Towards a Simpler Semantics for Systems Biology

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Abstract. *Computational semantics for molecular biology was introduced to assign activities to biomolecules based on their interactions with environments and other biomolecules. We distinguish between activity and biological function towards an epistemologically neutral semantics that aligns with computational processes. Object Petri Nets (OPNs) represent complex biomolecular activities as compositions of interactions at the nucleotide level. This article introduces a way to transform the networks that shows the equivalence between OPNs and simple Place/Transition (P/T) nets while preserving their semantics. It gives an intuitive understanding of this equivalence and shows OPNs implemented on P/T PNs.*

1. Introduction

In [Haeusler et al. 2023], we proposed a computational semantics for molecular biology. It assigns to any biological molecule a specific activity, i.e., a computational behaviour induced by each environment in which it can lie and the behaviour of other biomolecules that interact with it. The paper adverts to avoid the confusion between activity and biological function. For example, the helicase activity is seen as unwinding the DNA double-strand by breaking the hydrogen bonds between the complementary base pairs, allowing them to be separated, which is the double strand. It interacts with the DNA double-strand at the level of nucleotides and consumes ATP to perform its activity. The activity description should be epistemologically neutral, as with computational process activity. [Haeusler et al. 2023] uses Object Petri Nets, as defined in [Valk 2004], to describe each molecule activity. The article also points out that this intentional semantics is not ad-hoc and follows universal principles based on fundamental OPNs that provide the basic nucleotide interaction. In this way, it should be possible to express any biomolecular

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activity as a formal composition of these fundamental nucleotide-only based activities expressed employing OPNs.

In [Costa Neto et al. 2024], we showed that having models closer to the actual dynamics in molecular biology has potentially new and interesting conclusions regarding the behaviour of the system, in that work, we modelled at the codon level, which more closely resembles the observed behaviour for translation[1]. In [Haeusler et al. 2023] the authors propose to model the flow of genetic information at the nucleotide level, using OPNs, however, they carried the caveat of relying only on simulation to analyze behaviour, lacking more analytical tools.

The nets-within-nets (NwN) introduced by [Valk 2004] and used in [Haeusler et al. 2023] has been a popular extension of the more usual P/T Nets introduced by Carl Petri in 1962 [Petri 1962]. However popular, this new formalism lacks the rich analysis methods available for the plain P/T Nets [2]. In that regard, it would be advantageous to convert NwNs to vanilla P/T Nets back and forth to be capable of using the vast literature regarding analysis methods for the latter.

Focusing on the fundamental interactions happening at the level of the nucleotides and the semantical principle that any biomolecular activity is a composition of these basic object Petri nets, we would like to have tools to perform a formal analysis of such OPNs. As cited above, there are many tools to formally analyze vanilla P/T nets; thus, a mapping from OPNs to P/T nets that preserves semantics in some way can fill this gap and permit the best of both worlds, both an intuitive and less cumbersome modeling formalism (OPNs) and the rich literature and analysis tools available for the usual formalism.

The goal is to introduce the idea of an equivalence between the NwN and P/T Nets formalisms that preserve semantics. The goal is to provide intuition behind the equivalence. However, this work does not present the complete proof due to scope and space considerations.

2. Using Petri Nets and OPNs to formally describe Biomolecular activity

In this section, we consider the translation of a polypeptide by a mRNA and a tRNA, i.e., the translation of the polypeptide from the mRNA coding. We focus on attaching one tRNA and its amino acid in the polypeptide. We do not consider the use of ATP in this activity for a better explanation.

In Figure 1 we show an unmarked version of a Petri net that describes the activity of attaching an anticodon formed by the nucleotides assigned to P4, P5, and P6, respectively, to the codon determined by the three-nucleotide sequence P1, P2 and P3 of the mRNA, respectively, incorporating the aminoacid related to P8 in the polypeptide translation. Figure 2 shows the marking corresponding to the enabling of this activity and Figure 3 shows the product of this stage of the translation activity. The nets considered in this example could be describing the specific attachment of the amino acid lysine that has the codon AAG, so the anticodon is UUC. After the end of this stage of the translation, we

[1]We showed, that in this more detailed model, the system can have non-linear behaviour regarding consumption of amino acids, with possible implications to understanding how introducing mRNA in an environment may affect the mRNA already there in some cases.

[2]For a review of some of these methods, see [Murata 1989].

would have the lysine in the place P8, and the mRNA enabled to continue the translation. Finally, in this example, P1-P2-P3 would be A-A-G and P4-P5-P6 would be UUC.

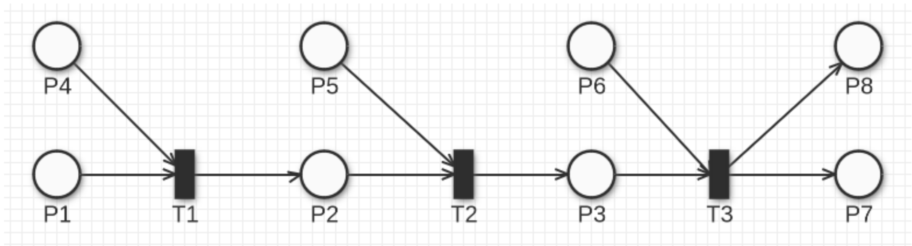

Figure 1. Part of a P/T PN describing the association of an anticodon (P4-P5-P6) of a free tRNAs with its corresponding three nucleotide part of a mRNA, i.e. the codon P1-P2-P3, capturing an amino acid, P8

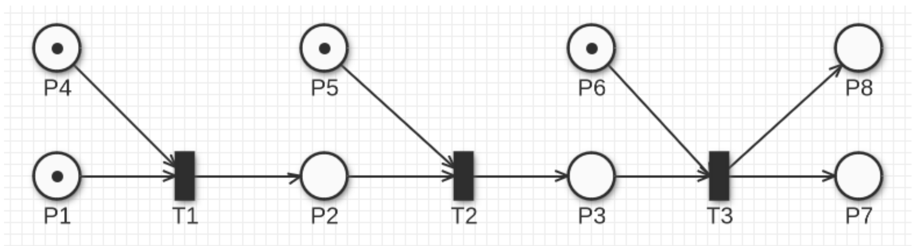

Figure 2. Marking denoting the existence of the anticodon (P4-P5-P6) of a free tRNA enabled to be attached to the three nucleotide codon sequence, P1-P2-P3

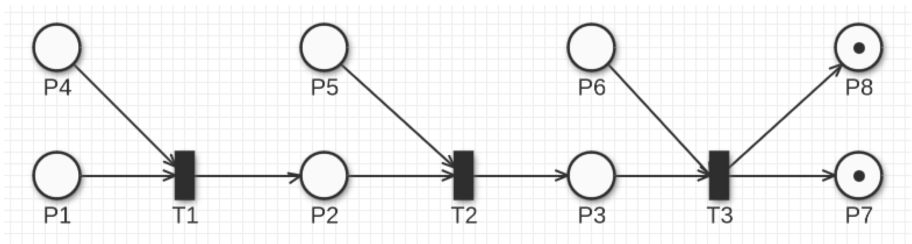

Figure 3. Marking denoting the existence of the anticodon (P4-P5-P6) of a free tRNA enabled to be attached to the three nucleotide codon sequence, P1-P2-P3

We note that the whole translation process can be described by an equivalent larger Petri net (PN). However, this way of representing the biomolecular translation activity of the combination of a mRNA and a set of tRNAs is less intuitive and modular. The equivalent PN is big and sparse and does not reflect the intention of this combination. We contend that a Petri net as depicted in Figure 4 capture better the intention of combining mRNA and tRNAs to produce protein. This is just the activity of a ribosome. The Object Petri Net in the Figure represents the ribosome's activity. The place mRNA has a token that is a Petri Net itself, as shown in Figure 6 PN based on the lower places in Figure 1, while each token in the place tRNA in Figure 4 is a tRNA as in Figure 5. The interaction between the token Petri Net and the higher level Petri nets is provided by the mechanisms defined for OPNs, illustrated in Figure 7, 8 and 9.

With the motivation of modelling processes crucial to life itself through OPNs, we will explore how to convert an OPN into a vanilla P/T Net in the next section, recalling the

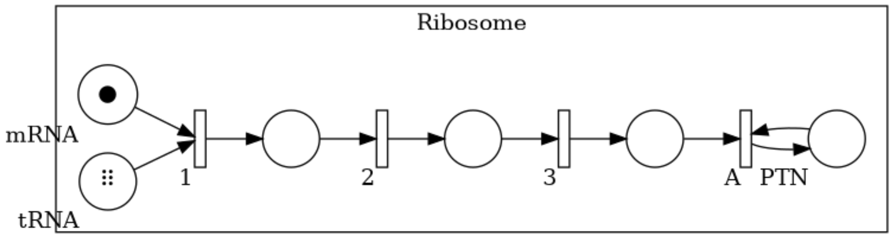

Figure 4. Object Petri Net representing the activity of a Ribosome.

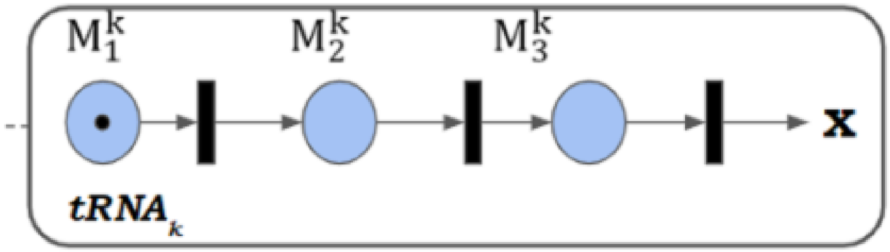

Figure 5. Object Petri Net representing the activity of a transfer ribonucleic acid.

idea introduced in the first section of using this equivalence to reclaim the vast analysis tools available for vanilla P/T Nets.

3. The best of both worlds

In the previous section, we explored the advantages of OPNs as an intuitive and modular framework for understanding the dynamics of biomolecular processes. Although intuitive and modular, it lacks the tractability of usual P/T Nets, so having a way of mapping OPNs to usual P/T Nets, preserving behaviour (i.e. semantics), would provide the best of both worlds. This is similar to how having higher level programming languages, with more abstraction, is easier to work with, rather than programming directly in machine language, but in the end, we need to descend to the machine level to be capable of running programs.

In this spirit, we begin with an OPN with some complexity and some interactions in Figure 10 and Figure 11 provides a step-by-step technique for converting OPNs of the NwN flavour into vanilla P/T Nets.

Theorem 3.1. *[Semantic Preservation from OPNs to PNs] For any OPN(NwN) π there is an equivalent vanilla P/T Net π', such that, for every marking (R, M) in π, there is a unique marking M' π' and for every possible action $(\hat{t}, i, t)$ in π, there is a unique transition t' in π'. Moreover, given a marking in π, an action is enabled iff the equivalent transition is enabled in the equivalent marking, and firing the action in π and the equivalent transition in π', results in equivalent markings.*

We cannot present here a full proof of the above proposition, as it would be out of scope for this work. Nonetheless, the procedure mentioned in Figures 10, 11 can be made precise and an inductive proof is sufficient to ensure the correctness of the statement.

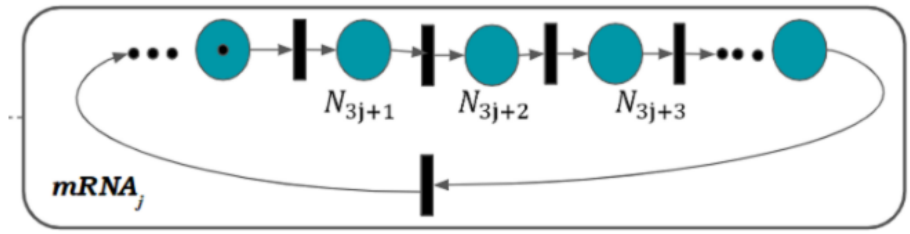

Figure 6. Object Petri Net representing the activity of a messenger ribonucleic acid.

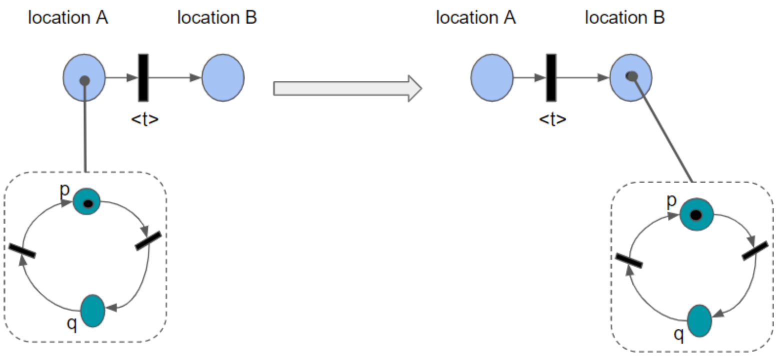

Figure 7. Object Petri Net transport action semantics

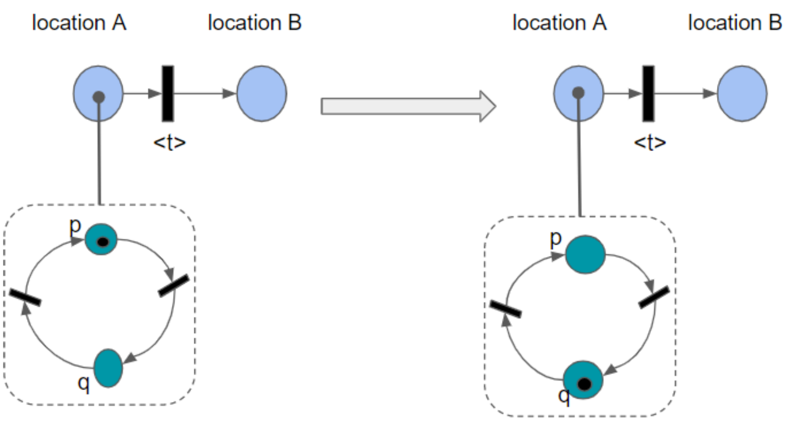

Figure 8. Object Petri Net autonomous action semantics

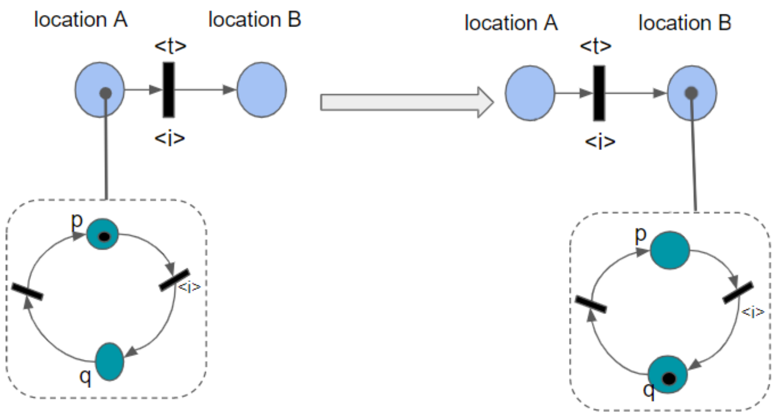

Figure 9. Object Petri Net interaction semantics

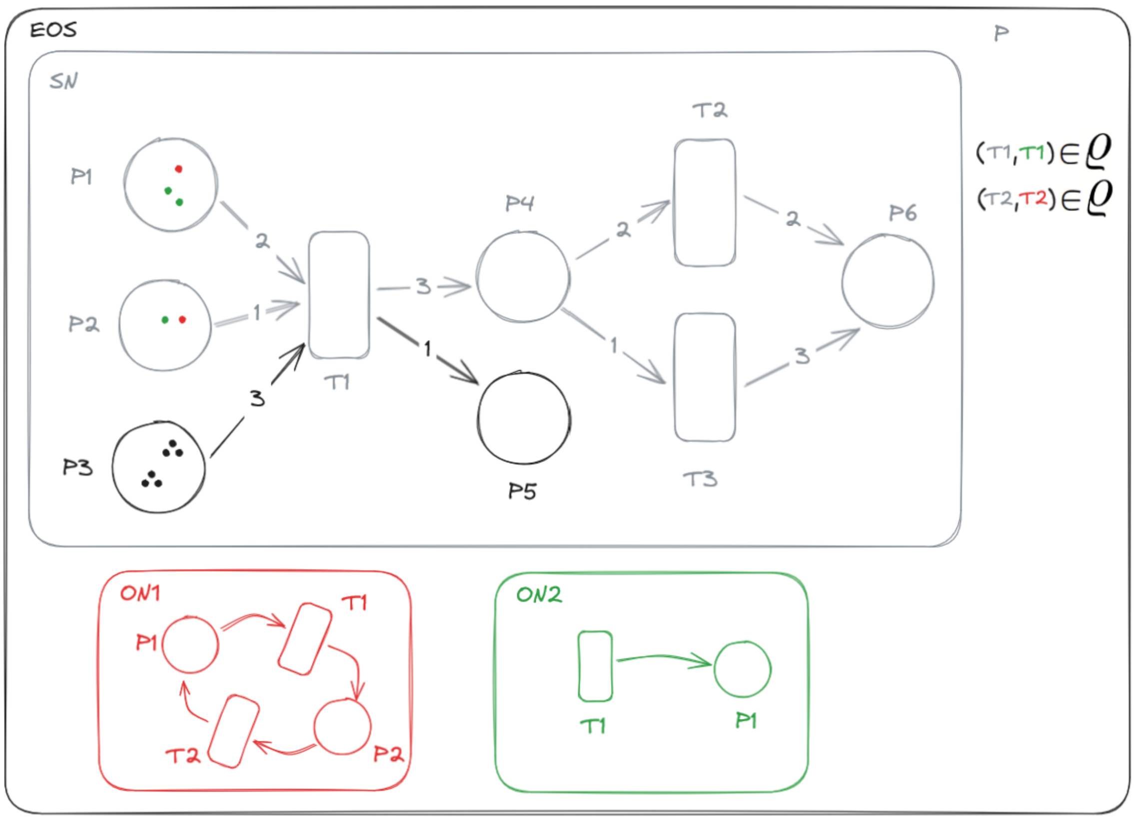

Figure 10. $EOS = (\mathcal{SN}, \{\mathcal{ON}_1, \mathcal{ON}_2\}, \varrho)$
with some initial marking, which has only an interaction action enabled

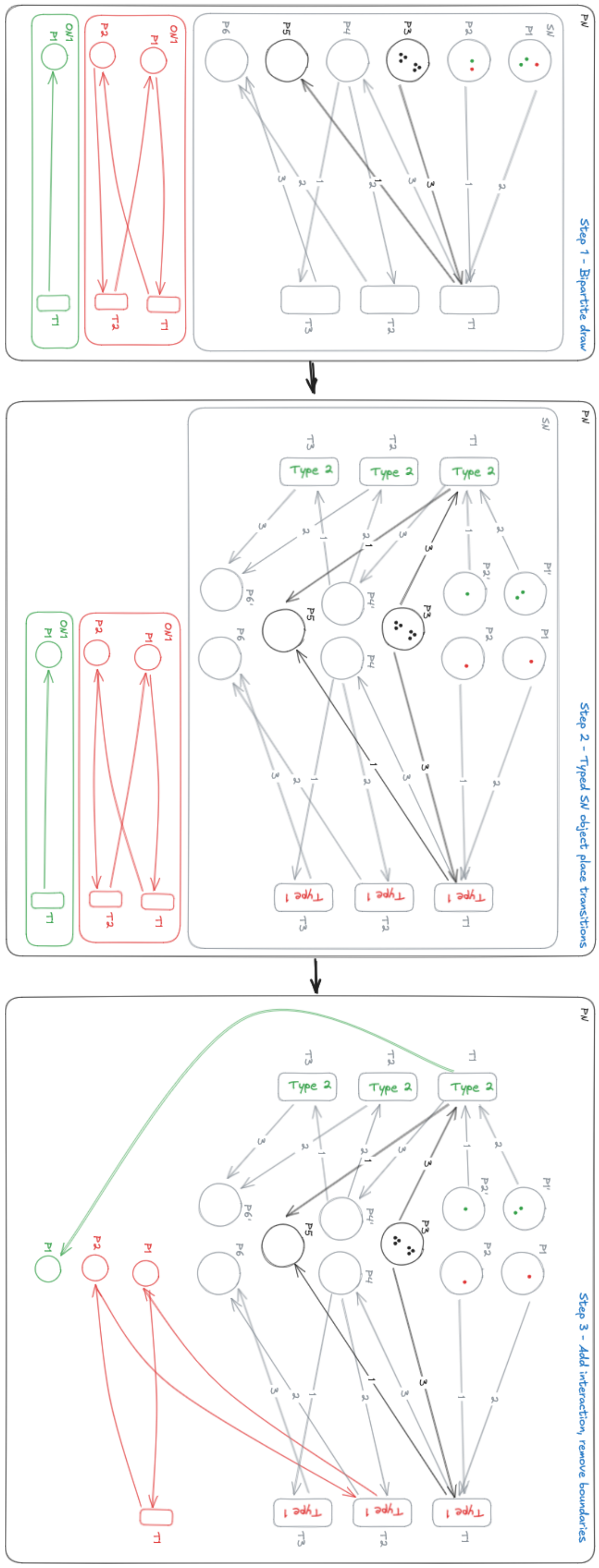

Figure 11. Intuitive visualization of how to convert an OPN (NwN) into a vanilla P/T Net

4. Computational Results and Discussion

With the above procedure in mind, the question of the utility of such a procedure may be raised, and its role in bioinformatics. In this section, we discuss some results in related works that draw from the use of the correspondence between OPNs and vanilla P/T Nets, in the context of protein translation.

In [Costa Neto et al. 2024] we transformed the proposed OPN in [Haeusler et al. 2023] into a vanilla P/T Net and used this to run Monte Carlo simulations. The experiments showed the theoretical possibility of having a detrimental effect of the abundance of mRNA, this was made possible by the level of detail of the model[3]. But this level of detail, without modularity, implies a lot of rework each time a new feature is to be added, with OPNs, it is possible to consider existing networks as tokens in a larger network or to extend the level of detail by making the tokens into networks themselves.

In [Guateque et al. 2024], the authors leveraged a close notion of equivalence, to turn OPNs into Coloured Petri Networks[4], with that, they were able to use available software to draw results from the model. This shows the usefulness of an equivalence, in particular for modelling complex systems as is usual in bioinformatics.

We understand this equivalence, can help drive forward further analysis of qualitative properties of biological networks that would be reasonable to expect, such as liveness or boundedness, among others. Also, several methods of analyzing the network such as reachability, transition matrices, etc[5]. And the equivalence may help keep modularity in the process.

5. Conclusion

In this work, we have remotivated the formal approach to modelling biomolecular activities using Object Petri Nets (OPNs), introduced in [Haeusler et al. 2023], and established their semantic equivalence with simple Place/Transition (P/T) nets. By distinguishing between activity and biological function, we maintain an epistemologically neutral framework that aligns with computational principles, offering a precise method to represent complex molecular interactions in a simpler than OPN's computational model. The transformation of OPNs into P/T nets, as introduced in this study, preserves their underlying semantics while enabling more accessible analysis through existing P/T net tools. This equivalence not only advances the formal understanding of biomolecular processes but also expands the applicability of well-established computational methods in molecular biology. Future work will focus on refining these transformations and exploring additional applications within broader biological contexts. The implemented tool described in the previous section and its use in the simulation of protein synthesis shows how the equivalence theorem facilitates the formal analysis of OPNs.

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[3] In this case, the process was simulated at the codon level.

[4] This would be an intermediate step in our procedure.

[5] For more properties and a comprehensive review of analytical methods see [Murata 1989]

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A. EOS structure and reference semantics

Although formally proving the equivalence is outside the scope of this work, it is instructive to explore the definitions for OPNs vs vanilla P/T Nets to better understand the intuitive notion of how to build the equivalence. Also, the definitions are relevant to make precise both what we mean by semantics in the formalisms and the OPNs formalism used here[6]. We follow [Valk 2004] closely, with some small differences that in no way change the original meaning of the definitions, but rather introduce nomenclature that makes it easier to understand the equivalence we propose.

Definition 1. *(EOS structure) An elementary object system (henceforth EOS) is a tuple $\mathcal{OS} = (\mathcal{SN}, \mathcal{ON}, \varrho)$, where $\mathcal{SN}$ is the system network, $\mathcal{ON}$ is a set of object networks and ϱ is the interaction relation between the transitions from the system net and of some transition in one of the object nets. More precisely:*

1. $SN = (\widehat{P}, \widehat{T}, \widehat{W})$, *where:*
   (a) $\widehat{P} = P_{bt} \cup P_{ob}$ *and* $P_{bt} \cap P_{ob} = \emptyset$*;*
   (b) $\widehat{T}$ *is the set of transitions;*
   (c) $\widehat{W} : (\widehat{P} \times \widehat{T}) \cup (\widehat{P} \times \widehat{T}) \to \mathbb{N}$ *is the arrow weight function.*
2. $\mathcal{ON} = \{\mathcal{ON}_1, \mathcal{ON}_2, \ldots, \mathcal{ON}_k\}$ *is the set of object nets, with each object net being a triple* $\mathcal{ON}_i = (P_i, T_i, W_i)$ *where the terms are the set of places, the set of transitions and the weight function for the i-th object net, respectively, with these elements defined as usual.*
3. $\varrho \subseteq \widehat{T} \times (\bigcup_{1 \leqslant i \leqslant k} T_i)$

Note that $\mathcal{SN}$ and each $\mathcal{ON}_i$ have similar definitions, with the distinction that $\mathcal{SN}$ may have different types of places and tokens and, as in [Valk 2004], the object nets are only allowed to have the usual *black tokens*. This results in a 2-level network system, which we will restrict ourselves to for the sake of simplicity.

[6]Which is that of an Elementary Object System (EOS), as used in [Valk 2004]

With the structure set, we can move on to the semantics of the EOS. In [Valk 2004], two main ideas are presented: reference semantics and value semantics, we will concern ourselves only with reference semantics in this work.

Definition 2. *(Marking/reference semantics) The marking for an EOS under reference semantics is a pair (R, M), where R is a special marking for the $\mathcal{SN}$ and M is an array with the markings for each $\mathcal{ON}_i$, more precisely:*

1. $R : \widehat{P} \to \mathbb{N} \cup \mathrm{Bag}^7(\mathcal{ON})$*, with* $R(\widehat{p}) \in \mathbb{N}$ *iff* $\widehat{p} \in P_{bt}$*, Through the* Bag *definition, we can assign to an object place different quantities of specific object nets.*
2. $M := \{(m_1, m_2, \ldots, m_k) \mid m_i \in \mathrm{Bag}^7(P_i)\}$

With this pair, we completely specify the state of each network in the system. The $\mathrm{Bag}(\mathcal{ON})$ is there to represent mathematically the notion of a multitude of objects in an object place, each object with its multiplicity. In the object networks, the notion of a marking is as usual, as there is no difference between the tokens in an object network.

We call the dynamic of the EOS the possible changes between states (i.e. markings). In the traditional P/T Net, this is determined entirely by the transitions, in an EOS, we may have combinations of simultaneous transitions in each of the networks. In our work, we call any possible individual transition or combination, an action, an action maps one marking (R, M) to another (R', M'), we will use the word action instead of transition when speaking of the EOS change of states[8]. This choice of giving a new name for the change of states at the EOS level will help when we begin mapping the EOS to a simple P/T Net. To keep notation consistent with respect to [Valk 2004] we will denote $(R, M)[\alpha\rangle(R', M')$ to state that the EOS has changed from state (R, M) by firing action α (defined below) and therefore reaching state (R', M'). We will not reproduce here the technical details for each definition but rather describe the intuitive notion for the possible actions.

Definition 3. *(Empty transition) Given a network with transition set T, we denote by τ an additional special transition, such that it does not change the state of that network. We define $T_\tau = T \cup \{\tau\}$, and we assume τ to be defined for any network and for its meaning to be clear from the context where it appears. The empty transition is defined as always being enabled in the network.*

Definition 4. *(Action)*[9] *We define an action to be an element* $a = (\hat{t}, j, t) \in \widehat{T_\tau} \times \{1, \ldots, k\} \times (\bigcup_{1 \leqslant i \leqslant k} T_{\tau i})$ *with the restriction that* $t \neq \tau \to t \in T_j$*.*

At first glance, this definition of action seems more complicated than necessary, after all, why shouldn't we define an action as simply being some transition occurring in some of the networks? If we did this, then actually the equivalence would be obvious, as it wouldn't matter the level of the transition, we could consider the networks separately. What makes the NwN/OPNs framework interesting, is the possibility of interaction between transitions in different networks, that is what our definition of action encompasses. To make it less abstract, below follows a classification of actions based on where they happen and how they interact[10].

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[7] Given a nonempty set A, we denote by $\mathrm{Bag}(A)$ the set of multisets of A, where a multiset of A is a function $s : A \to \mathbb{N}$.

[8] We understand this to be a better terminology to avoid confusion with the transitions that happen within the system and object nets.

[9] This is not defined explicitly in [Valk 2004], though it is used in the form of $[\hat{t}, t_i\rangle$ in a similar sense.

[10] In [Valk 2004] there's the possibility of interaction between object networks, this is not a problem for our equivalence, it just requires a slight modification in the definition of action, instead of taking the union of the transitions in the object networks, we would need the cartesian product.

Definition 5. *(Types of actions/ reference semantics)*

- *Interaction: the action belongs to the interaction relation ϱ, in this case, the transition in the system network and the transition in the object network can only be fired simultaneously.*
- *Transport: only a transition at the system network is fired and it does not interact with any object network, i.e. does not belong to ϱ. In this case, only the marking at the system network is changed, i.e. $R \neq R'$ and $M = M'$ (recall definition 2). It is enabled if the transition at the system network is enabled.*
- *Autonomous: only a transition at some object network is fired, and it does not interact with the system network. In this case, only the marking for that particular object network is changed.*

A.1. An isomorphic P/T Network

With the details of the definitions clear, we proceed to the main part of this work and give the main ideas to build the isomorphic network, though a full proof is outside of the scope of this work and will remain to be published in the future. But first, we need to address what we mean by an isomorphism here.

A.2. What do we need?

To say that two network formalisms are ”isomorphic”, morally we need to be able to translate back and forth between them, in our case, we need to convert both the states AND the firing sequences unambiguously, this means we need

- For each state (R, M) at the EOS, we need to have one and only one state for the P/T Net (i.e. a marking of the P/T Net) - that means we can translate the state of the network.
- For each possible change in state for the EOS (an action), we need to have one and only one possible change of state (i.e. a transition) for the P/T Net - that means we can translate the firing sequences
- For corresponding states, an action is enabled in the EOS iff the corresponding transition is enabled in the P/T Net
- Given corresponding states and corresponding actions-transitions, the resulting states must be in correspondence as well - this preserves the semantic effects of a firing sequence

A.3. Building the P/T Net

The realisation that these are the same is motivated by the fact that transition names matter little, what matters is the change in states they produce. Similarly, separating place sets should be tantamount to considering the entire place set and considering the changes of each transition in it. This is the essence of a plain P/T Net. We also note that we introduced the definition of an action precisely because they will correspond exactly to the transitions in the isomorphic net.

To simplify the definition, we assume that $P_{bt} = \varnothing$, this in no way restricts the semantics of the network, as we can always consider the black tokens to be empty object networks.

Definition 6. *Given and $EOS = (\mathcal{SN}, \{\mathcal{ON}_1, \mathcal{ON}_2, \ldots, \mathcal{ON}_k\}, \varrho)$, with $\mathcal{SN} = (\widehat{P}, \widehat{T}, \widehat{W})$ and $\mathcal{ON}_i = (P_i, T_i, W_i)$, we define an equivalent P/T Network (P', T', W') as:*

- $P' = (\widehat{P} \times \{1, \ldots, k\}) \cup (\bigcup_{1 \leqslant i \leqslant k} P_i)$
- $T' \subseteq \{(\hat{t}, j, t) | (\hat{t}, j, t) \in \widehat{T}_\tau \times \{1, \ldots, k\} \times (\bigcup_{1 \leqslant i \leqslant k} T_{\tau i}) \wedge t \neq \tau \rightarrow t \in T_j \wedge (t \neq \tau \wedge \hat{t} \neq \tau) \rightarrow (\hat{t}, t) \in \varrho)\}$, *which is exactly the set of actions as we defined.*
- $W'(p,t) = \begin{cases} \widehat{W}(\hat{p}, \hat{t}), & \textit{if } p = (\hat{p}, i) \in (\widehat{P} \times \{1, \ldots, k\}) \textit{ and } t = (\hat{t}, j, t) \in T' \textit{ with } i = j \\ W_i(p,t), & \textit{if } p \in P_i \textit{ and } t = (\hat{t}, j, t) \in T' \textit{ with } i = j \\ 0, & \textit{otherwise} \end{cases}$
- $W'(t,p)$ *is defined similarly*

With this definition of the isomorphic network, we have the same network resulting from the procedure in Figure 11. In the procedure, the step of drawing the network as a bipartite is merely a means to better visualize the equivalence.

This definition, put together with an inductive argument and a careful analysis of the results of firing transitions in each system, is enough to formalize theorem 3.1.