Causal $\pi$-Calculus for Biochemical Modelling*

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Abstract. We present a reduction semantics for the $\pi$-calculus from which causality and concurrency can be mechanically derived. We prove that our semantics agrees with the causal definitions presented in the literature. We then apply the causal reduction semantics in the domain of biochemical systems to study the interactions of components.

Keywords: Concurrency, Causality, Reduction Semantics, Bio-informatics, Formal Description of Biochemical Processes

1 Introduction

Causality in concurrency has received a lot of attention. Its supporters claim that it permits more accurate and often more concise representations of system behaviour. Degano & Priami \cite{DeganoPriami} proposed a structural operational semantics for the $\pi$-calculus that is interleaving in style, but has enough information to (mechanically) derive causal description.

Recently, Regev, Silverman & Shapiro \cite{RegevSilvermanShapiro} proposed the $\pi$-calculus as a model of biochemical processes, seen as network of proteins. The authors claim that the main advantage over other proposals (see among others \cite{PetriNets,DeganoPriami,Barthelemy,Comon}) is that the $\pi$-calculus permits to better integrate dynamics, molecular and biochemical details. This calculus has solid theoretical basis, widely investigated. Additionally, the $\pi$-calculus has a linguistic structure, unlike other approaches leading to similar descriptions (\textit{e.g.} Petri Nets \cite{PetriNets}). Further work lead to a more precise model \cite{Sangiorgi}, that describes also quantitative aspects of reactions, such as time and probability. Its authors use the stochastic $\pi$-calculus \cite{SangiorgiStochastic}, an extension of the original calculus with probabilistic distributions that govern the race conditions. Slight extensions are only needed to the standard reduction semantics to take care of the quantitative information (plus a further rule to model homodimerization).

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Although it offers a qualitative view of processes, causality seems to play a relevant role in understanding complex biochemical reactions. No reduction semantics was available expressing also causality. In this paper we offer such a causal semantics for the $\pi$-calculus, and we apply it to a small biological example. Our semantics can be considered unconventional, because our reductions do carry labels, from which the causality and the concurrency relations are mechanically derived. Indeed, we mimic the so-called enhanced operational semantics [3]. The information stored in reduction labels make our proposal flexible: also other aspects of processes can be derived from labels, in particular quantitative aspects [2]. Separation of concerns suggest us to discuss here only causality; for a survey on enhanced operational semantics, see [4].

Our example models a well-characterized biochemical process: the activation of the transcription factor NF-AT, which plays a crucial role in the process of T-cell activations. This process is particularly important in immunology and oncology. Our simulation reflects faithfully experiments in vitro, especially the two pathways activated by the T-cell antigene receptor (TCR) that lead to the activation of the transcription factors AP-1 and NF-AT.

This makes us confident that our proposal can be used both as a descriptive tool and as a prescriptive one. Also, the causal relation we extract from the computations of processes of the $\pi$-calculus has a meaningful graphical representation. These pictures seem to be superior to those commonly used by biologists to describe biochemical processes (e.g. KEGG [13] or EcoCyc [11]), because they explicitly describe pathway evolutions, originated from a formal model. Consequently, the attention is focused on the flow of reactions that occur in the process, rather then on reactants only. Furthermore, while other computational tools have been developed for the description of biological pathways, our approach appears particularly suitable to the analysis of signaling pathways mediated by protein-protein interactions based on the conversion of their individual molecular components from an off to an on state. Also, a formal description of the pathway should permit software simulations that offer cheap pre-views of tests before actually carrying them out.

As a matter of fact, the qualitative and the quantitative aspects are orthogonal to each other. So, the stochastic and the causal semantics can be combined together to yield even more detailed and accurate models of biochemical processes, taking care of the probability that reaction have to occur. As said above, our reduction semantics is flexible and supports both aspects (and more): the stochastic [18] and the causal descriptions of biological evolution can be specified within a single model.

The paper is organized as follows. In the next section we shall present our causal reduction semantics of the $\pi$-calculus, along with a comparison with similar work. In this extended abstract we only state our results and omit their proofs, that often are by structural induction. In Section 3 we shall briefly survey how biochemical processes may be represented as processes of the $\pi$-calculus; then we present our example and, driven by the model, we derive a graphical representation of the causal relations in the resulting pathways.