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Using Nets-Within-Nets for Modeling Differentiating Cells in the Epigenetic Landscape

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1 Introduction

In this work the authors propose the use of a high-level Petri net formalism for modeling developmental processes at the cell level, taking explicitly into account the role of epigenetic regulation. The term "epigenetics" can refer to all possible mechanisms "acting on the genomic information between genotype and phenotype" [1], changing the actual condition of a system without changing the underlying DNA sequence. "For example, even though the vast majority of cells in a multicellular organism share an identical genotype, organismal development generates a diversity of cell types with disparate, yet stable, profiles of gene expression and distinct cellular functions. Thus, cellular differentiation may be considered an epigenetic phenomenon, largely governed by changes in what is described as the "epigenetic landscape"" [1, 2]. The epigenetic landscape was initially proposed as a visual metaphor [2] for describing the scenario where developmental processes take place. Cell type differentiation is represented as increasingly irreversible, as ridges rise between the valleys where the different cells are traveling [3]. These two metaphoric terms refer to a quasi-potential scenario, as proposed in [6].

In computational terms, an epigenetic landscape can be interpreted as the ensemble of all possible regulation configurations a complex system can be in. Unfortunately, the huge number of variables involved in epigenetic regulation make this task extremely challenging.

The proposed model, based on Petri Nets, is designed to simulate and conceptually characterize the contributions of the epigenetic regulation from those of other mechanisms within the cells, including transcriptional and post-transcriptional regulation, and metabolism.

In this work we present the idea and the main properties of the model. Experimental results are not yet available but will be presented at the conference.

2 Motivation

The complexity of regulation mechanisms within the cell can be addressed choosing different formalisms [4]. Mathematical models, such as those based on differential equations [20], are potentially able to model several activities but suffer from high complexity in terms of modeling effort and computational requirements. Boolean Networks have been also efficiently exploited in modeling different regulation mechanisms.

Previously, we modeled enhanced gene regulatory networks (taking into account the contributions of post-transcriptional actors, such as miRNAs) by means of Boolean Networks [5]. However, Boolean models introduce a strong simplification of the modeled reality posing several limitations:

- the states of a node in the network are described by a Boolean value, while resources in a biological system are better described by continuous quantities;
- they do not support the composition of larger models from smaller ones, while information in the real system often has an encapsulated, modular and hierarchical organization;
- links between nodes are represented with weighted edges carrying either activation or inhibition; the interactions occurring in a biological network require more information than that to be properly described.
- they are deterministic, that is, the outcome of the execution is unique, whereas natural phenomena are intrinsically stochastic.

From these considerations the need emerges for a more suitable formalism for modeling a biological phenomenon and its dynamic evolution.

Developmental processes into the epigenetic landscape have already been addressed with mathematical models applied to gene regulatory networks [6]. Sharing the quantitative interpretation of the epigenetic landscape metaphor proposed there, we aim to further challenge the so-called central dogma of biology, proposing a more powerful computational model whose higher specificity and organization allows for a better representation and subsequent analyses.

3 Methods

Epigenetic mechanisms of regulation, which are able to affect the whole network within a cell by controlling the availability of genomic information, overimposes a hierarchically separate level of complexity on systems dynamics. That raises the need of a two-folded approach which allows for taking into account some prerogatives of one layer of regulation above the others. Moreover, the position of the cell into its epigenetic landscape is co-determined by the state of its regulatory network.

Since both these facets of dynamic regulation must be taken into account, the Nets-Within-Net formalism is proposed, which is a high-level Petri net model consisting of a system network whose tokens are, in turn, Petri nets.

3.1 Petri Nets

Petri nets can be used as a tool for describing distributed, concurrent asynchronous systems using a low degree of abstraction. The reason for their success as net models lies in their graphical representation, together with a well-defined semantics allowing formal analysis [7]. They've been assessed as valuable tools for modeling biological systems, and examples of their application can be find in the literature [8, 9, 10]. Petri nets are bipartite, weighted and directed graphs. Each node belongs to one out of two separate groups: places or transitions. Edges link nodes of different kind only, i.e., a place and a transition or vice-versa, and not two places or two transitions. Input places are those from which edges go to transitions, output places, conversely, are reached by edges from transitions. Each place can contain entities called tokens, which can move along edges and transitions to the next places of the net. The tokens move through a transition if it is enabled and it fires. Enabling occurs when in its input places the number of tokens exceeds a threshold associated with a transition. Each transition fires by activating its specific function, which regulates the way tokens move through it. In fact, each transition can be programmed for functioning in a specific way, under different requirements also in terms of token availability. The enabling of a transition does not directly imply its activation, but it is a necessary condition for it: a transition may fire only once it is enabled, but it will only fire after an interval of time which can be non-deterministic. This peculiar dynamical feature allows for the representation of concurrency in distributed systems, satisfying one of the requirements for a suitable representation of complex biological problems, where interactions among the elements of the same network tend to be parallel and asynchronous.

Some topological structures in the net are related to specific dynamical features. A group of places and transitions is defined as a trap if tokens entering such structures won't exit them. If tokens enter a net structure only to exit it and are not able to come back in, it is a structural deadlock. Sets of places and transitions involving a uniform number of tokens over time are called invariants and have a great importance for model analysis. Each of these can be related to specific dynamical features of biological systems: for example, traps can model cyclic structures in biological regulation that are activated by an input, structural deadlocks can refer to cyclic structures that might produce molecules by consuming themselves, while invariants can implement the assumption of mass conservation in biochemical reactions [11].

Given a topological structure, a Petri net is specified also by its initial marking, that is, the initial distribution of tokens in the places. As the network evolves, subsequent markings are formed, corresponding to some of the states the system can assume. The state space of a Petri net is defined as its reachability graph, i.e., the set of possible markings the initial marking can evolve into.

A transition is described as dead if it is not supposed to fire anymore, in the subsequent evolution of the network. Depending on the capability of a transition for firing, it can be described with different degrees of liveness, the higher corresponding to a transition, which always fires as the net evolves. The whole Petri net is described in terms of liveness depending on that of all its transitions.

A place can be bounded, in the sense that the number of tokens it can contain is limited. It is described as safe if such number is 1, and as *k*-bounded if it is *k*. [12]

Tokens can represent quantities of resources, discrete or continuous. Their transitions can fire once enabled, following deterministic, but also stochastic rules. This allows for the representation of real quantities in biological systems, taking into account the contribution of stochastic events to their evolution in time.

The model described so far is called also Place-Transition network, or low-level Petri net, and it is a suitable formalism for modeling biological networks better than, say, Boolean Networks. Still, it has only one kind of token. The capability of this model can be exploited for overcoming such limitation, building more suitable formalisms. In high-level Petri nets, each token contains complex information or data, providing much more potential for addressing real-world problems. A compact representation of this additional layer of information is achieved in colored Petri nets: to each token can be attached a different, arbitrarily complex data value, which is graphically represented as a color. Different color sets refer to the possible values of the tokens they contain. In this formalism, each place is described by a marking,which is a multi-set over the color set attached to the place. [7]

Petri nets can be used for building nets-within-nets, i.e., structures consisting of a system Petri net whose tokens are provided with a structure, which is based on Petri nets too [13]. Hence, a net can contain net items, being able to move in the system net and fire themselves trough its transitions. This allows for the description of mobility, hierarchy and encapsulation, since the net tokens move in a frame whose structure is independent from them, sets up functional constraints on their mobility, and can be nested. Net tokens can be considered as references to net items, if the system is described in terms of reference semantics. They can also be described in terms of their existence in different places and with different internal states, according to value semantics instead. In this frame, copies of a net token can be created to model concurrent execution. In nets-within-nets, net tokens can communicate via predefined interfaces, allowing for insights to the interplay of locality and concurrency [14, 15, 16, 17].

The choice of the Petri net formalism allows to overcome most limitations of Boolean Networks:

- the possible states of a place can be described with discrete but also continuous quantities;
- nested Petri nets properly represent hierarchically organized networks; the potential for describing encapsulation and motility in biological systems is expressed at its full in nets-within-nets;

- links between places are described by edges and transitions, whose functioning can be set up independently from that of the others, allowing for a suitable representation for the diversity of interactions described in biological systems;
- choosing to set a non-deterministic delay between enabling and firing for transitions makes the description of stochastic contributions to biological mechanisms possible.

Addressing the particular problem of a differentiating cell going through the epigenetic landscape, the nets-within-nets formalism is potentially able to satisfy the requirement for a representation of intrinsically intertwined, yet hierarchically separable levels of regulation.

In our model, the system Petri net represents the epigenetic landscape, each place referring to a specific epigenetic regulation state. Transitions represent the stages of a developmental process, which is a path undertaken by tokens. Each token is in turn a Petri net, representing the enhanced regulatory network of a specific cell, where the places are the molecules involved, and transitions are the interactions between them. Each cell adapts to the epigenetic constraints linked to the place it is in, and undergoes subsequent network evolution. An abstract and static representation of the model is provided in Fig. 1. Transitions in the outer net can be enabled by system regulations as well as by specific conformations of the net tokens in the respective input places. In this way, the transition of a cell from a state to another is co-regulated by both epigenetic and non-epigenetic factors, providing for a more realistic mimicry of the biological system. In fact, differentiation can be explained both in terms of external guidance and by means of intrinsic regulation, since the two are extensively intertwined. The dynamics of the system net, referring to a developmental scenario, or epigenetic landscape, and that of the individual cell, referring to specific differentiation processes, can be discerned one from the other. At the same time, their functioning is strictly intertwined, like in biological developmental processes.

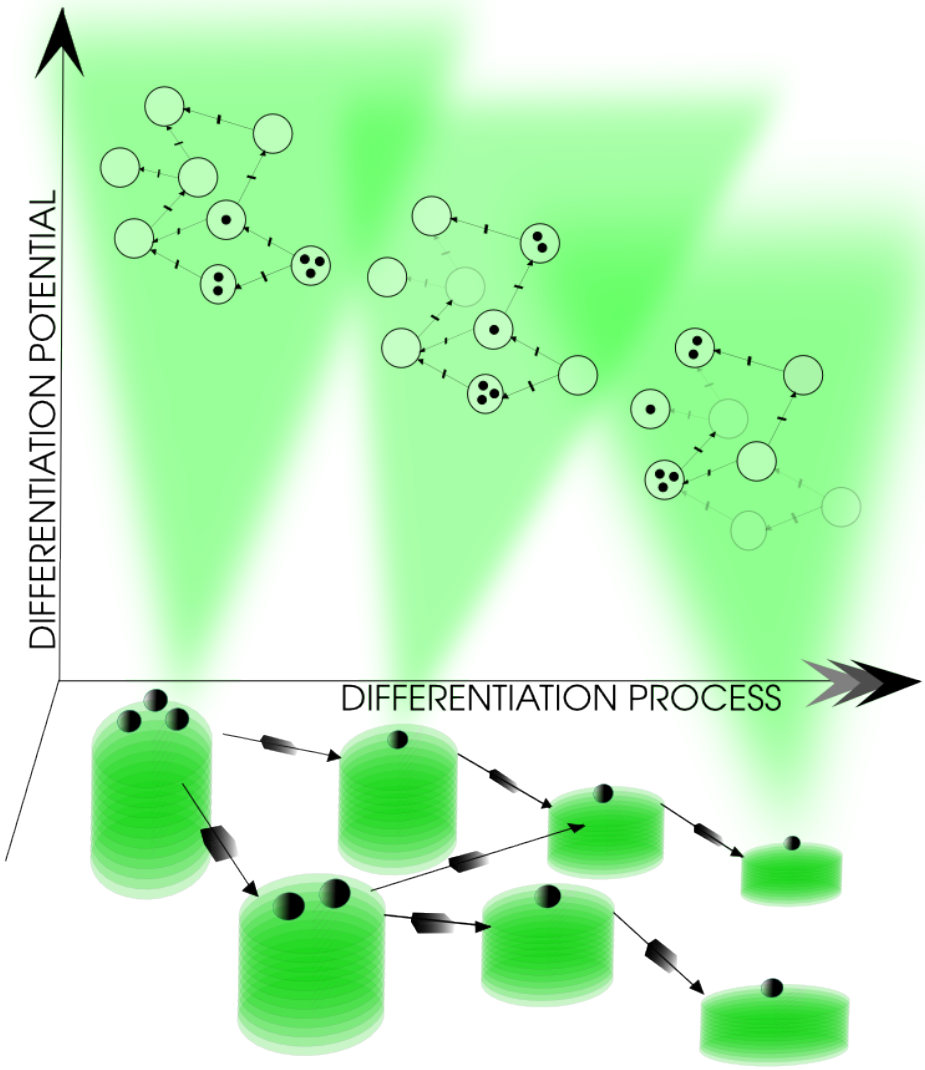

Fig. 1 This representation of the model shows the hierarchical relation between the system net and the net tokens. Each place of the system net imposes *de facto* topological modifications on the net tokens it contains, contextually de-activating some of their components. Traveling through the system net, each net token evolves indipendently, as shown by their different markings evolving also respect to the contraints of each system place. In the context of a developmental process, the vertical position of system places on the axis of differentiation potential refers to the *quasi-potential* landscape [6] they are described in, ranging from maximal stemness to complete differentiation of the net tokens it contains, along the differentiation process. For some net tokens (black spheres) a representation of the Petri net it refers to is provided.

4 Future perspectives

The model proposed can be employed for addressing specific matters in the frame of differentiation processes in both physiological and artificial contexts. Some of the applications Nets-within-nets can be suitable for are suggested:

- modeling the physiological differentiation processes in organismal developmental processes;
- modeling stem cell differentiation into their niches in adult tissues;
- modeling the induction of pluripotent stem cells from differentiated cells by means of genetic engineering (iPSC, [18]), or by chemicals (CiPSC, [19]) and the process of obtaining differentiated cells from them;
- studying the population distribution of the differentiating cells during tissue development;
- testing particular net tokens for their compatibility with particular places of the system net, for classifying them according to their position in the epigenetic landscape, during physiologic od pathogenic developmental processes of development, in a natural or artificial context.

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