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Efficient modelling of yeast cell cycles based on multisite phosphorylation using coloured hybrid Petri nets with marking-dependent arc weights

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HIGHLIGHTS

- We present a case study for using coloured hybrid Petri nets to model complex biological systems that exhibit hybrid and nonlinear behaviour.
- Coloured Petri nets have been extended to support marking-dependent arc weights.
- Comparing the results of hybrid and stochastic versions of the presented model reveals that they are equivalent, but the hybrid one is more efficient.
- Coloured hybrid Petri nets present an excellent tool to model complex biological systems such as cell cycle regulations.

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ABSTRACT

With the increasing interest in systems biology to investigate the dynamics and behaviour of biological reaction networks, the scales as well as the complexities of the models under study grew rapidly and continue to grow at even faster pace. Traditional single-scale simulation methods become more and more impractical and inefficient to study these complex reaction networks. A daunting example of biological systems that falls into this category is the cell cycle regulation. In order to accurately model repeated cell growth and division, the corresponding reaction network should exhibit some sort of nonlinearity. One of the techniques able to reproduce this nonlinear behaviour is to include a series of phosphorylation and dephosphorylation reactions of the regulating proteins. However, this modelling approach results in two main challenges: the existence of components with different abundance of molecules and substantially larger biochemical networks in terms of number of reactions and species, with many of them exposing equivalent structure and behaviour. In this paper, we address these two issues by exploiting the modelling power of coloured hybrid Petri nets ($\mathcal{HPN}^C$). $\mathcal{HPN}^C$ are a hybrid Petri net class that combines stochastic and deterministic events over a continuous time scale at the coloured level. Moreover, motivated by this case study we extend $\mathcal{HPN}^C$ to include marking-dependent arc weights instead of just having constant values to define such weights.

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1. Introduction

Cell cycle regulation [1–3] is an example of biological systems which require intensive investigations in order to disclose key factors affecting the interactions of their biological network components. Systems biology plays an important role in studying this and other similar biological systems for a better and deeper understanding of the mechanisms behind the functioning of certain biological networks. Many models have recently been constructed to elucidate the interactions between the different cell cycle components at the system level (see, e.g., [2,4–9]). The aim of the majority of these models is to reproduce the cell cycle behaviour observed and measured in the "wet-lab" using "dry-lab" experiments. This will indeed increase our understanding of the molecular interactions of cell cycle regulation. However, the biochemical network governing the cell cycle regulation is inherently nonlinear [3,4], and consists of several components that act in different ways. For instance, the growth of the cellular volume can be analysed deterministically, while the interactions between cell genes and mRNAs exhibit a notable fluctuation due to the existence of a limited number of copies, which has to be analysed stochastically [3]. Indeed, a cell cycle model is inherently hybrid.

During a cell cycle, the process of cell division involves replicating all cell components and afterwards dividing them more or less evenly between daughter and mother cell [1–3,5,9]. *The molecular noise due to species with low numbers of molecules influences the time point of the volume division* [4,7,8]. Such intrinsic noise is one factor affecting the variability in the cell age and size at division [7]. Intrinsic noise is merely due to the fluctuation of species with low number of molecules [7,8], which can be captured using stochastic simulation [10]. Indeed, cell division occurs within cells of very limited size (about 50 femtoliters) [4].

The process of a cell cycle consists of two main phases, synthesis (S phase) and mitosis (M phase) separated by two gaps: G_1 and G_2. The core component of the many constructed cell cycle models is the bistable switch circuit [9]. Positive and negative feedback loops create and flip the bistable switch states [2,4]. The "off" state corresponds to the G_1 phase, while the "on" state corresponds to the $S - G_2 - M$ phases [3].

The bistable switch is caused by the nonlinear behaviour of the reaction kinetics. There are plenty of models that tried to address and replicate the nonlinear behaviour of cell cycle regulation (see. e.g., [7–9]). In [4], the authors created a model to study the cell cycle regulation of budding yeast based on the mechanism of multisite phosphorylation of target proteins. Multisite phosphorylation has been originally studied in [11] and [12] as the source of nonlinearity. Nevertheless, two challenges face the modelling of cell cycle regulation using this approach: the larger number of reactions and species participating in the network, compared with other approaches, and the existence of species with different numbers of molecules. These issues are intricate to deal with applying traditional modelling paradigms. Therefore, many subsequent work tried to address the challenges above (see, e.g., [13–16]).

On the one hand, the number of reactions and species increased compared with similar models (e.g., [7]) due to the introduction of the phosphorylation and dephosphorylation reactions. For instance, the model in [4] encompasses 176 reactions and 60 metabolites. In contrast, many other reactions have been ignored to keep the model as simple as possible. A larger number of reactions and species inevitably increases the model complexity, and greatly prolongs the simulation runtime, particularly when the stochastic simulation approach [10] is used. However, many of these reactions expose similar behaviour. Therefore in [17], a model reduction technique has been applied to decrease the number of reactions. Nevertheless, a (graphical) language suitable to manage higher numbers of reactions and variables is of paramount importance.

On the other hand, the number of molecules of the various model species do exist in different abundance [4,7]. For example, each gene of the cell cycle network has only one copy and each mRNA has very few number of molecules. On the contrary, the network proteins exhibit higher number of molecules compared to the network genes and mRNAs. Thus, for such biochemical networks, it is not easy to adequately reproduce intrinsic noise with a single simulator type. In order to focus on the fluctuation of species with a few number of molecules, the corresponding reactions should be executed via stochastic simulations, while reactions related to proteins can be abstracted and executed via deterministic simulation in order to improve the overall simulation performance.

Hybrid Petri nets ($\mathcal{HPN}$) [18,19], which are an extension of basic Petri nets (cf. [20]), provide a great opportunity to model and explore biological and biochemical networks. They combine discrete and continuous entities for the convenient modelling of dynamic hybrid systems [21]. In [6,22–24] , $\mathcal{HPN}$ have been extended to support the special requirements of systems biologists. $\mathcal{HPN}$ have the power to tackle emerging challenges of modelling biological processes by offering to systems biologists the tools required to incorporate different simulation approaches for model execution, combined with the option to graphically construct the reaction networks.

Similarly, coloured Petri nets ($\mathcal{PN}^{\mathcal{C}}$) [25,26] play an important role in modelling complex biological networks by providing an efficient tool to concisely represent systems with repeated components as it has been proposed by many publications (see, e.g., [27–34]). Using $\mathcal{PN}^{\mathcal{C}}$, reaction subnetworks which share similar structures, but possibly with different quantitative information, can be represented as one subnetwork with different colours, each colour standing for a different subnetwork. Therefore $\mathcal{PN}^{\mathcal{C}}$ offer an abstraction tool that hides the details of similar subnetworks. Besides, a $\mathcal{PN}^{\mathcal{C}}$ model can be executed via any of the simulation algorithms well-established for Petri nets as it can be automatically unfolded into a low-level Petri net.

Coloured hybrid Petri nets ($\mathcal{HPN}^{\mathcal{C}}$) [31] combine hybrid Petri nets and coloured Petri nets into one net class to join the merits of the two Petri net classes. $\mathcal{HPN}^{\mathcal{C}}$ present an advanced tool to systems biologists for the graphical construction of