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研究課題名（和文）計算モデルを用いた哺乳類の概日リズムと細胞周期のカップリング機構の研究

研究課題名（英文）computational modelling of the entrainment of the mammalian cell cycle by the circadian clock

研究代表者

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研究成果の概要（和文）：この研究の当初の目的は、概日時計による細胞周期の引き込みモデルを作ることであったが、この研究の開始年に、そのようなモデルは他者により発表されたため、当初の計画の方向を若干変更した。即ち、彼らのモデルを活用し、引き込みを解析する論理モデルを作成するためのテンプレートとした。
彼らのモデルが複雑であることや、研究の初期段階で得られた結果により、回路機能解析手法にある限界があることが明らかになり、問題が当初の想定より解決が困難であることが分かった。しかしながら、哺乳類の新しい細胞周期モデルを開発することができ、その論文は欧州で開催される国際会議ECCB2016に受理された。

研究成果の概要（英文）：The initial aim of this project was to create a model coupling the circadian clock and the cell cycle networks. However, such a coupled model was published by Gerard and Goldbeter during the first year of this project. This unexpected turn of event led to substantial modifications of the initial project. Gerard and Goldbeter's model was used as a template to produce a logical model, with the prospect of applying tools and methods available in the logical formalism to analyze entrainment of the cell cycle by the circadian clock. This proved more difficult than expected, partly due to the complexity of the original model, and partly because preliminary results highlighted limitations in the circuit functionality analysis method. Nonetheless, within the context of this project, a new model of the mammalian cell cycle has been developed, and the corresponding paper has just been accepted to the ECCB 2016 conference, to be published in a forthcoming issue of Bioinformatics.

研究分野：Bioinformatics

キーワード：cell cycle　circadian rhythms　logical modeling　regulatory network　circuit functionality

1. 研究開始当初の背景

The cell division cycle is the process through which a cell reproduces itself, replicating its genetic material and sorting the copies to two daughter cells. In multicellular organisms, cell division is under tight control at each stage of development, and deregulation of this process is a major hallmark of cancer.

Circadian oscillations characterize biological activities that display cyclic variations over a 24 hours period. In mammals, the sleep-wake cycle is the most conspicuous manifestation of the circadian clock, but metabolic, cellular and molecular processes are also affected. Accordingly, perturbations of the circadian clock have been linked to various disorders, including diabetes, and cancer. The main components of the mammalian circadian clock are displayed on the figure opposite.

Like the cell division cycle, the circadian clock is controlled by a complex molecular oscillator. Recent works further uncovered the tight regulatory links from circadian rhythms to the cell cycle machinery, showing that many clock regulators (RORα, REV-ERB, PERs, BMAL1-CLOCK, BMAL1-NPAS, CRYs, TIM) also have an impact on cell cycle regulators (p21, c-myc, WEE1, ATM and ATR)[1].

Both systems are appealing for computational scientists and have been heavily studied from a systems biology point of view. Yet, at the time when this project was drafted, the connection between these two oscillators had hardly been explored by modelers.

References:

Borgs et al. Cell Cycle, 8(6):832–7, 2009.

2. 研究の目的

The main purpose of this project was thus to build a model coupling the mammalian cell cycle and circadian oscillators. Unfortunately, during the very first year of the project, such a coupled model, based on differential equations, was published independently by an other team [Gérard2012]. In this context, the project had to be reoriented.

While I kept working on a logical model of the mammalian cell cycle, I decided shift the main focus of the project to the analysis of the properties of Gérard and Goldbeter's new coupled model. The aim was to better understand the coupling mechanism, taking advantage of a well-researched, and now publicly available model. The modular structure of the model was supposed to help achieve fast progress, and I was particularly interested in exploring the roles of feedback circuits [Thieffry, 2007] in such a complex model.

References:

Gérard and Goldbeter, 2012. PLoS Comput. Biol. 8(5):e1002516
Thieffry, 2007. Briefings in Bioinformatics 8(4):220-225

3. 研究の方法

The logical formalism is a discrete modeling framework that has been successfully applied to a number of biological systems [See Abou-Jaoudé 2016 for a recent review], and for which a number of tools are available that have been used in this project. In particular, circuit functionality analysis [Naldi et al., 2007] and the model-checker NuSMV [Cimatti et al., 2002] have been applied to this project. Models were developed using the software GINsim [Chaouiya et al., 2012].

References:

Chaouiya et al., 2012. Methods Mol. Biol. 804, 463–479.
Cimatti et al., 2002. Lect. Notes Comp. Sci. 2404:359–364.
Naldi et al., 2007. Lect. Notes Comp. Sci. 4695:233–247.

4. 研究成果

Due to the necessary reorientation discussed above, the initial project could not be carried out as initially planned, and as a consequence the results could not match the expected outcome of the project. In particular, the project led to a single publication, recently accepted for the ECCB conference later this year (see reference below). This article presents an extended and updated version of an earlier logical model of the mammalian cycles, introducing several new variables and interactions. Perhaps more importantly, the paper illustrates an application of model-checking techniques to evaluate complex dynamic properties of logical models.

Besides this publication, the project generated a number of conceptual advances and preliminary results which I introduce below.

First, adaptation of the Gérard-Goldbeter model proved a challenging task. Due to the difference in terms of modeling framework, the modular nature of the model proved a hindrance rather than an asset: indeed, module definition in the continuous and discrete formalism seem to follow unexpectedly different principles, and we could not directly transpose the original modules in the new modeling framework. A model has finally been developed, but it proved too unreliable and difficult to evaluate to warrant publication, and had to be discarded.

Second, analysis of this preliminary model revealed limitations in the current definitions of circuit functionality. Some of these limitations have recently been

discussed [Comet et al., 2013], but were not widely known at the start of this project. In particular, we were surprised to observe that some states within the main complex attractor showed no functional negative circuit, and indeed not functional circuit at all.

These observations have prompted the development of new lines of research on modularity and the roles of regulatory circuits, towards a new definition of circuit functionality. This research is still in the early stages and will extend well beyond the scope of this project, but promising preliminary results suggest that valuable insights may be obtained from these new plans.

References:

Comet et al., 2013. Bull. Math. Biol. 75(6):906-19.

5. 主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計　　件）

〔学会発表〕（計　1　件）

1) Pauline Traynard, Adrien Fauré, François Fages and Denis Thieffry (2016), Logical model specification aided by model-checking techniques: application to the mammalian cell cycle regulation. Accepted by the 15th European Conference on Computational Biology (Sept. 5-7 2016, The Hague, Netherlands), to be published in Bioinformatics.

〔図書〕（計　　件）

6. 研究組織

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