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On robustness of phase resetting to cell division under entrainment ☆

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HIGHLIGHTS

- Studied the problem of phase synchronization for a population of genetic oscillators under cell division.
- Derived analytical conditions for phase synchronization using PRC formalism.
- Demonstrated the theoretical results through numerical experiments.

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ABSTRACT

The problem of phase synchronization for a population of genetic oscillators (circadian clocks, synthetic oscillators, *etc.*) is considered in this paper, taking into account a cell division process and a common entrainment input in the population. The proposed analysis approach is based on the Phase Response Curve (PRC) model of an oscillator (the first order reduced model obtained for the linearized system and inputs with infinitesimal amplitude). The occurrence of cell division introduces state resetting in the model, placing it in the class of hybrid systems. It is shown that without common entraining input in all oscillators, the cell division acts as a disturbance causing phase drift, while the presence of entrainment guarantees boundedness of synchronization phase errors in the population. The performance of the obtained solutions is demonstrated via computer experiments for two different models of circadian/genetic oscillators (*Neurospora's* circadian oscillation model and the *repressilator*).

1. Introduction

The interest in the analysis and synthesis of genetic oscillators is continuously growing these last decades (Guevara et al., 1981; Kuramoto, 1984; Tass, 1999; Winfree, 1980). Any periodic oscillation is characterized by its frequency (or frequency spectrum), phase and amplitude. The amplitude and frequency are mainly governed by external stimulus applied to oscillators, a phenomenon called *entrainment* (Izhikevich, 2007; Pikovsky et al., 2001), while the phase value is dependent on properties of the oscillator and characteristics of entrainment. This phase feature has attracted the attention of many researchers and in particular, the phase synchronization phenomenon studies are very popular (Izhikevich, 2007; Pikovsky et al., 2001). Phase synchronization is frequently observed in networks of oscillators, like a colony of the smallest free-living eukaryotes (Thommen et al., 2010), the mammalian circadian pacemaker neural network (Antle et al., 2007; Zhao, 2010) or networks of neural oscillators (Smeal et al., 2010; Tass, 1999; Canavier and Achuthan, 2010), to mention a few. Controlled phase resetting has been studied in Bagheri et al. (2007), Danzl and Moehlis (2008), Efimov et al. (2009), and Efimov (2011) and for a population of oscillators in Efimov (2015).

A simple but effective approach for analysis of phase resetting and dynamics for a single oscillator is based on PRC (Glass et al., 2002; Govaerts and Sautois, 2006; Izhikevich, 2007). The infinitesimal PRC map is calculated for the system linearized around the limit cycle and inputs with small amplitudes. If the entraining input is a series of pulses, then a Poincaré phase map based on PRC can be calculated to predict the phase behavior (Izhikevich, 2007). Such a reduced phase model has been used in Efimov et al. (2009) and Efimov (2015) for pulse amplitude and timing calculation for a controlled phase resetting.

Another interesting problem has emerged recently in Gonze (2013), it concerns the influence of cell division on the behavior of genetic oscillators. It has been observed that oscillations persist

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across cell divisions in *Repressilator* (Elowitz and Leibler, 2000), similarly for circadian oscillations in cyanobacteria cells (Mihalcescu et al., 2004). In Nagoshi et al. (2004), the persistence of circadian oscillations in culture fibroblasts under cell division has been demonstrated, and it has been noted that cell division can shift the phase in circadian cycle. A rapid phase decorrelation between daughter cells has been remarked in Geva-Zatorsky et al. (2006) for oscillations in the p53/Mdm2 system. Moreover, experimental study that demonstrated synchronization of budding yeast cells using periodic cyclins and its validation with a complex stochastic model can be found in Charvin et al. (2009) and Oguz et al. (2014) respectively. Since cell division introduces a discontinuity in the oscillator dynamics (that is usually described by a system of nonlinear differential equations), then the analysis of division influence leads to the study of a hybrid or impulsive nonlinear oscillating system, which is a rather complicated problem (Churilov et al., 2014; Efimov et al., 2014). In Gonze (2013), this problem has been investigated using a stochastic simulation approach, and in Tourigny (2014), the geometric phase approach has been adopted from quantum mechanics.

The goal of the present work is to analyze the phase behavior and synchronization under cell division in genetic oscillators using the PRC formalism. A motivating example given by a simple biological model of circadian oscillations in *Neurospora* is studied in Section 2. The analysis of cell division influence on the phase dynamics is presented in Section 3. An illustration by simulations of the obtained results is given in Section 4. General results about phase dynamics are summarized in the Appendix.

2. Motivating example

Let us consider a simple biological model of circadian oscillations in *Neurospora* in the following form Leloup et al. (1999):

$$\begin{aligned}\dot{M}(t) &= (v_s+u(t))\frac{K_I^n}{K_I^n+F_N^n(t)}-v_m\frac{M(t)}{K_m+M(t)},\\ \dot{F}_C(t) &= k_s M(t)-v_d\frac{F_c(t)}{K_d+F_c(t)}-k_1F_c(t)+k_2F_n(t),\\ \dot{F}_N(t) &= k_1F_c(t)-k_2F_N(t),\end{aligned} \tag{1}$$

where $M(t)$, $F_c(t)$ and $F_N(t)$ are the concentrations (defined with respect to the total cell volume) of the *frq* mRNA, the cytosolic and nuclear forms of FRQ, respectively. The parameter v_s defines the rate of *frq* transcription (this parameter increases in the light phase) while the influence of light (the external entraining input in the model (1)) is denoted by $u(t)\geq 0$. A description of the other parameters appearing in these equations can be found in Leloup et al. (1999). The following values of parameters are proposed there: $v_m=0.505$ nM h^{-1}, $v_d=1.4$ nM h^{-1}, $k_s=0.5$ h^{-1}, $k_1=0.5$ h^{-1}, $k_2=0.6$ h^{-1}, $K_m=0.5$ nM, $K_I=1$ nM, $K_d=0.13$ nM, $n=4$ and $1\leq v_s+u(t)\leq 2.5$.

For all these values, the system (1) for $u(t)=0$ has single unstable equilibrium and globally attractive limit cycle that represents a rhythmic behavior of the circadian rhythm in *Neurospora* with a period $T>0$. It is a continuous-time dynamical system that for any initial conditions $M(0)>0$, $F_C(0)>0$ and $F_N(0)>0$ has a continuous positive solution for all $t\geq 0$. To model the cell division in (1), it is necessary to introduce an increasing series of time instants $t_k>0$, $k=1,2,\ldots$, with a division at each t_k. During the division, the state variables are resetted (Gonze, 2013), *i.e.* $M(t_k^+)=\lambda_k^M M(t_k)$, $F_C(t_k^+)=\lambda_k^{F_C}F_C(t_k)$ and $F_N(t_k^+)=\lambda_k^{F_N}F_N(t_k)$, where $M(t_k^+)$ is the value of the concentration M after division at instant t_k; $\lambda_k^M>0$, $\lambda_k^{F_C}>0$ and $\lambda_k^{F_N}>0$ are parameters.

The cell division cycle can be larger than the period of oscillations T (Tourigny, 2014) or similar, as in proliferating human cells (Bernard and Herzel, 2006) where the circadian clock is a major synchronizing factor, which orchestrates daily rhythms regulating the cell division cycle; or two times faster as in cyanobacteria (Mori et al., 1996). The values λ_k^M, $\lambda_k^{F_C}$, $\lambda_k^{F_N}$ have been selected around 0.5 in Gonze (2013) (for the Goodwin model), but in Cookson et al. (2010) it has been observed *in vivo* that concentrations do not jump significantly after cell division. In the present work, we will adopt the latter hypothesis by taking λ_k^M, $\lambda_k^{F_C}$, $\lambda_k^{F_N}$ close to 1.

The modeling of such a hybrid oscillator corresponds to a mother cell in the population, then after each division the daughter cells have a similar dynamics and forthcoming divisions augment the population. It is assumed that division instants t_k for each cell are different, then the phase synchronization behavior in a population (suppose that there is no interconnection between cells) can be analyzed using (1). If the phase converges to a steady-state in this hybrid system under some conditions, then the population will be phase synchronized in some sense. In our current work, we have considered in-phase synchronization. For details about various kinds of phase synchronization (anti-phase, in-phase, arbitrary phase locking) consult Pikovsky and Rosenblum (2007).

Taking the previously mentioned parameter values and $v_s=1.11$, the period of the autonomous oscillation of (1) is obtained as $T=19.25$ h. For these values of parameters and for the case $u(t)=0$ and $t_k=kT-\upsilon_k$, $k\geq 1$, where $\upsilon_k\in[0.15T,0.30T]$ is a uniformly distributed random variable, the results of the *Neurospora's* circadian oscillation model simulation for the same initial conditions and different realizations of υ_k for 4 different cells undergoing divisions can be seen in Fig. 1. As we can conclude from these results the phase is diverging as it has been noted in Nagoshi et al. (2004), Geva-Zatorsky et al. (2006) and in some experiments of Gonze (2013). Next, by taking $u(t)=\max\{0,0.2\sin F(\omega t)\}\left(\omega=2\pi T^{-1}\right)$ as the common external entraining input and repeating the same experiments, the results are given in Fig. 2. From this figure, it is evident that the oscillations converge to a common entrained mode.

The robustness of this common entrained mode can be checked through simulation of a large population of cells. This can be seen in Fig. 3. The population consists of 100 cells, the transcription rate represented by the uniformly distributed random variable, $v_s\in[1.1,1.3]$ and the cell division time parameters $v_k\in[0.15T,0.3T]$. Histograms of v_k and v_s can be seen in Fig. 3 (bottom). From Fig. 3, it is evident that the oscillations converge to a common entrained mode in the case of a large population well despite of simultaneous variations in the cell division time and transcription rate. So, from the simulation experiments it can be seen that the common entrained mode is quite robust.

In this paper, we will try to find conditions providing both these two types of phase behavior (Figs. 2 and 1) using the PRC phase model for small inputs *i.e.* inputs with small amplitude.

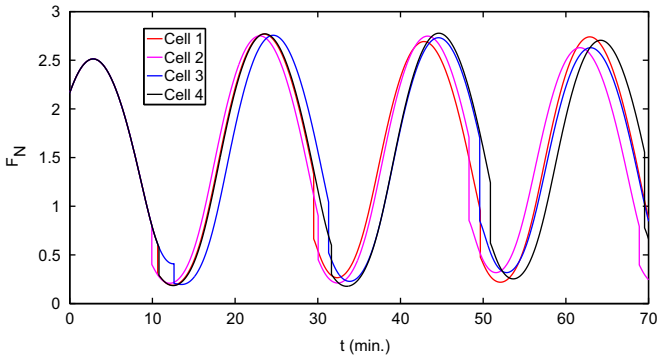

Fig. 1. Oscillations of different single cells with cell divisions and without any common input.