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Role of transcriptional bursts in cellular oscillations

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ABSTRACT

Genetic oscillators are present in the cells of many organisms and control several biological processes. The common feature of such oscillators is the presence of a protein which represses the transcription of its own gene. Recently, it has been shown that for many genes transcription is not a continuous process, but that it proceeds in bursts. We study here the relationship between bursty transcription and the robustness of protein oscillations. We concentrate on the temporal profile of mRNA production by studying regimes where this profile changes but the amount of mRNA produced is kept fixed. For systems with different degrees of cooperativity we show that in general bursts are associated with more robust oscillations, but when they are too short and intense they can have the opposite effect. In other words, we show that, in terms of the regularity of the oscillations generated, there is an optimal value for the intensity of the bursts.

1. Introduction

Given the relatively low copy number of molecules involved, stochasticity usually plays an important role in the cell cycle. Because only one or two copies of each gene are present in a cell, the production of messenger mRNA (also called gene expression) is a process where stochastic effects are particularly relevant (Raj and van Oudenaarden, 2008). Experimental studies carried out on several organisms, ranging from yeast (Becskei et al., 2005) and *E. coli* (Elowitz et al., 2002) to mammals (Raj et al., 2006; Suter et al., 2011), have found that the number of mRNA molecules presents large variations from cell to cell. Moreover, it has been shown that in general gene expression proceeds in short but intense bursts followed by relatively long periods during which the gene is 'silent'. However, it is not yet clear whether this bursty transcriptional dynamics is governed by processes acting on the whole genome or whether these processes are gene-specific (Sanchez and Golding, 2013).

The first question that arises is what can be the benefits (if any) of having large levels of noise in gene expression (Raj and van Oudenaarden, 2008). It has been shown that stochastic expression of a very specific gene is necessary for the development of the retinal mosaic that is so characteristic of the fruit fly (Drosophila) (Wernet et al., 2006). One early example of mathematical modelling has suggested that stochastic gene expression can also underlie the phenotypic variations that are observed in some colonies of both eukaryotic and prokaryotic cells (McAdams and Arkin, 1997). In turn, other mathematical models (Kussell and Leibler, 2005) have shown that such phenotypic variability could confer an adaptive advantage in fluctuating environments. This was later confirmed by experiments with yeast strains (Acar et al., 2008).

Noise in gene expression induces large fluctuations in the abundances of the proteins encoded. For most proteins, however, there is a well defined steady state about which this fluctuation occurs. But there are some proteins whose abundance is known to have a cyclical variation throughout the day. The best example are the proteins involved in the circadian clock (Panda et al., 2002), but there are other proteins whose abundance oscillates with shorter, ultradian, periods (see e.g. Bar-Or et al., 2000). The basic mecha-

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nism of these oscillators is a feedback loop involving one or more proteins that repress the transcription of their own genes. Bursty transcription seems to be the dominant form of gene expression (at least for humans (Dar et al., 2012)) and it has recently been shown that this may also be the case for circadian genes (Ono et al., 2015; Suter et al., 2011).

One important difference between circadian and non circadian genes is that in the former the bursts in transcription can be caused by the very protein that the gene encodes. The relationship between protein abundance and transcriptional bursting is thus much less straightforward. The circadian clock is composed of many cellular oscillators, and it controls many behaviours. As a consequence, the cellular clocks should be as accurate as possible. It is then natural to ask what is the relationship between the fundamental stochasticity of transcriptional bursting and the regularity of protein oscillations and, moreover, whether it imposes any fundamental limit on these oscillations. These are the questions that we address in this paper.

We study the stochastic version of a simple genetic oscillator with one feedback loop for a protein that can pass through two different states. In order to study the effect of cooperativity in the repression of the gene, we consider systems with three different degrees of cooperativity. In Section 2 we present the stochastic model and the deterministic equations associated with it. In Section 3 we give a quantification of the quality of oscillations and relate it to the amount of bursting. Section 4 provides a simplified theoretical treatment, for a better understanding of the results given in the previous section. In the last section we summarize and discuss our main results.

2. Model of a genetic oscillator

We consider a genetic oscillator composed by a protein, its messenger RNA and the gene that expresses it. We assume that, when it is not being repressed, the gene is in the active state (noted as D_0). In other words, we assume that the gene is always associated with its activator. This models the fact that, in some circadian oscillators, the activator of the gene is constitutively expressed in the cell (Houl et al., 2006). When active, the gene 'produces' mRNA (M) at a rate k_1. We assume that the protein passes through two states before being degraded. Translation takes place at a rate k_3, generating the first state of the protein (P_1). This is then converted into the second state of the protein (P_2) at a rate k_4. This models the phosphorylations that circadian proteins are known to undergo (Panda et al., 2002), or its entrance to the nucleus. When in the second state, the protein closes the feedback loop by repressing the activator, thus turning off the gene (R).

In most deterministic circadian models it is assumed that there is some degree of cooperativity in the repression of the activator by P_2 (Goldbeter, 1995). This is usually modelled by introducing a Hill term in the differential equation for M. In our stochastic model cooperativity is enforced by assuming that n copy molecules of P_2 are needed to repress the activator. Thus, the gene passes through n different states (D_i, $i = 0, \ldots, n-1$) before being completely repressed. For simplicity we assume that the rate of production of mRNA is the same in all active states. In this paper we have studied the cases of $n = 1$ (no cooperativity), $n = 2$, and $n = 3$. In the following all the equations will be written for the case $n = 3$ but the modifications necessary for the other cases are straightforward.

We have also assumed that the degradation of the protein is mediated by an enzyme (E), whose abundance is assumed to be constitutive and given by E_0. The protein and the enzyme form a complex C which degrades the protein at rate k_6, thus freeing a copy of the enzyme. This is a gross simplification of the complex degradation paths of a protein, but at least it allows us to model the saturation of those paths. Furthermore, it has been shown that degradation terms of this form are in many cases necessary to have oscillations in a dynamical system (Kurosawa and Iwasa, 2002). For simplicity, and also because the small copy number of mRNA is unlikely to saturate its degradation paths, we have assumed that mRNA is degraded at a fixed rate k_2.

For $n = 3$, the reactions that take place in our stochastic model are:

$$
\begin{aligned}
&D_0 \xrightarrow{k_1} D_0 + M,\\
&D_1 \xrightarrow{k_1} D_1 + M,\\
&D_2 \xrightarrow{k_1} D_2 + M,\\
&M \xrightarrow{k_2} \emptyset,\\
&M \xrightarrow{k_3} M + P_1,\\
&P_1 \xrightarrow{k_4} P_2,\\
&P_2 + E \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} C \xrightarrow{k_6} E,\\
&D_0 + P_2 \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} D_1,\\
&D_1 + P_2 \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} D_2,\\
&D_2 + P_2 \underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} R.
\end{aligned}
$$

To obtain the system for $n = 2$ the reactions producing D_2 are eliminated and D_2 is replaced by D_1. A similar modification regarding D_1 must be performed to obtain the system for $n = 1$. In the following the expressions will be given for the case $n = 3$, unless otherwise noted. The generalizations for lower values of cooperativity are straightforward. The simulations for this system were performed using the Gillespie algorithm (Gillespie, 1976). We tested four different parameter sets for each value of n.

The evolution of the averages over the stochasticity is given by the following set of equations:

$$
\begin{aligned}
\dot{D}_0 &= -k_7 D_0 P_2 + k_{-7} D_1,\\
\dot{D}_1 &= k_7 D_0 P_2 - k_{-7} D_1 - k_8 D_1 P_2 + k_{-8} D_2,\\
\dot{D}_2 &= k_8 D_1 P_2 - k_{-8} D_2 - k_{off} D_2 P_2 + k_{on} R,\\
\dot{M} &= k_1 (D_0 + D_1 + D_2) - k_2 M,\\
\dot{P}_1 &= k_3 M - k_4 P_1,\\
\dot{P}_2 &= k_4 P_1 - k_5 P_2 E + k_{-5} C - k_7 D_0 P_2 + k_{-7} D_1 +\\
&\quad -k_8 D_1 P_2 + k_{-8} D_2 - k_{off} D_2 P_2 + k_{on} R,\\
\dot{E} &= -k_5 P_2 E + k_{-5} C + k_6 C,\\
\dot{C} &= k_5 P_2 E - k_{-5} C - k_6 C,\\
\dot{R} &= k_{off} D_2 P_2 - k_{on} R,
\end{aligned}
\tag{1}
$$

with the initial condition at $t = 0$,

$$
(D_0, D_1, D_2, M, P_1, P_2, E, C, R) = (D, 0, 0, 0, 0, 0, E_0, 0, 0). \tag{2}
$$

All the variables in these equations represent volumetric concentrations. The fact that the amount of enzyme and DNA remain constant induces the constraints $E_0 = E(t) + C(t)$ and $D = D_0(t) + D_1(t) + D_2(t) + R(t)$. In each cell there are only one or two copies of each gene but, for the sake of simplicity, we will assume in the following that $D = 1$. Notice that this forces us to assume that the unit volume used in the volumetric concentrations is the volume of the whole cell.

It can be shown that the system given by Eqs. (1) has always a single fixed point (and the same happens when the degree of