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# Oscillations in the expression of a self-repressed gene induced by a slow transcriptional dynamics.

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We revisit the dynamics of a gene repressed by its own protein in the case where the transcription rate does not adapt instantaneously to protein concentration but is a dynamical variable. We derive analytical criteria for the appearance of sustained oscillations and find that they require degradation mechanisms much less nonlinear than for infinitely fast regulation. Deterministic predictions are also compared with stochastic simulations of this minimal genetic oscillator.

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Networks of genes interacting via regulatory proteins are highly nonlinear dynamical systems which display a rich variety of dynamical behaviors [1, 2]. In particular, oscillating gene expression has been linked to cellular processes such as circadian rhythms [3, 4], control of DNA repair [5], signal transduction or somite segmentation [6]. The study of the somite clock, which involves a gene repressed by its own protein (*Hes1*) [6], has recently revived an old problem of theoretical biology: the dynamics of a single gene regulating its expression through a negative feedback loop [3, 4, 7, 8, 9, 10, 11, 12]. The common wisdom is that oscillations can appear in this genetic circuit only when an additional step is inserted in the loop [8]. In the Goodwin and Bliss oscillators [7, 8, 9], the gene protein catalyzes synthesis of the actual repressor. In early circadian models based on a self-regulated gene, multiple phosphorylation of the repressor [3] or its nucleocytoplasmic transport [4] have been found to be key oscillatory ingredients. In fact, the introduction of a time delay in the one-gene circuit model (accounting for protein transport or more generally a cascade of intermediate steps [13]) is sufficient to destabilize it [10, 11, 12]. As will be of particular interest here, oscillations may also be induced by strongly nonlinear degradation mechanisms [14].

However, these studies have generally assumed that the protein-DNA interactions controlling gene activation are fast compared to transcription or translation, and thus that transcription rate reacts instantaneously to protein concentration. This is not always justified, as transcription is a complex process [15]. In particular, there is evidence of transcriptional bursting at slow time scales both in prokaryotes [16] and in eukaryotes [17] as well as of transcriptional memory [17]. On the theoretical side, François and Hakim have identified a simple genetic

module where a non-instantaneous transcription rate is crucial for the appearance of oscillations [18].

In this Letter, we investigate how transcriptional dynamics modifies the behavior of a self-repressed gene. For simplicity, we study the case of an elementary kinetic equation describing regulation through protein-DNA interaction [18], which can also be viewed as an effective description of transcriptional memory in more complex mechanisms. An analytical expression of the oscillation threshold is derived and allows us to show that when the gene response time scale is appropriately tuned, oscillations can be induced by degradation mechanisms much less nonlinear than for infinitely fast regulation. We also carry out stochastic simulations of our model to determine how the results of our deterministic analysis carry over to low copy number situations.

Our study is based on the following three-variable model describing the genetic circuit represented in Fig. 1:

$$\dot{G} = \theta_0(1 - G) - \alpha_0 C(P)G \quad (1a)$$

$$\dot{P} = n\dot{G} + \beta_0 M - \delta_P F(P) \quad (1b)$$

$$\dot{M} = \mu_0 + \lambda_0 G - \delta_M H(M) \quad (1c)$$

where  $G$ ,  $P$  and  $M$  represent gene activity, protein and RNA copy numbers, respectively. Eq (1a) describes the kinetics of protein-DNA binding at rate  $\alpha_0$  and unbinding at rate  $\theta_0$  [18]. Possible cooperativity effects are taken into account via the function  $C(P)$  and the number  $n$  of proteins binding to DNA. Single-protein regulation corresponds to  $C(P) = P$ ,  $n = 1$ . More generally, we view Eq (1a) as describing the dynamics of an effective gene state  $G$  slowly relaxing towards an equilibrium value which is the usual gene regulation function  $G = 1/[1 + C(P)/C(P_0)]$ , with  $P_0$  the half-expression

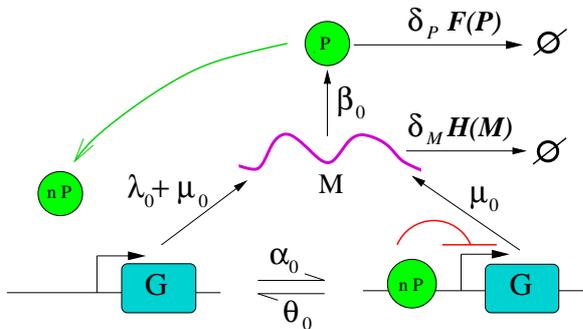


FIG. 1: Reaction diagram of the self-regulated gene circuit.

threshold. In Eq. (1b), the first term corresponds to binding/unbinding, the second and third terms describe translation and degradation. Eq. (1c) describes transcription at rate  $\mu_0 + \lambda_0 G$  and RNA degradation. In order to understand how oscillations can be induced by tuning protein and RNA degradation, we derive the oscillation criterion for arbitrary degradation functions  $F(P)$  and  $H(M)$  having unit derivative at zero so that  $\delta_P$  and  $\delta_M$  are the degradation rates at low copy number.

By renormalizing time, variables, parameters, cooperativity and degradation functions according to:

$$t = \frac{t'}{\delta_M}, G = g, P = pP_0, M = mM_0, \quad (2a)$$

$$P_0 = C^{-1} \left( \frac{\theta_0}{\alpha_0} \right), M_0 = \frac{\delta_P P_0}{\beta_0}, \theta = \frac{\theta_0}{\delta_M}, \quad (2b)$$

$$\alpha = \frac{\theta_0}{P_0 \delta_M}, \delta = \frac{\delta_P}{\delta_M}, \lambda = \frac{\lambda_0}{M_0 \delta_M}, \mu = \frac{\mu_0}{M_0 \delta_M} \quad (2c)$$

$$c(p) = \frac{C(P)}{C(P_0)}, f(p) = \frac{F(P)}{P_0}, h(m) = \frac{H(M)}{M_0}, \quad (2d)$$

Eqs. (1) can be rewritten in dimensionless form

$$g' = \theta [1 - g(1 + c(p))] \quad (3a)$$

$$p' = n\alpha [1 - g(1 + c(p))] + \delta [m - f(p)] \quad (3b)$$

$$m' = \mu + \lambda g - h(m) \quad (3c)$$

where  $x' = dx/dt'$ . When  $f$  and  $g$  are monotonous and  $h(f(\infty)) > \mu$ , model (3) has a single steady state  $(g_*, p_*, m_*)$  satisfying the fixed point equations:

$$g_* = \frac{1}{1 + c(p_*)}, m_* = f(p_*), g_* = \frac{h(m_*) - \mu}{\lambda}. \quad (4)$$

Note that the steady state depends only on parameters  $\lambda$  and  $\mu$  as well as on functions  $c$ ,  $f$  and  $h$ , whereas parameters  $\theta$ ,  $\alpha$ ,  $\delta$  control time scales. The behavior of the degradation and cooperativity functions in the neighborhood of the steady state is described by the slopes

$$s = \left. \frac{df(p)}{dp} \right|_{p=p_*}, u = \left. \frac{dh(m)}{dm} \right|_{m=m_*}, v = \left. \frac{dc(p)}{dp} \right|_{p=p_*}$$

In the case of linear degradation [ $f(p) = p$ ,  $h(m) = m$ ], we have  $u = s = 1$ . Small or even negative values of the slopes  $s$  and  $u$  (due to, e.g., saturation) generally denote strongly nonlinear degradation mechanisms [2, 14].

To assess whether Eqs. (3) can display sustained oscillations, we have searched for parameter values where the fixed point loses stability to a periodic solution via a Hopf bifurcation, where a pair of conjugate eigenvalues of the fixed point stability matrix cross the imaginary axis. For the sake of simplicity, we assume here perfect repression ( $\mu = 0$ ) and a large threshold  $P_0$  ( $\alpha \sim 0$ ). Under this approximation, we find using the Routh-Hürwitz stability criterion [19] that a Hopf bifurcation of the fixed point specified by (4) occurs when the quantity

$$\mathcal{H} = \sigma + g_* (-\delta \lambda v g_*^2 + \sigma^2) \tau + \pi g_*^2 \sigma \tau^2 \quad (5)$$

crosses zero to become negative, where  $\tau = 1/\theta$  is the gene response time (strictly speaking, the mean residence time of the repressor), and the sum  $\sigma = \delta s + u$  and product  $\pi = \delta s u$  are symmetric functions of degradation rates  $\delta s$  and  $u$ . Since cooperativity essentially acts to change feedback strength from  $\delta \lambda$  to  $\delta \lambda v$ , we assume for simplicity single protein regulation in the remainder of this paper [ $c(p) = p$ ,  $v = 1$ ], keeping in mind that higher feedback strengths can be obtained through cooperativity. Eq. (5) shows that a strong feedback strength destabilizes the system while high degradation rates (large  $\sigma$  and  $\pi$ ) generally tend to stabilize it. In the single protein case,  $\mathcal{H}$  is unconditionally positive when both protein and RNA are linearly degraded and no oscillations can occur. Conversely, when protein and RNA degradations are completely saturated ( $s = u = \sigma = 0$ ),  $\mathcal{H} = -\tau \delta \lambda g_*^3$  is *unconditionally negative*, indicating that oscillations then appear systematically. The behavior in intermediate cases depends on the value of the response time  $\tau$ .

In the classical case where  $\tau = 0$ ,  $\mathcal{H} = \sigma$  and oscillations appear for  $\sigma < 0$  only. It is indeed known that negative effective degradation rates can lead to oscillations [2, 14]. We thus restrict ourselves to showing that at finite  $\tau$ , oscillations can occur for  $u, s > 0$ , as we shall see below. More precisely, we want to understand how oscillations can occur far away from the saturated cases  $u = 0$  or  $s = 0$ . To this end, we will use as an index the geometric average of the slopes  $\nu = \sqrt{us} = \sqrt{\pi/\delta}$  (in the linear case,  $\nu = 1$ ), seeking to determine the maximum value of  $\nu$  at which oscillations can be observed, and for which values of  $\tau$  this extremum is achieved.

The quantities  $\sigma$  and  $\pi$  play complementary roles. The total degradation rate  $\sigma$  controls instability onset for small to moderate  $\tau$ . Moreover, Eq. (5) indicates that when  $\sigma, \pi > 0$ , a necessary condition for oscillations is

$$\sigma < \sigma_c = g_* \sqrt{\delta \lambda} = \frac{g_* \sqrt{2}}{t_{sw}} \quad (6)$$

where  $t_{sw}$  is the time during which a fully active gene synthesizes the amount of protein corresponding to half-

repression threshold, starting from zero. The degradation rate product  $\pi$  is relevant only for large  $\tau$ , blocking oscillations if it is too large. In particular,  $\pi = 0$  guarantees the onset of oscillations for sufficiently large  $\tau$  whenever (6) holds. For  $u, s > 0$  and a given value of  $\sigma$ ,  $\pi$  can take any value between  $\sigma^2/4$  and 0 depending on whether the two degradation rates are equal or completely unbalanced, one being equal to zero and the other to  $\sigma$ . We use below  $\epsilon = 2\sqrt{\pi}/\sigma \in [0, 1]$  as a balance indicator.

Remarkably, we note that under the rescaling

$$\sigma = \sigma_c \Sigma, \quad \pi = \left(\frac{\epsilon \sigma_c}{2}\right)^2 \Sigma^2, \quad \tau = \frac{T}{g_* \sigma_c} \quad (7)$$

suggested by (6), the oscillation condition can be rewritten without explicit parameter dependence:

$$\mathcal{H}_\epsilon(\Sigma, T) = \Sigma \times \left[ \frac{\epsilon^2 \Sigma^2}{4} T^2 + \left( \Sigma - \frac{1}{\Sigma} \right) T + 1 \right] < 0 \quad (8)$$

and defines a series of curves  $\Sigma_\epsilon(T)$  specifying the degradation rate  $\Sigma$  at oscillation threshold as a function of response time  $T$  and balance index  $\epsilon$ . For a given  $\epsilon$ , oscillations are found for  $\Sigma \leq \Sigma_\epsilon(T)$  and at fixed  $T$ ,  $\Sigma_\epsilon(T)$  decreases monotonously with  $\epsilon$ . Fig. 2 shows the limit curves  $\Sigma_1(T)$  and  $\Sigma_0(T)$  which are particularly important to understand the bifurcation diagram: for all values of  $\epsilon$ , the circuit always (resp., never) oscillates when  $\Sigma < \Sigma_1(T)$  [resp.,  $\Sigma > \Sigma_0(T)$ ]. To assess the relevance of our analysis, we have also searched the parameter space of Eqs. (3) for oscillatory behavior, assuming for definiteness degradation of the protein by an allosteric enzyme and Michaelis-Menten degradation for RNA:

$$f(p) = \frac{p \times (a + p/\kappa)}{a + 2a(p/\kappa) + (p/\kappa)^2}, \quad h(m) = \frac{\chi m}{\chi + m} \quad (9)$$

The points in the  $(\Sigma, T)$  plane associated to oscillating parameter sets are displayed as black dots in Fig. 2. Even though our numerical simulations were carried out with  $\mu, \alpha \neq 0$ , the agreement is excellent: all dots are found below the  $\Sigma_0(T)$  curve and the few that are significantly above the  $\Sigma_1(T)$  have generally one small degradation rate. We are thus confident that our analysis allows us to make general statements about the behavior of Eqs. (3).

Two regions can be distinguished in Fig. 2. For  $T < 1$ , the instability threshold  $\Sigma_\epsilon(T)$  increases rapidly with  $T$  and its dependence on  $\epsilon$  is negligible. For small  $T$ , we find that  $\Sigma_\epsilon(T) \sim T$ , which given (7) translates back to

$$\sigma < \lambda g_*^3 \delta \tau \quad (10)$$

Interestingly, it was also noted in [13] that a quantity similar to  $\delta \tau$  must be large enough for coherent stochastic oscillations to develop in a self-regulated gene where protein production requires a large number of steps.

In the  $T > 1$  region,  $\Sigma_\epsilon(T)$  reaches its maximum value  $\Sigma_m(\epsilon) = 1/\sqrt{\epsilon + 1}$  at  $T = T_m(\epsilon) = 2\sqrt{\epsilon + 1}/\epsilon$ , and then

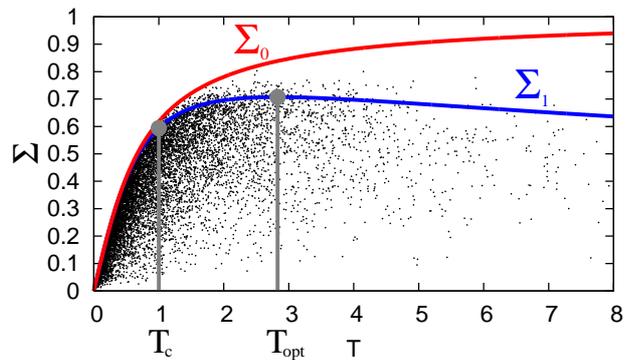


FIG. 2: Bifurcation diagram of (3) in the  $(\Sigma, T)$  plane according to (8). A system with balance index  $\epsilon$  oscillates for  $\Sigma < \Sigma_\epsilon(T)$ . Black dots indicate oscillating parameter sets of (3), with  $\theta, \delta \in [10^{-1}, 10]$ ,  $\theta/\alpha \in [10, 1000]$ ,  $\lambda \in [1, 10^3]$ ,  $\lambda/\mu \in [10, 10^3]$  and assuming the degradation mechanisms in (9) with  $a \in [10^{-6}, 1]$ .  $T_c = 1$  denotes the time scale beyond which transcriptional dynamics cannot be neglected and  $T_{opt} = 2\sqrt{2}$  is the location of the maximum of  $\Sigma_1(T)$ .

decreases as  $T^{-1}$  for  $T \rightarrow \infty$ , except for  $\epsilon = 0$  where it monotonously increases towards  $\Sigma = 1$ . At fixed  $\Sigma$ , oscillations are thus found in a finite range of  $T$ , which widens gradually, and is eventually infinite, as  $\epsilon \rightarrow 0$ .

Although higher values of  $\Sigma$  at threshold can be obtained for smaller  $\epsilon$  (Fig. 2), these actually correspond to smaller values of the index  $\nu \sim \epsilon \Sigma$  that we have chosen to measure the distance to a saturated situation (either  $s = 0$  or  $u = 0$ ). It is easily shown that the highest value of  $\nu$  at threshold is reached for  $\epsilon = 1$ , at the maximum of the  $\Sigma_1(T)$  curve located at  $T_{opt} = 2\sqrt{2}$ , and reads

$$\nu_{opt} = \frac{g_* \sqrt{\lambda}}{2\sqrt{2}} \quad (11)$$

Thus, our simple analysis indicates that there is a resonance-like phenomenon in the dynamics of a self-regulated gene with dynamical transcription rate: this circuit bifurcates most easily to periodic behavior, or more generally is least stable, at a finite value of the gene relaxation time given by

$$\tau_{opt} = 2\sqrt{2} \tau_c, \quad \tau_c = \frac{1}{g_*^2 \sqrt{\delta \lambda}} = \delta_M \times \frac{1}{g_*^2} \sqrt{\frac{P_0}{\lambda_0 \beta_0}}, \quad (12)$$

its dynamical behavior departing significantly from the infinitely fast regulation case for  $\tau > \tau_c$  [note that  $\tau_c = t_{sw}/(g_*^2 \sqrt{2})$ ]. This suggests that the transcriptional dynamics of a gene can be neglected only when  $\tau_c$  is unrealistically large. Because  $g_*$  depends on  $\lambda, \mu$ , and degradation functions through (4), computing lower bounds on  $\tau_c$  using (12) requires the degradation mechanisms to be specified. Still, fixing  $\lambda_0 = \beta_0 = 10 \text{ mn}^{-1}$ ,  $P_0 = 100$ , and  $g_*^2 = 0.5$ , one gets a very realistic  $t_c = \tau_c/\delta_M = 2 \text{ mn}$ . Near resonance ( $\Sigma > 0.5$ ), oscillation periods vary typically between  $\tau/4$  and  $5\tau$ .

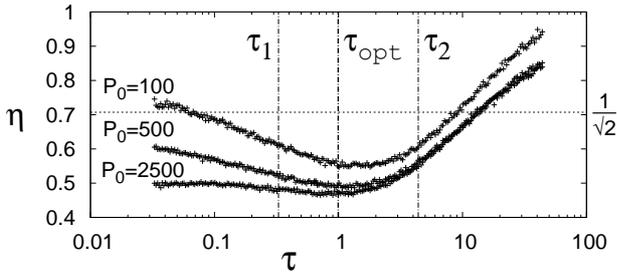


FIG. 3: Coefficient of variation of interpeak time intervals  $\eta$  vs. mean residence time  $\tau$  for a stochastic simulation of (3)+(9) rescaled to original variables  $G, P, M$  at three values of threshold  $P_0$  (from top to bottom,  $P_0 = 100, 500, 2500$ ). Parameter values correspond to  $\delta = 1, \theta = 1, \alpha = \theta/P_0, \lambda = 21.54, \mu = 0.085, \chi = 95.5, \kappa = 21.68, a = 10^{-6}$ .  $\tau_1$  and  $\tau_2$  are the boundaries of the deterministic oscillation domain.

Since a common interpretation of the diagram of Fig. 1 is that there are only two gene states (bound or unbound) [20], the relevance of our deterministic analysis might be questioned. If  $g$  is viewed as a temporal average of gene activity, however, our results are valid when the mean residence time  $\tau$  becomes small compared to the oscillation period, so that there are many binding/unbinding events by cycle [21]. Moreover, transcription is a complex process involving a number of distinct steps [15], and Eq. (1a) is a simple way to model memory effects arising from cooperativity in the transcription machinery [17].

In any case, we now show that even when  $G$  is a stochastic variable jumping between 0 and 1, our main result, namely the existence of a time scale near  $\tau_{\text{opt}}$  at which oscillations are enhanced, still holds. To this end we have carried out stochastic simulations of Eqs. (1) for different values of the mean residence time  $\tau$  at fixed  $P_0$ . One then no longer observes regular oscillations as in the deterministic model, but a sequence of irregularly spaced peaks in protein concentration. A natural question is then whether the protein peaks occur more regularly at parameter values where the deterministic model oscillates, in particular when  $\tau = \tau_{\text{opt}}$ .

We define interpeak times as the time intervals  $\Delta t$  between two crossings of  $P = 1.2P_{\text{avg}}$  separated by at least one crossing of  $P = 0.8P_{\text{avg}}$ , with  $P_{\text{avg}}$  the mean protein level (thus imposing a minimum amplitude of 40%). Their distribution is characterized by the coefficient of variation  $\eta = \frac{\sigma_{\Delta t}}{\langle \Delta t \rangle}$ . Without feedback loop,  $\Delta t$  is the sum of two Poissonian variables, and  $\eta \in [1/\sqrt{2}, 1]$ . A typical variation of  $\eta$  with  $\tau$  in our system is shown in Fig. 3. It definitely suggests that the deterministic analysis remains relevant in the stochastic regime. Indeed, there is clearly a time scale near  $\tau_{\text{opt}}$  where interpeak time fluctuations are minimal. Note that  $\eta < 1/\sqrt{2}$  in a large interval around the oscillation domain.

In conclusion, we have shown that a nontrivial tran-

scriptional dynamics can destabilize a self-regulated gene. Although it is known that nonlinear degradation mechanisms can induce oscillations in this system, we observe a resonance-like effect such that a much weaker nonlinearity is required when the gene response time matches a characteristic time. Its expression can be computed analytically, which allows us to identify the parameter regions where this effect cannot be neglected. Stochastic simulations confirm the relevance of this time scale in the dynamics of the self-regulated gene. This shows that transcriptional dynamics must be considered as a possible source of oscillatory behavior besides other deterministic [1, 2, 3, 4, 10, 11, 12, 14] and stochastic [22, 23] effects.

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