Bimodality without feedback: Noise-induced transitions in the repressed gene with extrinsic log-normal noise

Gerardo Aquino and Andrea Rocco
Department of Microbial and Cellular Sciences, Faculty of Health and Medical Sciences, University of Surrey, GU2 7XH, Guildford, UK

Extrinsic noise-induced transitions have been largely investigated in a variety of chemical and physical systems. The key properties that make these systems mathematically tractable is that the noise appears linearly in the dynamical equations and it is assumed Gaussian and white. Here we consider the simplest unit of gene regulation, the repressed gene, which is instead characterized by nonlinear dependencies on external parameters, leading to corresponding nonlinear extrinsic noise. We adopt a general methodology to address this nonlinearity based on assuming that the fluctuations exhibit a finite and large correlation time. We also relax the Gaussian assumption, and consider the more biologically relevant log-normal noise. We find that in contrast to Gaussian noise, log-normal noise leads to noise-induced transitions, with the system becoming bimodal. We emphasize that no feedback loops are present in the system, and therefore our findings identify a novel class of noise-induced transitions, based on both features of noise nonlinearity and boundedness.

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Bistability is a feature dramatically relevant for the functioning of living systems [1]. Deterministic bistability is realized in gene regulatory networks by the inclusion of specific topological features, such as feedback loops, which provide for the simultaneous existence of two, or more, stable steady states. In fact, feedback loops are known to underlie a number of processes involved in cellular decision making, ranging from the LAC operon [2], to quorum sensing [3], to cell differentiation [4].

However, in physical and chemical systems topological features are not the only known determinants of bistable behaviour. Extrinsic noise has been investigated now for a while, and it has emerged as an active dynamical player, which can produce so-called noise-induced transitions to bimodal dynamics in systems otherwise deterministically monostable [5]. In contrast, no noise-induced transitions have been identified in biological systems not including feedback loops, despite the effect of extrinsic noise having been investigated extensively [6–8].

In most systems, the search and the possible emergence of such transitions relies on the multiplicative nature of the corresponding stochastic dynamics, which is mathematically well characterized when the noise appears linearly in the system’s dynamical equations, and it is gaussian and white.

These assumptions are not free of criticism. First, regulatory processes of gene expression are usually described in terms of strongly nonlinear dynamics, such as Hill functions. If the parameter affected by noise appears nonlinearly in the dynamical equations, the mathematical treatment of the corresponding stochastic dynamics for white noise becomes very hard, if not impossible [9]. Second, the gaussian approximation is of limited applicability for fluctuations affecting parameters which are strictly positive. This problem has been recognized in some recent literature dealing with so-called bounded noise [9–11], and in the case of linear noise, noise-induced transitions have been identified in different systems [12–14]. And third, the white character of extrinsic noise is largely questionable for gene regulatory networks, where the typical correlation times of extrinsic noise can extend up to and well above typical cell cycle times [15].

In this Letter we take up these issues, and show that nonlinear log-normal noise provokes noise-induced transitions in a gene regulatory system in absence of feedback loops. We do so by extending to nonlinear noise a well established formalism, first developed in [16] and applied later in a variety of chemical and physical systems [17]. The formalism is based on relaxing the assumption of white noise, and on focusing instead on fluctuations characterized by a correlation time much longer than all other relaxational timescales in the system. This is indeed the typical situation when modelling extrinsic noise in gene regulation [15].

We start by considering the repressed gene, a gene which is constitutively expressed at its maximal expression rate, but it is regulated by a transcription factor, the repressor, that represses protein synthesis by acting as an external control parameter (Fig. 1).

![FIG. 1: The repressed gene. The expression level of gene $G_x$ is downregulated by the binding of the repressor $R$ to the the DNA binding site BS. We make the assumption that when active, gene $G_x$ synthesizes the protein $x$ in one single step of combined transcription and translation.](image-url)
We describe this system by decomposing the rate equation for the protein $x$ into a production term, described phenomenologically in terms of a Hill function, and a degradation term, straightforwardly written according to the Law of Mass Action:

$$\frac{dx}{dt} = f(x, R) = \frac{g}{1 + \rho R} - kx. \quad (1)$$

Here $\rho$ is the association constant of $R$ to DNA, which describes the strength of the repressor binding to its binding site, $g$ is the maximal expression rate for gene $G_x$, and $k$ is the degradation rate of the protein $x$. These dynamics describe the down regulation of the gene $G_x$ by the repressor $R$, which acts as an external control parameter.

Due to the much shorter half-life of mRNA with respect to that of proteins [8], we here assume that translation and transcription are lumped together in one single step, so that when the gene is in the active state it synthesizes directly the protein $x$. The dynamics specified by the function $f(x, R)$ is characterized by a timescale $\tau_x$, which in the specific case considered here is simply given by the protein inverse degradation rate, $\tau_x = 1/k$.

Let us now consider fluctuations acting on $R$. The nature of these fluctuations is multiple, and their modelling is entirely phenomenological, as we are not assuming or describing any specific molecular mechanism underlying their occurrence. While the Central Limit Theorem would suggest to model them as a Gaussian process, this choice is questionable for fluctuations affecting a strictly positive parameter. In fact, extrinsic fluctuations are well described by log-normal distributions [13, 19], which are also regarded as phenomenological possible candidates to interpret universal features in bacteria and yeast [20, 21]. Furthermore, irrespective of the chosen distribution, the nonlinear dependency of Eq. (1) on $R$ makes the corresponding white noise limit mathematically ill-defined [5].

In order to tackle these issues, first we properly define the nonlinear noise terms in (1) by relaxing the white properties of the noise, and considering coloured noises instead, characterized by a finite correlation time $\tau \gg \tau_x$.

Secondly, we describe log-normal fluctuations, and analyze their effect on the system, compared to the Gaussian noise case.

Thus we supplement Eq. (1) with a complementary equation that describes the fluctuations affecting the parameter $R$:

$$\frac{dR}{dt} = \frac{1}{\tau} \mu(R) + \sqrt{\frac{D}{\tau}} \nu(R) \xi. \quad (2)$$

Here the functions $\mu(R)$ and $\nu(R)$ are kept generic for the moment, but can be chosen so as to reproduce different types of fluctuations, including Gaussian and non-Gaussian noises. The rescaling by the factors $1/\tau$ is introduced so as to slow-down the fluctuations and allows us to carry out a systematic expansion in powers of $1/\sqrt{\tau}$, for $\tau \gg \tau_x$. Finally, the variable $\xi = \xi(t)$ is gaussian, zero average, white noise, with correlator given by

$$\langle \xi(t)\xi(t') \rangle = 2\delta(t - t'). \quad (3)$$

The Master Equation of the system specified by Eqs. (1) and (2) results in

$$\frac{\partial w_i(x, R)}{\partial t} = -\frac{\partial}{\partial x} \left[ f(x, R) w_i(x, R) \right] - \frac{1}{\tau} \frac{\partial}{\partial R} \left[ \left\{ (\mu(R) + D\nu(R)\nu'(R) \right\} w_i(x, R) \right] + \frac{D}{\tau} \frac{\partial^2}{\partial R^2} \left[ \nu^2(R) w_i(x, R) \right], \quad (4)$$

where $w_i(x, R)$ is the joint probability density for the $x$ and $R$ variables. The term proportional to $\nu(R)\nu'(R)$ is the so-called Stratonovich drift, corresponding to having so-called "switching-curve approximation", and expand the stationary solution $w_s(x, R)$ of (4) in inverse powers of the correlation time $\tau$ of the $R$ process:

$$w_s(x, R) = w_0(x, R) + \frac{1}{\tau^{1/2}} w_1(x, R)$$

$$+ \frac{1}{\tau} w_2(x, R) + \mathcal{O} \left( \frac{1}{\tau^{3/2}} \right). \quad (5)$$

We then obtain to the zeroth order in $1/\tau$

$$w_0(x, R) = w(R) \delta(x - u(R)), \quad (6)$$

where $u(R)$ is defined so that $f(u(R), R) = 0$. By assuming that $w_0(x, R)$ is normalized, $w(R)$ in (6) can be identified by solving to order $\tau^{-1}$ the stationary Fokker-Planck Equation associated to (2) and supplemented with the Stratonovich interpretation:

$$0 = D \frac{\partial^2}{\partial R^2} \left[ \nu^2(R) w(R) \right]$$

$$- \frac{\partial}{\partial R} \left[ \left\{ (\mu(R) + D\nu(R)\nu'(R) \right\} w(R) \right]. \quad (7)$$

The marginalized probability density $p(x)$ for the $x$ process can then be obtained as

$$p(x) = \int w_0(x, R)dR = \int w(R)\delta(x - u(R))dR. \quad (8)$$

By using $\delta(\varphi(x)) = \delta(x - x_0)/|\varphi'(x_0)|$, where $x_0$ is the root of $\varphi(x)$, $\varphi(x_0) = 0$, we readily obtain:

$$p(x) = w(u^{-1}(x)) \left| \frac{du^{-1}(x)}{dx} \right|. \quad (9)$$
The probability density \( w(R) \) can be computed from \( \frac{N}{\nu(u^{-1}(x))} \left| \frac{du^{-1}(x)}{dx} \right| \exp \left\{ \frac{1}{D} \int u^{-1}(x) \mu(y) dy \right\} \),\(^{(10)}\) where \( N \) is a normalization constant.

The mode(s) of the probability density \( p(x) \) represent the natural extension of the stable steady state of the corresponding deterministic system, and can be computed explicitly by differentiating \( p(x) \). This leads readily to

\[
\mu - D \nu' - D u'' \left( \frac{du^{-1}(x)}{dx} \right) u'' = 0, \quad (11)
\]

where \( \mu = \mu(u^{-1}(x)), \nu = \nu(u^{-1}(x)), \) and \( u'' = u''(u^{-1}(x)). \)

Eq. \( (11) \) is an extension of the standard equation identifying the modes of a multiplicative stochastic process supplemented with the Stratonovich prescription. The extra term \(- D u'' \left( \frac{du^{-1}(x)}{dx} \right) u'' \) in \( (11) \) accounts for dynamical modifications of the deterministic system which are induced by the slow fluctuations. This term is identically zero only in the case when the the relationship between the variable \( R \) and the variable \( x \) is linear (so that \( u'' = 0 \)), while in all other cases nontrivial modifications of the dynamics can be expected. However, whether these modifications will correspond to a mere shift of parameter values, a change of stability properties of the deterministic attractor states, or a change in their number (namely a pure noise-induced transition) will need to be assessed case by case, once the dynamics of the \( x \) and \( R \) processes are specified. We are going to show here two cases in which a noise-induced transition occurs, and does not, respectively.

Let us consider first the repressed gene model given by Eq. \( (1) \), with log-normal noise on \( R \). In this case the function \( u(R) \) is defined by

\[
\frac{g}{1 + \rho R} - k u(R) = 0 \Rightarrow u^{-1}(x) = \frac{g}{k \rho x} - \frac{1}{\rho}, \quad (12)
\]

and we define

\[
R \rightarrow R(t) = \bar{R} e^{\eta(t)} e^{-D/2}, \quad (13)
\]

where \( \eta(t) \) is the standard Ornstein-Uhlenbeck noise, with the Langevin representation

\[
\frac{d\eta}{dt} = -\frac{\eta}{\tau} + \sqrt{\frac{D}{\tau}} \xi(t). \quad (14)
\]

Here \( \xi(t) \) is zero average Gaussian white noise. The definition \( (13) \) guarantees that \( \langle R \rangle = \bar{R}, \) since \( \langle e^{\eta(t)} \rangle = e^{D/2}. \) The fluctuations on \( R \) can then be described by

\[
\frac{dR}{dt} = -\frac{R}{\tau} \left[ \ln R - \ln \bar{R} + \frac{D}{2} \right] + \sqrt{\frac{D}{\tau}} R \xi(t) \quad (15)
\]

and are characterized by the stationary log-normal distribution:

\[
w(R) = \frac{1}{\sqrt{2\pi D R}} \frac{1}{\bar{R}} \exp \left\{ -\frac{1}{2D} \left( \ln R - \ln \bar{R} + \frac{D}{2} \right)^2 \right\}. \quad (16)
\]

By direct integration of Eq. \( (10) \), we readily obtain

\[
p(x) = \frac{g}{\sqrt{2\pi D x}} \frac{1}{\rho} \left[ \ln \frac{g}{k \rho x} - \frac{1}{\rho} \right] - \ln \bar{R} + \frac{D}{2} \right)^2 \right\} \quad (17)
\]

and, for \( x \neq 0 \) and \( x \neq g/k \), from Eq. \( (11) \)

\[
g \ln \left( \frac{g}{k \rho x} - \frac{1}{\rho} \right) - g \ln \bar{R} - \frac{g D}{2} + 2Dkx = 0. \quad (18)
\]

As an illustration of these dynamics, we consider a prototypical bacterial gene with the following biologically grounded parameter values. We estimate the effective maximal gene expression parameter as \( g \approx g_p g_M / k_M = 10^{-2} \) s\(^{-1}\), where \( g_p \) and \( g_M \) are transcriptional and translational rates respectively, and \( k_M \) is the degradation
rate of mRNA. This choice is compatible with a moderate transcriptional and translational activity and typical mRNA degradation rates in bacteria [22]. Also, we set $k = 10^{-4}$ s$^{-1}$, which corresponds to a protein half-life in the range of 2 hours, and a typical dissociation constant of transcription factors to DNA $\rho = 10$ nM$^{-1}$ [23]. We also fix $\bar{R} = 0.8$ nM, which together with the chosen $\rho$ gives on average a moderate repression activity of $R$ on gene $G_x$. The timescale of the fluctuations $\tau$ is crucial for the matching of our theoretical predictions with the numerical results. Given $k = 10^{-4}$ s$^{-1}$, we set $\tau = 10^5$ s, to capture the dynamics of slow fluctuations of $R$. Noise intensities $D$ in the range $1-10$ are chosen to reproduce fairly large fluctuations, as observed in single cells [24].

Simulations show an excellent agreement with the theoretical predictions, as shown in Fig. [2]. Further to the excellent matching of the full distribution for $R$, the predictions for the modes as given by Eq. (15) is also verified. In Fig. 3 we show the extrema of the stationary probability (17) as function of $\bar{R}$ for different noise intensities, obtained by the numerical solution of Eq. (18) with parameter values as in Fig. 2. The curve associated to $D = 0$ (deterministic case) is single valued for all values of $\bar{R}$, with further increase of $D$ provoking the appearance of a second stable mode for intermediate $\bar{R}$ values.

For comparison, we also consider Gaussian fluctuations on the parameter $R$, by assuming $R \to \bar{R} + \eta(t)$, where $\eta(t)$ is the standard Ornstein-Uhlenbeck process, whose dynamics is given by Eq. (14). Again by direct integration of Eq. (10), we readily obtain

$$p(x) = \frac{1}{\sqrt{2\pi D}} \left( \frac{g}{k\rho x^2} \right) \exp \left\{ -\frac{1}{2D} \left( \frac{g}{k\rho x} - \frac{1}{\rho} - \bar{R} \right)^2 \right\}$$ (19)

The resulting $p(x)$ is non trivial in this case as well, as the original Gaussian noise is transformed nonlinearily into the non-Gaussian probability density [19]. Simulations agree also in this case very well with the analytical predictions. However, in this case only one positive mode is present, which extends the deterministic solution. In fact, for $x \neq 0$, Eq. (11) becomes

$$2Dk^2\rho^2x^2 + g(1 + \rho\bar{R})kx - g^2 = 0$$ (20)

which for $D \neq 0$ accounts for the two real solutions:

$$x_{1,2} = -\frac{g}{4Dk\rho^2}(1 + \bar{R}\rho)$$

$$\pm \sqrt{\left[ \frac{g}{4Dk\rho^2}(1 + \bar{R}\rho) \right]^2 + \frac{g^2}{2Dk^2\rho^2}}$$ (21)

The solution of (20) for $D = 0$ coincides trivially with the solution of the deterministic case, with $x_1$ being the stochastic continuation of it. The $x_2$ branch emerges instead for $D > 0$, signalling that no transition is taking place in the system at finite $D$ (the only critical point being the trivial one, $D = D_c = 0$). Despite the appearance of a second mode, this is to be biologically discarded because at negative $x$ values.

In conclusion, we have introduced an efficient methodology to deal with nonlinear extrinsic noise when the correlation time of the fluctuations is large. Our results generalize the concept of noise-induced transitions exclusively due to multiplicative noise terms, and related to the so-called Stratonovich drift in the Gaussian and white limit. In fact, in the two examples analysed here, the Stratonovich drift does not provoke any qualitative change in the dynamics of the system, as the driving noise is unimodal in all cases. The extra correction terms identified are instead responsible for the possible onset of noise-induced transitions that may or may not occur depending on the general features of the driving noise distribution. While nonlinear Gaussian noise does not provoke any biologically relevant transition to bimodality, nonlinear log-normal noise appears to produce more interesting effects.

Our results show that particular care should be taken when reconstructing gene regulatory networks under...
the evidence of bimodal distributions of gene expression levels. The usual implication that these require a wiring diagram including feedback loops may be false, as the same bimodality may be produced by nonlinear extrinsic noise. The novel mechanism for noise-induced transitions here described is promising and worthy of further analysis and experimental validation. It will contribute to our fundamental understanding of the relevance of noise in biological systems.

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* Electronic address: a.rocco@surrey.ac.uk

[1] J.R. Pomerening, Curr. Opin. Biotechnol. 19, 381 (2008).
[2] M. Santillan, M.C. Mackey, E.S. Zeron, Biophysical J. 92, 3830 (2007).
[3] J.W. Williams, X. Cui, A. Levchenko, A.M. Stevens, Mol. Sys. Biol. 4, 234 (2008).
[4] J.E. Ferrell, Curr. Biol. 22, R458 (2012).
[5] W. Horsthemke and R. Lefever, Noise-Induced Transitions, Springer (2006).
[6] M. Samoilov, S. Plyasunov, A.P. Arkin, PNAS 102, 2310 (2005).
[7] E. Pujadas and A.P. Feinberg, Cell 148, 1123 (2012).
[8] M. Weber and J. Buceta, PLOS One 8, e73487 (2013).
[9] S. de Franciscis, G. Caravagna, A. d’Onofrio, Nat. Comput. 13, 297 (2014).
[10] L. Borland, Phys. Lett. A 245, 67 (1998).
[11] R.V. Bobryk, A. Chrzesczczyk, Phys A 358, 263 (2005).
[12] H.S. Wio, R. Toral, Physica D 193, 161 (2004).
[13] A. d’Onofrio, Phys. Rev. E 81, 021923 (2010).
[14] A. d’Onofrio, A. Gandolfi, Phys. Rev. E 82, 061901 (2010).
[15] N. Rosenfeld, J.W. Young, U. Alon, P.S. Swain, M.B. Elowitz, Science 307, 1962 (2005).
[16] L. Arnold, W. Horsthemke, R. Lefever, Z. Physics B 29, 367 (1978).
[17] L.E. Reichl and W.C. Schieve, Instabilities, bifurcation, and Fluctuations in Chemical Systems, University of Texas Press, Austin (1982).
[18] N. Rosenfeld, M.B. Elowitz, U. Alon, J. Mol. Biol. 323, 785 (2002).
[19] V. Shahrezaei, J.F. Ollivier, P.S. Swain, Mol. Sys. Bio. 4, 196 (2008).
[20] H. Salman et al., Phys. Rev. Lett. 108, 238105 (2012).
[21] N. Brenner et al., Phys. Rev. E 92, 042713 (2015).
[22] M Thattai and A. van Oudenaarden, PNAS 98, 8614 (2001).
[23] A. Loinger, A. Lipshtat, N.Q. Balaban, O. Biham, Phys Rev. 75, 021904 (2007).
[24] L. Cai, N. Friedman, X.S. Xie, Nature 440, 358 (2006).