MODELING DELAYS IN STATE TRANSITION OF A BISTABLE GENETIC SWITCH UNDER THE INFLUENCE OF EXTRINSIC NOISE

Jaroslav Albert and Marianne Rooman
BioSystems, BioModeling and Bioprocesses, Université Libre de Bruxelles
CP 165/61 avenue Roosevelt 50, 1050 Bruxelles, Belgium

Keywords: Bistable genetic switches, Delays, Modeling gene expression, Moise, Robustness.

Abstract: Among other functions, bistable genetic switches serve as decision-makers, accepting or rejecting noisy input signals. In some instances, e. g. during developmental stages, it is imperative that, once an input signal is accepted, the gene's expression remains virtually unchanged for a certain period of time before evolving to its other stationary state. In this paper, we aim to tackle the question of what causes this delay to occur. We look at a particular model of a bistable switch and study the conditions which lead to delayed state transitions. Given that every biological system is subject to noise, it is imperative that any model capable of explaining and predicting these delays is robust against random parameter perturbations. Therefore, in order to test the robustness of the model, we subject the system to random noise and show that for particular combinations of parameter values, its effects on the delays are negligible. It is demonstrated that the ratio of protein to mRNA degradation rates plays a critical role in the system's confidence to generate accurate delays.

1 INTRODUCTION

For a long time, bistable switches have been the focus of extensive research in both experimental and theoretical domains ((Griffith (1968); Kauffman (1975); Watson (1976); Meinhardt and Gierer (1980); Cherry and Adler (2000); Gardner et al. (2000))). One area of study has focused on the ability of switches to distinguish important input signals from random noise ((Fritz et al. (2007))), while in other studies noise was shown to play a positive role in regulating gene expression and amplification of protein production ((Hasty et al. (2000))) and inducing state transitions ((Horsthemke and Lefever (1984))). Although a lot of progress has been made towards understanding the dynamics of bistable switches in noisy environments and the conditions under which they can reliably operate ((Guantes and Poyatos (2008))), much less attention has been payed to the ability of some switches to delay their transition from one stationary state to another. In this paper, we aim to explore this phenomenon.

First, we examine the properties of a bistable switch in terms of an analogy to a particle, moving in one-dimensional potential while being resisted by a frictional force. The shape of the potential, which is a function of only two effective model parameters, is shown to be the only factor in determining whether or not switching occurs. Next, we model the dynamics of the switch in the presence of noise, acting on the model parameters, and study its effects on delays. Finally, the most suitable conditions, i. e. the range of parameter values, for inducing delays under the influence of noise are discussed.

2 MODEL STRUCTURE OF A BISTABLE SWITCH

Us and ((Trotta et al. (2010))) have independently analyzed the mechanism of delayed switching based on the Griffith model discussed below. Here, we briefly summarize our analysis.

The evolution of a bistable switch can be captured by the following set of differential equations first proposed by Griffith ((Griffith (1968))):

$$\dot{x} = r\frac{(\gamma y)^2}{1+(\gamma y)^2} - k_x x + r_0, \quad (1)$$

$$\dot{y} = Kx - k_y y, \quad (2)$$

where x and y are the mRNA and protein concen-

Albert J. and Rooman M..
MODELING DELAYS IN STATE TRANSITION OF A BISTABLE GENETIC SWITCH UNDER THE INFLUENCE OF EXTRINSIC NOISE.
DOI: 10.5220/0003133402780282
In *Proceedings of the International Conference on Bioinformatics Models, Methods and Algorithms* (BIOINFORMATICS-2011), pages 278-282
ISBN: 978-989-8425-36-2

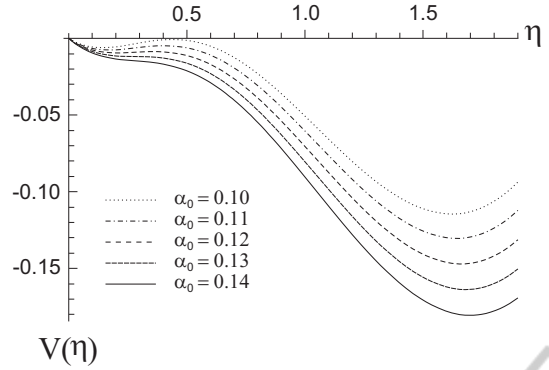

Figure 1: Potential curves corresponding to $\alpha_0 = 0.10$, 0.11, 0.12, 0.13, 0.14 and $\alpha = 2.1$.

tration levels respectively. In respective order, the model parameters in Eq. (1), r, γ, k_x and r_0, stand for the maximum transcription rate, the inverse dissociation factor, degradation rate of mRNA, and the minimum or basal transcription rate. In Eq. (2), K is the rate of translation while k_y is the degradation rate of the translated protein. For simplicity, we redefine all quantities in Eqs. (1) and (2) as follows:

$$\alpha \equiv \frac{K\gamma r}{k_x k_y},\ \alpha_0 \equiv \frac{K\gamma r_0}{k_x k_y},\ \beta \equiv \frac{k_y}{k_x},\ \xi \equiv \frac{K\gamma x}{k_y},\ \eta \equiv \gamma y. \tag{3}$$

This leads to a set of equations with fewer parameters:

$$\dot{\xi} = \alpha\frac{\eta^2}{1+\eta^2} - \xi + \alpha_0, \quad \dot{\eta} = \beta(\xi - \eta), \tag{4}$$

where the dot denotes derivative with respect to $\tau = k_x t$.

In order to get a sense for the model structure and its implications on the system dynamics, we first differentiate Eq. (2), and then, solving algebraicly for $\dot{\xi}$ and ξ in terms of $\dot{\eta}$ and η, write a second order differential equation entirely in terms of η as

$$\ddot{\eta} = -\nu\dot{\eta} - \frac{\partial}{\partial\eta}V(\eta), \tag{5}$$

where

$$V(\eta) = -\beta\left[\alpha(\eta - \tan^{-1}\eta) - \frac{\eta^2}{2} + \alpha_0\eta\right], \tag{6}$$

and $\nu = 1+\beta$. Equation (5) describes a particle acted on by two forces: $-\partial V(\eta)/\partial\eta$ and a frictional force $\nu\dot{\eta}$. Since β in Eq. (6) is merely a multiplicative factor, it plays no role in determining the shape of the potential. Figure 1 shows the shape of $V(\eta)$ as a function of α and α_0.

With rising α_0, the potential barrier between the two minima decreases and disappears completely when the first local minimum and maximum converge into a zero inflection point: $\partial^2 V(\eta)/\partial\eta^2 = 0$ or

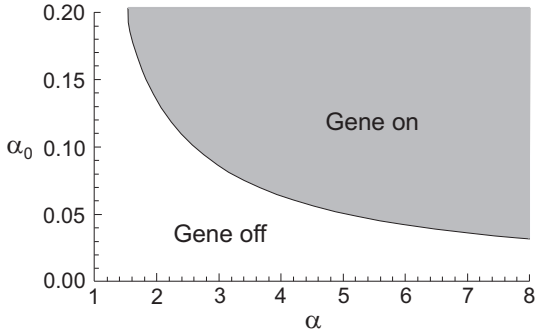

Figure 2: A section of the parameter space (α, α_0). Any combination of parameters which falls onto the shaded region guarantees gene activation. For a fixed value of β, each point in this region corresponds to a particular delay.

$$\frac{2\alpha\eta}{(1+\eta^2)^2} - 1 = 0. \tag{7}$$

If we let η_0 denote the first real solution to this equation, then the necessary condition for a transition to the global minimum becomes

$$\left.\frac{\partial V(\eta)}{\partial\eta}\right|_{\eta=\eta_0} = -\alpha\frac{\eta_0^2}{1+\eta_0^2} + \eta_0 - \alpha_0 < 0. \tag{8}$$

Figure 2 shows the region in parameter space that allows this transition to occur. Since α and α_0 together contain all the other model parameters, the condition expressed in Eq. (8) can provide biologically relevant information about the state of the genetic switch.

The time it takes the system to evolve from one minimum to the other depends on the slope at the inflection point η_0 and the coefficient of friction ν. The less negative this slope and the larger ν, the longer it takes to make this transition. By selecting values for the model parameters, one can set the gene, much like an alarm clock, to become activated after a desired time.

3 DELAYED STATE TRANSITIONS IN THE PRESENCE OF NOISE

Noise is an unavoidable part of all biological systems. Hence, only those models that can reproduce a system's behavior under noisy conditions can be said to have any biological significance. We distinguish between two types of noise: intrinsic and extrinsic.

3.1 Intrinsic Versus Extrinsic Noise

Intrinsic noise comes about as a consequence of random collisions among DNA, RNAs, proteins, and small molecules within the cell ((Hasty et al. (2000))). In small systems, i. e. systems with low concentration levels of mRNA and Protein, and small cell volumes, these collisions cause the concentration levels to fluctuate with frequencies comparable to the macroscopic rates of transcription, translation, and degradation (see (Koern et al. (2005)) for a review). In the opposite limit however, the system dynamics tend towards the deterministicly predicted behavior as, for example, described by differential equations ((Kampen (1992))).

Extrinsic noise arises from slow (compared to typical collision frequencies) fluctuations of one or more of the macroscopic parameters as a response to changes in the chemical environment ((Hasty et al. (2001))). As an example, one can consider a postranslational modification of a particular protein, causing its degradation rate to change ((Guantes and Poyatos (2008); **?**)). The specific molecules responsible for this modification will fluctuate in concentration due to macroscopic effects such as spacial inhomogeneity and cell division, and will modify the differential equations through an addition of a random function added to the protein degradation rate. Similar arguments can be applied to all other parameters.

3.2 Effects of Extrinsic Noise on Time Delays

We model the effects of extrinsic noise on time delays by multiplying one model parameter at a time by a stochastic term $1+\delta(\tau)$, where $\delta(\tau)$ is a piecewise continuous function whose value changes according to a Gassian distribution with variance σ_n^2. The changes in $\delta(\tau)$ are separated by time intervals whose values are assigned probabilistically according to the Poisson distribution. This function is analogous the one representing the velocity of a Brownian particle moving along one-dimension.

Without an external input, i. e. a chemical acting on one of the parameters, α and α_0 are set to 2.1 and 0.1 respectively for five cases of β: $0.1, 0.3, 0.5, 0.7, 0.9$. The exact combination of the parameter values for r, γ, k_x, r_0, K, and k_y is irrelevant as long as the chosen values of α, α_0 and β are respected. For the parameter that is varied - here called the control parameter - twentyfive combinations of noise variance σ_n^2 and frequency f are chosen, corresponding to $\sigma_n = 0.05, 0.1, 0.15, 0.2, 0.25$ and $f^{-1} = 0.02, 0.04, 0.06, 0.08, 0.1$. Twelve values

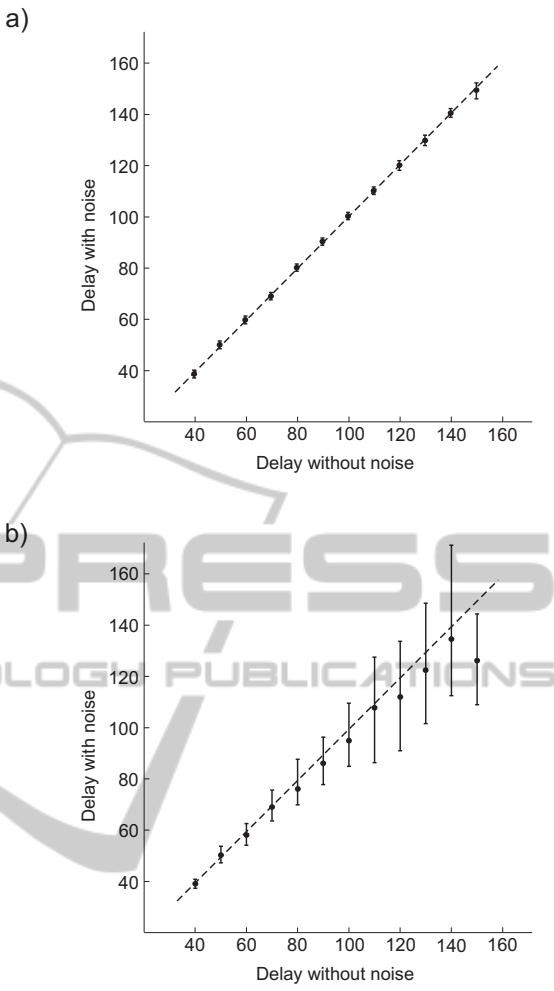

Figure 3: Exact delays d_{Ex} versus the average delays d_{Av} for k_y as the control parameter subject to noise with $\sigma_n = 0.15$, $f^{-1} = 0.04$. In a) $\beta = 0.1$ and b) $\beta = 0.7$. The total variance $\sigma_L + \sigma_R$ for each delay shown in the two figures demonstrates the importance of β on the delays.

are selected for each control parameter in such a way that, in the absence of noise, the delays range from 40 to 150 (in arbitrary units) by steps of ten. For every one of the twelve values of a control parameter, we compute the delay d thirty times, and record their average d_{Av}. The left (right) standard deviation σ_L (σ_R), which corresponds to all points satisfying $d < d_{Av}$ ($d > d_{Av}$) is also computed. Figure 3 illustrates the comparison between the delays in the presence versus the absence of noise for two values of β.

To have a quantitative measure of how well the delays of the stochastic system match up with the exact delays, we define

$$Q = \sqrt{\left(\frac{\sigma_L + \sigma_R}{d_{Av}}\right)^2 + \left(\frac{d_{Av} - d_{Ex}}{d_{Ex}}\right)^2}, \qquad (9)$$

where d_{Ex} stands for the exact delay in the absence of noise. The bar charts in figures 4 a, b, and c show the values of Q for all parameters (see figure captions) and for three different delays, $d_{Ex} = 40, 10, 15$, respectively.

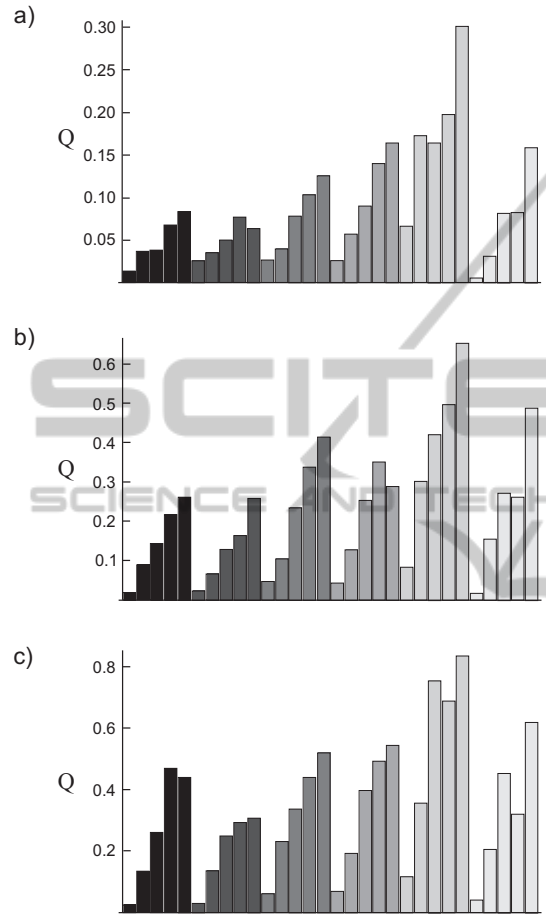

Figure 4: Bar charts showing Q along the vertical axis for three different delays: a) $d_{Ex} = 40$, b) $d_{Ex} = 100$, and c) $d_{Ex} = 150$. Each shade of gray represents one parameter in the order (left to right) r, r_0, k_x, γ, K, and k_y. Within each shade, the columns correspond to the five values of β: 0.1, 0.3, 0.5, 0.7, 0.9.

4 CONCLUSIONS

We have studied the effects of extrinsic noise on the activation delays of a genetic switch. Our analysis shows that, although any of the parameters in the model can be manipulated to generate delays, not all parameters are equally robust against external noise. In particular, looking at the average $\bar{Q} = \sum_\beta Q$ for each parameter, one finds that K, the translation rate, is most suseptible to external noise and therefore least suitable for generating delays. On the other hand, r and r_0, having the lowest $\bar{Q}$ among all parameters, can be used to induce delays with the highest confidence.

Two observations should be made: first, the above results indicate that all parameters gain robustness with decreasing β; and second, Q falls as the delays increase. Therefore, knowing β for a particular gene, one can estimate the likelyhood of that gene to play a role in generating delays. In most cases, β is always less than 1 ((Hargrove and Schmidt (1989))) and can be as small as 0.007 ((Yamamoto et al. (1988))). However, for some proteins and their corresponding mRNA's, such as the Glucocorticoid receptor ((Rosewicz et al. (1988))) and Ornithine decarboxylase ((Rogers et al. (1986))), it can range from 1 up to 4. Although in the deterministic case the delays can reach infinity, in the presence of noise Q increases as a function of d_{Ex}, which suggests a limit on the length of time the switch can be reliably delayed.

As a final comment, we point out that some models of the genetic switch neglect the translational time lapse between the synthesis of mRNA and the corresponding protein. Under this assumption the two quantities ξ and η in Eqs. (4) can be equated, which leads to a single equation for ξ. Mathematically, this simplification can be justified only for $\beta \gg 1$. As this limit is unrealistic for most biological systems, one may conclude that in the context of delayed switching, Eqs. (4) constitute the minimal model required to explain long time activation delays.

ACKNOWLEDGEMENTS

We thank L. Trotta, E. Bullinger, M. Kinnaert and T. Konopka for useful discussions.

REFERENCES

J. S Griffith, *J. theor. Biol.* vol. 20, no. 2, pp. 65-88 (1968)

S. Kauffman, *Ciba Foundation Symp.* vol. 29, p. 201 (1975), Amsterdam: Elsevier.

J. D. Watson, *Molecular Biology of the Gene* W. A. Benjamin, Inc.(1976) Manlo Park

H. Meinhardt,A. Gierer, *J. theor. Biol.* vol. 85, p. 429-450 (1980)

J. L. Cherry, F. R. Adler, *J. theor. Biol.* vol. 203, p. 117-133 (2000)

T. S. Gardner, C. R. Cantor, J. J. Collins, *Nature* vol. 403, p. 339-342 (2000)

G. Fritz, N. E. Buchler, T. Hwa, U. Gerland, *Syst. Synth. Biol.* vol. 1, p. 89-98 (2007)

J. Hasty, J. Pradines, M. Dolnik, J. J. Collins, *PNAS* vol. 97, no. 5, p. 2075-2080 (2000)

W. Horsthemke, R. Lefever, *Noise-Induced Transitions* Springer-Verlag (1984) Berlin

R. Guantes, J. F. Poyatos, *PLOS Comp. Biol.* vol. 4, Issue 11, e1000235 (2008)

L. Trotta, R. Sepulchre, E. Bullinger, accepted to the 2010 IEEE Conference on Decision and Control (2010)

M. Koern, T. C. Elston, W.j. Blake, J.J. Collins, *Nature Reviews* vol. 6, p. 451-464 (2005)

N. G. vanKampen, *Stochastic Processes in Physics and Chemistry* North-Holland Personal Library, (1992) Amsterdam

J. Hasty, F. Isaacs, M. Dolnik, D. McMillen, J. J. Collins, *Chaos* vol. 11, p. 207-220 (2001)

J. Wang, J. Zhanf, Z. Yuan, T. Zhuo, *BMC Systems Biology* vol. 1, p. 50 (2007)

J. L. Hargrove, F. H. Schmidt, *The FASEB Journal* vol. 3, p. 2360-2370 (1989)

M. Yamamoto, S. Kure, J. D. Engel, K. Hiraga, *J. Biol. Chem.* vol. 263, p. 15973-15979 (1988)

S. Rosewicz, A. R. McDonald, B. A. Maddux, I. D. Goldfine, R. L. Miesfeld, C. D. Lugsdon *J. Biol. Chem.* vol. 263, p. 2581-2584 (1988)

S. Rogers, R. Wells, M. Rechsteiner, *Science* vol. 234, p. 364-368 (1986)