Stochastic resonance in an intracellular genetic perceptron

Russell Bates,[1] Oleg Blyuss,[2] and Alexey Zaikin[1,2,3,4]
[1]*Department of Mathematics, University College London, United Kingdom*
[2]*Institute for Women's Health, University College London, United Kingdom*
[3]*Department of Mathematics, King AbdulAziz University, Jeddah, Saudi Arabia*
[4]*Lobachevsky State University of Nizhniy Novgorod, Nizhniy Novgorod, Russia*
(Received 3 September 2013; published 26 March 2014)

Intracellular genetic networks are more intelligent than was first assumed due to their ability to learn. One of the manifestations of this intelligence is the ability to learn associations of two stimuli within gene-regulating circuitry: Hebbian-type learning within the cellular life. However, gene expression is an intrinsically noisy process; hence, we investigate the effect of intrinsic and extrinsic noise on this kind of intracellular intelligence. We report a stochastic resonance in an intracellular associative genetic perceptron, a noise-induced phenomenon, which manifests itself in noise-induced increase of response in efficiency after the learning event under the conditions of optimal stochasticity.

DOI: 10.1103/PhysRevE.89.032716 PACS number(s): 87.18.Cf, 05.40.Ca, 89.75.−k

I. INTRODUCTION

Multicellular systems, e.g., neural networks of a living brain, can learn and be intelligent. Some of the principles of this intelligence have been mathematically formulated in the study of artificial intelligence (AI), starting from the basic Rosenblatt's and associative Hebbian perceptrons and resulting in modern artificial neural networks with multilayer structure and recurrence. In some sense, AI has mimicked the function of natural neural networks. But could this AI be implemented on a genetic level inside one cell, hence, working as an *intracellular* AI? Now we observe the translation of these principles to a new, much smaller scale inside the cell. Indeed, even single cells or unicellular organisms are able to perform tasks such as decision-making and learning by utilizing their genetic regulatory frameworks, i.e., as a sequence of chemical reactions. As a proof-of-principle, it was shown that a neural network can be built on the basis of chemical reactions or linked chains of chemical reactions can act as Turing machines or neural networks [1]. Bray has demonstrated that a cellular receptor can be considered as a perceptron with weights learned via genetic evolution [2] and shown that protein molecules may work as computational elements in living cells [3]. Qian *et al*. have experimentally shown that neural network computations, e.g., a Hopfield-type memory, can be implemented with DNA gate architecture and DNA strand displacement cascades [4]. Without any doubt, complex bimolecular circuits can provide individual cells with the "intelligent" behavior required for survival.

Associative learning, mostly known with respect to Pavlov's dog's ablility to associate the ringing of a bell with getting meat, can also occur on the intracellular scale, as was first formally shown by Gandhi [5]. Later it was shown that real genomic interconnections of the bacterium *Eschericia coli* can function as a liquid-state machine learning associatively how to respond to a wide range of environmental inputs [6]. In 2008 Saigusa *et al*. showed experimentally that the amoebae can anticipate periodic events [7], conversely explaining this by the onset and sustaining of intracellular periodic oscillations. Finally, in 2008 Fernando *et al*. suggested a scheme of the single-cell genetic circuit, which can associatively learn association between two stimuli within the cellular life [8].

On the other hand, it has been demonstrated that gene expression is genuinely a noisy process [9]. Stochasticity of a gene expression, both intrinsic and extrinsic, has been experimentally measured, e.g., in Ref. [10], and modeled either with stochastic Langevin-type differential equations or with Gillespie-type algorithms to simulate the single chemical reactions underlying this stochasticity [11]. Naturally, the question arises as to what the fundamental role of noise in intracellular intelligence is. Can stochastic fluctuations only corrupt the information processing in the course of learning or can they also help cells to "think"? Indeed, recently it was shown that counterintuitively under certain conditions in nonlinear systems noise can lead to ordering, e.g., in the effect of stochastic resonance (SR) [12], which has found many manifestations in biological systems, in particular to improve the hunting abilities of the paddlefish [13], to enhance human balance control [14], to help brain's visual processing [15], or to increase the speed of memory retrieval [16]. Here we will show that, surprisingly, the correct amount of noise in intracellular genetic intelligence can produce an improvement in performance in certain situations or tasks, hence, demonstrating stochastic resonance in an intracellular genetic perceptron (SRIGP).

II. THE MODEL

To show this we will use the model of the associative genetic perceptron suggested in Ref. [8] (Fig. 1), which is able to learn associatively in the manner of Pavlov's dogs. Pavlovian conditioning is the process in which a response typically associated with one stimulus can become associated with a second independent stimulus by repeated, simultaneous presentation of the two stimuli. After a sufficient amount of learning events (simultaneous presentation of stimuli resulting in a response) the presentation of the second stimulus should be able to elicit a response by itself. A scheme of the gene regulatory circuit demonstrating this ability is shown in Fig. 1. This scheme is completely symmetric except for the fact that in

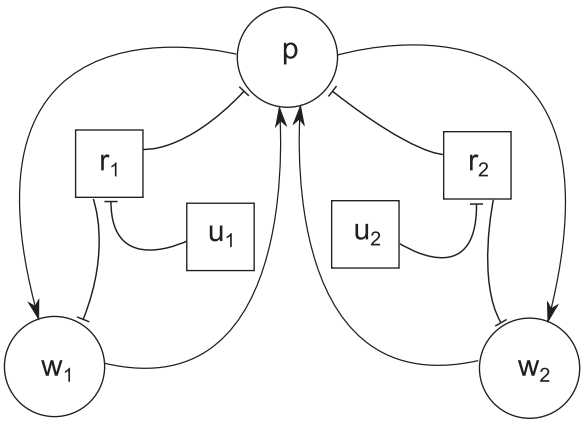

FIG. 1. Schematic representation of an intracellular associative genetic perceptron: nodes represent proteins, black lines represent activatory (pointed arrow) and inhibitory (flat-ended arrow) transcriptional interactions. Square boxes are molecules whose production is not regulated within this circuit but is important to the regulation of the circular nodes.

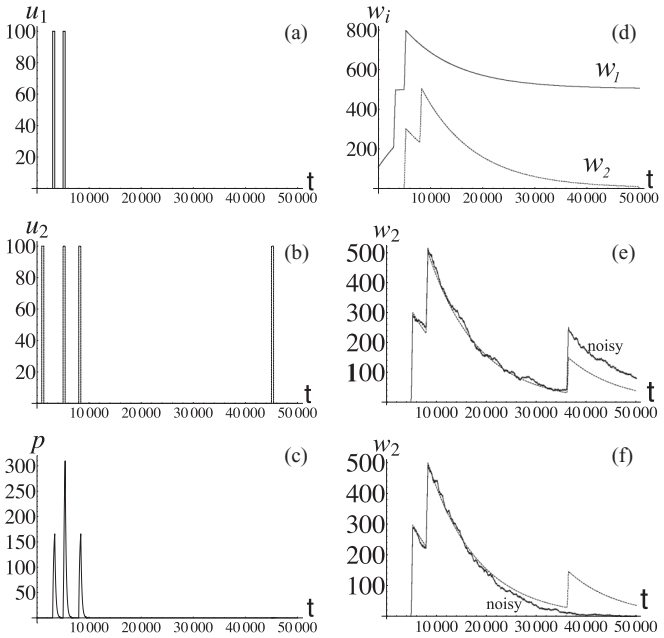

FIG. 2. Learning the association of two stimuli. Plots of concentration of inputs u_1, u_2 and output p vs. time t. (a) u_1, (b) u_2, (c) p, and (d) w_1 and w_2. Noisy (solid) and nonnoisy (dashed) simulations for w_2. (e) An excitation event happens at $t = 36\,000$. At the time of excitation the noisy path very slightly exceeds the nonnoisy path leading to a much greater excitatory jump in w_2, thus a better "learning event"; (f) the converse is also possible.

the left part of the scheme with proteins u_1, r_1, w_1, responsible for main stimulus (as "meat"), the basal expression of w_1 is always present, whereas in the right part of the scheme with proteins u_2, r_2, w_2, responsible for the "bell" stimulus, initially there is no basal expression of w_2, and a concentration of this protein is zero. The flat-headed arrow connecting the u_i and r_i molecules does not represent gene inhibition but the effect will be similar. What it represents is the fact that u_i will bind with an r_i molecule, thus preventing the r_i molecule from inhibiting genes w_i.

The system is governed by a set of coupled stochastic differential equations (SDEs) based on typical mathematical description of activation and inhibition of gene expression through the Hill functions [17]; see for detail of the model Ref. [8]:

$$\begin{aligned}
\frac{dp}{dt} &= v_p\left[\left(\frac{w_1^4}{K_w^4+w_1^4}\right)\left(1-\frac{r_1^2}{K_r^2+r_1^2}\right)\right] \\
&\quad + v_p\left[\left(\frac{w_2^4}{K_w^4+w_2^4}\right)\left(1-\frac{r_2^2}{K_r^2+r_2^2}\right)\right] - \delta_p p + \sigma_p\xi_p \\
\frac{dw_1}{dt} &= \left(\frac{p^2}{K_p^2+p^2}\right)\left(1-\frac{r_1^2}{K_r^2+r_1^2}\right) - \delta_w w_1 + \epsilon_1 + \sigma_{w_1}\xi_{w_1} \\
\frac{dw_2}{dt} &= \left(\frac{p^2}{K_p^2+p^2}\right)\left(1-\frac{r_2^2}{K_r^2+r_2^2}\right) - \delta_w w_2 + \sigma_{w_2}\xi_{w_2}, \quad (1)
\end{aligned}$$

where

$$r_i(t) = \frac{R}{k+u_i(t)} \quad (2)$$

describes the effect of stimulus, and noise is represented by correlated in time Gaussian variables $\xi_p, \xi_{w_1}, \xi_{w_2}$, for all $\langle\xi(t)\xi(t')\rangle = \sigma\delta(t-t')$. The intensities σ_{p,w_1,w_2} depend additionally on the variables as in chemical Langevin equation [11], thus making noise multiplicative in these SDEs. The reaction governing the relationship between r_i and u_i is assumed to be much faster than the gene expression rates so is simply given as an instantaneous conversion to the equilibrium concentration. This equation is taken from what is known as Michaelis-Menten enzyme kinetics, where k represents some kind of equilibrium ratio between the two molecules compared to their bound complex and total number of molecules r_i is a constant. The ϵ_1 term in the w_1 equation represents the asymmetry of the system. It is this "basal rate" of growth that gives us an "unconditioned" stimuli whereby w_1 will always have some nonzero base value. It is this property that allows any input of u_1 to stimulate a response in p, and it is the lack of this basal rate that means initially any isolated input of w_2 will not elicit a response. The constants of this system are as follows: $v_p = 1$, $v_w = 1$, $\delta_p = 0.005$, $\delta_w = 0.0001$, $\epsilon_1 = 0.05$, $K_w = 50$, $K_p = 50$, $K_r = 0.05$, $R = 10$, and $k = 10$ [8].

Without noise, with all σ equal to 0, we can understand the dynamics more easily by simulating these genetic networks and watching how the variables respond to "pulses" of the inputs $u_{1,2}$ at various points in time [see Figs. 2(a)–2(d)]. This collection of images summarizes the dynamics that we desired from this system. An initial pulse of u_2 elicits no response from the system at $t \approx 1000$; this is the conditioned stimulus. At $t \approx 3000$ a pulse of u_1 stimulates a response from the system, the unconditioned stimulus. At $t \approx 5000$ we observe synchronized pulses of both u_1 and u_2; at this point the association is "learned." This is evidenced by the sudden increase in w_2 at this point. At $t \approx 8000$ we see a lone pulse of u_2 eliciting a response in p on its own. This shows that the system has now "learnt" and has fundamentally changed its functionality. Later on at $t \approx 43\,000$ it returns to a state where u_2 does not elicit a response. This is observable in the fact

that w_2 has decayed too close to 0 again and is explained by the fact that within the cell gene products such as w_2 will be recycled and thus the concentration of these molecules will decay exponentially if they are no longer being produced.

III. STOCHASTIC RESONANCE

Next let us investigate how noise will affect the dynamics. The response of the system to an input of unconditioned stimulus u_2 is highly dependent on the quantity of w_2 and due to the sharp switching nature of the Hill functions, small differences can cause much larger excitation behavior. As our w_2 quantity will now behave as a stochastic trajectory it would be of interest to examine how this will affect its value at the time of an input pulse. As Figs. 2(e) and 2(f) show, respectively, noise can improve the learning event, and the converse is also possible. To study averaging influence of noise there are two performance measures which we will consider. First, we would like to consider the likelihood of eliciting a response from an input that is just out of the memory range of the nonnoisy system. Second, we would like to consider the noisy system's ability to respond to a sequence of such inputs.

By performing repeated simulations and calculating the average response, we can plot the probability of eliciting a response against the intensity of noise. A response is classified as the output quantity p exceeding a value of 40 during the input pulse. To define a successful firing event we require that the output exceeds the designated threshold of 40 within the input duration, but we will also require that it settles down quickly and does not exceed a lower threshold 5 during the interval between pulses, namely, in the 7000 s preceding the pulse p. This requirement allows us to treat the high noise limit as a failure of functionality. This is important as we are only interested in the output exceeding the threshold as a response to the input and not simply as a consequence of a highly noisy system, and we cannot treat it truly as a response if it cannot be easily distinguished from an interval.

In the first case, we are interested in eliciting simply a single response that lies out of range of the nonnoisy system. A likelihood of triggering first response L is shown in Fig. 3(a). This is the classic stochastic resonance bell curve, in our case explained by the mechanism of threshold stochastic resonance without period force [18]. An initial increase in effectiveness followed by a decrease due to a loss of order in the higher noise range, hence, demonstrating SRIGP.

In the second case we present the system with a set of ten evenly spaced input pulses, again the initial one is just out of range of the nonnoisy system. In the best case the system responds to all ten pulses; see Fig. 3(b). Repeated simulations are performed and we can plot the expected number of responses against the intensity of noise added, as in Fig. 3(c). Again we observe this characteristic bell-shaped curve of improvement followed by regression after an optimal point.

The points at which we are considering input pulses to occur are at the limits of the systems memory, this implies that we are dealing with low concentrations of w_2. This means that the existence of the stochastic resonance bell curve can be understood from identifying the upward biasing of the noisy Hill function as likely to cause some improvement. The Hill function relevant to our decaying w_2 molecules is

$$\frac{w_2^4}{K_w^4 + w_2^4}. \tag{3}$$

From this we can clearly see the sharp switching nature of this function that is ultimately responsible for the excitability of the system. Above $w_2 = 100$ we see that the function is essentially constant at 1. This is why we will get a uniform response regardless of our value of w_2 provided that value is sufficient. Below $w_2 = 100$ there is a sharp drop-off until below $w_2 = 20$ we are essentially at 0. It is worth observing that at low concentrations we have a highly asymmetric function, any effect of noise is most likely going to take advantage of this bias. We can explore this bias analytically. Let our Hill function be

$$g(x) = \frac{x^4}{K^4 + x^4}.$$

Now let $X \sim \mathcal{N}(x_0, \sigma^2)$ be our random variable for the intrinsic noise in the system when we have $w = x_0$. Let $f(x)$ be the probability distribution function for the normal distribution with mean x_0 and variance σ_0^2:

$$f(x) = \frac{1}{\sqrt{2\pi\sigma_0^2}} e^{-\frac{(x-x_0)^2}{2\sigma_0^2}}.$$

We know that $\mathbb{E}[X] = x_0$ and that for $g(X)$

$$\mathbb{E}[g(X)] = \int_0^\infty f(x)g(x)\,dx.$$

By considering

$$h(x_0) = \mathbb{E}[g(X)] - g(x_0),$$

we see the following; see Fig. 3(d). For values of $w = x_0$ less than approximately 10 we see an upward biasing of the noise with respect to our Hill function. This is plotted for $\sigma_0 =$

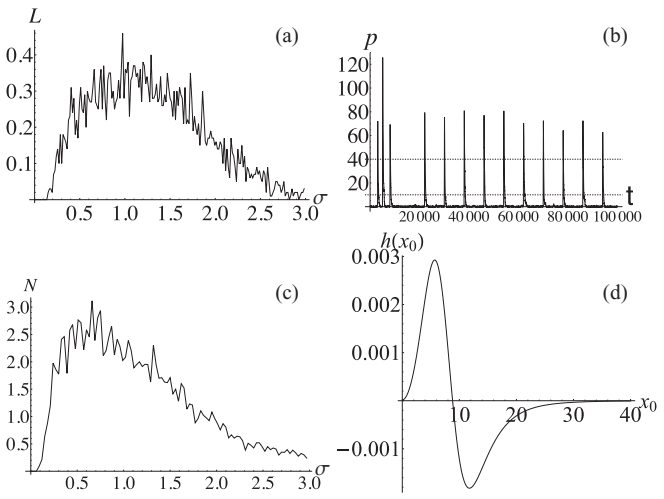

FIG. 3. SR in genetic perceptron. (a) Likelihood of first response L vs. noise intensity σ; (b) demonstration of a perfect 10 out of 10 response to the series of inputs, with an upper and lower threshold both marked on; (c) average number N of responses, out of 10, vs. noise intensity; (d) numerical plot of $h(x_0)$ vs. x_0.

0.5 but holds for all values, the amplitude of the oscillations increasing with σ_0. What this means is that the expectation of the Hill function for a noisy variable at small concentrations will be larger than the value of the Hill function for a nonnoisy variable. This suggests that the influence of noise may provide us with some constructive effects.

IV. DISCUSSION

In summary, the investigations into the associative perceptron have shown a significant improvement in two different measures of functionality due to noise. In the first instance we saw a marked improvement in the likelihood of eliciting a response from an input out of the memory range of the nonnoisy system. Second, we noticed an increase in the effectiveness also when considering the ability to repeatedly respond to inputs. In both cases there was a stochastic resonance bell curve demonstrating an optimal level of noise for the task. The improvement in excitory behavior comes as a result of the strong asymmetry of the Hill functions, identified earlier as the crucial term in the equation when it comes to this kind of dynamics. While our noise is unbiased in whether it will increase or decrease the concentration value, as it normally distributed, the fact that this variable is then applied to Hill functions means that small increases in the positive direction have much more impact than those in the negative direction. This was demonstrated using the expectation of a function of random variables and we were able to prove that this biasing does indeed exist for small concentrations. In the case of eliciting a first response, it was noticed that the optimal noise actually corresponded to a scaling factor of approximately 1 to the initially derived intensity of noise.

Our demonstration of SR at the level of intracellular behavior gives insights into fundamental role of stochasticity in gene expression. It seems that the ability of cells to "think" has been probably evolved for functional success and adapted evolutionarily to the present noise. Indeed, an optimal amount of noise extends the memory of successful associative learning. Malfunction of this adaptation could be a possible cause of cancer as a failure to use an optimal amount of noise can lead to the wrong classification of intracellular signals. Manifestation of intracellular intelligence may change our views on the functionality of the brain, because it bears witness to neural network functionality not only between its cells but also inside one single cell. In its turn, the possibility of stochastic resonance on the intracellular scale means that our brain can effectively utilize not only the external noise but also the intrinsic noise of gene expression. Finally, construction of intelligent intracellular gene-regulating networks is the hot topic of synthetic biology [19], and here we have shown that unavoidable noise can be constructively used in such design.

ACKNOWLEDGMENT

A.Z. acknowledges support from the Deanship of Scientific Research (DSR), King Abdulaziz University (KAU), Jeddah, under Grant No. 20/34/Gr and from Russian Foundation for Basic Research (Grant No. 14-02-01202).

[1] A. Hjelmfelt and J. Ross, Physica D: Nonlin. Phenom. **84**, 180 (1995).
[2] D. Bray and S. Lay, Biophys. J. **66**, 972 (1994).
[3] D. Bray, Nature **376**, 307 (1995).
[4] L. Qian, E. Winfree, and J. Bruck, Nature **475**, 368 (2011).
[5] N. Gandhi, G. Ashkenasy, and E. Tannenbaum, J. Theor. Biol. **249**, 58 (2007).
[6] B. Jones, D. Stekel, J. E. Rowe, and C. Fernando, in *Proceedings of IEEE Symposium on Artificial Life* (IEEE, Piscataway, NJ, 2007), Vol. 187.
[7] T. Saigusa, A. Tero, T. Nakagaki, and Y. Kuramoto, Phys. Rev. Lett. **100**, 018101 (2008).
[8] C. T. Fernando *et al.*, J. R. Soc. Inter. **6**, 463 (2008).
[9] H. H. McAdams and A. Arkin, Trends Genet. **15**, 65 (1999).
[10] M. B. Elowitz, Science **297**, 1183 (2002).
[11] D. T. Gillespie, J. Chem. Phys. **113**, 297 (2000).
[12] R. Benzi, A. Sutera, and A. Vulpiani, J. Phys. A **14**, L453 (1981); C. Nicolis, Sol. Phys. **74**, 473 (1981); L. Gammaitoni, P. Hänggi, P. Jung, and F. Marchesoni, Rev. Mod. Phys. **70**, 223 (1998).
[13] D. F. Russell, L. A. Wilkens, and F. Moss, Nature **402**, 291 (1999).
[14] A. A. Priplata *et al.*, Lancet **362**, 1123 (2003).
[15] T. Mori and S. Kai, Phys. Rev. Lett. **88**, 218101 (2002).
[16] M. Usher and M. Feingold, Biol. Cybern. **83**, L011 (2000).
[17] J. N. Weiss, FASEB J. **11**, 835 (1997).
[18] E. Simonotto, M. Riani, C. Seife, M. Roberts, J. Twitty, and F. Moss, Phys. Rev. Lett. **78**, 1186 (1997).
[19] T. K. Lu, A. S. Khalil, and J. J. Collins, Nat. Biotechnol. **27**, 1139 (2009).