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Dynamical decision making in a genetic perceptron

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HIGHLIGHTS

- We study dynamical classification in a genetic perceptron with noise.
- Noise, bistability and threshold perturbation separately degrade classifier accuracy.
- Noise in the presence of bistability or threshold perturbation may improve accuracy.
- Noise may play a constructive role in intracellular decision making.

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ABSTRACT

Decision making is an essential element of cell functioning, which determines milestones of its evolution including differentiation, apoptosis and possible transition to cancerous state. Recently the concept of stochastic resonance in decision making (SRIDM) was introduced, demonstrated and explained using a synthetic genetic classifier circuit as an example. It manifests itself as a maximum in the dependence of classification accuracy upon noise intensity, and was caused by the concurrent action of two factors, both coarsening the classification accuracy by themselves, but found to extenuate the effect of each other: perturbation of classifier threshold and additive noise in classifier inputs. In the present work we extend the SRIDM concept to dynamical decision making, in which a classifier keeps track of the changeable input. We reproduce the stochastic resonance effect caused by noise and threshold perturbation, and demonstrate a new mechanism of SRIDM, which is associated with bistability and not connected with threshold perturbation.

1. Introduction

The functioning of a living cell in a multicellular organism is essentially a sequence of decisions [1]. Decision making is involved in differentiation [2], morphogenic pattern formation [3,4], apoptosis [5]. A possible cause of turning a cell into a cancerous state may also be attributed to (erroneous) decision making [6]. Decisions are made by the cell's internal regulatory circuitry in response to intra- or extracellular signals. It is known that genetic circuits can act as perceptrons [7], which are basic decision-making units. One of the key players in the intracellular decision making process is noise, which inevitably occurs in genetic expression due to essentially discrete nature of involved chemical reactions [8,9]. Recently it was shown that noise can play a constructive role in cellular decision making, improving the rate of correct decisions under certain conditions [10].

A simple genetic network which implements a two-input genetic perceptron was designed in [10]. Basically, it is a weighted linear classifier with a threshold detector at the output. The inputs to the circuit are initial concentrations of two transcription factors. The output is determined by the established state of the system. By means of analysis and numerical simulation the effect of stochastic resonance in a linear classifier with perturbed threshold and additive noise in the inputs was demonstrated and quantified. Namely, a certain two-input linear classifier is chosen as a reference one, whose output is assumed to be the "correct" answer. Expectedly, perturbing the output threshold value leads to the appearance of incorrect answers. Likewise, introducing random additives to the inputs of the unperturbed classifier ("input noise") has the same effect. That said, in [10] it was found that adding input noise to a classifier with *perturbed* threshold may lead to

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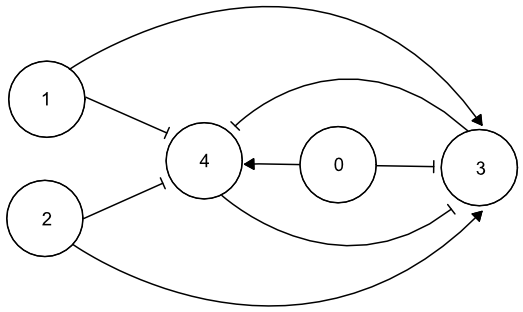

Fig. 1. Scheme of the genetic perceptron circuit.

increasing the correct classification rate, exhibiting a maximum in the dependence of the latter upon input noise intensity (effect identified in [10] as stochastic resonance in a classifier).

Although a dynamical model of the genetic classifier circuit was considered in [10], basically, no dynamical effects were studied, since the inputs were assumed to be constant, and the classifier output was essentially a function of the inputs. In the present work we extend the study of a genetic classifier with noise to account for dynamical effects.

We define and address the problem of dynamical classification, in which the classifier inputs remain constant for a certain time interval, but vary abruptly between such intervals in a sequence. This setting creates new sources of classification errors. First, due to the inertia (delay) of the genetic response, the system may fail to respond to input changes, if they occur too rapidly. Second, if the threshold circuit has bistable dynamics, then the output exhibits hysteretic behaviour, which implies that the output value may depend on the previous state of the system regardless of the delay effects. Furthermore, the dynamical classification problem setting calls for taking into account the (dynamical) gene expression noise by considering the model in the form of stochastic differential equations.

We start with studying the effects of inertia and bistability upon dynamical classification by measuring the simulated classification accuracy (correct classification rate) upon the duration of constant input presentation, and a classifier circuit parameter which determines bistability. Then we reproduce the stochastic resonance effect known from [10] (in a classifier with perturbed threshold and noise in the inputs) in the dynamical setting. Finally, we explore the effect of dynamical transcription noise and show that it may improve classification accuracy by reducing the destructive effect of hysteresis (bistability) in a classifier without threshold perturbation. This effect can also be identified as stochastic resonance, but of different nature than one found in [10].

2. Classifier model

We use the genetic perceptron scheme and model suggested in [10]. The scheme of the circuit is presented in Fig. 1. Genes 1 and 2 stand for classifier inputs, while the self-inducing and mutually repressing genes 3 and 4 form the thresholding unit which presents the classification result: we denote the outcome as "positive" when established expression of gene 3 is higher than that of gene 4, and as "negative" otherwise. Gene 0 is used to control the value of the classification threshold.

Following [10], we use the Kaneko model [11] to describe the circuit dynamics by ordinary differential equations

$$\dot{m}_i = f\left(\sum_j A_{ij} p_j - \theta_i\right) - m_i \tag{1a}$$

$$\dot{p}_i = m_i - p_i, \quad i = 0 \ldots 4, \tag{1b}$$

where dynamic variables p_i and m_i denote normalized concentrations of protein and mRNA corresponding to the ith gene (we assume their values to be restricted to the interval [0, 1], since all solutions converge to this region of phase space). A sigmoid function $f(x)$ is switching from 0 to 1 when its argument changes sign from negative to positive:

$$f(x) = \frac{1}{1 + e^{-\beta x}}. \tag{2}$$

In the simulations we take $\beta = 40$. Parameters $\theta_0, \theta_1, \theta_2$ are used to set the output threshold and the inputs of the classifier (see below), and $\theta_3 = \theta_4 = 0$. Matrix A_{ij} describes the interactions between the genes according to the scheme in Fig. 1:

$$A = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ -1 & 1 & 1 & a & -a \\ 1 & -1 & -1 & -a & a \end{pmatrix}. \tag{3}$$

Positive parameter $a > 0$ determines the strength of mutual suppression between genes 3 and 4, all other interactions assumed to be unity.

Since genes 0, 1 and 2 are not regulated by any other genes, their dynamics decouple from the rest of the circuit. Using (1b) to exclude variables m_i from (1a), we write down the corresponding equations in the form

$$\ddot{p}_i + 2\dot{p}_i = f(-\theta_i) - p_i, \quad i = 0, 1, 2. \tag{4}$$

When parameters θ_i, $i = 0, 1, 2$ are constant, the stable equilibrium concentrations of p_i are

$$p_i^e = f(-\theta_i), \quad i = 0, 1, 2. \tag{5}$$

These equilibrium concentrations can be easily controlled by substituting for θ_i their expression from (5) via desired values of p_i^e:

$$\theta_i = \frac{1}{\beta} \log\left(\frac{1}{p_i^e} - 1\right), \quad i = 0, 1, 2. \tag{6}$$

If parameters θ_i are varied in time, then (4) will exhibit some inertia (delay) in the response of concentrations p_i to changes in θ_i.

Dynamics of output genes 3 and 4 is described by equations

$$\ddot{p}_3 + 2\dot{p}_3 = f(\quad (p_1 + p_2 - p_0) + a(p_3 - p_4)) - p_3 \tag{7a}$$

$$\ddot{p}_4 + 2\dot{p}_4 = f(-(p_1 + p_2 - p_0) + a(p_4 - p_3)) - p_4, \tag{7b}$$

where p_0, p_1 and p_2 are determined by (4) and play here the role of external parameters (generally speaking, variable in time).

In the setting of [10] (static classification), where inputs p_1 and p_2 as well as threshold p_0 are constant in time, and initial concentrations $p_3(0)$ and $p_4(0)$ are equal, the relation between equilibrium values of p_3^e and p_4^e is determined by the sign of the linear expression $p_1 + p_2 - p_0$:

$$p_3^e > p_4^e, \quad \text{if } p_1 + p_2 > p_0, \tag{8a}$$

$$p_3^e < p_4^e, \quad \text{if } p_1 + p_2 < p_0. \tag{8b}$$

Cases (8a,b) are denoted as the positive and the negative decisions of the classifier, respectively. This is the linear classification rule for static classification setting [10].

3. Dynamical classification

In order to define dynamical classification, we assume that different inputs are presented to the classifier sequentially, so that during each presentation the parameters θ_1, θ_2 are constant and calculated according to (6). The classifier decisions are defined

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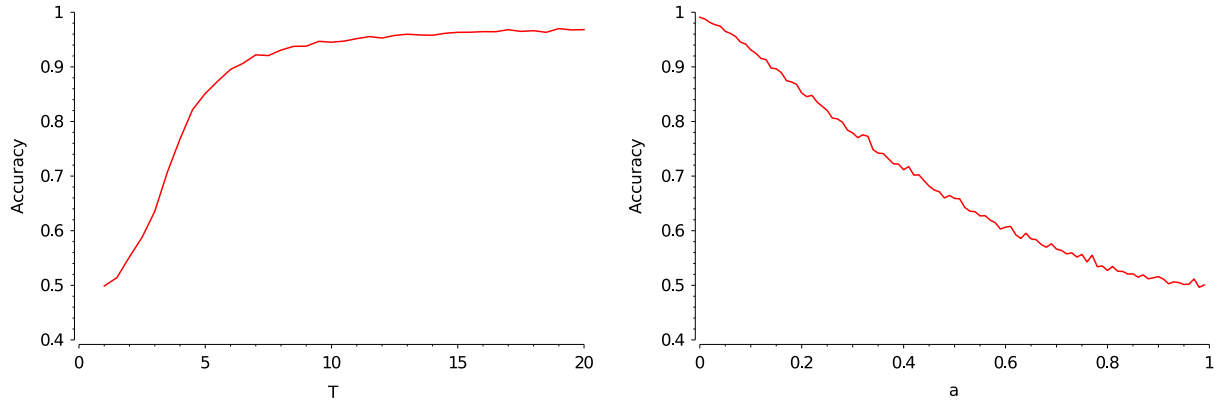

Fig. 2. Accuracy of dynamic classification versus duration of input presentation T at $a = 0.1$ (left panel) and versus coupling parameter a at $T = 10$ (right panel).

similarly to (8a,b) with the output read out at the end of each input presentation:

$$\text{Classifier answer}_i = \begin{cases} +, & \text{if } p_3(t_i^{\text{end}}) > p_4(t_i^{\text{end}}) \\ -, & \text{if } p_3(t_i^{\text{end}}) < p_4(t_i^{\text{end}}), \end{cases} \tag{9}$$

where t_i^{end} is the end of the time interval of ith input presentation. The reference, or "correct" answer is defined according to the linear classifier rule:

$$\text{Correct answer}_i = \begin{cases} +, & \text{if } p_1^i + p_2^i > p_0 \\ -, & \text{if } p_1^i + p_2^i < p_0, \end{cases} \tag{10}$$

where (p_1^i, p_2^i) is the ith input sample. We define the classification accuracy, or correct classification rate, as the ratio of correct classifier decisions to total number of classified samples.

Two sources of errors in dynamical classification are bistability and inertia of the classifier. If ith input falls into the bistability region, then the classifier will actually repeat its $(i-1)$th decision regardless of the ith input value. Since the bistability region in (7) expands with increasing a, the classification accuracy dependence upon a is expected to be falling. At the same time, classifier inertia may lead to errors regardless of bistability: if the duration of input presentation is less than the response time of the classifier (determined by the duration of transient process), then the correct classifier state may fail to establish during the input presentation time.

To reveal the classification accuracy dependence upon interaction parameter a and duration of input presentation T we performed simulations of dynamical classification. To measure classification accuracy at given parameter values we generated a sequence of N_s random inputs (p_1^i, p_2^i), $i = 1, \ldots, N_s$, $N_s = 10^4$, where all quantities p_1^i, p_2^i were sampled from a uniform distribution on the segment $[0, 1]$. These inputs were presented to the classifier sequentially by adjusting parameters θ_1, θ_2 according to (6), so that the parameters are constant during each interval of length T and change their value abruptly between intervals. In all simulations we set $\theta_0 = -100$, so that classification threshold $p_0 \approx 1$. For each input we compute the reference answer according to (10) and compare it to the actual classifier output (9). Then classification accuracy is calculated for the total sequence. Two series of simulations were performed. In the first one we set $a = 0.1$ and vary T from 1 to 20 (Fig. 2, left panel). In the second one we fix $T = 10$ and vary a from 0.01 to 0.99 (Fig. 2, right panel). The results confirm the expected increasing dependence of accuracy upon T and its decreasing dependence upon a. In particular, values $T = 10$ and $a = 0.1$ reliably provide accuracy above 0.9. We use these values in our further simulations, unless stated otherwise.

4. Effect of noise and stochastic resonance in dynamical classification

We start with considering "static" noise in the inputs, which distorts each single input (p_1^i, p_2^i) by a random additive quantity which remains constant during each input presentation and varies independently between inputs. Namely, distorted input $(\tilde{p}_1^i, \tilde{p}_2^i)$ is specified by

$$\tilde{p}_1^i = w_{[0,1]}(p_1^i + \xi_i) \tag{11a}$$

$$\tilde{p}_2^i = w_{[0,1]}(p_2^i + \eta_i), \tag{11b}$$

where ξ_i and η_i are independent Gaussian random variates with zero mean and dispersion σ^2, and $w_{[0,1]}(x)$ is truncating function

$$w_{[0,1]}(x) = \begin{cases} 0, & \text{if } x < 0 \\ x, & \text{if } x \in [0, 1] \\ 1, & \text{if } x > 1. \end{cases} \tag{12}$$

In order to seek for the effect of Stochastic resonance in genetic decision making (SRIDM), which was discovered and explained in case of static classification in [10], we consider a dynamical classifier with perturbed threshold, which implies using perturbed parameter $\tilde{\theta}_0$ in place of θ_0 according to

$$\tilde{\theta}_0 = \frac{1}{\beta} \log\left(\frac{1}{p_0 + \varepsilon} - 1\right), \tag{13}$$

where p_0 is unperturbed threshold, and ε is (determinate) threshold perturbation.

Similarly to simulations in the previous section, for each measurement of classification accuracy we generate a sequence of random inputs (p_1^i, p_2^i), $i = 1, \ldots, N_s$, $N_s = 10^4$. For each input the reference answer (10) is found. In the course of the simulation distorted inputs $(\tilde{p}_1^i, \tilde{p}_2^i)$ according to (11a,b) are sequentially presented to the classifier (by setting the corresponding values for θ_1, θ_2 according to (6)). Each classification result is compared to the reference one, and classification accuracy is calculated for the total sequence.

We performed two series of simulations with noise intensity σ varied from 0 to 1, the first one with unperturbed classifier threshold $p_0 \approx 1$, $\theta_0 = -100$ (Fig. 3, blue solid line), and the second one with perturbed threshold according to (13) with $\varepsilon = -0.3$ (Fig. 3, red dashed line). The latter curve exhibits a local maximum, which can be interpreted as a manifestation of SRIDM in dynamical classification.

Now we take into account dynamic transcriptional noise by adding noisy terms to the right-hand part of dynamical equations (1a) which take the form of Langevin equations

$$\dot{m}_i = f\left(\sum_j A_{ij} p_j - \theta_i\right) - m_i + \xi_i(t), \quad i = 0 \ldots 4, \tag{14}$$

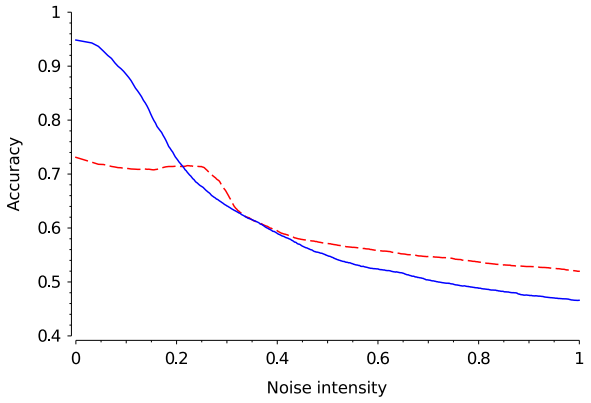

Fig. 3. SRIDM effect in dynamic classification. Classification accuracy versus noise intensity σ, static distortion of inputs with unperturbed (blue solid line) and perturbed (red dashed line) threshold. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

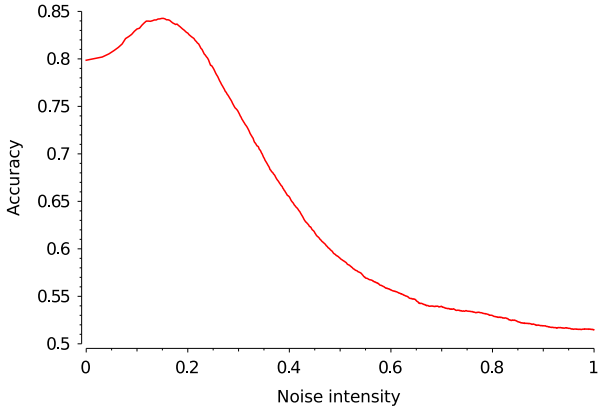

Fig. 4. SRIDM effect due to dynamical noise without perturbation of threshold. Classification accuracy versus noise intensity σ.

where $\xi_i(t)$ are independent Gaussian white noises with dispersion σ^2.

We performed a series of simulations with noise intensity σ varied from 0 to 1 without threshold perturbation, at $a = 0.3$, $N_s = 10^4$, all other parameters and methods same as in previous simulations. Result is presented in Fig. 4. The curve exhibits a local maximum which again can be referred to as stochastic resonance in decision making, but this time it is not caused by threshold perturbation. Thus, this kind of SRIDM is of completely different nature than that observed in Fig. 3 and explained in [10].

In order to explain this phenomenon, we recall bistability as one of the key sources of errors in dynamical classification. When at a certain input the system finds itself in the bistable regime, in the absence of noise it is unable to change the decision readout from the one inherited from the previous input. At the same time, when noise is present, switchings between stable states become possible [12]. This may improve the correct classification rate for inputs falling within the bistability region, thus leading to the appearance of a local maximum in the dependence of classification accuracy upon noise intensity.

5. Conclusions

We formulated the problem of dynamical classification in a genetic classifier circuit with variable inputs. We studied the effects of inertia and bistability upon classification accuracy. We reproduced the stochastic resonance effect in a dynamical classifier with perturbed threshold and noise in the inputs. Finally, we have shown that dynamical noise may improve classification accuracy by reducing the destructive effect of bistability in a classifier without threshold perturbation. This effect can also be referred to as stochastic resonance, but of different nature than that caused by perturbed classifier threshold.

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