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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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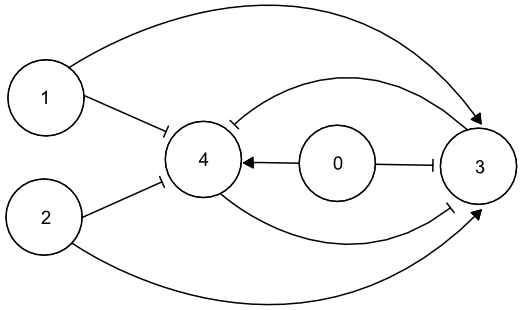

Fig. 1. Scheme of the genetic perceptron circuit.

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

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

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

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