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A Hardware-Efficient Gene Network Model based on Asynchronous Bifurcation Processor

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Abstract—In this paper, a novel gene network model based on an asynchronous bifurcation processor is presented. It is shown that an isolated gene network model generates periodic oscillations of mRNA, protein, inhibitor, and neuropeptide concentrations. Then a network of the gene network (corresponding to a network of cells) is presented, where each gene network is coupled via a mean field of the neuropeptides. It is shown that the network of the cells can reproduce typical nonlinear phenomena related to circadian rhythms such as mutual synchronization of coupled gene networks and forced synchronization of coupled gene networks to a periodic light stimulation.

1. Introduction

The circadian rhythm is a biological rhythmic phenomena, where mammalian circadian rhythms typically have periods of about 24-h (24 hours). The circadian rhythm is generated by a network of suprachiasmatic nucleus (SCN) neurons [1]-[3]. A gene network in the single SCN neuron forms a closed-loop nonlinear dynamical system, which leads to periodic oscillations of mRNA, protein, and neurotransmitter concentrations. If the SCN neurons are isolated, oscillation periods of the mRNA concentrations have a relatively wide distribution. However, in the suprachiasmatic nucleus, the SCN neurons are coupled via neurotransmitters and the oscillation periods of the mRNA concentrations have a sharp distribution near (but not identical with) 24-h. In addition, if a light-and-dark stimulation with period 24-h is applied to a mammalian visual system, the suprachiasmatic nucleus is affected by the stimulation and then the periods of the mRNA concentrations in the coupled SCN neurons are sharply locked to 24-h. It should be emphasized that the gene networks play important roles not only in the generation of the circadian rhythm but also in many brain functions [3], i.e., investigation of the circadian rhythm is an entrance into studies of roles of gene networks in brain functions. On the other hand, our group has been developing a neural system modeling approach based on the nonlinear dynamics of an asynchronous cellular automaton, where nonlinear dynamics (especially, bifurcations) of neural systems are reproduced by the asynchronous cellular automaton with low hardware cost [4]-[6]. Our group is conceptually referring to such a hardware platform as "asynchronous bifurcation processor (ABP)." So, in this paper, a novel gene network model based on the ABP is presented. It is shown that the network can reproduce generations of typical circadian rhythms.

2. ODE Gene Network Model

Let

$$t \in \boldsymbol{R}$$

represent a continuous time and let

$$X_i \in \boldsymbol{R}^+ = \{x | x \in \boldsymbol{R}, x > 0\},$$

$$Y_i \in \boldsymbol{R}^+, \quad Z_i \in \boldsymbol{R}^+, \quad V_i \in \boldsymbol{R}^+$$

represent mRNA concentration of a clock gene, the resulting protein concentration, concentration of nuclear form of the protein (inhibitor concentration), and neuropeptide concentration, respectively. A basic ODE gene network model is described by the following set of equations [1].

$$\begin{aligned}
\frac{dX_i}{dt} &= v_1 \frac{K_1^n}{K_1^n + Z_i^n} - v_2 \frac{X_i}{K_2 + X_i} + v_c \frac{KF}{K_c + KF} + L, \\
\frac{dY_i}{dt} &= k_3 X_i - v_4 \frac{Y_i}{K_4 + Y_i}, \\
\frac{dZ_i}{dt} &= k_5 Y_i - v_6 \frac{Z_i}{K_6 + Z_i}, \\
\frac{dV_i}{dt} &= k_7 X_i - v_8 \frac{V_i}{K_8 + V_i}, \\
F &= \frac{1}{D} \sum_{i=1}^{D} V_i,
\end{aligned}$$

where L represents a light stimulation with period 24-h; D represents the number of cells; F represents a mean field of the neuropeptide; and $v_1, \cdots, v_8$, $K_1, \cdots, K_8$, v_c, and K_c are parameters. Fig. 1 shows typical time waveforms of the ODE gene network model. Fig. 1(a) shows time waveforms of concentrations X_1 and X_2 of mRNAs in two cells. In Fig. 1(b), the cells are coupled via the mean field F of the neuropeptide. In this case, the mRNA concentrations X_1 and X_2 are synchronized. In Fig. 1(c), the coupled cells accept an external light stimulation L with period 24-h . In

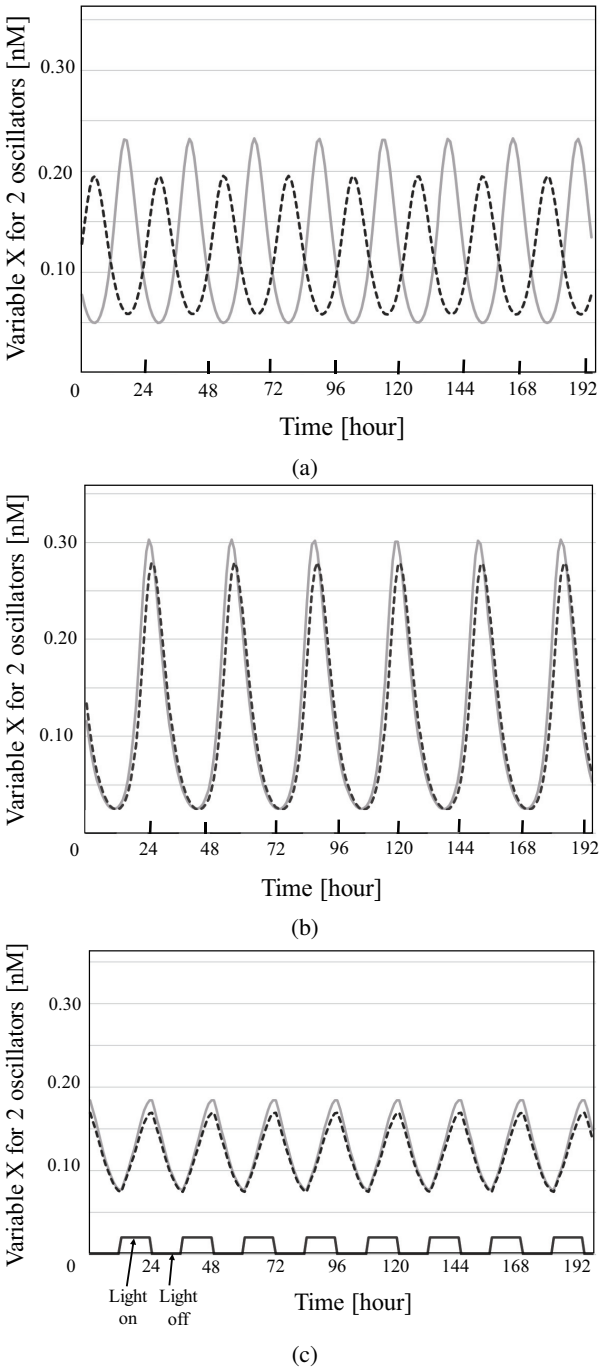

Figure 1: Typical waveforms of the ODE gene network model [1]. The parameter values are $K = 0.5$, $v1 = 0.7/0.73$, $K1 = 1.0/1.01$, $n = 4.0$, $v2 = 0.35/0.33$, $K2 = 1.0/0.98$, $k3 = 0.7/0.72$, $v4 = 0.35$, $K4 = 1.0/1.01$, $k5 = 0.7/0.73$, $v6 = 0.35$, $K6 = 1.0/1.04$,, $k7 = 0.35$, $v8 = 1.0/0.97$, $K8 = 1.0/1.01$, $vc = 0.4/0.41$, and $Kc = 1.0/1.05$. (a) Time waveforms of mRNA concentrations X_1 and X_2 of two uncoupled cells. (b) Synchronized time waveforms of mRNA concentrations X_1 and X_2 of two coupled cells. (c) Time waveforms of mRNA concentrations X_1 and X_2 of two coupled cells under external stimulation of light. The mRNA concentrations X_1 and X_2 are synchronized to the light.

this case, the periods of oscillations of the mRNA concentrations X_1 and X_2 coincide with the period 24-h of the light stimulation L.

3. Gene Network Model based on Asynchronous Bifurcation Processor

In this section, a gene network model based on the asynchronous bifurcation processor (ABP) is proposed. The model has the following discrete states.

$$X_i \in \boldsymbol{A}_N = \{0, \ldots, N-1\},\ \ Y_i \in \boldsymbol{A}_N,\ \ Z_i \in \boldsymbol{A}_N,\ \ V_i \in \boldsymbol{A}_N,$$
$$P_i \in \boldsymbol{A}_M = \{0, \ldots, M-1\},\ \ Q_i \in \boldsymbol{A}_M,\ \ R_i \in \boldsymbol{A}_M,\ \ S_i \in \boldsymbol{A}_M,$$

where N and M are positive integers, which determine the resolution of the state space. Same as the ODE model, the discrete states X_i, Y_i, Z_i, and V_i correspond to mRNA concentration of a clock gene, the resulting protein concentration, concentration of nuclear form of the protein (inhibitor concentration), and neuropeptide concentration, respectively. The other discrete states P_i, Q_i, R_i, and S_i are used to control velocities of the discrete states X_i, Y_i, Z_i, and V_i, respectively. In order to realize a vector field of a gene network, the following discrete functions are introduced.

$$F_{X_i}(X_i, Y_i, Z_i, V_i) = \begin{cases} M-1 \\ \quad if\ \ Int(\frac{l}{g_x(X_i,Y_i,Z_i,V_i)T_{X_i}}) \geq M-1, \\ -(M-1) \\ \quad if\ \ Int(\frac{l}{g_x(X_i,Y_i,Z_i,V_i)T_{X_i}}) \leq -(M-1), \\ Int(\frac{l}{g_x(X_i,Y_i,Z_i,V_i)T_{X_i}}) \\ \quad otherwise. \end{cases}$$

$$F_{Y_i}(X_i, Y_i, Z_i, V_i) = \begin{cases} M-1 \\ \quad if\ \ Int(\frac{l}{g_y(X_i,Y_i,Z_i,V_i)T_{Y_i}}) \geq M-1, \\ -(M-1) \\ \quad if\ \ Int(\frac{l}{g_y(X_i,Y_i,Z_i,V_i)T_{Y_i}}) \leq -(M-1), \\ Int(\frac{l}{g_y(X_i,Y_i,Z_i,V_i)T_{Y_i}}) \\ \quad otherwise. \end{cases}$$

$$F_{Z_i}(X_i, Y_i, Z_i, V_i) = \begin{cases} M-1 \\ \quad if\ \ Int(\frac{l}{g_z(X_i,Y_i,Z_i,V_i)T_{Z_i}}) \geq M-1, \\ -(M-1) \\ \quad if\ \ Int(\frac{l}{g_z(X_i,Y_i,Z_i,V_i)T_{Z_i}}) \leq -(M-1), \\ Int(\frac{l}{g_z(X_i,Y_i,Z_i,V_i)T_{Z_i}}) \\ \quad otherwise. \end{cases}$$

$$F_{V_i}(X_i, Y_{,i}, Z_i, V_i) = \begin{cases} M-1 \\ \quad if\ \ Int(\frac{l}{g_v(X_i,Y_i,Z_i,V_i)T_{V_i}}) \geq M-1, \\ -(M-1) \\ \quad if\ \ Int(\frac{l}{g_v(X_i,Y_i,Z_i,V_i)T_{V_i}}) \leq -(M-1), \\ Int(\frac{l}{g_v(X_i,Y_i,Z_i,V_i)T_{V_i}}) \\ \quad otherwise. \end{cases}$$

where

$$g_x(X_i, Y_{,i}, Z_i, V_i) = l(v_1 \frac{K_1^n}{K_1^n + Z_i^n} - v_2 \frac{X_i}{K_2 + X_i} + v_c \frac{KF}{K_c + KF} + L),$$

$$g_y(X_i, Y_{,i}, Z_i, V_i) = l(k_3 X_i - v_4 \frac{Y_i}{K_4 + Y_i}),$$

$$g_z(X_i, Y_{,i}, Z_i, V_i) = l(k_5 Y_i - v_6 \frac{Z_i}{K_6 + Z_i}),$$

$$g_v(X_i, Y_{,i}, Z_i, V_i) = l(k_7 X_i - v_8 \frac{V_i}{K_8 + V_i}),$$

$$F = \frac{l}{D} \sum_{i=1}^{D} V_i.$$

The presented model accepts the following four periodic internal clocks $C_{X_i}(t)$, $C_{Y_i}(t)$, $C_{Z_i}(t)$ and $C_{V_i}(t)$ with periods $T_{X_i} > 0$, $T_{Y_i} > 0$, $T_{Z_i} > 0$, and $T_{V_i} > 0$, respectively, which are generated by uncoupled clock generators.

$$C_{X_i}(t) = \begin{cases} 1 & if \ \ t = 0, T_{X_i}, 2T_{X_i}, \ldots, \\ 0 & if \ \ otherwise. \end{cases}$$

$$C_{Y_i}(t) = \begin{cases} 1 & if \ \ t = 0, T_{Y_i}, 2T_{Y_i}, \ldots, \\ 0 & if \ \ otherwise. \end{cases}$$

$$C_{Z_i}(t) = \begin{cases} 1 & if \ \ t = 0, T_{Z_i}, 2T_{Z_i}, \ldots, \\ 0 & if \ \ otherwise. \end{cases}$$

$$C_{V_i}(t) = \begin{cases} 1 & if \ \ t = 0, T_{V_i}, 2T_{V_i}, \ldots, \\ 0 & if \ \ otherwise. \end{cases}$$

These clocks trigger the following asynchronous transitions of the discrete states.

$$If \ C_{X_i}(t) = 1, then$$
$$P_i(t_+) := \begin{cases} P_i(t) + 1 & if \ P_i(t) < |F_{X_i}|, \\ 0 & if \ P_i(t) \geq |F_{X_i}|. \end{cases}$$
$$If \ C_{Y_i}(t) = 1, then$$
$$Q_i(t_+) := \begin{cases} Q_i(t) + 1 & if \ Q_i(t) < |F_{Y_i}|, \\ 0 & if \ Q_i(t) \geq |F_{Y_i}|. \end{cases}$$
$$If \ C_{Z_i}(t) = 1, then$$
$$R_i(t_+) := \begin{cases} R_i(t) + 1 & if \ R_i(t) < |F_{Z_i}|, \\ 0 & if \ R_i(t) \geq |F_{Z_i}|. \end{cases}$$
$$If \ C_{V_i}(t) = 1, then$$
$$S_i(t_+) := \begin{cases} S_i(t) + 1 & if \ S_i(t) < |F_{V_i}|, \\ 0 & if \ S_i(t) \geq |F_{V_i}|. \end{cases}$$

$$If \ C_{X_i}(t) = 1, and \ P_i(t) \geq |F_{X_i}|, then$$
$$P_i(t_+) := \begin{cases} X_i(t) + 1 \\ \quad if \ X_i(t) \neq N - 1 \ and \ F_{X_i} \geq 0, \\ X_i(t) - 1 \\ \quad if \ X_i(t) \neq 0 \ and \ F_{X_i} < 0, \\ X_i(t) \\ \quad otherwise. \end{cases}$$
$$If \ C_{Y_i}(t) = 1, and \ Q_i(t) \geq |F_{Y_i}|, then$$
$$Q_i(t_+) := \begin{cases} Y_i(t) + 1 \\ \quad if \ Y_i(t) \neq N - 1 \ and \ F_{Y_i} \geq 0, \\ Y_i(t) - 1 \\ \quad if \ Y_i(t) \neq 0 \ and \ F_{Y_i} < 0, \\ Y_i(t) \\ \quad otherwise. \end{cases}$$
$$If \ C_{Z_i}(t) = 1, and \ R_i(t) \geq |F_{Z_i}|, then$$
$$R_i(t_+) := \begin{cases} Z_i(t) + 1 \\ \quad if \ Z_i(t) \neq N - 1 \ and \ F_{Z_i} \geq 0, \\ Z_i(t) - 1 \\ \quad if \ Z_i(t) \neq 0 \ and \ F_{Z_i} < 0, \\ Z_i(t) \\ \quad otherwise. \end{cases}$$
$$If \ C_{V_i}(t) = 1, and \ S_i(t) \geq |F_{V_i}|, then$$
$$S_i(t_+) := \begin{cases} V_i(t) + 1 \\ \quad if \ V_i(t) \neq N - 1 \ and \ F_{V_i} \geq 0, \\ V_i(t) - 1 \\ \quad if \ V_i(t) \neq 0 \ and \ F_{V_i} < 0, \\ V_i(t) \\ \quad otherwise. \end{cases}$$

Fig. 2 shows typical time waveforms of the proposed model. Fig. 2(a) shows time waveforms of concentrations X_1 and X_2 of mRNAs in two uncoupled cells. In Fig. 2(b), the cells are coupled via the mean field F of the neuropeptide. In this case, the mRNA concentrations X_1 and X_2 are synchronized. In Fig. 2(c), the coupled cells accept an external light stimulation L with a period corresponding to 24-h. In this case, the periods of oscillations of the mRNA concentrations X_1 and X_2 coincide with the period of the light stimulation L. Comparing Fig. 2 with Fig. 1, it can be confirmed that the proposed model can reproduce generations of the typical circadian rhythms.

4. Conclusion

In this paper, the gene network model based on the ABP is proposed. It was shown that the model can reproduce the features of the circadian rhythm such as the mutual synchronization phenomena of coupled gene networks and

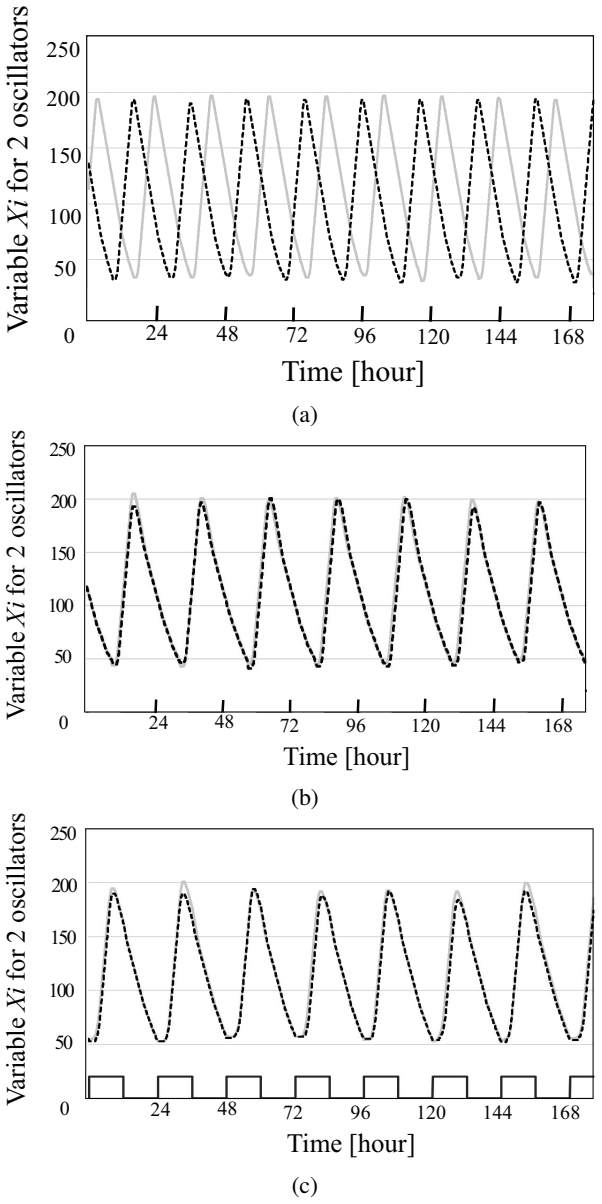

Figure 2: Typical waveforms of the proposed gene network model. The parameter values are l = 10000, K = 0.8, $v1$ = 0.7/0.73, $K1$ = 1.0/1.01, n = 4.0, $v2$ = 0.35/0.33, $K2$ = 1.0/0.98, $k3$ = 0.7/0.72, $v4$ = 0.35, $K4$ = 1.0/1.01, $k5$ = 0.7/0.73, $v6$ = 0.35, $K6$ = 1.0/1.04,, $k7$ = 0.35, $v8$ = 1.0/0.97, $K8$ = 1.0/1.01, vc = 0.4/0.41, and Kc = 1.0/1.05, T_{X_i} = 18, T_{Y_i} = 17, T_{Z_i} = 4,and T_{V_i} = 2. (a) Time waveforms of mRNA concentrations X_1 and X_2 of two uncoupled cells. (b) Synchronized time waveforms of mRNA concentrations X_1 and X_2 of two coupled cells. (c) Time waveforms of mRNA concentrations X_1 and X_2 of two coupled cells under external stimulation of light. The mRNA concentrations X_1 and X_2 are synchronized to the light. Comparing (a)-(c) with those in Fig. 2, it can be confirmed that the proposed model can reproduce generations of the typical circadian rhythms.

the forced synchronization to the light stimulation. Future problems include: (a) analysis of large scale gene networks, (b) hardware implementation, and (c) comparison of hardware cost with previous models. This work was partially supported by JSPS KAKENHI Grant Number 15K00352.

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