A novel ergodic cellular automaton gene network model towards efficient hardware-based genome simulator

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Abstract—In this paper, a novel ergodic cellular automaton model of Hes1 mRNA and Hes1 protein network is presented. Detailed analyses reveal that the presented network model can reproduce a typical nonlinear bifurcation phenomenon observed in a conventional delay differential equation model of the Hes1 mRNA and Hes1 protein network. Furthermore, the presented network model is implemented by a field programmable gate array and its operation is validated by experiments. It is shown that the presented network model consumes much fewer circuit elements and much lower power compared to the delay differential equation network model. Hence the results of this paper will provide fundamental knowledge to design an efficient hardware-based gene network simulator.

I. INTRODUCTION

Various gene network simulators have been developed with emphases on applications to drug discovery and personalized medicine \cite{1}-\cite{3}. For example, Fig. 1(a) shows an example of software-based gene network simulators for understanding the control mechanism by monitoring the change of each component in a biological network \cite{1}. In these simulators, the dynamics and kinetics of the gene networks are often modeled by nonlinear differential equations with time delays \cite{4}. However, numerical simulation of the delay differential equation (DDE) requires a huge number of hardware resources (e.g., memories and processors) and consumes high power because a lot of delayed state variables must be used to execute arithmetic operations in the simulation. Therefore, this paper focuses on the following fundamental problem.

How to design a hardware-based gene network simulator that consumes few hardware resources and low power?

Recently, in the nonlinear circuits and systems society, hardware-efficient design methods of biomimetic electronic circuits based on ergodic cellular automata have been proposed \cite{5}-\cite{10}. It has been shown that the ergodic cellular automaton biomimetic model consumes much fewer circuit elements and much lower power compared to conventional digital-processor-based biomimetic models \cite{5}-\cite{10}. Therefore, in this paper, a novel ergodic cellular automaton gene network model is presented as follows. In Section II, as a preparation, a conventional DDE model of Hes1 mRNA and Hes1 protein network is introduced \cite{11}. It is shown that the dynamic behavior of the DDE network model dramatically changes with respect to the change of a parameter value. From the viewpoint of the nonlinear dynamical system theory, the change of behavior is known to be caused by a supercritical Andronov-Hopf bifurcation \cite{4}. In Section III, the novel ergodic cellular automaton model of the Hes1 mRNA and Hes1 protein network is presented. Detailed analyses reveal that the presented network can reproduce the Andronov-Hopf bifurcation of the DDE network model and predict the critical parameter value at which the bifurcation occurs. In Section IV, the presented network model is implemented by a field programmable gate array (FPGA), and its operation is validated by experiments. It is shown that the presented network model is much more hardware-efficient (i.e., consumes much fewer circuit elements and much lower power) compared to the DDE network model. These results suggest that the presented network model can be used as a hardware-efficient simulator of the Hes1 mRNA and Hes1 protein network instead of the conventional DDE network model.

II. A CONVENTIONAL DDE GENE NETWORK MODEL

In this section, the following delay differential equation (DDE) model of Hes1 mRNA and Hes1 protein network is introduced \cite{11}.

\[
\begin{align*}
\dot{x} &= 1/(1+y(t-\tau)^n) - x, \\
\dot{y} &= (bx - y)/a,
\end{align*}
\]

where $t \in \mathbb{R}$ is a continuous time; $x \in \mathbb{R}$ and $y \in \mathbb{R}$ are continuous state variables representing concentrations of Hes1 mRNA and Hes1 protein, respectively; $\dot{x} = dx/dt$ and $\dot{y} = dy/dt$; $a \in \mathbb{R}$ and $b \in \mathbb{R}$ are parameters; $n$ is an integer representing Hill coefficient; and $\tau > 0$ is a time delay.
Fig. 2: Typical time waveforms of the DDE model of Hes1 mRNA and Hes1 protein network [11]. (a,b,n) = (1, 3, 11). (a) Stable equilibrium point. \( \tau = 0.3 \). (b) Stable periodic orbit. \( \tau = 0.75 \).

Fig. 3: Characteristics of the peak-to-peak value \( y_{pp} \) of the Hes1 protein concentration \( y \) with respect to the time delay \( \tau \). The values of the parameters \( (a,b,n) \) are the same as those in Fig. 2. (a) \( \tau = 0.3 \). (b) \( \tau = 0.75 \). (c) \( \tau = 0.54 \).

Fig. 4 depicts typical time waveforms of the DDE network model obtained by a forward Euler method. The DDE network model exhibits the following phenomena:

- In the case of Fig. 2(a), the DDE network model exhibits a stable equilibrium point.
- In the case of Fig. 2(b), the time delay \( \tau \) is increased and then the stable equilibrium point in Fig. 2(a) is changed into a stable periodic orbit in Fig. 2(b). This change of phenomena is caused by a supercritical Andronov-Hopf bifurcation [4].
- Fig. 3 shows the characteristics of the peak-to-peak value \( y_{pp} \) of the Hes1 protein concentration \( y \) for the time delay \( \tau \). The DDE network model exhibits the supercritical Andronov-Hopf bifurcation at \( \tau \approx 0.54 \).

In the next section, a novel hardware-efficient network model that can reproduce the bifurcation phenomenon is presented.

III. NOVEL HARDWARE-EFFICIENT ERGODIC CELLULAR AUTOMATON GENE NETWORK MODEL

In this section, the novel ergodic cellular automaton model of the Hes1 mRNA and Hes1 protein network is presented. Fig. 4 shows a schematic circuit diagram of the presented network model. As shown in the figure, the presented network model has registers, which store the following discrete state variables.

\[
X \in Z_N = \{0, 1, \ldots, N - 1\}, \quad Y \in Z_N, \\
Y_1 \in Z_N, \quad Y_2 \in Z_N, \quad \ldots \quad, \quad Y_D \in Z_N,
\]

where \( N \) is a positive integer determining the resolution of the state variables and \( D \) is a positive integer determining the resolution of the time delay. The state variables \( X \) and \( Y \) correspond to the Hes1 mRNA concentration \( x \) and the Hes1 protein concentration \( y \) of the DDE network model in Eq. (1), respectively. As shown in Fig. 4, the presented network model has other registers, which store the following discrete auxiliary variables.

\[
P \in Z_M = \{0, \ldots, M - 1\}, \quad Q \in Z_M,
\]

where the auxiliary variables \( P \) and \( Q \) work as state-dependent frequency dividers, which adjust transition speeds of the discrete state variables \( X \) and \( Y \), respectively. As shown in Fig. 4, the presented model receives the following two periodic clocks \( C \) and \( C_{\text{delay}} \) (see also Fig. 5).

\[
C(t) = \sum_{k=0}^{\infty} p(t - kT_C), \quad C_{\text{delay}}(t) = \sum_{k=0}^{\infty} p(t - kT_{\text{delay}}),
\]

where \( T_C > 0 \) and \( T_{\text{delay}} > 0 \) are periods of the clocks \( C \) and \( C_{\text{delay}} \), respectively, and \( p(t) \) is an instantaneous pulse defined by \( p(0) = 1 \) and \( p(t) = 0 \) for \( t \neq 0 \), which corresponds to a positive edge of a rectangular-shaped clock. As shown in Fig. 4, the presented network model receives two binary signals \( S_X \in \{0, 1\} \) and \( S_Y \in \{0, 1\} \), which are
called switch signals. In this paper, the following periodic binary signals are used as the switch signals $S_X$ and $S_Y$ (see also Fig. 5).

$$S_X(t) = \sum_{k=0}^{\infty} q(t - kT_x - \Phi_X, W_X),$$

$$S_Y(t) = \sum_{k=0}^{\infty} q(t - kT_y - \Phi_Y, W_Y),$$

where $T_x$ and $T_y$ are periods; $\Phi_X$ and $\Phi_Y$ are initial phases; $W_X$ and $W_Y$ are pulse widths; and $q$ is a rectangular-shaped pulse defined by $q(t, W) = 1$ for $0 \leq t \leq W$ and $q(t, W) = 0$ otherwise. The clocks $C$ and $C_{delay}$ trigger the following transitions of the discrete state variables (see also Fig. 5).

**Transitions of discrete state variables:**

If $C(t) = 1$ and $S_X(t) = 1$ then,

$$X(t^+) = X(t) + F_X(X(t), Y_D(t), P(t)),$$

If $C(t) = 1$ and $S_Y(t) = 1$ then,

$$Y(t^+) = Y(t) + F_Y(X(t), Y(t), Q(t)),$$

If $C_{delay}(t) = 1$ then,

$$Y_1(t^+) = Y(t) \text{ and } Y_2(t^+) = Y_{d-1}(t^+),$$

where $t^+ = \lim_{\varepsilon \rightarrow 0} + \varepsilon$, $\varepsilon > 0$, and $d = 2, 3, \ldots, D$. Here, $F_X: \mathbb{Z}_N^+ \times \mathbb{Z}_M \rightarrow \{-1, 0, 1\}$ and $F_Y: \mathbb{Z}_N^+ \times \mathbb{Z}_M \rightarrow \{-1, 0, 1\}$ are discrete functions determining the nonlinear vector field of the presented network model and thus they are referred to as discrete vector field functions. To reproduce the nonlinear bifurcation phenomenon of the DDE network model in Eq. (1), we propose to design the discrete vector field functions $F_X$ and $F_Y$ as follows.

$$F_X(X, Y_D, P) =
\begin{cases}
1 & \text{if } F_X(X, Y_D) \geq 0 \text{ and } P \geq |F_X(X, Y_D)|, \\
-1 & \text{if } F_X(X, Y_D) < 0 \text{ and } P \geq |F_X(X, Y_D)|, \\
0 & \text{otherwise},
\end{cases}$$

$$F_Y(X, Y, Q) =
\begin{cases}
1 & \text{if } F_Y(X, Y) \geq 0 \text{ and } Q \geq |F_Y(X, Y)|, \\
-1 & \text{if } F_Y(X, Y) < 0 \text{ and } Q \geq |F_Y(X, Y)|, \\
0 & \text{otherwise},
\end{cases}$$

where the functions $F_X: \mathbb{Z}_N^+ \rightarrow \mathbb{Z}_M^+ = \{-M-1, \ldots, 0, \ldots, M-1\}$ and $F_Y: \mathbb{Z}_N^+ \rightarrow \mathbb{Z}_M^+$ are designed as

$$F_X(X, Y_D) = \text{Int}(f_X(X, Y_D)^{-1} T_X^{-1}),$$

$$F_Y(X, Y) = \text{Int}(f_Y(X, Y)^{-1} T_Y^{-1}).$$

Here, the functions $F_X$ and $F_Y$ are saturated at $-(M-1)$ and $M-1$; the function $\text{Int}(x)$ gives the integer part of $x$; and the functions $f_X$ and $f_Y$ are designed as

$$f_X(X, Y_D) = \alpha_x(1/(1 + (Y_D \beta_x^{-1})^n)) - X \beta_x^{-1},$$

$$f_Y(X, Y) = \alpha_y((b x \beta_x^{-1} - Y \beta_y^{-1}) a^{-1}),$$

where $\alpha_x$, $\alpha_y$, $\beta_x$, and $\beta_y$ are parameters for scaling. Additionally, the clock $C$ triggers the following transitions of the discrete auxiliary variables $P$ and $Q$ (see also Fig. 5).

**Transitions of discrete auxiliary variables:**

If $C(t) = 1$ and $S_X(t) = 1$ then,

$$P(t^+) = \begin{cases} P(t) + 1 & \text{if } F_X(X(t), Y_D(t), P(t)) = 0, \\ 0 & \text{otherwise}, \end{cases}$$

If $C(t) = 1$ and $S_Y(t) = 1$, then,

$$Q(t^+) = \begin{cases} Q(t) + 1 & \text{if } F_Y(X(t), Y(t), Q(t)) = 0, \\ 0 & \text{otherwise}. \end{cases}$$

Fig. 6 depicts typical time waveforms of the presented network model. The presented network model exhibits the following phenomena.

- In Fig. 6(a), the discrete state variables $X$ and $Y$ stay in sufficiently small regions and their peak-to-peak values $X_{pp}$ and $Y_{pp}$ are smaller than or equal to reference values $\varepsilon_X$ and $\varepsilon_Y$, where $\varepsilon_X = 2$ and $\varepsilon_Y = 2$ are used hereafter. This phenomenon corresponds to the stable equilibrium point of the DDE network model in Fig. 2(a).
- In Fig. 6(b), the discrete state variables $X$ and $Y$ oscillate and their peak-to-peak values $X_{pp}$ and $Y_{pp}$ exceed the reference values $\varepsilon_X$ and $\varepsilon_Y$, respectively. This phenomenon corresponds to the stable periodic orbit of the DDE model in Fig. 2(b).

Fig. 7 shows the characteristics of the peak-to-peak value $Y_{pp}$ of the discrete state variable $Y$ with respect to the time delay $T_{delay}$. As the time delay is increased, the peak-to-peak value $Y_{pp}$ exceeds the reference value $\varepsilon_Y$ at $T_{delay} \approx 0.534$. Therefore the presented network model is regarded to exhibit a super-critical Andronov-Hopf bifurcation at the time delay $T_{delay} \approx 0.534$.

Recall that, as shown in Fig. 3, the DDE network model in Eq. (1) exhibits the supercritical Andronov-Hopf bifurcation at the time delay $\tau = 0.540$. Hence it can be concluded that the presented network model can reproduce the bifurcation phenomenon of the conventional DDE network model and thus it can be used as a gene network simulator.
IV. IMPLEMENTATION AND COMPARISONS

The dynamic equations of the presented network model in Eqs. (6) and (11) were handwritten in a register transfer level Verilog-HDL code, which was compiled by Xilinx’s design suite Vivado 2021.2. The generated bitstream file was used to implement Xilinx’s field programmable gate array (FPGA) device XC7a100T-1CSG324C. Fig. 8 shows typical time waveforms of the presented network model implemented by the FPGA. It can be seen that the implemented model operates properly. For comparison, a forward Euler formula of the DDE model was also implemented in the same manner, where the bit lengths of the state variables $x$ and $y$ were shortened as short as possible under the condition that the model exhibited the bifurcation properly. Table I summarizes comparison results. It can be seen that the presented network model is much more hardware-efficient.

V. DISCUSSIONS AND CONCLUSIONS

Recall that the presented network model can reproduce the bifurcation phenomenon of the DDE network model as shown in Figs. 3 and 7. In addition, we have confirmed that the presented network model can reproduce the bifurcation phenomenon for a wide parameter range. Recall also that the presented network model is much more hardware-efficient compared to the DDE network model as shown in Table I. Therefore, these results suggest that the ergodic cellular automaton network is better suited to build a hardware-efficient gene network simulator compared to differential equation networks. To develop a hardware-efficient large-scale genome simulator based on the ergodic cellular automaton, the following problems should be investigated: (a) development of systematic design and implementation methods of large-scale networks of ergodic cellular automata with multi-scale time delays, and (b) development of an efficient analysis method of the large-scale ergodic cellular automaton networks.

REFERENCES