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Discrete and ultradiscrete models for biological rhythms comprising a simple negative feedback loop

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HIGHLIGHTS

- We propose discrete model with two variables comprising negative feedback.
- Discrete model generates self-sustained oscillations for some conditions.
- We derive ultradiscrete model from discrete model.
- Ultradiscrete model generates self-sustained oscillations for some conditions.
- Ultradiscrete model includes a Boolean system as a special case.

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ABSTRACT

Many biological rhythms are generated by negative feedback regulation. Griffith (1968) proved that a negative feedback model with two variables expressed by ordinary differential equations do not generate self-sustained oscillations. Kurosawa et al. (2002) expanded Griffith's result to the general type of negative feedback model with two variables. In this paper, we propose discrete and ultradiscrete feedback models with two variables that exhibit self-sustained oscillations. To obtain the model, we applied tropical discretization and ultradiscretization to a continuous model with two variables and then investigated its bifurcation structures and the conditions of parameters for oscillations. We found that when the degradation rate of the variables is lower than their synthesis rate, the proposed models generate oscillations by Neimark–Sacker bifurcation. We further demonstrate that the ultradiscrete model can be reduced to a Boolean system under some conditions.

1. Introduction

Numerous examples of self-sustained oscillations are known at the molecular to ecological levels, including cell division cycles, segmentation clocks (Hirata et al., 2002), oscillations of p53 expression (Lahav et al., 2004), and periodical outbreaks of insects (Liebhold et al., 2000). Many of these biological rhythms are generated by negative feedback loops. At the molecular level, autonegative feedback loops of clock genes, such as *per*, *frq*, *cca1* and *kai*, produce circadian rhythms (Aronson et al., 1994; Ishiura et al., 1998; McWatters and Devlin, 2011; Partch et al., 2014). Negative feedback loops in a genetic circuit are very common such that they are well known as a network motif (Alon, 2007). More than 40% transcription factors in *Escherichia coli* repress their own gene expression (Shen-Orr et al., 2002; Rosenfeld et al., 2002). At the macroscopic level, a predator–prey system in an ecosystem can be regarded as a negative feedback loop. The oscillations in population size have been intensively examined from not only theoretical but also experimental viewpoints (Fussmann et al., 2000).

The range of number of reactions that constitute negative feedback loops is broad. Some repressors can directly repress their own expression. The HES1 protein, which is responsible for the segmentation clock, can directly repress its own expression by binding to the promoter of the *hes1* gene (Hirata et al., 2002). In contrast, the circadian clock genes form a complex negative feedback loop with several steps, including multiple phosphorylation and nuclear transportation (Partch et al., 2014).

In this paper, we focus on the negative feedback loop comprising two elements in biological networks. Griffith (1968) proved that no oscillations are generated by the negative feedback model

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described as $\dot{M} = \frac{a}{1+KE^m} - bM$, $\dot{E} = cM - dE$ through Bendixson criterion.

Kurosawa et al. (2002) expanded Griffith's model to the generalized case. They proved that no oscillations are produced by the general class of negative feedback loop described as follows:

$$\frac{dx_1}{dt} = f(x_2) - h(x_1), \tag{1a}$$

$$\frac{dx_2}{dt} = g(x_1) - k(x_2), \tag{1b}$$

where $f(x_2)$ is a monotonically decreasing function, and $g(x_1)$, $h(x_1)$, and $k(x_2)$ are monotonically increasing functions. The proof was given by the construction of the Lyapunov function for Eqs. (1). This model corresponds to the case of a common feedback loop of a single gene through transcription and translation. Suppose x_1 to be the amount of messenger RNA and x_2 to be that of protein. $\frac{df}{dx_2}$ is negative, given that proteins decrease the rate of gene expression via negative feedback. $\frac{dg}{dx_1}$ is positive, given that proteins are produced via the translation of mRNA. $\frac{dh}{dx_1} > 0$ and $\frac{dk}{dx_2} > 0$ should hold because of the degradation of the mRNA and proteins. These conditions should also be satisfied in the simple case of a predator–prey relationship. When x_1 and x_2 represent the populations of prey and predator, respectively, $\frac{df}{dx_2} < 0$ and $\frac{dg}{dx_1} > 0$ hold owing to predation, and $\frac{dh}{dx_1} > 0$ and $\frac{dk}{dx_2} > 0$ hold because of their death.

In the negative feedback with n variables as follows:

$$\frac{dx_1}{dt} = f_1(x_n) - h_1(x_1), \tag{2a}$$

$$\frac{dx_2}{dt} = f_2(x_1) - h_2(x_2), \tag{2b}$$

$$\vdots$$

$$\frac{dx_n}{dt} = f_n(x_{n-1}) - h_n(x_n), \tag{2c}$$

the necessary condition for instability is

$$\frac{\beta_1\beta_2\cdots\beta_n}{\alpha_1\alpha_2\cdots\alpha_n} > \left(\sec\left(\frac{\pi}{n}\right)\right)^n, \tag{3}$$

where $\alpha_i = \frac{dh_i(x_i)}{dx_i}(i = 1, 2, \ldots, n)$, $\beta_i = \frac{df_i(x_{i-1})}{dx_{i-1}}(i = 2, 3, \ldots, n)$ and $\beta_1 = -\frac{df_1(x_n)}{dx_n}$. This condition is known as the secant condition (Tyson and Othmer, 1978; Thron, 1991; Sontag, 2006). In particular, if $n=2$, any values of α_i and β_i cannot satisfy the condition (3) because the right-hand side of Eq. (3) is infinity. This result is consistent with Kurosawa et al. (2002).

The proof that negative feedback with two variables cannot generate oscillation is limited to ordinary differential equations (ODEs). Some researchers have recently focused on cases where ODEs are not applicable. For example, gene expression noise is unavoidable, owing to the low copy numbers of most genes. The effect of molecular noise on the oscillation was assessed via stochastic simulation (Barkai and Leibler, 2000; Gonze et al., 2002; Nishino et al., 2013). Although impossibility of oscillations was proved for ODE model of negative feedback with two variables, whether the other model for negative feedback with two variables can show self-sustained oscillations has not yet been investigated.

Besides ODEs, discrete and ultradiscrete systems are used to model dynamical systems. A discrete system treats the independent variables such as time and space as discrete numbers and is represented as a difference equation (Elaydi, 2005). An ultradiscrete system treats both independent and dependent variables as discrete numbers (Tokihiro et al., 1996). The qualitative behaviors may not generally be conserved by discretizing or ultradiscretizing ODEs. For example, although the logistic equation described as an ODE is attracted to an equilibrium point, the logistic map obtained by the forward discretization of the logistic equation shows a chaotic behavior (May, 1976).

In the present study, we focus on discrete and ultradiscrete negative feedback models with two variables. These models can oscillate under some parameter conditions. We also investigated the types of bifurcation and parameter conditions for the oscillations.

2. Discretization

In this section, we discretize a negative feedback model with two variables and study its bifurcation structure.

2.1. Model

We consider the negative feedback model with two variables, which is reduced from the three-variable model proposed by Kurosawa et al. (2002), as follows:

$$\frac{dM}{dt} = \frac{k}{1+\left(\frac{P}{h}\right)^n} - aM, \tag{4a}$$

$$\frac{dP}{dt} = sM - vP. \tag{4b}$$

If Eqs. (4) represent a genetic feedback loop, then M and P correspond to amounts of mRNA and protein, respectively. We assume that the parameters k, a, s, v, n, and h are positive. Because Eqs. (4) are included in the class of (1), Eqs. (4) have no limit cycle solutions. To nondimensionalize Eqs. (4), we define the dimensionless variables $M = \frac{k}{v}x$, $P = \frac{ks}{v^2}y$, $t = \frac{1}{v}\tau$ and dimensionless parameters $b = \frac{a}{v}$ and $c = \frac{hv^2}{ks}$. Then, Eqs. (4) are transformed into

$$\frac{dx}{d\tau} = \frac{1}{1+\left(\frac{y}{c}\right)^n} - bx, \tag{5a}$$

$$\frac{dy}{d\tau} = x - y. \tag{5b}$$

By applying tropical discretization (Murata, 2013) to Eqs. (5), we obtain

$$\frac{x_{T+1} - x_T}{\delta} = \frac{\frac{1}{1+\left(\frac{y_T}{c}\right)^n} - bx_T}{1+b\delta}, \tag{6a}$$

$$\frac{y_{T+1} - y_T}{\delta} = \frac{x_T - y_T}{1+\delta}, \tag{6b}$$

or,

$$x_{T+1} = \frac{x_T + \frac{\delta}{1+\left(\frac{y_T}{c}\right)^n}}{1+b\delta}, \tag{7a}$$