Stability of Cyclic Gene Models for Systems Involving Repression

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We consider a Goodwin-type model for cyclic gene systems involving endproduct repression. The model is described by a very general system of functional differential equations which include as special cases continuous analogues of cyclic models studied previously via computer simulation by other investigators (Fraser & Tiwari, 1974). We establish global stability of equilibrium solutions with arguments which are valid for any number (odd or even) of genes in the cyclic loop.

1. Introduction

Since the early work of Goodwin (1963, 1965) a substantial number of investigations of theoretical models for protein synthesis have been detailed in the literature (see the bibliographies in Hess & Boiteux, 1971; Walter, 1972; Chance, Pye, Ghosh & Hess, 1973; Othmer, 1976; Tyson & Othmer, 1977; Banks & Mahaffy, 1978*a*). The central focus of many of these investigations concerns the existence or non-existence of sustained oscillations for the models considered. One class of models that has received attention is based on negative feedback (end product repression) mechanisms such as those known to occur in a number of biosynthetic pathways [e.g. see the pathways for histidine and tryptophan in Lehninger, (1975)]. In addition to developing ordinary differential equation models for single gene repressible systems, Goodwin in his earlier work suggested that repressible system models involving several gene loci coupled in some way might prove of value in the study of epigenetic oscillations. Analog computer simulations of some of those early Goodwin models (which contained no damping terms) did produce oscillatory behavior. In subsequent efforts Fraser & Tiwari (1974) studied a version of the Goodwin models modified to include damping terms and time delays (the latter to account for times between transcription and

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initiation of translation, translation and transport times, etc.). They carried out digital computer simulation studies of deterministic cyclic gene models with loops of 2, 3, 4, and 5 genes. On the basis of these simulations, they conjectured that "cyclic gene systems with an odd number of genes will show undamped oscillation" if certain model parameters are appropriately chosen.

In this paper, we consider continuous analogues of these cyclic gene systems and offer conclusive arguments that these systems (in the case of both odd and even numbers of genes) possess unique globally asymptotically stable equilibrium states. In fact, we establish these results for a somewhat more general class of models which allow for a very general hereditary mechanism and which include ordinary differential equation models (no delays) and differential–difference equation models (finite discrete delays as studied by Fraser & Tiwari) as special cases. While our models entail quite general hereditary terms, our arguments employ only very elementary (linear differential inequalities) mathematical techniques.

2. Stability Results for Mathematical Models of Repressible Cyclic Gene Systems

The model which we consider in this paper is a cyclic gene model suggested by the earlier investigations of Goodwin (1963, 1965) and Fraser & Tiwari (1974). We assume one has n genes which control synthesis of endproducts
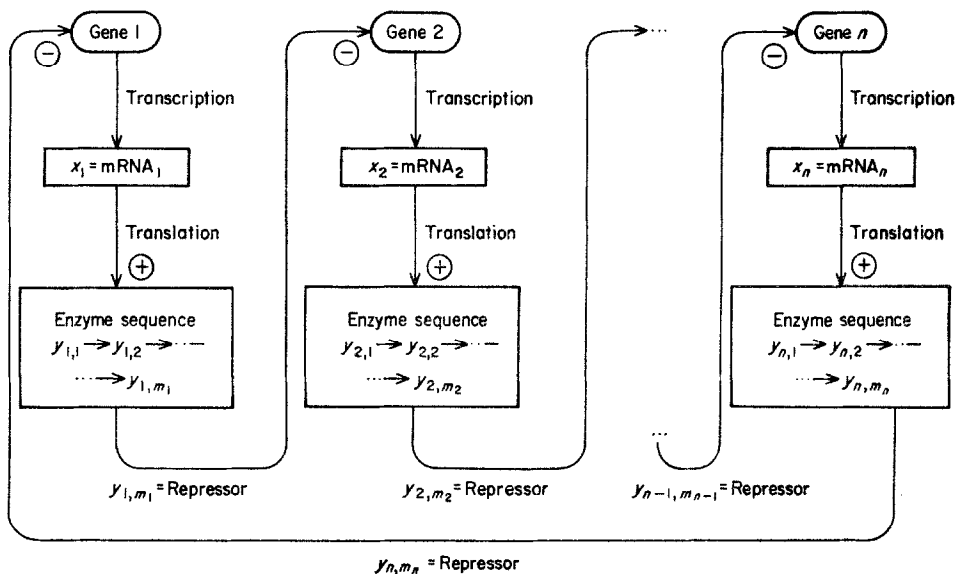

FIG. 1. Cyclic gene models with repression.

and which are coupled as depicted in Fig. 1. Specifically, we assume in this model that the first gene is transcribed producing a mRNA (x_1) which in turn is translated to produce a protein. This protein is the first enzyme in a sequence (of length m_1) which produces as endproduct a repressor (y_{1,m_1}). This endproduct acts as a repressor to shut down transcription of the second gene. When the second gene is transcribed, a mRNA (x_2) is produced which is translated to form a protein acting as the first enzyme in a sequence (of length m_2) for the second gene. The resulting endproduct acts as a repressor for gene 3, etc. Finally, a similar sequence occurs for the nth gene and results in a repressor for gene 1.

If one considers models in which the mRNA's are translated to form the repressor proteins directly (i.e. the enzyme sequences all have length $m_i = 1$ so that $y_{i,m_i} \equiv y_i$ is the repressor), Goodwin-type models with damping are described (with an appropriate scaling of parameters) by ordinary differential equations:

$$\dot{x}_1(t) = \frac{a_1}{1+k_1 y_n(t)} - b_1 x_1(t)$$

$$\dot{y}_1(t) = \alpha_1 x_1(t) - \beta_1 y_1(t) \tag{1}$$

$$\dot{x}_i(t) = \frac{a_i}{1+k_i y_{i-1}(t)} - b_i x_i(t)$$

$$\dot{y}_i(t) = \alpha_i x_i(t) - \beta_i y_i(t), \qquad i = 2, \ldots, n.$$

If one incorporates discrete delays into this model to take into account the time involved in transcription, translation, and transport within the cell, one obtains a continuous analogue of the model studied by Fraser & Tiwari (1974) using computer simulations. The resulting model is given by differential-difference equations:

$$\dot{x}_1(t) = \frac{a_1}{1+k_1 y_n(t-\tau_1)} - b_1 x_1(t)$$

$$\dot{y}_1(t) = \alpha_1 x_1(t-\gamma_1) - \beta_1 y_1(t)$$

$$\dot{x}_i(t) = \frac{a_i}{1+k_i y_{i-1}(t-\tau_i)} - b_i x_i(t) \tag{2}$$

$$\dot{y}_i(t) = \alpha_i x_i(t-\gamma_i) - \beta_i y_i(t), \qquad i = 2, \ldots, n.$$

However, it is perhaps more accurate to use distributed delay terms instead of the discrete delays in equations (2) when modeling such phenomena. Some authors (e.g. see Caperon, 1969; MacDonald, 1977) have done this and, indeed, the appropriateness of such terms can be argued on the basis of both basic modeling principles and evidence obtained when fitting other types of

delay-phenomena models to experimental data for enzyme regulated pro-
cesses in micro-organisms (Caperon, 1969). To modify the model given by
equations (2) in this way one only replaces each of the discrete delay terms of
the form $z(t-\tau)$ by an integral term

$$\int_{-r}^{0} z(t+\theta)\,\zeta(\theta)\,d\theta$$

which "distributes" the delay over the time interval $[t-r, t]$ via a weighting
function ζ.

We shall consider a model which includes as special cases the models (1),
(2) and modifications of (2) using distributed delay terms. The hereditary
terms are assumed to consist of a finite number of discrete delay terms
(including as one of these a term for $\tau = 0$) plus a distributed term. That is,
using the notation z^t to denote the function $\theta \rightarrow z(t+\theta)$ for $-r \leq \theta \leq 0$, our
hereditary or delay terms have the form

$$L(z^t) = \int_{-r}^{0} z(t+\theta)\,d\mu(\theta) = \sum_{k=0}^{v} c_k z(t-h_k) + \int_{-r}^{0} z(t+\theta)\,\zeta(\theta)\,d\theta \quad (3)$$

where $0 = h_0 < h_1 < \ldots < h_v = r$ and the constants $\{c_k\}$ are non-negative
as is the scalar function ζ. (In this case the measure μ consists of a finite
number of saltus functions plus an absolutely continuous part.) The general
model which includes (1) and (2) as special cases is given by the hereditary
(functional) differential equations

$$\dot{x}_1(t) = \frac{a_1}{1+k_1 L_1(y_n^t)} - b_1 x_1(t),$$

$$\dot{y}_1(t) = \alpha_1 L_1^2(x_1^t) - \beta_1 y_1(t),$$

$$\dot{x}_i(t) = \frac{a_i}{1+k_i L_i^{-1}(y_{i-1}^t)} - b_i x_i(t), \quad\quad\quad (4)$$

$$\dot{y}_i(t) = \alpha_i L_i^2(x_i^t) - \beta_i y_i(t), \quad i = 2, \ldots, n,$$

where

$$L_i^j(\eta) = \int_{-r}^{0} \eta(\theta)\,d\mu_i^j(\theta)$$

$$= \sum_{k=0}^{v} c_{ik}^j \eta(-h_k) + \int_{-r}^{0} \eta(\theta)\,\zeta_i^j(\theta)\,d\theta \quad (5)$$

with $c_{ik}^j \geq 0$, $\zeta_i^j(\theta) \geq 0$.

Appropriate initial data consist of non-negative initial functions ϕ_i, ψ_i so
that (4) is to be solved for $t > 0$ subject to $x_i(\theta) = \phi_i(\theta)$, $y_i(\theta) = \psi_i(\theta)$,
$-r \leq \theta \leq 0$, $i = 1, 2, \ldots, n$.

Referring again to Fig. 1, we see that equation (4) corresponds to the schematic with $m_i = 1$ for $i = 1, \ldots, n$. We restrict our arguments below to this case, but point out that all our arguments and results extend easily and in a straightforward manner to the case where the m_i are allowed to be arbitrary but fixed finite positive integers (see Banks & Mahaffy, 1978b). Our restriction here to the case $m_i = 1$ is solely for ease in exposition.

Let us turn now to a careful analysis of the system (4) where we assume that the parameters a_i, b_i, k_i, α_i, β_i, $i = 1, \ldots, n$, are positive and finite. Since each of the measures μ_i^j in equation (5) is of finite variation we may further assume (by a rescaling of the k_i and α_i) that each of these measures is a probability measure on $[-r, 0]$. That is, we may assume without loss of generality that $L_i^j(1) = 1$. We note that the assumptions in equation (5) yield that $L_i^j(\eta_1) \geq L_i^j(\eta_2)$ whenever $\eta_1(\theta) \geq \eta_2(\theta)$, $-r \leq \theta \leq 0$.

The main result of this paper is summarized in the following theorem. The arguments to establish this stability result are similar in spirit to those used in (Banks & Mahaffy, 1978a) in investigations of single gene models.

Theorem

The system (4) has a unique equilibrium point $\bar{x}_i$, $\bar{y}_i$, $i = 1, \ldots, n$, in the orthant $\mathscr{P} = \{(x, y) \in R^n \times R^n | x_i \geq 0, \ y_i \geq 0, \ i = 1, \ldots, n\}$. Given any continuous initial data (ϕ, ψ) satisfying $(\phi(\theta), \psi(\theta)) \in \mathscr{P}$, $-r \leq \theta \leq 0$, there exists a unique solution (x, y) of equation (4) for all $t > 0$ which satisfies $(x(t), y(t)) \in \mathscr{P}$ for $t > 0$. Furthermore, as $t \to \infty$ we have $x(t) \to \bar{x} = (\bar{x}_1, \ldots, \bar{x}_n)$, $y(t) \to \bar{y} = (\bar{y}_1, \ldots, \bar{y}_n)$.

Given continuous initial data one can establish existence, uniqueness, and non-negativity of solutions to equations (4) using quite standard techniques {e.g. construction of Picard iterates in the positive cone of continuous "state" functions $C([-r, 0], \mathscr{P})$, etc.}. Since the details of these rather classical ideas are presented in (Banks–Mahaffy, 1978b) for systems which include equations (4) as a special case, we shall not repeat the arguments here.

Equilibrium solutions of (4) will be constants $\bar{x}_i$, $\bar{y}_i$, $i = 1, \ldots, n$, which must satisfy [recall $L_i^j(\bar{x}) = \bar{x}$ for any constant function $\bar{x}$]

$$\frac{a_1}{1 + k_1 \bar{y}_n} = b_1 \bar{x}_1$$

$$\alpha_1 \bar{x}_1 = \beta_1 \bar{y}_1$$

$$\frac{a_i}{1 + k_i \bar{y}_{i-1}} = b_i \bar{x}_i,$$

$$\alpha_i \bar{x}_i = \beta_i \bar{y}_i, \quad i = 2, \ldots, n.$$

Adopting the convention that $\bar{x}_0 \equiv \bar{x}_n$, $\bar{y}_0 \equiv \bar{y}_n$, $\alpha_0 \equiv \alpha_n$, $\beta_0 \equiv \beta_n$, we may re-write these relationships as

$$\frac{a_i}{1+k_i\bar{y}_{i-1}} = b_i\bar{x}_i \tag{6}$$

$$\alpha_i\bar{x}_i = \beta_i\bar{y}_i, \quad i = 1, 2, \ldots, n,$$

$$\bar{x}_i = \frac{a_i}{b_i}\left\{\frac{1}{1+k_i\bar{y}_{i-1}}\right\} = \frac{a_i/b_i}{1+k_i(\alpha_{i-1}/\beta_{i-1})\bar{x}_{i-1}} = \frac{A_i}{B_i+C_i\bar{x}_{i-1}}, i = 1, 2, \ldots, n, \tag{7}$$

where A_i, B_i, C_i are appropriately defined positive constants.

Thus, using equation (7) and defining appropriately positive constants $D_i, E_i, F_i, G_i, i = 1, \ldots, n-1$, we find

$$
\begin{aligned}
\bar{x}_1 &= \frac{A_1}{B_1+C_1\bar{x}_n} = \frac{A_1}{B_1+C_1[A_n/(B_n+C_n\bar{x}_{n-1})]} \\
&= \frac{D_{n-1}+E_{n-1}\bar{x}_{n-1}}{F_{n-1}+G_{n-1}\bar{x}_{n-1}} = \frac{D_{n-1}+E_{n-1}[A_{n-1}/(B_{n-1}+C_{n-1}\bar{x}_{n-2})]}{F_{n-1}+G_{n-1}[A_{n-1}/(B_{n-1}+C_{n-1}\bar{x}_{n-2})]} \\
&= \frac{D_{n-2}+E_{n-2}\bar{x}_{n-2}}{F_{n-2}+G_{n-2}\bar{x}_{n-2}} \\
&= \ldots \\
&= \frac{D_1+E_1\bar{x}_1}{F_1+G_1\bar{x}_1}.
\end{aligned} \tag{8}
$$

Hence, $\bar{x}_1$ satisfies

$$G_1\bar{x}_1^2+(F_1-E_1)\bar{x}_1-D_1 = 0 \tag{9}$$

which (since $D_1, E_1, F_1, G_1 > 0$) has a unique positive real root. It then follows from arguments using equations (6) that unique positive solutions $\bar{y}_1, \bar{x}_2, \bar{y}_2, \ldots, \bar{x}_n, \bar{y}_n$ are obtained, yielding the unique positive equilibrium solution claimed.

It remains to consider behavior of solutions as $t \to \infty$. Given a fixed solution of (4), we shall argue the existence of monotonic sequences of positive numbers $\{U_i^m\}_{m=1}^\infty$, $\{V_i^m\}_{m=1}^\infty$, $\{R_i^m\}_{m=1}^\infty$, $\{S_i^m\}_{m=1}^\infty$, $i = 1, 2, \ldots, n$, such that $U_i^m \nearrow \bar{x}_i$, $V_i^m \searrow \bar{x}_i$, $R_i^m \nearrow \bar{y}_i$, $S_i^m \searrow \bar{y}_i$, $i = 1, 2, \ldots, n$, as $m \to \infty$. We shall establish that these sequences are such that for any fixed m_0 there exists T_{m_0} so that the given solution of (4) satisfies

$$
\begin{aligned}
U_i^{m_0} &\leq x_i(t) \leq V_i^{m_0} \\
R_i^{m_0} &\leq y_i(t) \leq S_i^{m_0},
\end{aligned} \tag{10}
$$

for all $t \geq T_{m_0}$ and $i = 1, 2, \ldots, n$. This then will yield the desired behavior for the solution.

In our arguments below, we shall continually make use of the following simple differential inequalities (Coppel, 1965, p. 28): If $\dot\omega(t) \leq A - B\omega(t)$ for $t \geq \tau$, then $\omega(t) \leq W(t)$ for $t \geq \tau$, where W is the solution of $\dot W(t) = A - BW(t)$, $W(\tau) = \omega(\tau)$. Also, $\dot\omega(t) \geq A - B\omega(t)$ for $t \geq \tau$ implies $\omega(t) \geq W(t)$ for $t \geq \tau$, where W is as just defined. We shall also repeatedly employ the fact that if $\dot W(t) = A - BW(t)$ and $W(\tau) = W_0$, then $W(t) = A/B + (W_0 - A/B)\,e^{-B(t-\tau)}$ for $t \geq \tau$.

We begin our arguments by considering a fixed solution of equations (4) corresponding to fixed non-negative initial data. By our previous comments, the solution will exist and remain non-negative for all $t \geq 0$. In our constructive arguments below, in choosing the monotonic sequence $\{\varepsilon_m\}$, we make the choice at each step such that $0 < \varepsilon_m < 1/m$ and hence $\varepsilon_m \searrow 0$.

Let v_i^1 be the solution of $\dot z = a_i - b_i z$, $z(0) = x_i(0)$, $1 \leq i \leq n$. Then, since $L_i^1(y_j^r) \geq 0$, $1 \leq i \leq n$, $1 \leq j \leq n$, for all t, we find that $\dot x_i(t) \leq a_i - b_i x_i(t)$ for $t > 0$. Thus, our differential inequality implies

$$x_i(t) \leq v_i^1(t) = a_i/b_i + \{x_i(0) - a_i/b_i\}\,e^{-b_i t}, \quad 1 \leq i \leq n.$$

Hence, choosing ε_1 with $0 < \varepsilon_1 < 1$, there exists $t_1 > 0$ such that

$$x_i(t) \leq V_i^1 \equiv a_i/b_i + \varepsilon_1 \quad \text{for} \quad t \geq t_1, \quad 1 \leq i \leq n.$$

We next let s_i^1 be the solution for $t > t_1 + r$ of $\dot z = \alpha_i V_i^1 - \beta_i z$, $z(t_1 + r) = y_i(t_1 + r)$, $1 \leq i \leq n$, so that for $t \geq t_1 + r$,

$$s_i^1(t) = (\alpha_i/\beta_i)V_i^1 + \{y_i(t_1 + r) - (\alpha_i/\beta_i)V_i^1\}\,e^{-\beta_i\{t - (t_1 + r)\}}, \quad 1 \leq i \leq n.$$

Choosing $\varepsilon_2 < \varepsilon_1$ there exists $t_2 > t_1 + r$ such that

$$s_i^1(t) \leq S_i^1 \equiv (\alpha_i/\beta_i)V_i^1 + \varepsilon_2, \quad 1 \leq i \leq n,$$

for $t \geq t_2 > t_1 + r$. Since $x_i(t+\theta) \leq V_i^1$ for $t+\theta \geq t_1$, $1 \leq i \leq n$, we find $L_i^2(x_i^t) \leq V_i^1$ for $t \geq t_1 + r$ so that

$$\dot y_i(t) \leq \alpha_i V_i^1 - \beta_i y_i(t) \quad \text{for} \quad t \geq t_1 + r, 1 \leq i \leq n.$$

Thus, it follows that

$$y_i(t) \leq S_i^1 \quad \text{for} \quad t \geq t_2 > t_1 + r, 1 \leq i \leq n.$$

We now define u_i^1 to be the solution for $t \geq t_2 + r$ of

$$\dot z = \frac{a_i}{1 + k_i S_{i-1}^1} - b_i z$$

$$z(t_2 + r) = x_i(t_2 + r), \quad 1 \leq i \leq n,$$

where we hereafter adopt the convention that a subscript of zero on any quantity is identified with a subscript of n on that quantity; e.g. $S_0^1 \equiv S_n^1$. Then choosing $\varepsilon_3 < \varepsilon_2$ so that

$$U_i^1 \equiv \frac{a_i}{b_i[1 + k_i S_{i-1}^1]} - \varepsilon_3 > 0, \quad 1 \leq i \leq n,$$

we have there exists $t_3 > t_2 + r$ so that

$$u_i^1(t) = \frac{a_i}{b_i[1+k_iS_{i-1}^1]} + \left\{ x_i(t_2+r) - \frac{a_i}{b_i[1+k_iS_{i-1}^1]} \right\} e^{-b_i\{t-(t_2+r)\}}$$

$$\geq U_i^1 \quad \text{for} \quad t \geq t_3 > t_2 + r, \quad 1 \leq i \leq n.$$

Since $y_{i-1}(t+\theta) \leq S_{i-1}^1$ for $t+\theta \geq t_2$, $1 \leq i \leq n$, we find that $L_i^1(y_{i-1}^t) \leq S_{i-1}^1$ for $t \geq t_2+r$ so that

$$\dot{x}_i(t) \geq \frac{a_i}{1+k_iS_{i-1}^1} - b_ix_i(t) \quad \text{for} \quad t \geq t_2 + r.$$

Thus, we have

$$x_i(t) \geq U_i^1 \quad \text{for} \quad t \geq t_3 > t_2 + r, 1 \leq i \leq n.$$

Let r_i^1 be the solution of $\dot{z} = \alpha_iU_i^1 - \beta_iz$, $z(t_3+r) = x_i(t_3+r)$ so that for ε_4 chosen with $\varepsilon_4 < \varepsilon_3$ and $(\alpha_i/\beta_i)U_i^1 - \varepsilon_4 > 0$, there exists $t_4 > t_3 + r$ such that

$$r_i^1(t) = (\alpha_i/\beta_i)U_i^1 + \{x_i(t_3+r) - (\alpha_i/\beta_i)U_i^1\} e^{-\beta_i\{t-(t_3+r)\}}$$

$$\geq R_i^1 \equiv (\alpha_i/\beta_i)U_i^1 - \varepsilon_4$$

for $t \geq t_4 > t_3 + r$, $1 \leq i \leq n$. Since $x_i(t+\theta) \geq U_i^1$ for $t+\theta \geq t_3$, we have $\dot{y}_i(t) \geq \alpha_iU_i^1 - \beta_iy_i(t)$ for $t \geq t_3 + r$ and thus

$$y_i(t) \geq R_i^1 \quad \text{for} \quad t \geq t_4 > t_3 + r, 1 \leq i \leq n.$$

Continuing in this procedure, we let v_i^2 be the solution of

$$\dot{z} = \frac{a_i}{1+k_iR_{i-1}^1} - b_iz, \qquad t \geq t_4 + r,$$

$$z(t_4+r) = x_i(t_4+r), \qquad 1 \leq i \leq n.$$

For $\varepsilon_5 < \varepsilon_4$ chosen there exists $t_5 > t_4 + r$ such that

$$v_i^2(t) \leq V_i^2 \equiv \frac{a_i}{b_i[1+k_iR_{i-1}^1]} + \varepsilon_5 \quad \text{for} \quad t \geq t_5.$$

Since $y_{i-1}(t+\theta) \geq R_{i-1}^1$ for $t+\theta \geq t_4$, we have $1 + k_iL_i^1(y_{i-1}^t) \geq 1 + k_iR_{i-1}^1$ for $t \geq t_4 + r$. Hence,

$$\dot{x}_i(t) \leq \frac{a_i}{1+k_iR_{i-1}^1} - b_ix_i(t), \qquad t \geq t_4 + r$$

and thus

$$x_i(t) \leq V_i^2 \quad \text{for} \quad t \geq t_5 > t_4 + r.$$

In a similar manner one can continue these arguments to obtain without difficulty the existence of sequences ε_6, ε_7 ... and t_6, t_7, ..., such that

$$y_i(t) \leq S_i^2 \equiv (\alpha_i/\beta_i)V_i^2 + \varepsilon_6 \qquad \text{for} \quad t \geq t_6 > t_5 + r,$$

$$x_i(t) \geq U_i^2 \equiv \frac{a_i}{b_i[1 + k_i S_{i-1}^2]} - \varepsilon_7 > 0 \quad \text{for} \quad t \geq t_7 > t_6 + r,$$

$$y_i(t) \geq R_i^2 \equiv (\alpha_i/\beta_i)U_i^2 - \varepsilon_8 > 0 \qquad \text{for} \quad t \geq t_8 > t_7 + r,$$

$$x_i(t) \leq V_i^3 \equiv \frac{a_i}{b_i[1 + k_i R_{i-1}^2]} + \varepsilon_9 \qquad \text{for} \quad t \geq t_9 > t_8 + r,$$

etc. One thus obtains sequences $\{t_j\}$, $\{V_i^m\}_{m=1}^\infty$, $\{S_i^m\}_{m=1}^\infty$, $\{U_i^m\}_{m=1}^\infty$, $\{R_i^m\}_{m=1}^\infty$, $1 \leq i \leq n$, such that $t_j < t_{j+1}$, the V_i^m, S_i^m, U_i^m, R_i^m are all positive, and

$$
\begin{aligned}
x_i(t) &\leq V_i^m &&\text{for} \quad t \geq t_{4m-3}, \\
y_i(t) &\leq S_i^m &&\text{for} \quad t \geq t_{4m-2}, \\
x_i(t) &\geq U_i^m &&\text{for} \quad t \geq t_{4m-1}, \\
y_i(t) &\geq R_i^m &&\text{for} \quad t \geq t_{4m},
\end{aligned}
\qquad (11)
$$

for $m = 1, 2, \ldots$, and $1 \leq i \leq n$.

It follows immediately from equations (11) and our constructive arguments that the statement involving (10) holds. To complete our arguments we must demonstrate that $V_i^m \searrow \bar{x}_i$, $S_i^m \searrow \bar{y}_i$, $U_i^m \nearrow \bar{x}_i$, $R_i^m \nearrow \bar{y}_i$, as $m \to \infty$, $1 \leq i \leq n$.

If we define $R_i^0 \equiv 0$, it is easy to see that the following recursive relationships obtain:

$$
\begin{aligned}
V_i^m &= \frac{a_i}{b_i[1 + k_i R_{i-1}^{m-1}]} + \varepsilon_{4m-3}, \\
S_i^m &= (\alpha_i/\beta_i)V_i^m + \varepsilon_{4m-2}, \\
U_i^m &= \frac{a_i}{b_i[1 + k_i S_{i-1}^m]} - \varepsilon_{4m-1}, \\
R_i^m &= (\alpha_i/\beta_i)U_i^m - \varepsilon_{4m},
\end{aligned}
\qquad (12)
$$

for $1 \leq i \leq n$ and $m = 1, 2, \ldots$. Using these recursive formulae and the monotonicity of $\{\varepsilon_m\}$, one can give an easy inductive argument that $V_i^{m+1} < V_i^m$, $S_i^{m+1} < S_i^m$, $U_i^{m+1} > U_i^m$, $R_i^{m+1} > R_i^m$, $1 \leq i \leq n$, $m = 1, 2, \ldots$. Since the monotone sequences $\{V_i^m\}$, $\{S_i^m\}$, $\{U_i^m\}$, $\{R_i^m\}$ are clearly bounded, one obtains existence of the limits

$$
\begin{aligned}
\bar{V}_i &= \lim_{m \to \infty} V_i^m \\
\bar{S}_i &= \lim_{m \to \infty} S_i^m \\
\bar{U}_i &= \lim_{m \to \infty} U_i^m \\
\bar{R}_i &= \lim_{m \to \infty} R_i^m
\end{aligned}
$$

for $1 \leq i \leq n$. Furthermore, these limits are finite and non-negative. Passing to the limits in equations (12), one finds

$$\overline{V}_i = \frac{a_i}{b_i[1+k_i\overline{R}_{i-1}]},$$

$$\overline{S}_i = (\alpha_i/\beta_i)\overline{V}_i,$$

$$\overline{U}_i = \frac{a_i}{b_i[1+k_i\overline{S}_{i-1}]},$$

$$\overline{R}_i = (\alpha_i/\beta_i)\overline{U}_i,$$

(13)

for $1 \leq i \leq n$. Recalling equations (6) and (7), one has that equations (13) can be used to write

$$\overline{V}_i = \frac{a_i/b_i}{1+k_i(\alpha_{i-1}/\beta_{i-1})\overline{U}_{i-1}} = \frac{A_i}{B_i+C_i\overline{U}_{i-1}}$$

and

$$\overline{U}_i = \frac{a_i/b_i}{1+k_i(\alpha_{i-1}/\beta_{i-1})\overline{V}_{i-1}} = \frac{A_i}{B_i+C_i\overline{V}_{i-1}}$$

for $1 \leq i \leq n$. Hence, defining the positive constants D_i, E_i, F_i, G_i as in equations (8) and (9), one obtains

$$\begin{aligned}
\overline{V}_1 &= \frac{A_1}{B_1+C_1\overline{U}_n} = \frac{A_1}{B_1+C_1[A_n/(B_n+C_n\overline{V}_{n-1})]} \\
&= \frac{D_{n-1}+E_{n-1}\overline{V}_{n-1}}{F_{n-1}+G_{n-1}\overline{V}_{n-1}} \\
&= \frac{D_{n-2}+E_{n-2}\overline{U}_{n-2}}{F_{n-2}+G_{n-2}\overline{U}_{n-2}} \\
&= \cdots \\
&= \frac{D_1+E_1X}{F_1+G_1X},
\end{aligned}$$

where

$$X = \begin{cases} \overline{V}_1 & \text{if } n \text{ even} \\ \overline{U}_1 & \text{if } n \text{ odd}. \end{cases}$$

By symmetry one also has

$$\overline{U}_1 = \frac{D_1+E_1Y}{F_1+G_1Y}, \quad \text{where} \quad Y = \begin{cases} \overline{U}_1 & \text{if } n \text{ even} \\ \overline{V}_1 & \text{if } n \text{ odd}. \end{cases}$$

In the case n is even, we thus have that $\overline{U}_1$, $\overline{V}_1$ are non-negative solutions of the quadratic

$$X = \frac{D_1+E_1X}{F_1+G_1X}$$

which [see equations (8) and (9)] yields $\overline{U}_1 = \overline{V}_1 = \bar{x}_1$. In the case n is odd we have that $\overline{U}_1$, $\overline{V}_1$ are non-negative solutions of the quadratic

$$X = \frac{D_1 + E_1[(D_1 + E_1 X)/(F_1 + G_1 X)]}{F_1 + G_1[(D_1 + E_1 X)/(F_1 + G_1 X)]}$$

which, after some simple algebra, reduces to

$$(E_1 + F_1)\{G_1 X^2 + (F_1 - E_1)X - D_1\} = 0.$$

Thus, in light of equation (9), we find in this case also that $\overline{U}_1 = \overline{V}_1 = \bar{x}_1$.

Once one has established that $\overline{U}_1 = \overline{V}_1 = \bar{x}_1$, it follows immediately from equations (13) and (6) that $\overline{S}_1 = \overline{R}_1 = \bar{y}_1$, $\overline{V}_2 = \overline{U}_2 = \bar{x}_2$, $\overline{S}_2 = \overline{R}_2 = \bar{y}_2, \ldots, \overline{V}_n = \overline{U}_n = \bar{x}_n$, $\overline{S}_n = \overline{R}_n = \bar{y}_n$. When combined with our previous observations and arguments, this finally completes the proof for our theorem.

3. Conclusions

We have considered cyclic gene models with repression which include as special cases continuous analogues of the cyclic models studied by Fraser & Tiwari (1974) via digital simulation. These computer simulations led Fraser and Tiwari to conjecture that such cyclic systems with an odd number of genes might exhibit oscillatory behavior if certain model parameters were carefully chosen. Our analysis shows that continuous analogues of the Fraser–Tiwari systems do not differ in their qualitative behavior, regardless of whether n is odd or even, and independent of the choice of permissible model parameter values. Indeed, for these systems sustained self-oscillations are not possible.

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