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5 **DYNAMICS OF A SEGMENTATION CLOCK MODEL**
6 **WITH DISCRETE AND DISTRIBUTED DELAYS**

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12 In this paper, we study the effects of time delays on the dynamics of a segmentation
13 clock model with both discrete and distributed delays. Two cases are considered. The
14 first case corresponds to the model with only distributed delay. The second case involves
15 both discrete and distributed delay. Local stability analysis is carried out for all cases.
16 Numerical simulations are also performed to illustrate the results.

17 *Keywords:* Pattern formation; gene expression; somitogenesis; distributed and discrete
18 delays.

19 **1. Introduction**

Somites are the segmental units that lie along the AP axis of vertebrate embryos. Further differentiation of the somites gives rise to skeletal muscles, vertebrae and ribs. The segmentation occurs periodically at the anterior end of the presomitic mesoderm (PSM). This periodic segmentation has been suggested to be regulated by a molecular clock [6]. From the molecular point of view, formation of the somites begins with the establishment of prepattern of gene expression. In 1997, Palmeirim *et al.* reported the chick basic helix-loop-helix (bHLH) gene *chairy1* [19]. *Chairy1* expression initiates as a broad band in the posterior of PSM, moves anteriorly and reaches the anterior end of PSM. This wave-like propagation of gene expression is not caused by cell movement but rather by the synchronized oscillations of *chairy1* expression. Its mRNA exhibits cyclic waves of expression whose temporal periodicity corresponds to the formation time of one somite (90 min). Similar dynamical expression of genes has also been observed in other embryos. These are known as cyclic genes as their expressions oscillate with the same frequency it takes to form one somite. In zebrafish embryos, Holley *et al.* performed a detailed study of *her1* expression within the PSM. *Her1* gene is reported to oscillate with a period of 30 minutes, in agreement with the time it takes to form one somite

2 *P. Feng*

in zebrafish embryos [9]. Jouve *et al.* [12] reported Hes1 in mouse embryos which oscillates with a period of 120 minutes. Bessho and the coauthors found that the expression of Hes7 in mouse also oscillates in a 2-h cycle [4]. In Hes7-deficient mice, they reported abnormal segmentation that leads to severe defects of axial skeletons. The ribs were fused and bifurcated and the symmetry of right-left was lost. Hirata and co-workers have also investigated the role of Hes7 by generating mice expressing mutant Hes7 with longer half life of approximately 30 minutes comparing to approximately 22 minutes for wild-type Hes7. In these mice, somite segmentation and oscillatory gene expression became severely disorganized after a few normal cycles. They further simulated this effect mathematically using the following model. They concluded that the instability of Hes7 is essential for sustained oscillation and for its function as a segmentation clock [11]. They applied the following mathematical model describing the number of protein and mRNA of Hes7:

$$\frac{dp}{dt} = am(t - \tau_p) - bp(t),$$

$$\frac{dm}{dt} = f(p(t - \tau_m))ds - cm(t),$$

1 where $p(t)$ and $m(t)$ represent the number of Hes7 protein and mRNA, respectively.
 2 τ_p represents the time lag between the initiation of the translation and the appear-
 3 ance of a mature protein. τ_m represents the time lag between transcription and the
 4 appearance of a mature mRNA molecule. b and c represents the degradation rates
 5 of the protein and mRNA, respectively.

A similar model was also used for the *her1* gene in zebrafish embryo. The mathematical model was further analyzed by Feng [7]. It was found that a Hopf bifurcation occurs when the total delay $\tau = \tau_p + \tau_m$ surpasses a critical value. If the ratio τ_m/τ_p is used as a bifurcation parameter, the bifurcation point r_0 is found to depend on τ_p . This model also assumes that (i) translation is nonsaturating; (ii) the movement of protein molecules between the cytoplasm and cell nucleus is instantaneous and (iii) the delays in transcription and translation take discrete values. Monk (2003) suggests that a more realistic assumption would be that the delay is uniformly

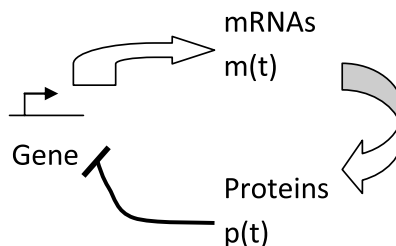


Fig. 1. Schematic representation of gene regulation: Gene is transcribed into mRNA which is translated into protein. By binding to the promoter of the gene the protein represses further transcription of gene.

distributed [15]. This results in the following revised equation incorporating both discrete and distributed delays:

$$\begin{aligned}\frac{dp}{dt} &= am(t - \tau_p) - bp(t), \\ \frac{dm}{dt} &= \int_{-\infty}^t g(t-s)f(p(s)) - cm(t),\end{aligned}$$

1 where τ_p represents the time lag between the initiation of the translation and the
2 appearance of a mature protein; b and c represent the degradation rates of proteins
3 and mRNAs, respectively; a is the translation constant. $f(p)$ is a sigmoid function
4 which models the switch-like phenomena during this process. We take

$$5 \quad f(p) = \frac{k\theta^h}{\theta^h + p^h},$$

6 where θ represents the critical protein concentration at which the transcription rate
7 is at half of its base value and h is the hill coefficient that characterizes the degree
8 of cooperativity of repression activity of agents involved in the inhibition of Hes7
9 transcription. However, the complexity of transcription regulation does not allow for
10 direct evaluation of the cooperativity coefficient. In [2], the authors found plausible
11 ranges of the value of h by analyzing the self-repression. A similar analysis shows h
12 should take values between 2 and 5. In [10], the authors used $h = 2$. In fact, h can
13 also be used as a bifurcation parameter. It can be shown that there exists a critical
14 value of h beyond which the steady state is unstable and a limit cycle appears.
15 This type of function has also been widely used in many neural network models.
16 One such system is the Goodwin model [8] which requires a large and unrealistic
17 cooperativity coefficient of at least 9 to induce oscillations [2]. In [15], the author
18 numerically simulated the system with discrete delay τ_p and pointed out that the
19 period of the oscillation is insensitive to the distributions in delay.

20 The distributed delay was first introduced into biological modelling by Volterra
21 in the 1930s and it is generally regarded to be more realistic than discrete delay.
22 Similar models involving distributed delays have been used in neuron networks,
23 see, for example [17, 20] and references therein. Here we shall apply the Gamma
24 distribution delay kernel

$$25 \quad g(t) = \frac{\alpha^n t^{n-1} e^{-\alpha t}}{(n-1)!}, \quad n = 1, 2, \dots$$

26 where $\alpha > 0$ is a constant. The average delay for this type of kernel is $T = \frac{n}{\alpha}$.

27 In particular, the weak kernel ($n = 1$)

$$28 \quad g(t) = \alpha e^{-\alpha t}$$

29 and the strong kernel ($n = 2$)

$$30 \quad g(t) = \alpha^2 t e^{-\alpha t}$$

31 are often used and we shall focus primarily on these two kernels.

4 *P. Feng*

We denote the equilibrium of system by $E^* = (p^*, m^*)$ which is given by the solutions of

$$\begin{aligned} am - bp &= 0, \\ \frac{k\theta^h}{\theta^h + p^h} - cm &= 0. \end{aligned}$$

1 It is easy to determine that p^* is the unique positive solution of

$$2 \quad bcp^{h+1} + bc\theta^h p - ka\theta^h = 0.$$

3 The outline of the paper is as follows. In Sec. 2, we consider the system without
4 discrete delay. We discuss the possible Hopf bifurcation under both weak and strong
5 kernels. In Sec. 3, we consider the system with both discrete and distributed delays.
6 Again, we shall study both kernels. In Sec. 4, we perform several numerical simu-
7 lations to illuminate our results. Further discussion of implications of our results is
8 given in the last section.

9 **2. Hopf Bifurcation without Discrete Delay**

10 In this section, we study the existence of bifurcating periodic solutions without the
11 presence of discrete delay.

12 **2.1. Weak kernel**

13 To apply the linear chain trick on the integro-differential equation, we define

$$14 \quad w(t) = \int_{-\infty}^t \alpha e^{-\alpha(t-s)} f(p(s)) ds.$$

The original system then becomes

$$\begin{aligned} \frac{dp}{dt} &= am(t) - bp(t), \\ \frac{dm}{dt} &= w(t) - cm(t), \\ \frac{dw}{dt} &= \alpha(f(p(t)) - w(t)). \end{aligned}$$

15 The equilibrium of this system is given by $F^* = (p^*, m^*, w^*)$ where $w^* = f(p^*)$.
16 Moreover the stability of F^* is equivalent to the stability of E^* , see [14].

17 To linearize the system, we let

$$18 \quad P = p - p^*, \quad M = m - m^*, \quad W = w - w^*.$$

The linearized system takes the form:

$$\begin{aligned}\frac{dP}{dt} &= aM(t) - bP(t), \\ \frac{dM}{dt} &= W(t) - cM(t), \\ \frac{dW}{dt} &= \alpha(-dP(t) - W(t)),\end{aligned}$$

1 where $d = -f'(p^*) = \frac{k\theta^h h p^{*h-1}}{[\theta^h + p^{*h}]^2}$. The associated characteristic equation of this
2 system is

$$3 \begin{vmatrix} -b - \lambda & a & 0 \\ 0 & -c - \lambda & 1 \\ -\alpha d & 0 & -\alpha - \lambda \end{vmatrix} = 0.$$

4 Expanding this expression, we arrive at the following characteristic equation

$$5 \lambda^3 + A\lambda^2 + B\lambda + C = 0, \quad (2.1)$$

6 where

$$7 A = b + c + \alpha, \quad B = \alpha(b + c) + bc, \quad C = \alpha(bc + ad).$$

8 We define

$$9 \phi(\alpha) = A(\alpha)B(\alpha) - C(\alpha).$$

10 The Routh–Hurwitz criteria implies that the equilibrium F^* is locally asymptotically stable if $\phi(\alpha) > 0$. A detailed calculation yields that this is equivalent to
11 either
12

13 (i) $bc < ad$ or

14 (ii) $bc > ad$, $(b + c)^2 + ad > 2(b + c)\sqrt{bc}$ and $\alpha > \alpha_0$ where α_0 is given by

$$15 \alpha_0 = \frac{ad - (b + c)^2 + \sqrt{\Delta}}{2(b + c)}, \quad \text{with } \Delta = [(b + c) - \sqrt{bc}]^2 - (bc - ad).$$

16 At the bifurcation point α_0 , the characteristic equation has a pair of purely
17 imaginary roots

$$18 \lambda_{1,2} = \pm \sqrt{B(\alpha_0)}i,$$

19 and a real root $\lambda_3 = -A(\alpha_0) < 0$.

20 Differentiating (2.1) implicitly yields

$$21 \frac{d\lambda}{d\alpha} = -\frac{\lambda^2 + (b + c)\lambda + bc + ad}{3\lambda^2 + 2A\lambda + B}.$$

22 Thus

$$23 \frac{d}{d\alpha} \text{Re}(\lambda)|_{\alpha=\alpha_0} = -\frac{2A(\alpha_0)B(\alpha_0)(b + c) - 2B(\alpha_0)(bc + ad - B(\alpha_0))}{P^2 + Q^2},$$

6 *P. Feng*

1 where $P = 2B(\alpha_0)$, $Q = 2A(\alpha_0)\sqrt{B(\alpha_0)}$. A direct calculation of the numerator
2 yields

$$3 \quad \frac{d}{d\alpha} \operatorname{Re}(\lambda)|_{\alpha=\alpha_0} = -\frac{\sqrt{\Delta}}{P^2 + Q^2} < 0.$$

4 This guarantees the bifurcation to a limit cycle at $\alpha = \alpha_0$. In summary, we have
5 the following theorem.

6 **Theorem 2.1.** *If (i) $bc < ad$ or (ii) $bc > ad$, $(b+c)^2 + ad > 2(b+c)\sqrt{bc}$ and*
7 *$\alpha > \alpha_0$ where α_0 is given by*

$$8 \quad \alpha_0 = \frac{ad - (b+c)^2 + \sqrt{\Delta}}{2(b+c)}, \quad \text{with } \Delta = [(b+c) - \sqrt{bc}]^2 - (bc - ad).$$

9 *then the steady-state solution (p^*, m^*) is asymptotically stable.*

10 *If $bc > ad$, $(b+c)^2 + ad > 2(b+c)\sqrt{bc}$ and $\alpha \in [0, \alpha_0)$, then the steady state is*
11 *unstable. Hopf bifurcation occurs when $\alpha = \alpha_0$.*

12 2.2. Strong kernel

13 If $g(t)$ is the strong kernel, i.e. $g(t) = \alpha^2 t e^{-\alpha t}$, then by letting

$$14 \quad w_2(t) = \int_{-\infty}^t \alpha^2 (t-s) e^{-\alpha(t-s)} f(p(s)) ds$$

15 and

$$16 \quad w_1(t) = \int_{-\infty}^t \alpha e^{-\alpha(t-s)} f(p(s)) ds,$$

we have the following equivalent system

$$\frac{dp}{dt} = am(t) - bp(t),$$

$$\frac{dm}{dt} = w_2(t) - cm(t),$$

$$\frac{dw_2}{dt} = \alpha(w_1(t) - w_2(t)),$$

$$\frac{dw_1}{dt} = \alpha(f(p(t)) - w_1(t)).$$

17 The associated characteristic equation to the linearized system is

$$18 \quad \begin{vmatrix} -b - \lambda & a & 0 & 0 \\ 0 & -c - \lambda & 1 & 0 \\ 0 & 0 & -\alpha - \lambda & \alpha \\ -\alpha d & 0 & 0 & -\alpha - \lambda \end{vmatrix} = 0.$$

1 Expansion of the above equation yields

$$2 \quad \lambda^4 + C_1\lambda^3 + C_2\lambda^2 + C_3\lambda + C_4 = 0 \quad (2.2)$$

with

$$\begin{aligned} C_1 &= b + c + 2\alpha; \\ C_2 &= \alpha^2 + 2\alpha(b + c) + bc; \\ C_3 &= \alpha^2(b + c) + 2abc; \\ C_4 &= \alpha^2(bc + ad). \end{aligned}$$

3 The Routh–Hurwitz criteria implies that the equilibrium is locally asymptoti-
4 cally stable if

$$5 \quad \phi_1(\alpha) := C_1(\alpha)C_2(\alpha)C_3(\alpha) - C_3^2(\alpha) - C_1^2(\alpha)C_4(\alpha) > 0.$$

Let λ_i ($i = 1, 2, 3, 4$) be the roots of the characteristic equation. Then we have

$$\sum_{i=1}^4 \lambda_i = -C_1; \quad \sum_{i \neq j} \lambda_i \lambda_j = C_2; \quad (2.3)$$

$$\sum_{i \neq j \neq k} \lambda_i \lambda_j \lambda_k = -C_3; \quad \lambda_1 \lambda_2 \lambda_3 \lambda_4 = C_4. \quad (2.4)$$

If there exists α^* such that $\phi_1(\alpha^*) = 0$, then by Routh–Hurwitz criteria and the last equation above, there exists at least one root that's pure imaginary. Thus we may assume $\lambda_2 = -\lambda_1 = -Im(\lambda_1)$. Therefore, at α^* , the equations above take the following simplified form:

$$\lambda_3 + \lambda_4 = -C_1; \quad Im(\lambda_1)^2 + \lambda_3 \lambda_4 = C_2; \quad (2.5)$$

$$(\lambda_3 + \lambda_4)Im(\lambda_1)^2 = -C_3; \quad \lambda_3 \lambda_4 Im(\lambda_1)^2 = C_4. \quad (2.6)$$

6 If λ_3 and λ_4 are complex conjugate, then clearly, $Re(\lambda_3) < 0$. If they are both
7 real, it follows from the above equations that they must be both negative. Finally,
8 the implicit differentiation of the characteristic equation yields

$$9 \quad \frac{d\lambda}{d\alpha} = \frac{2\lambda^3 + [2\alpha(b + c) + 2bc]\lambda^2 + [2\alpha + 2(b + c)]\lambda + 2\alpha(ab + cd)}{4\lambda^3 + 3C_1\lambda^2 + 2C_2\lambda + C_4}. \quad (2.7)$$

Moreover, we have

$$\begin{aligned} \frac{d\phi_1(\alpha)}{d\alpha} &= C_2C_3 \frac{dC_1}{d\alpha} + C_1C_3 \frac{dC_2}{d\alpha} + C_1C_2 \frac{dC_3}{d\alpha} - 2C_3 \frac{dC_3}{d\alpha} \\ &\quad - C_1^2 \frac{dC_4}{d\alpha} - 2C_1C_4 \frac{dC_1}{d\alpha}. \end{aligned} \quad (2.8)$$

10 Hence

$$11 \quad \frac{d}{d\alpha} Re(\lambda)|_{\alpha^*} = -\frac{C_1}{2C_1^3C_3 + 2Im(\lambda)^2(2C_3 - C_1C_2)^2} \frac{d\phi_1}{d\alpha}|_{\alpha^*}. \quad (2.9)$$

12 In summary, we have the following theorem.

8 *P. Feng*

1 **Theorem 2.2.** *If $\phi_1(\alpha) > 0$, then the equilibrium (p^*, m^*) is locally asymptotically*
 2 *stable. Moreover, if there exists α^* such that $\phi_1(\alpha^*) = 0$, then as α passes through*
 3 *α^* , a Hopf bifurcation occurs if $\frac{d\phi_1}{d\alpha}|_{\alpha^*} \neq 0$.*

4 For the special case $b = c$, the characteristic equation can be simplified as

$$5 \quad (b + \lambda)^2(\alpha + \lambda)^2 + \alpha^2 ad = 0. \quad (2.10)$$

6 **Remark 2.3.** In fact, one may rescale the original equation to simplify it to this
 7 case, see [2].

8 In this case, we have the following result.

9 **Theorem 2.4.** *If $(2b + ad/b)^2 > 4b^2$, then (p^*, m^*) is locally asymptotically stable*
 10 *for $\alpha \in (0, \alpha_1) \cup (\alpha_2, +\infty)$ and is unstable for $\alpha \in (\alpha_1, \alpha_2)$. α_1, α_2 are given by*

$$11 \quad \alpha_1 = \frac{1}{2}[C_5 - \sqrt{C_5^2 - 4b^2}], \quad \alpha_2 = \frac{1}{2}[C_5 + \sqrt{C_5^2 - 4b^2}]$$

12 *with $C_5 = (2b + ad/b)$. α_1 and α_2 are Hopf bifurcation values. If $(2b + ad/b)^2 < 4b^2$,*
 13 *then (p^*, m^*) is always asymptotically stable.*

14 3. Hopf Bifurcation with Discrete Delay

15 In this section, we consider the system with both discrete and distributed delays.
 16 We shall apply similar techniques, namely, the linear chain trick and study the
 17 associated quasi-polynomial characteristic equation.

18 3.1. Weak kernel

19 We define

$$20 \quad w(t) = \int_{-\infty}^t \alpha e^{-\alpha(t-s)} f(p(s)) ds.$$

The original system then becomes

$$\frac{dp}{dt} = am(t - \tau_p) - bp(t),$$

$$\frac{dm}{dt} = w(t) - cm(t),$$

$$\frac{dw}{dt} = \alpha(f(p(t)) - w(t)).$$

The linearized system takes the form:

$$\frac{dP}{dt} = aM(t - \tau_p) - bP(t),$$

$$\frac{dM}{dt} = W(t) - cM(t),$$

$$\frac{dW}{dt} = \alpha(-dP(t) - W(t)),$$

1 where $d = -f'(p^*) = \frac{k\theta^h h p^{*h-1}}{[\theta^h + p^{*h}]^2}$. The associated characteristic equation of this
2 system is

$$3 \begin{vmatrix} -b - \lambda & ae^{-\tau_p \lambda} & 0 \\ 0 & -c - \lambda & 1 \\ -\alpha d & 0 & -\alpha - \lambda \end{vmatrix} = 0.$$

4 Expanding this expression, we arrive at the following characteristic equation

$$5 \lambda^3 + A\lambda^2 + B\lambda + C + De^{-\tau_p \lambda} = 0,$$

6 where

$$7 A = b + c + \alpha, \quad B = \alpha(b + c) + bc, \quad C = \alpha bc, \quad D = -\alpha ad < 0.$$

Let $\lambda = \xi + i\omega$ be a solution to this quasi-polynomial characteristic equation. We can rewrite the equation in terms of the real and imaginary parts as

$$\begin{aligned} \xi^3 - 3\xi\omega + A\xi^2 - A\omega^2 + B\xi + C + De^{-\xi\tau_p} \cos(\omega\tau_p) &= 0 \\ 3\xi^2\omega - \omega^3 + 2A\xi\omega + B\omega - De^{-\xi\tau_p} \sin(\omega\tau_p) &= 0. \end{aligned}$$

Setting $\xi = 0$, we have

$$\begin{aligned} -A\omega^2 + C + D \cos(\xi\tau_p) &= 0 \\ -\omega^3 + B\omega - D \sin(\omega\tau_p) &= 0. \end{aligned}$$

8 Thus

$$9 (-A\omega^2 + C)^2 + (-\omega^3 + B\omega)^2 = D^2,$$

10 or equivalently,

$$11 \omega^6 + (A^2 - 2B)\omega^4 + (B^2 - 2AC)\omega^2 + C^2 - D^2 = 0. \quad (3.1)$$

12 Note that if $C^2 - D^2 < 0$, then the left hand side is negative at $\omega = 0$. It is positive
13 for $|\omega|$ sufficiently large. Thus it has at least one positive root.

14 Applying the next lemma, we show that there is no real root to this equation
15 when $C^2 - D^2 > 0$.

16 **Lemma 3.1.** [13] *The cubic equation*

$$17 x^3 + a_1x^2 + a_2x + a_3 = 0$$

18 *has at least one single positive root when $a_3 > 0$ if and only if*

- 19 (1) *Either $a_1 < 0$, $a_2 \geq 0$, $a_1^2 > 3a_2$ or $a_2 < 0$;*
20 *and*
21 (2) $\frac{4}{27}a_2^3 - \frac{1}{27}a_1^2a_2^2 + \frac{4}{27}a_1^3a_3 - \frac{2}{3}a_1a_2a_3 + a_3^3 < 0$.

22 For Eq. (11),

$$23 a_1 = A^2 - 2B = b^2 + c^2 + \alpha^2 > 0$$

10 *P. Feng*

1 and

$$2 \quad a_2 = B^2 - 2AC = \alpha^2(b^2 + c^2) + b^2c^2 > 0.$$

3 Thus if $C^2 - D^2 > 0$, then the cubic equation does not have any positive solution.
4 Let ω_+ be the solution to (3.1). We denote

$$5 \quad F(\lambda, \tau_p) = \lambda^3 + A\lambda^2 + B\lambda + C + De^{-\tau_p\lambda}. \quad (3.2)$$

6 The implicit differentiation yields

$$7 \quad \frac{d\lambda}{d\tau_p} = -\frac{\partial F}{\partial \lambda} \bigg/ \frac{\partial F}{\partial \tau_p} = \frac{D\lambda e^{-\tau_p\lambda}}{3\lambda^2 + 2A\lambda + B - D\tau_p e^{-\tau_p\lambda}}.$$

8 At $\tau_p = \tau_0$, $\lambda = i\omega_+$, it follows that

$$9 \quad \frac{d}{d\tau_p} \operatorname{Re}(\lambda)|_{\tau_p=\tau_0} = \frac{\omega_+^2(3\omega_+^4 + 2(A^2 - 2B)\omega_+^2 + B^2 - 2AC)}{P^2 + Q^2}, \quad (3.3)$$

10 where

$$11 \quad P = -3\omega_+^2 + B + \tau_0(-A\omega_+^2 + C),$$

12 and

$$13 \quad Q = 2A\omega_+ + \tau_0(-\omega_+^3 + B\omega_+).$$

14 Note that the numerator in Eq. (3.3) is not zero if $f'(\omega_+) \neq 0$ where

$$15 \quad f(x) = x^3 + (A^2 - 2B)x^2 + (B^2 - 2AC)x + C^2 - D^2$$

16 which is directly related to the characteristic Eq. (3.1) (by setting $\omega^2 = x$).

17 Hence we arrive at the following conclusion.

18 **Theorem 3.2.** *If $bc < -ad$, and ω_+ is the least simple root of Eq. (3.1), then a*
19 *Hopf bifurcation occurs as τ_p passes through $\tau_0 = \frac{1}{\omega_+} \arccos\{\frac{A\omega_+^2 - C}{D}\}$. Here*

$$20 \quad A = b + c + \alpha, \quad C = abc, \quad D = -\alpha ad.$$

21 3.2. Strong kernel

22 If $g(t)$ is the strong kernel, i.e. $g(t) = \alpha^2 t e^{-\alpha t}$, then by letting

$$23 \quad w_2(t) = \int_{-\infty}^t \alpha^2 (t-s) e^{-\alpha(t-s)} f(p(s)) ds$$

24 and

$$25 \quad w_1(t) = \int_{-\infty}^t \alpha e^{-\alpha(t-s)} f(p(s)) ds,$$

we have the following equivalent system

$$\begin{aligned}\frac{dp}{dt} &= am(t - \tau_p) - bp(t), \\ \frac{dm}{dt} &= w_2(t) - cm(t), \\ \frac{dw_2}{dt} &= \alpha(w_1(t) - w_2(t)), \\ \frac{dw_1}{dt} &= \alpha(f(p(t)) - w_1(t)).\end{aligned}$$

1 The associated characteristic equation to the linearized system is

$$2 \begin{vmatrix} -b - \lambda & ae^{-\tau_p \lambda} & 0 & 0 \\ 0 & -c - \lambda & 1 & 0 \\ 0 & 0 & -\alpha - \lambda & \alpha \\ -\alpha d & 0 & 0 & -\alpha - \lambda \end{vmatrix} = 0.$$

3 Expansion of the above equation yields

$$4 (b + \lambda)(c + \lambda)(\alpha + \lambda)^2 + \alpha^2 a d e^{-\tau_p \lambda} = 0.$$

5 To simplify our analysis, we choose the same degradation rates for both protein and
6 mRNA. This is a reasonable simplification, see, for example [2]. The characteristic
7 equation then becomes

$$8 (b + \lambda)(\alpha + \lambda) = \pm \alpha \sqrt{ad} e^{-\lambda \tau_p / 2}.$$

9 For convenience, we introduce some new notations:

$$10 A = b + \alpha, \quad B = b\alpha, \quad C = \alpha \sqrt{ad}, \quad \bar{\tau} = \tau_p / 2.$$

11 The characteristic equation then takes the following form

$$12 \lambda^2 + A\lambda + B \pm C i e^{-\bar{\tau} \lambda} = 0.$$

13 For the positive case, we conclude that if either

$$14 B^2 - C^2 > 0, \quad -A^2 + 2B < 0$$

15 or

$$16 (-A^2 + 2B)^2 < 4(B^2 - C^2)$$

17 holds, then all roots have negative real parts for all $\bar{\tau}$.

18 If

$$19 B^2 - C^2 < 0$$

20 or

$$21 -A^2 + 2B > 0, \quad (-A^2 + 2B)^2 = 4(B^2 - C^2)$$

12 *P. Feng*

1 then the equation has a pair of purely imaginary roots

$$2 \quad \pm i\xi_+$$

3 with

$$4 \quad \xi_+ = \sqrt{\frac{1}{2}(-A^2 + 2B) + [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}}.$$

5 when

$$6 \quad \bar{\tau} = \tau_{n,1}^+ = \frac{1}{\xi_+} \arcsin\left(\frac{\xi_+^2 - B}{C}\right) + \frac{2n\pi}{\xi_+}.$$

7 If

$$8 \quad B^2 - C^2 > 0, \quad -A^2 + 2B > 0, \quad (-A^2 + 2B)^2 > 4(B^2 - C^2)$$

9 then the equation has a second pair of purely imaginary roots

$$10 \quad \pm i\xi_-$$

11 with

$$12 \quad \xi_- = \sqrt{\frac{1}{2}(-A^2 + 2B) - [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}},$$

13 when

$$14 \quad \bar{\tau} = \tau_{n,2}^+ = \frac{1}{\xi_-} \arcsin\left(\frac{\xi_-^2 - B}{C}\right) + \frac{2n\pi}{\xi_-}.$$

15 For the negative case, we have very similar results. If

$$16 \quad B^2 - C^2 > 0, \quad -A^2 + 2B < 0$$

17 or

$$18 \quad (-A^2 + 2B)^2 < 4(B^2 - C^2)$$

19 holds, then all roots have negative real parts for all $\bar{\tau}$.

20 If

$$21 \quad B^2 - C^2 < 0$$

22 or

$$23 \quad -A^2 + 2B > 0, \quad (-A^2 + 2B)^2 = 4(B^2 - C^2)$$

24 then the equation has a pair of purely imaginary roots

$$25 \quad \pm i\eta_+$$

26 with

$$27 \quad \eta_+ = \sqrt{\frac{1}{2}(-A^2 + 2B) + [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}}.$$

1 when

$$2 \quad \bar{\tau} = \tau_{n,1}^- = -\frac{1}{\eta_+} \arcsin\left(\frac{\eta_+^2 - B}{C}\right) + \frac{2n\pi}{\eta_+}.$$

3 If

$$4 \quad B^2 - C^2 > 0, \quad -A^2 + 2B > 0, \quad (-A^2 + 2B)^2 > 4(B^2 - C^2)$$

5 then the equation has a second pair of purely imaginary roots

$$6 \quad \pm i\eta_-$$

7 with

$$8 \quad \eta_- = \sqrt{\frac{1}{2}(-A^2 + 2B) - [1/4(-A^2 + B)^2 - (B^2 - C^2)]^{1/2}},$$

9 when

$$10 \quad \bar{\tau} = \tau_{n,2}^- = -\frac{1}{\eta_-} \arcsin\left(\frac{\eta_-^2 - B}{C}\right) + \frac{2n\pi}{\eta_-}.$$

11 In conclusion, we have obtained the following theorem.

12 **Theorem 3.3.** (i) If $B^2 - C^2 > 0, -A^2 + 2B < 0$ or $(-A^2 + 2B)^2 < 4(B^2 - C^2)$,
13 then the steady state (p^*, m^*) is asymptotically stable for all discrete delays;

14 (ii) If $B^2 - C^2 < 0$ or $-A^2 + 2B > 0, (-A^2 + 2B)^2 = 4(B^2 - C^2)$, then the steady
15 state is asymptotically stable for $\bar{\tau} \in [0, \min\{\tau_{0,1}^+, \tau_{0,1}^-\})$. Otherwise, the steady
16 state is unstable and $\tau_{n,1}^+$ and $\tau_{n,2}^-$ are the bifurcation points;

17 (iii) If $B^2 - C^2 > 0, -A^2 + 2B > 0, (-A^2 + 2B)^2 > 4(B^2 - C^2)$, then the
18 steady state is asymptotically stable for $\bar{\tau} \in [0, \min\{\tau_{0,1}^+, \tau_{0,1}^-\})$. When $\bar{\tau} \in$
19 $[\min\{\tau_{n,1}^+, \tau_{n,1}^-\}, \max\{\tau_{n,2}^+, \tau_{n,2}^-\}]$, the steady state is unstable, when $\bar{\tau} \in$
20 $[\max\{\tau_{n,2}^+, \tau_{n,2}^-\}, \min\{\tau_{n+1,2}^+, \tau_{n+1,2}^-\}]$, the steady state is stable.

21 4. Numerical Simulations

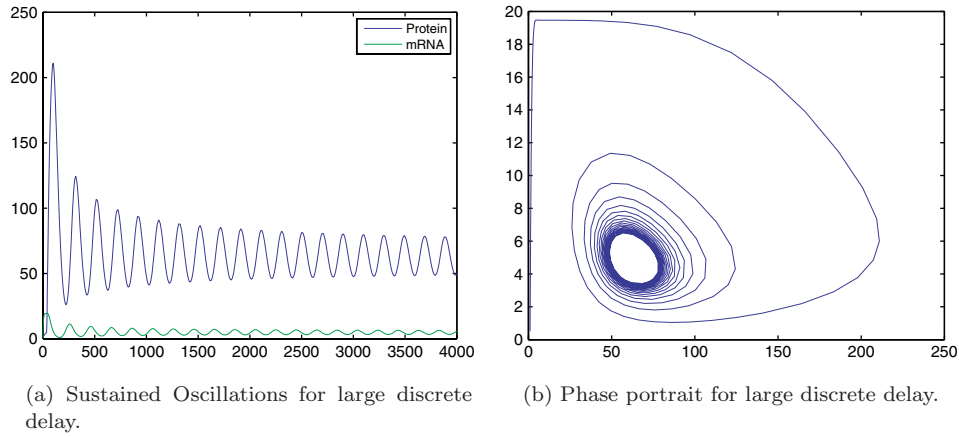
22 In this section, we illustrate the validity of our results and study the effect of
23 different parameters.

24 These parameters are obtained from Hirata *et al.* [11] and Monk [15]. We shall
25 remark here that our system is highly sensitive to changes in the Hills coefficient.
26 In [11], h was taken to be 2 indicating that Hes7 has only one binding sites in its
27 promoter. However, Bessho *et al.* established there are three regulatory elements
28 in the promoter region. In general, it is rarely the case that the Hill coefficient
29 is exactly the same as the number of binding site. It is suggested in [22], a more
30 reasonable choice will be between 2 and 3. For our simulations, we choose $h = 2.6$.
31 It is possible to obtain an explicit formula for a critical Hill coefficient beyond which
32 the steady state is unstable and a limit cycle appears [2].

33 All the figures in this section are obtained using the model with both discrete
34 and distributed delays. Our simulations are done through **dde23**, a delay differential

Table 1. Estimated parameters for her7 gene.

Parameter	Value	Description
a	0.45 molecules/min	Transcription rate
b	0.0347 or 0.0231 molecules/min	0.0347 for wild-type and 0.0231 for Hes7K14R
c	0.231 molecules/min	mRNA degradation rate
k	4.5 molecules/cell · min	
h	2.6	Hill cooperativity factor
θ	40 molecules	DNA dissociation constant
τ_p	20-40 min	Translation delay
α	controlled	

Fig. 2. (a) $\tau_p = 35$, $\alpha = 2/40$.

1 equation solver, which is now part of Matlab official release. We would like to refer
 2 the readers to the following website: <http://www.runet.edu/thompson/webddes/>.
 3 In Fig. 2, we obtain the sustained oscillations for discrete delay of 35 minutes.
 4 In Fig. 3, we obtain damped oscillations for a relatively smaller discrete delay
 5 of 30 minutes. In both cases, the distributed coefficient is $\alpha = 1/20$. In Fig. 4,
 6 the discrete delay is kept at 30 minutes, by increasing distributed coefficient to
 7 $\alpha = 2/15$, we obtained a sustained oscillations. When α is being increased even
 8 further to 2, the stability is regained and we obtained damped oscillation in Fig. 5.
 9 This illustrated the stability switch that we established in Theorem 5.

10 We now turn our attention to the effect of the degradation rate of the Hes7 pro-
 11 tein which directly related to the half-life of the protein. The numerical simulations
 12 we have done so far are based on the wild-type Hes7 with half-life of 20 minutes.
 13 The simulations below shows that the oscillations are always damped for mutant
 14 Hes7K14R which has a longer half-life of 30 minutes ($b \approx 0.0231$). For Fig. 6, we
 15 simulated the case for $\tau_p = 35$ and $\alpha = 1/20$. We obtained a damped oscillation,
 16 indicating the stability of the equilibrium. For Fig. 7, we simulated the case for

Dynamics of a Segmentation Clock Model with Discrete and Distributed Delays 15

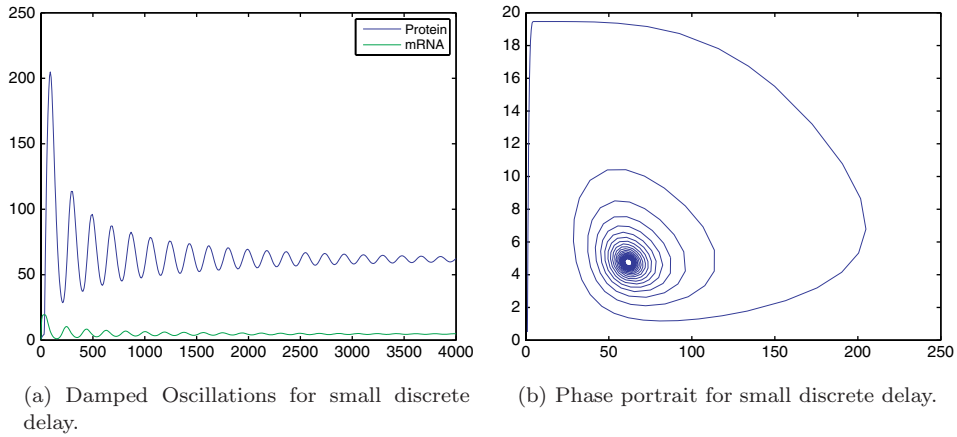


Fig. 3. (a) $\tau_p = 30$, $\alpha = 2/40$.

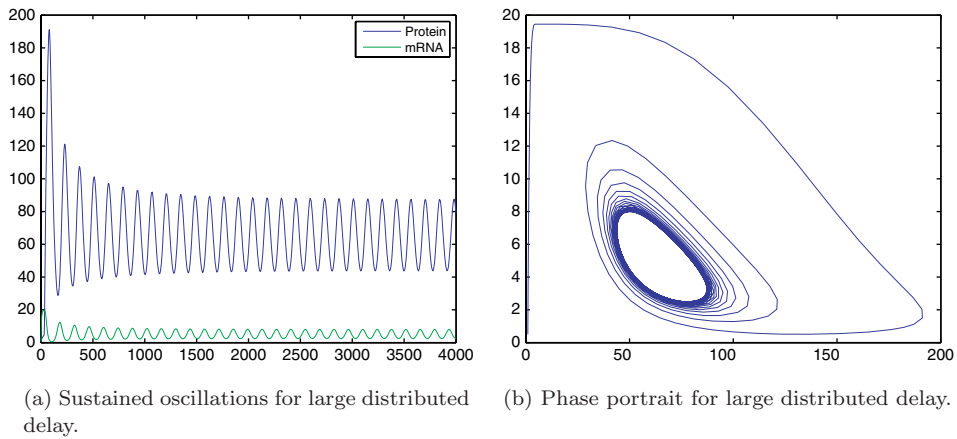


Fig. 4. (a) $\tau_p = 30$, $\alpha = 2/15$.

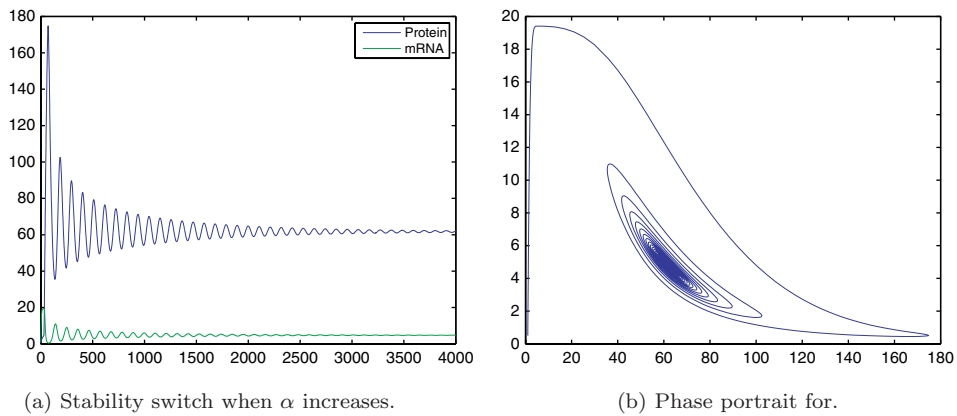
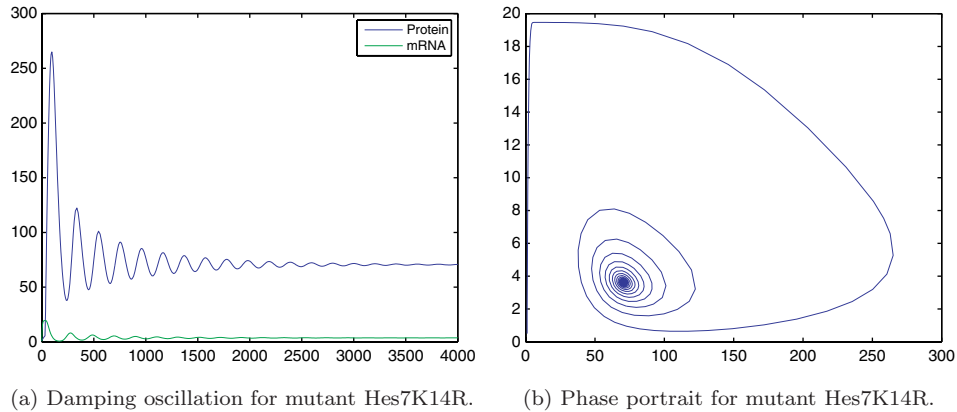
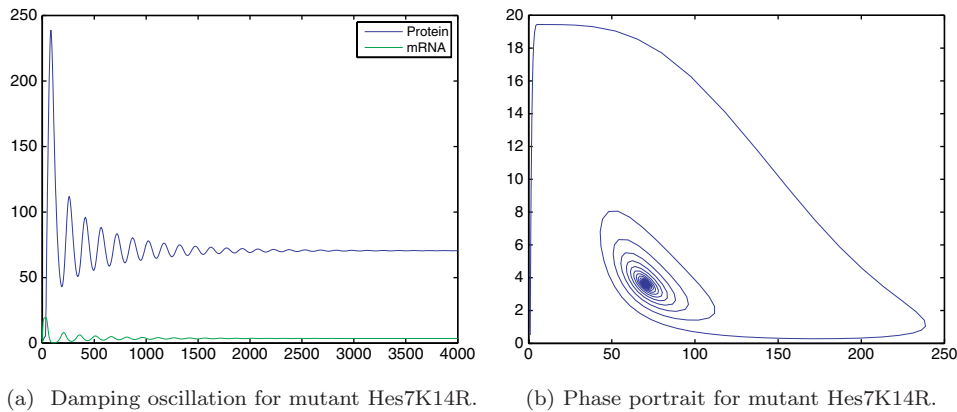


Fig. 5. (a) $\tau_p = 30$, $\alpha = 2$.

16 *P. Feng*Fig. 6. (a) $\tau_p = 35$, $\alpha = 2/40$.Fig. 7. (a) $\tau_p = 30$, $\alpha = 2/15$.

1 $\tau_p = 30$, $\alpha = 2/15$. The oscillation is still damped. Note that the oscillations are
 2 both sustained with $b = 0.347$. These simulations strongly suggest that the half-life
 3 of the protein plays an important role in somite segmentation clock.

4 **5. Conclusions**

5 In this paper, we investigated a mathematical model for gene transcription net-
 6 works. We have considered the model with both discrete and distributed delays.
 7 Stability of the steady state solutions and the oscillations around the steady-state
 8 solutions have been studied. The existence of sustained oscillations has been shown
 9 by Hopf bifurcation analysis.

10 In Hirata (2004), they predicated that the oscillations depend crucially on the
 11 instability of the protein. In their work, they generated mice expressing mutant Hes7
 12 with a longer half-life of approximately 30 minutes, comparing to approximately

22 minutes in the wild-type mouse. Somite segmentation and oscillatory gene expression became severely disorganized after a few cycles. Our theoretical results, along with numerical simulations, agree with their observation that instability of Hes7 is essential for sustained oscillation and for its function as a segmentation clock.

For the case when there is only a single discrete delay, we found that when the delay passes a threshold, the steady-state solution loses stability and Hopf bifurcation occurs. In the case of both discrete and distributed delay, we found that the distributed delay is dominated by the discrete delay. This result confirms Hirata's claim that the instability of Hes7 is crucial for the somite segmentation clock. We have also established the stability switches similar to results in [5, 3].

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18 *P. Feng*

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