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PERIODIC OSCILLATIONS OF BLOOD CELL POPULATIONS IN CHRONIC MYELOGENOUS LEUKEMIA*

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Abstract. Periodic chronic myelogenous leukemia and cyclical neutropenia are two hematological diseases that display oscillations in circulating cell numbers with a period far in excess of what one might expect based on the stem cell cycle duration. Motivated by this observation and a desire to understand how long period oscillations can arise, we analytically prove the existence and stability of long period oscillations in a G_0 phase cell cycle model described by a nonlinear differential delay equation. This periodic oscillation p_∞ can be analytically constructed when the proliferative control is of a "bang-bang" type (the Hill coefficient involved in the nonlinear feedback is infinite). We further obtain a contractive return map (for the semiflow generated by the functional differential equation) in a closed and convex cone containing p_∞ when the proliferative control is smooth (the Hill coefficient is large but finite). The fixed point of this contractive map gives the long period oscillation previously observed both numerically and experimentally.

Key words. cell proliferation, G_0 cell cycle model, periodic chronic myelogenous leukemia, long period oscillations, delay differential equations, Hill function, Walther's method

AMS subject classifications. 34C25, 34K18, 37G15

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1. Introduction.

Periodic hematological diseases have attracted a significant amount of modeling attention from mathematicians, notably the disorders periodic autoimmune hemolytic anemia [3, 17] and cyclical thrombocytopenia [27, 29]. Periodic hematological diseases of this type, in which only a single cell type is typically involved, usually display a periodicity in circulating cell numbers between two and four times the bone marrow production delay. This clinical observation has a clear explanation within a modeling context [10].

Other periodic hematological diseases such as cyclical neutropenia [4, 10, 11, 15, 16, 18] and periodic chronic myelogenous leukemia (PCML) [8] have more than one circulating blood cell type (i.e., white cells, red blood cells, and platelets) that display oscillatory levels. The oscillations in cell numbers in these two diseases have period durations ranging from weeks to months in general and are thought to originate in the pluripotential stem cell compartment [10]. In the particular case of PCML, the period can range from 40 to 80 days. Two lines of evidence indicate that the PCML oscillations originate in the stem cell population based in the bone marrow. The first suggestion that this is the case comes from the presence of the Philadelphia

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chromosome in all hematopoietic cells in PCML [5, 7, 9, 12, 30]. Second, in PCML it is observed that white blood cells, erythrocytes, and platelets all oscillate with the same period [8].

"How do 'short' cell cycles give rise to 'long' period oscillations?" This question has arisen from the observation of circulating blood cell oscillations in PCML [8]. There is an enormous difference between the relatively short cell cycle duration, which ranges between 1 and 4 days [13, 18, 19], and the long period oscillations in PCML (between 40 and 80 days) [8]. The link between these relatively short cycle durations and the long periods of peripheral cell oscillations in PCML is unclear and has been neither biologically explained nor understood.

Using a G_0 model of the cell cycle [6, 20, 28], an attempt to answer this question has been made in [1, 25, 24], where the role of various model parameters on the period and amplitude of the cellular oscillations was examined. When cellular reentry from G_0 into the proliferative phase is subject to "bang-bang" control (technically, where the Hill coefficient in the model re-entry rate n is infinite—see below), qualitatively the cell cycle regulation parameters have a major influence on the oscillation amplitude, while the oscillation period is primarily determined by the cell death and differentiation parameters. Under this strong assumption, the cell cycle model is described by a piecewise linear scalar delay differential equation that, after nontrivial but straightforward calculations, has a periodic solution with large period and amplitude and strong stability properties.

Here, we prove analytically that similar conclusions hold in the more biologically realistic case that the re-entry rate is a smooth monotone function. We construct a convex closed cone containing the periodic solution when $n = \infty$ and a contractive return map defined on this cone such that a fixed point of the return map gives a stable periodic solution of the model equation when n is large. This method was first developed by Walther [31, 32] for a scalar delay differential equation with constant linear instantaneous friction and a negative delayed feedback, and was later extended to state-dependent delay differential equations [33, 34] and to delay differential systems [34, 36]. This method was further developed in [23] by incorporating some ideas from classical asymptotic analysis and using matching methods. Applications of this method to the present cell cycle model are nontrivial since both the instantaneous loss and the delayed production of stem cells involve the nonlinearity and there is no analytic formula for the periodic solution in the limiting case ($n = \infty$).

This paper is organized as follows. In section 2 we present the model in detail. Section 3 summarizes previous results from [24] in the case where the Hill coefficient n is infinite. Then, we introduce a more general result for the perturbed delay equation given in section 4, and we present our main results in section 5 including the full asymptotic expansion for the periodic solutions.

2. Description of the model. The G_0 model of the cell cycle (see Figure 2.1 for a depiction) is conceptually based on the work of Lajtha [14] and was first developed by Burns and Tannock [6]. It can be derived from an age structured system of two coupled partial differential equations, along with appropriate boundary and initial conditions [15, 16, 21, 26]. Integrating along characteristics [35] these equations can be transformed into a pair of coupled nonlinear first-order differential delay equations [15, 16, 18]. The resulting model depicted in Figure 2.1 consists of a proliferating phase cellular population $P(t)$ at time t and a G_0 resting phase, with a population of cells $N(t)$. The proliferative phase cells consist of cells in the G_1 phase of the cell cycle, the DNA synthesis (S) phase, G_2, and mitosis M. In this proliferative phase,

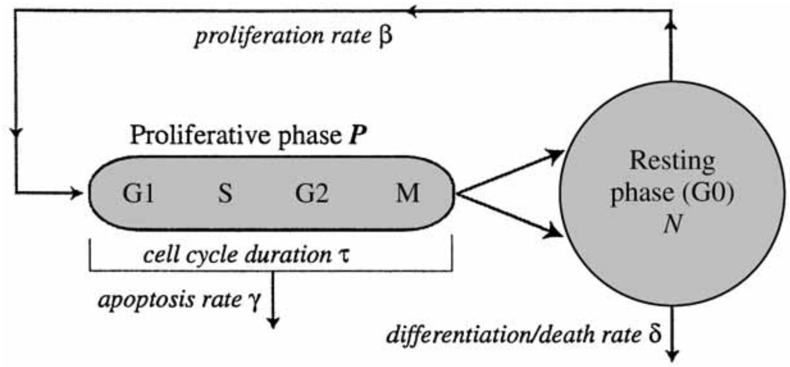

FIG. 2.1. *A schematic representation of the G_0 stem cell model. Proliferating phase cells (P) include those cells in G_1, S (DNA synthesis), G_2, and M (mitosis), while the resting phase (N) cells are in the G_0 phase. δ is the rate of differentiation into all the committed populations arising from the stem cells, and γ represents the apoptotic loss of proliferating phase cells. β is the rate of cell re-entry from G_0 into the proliferative phase, and the cell cycle time τ is the duration of the proliferative phase. See* [15, 16, 18] *for further details.*

cells are committed to undergo cell division a constant time τ after their entry into G_1. The choice of a constant cell cycle time τ simplifies the problem, though some models with a nonconstant value of τ have been examined [2, 4]. The proliferative phase death rate γ is due to apoptosis (programmed cell death). At the point of cytokinesis (cell division), a cell divides into two daughter cells, both of which are assumed to enter the resting (N) phase. In this phase, cells cannot divide but they may have one of three possible fates: differentiate at a constant rate δ, re-enter the proliferative phase at a rate β, or remain in G_0. The re-entry rate β is a nonlinear function of the cellular density and the central focus of this study.

The full model, described by a coupled nonlinear first-order delay equation, takes the form

$$\frac{dP(t)}{dt} = -\gamma P(t) + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau \tag{2.1}$$

and

$$\frac{dN(t)}{dt} = -[\beta(N) + \delta]N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau, \tag{2.2}$$

where $N_\tau = N(t-\tau)$. The resting (G_0) to proliferative phase feedback rate β is taken to be a monotone Hill function of the form

$$\beta(N) = \frac{\beta_0\theta^n}{\theta^n + N^n}.$$

In (2.2), the first term represents the loss of nonproliferating cells to the proliferative phase (flux $\beta(N)N$) and to differentiation (flux δN). The second term represents the production of G_0 phase cells from the proliferating stem cells. The factor 2 accounts for the amplifying effect of cell division while $e^{-\gamma\tau}$ accounts for the attenuation in the proliferative phase due to apoptosis. Note that we need to study only the dynamics of the G_0 phase resting population (governed by (2.2)) since the proliferating phase dynamics (governed by (2.1)) are driven by the dynamics of the resting cells. This is strictly a consequence of the fact that we have assumed β to be a function of N alone [21, 22].

Introducing the dimensionless variable $x = N/\theta$, we can rewrite (2.2) as

$$\frac{dx}{dt} = -[\beta(x) + \delta]x + k\beta(x_\tau)x_\tau, \tag{2.3}$$

where

$$\beta(x) = \beta_0 \frac{1}{1 + x^n}, \tag{2.4}$$

and $k = 2e^{-\gamma\tau}$. The steady states x_* of (2.3) are given by the solution of $dx/dt \equiv 0$. Thus we have $x_* \equiv 0$, and

$$x_* = \left(\beta_0 \frac{k-1}{\delta} - 1\right)^{1/n}. \tag{2.5}$$

Here we require

$$\tau < -\frac{1}{\gamma} \ln \frac{\delta + \beta_0}{2\beta_0},$$

so $\beta_0 \frac{k-1}{\delta} > 1$ in (2.5) and the second nontrivial steady state will be positive. Note that when $n \to \infty$, $x_* \to 1$ in (2.5) and $\beta(x)$ tends to a piecewise constant function (the Heaviside step function).

A solution of (2.3) is a continuous function $x : [-\tau, +\infty) \to \mathbf{R}_+$ obeying (2.3) for all $t > 0$. The continuous function $\varphi : [-\tau, 0] \to \mathbf{R}_+, \varphi(t) = x(t)$ for all $t \in [-\tau, 0]$, is called the initial condition for x. Using the method of steps, it is easy to prove that for every $\varphi \in C([-\tau, 0])$, where $C([-\tau, 0])$ is the space of continuous functions on $[-\tau, 0]$, there is a unique solution of (2.3) subject to the initial condition φ.

3. Periodic solutions: Limiting nonlinearity. In this section we study the dynamics of (2.3) when $\beta(x)$ is the step function

$$\beta(x) = \begin{cases} 0, & x \geq 1, \\ \beta_0, & x < 1. \end{cases}$$

By a solution of (2.3) in this case, we mean a continuous function $x(t)$ on the interval $[-\tau, \infty)$ which is piecewise differentiable and satisfies (2.3) for $t \in [0, \infty)$ except at the point t where $x(t)$ or $x(t - \tau)$ is equal to 1. For any initial data $\varphi \in C[-\tau, 0]$, it is not difficult to obtain a unique solution $x(t)$ by using the method of steps. As in [24], we introduce two constants

$$\alpha = \beta_0 + \delta, \quad \Gamma = 2\beta_0 e^{-\gamma\tau} = k\beta_0.$$

Inserting the step function $\beta(x)$ into (2.3), we obtain

$$\frac{dx}{dt} = \begin{cases} -\delta x, & 1 < x, x_\tau, \\ -\alpha x, & 0 < x < 1 < x_\tau, \\ -\alpha x + \Gamma x_\tau, & 0 < x, x_\tau < 1, \\ -\delta x + \Gamma x_\tau, & 0 < x_\tau < 1 < x, \end{cases} \tag{3.1}$$

where $x_\tau = x(t - \tau)$.

For (3.1), we choose the initial function $\varphi(t) \geq 1+\eta$ for $t \in [-\tau, 0)$ and $\varphi(0) = 1+\eta$ where η is a small positive constant specified later. By the continuity of the solution x, we have from (3.1) the existence of t_1 such that $x(t)$ and $x(t-\tau)$ are greater than 1 for $t \in [0, t_1)$ and $x(t_1) = 1$. The solution $x(t)$ then satisfies

$$\frac{dx}{dt} = -\delta x \quad \text{for} \quad t \in [0, t_1]. \tag{3.2}$$

Thus solving the above equation, we have $x(t) = \varphi(0)e^{-\delta t} = (1+\eta)e^{-\delta t}$. It follows that

$$t_1 = \frac{\ln \varphi(0)}{\delta} = \frac{\ln(1+\eta)}{\delta}. \tag{3.3}$$

In the next interval of time, defined by $(t_1, t_1+\tau)$, we have $x(t-\tau) > 1$. From the first two lines in (3.1), the solution is decreasing and thus crosses the level $x = 1$. The dynamics are given by

$$\frac{dx}{dt} = -\alpha x \tag{3.4}$$

as long as $x(t) < 1$. The solution is then given by $x(t) = e^{-\alpha(t-t_1)}$ for $t \in [t_1, t_1+\tau]$ and $x(t_1+\tau) = e^{-\alpha\tau}$ independent of the initial function $\varphi(t)$. Thus, the dynamics eventually destroy all memory of the initial function.

The solution in the next interval will be such that $x, x_\tau < 1$. In order that (3.1) has periodic solutions, we impose an extra condition on Γ and α so that

$$-\alpha x + \Gamma x_\tau > 0. \tag{3.5}$$

Otherwise, if $-\alpha x + \Gamma x_\tau \leq 0$, then the solution may tend to zero as t approaches infinity and thus we cannot expect a periodic solution. In particular, if

$$-\alpha x + \Gamma x_\tau \approx 0,$$

then the solution may stay below the line $x = 1$ so long that the resulting analysis becomes very complicated. Note that for $t \in [t_1+\tau, t_1+2\tau]$, we have $x(t-\tau) = e^{-\alpha(t-t_1-\tau)}$. Then if $x(t) < 1$, from (3.1), we have $\frac{dx}{dt} = -\alpha x + \Gamma x_\tau = -\alpha x + \Gamma e^{-\alpha(t-t_1-\tau)}$ which gives

$$x(t) = e^{-\alpha(t-t_1-\tau)}(e^{-\alpha\tau} + \Gamma(t-t_1-\tau)). \tag{3.6}$$

For the sake of simplicity, we impose an extra condition on Γ:

$$\Gamma > \max\left\{\frac{1}{\tau}(e^{\alpha\tau} - e^{-\alpha\tau}), \alpha e^{\alpha\tau}\right\}. \tag{3.7}$$

Note that condition (3.7) clearly holds if β_0 is large.

Equation (3.6) is only valid if the value of $x(t)$ is less than or equal to 1. However when we directly replace t in (3.6) by $t_1+2\tau$, we have $x(t_1+2\tau) = e^{-\alpha\tau}(e^{-\alpha\tau}+\Gamma\tau) > 1$. Thus we need to use (3.6) to find a point $t_2 \in (t_1+\tau, t_1+2\tau)$ such that $x(t_2) = 1$ and (3.6) is valid for $t \in [t_1+\tau, t_2]$. Assume $t_2 = t_1+\tau+u$, $u \in (0, \tau)$. Then from (3.6) we have

$$e^{\alpha u} = e^{-\alpha\tau} + \Gamma u. \tag{3.8}$$

Equation (3.8) is a transcendental equation and cannot be solved explicitly. However, the existence of a positive solution $u \in (0, \tau)$ is obvious given (3.7). Therefore (3.5) holds for $t \in [t_1 + \tau, t_2]$ (due to the fact that $x(t-\tau) \geq e^{-\alpha\tau}$).

Next for $t \in (t_2, t_2 + \tau)$, we claim that

$$x(t) > 1. \tag{3.9}$$

Indeed, from the above analysis, we know that $e^{-\alpha\tau} < x(t-\tau) < 1$ and at the particular point t_2, $x(t_2 + 0) = \lim_{t \to t_2 + 0} x(t) = 1$, so $x(t_2 - \tau) \geq e^{-\alpha\tau}$. By (2.3) and (3.7) we have

$$x'(t_2 + 0) = -[\beta(x) + \delta]x + k\beta(x_\tau)x_\tau > -\alpha + \Gamma x_\tau > 0.$$

The solution $x(t)$ is differentiable with respect to t as long as $x(t)$ and $x(t-\tau)$ are not equal to 1. To see our claim suppose, by contradiction, that there exists a point $h \in (t_2, t_2 + \tau)$ such that $x(h) = 1$, $x'(h - 0) \leq 0$, and $x(t) > 1$ for $t \in (t_2, h)$. Then using (3.1), we have by (3.7) that

$$x'(h-0) = -\delta + \Gamma x(h - \tau) \geq -\delta + \Gamma e^{-\alpha\tau} > 0.$$

This is a contradiction, and our claim is true.

Splitting $[t_2, t_2 + \tau]$ into two subintervals $[t_2, t_1 + 2\tau]$ and $[t_1 + 2\tau, t_2 + \tau]$, we can give explicit formulae for the solution $x(t)$ as follows.

For $t \in [t_2, t_1 + 2\tau]$, we know that $x(t - \tau) = e^{-\alpha(t - t_1 - \tau)} < 1$. The dynamics are thus given by

$$\frac{dx}{dt} = -\delta x + \Gamma x_\tau = -\delta x + \Gamma e^{-\alpha(t - t_1 - \tau)},$$

which has the solution

$$x(t) = e^{-\delta\tau(t - t_2)} \left\{ 1 - \frac{\Gamma}{\beta_0} e^{\alpha(t_1 + \tau) - \delta t_2} \left(e^{-\beta_0 t} - e^{-\beta_0 t_2} \right) \right\}. \tag{3.10}$$

Moreover, since the solutions are differentiable provided that $x(t)$ and $x(t-\tau)$ are not equal to 1, and the solutions are continuous everywhere, for $t \in [t_1 + 2\tau, t_2 + \tau]$ we have

$$\begin{aligned} \frac{dx}{dt} &= -\delta x + \Gamma x_\tau \\ &= -\delta x + \Gamma e^{-\alpha(t - t_1 - 2\tau)}(e^{-\alpha\tau} + \Gamma(t - t_1 - 2\tau)), \end{aligned}$$

so

$$x(t) = e^{-\delta(t - t_1 - 2\tau)} \left[x(t_1 + 2\tau) + \Gamma \left(j(t) - j(t_1 + 2\tau) \right) \right],$$

where

$$j(t) = \frac{1}{(\delta - \alpha)} \left(e^{-\alpha\tau} + \Gamma(t - t_1 - 2\tau) - \frac{\Gamma}{\delta - \alpha} \right) e^{(\delta - \alpha)(t - t_1 - 2\tau)}.$$

After the time $t_2 + \tau$, both x_τ and x are greater than 1, and the solution satisfies

$$x' = -\delta x \tag{3.11}$$

as long as $x(t) > 1$ and thus is decreasing. Therefore, there exists a point, say, $t = d$, so that $x(d) = 1$. Note that in the interval $[t_2, d]$, the graph of the solution $x(t)$ is independent of the initial function $\varphi(t)$. Now we can use (3.9) and (3.11) to choose a small positive constant $\eta < 1$ such that the following hold:

1. We have

$$t_1 = \frac{\log(1+\eta)}{\delta} < \tau; \tag{3.12}$$

2. we have

$$\Gamma > \max\left\{\frac{1}{\tau}(e^{\alpha\tau} - e^{-\alpha\tau}), \alpha(1+\eta)e^{\alpha\tau}\right\}, \tag{3.13}$$

   and $x(t)$ reaches $1+\eta$ at a point $t_3 \in (t_2, t_2+\tau)$; and
3. there is a point T_x, $t_3+\tau < T_x < d$ so that

$$x(T_x) = 1+\eta,\ x(T_x+s) > 1+\eta,\ s \in [-\tau, 0). \tag{3.14}$$

With this choice of η, we have $x(t) > 1+\eta$ for $t \in (t_3, T_x)$ and the solution is strictly increasing for $t \in [t_2, t_3]$ (due to (3.13)). Finally, when we continue to solve (3.1) step by step, we have $x(t) = x(t+T_x)$ for $t \geq 0$. Summarizing the above analysis, we have the following result.

THEOREM 3.1. *Suppose that* Γ *satisfies* (3.7). *Assume that* x *is the solution of* (3.1) *subject to the initial condition* $\phi \geq 1+\eta$ *where* η *is chosen to satisfy* (3.12), (3.13), *and* (3.14). *Then the solution* x *satisfies* $x(t) = x(t+T_x)$ *for* $t \geq 0$.

4. Periodic solutions: General nonlinearity.

4.1. Perturbed delay equation. With the preceding analysis of the G_0 phase cell cycle model when the feedback function β is a Heaviside step function, we turn to a consideration of the general continuous nonlinearity. More precisely, we consider

$$\frac{dy}{dt} = -[\beta(y)+\delta]y + k\beta(y_\tau)y_\tau, \tag{4.1}$$

returning to the original problem with $\beta = \beta_0 \frac{1}{1+y^n}$. Let $\varepsilon = 1/n$. Then we can rewrite the Hill function as

$$\beta_\varepsilon(y) = \beta_0 \frac{1}{1+y^{1/\varepsilon}}.$$

Let the initial function φ be chosen from the closed convex set

$$A_\eta = \{\varphi \in C([-\tau, 0]) : 1+\eta \leq \varphi(t) \quad \text{for} \quad t \in [-\tau, 0], \quad \text{and} \quad \varphi(0) = 1+\eta\},$$

where $\eta < 1$ is a small positive constant as chosen in the previous section. For given φ in A_η, we have a unique solution to (4.1). The relations

$$F_\varepsilon(t, \varphi) = y_t,\ y_t = y(t+s),\ -\tau \leq s \leq 0,\ t \geq 0,$$

define a continuous semiflow $F = F_\varepsilon$ on $C([-\tau, 0])$.

As a technical preparation, we now describe some elementary properties of the Hill function we employ here.

Lemma 4.1. *Assume* $\varepsilon = \frac{1}{n} < 1$. *The following inequalities hold:*

(a) *If* $y > \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)}$, *then*

$$\beta_\varepsilon(y) < \beta_0\varepsilon, \quad y\beta_\varepsilon(y) < \beta_0\varepsilon$$

and if $0 < y < \varepsilon^\varepsilon$, *then*

$$\beta_0 > \beta_\varepsilon(y) > \beta_0(1-\varepsilon) \quad \textit{and} \quad |y\beta_\varepsilon(y) - \beta_0 y| < \beta_0\epsilon. \tag{4.2}$$

(b) *Also,*

$$\left|\frac{d(y\beta_\varepsilon(y))}{dy}\right| < \beta_0\varepsilon \quad \textit{for} \ \ y > \left(\frac{1}{\varepsilon}\right)^{2\varepsilon},$$

and

$$\left|\frac{d(y\beta_\varepsilon(y) - \beta_0 y)}{dy}\right| < \beta_0\varepsilon \quad \textit{for} \ \ 0 < y < \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon}.$$

Proof. (a) If $y > \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)}$, then

$$\beta_\varepsilon(y) = \frac{\beta_0}{1+y^{1/\varepsilon}} < \frac{\beta_0}{y^{1/\varepsilon}} < \frac{\beta_0}{\left(\frac{1}{\varepsilon}\right)^{1/(1-\varepsilon)}} < \beta_0\varepsilon,$$

and

$$y\beta_\varepsilon(y) = \frac{\beta_0 y}{1+y^{1/\varepsilon}} < \frac{\beta_0}{y^{\frac{1}{\varepsilon}-1}} < \beta_0\varepsilon.$$

If $0 < y < \varepsilon^\varepsilon$, then

$$\beta_0 > \beta_\varepsilon(y) = \frac{\beta_0}{1+y^{1/\varepsilon}} > \beta_0(1-y^{1/\varepsilon}) \geq \beta_0(1-\varepsilon),$$

and

$$|y\beta_\varepsilon(y) - \beta_0 y| = \left|\beta_0 \frac{y^{1/\varepsilon+1}}{1+y^{1/\varepsilon}}\right| < \beta_0 y^{1/\varepsilon+1} < \beta_0\varepsilon.$$

(b) If $y > (1/\varepsilon)^{2\varepsilon}$, then

$$\left|\frac{d\left(y\beta_\varepsilon(y)\right)}{dy}\right| = \beta_0 \frac{\left|\left(\frac{1}{\varepsilon}-1\right)y^{1/\varepsilon}-1\right|}{(1+y^{1/\varepsilon})^2} \leq \beta_0\left(\frac{1}{\varepsilon}-1\right)y^{-1/\varepsilon} < \beta_0\varepsilon.$$

Since

$$f(x) = \frac{\left(1+\frac{1}{\varepsilon}\right)x + \frac{1}{\varepsilon}x^2}{1+x}$$

is strictly increasing for $x \in (0, \frac{\varepsilon^2}{1+\varepsilon})$ and $f(\frac{\varepsilon^2}{1+\varepsilon}) < \varepsilon$, we obtain

$$\left|\frac{d\left(y\beta_\varepsilon(y) - \beta_0 y\right)}{dy}\right| = \beta_0 \frac{(1+\frac{1}{\varepsilon})y^{1/\varepsilon} + \frac{1}{\varepsilon}y^{2/\varepsilon}}{1+y^{1/\varepsilon}} < \beta_0\varepsilon$$

for $0 < y < (\frac{\varepsilon^2}{1+\varepsilon})^\varepsilon$. $\square$

We found that for (3.1), if $\varphi \in A_\eta$, then the solution will return to A_η after finite time. The following lemma shows a similar property for (4.1).

LEMMA 4.2. *Let y be the solution of* (4.1) *with an initial function $\varphi \in A_\eta$. Then there exists a point $T_y > 0$ such that $y(T_y) = 1 + \eta$ and*

$$y(t) \geq 1 + \eta \quad \text{for } t \in [T_y - \tau, T_y]. \tag{4.3}$$

Moreover, there exists a constant $\varepsilon_1, \varepsilon_1 \in (0, 1)$, such that for each $\varepsilon \in (0, \varepsilon_1)$, we have

$$T_y = T_x + O(\varepsilon \log \varepsilon) \tag{4.4}$$

and

$$y(t) = x(t) + O(\varepsilon \log \varepsilon), \tag{4.5}$$

uniformly for $t \in [0, T_x]$ and $\varphi \in A_\eta$, where T_x is the period of the periodic solution x to (3.1) *obtained in Theorem* 3.1.

Proof of Lemma 4.2. We first claim that there exist three points η_1, t_1^y, η_2, $0 < \eta_1 < t_1^y < \eta_2$, which are dependent on ε and φ, such that

$$y(\eta_1) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon} > 1, \;\; y(t_1^y) = 1, \;\; y(\eta_2) = \left(\frac{\varepsilon^2}{1 + \varepsilon}\right)^{\varepsilon} < 1. \tag{4.6}$$

Indeed, if $y(t) > (\frac{1}{\varepsilon})^{2\varepsilon} > \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)} > 1$ and $y(t - \tau) > (\frac{1}{\varepsilon})^{2\varepsilon} > (\frac{1}{\varepsilon})^{\varepsilon/(1-\varepsilon)}$, then we have by Lemma 4.1 that

$$\beta_\varepsilon(y(t))y(t) < \beta_0 \varepsilon, \;\; \beta_\varepsilon(y(t - \tau))y(t - \tau) < \beta_0 \varepsilon$$

and

$$\begin{aligned} \frac{dy(t)}{dt} &= -(\delta + \beta_\varepsilon(y(t)))y(t) + k\beta_\varepsilon(y(t - \tau))y(t - \tau), \\ &= -\delta y(t) + O(\varepsilon) \\ &< -\frac{\delta}{2} \;\text{ for } \varepsilon \in (0, \sigma_1). \end{aligned} \tag{4.7}$$

Here σ_1 is chosen so that for each $\varepsilon \in (0, \sigma_1)$, we have $-\delta y(t) + O(\varepsilon) < -\frac{\delta}{2}$. This means that y is decreasing as long as $y(t) \geq (\frac{1}{\varepsilon})^{2\varepsilon} > (\frac{1}{\varepsilon})^{\varepsilon/(1-\varepsilon)}$. Therefore there is a point $\eta_1 > 0$ so that $y(\eta_1) = (1/\varepsilon)^{2\varepsilon}$ and $1 + \eta > y(t) > (1/\varepsilon)^{2\varepsilon}$ for $t \in (0, \eta_1)$. Using $\frac{dy}{dt} = -\delta y + O(\varepsilon)$ and $y(0) = 1 + \eta$, we also have

$$\eta_1 = \frac{\log(1 + \eta)}{\delta} + O(-\varepsilon \log \varepsilon) = t_1 + O(-\varepsilon \log \varepsilon). \tag{4.8}$$

Here the term $O(-\varepsilon \log \varepsilon)$ holds uniformly for all the initial functions φ in A_η. Next in the interval $(\eta_1, \eta_1 + \tau)$, we have $\beta_\varepsilon(y(t - \tau))y(t - \tau) = O(\varepsilon)$ and

$$\begin{aligned} \frac{dy(t)}{dt} &= -(\delta + \beta_\varepsilon(y(t)))y(t) + k\beta_\varepsilon(y(t - \tau))y(t - \tau) \\ &< -\delta y(t) + k\beta_\varepsilon(y(t - \tau))y(t - \tau) \\ &= -\delta y(t) + O(\varepsilon) \\ &< -\frac{\delta}{2} \text{ for } \varepsilon \in (0, \sigma_2) \end{aligned}$$

as long as $y(t) \geq (\frac{\varepsilon^2}{1+\varepsilon})^\varepsilon$. Here σ_2 is chosen so that for each $\varepsilon \in (0, \sigma_2)$, we have

$$-\delta y(t) + O(\varepsilon) < -\delta \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^\varepsilon + O(\varepsilon) < -\frac{\delta}{2}.$$

This means that the solution is decreasing and there exist two points t_1^y, η_2, $\eta_1 < t_1^y < \eta_2$, such that

$$y(t_1^y) = 1, \;\; y(\eta_2) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^\varepsilon.$$

By the mean value theorem, it is easy to show that

$$|y(\eta_1) - y(\eta_2)| \geq \frac{\delta}{2} |\eta_1 - \eta_2|$$

or, equivalently,

$$\eta_2 - \eta_1 \leq \frac{2}{\delta}(y(\eta_1) - y(\eta_2)) = \frac{2}{\delta}\left[\left(\frac{1}{\varepsilon}\right)^{2\varepsilon} - \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^\varepsilon\right] = O(-\varepsilon \log \varepsilon).$$

Therefore,

$$0 < t_1^y - \eta_1 < \eta_2 - \eta_1 = O(-\varepsilon \log \varepsilon). \tag{4.9}$$

Now using (4.1) for $t \in [0, \eta_1]$, we have

$$y' = -\delta y + O(\varepsilon), \; y(0) = 1 + \eta,$$

which gives

$$y(t) = (1+\eta)e^{-\delta t} + O(\varepsilon).$$

We claim that

$$y(t) = x(t) + O(\varepsilon) \tag{4.10}$$

uniformly for $t \in [0, \xi_1]$ and $\varphi \in A_\eta$, where

$$\xi_1 = \min\{t_1, \eta_1\}.$$

Indeed, this is true, since $x(t) = (1+\eta)e^{-\delta t}$ for $t \in [0, t_1]$.

Next for $t \in [\xi_1, \eta_2]$, using an argument that the length of the interval $[t_1, \eta_1]$ is of order $O(-\varepsilon \log \varepsilon)$, and both $|x'(t)|$ and $|y'(t)|$ are bounded by a constant, say, M, which is independent of ε and η, we conclude from (4.10) that

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon). \tag{4.11}$$

For $t \in [\eta_2, \tau + \xi_1]$, we can show that $y(t-\tau) > (1/\varepsilon)^{2\varepsilon}$. Note that $\eta_2 \leq \xi_1 + \tau$ since $\eta_2 - \xi_1 = O(\varepsilon \log \varepsilon)$ and τ is a constant. Here we have assumed that $\varepsilon \in (0, \sigma_3)$, where σ_3 is small enough so that for each $\varepsilon \in (0, \sigma_3)$, we have $O(\varepsilon \log \varepsilon) < \tau$. By Lemma 4.1, we have

$$y(t-\tau)\beta(y(t-\tau)) = O(\varepsilon).$$

Using (4.1) we know that

$$-\alpha y + O(\varepsilon) \le y' \le -\delta y + O(\varepsilon),$$

and thus the solution $y(t) \ge (\varepsilon^2/(1+\varepsilon))^{\varepsilon} e^{-\alpha\tau} + O(\varepsilon)$ and its derivative

$$y'(t) \le -\delta(\varepsilon^2/(1+\varepsilon))^{\varepsilon} e^{-\alpha\tau} + O(\varepsilon) < 0 \text{ for } \varepsilon \in (0, \sigma_4),$$

where σ_4 is chosen so that for each $\varepsilon \in (0, \sigma_4)$, we have $-\delta(\varepsilon^2/(1+\varepsilon))^{\varepsilon} e^{-\alpha\tau} + O(\varepsilon) < 0$. So $y(t)$ is decreasing for $t \in [\eta_2, \tau + \xi_1]$. Note that $0 < y < y(\eta_2) \le \varepsilon^{\varepsilon}$ so that (4.2) in Lemma 4.1 holds. Thus we can derive from (4.1) that

$$y'(t) = -\alpha y(t) + O(\varepsilon) \tag{4.12}$$

for $t \in [\eta_2, \tau + \xi_1]$. Coupling this equation with (3.4) and using (4.11) at the point $t = \eta_2$ give

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon)$$

for $t \in [\eta_2, \tau + \xi_1]$.

For $t \in [\tau + \xi_1, \tau + \eta_2]$, again using the fact that both the derivatives of x and y are bounded and the length of this interval is of order $O(-\varepsilon \log \varepsilon)$, we have

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon).$$

For $t \ge \tau + \eta_2$, the solution y begins to increase since Γ satisfies (3.7). To be precise, we have $\beta_\varepsilon(y(t)) < \beta_0$, $\beta_\varepsilon(y(t-\tau))y(t-\tau) = \beta_0 y(t-\tau) + O(-\varepsilon \log \varepsilon)$ and

$$\begin{aligned} y'(t) &= -(\delta + \beta_\varepsilon(y(t)))y(t) + k\beta_\varepsilon(y(t-\tau))y(t-\tau) \\ &\ge -\alpha y(t) + k\beta_0 y(t-\tau) + O(-\varepsilon \log \varepsilon) \\ &= -\alpha y(t) + \Gamma x(t-\tau) + O(-\varepsilon \log \varepsilon) \\ &\ge -\alpha(1+\eta) + \Gamma e^{-\alpha\tau} + O(-\varepsilon \log \varepsilon) \\ &> 0 \quad \text{ for } \varepsilon \in (0, \sigma_5) \end{aligned}$$

as long as $y(t) \le 1 + \eta$ and $t \le 2\tau + \eta_2$. Here σ_5 is sufficiently small so that for each $\varepsilon \in (0, \sigma_5)$, we have $-\alpha(1+\eta) + \Gamma e^{-\alpha\tau} + O(-\varepsilon \log \varepsilon) > 0$. Using similar arguments as above, we conclude that there exist three points η_3, t_2^y, η_4, with $\eta_3 < t_2^y < \eta_4$ such that

$$y(\eta_3) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon}, \quad y(t_2^y) = 1, \quad y(\eta_4) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon},$$

$$\eta_3 = t_2^y + O(-\varepsilon \log \varepsilon), \quad \eta_4 = t_2^y + O(-\varepsilon \log \varepsilon), \tag{4.13}$$

and

$$t_2^y = t_2 + O(-\varepsilon \log \varepsilon). \tag{4.14}$$

We can continue this process to find that y will satisfy

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon)$$

for $t \in [0, \tau + \xi_2]$, where $\xi_2 = \min\{t_2, \eta_3\}$. From the expression for x, we know from the preceding equation that there exists a point $t_3^y \in (\eta_4, \tau+\xi_2)$ such that $y(t_3^y) = 1+\eta$ and $t_3^y = t_3 + O(-\varepsilon \log \varepsilon)$.

For $t \in [\tau+\xi_2, \tau+\eta_4]$, using the same argument as in the interval $[\tau+\xi_1, \tau+\eta_2]$, we again have

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon). \tag{4.15}$$

Finally for $t \geq \tau+\eta_4$, the solution is decreasing and will reach the value $1+\eta$ at some point T_y. In the whole interval $[0, T_x]$, if we choose $\varepsilon_1 = \min\{\sigma_i, 1 \leq i \leq 5\}$, then we can show as before that for each $\varepsilon \in (0, \varepsilon_1)$, we have

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon),\ x \in [0, T_x], \tag{4.16}$$

and

$$T_y = T_x + O(-\varepsilon \log \varepsilon). \tag{4.17}$$

Furthermore, we also have $y(T_y) = 1+\eta$ and

$$y(t) \geq 1+\eta \text{ for } [T_y - \tau, T_y]. \quad \square \tag{4.18}$$

Remark 4.3. By Lemma 4.2 and (4.1) we have two positive constants M_1 and M_2 which are independent of ε and the initial data φ so that for $t \geq 0$,

$$|y(t)| \leq M_1 \tag{4.19}$$

and

$$\left|\frac{dy(t)}{dt}\right| \leq M_2. \tag{4.20}$$

Now we are ready to define a continuous return map

$$R : A_\eta \ni \varphi \to y_{q(\varphi)} = F_\varepsilon(q(\varphi), \varphi) \in A_\eta,$$

where $q(\varphi) = T_y$. To verify that there exists a unique fixed point in A_η for the map R, we need to show that the map R is contractive, i.e., derive an estimation for the Lipschitz constant and show that the Lipschitz constant is less than 1.

4.2. Lipschitz constant for the map $\mathbb{R}$. The Lipschitz constant of a given map $T : D_T \to Y$, $D_T \subset X$, where X and Y are normed linear spaces, is given by

$$L(T) = \sup_{u \in D_T, v \in D_T, u \neq v} \frac{||T(u) - T(v)||}{||u - v||}.$$

In the case where $D_T = X = Y = \mathbb{R}$, $[u_1, u_2] \subset \mathbb{R}$, and $f = T$, we set

$$L_{[u_1,u_2]}(f) = L(f|[u_1, u_2]).$$

If $f(u) = u\beta_\varepsilon(u)$, $u \in \mathbb{R}$, we define the following four Lipschitz constants:

$$\begin{aligned} L_1^\varepsilon = &\quad L_{[1+\eta,+\infty)}(u\beta_\varepsilon(u)), \\ L_2^\varepsilon = &\quad L_{[(\frac{1}{\varepsilon})^{2\varepsilon},+\infty)}(u\beta_\varepsilon(u)), \\ L_3^\varepsilon = &\quad L_{(0,+\infty)}(u\beta_\varepsilon(u)), \\ L_4^\varepsilon = &\quad L_{(0,(\frac{\varepsilon^2}{1+\varepsilon})^\varepsilon)}(u\beta_\varepsilon(u)). \end{aligned}$$

Similarly for the function $f(u) = u\beta_\varepsilon(u) - \beta_0 u$, $u \in \mathbb{R}$, we define the following Lipschitz constant for later use:

$$L_5^\varepsilon = L_{(0,(\frac{\varepsilon^2}{1+\varepsilon})^\varepsilon)}(u\beta_\varepsilon(u) - \beta_0 u).$$

When $\varepsilon << 1$, we have

$$L_1^\varepsilon = O\left(\frac{1}{\varepsilon(1+\eta)^{1/\varepsilon}}\right), \quad L_2^\varepsilon = O(\varepsilon), \quad L_3^\varepsilon = O(1/\varepsilon), \quad L_4^\varepsilon = O(1), \quad L_5^\varepsilon = O(\varepsilon). \tag{4.21}$$

THEOREM 4.4. *There exists ε_2, $\varepsilon_2 \in (0, \varepsilon_1)$, such that for each $\varepsilon \in (0, \varepsilon_2)$ the Lipschitz constant L_R^ε of the map R is less than 1. In particular, we have*

$$\lim_{\varepsilon \to 0} L_R^\varepsilon = 0.$$

Proof. Step 1. Take $\phi, \bar{\phi}$ in A_η. Using a similar argument as in the proof of Lemma 4.2, we conclude that there exist η_1, η_2 and $\bar{\eta}_1, \bar{\eta}_2$ such that

$$y^\phi(\eta_1) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon}, \; y^\phi(\eta_2) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^\varepsilon, \; \eta_1 - \eta_2 = O(-\varepsilon \log \varepsilon)$$

and

$$y^{\bar{\phi}}(\bar{\eta}_1) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon}, \; y^{\bar{\phi}}(\bar{\eta}_2) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^\varepsilon, \; \bar{\eta}_1 - \bar{\eta}_2 = O(-\varepsilon \log \varepsilon).$$

Let

$$\eta_{\min} = \min\{\eta_1, \bar{\eta}_1\}$$

and

$$\eta_{\max} = \max\{\eta_2, \bar{\eta}_2\}.$$

Then by (4.8) and (4.9) we have

$$\begin{aligned} &\eta_{\min} = t_1 + O(-\varepsilon \log \varepsilon), \qquad \eta_{\max} = t_1 + O(-\varepsilon \log \varepsilon), \quad \text{and} \\ &\eta_{\max} - \eta_{\min} = O(-\varepsilon \log \varepsilon). \end{aligned} \tag{4.22}$$

Since $t_1 = \log(1+\eta)/\delta < \tau$, from (4.22) we have that $\eta_{\min} < \tau$ and $\eta_{\max} < \tau$. Here we have chosen $\sigma_6 > 0$ sufficiently small so that for each $\varepsilon \in (0, \sigma_6)$

$$\eta_{\max} = \log(1+\eta)/\delta + O(-\varepsilon \log \varepsilon) < \tau.$$

For $t \in [0, \eta_{\min}]$, using (4.1) for $y^\phi(t)$ and $y^{\bar{\phi}}(t)$ gives

$$\frac{dy^\phi(t)}{dt} = -[\delta + \beta_\varepsilon(y^\phi(t))]y^\phi(t) + k\beta_\varepsilon(y^\phi(t-\tau))y^\phi(t-\tau) \tag{4.23}$$

and

$$\frac{dy^{\bar{\phi}}(t)}{dt} = -[\delta + \beta_\varepsilon(y^{\bar{\phi}}(t))]y^{\bar{\phi}}(t) + k\beta_\varepsilon(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau). \tag{4.24}$$

Now we estimate the difference between $y^{\phi}(t)$ and $y^{\bar{\phi}}(t)$. Subtracting (4.24) from (4.23) yields

$$
\begin{aligned}
(y^{\phi}(t) - y^{\bar{\phi}}(t))' = &-\delta(y^{\phi}(t) - y^{\bar{\phi}}(t)) \\
&-[\beta_{\varepsilon}(y^{\phi}(t))y^{\phi}(t) - \beta_{\varepsilon}(y^{\bar{\phi}}(t))y^{\bar{\phi}}(t)] \\
&+k[\beta_{\varepsilon}(y^{\phi}(t-\tau))y^{\phi}(t-\tau) - \beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau)].
\end{aligned} \tag{4.25}
$$

Substituting the inequalities

$$|\beta_{\varepsilon}(y^{\phi}(t))y^{\phi}(t) - \beta_{\varepsilon}(y^{\bar{\phi}}(t))y^{\bar{\phi}}(t)| \le L_2^{\varepsilon}|y^{\phi}(t) - y^{\bar{\phi}}(t)|$$

and

$$|\beta_{\varepsilon}(y^{\phi}(t-\tau))y^{\phi}(t-\tau) - \beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau)| \le L_1^{\varepsilon}||\phi - \bar{\phi}||$$

into (4.25), we have

$$(y^{\phi}(t) - y^{\bar{\phi}}(t))' \le (\delta + L_2^{\varepsilon})\,|y^{\phi}(t) - y^{\bar{\phi}}(t)| + kL_1^{\varepsilon}||\phi - \bar{\phi}||. \tag{4.26}$$

Integrating (4.26) from 0 to t gives

$$(y^{\phi}(t) - y^{\bar{\phi}}(t)) \le \int_0^t \Big((\delta + L_2^{\varepsilon})\,|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_1^{\varepsilon}||\phi - \bar{\phi}||\Big)\,ds.$$

Similarly, we have

$$-(y^{\phi}(t) - y^{\bar{\phi}}(t)) \le \int_0^t \Big((\delta + L_2^{\varepsilon})\,|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_1^{\varepsilon}||\phi - \bar{\phi}||\Big)\,ds.$$

Thus, we have found that

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_0^t \Big((\delta + L_2^{\varepsilon})\,|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_1^{\varepsilon}||\phi - \bar{\phi}||\Big)\,ds. \tag{4.27}$$

From Gronwall's inequality, we obtain

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le C_1||\phi - \bar{\phi}||, \tag{4.28}$$

where

$$C_1 = \frac{e^{(\delta + L_2^{\varepsilon})\eta_{\min}} - 1}{\delta + L_2^{\varepsilon}} kL_1^{\varepsilon}. \tag{4.29}$$

Step 2. For $t \in [\eta_{\min}, \eta_{\max}]$, we have

$$|\beta_{\varepsilon}(y^{\phi}(t))y^{\phi}(t) - \beta_{\varepsilon}(y^{\bar{\phi}}(t))y^{\bar{\phi}}(t)| \le L_3^{\varepsilon}|y^{\phi}(t) - y^{\bar{\phi}}(t)|$$

and

$$|\beta_{\varepsilon}(y^{\phi}(t-\tau))y^{\phi}(t-\tau) - \beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau)| \le L_1^{\varepsilon}||\phi - \bar{\phi}||.$$

Thus from (4.23) and (4.24) we obtain, as before,

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_{\eta_{\min}}^t \Big((\delta + L_3^{\varepsilon})\,|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_1^{\varepsilon}||\phi - \bar{\phi}||\Big)\,ds + C_1||\phi - \bar{\phi}||.$$

Then by Gronwall's inequality, we have

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le C_2||\phi - \bar{\phi}||, \tag{4.30}$$

where

$$C_2 = C_1 e^{(\delta+L_3^{\varepsilon})(\eta_{\max}-\eta_{\min})} + \frac{e^{(\delta+L_3^{\varepsilon})(\eta_{\max}-\eta_{\min})}-1}{\delta+L_3^{\varepsilon}} kL_1^{\varepsilon} > C_1. \tag{4.31}$$

Remember that $\eta_{\min} \le \tau$ since $t_1 < \tau$ in (3.14) and $\eta_{\min} = t_1 + O(-\varepsilon \log \varepsilon)$. Moreover $\eta_{\max} \le \tau$ since $\eta_{\max} = t_1 + O(-\varepsilon \log \varepsilon)$ from (4.22).

Step 3. For $t \in [\eta_{\max}, \tau + \eta_{\min}]$,

$$|\beta_{\varepsilon}(y^{\phi}(\tau))y^{\phi}(t) - \beta_0 y^{\phi}(t) - (\beta_{\varepsilon}(y^{\bar{\phi}}(t))y^{\bar{\phi}}(t) - \beta_0 y^{\bar{\phi}}(t))| \le L_5^{\varepsilon}|y^{\phi}(t) - y^{\bar{\phi}}(t)|$$

and

$$|\beta_{\varepsilon}(y^{\phi}(t-\tau))y^{\phi}(t-\tau) - \beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau)| \le L_2^{\varepsilon}C_2||\phi - \bar{\phi}||.$$

It is thus easy to derive

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_{\eta_{\max}}^{t} \Big((\alpha + L_5^{\varepsilon})|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_2^{\varepsilon}C_2||\phi - \bar{\phi}||\Big)\, ds + C_2||\phi - \bar{\phi}||$$

and to conclude that (since $\tau + \eta_{\min} - \eta_{\max} < \tau$)

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le C_3||\phi - \bar{\phi}||, \tag{4.32}$$

where

$$C_3 = C_2 e^{\alpha\tau + \tau L_5^{\varepsilon}} + \frac{e^{\alpha\tau+\tau L_5^{\varepsilon}}-1}{\alpha + L_5^{\varepsilon}} kL_2^{\varepsilon}C_2 > C_2. \tag{4.33}$$

Step 4. When $t \ge \tau + \eta_{\min}$, we have from (4.13) and (4.14) that there exist $\eta_3 < \eta_4$ and $\bar{\eta}_3 < \bar{\eta}_4$ such that

$$y^{\phi}(\eta_3) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon},\ y^{\phi}(\eta_4) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon},\ \eta_4 - \eta_3 = O(-\varepsilon \log \varepsilon)$$

and

$$y^{\bar{\phi}}(\bar{\eta}_3) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon},\ y^{\bar{\phi}}(\bar{\eta}_4) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon},\ \bar{\eta}_4 - \bar{\eta}_3 = O(-\varepsilon \log \varepsilon).$$

Let

$$\eta_{\min}^3 = \min\{\eta_3, \bar{\eta}_3\},\ \eta_{\max}^4 = \max\{\eta_4, \bar{\eta}_4\}.$$

Then by (4.13) and (4.14) we have

$$\eta_{\min}^3 = t_2 + O(-\varepsilon \log \varepsilon),\ \eta_{\max}^4 = t_2 + O(-\varepsilon \log \varepsilon),\ \eta_{\max}^4 - \eta_{\min}^3 = O(-\varepsilon \log \varepsilon). \tag{4.34}$$

Since $t_2 > t_1 + \tau$, we can choose $\sigma_7 > 0$ sufficiently small so that for each $\varepsilon \in (0, \sigma_7)$ the inequality

$$\tau + \eta_{\max} < \eta_{\min}^3$$

holds. For $t \in [\tau + \eta_{\min}, \eta^3_{\min}]$, we similarly have

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_{\tau+\eta_{\min}}^{t} \Big((\alpha + L_5^{\varepsilon})|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_3^{\varepsilon} C_3 ||\phi - \bar{\phi}|| \Big)\, ds + C_3||\phi - \bar{\phi}||$$

and

$$|y^{\phi} - y^{\bar{\phi}}| \le C_4||\phi - \bar{\phi}||, \tag{4.35}$$

where

$$C_4 = C_3 e^{(\alpha+L_5^{\varepsilon})(\eta^3_{\min} - \tau - \eta_{\min})} + \frac{e^{(\alpha+L_5^{\varepsilon})(\eta^3_{\min} - \tau - \eta_{\min})} - 1}{\alpha + L_5^{\varepsilon}} kL_3^{\varepsilon} C_3 > C_3. \tag{4.36}$$

Step 5. For $t \in [\eta^3_{\min}, \eta^4_{\max}]$, from (4.22) and (4.34) it is easy to demonstrate that $\eta_{\max} \le t - \tau \le \eta^3_{\min}$. Thus we have

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_{\eta^3_{\min}}^{t} \Big((\delta + L_3^{\varepsilon})|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_4^{\varepsilon} C_4 ||\phi - \bar{\phi}|| \Big)\, ds + C_4||\phi - \bar{\phi}||.$$

Then it follows that

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le C_5||\phi - \bar{\phi}||, \tag{4.37}$$

where

$$C_5 = C_4 \left(e^{(\delta+L_3^{\varepsilon})(\eta^4_{\max} - \eta^3_{\min})} + \frac{e^{(\delta+L_3^{\varepsilon})(\eta^4_{\max} - \eta^3_{\min})} - 1}{\delta + L_3^{\varepsilon}} kL_4^{\varepsilon} \right). \tag{4.38}$$

Step 6. For $t \in [\eta^4_{\max}, \tau + \eta^4_{\max}]$, we claim that $y^{\phi}(t) \ge (1/\varepsilon)^{2\varepsilon}$ and $y^{\bar{\phi}}(t) \ge (1/\varepsilon)^{2\varepsilon}$. We prove this claim only for the function y^{ϕ}, because the proof for the function $y^{\bar{\phi}}$ is similar and hence omitted. Note that $t_3 > \eta^4_{\max} = t_2 + O(-\varepsilon \log \varepsilon)$ for each $\varepsilon \in (0, \sigma_8)$ where σ_8 is chosen so that $t_3 > t_2 + O(-\sigma_8 \log \sigma_8)$. Using $y^{\phi}(t) = x(t) + O(-\varepsilon \log \varepsilon)$, with $y^{\phi}(t - \tau) = x(t - \tau) + O(-\varepsilon \log \varepsilon) \ge e^{-\alpha\tau} + O(-\varepsilon \log \varepsilon)$, and (3.7) and (4.34), we have from (4.1) that $dy^{\phi}(t)/dt > 0$ for $t \in [\eta^4, t_3]$, and thus y^{ϕ} is increasing and satisfies $y^{\phi}(\eta^4_{\max}) \ge y^{\phi}(\eta_4) \ge (1/\varepsilon)^{2\varepsilon}$. For $t \in [t_3, \tau + \eta^4_{\max}]$, $x(t) \ge 1 + \eta$. Then using Lemma 4.2 again we have

$$y^{\phi}(t) = x(t) + O(-\varepsilon \log \varepsilon) > \left(\frac{1}{\varepsilon}\right)^{2\varepsilon}$$

provided $\varepsilon \in (0, \sigma_9)$, where σ_9 is sufficiently small so that the above formula holds for $\varepsilon \in (0, \sigma_9)$. Therefore, we obtain

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le \int_{\eta^4_{\max}}^{t} \Big((\delta + L_2^{\varepsilon})|y^{\phi}(s) - y^{\bar{\phi}}(s)| + kL_3^{\varepsilon} C_5 ||\phi - \bar{\phi}|| \Big)\, ds + C_5||\phi - \bar{\phi}||$$

and

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \le C_6||\phi - \bar{\phi}||, \tag{4.39}$$

where

$$C_6 = C_5 \left(e^{(\delta+L_2^{\varepsilon})\tau} + \frac{e^{(\delta+L_2^{\varepsilon})\tau} - 1}{\delta + L_2^{\varepsilon}} kL_3^{\varepsilon} \right). \tag{4.40}$$

Step 7. When $t \geq \tau + \eta^4_{\max}$, both y and $\bar{y}$ are decreasing and will take the value $1+\eta$ after a finite time. Suppose that s and $\bar{s}$ satisfy

$$y^{\phi}(s) = 1+\eta,\ y^{\bar{\phi}}(\bar{s}) = 1+\eta.$$

For the rest of the proof, we consider only the case $s < \bar{s}$, since the case when $s \geq \bar{s}$ can be similarly dealt with and the proof is omitted. By (4.4) and (4.34), we also obtain

$$s - (\tau + \eta^4_{\max}) = T_x - (\tau + t_2) + O(-\varepsilon \log \varepsilon)$$

and

$$\bar{s} - (\tau + \eta^4_{\max}) = T_x - (\tau + t_2) + O(-\varepsilon \log \varepsilon),$$

where T_x is the period of the function x. Because the distance between $\tau + \eta^4_{\max}$ and s may be greater than τ, we need to split the interval $[\tau + \eta^4_{\max}, s]$ into subintervals $[\tau + \eta^4_{\max}, 2\tau + \eta^4_{\max}]$, $[2\tau + \eta^4_{\max}, 3\tau + \eta^4_{\max}], \ldots, [m\tau + \eta^4_{\max}, s]$, where the length of each interval is exactly τ except the last one. Here m is the largest integer less than or equal to $(s - (\tau + \eta^4_{\max}))/\tau$. We can successively estimate $|y^{\phi} - y^{\bar{\phi}}|$ on the above subintervals to obtain

$$|y^{\phi}(t) - y^{\bar{\phi}}(t)| \leq C_7 ||\phi - \bar{\phi}||,\ t \in [\tau + \eta^4_{\max}, s], \tag{4.41}$$

with

$$C_7 = C_6 \left(e^{(\delta + L_2^{\varepsilon})\tau} + \frac{e^{(\delta + L_2^{\varepsilon})\tau} - 1}{\delta + L_2^{\varepsilon}} k L_2^{\varepsilon} \right)^{T_x}. \tag{4.42}$$

For $t \in [s, \bar{s}]$, the function $y^{\bar{\phi}}$ satisfies

$$y^{\bar{\phi}}(\bar{s}) = 1 + \eta \text{ and } y^{\bar{\phi}}(t) = 1 + \eta + O(-\varepsilon \log \varepsilon),$$

because the length of the interval $[s, \bar{s}]$ is of order $O(-\varepsilon \log \varepsilon)$ and the derivative of $y^{\bar{\phi}}$ is bounded; c.f. Remark 4.3. On the other hand, since $s = T_x + O(-\varepsilon \log \varepsilon)$, $\bar{s} = T_x + O(-\varepsilon \log \varepsilon)$, $x(t) \geq 1 + \eta$ for $t \in [t_3, T_x]$, and $y^{\bar{\phi}}(t) = x(t) + O(-\varepsilon \log \varepsilon)$ for $t \in [0, T_x]$, we know by (4.20) that for $t \in [s, \bar{s}]$,

$$y^{\bar{\phi}}(t - \tau) \geq \left(\frac{1}{\varepsilon}\right)^{2\varepsilon}$$

and

$$k\beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau)) y^{\bar{\phi}}(t-\tau) = O(-\varepsilon \log \varepsilon).$$

Therefore, from (4.1) we know that for $t \in [s, \bar{s}]$ the function $y^{\bar{\phi}}$ is decreasing and

$$\begin{aligned}
\left| \frac{dy^{\bar{\phi}}(t)}{dt} \right| &= \left| -(\delta + \beta_{\varepsilon}(y^{\bar{\phi}}(t))) y^{\bar{\phi}}(t) + k\beta_{\varepsilon}(y^{\bar{\phi}}(t-\tau)) y^{\bar{\phi}}(t-\tau) \right| \\
&\geq |-\delta(1+\eta) + O(-\varepsilon \log \varepsilon)| \\
&\geq \frac{\delta(1+\eta)}{2}.
\end{aligned}$$

Here we have assumed that ε is in the interval $(0, \sigma_{10})$, where σ_{10} is chosen so that for each $\varepsilon \in (0, \sigma_{10})$, the inequality

$$-\delta(1+\eta) + O(-\varepsilon \log \varepsilon) < -\frac{\delta(1+\eta)}{2}$$

holds. Applying the mean value theorem to the function $y^{\bar{\phi}}$ yields the existence of $\rho \in [s, \bar{s}]$ such that

$$|y^{\bar{\phi}}(\bar{s}) - y^{\bar{\phi}}(s)| = |(y^{\bar{\phi}})'(\rho)(\bar{s} - s)| \geq \frac{\delta(1+\eta)}{2}\, |\bar{s} - s|$$

or, by (4.41),

$$\begin{aligned} |\bar{s} - s| &\leq \frac{2}{\delta(1+\eta)} |y^{\bar{\phi}}(\bar{s}) - y^{\bar{\phi}}(s)| = \frac{2}{\delta(1+\eta)} |y^{\phi}(s) - y^{\bar{\phi}}(s)|, \\ &\leq \frac{2C_7}{\delta(1+\eta)} ||\phi - \bar{\phi}||. \end{aligned} \tag{4.43}$$

Our ultimate goal is to derive an estimate of $|y_{\bar{s}}^{\bar{\phi}}(\theta) - y_s^{\phi}(\theta)|$ where $\theta \in [-\tau, 0]$. Indeed, we have

$$|y_{\bar{s}}^{\bar{\phi}}(\theta) - y_s^{\phi}(\theta)| \leq |y_{\bar{s}}^{\bar{\phi}}(\theta) - y_s^{\bar{\phi}}(\theta)| + |y_s^{\bar{\phi}}(\theta) - y_s^{\phi}(\theta)|. \tag{4.44}$$

The first term of the right-hand side is bounded by

$$\int_{s+\theta}^{\bar{s}+\theta} \frac{dy^{\bar{\phi}}(t)}{dt} dt \leq M_2 \, |\bar{s} - s| \, ,$$

where M_2 is the maximum value of the derivative of the function $y^{\bar{\phi}}$; c.f. Remark 4.3. The second term of (4.44) is bounded by $C_7 ||\phi - \bar{\phi}||$. Thus from (4.44), we have

$$|y_{\bar{s}}^{\bar{\phi}}(\theta) - y_s^{\phi}(\theta)| \leq C_7 \left(1 + \frac{2M_2}{\delta(1+\eta)}\right) ||\phi - \bar{\phi}||. \tag{4.45}$$

Using (4.21), we conclude from (4.29), (4.31), (4.33), (4.36), (4.38), (4.40), and (4.42) that

$$\lim_{\varepsilon \to 0} L_R^{\varepsilon} = \lim_{\varepsilon \to 0} C_7 \left(1 + \frac{2M_2}{\delta(1+\eta)}\right) = 0 < 1.$$

Therefore we conclude that there exists $\varepsilon_2 < \min\{\varepsilon_1, \sigma_6, \sigma_7, \sigma_8, \sigma_9, \sigma_{10}\}$ so that for each $\varepsilon \in (0, \varepsilon_2)$, the Lipschitz constant L_R^{ε} of the map R is less than 1. This completes our proof. ∎

For $L_R^{\varepsilon} < 1$, the return map R is contractive and there exists a unique fixed point ϕ in A_η. Thus we have demonstrated the existence of a unique slowly oscillating periodic solution for (4.1). The stability and exponential attractivity of this unique periodic orbit can be established using the standard techniques developed in [31, 32, 33, 34, 36].

5. Asymptotic expansions for the periodic solution. In the previous section we used fixed point theory to prove that there exists a unique periodic orbit for (4.1). We now carry out a quantitative analysis of this periodic solution as $\varepsilon < \varepsilon_2$.

Since the map R is contractive and the Lipschitz constant L_R^ε is exponentially decaying as $\varepsilon \to 0$, we are able to give an asymptotic expansion for this particular solution for $t \in [-\tau, 0]$ with error bound beyond all integer orders of ε.

If we take the initial function given by $\phi = 1+\eta$, then we have a solution $y^{1+\eta}(\cdot)$ which is not periodic. But by Lemma 4.2, we have $y^{1+\eta}(t) = x(t) + O(-\varepsilon \log \varepsilon)$ for $t \in [0, T_x]$, and a $T_{1+\eta} > 0$ such that

$$y^{1+\eta}_{T_{1+\eta}}(0) = 1+\eta, \quad y^{1+\eta}_{T_{1+\eta}}(\theta) > 1+\eta, \qquad \theta \in [-\tau, 0).$$

It is obvious that $y^{1+\eta}_{T_{1+\eta}}(\theta) \in A_\eta$.

Assume that y is the periodic solution to (4.1) and satisfies $y(\theta) \in A_\eta$ for $\theta \in [-\tau, 0]$. Suppose also that $y(\theta)$ has the following asymptotic expansion:

$$y(\theta) = \sum_{i=0}^{\infty} \phi_i(\theta),\ \theta \in [-\tau, 0]. \tag{5.1}$$

The function ϕ_0 is given by $y^{1+\eta}_{T_{1+\eta}}$, and $\phi_i, i \geq 1$, with the norm $||\phi|| = \max_{-\tau \le \theta \le 0} |\phi(\theta)|$, will be constructed below. Let $y^{\phi_0}_{T_0}$ denote the image of the return map R at ϕ_0, i.e.,

$$y^{\phi_0}_{T_0}(\theta) = R(\phi_0) = F_\varepsilon(T_0, \phi_0),\ \theta \in [-\tau, 0],$$

where $T_0 > 0$ satisfies

$$y^{\phi_0}_{T_0}(0) = 1+\eta,\ y^{\phi_0}_{T_0}(\theta) > 1+\eta,\ \theta \in [-\tau, 0).$$

Similarly, by induction, we set

$$\phi_1 = R(\phi_0) - \phi_0 = y^{\phi_0}_{T_0} - \phi_0,$$

$$y^{\phi_1}_{T_1}(\theta) = R(\phi_1) = F_\varepsilon(T_1, \phi_1),$$

$$\phi_n(\theta) = R^n(\phi_0) - R^{n-1}(\phi_0) \text{ for } n \geq 2,$$

$$y^{\phi_n}_{T_n}(\theta) = R(\phi_n) = F_\varepsilon(T_n, \phi_n) \text{ for } n \geq 2,$$

where T_n satisfies

$$y^{\phi_n}_{T_n}(0) = 1+\eta,\ y^{\phi_n}_{T_n}(\theta) > 1+\eta,\ \theta \in [-\tau, 0),\ n \geq 1.$$

Thus we have

$$\begin{aligned} |\phi_n(\theta) - \phi_{n-1}(\theta)| &\leq L_R^\varepsilon |\phi_{n-1}(\theta) - \phi_{n-2}(\theta)| \\ &\leq (L_R^\varepsilon)^{n-1} |\phi_1(\theta) - \phi_0(\theta)|. \end{aligned}$$

Therefore, $y(\theta) = \sum_{i=0}^{\infty} \phi_i(\theta)$ is uniformly convergent for $\theta \in [-\tau, 0]$ and it is the fixed point of R.

We now give an asymptotic expansion for the period of the periodic solution y. Using (4.43), we have

$$|T_i - T_{i-1}| \le \frac{2C_7}{\delta(1+\eta)} ||\phi_i - \phi_{i-1}||,$$

which means that the series

$$T_0 + \sum_{j=1}^{\infty} (T_j - T_{j-1})$$

is absolutely convergent to some constant, say, T_ε. Since L_R is exponentially decaying as $\varepsilon \to 0$, it is easy to see that the value of T_ε is dominated by T_0 in the sense that $T_\varepsilon - T_0$ is exponentially small as $\varepsilon \to 0$. Likewise the value of $y(\theta)$ in (5.1) is dominated by ϕ_0 with an exponential error bound as $\varepsilon \to 0$. Thus when $t \in [0, T_0]$, we know that the periodic solution $y(t)$ is also dominated by $y^{\phi_0}(t)$. Therefore the estimate of $y^{\phi_0}(t)$ and T_0 becomes significant. From Lemma 4.2 we have the following rough result for $y^{\phi_0}(t)$ and T_0:

$$y^{\phi_0}(t) = x(t) + O(-\varepsilon \log \varepsilon),\ T_0 = T_x + O(-\varepsilon \log \varepsilon).$$

We now give refined estimates for $y^{\phi_0}(t)$ and T_0 using the above information. As in the proof of Lemma 4.2, we split the interval $[0, T_0]$ into subintervals and estimate $y^{\phi_0}(t)$ on each subinterval successively. We demonstrate this process on the first subinterval for the purpose of illustration. Remember that the initial data are taken to be ϕ_0 which is greater than $1+\eta$ when t lies in the interval $[-\tau, 0)$. Let $t_1^{\phi_0}, \eta_1$, and η_2 be the values as defined in the proof of Lemma 4.2. Thus $t_1^{\phi_0}$ satisfy $y^{\phi_0}(t_1^{\phi_0}) = 1$. Integrating (4.1) from 0 to t, $t \in [0, t_1^{\phi_0}]$, gives

$$\begin{aligned} y^{\phi_0}(t) - y^{\phi_0}(0) = &-\delta \int_0^t y^{\phi_0}(s)ds - \int_0^t \beta_\varepsilon(y^{\phi_0}(s)) y^{\phi_0}(s)ds \\ &+ k \int_0^t \beta_\varepsilon(y^{\phi_0}(s-\tau)) y^{\phi_0}(s-\tau)ds. \end{aligned} \tag{5.2}$$

Since $t_1^{\phi_0} = t_1 + O(-\varepsilon \log \varepsilon)$ and $t_1 < \tau$, it is easy to see that the last term of the right-hand side of (5.2) is small and of $O(\varepsilon)$. Next we claim that

$$\int_0^t \beta_\varepsilon(y^{\phi_0}(s)) y^{\phi_0}(s)ds = O(\varepsilon), \quad t \in [0, t_1^{\phi_0}]. \tag{5.3}$$

Indeed when $t \in [0, t_1^{\phi_0}]$, we have $k\beta y^{\phi_0}(t-\tau) y^{\phi_0}(t-\tau) = O(\varepsilon)$. Then from (4.1) we have

$$-\alpha(1+\eta) \le \frac{dy^{\phi_0}(t)}{dt} = -[\beta_\varepsilon(y^{\phi_0}(t)) + \delta] y^{\phi_0}(t) + O(\varepsilon) \le -\delta + O(\varepsilon). \tag{5.4}$$

Thus from (5.4) and the fact that

$$\begin{aligned} \left| \int_0^t \beta_\varepsilon(y^{\phi_0}(s)) y^{\phi_0}(s) \frac{dy^{\phi_0}}{ds} ds \right| &\le \left| \int_0^{t_1^{\phi_0}} \beta_\varepsilon(y^{\phi_0}(s)) y^{\phi_0}(s) \frac{dy^{\phi_0}}{ds} ds \right| \\ &= \left| \int_{1+\eta}^1 \frac{\beta_0 u}{1+u^{1/\varepsilon}} du \right| \\ &= O(\varepsilon), \end{aligned}$$

we know that $\int_0^t \beta_\varepsilon(y^{\phi_0}(s))y^{\phi_0}(s)ds$ is also of $O(\varepsilon)$ and the claim (5.3) is true. It follows then from (5.2) that for $t \in [0, t_1^{\phi_0}]$,

$$y^{\phi_0}(t) \; = -\delta \int_0^t y^{\phi_0}(t)dt + 1 + \eta + O(\varepsilon).$$

Using Gronwall's inequality, we obtain

$$y^{\phi_0}(t) = (1 + \eta + O(\varepsilon))e^{-\delta t},$$

which implies

$$y^{\phi_0}(t) = x(t) + O(\varepsilon),\, t \in [0, t_1^{\phi_0}]. \tag{5.5}$$

Continuing the above process, we can prove that (5.5) holds in the entire interval $[0, T_0]$. Furthermore, we also have

$$T_0 = T_x + O\left(\varepsilon\right),$$

which completes our refined estimate.

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