PERIODIC OSCILLATIONS OF BLOOD CELL POPULATIONS IN CHRONIC MYELOGENOUS LEUKEMIA

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Abstract. We develop some techniques to prove analytically the existence and stability of long period oscillations of stem cell populations in the case of periodic chronic myelogenous leukemia. Such a periodic oscillation p_∞ can be analytically constructed when the hill coefficient involved in the nonlinear feedback is infinite, and we show it is possible to obtain a contractive returning map (for the semiflow defined by the modeling functional differential equation) in a closed and convex cone containing p_∞ when the hill coefficient is large, and the fixed point of such a contractive map gives the long period oscillation previously observed both numerically and experimentally.

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

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

1. Introduction. "How do 'short' cell cycles give rise to 'long' period oscillations?" This question has arisen from the observation of blood cell population oscillations in the case of periodic myelogenous leukemia (PCML) [7], a blood disease to be discussed in some details below. Indeed, it has long been observed in the bone marrow that there is an enormous difference between the relatively short cell cycle duration which ranges between 1 to 4 days [12], [17] , [18] and the long period oscillations in PCML (between 40 to 80 days) [7]. The link between these relatively short cycle durations and the long periods of peripheral cell oscillations is unclear, to the best of our knowledge, has neither been biologically explained nor understood. An attempt to answer this question has been made by Pujo-Menjouet and Mackey in [23] and Pujo-Menjouet et al. in [22], where they investigated the role of each parameter of the mathematical model involved in the cell cycle and the influence of each parameter on the long period and the amplitude of the peripheral cell oscillations. They showed qualitatively that the cell cycle regulation parameters have major influence on the oscillation amplitude while the oscillation period is correlated with the cell death and differentiation parameters, and they obtained these results in the particular case where the hill coefficient involved in the model formulation is infinite. Our objective here is to prove analytically that the similar conclusions and results remain true in the more biologically realistic case where the hill coefficient is finite.

More specifically, from the previous studies, it is known that the evolution of

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the cells in resting phase involves the Hill function in both the term representing the instantaneous loss of proliferating cells to cell division and to differentiation and the term representing the delayed production of proliferating stem cells. A key parameter in the Hill function is the integer n which is usually large, and this Hill function reduces to the Heaviside step function when $n = \infty$. As will be shown, the underlying system with $n = \infty$ becomes a piecewise linear scalar delay differential equation that, after non-trivial but straightforward calculations, has a periodic solution of large periods and amplitudes with very strong stability and attractivity properties. The main purpose of this paper is to construct a convex closed cone containing the aforementioned periodic solution (when $n = \infty$) and a contractive returning map defined on this cone such that a fixed point of such a returning map gives a stable periodic solution of the model equation for the cells in resting phase when n is large. This method was first developed in Walther [29], [30] 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 [31],[32] and to delay differential systems [32], [34]. This method was further enhanced recently in [21] by incorporating some ideas from classical asymptotic analysis and matching method. Applications of this method to the model for cells in the resting phase seem to be highly non-trivial since both the instantaneous loss of proliferating cells and the delayed production of proliferating stem cells involve the nonlinearity and there is no analytic formula for the periodic solution in the limiting case ($n = \infty$).

We should emphasize that periodic hematological diseases have attracted a significant amount of modelling attention in various domain such as periodic auto-immune hemolytic anemia [2], [16] and cyclical thrombocytopenia [25], [27]. It has been observed that the periodic hematological diseases of this type involve periodicity between two and four times the bone marrow production delay. This observation has a clear explanation within a modelling context. Some other hematological diseases such like cyclical neutropenia ([3], [9], [10], [14], [15], [17]) and chronic myelogenous leukemia [7] involve more than one blood cell type (*i.e.* white cells, red blood cells and platelets). It is believed that the oscillations in these diseases originate in the pluripotential stem cell compartment and have very long period durations (of order of weeks to months) in general. In the particular case of the periodic chronic myelogenous leukemia, the period can range from 40 to 80 days and two lines of evidence appear to prove that the oscillations are due to a destabilization of the stem cell population based in the bone marrow. The first evidence is due to the gene mutation in the Philadelphia chromosome and responsible for the disease . The mutated cells have been observed in all the blood cell lineages [4], [6], [8], [11], [28]. The second line of evidence is given in [7] where the authors collected clinical data from the literature, and proved that white blood cells, erythrocytes and platelets oscillate with the same period.

Periodic chronic myelogenous leukemia (or PCML) takes its name from the clinical character and the type of leukemia it describes. Leukemia is a malignant disease characterized by uncontrolled proliferation of immature and abnormal white blood cells in the bone marrow, the blood, the spleen and the liver. Its character can be chronic (in the early stage of myelogenous leukemia) or acute (in the late stage). The type of cells involved are myeloid, lymphoid or monocytic depending on the damaged branch of blood cell production. The stem cell model by Pujo-Menjouet and Mackey in [23] and Pujo-Menjouet et al. in [22] (also called G_0 model due to the consideration of the G_0 resting phase in the cell cycle) is developed in order to describe the mechanism of the disease under consideration [5], [19], [26].

The remaining part of this paper is organized as follows. In Section 2 we present the model in detail. In Section 3 we recall some previous results from Pujo-Menjouet et al. in [22] in the case where the Hill coefficient n is infinite. Then, we introduce a more general result on 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, whose early features are due to Lajtha [13] and Burns and Tannock [5], is derived from an age structured coupled system of two partial differential equations, coupled with some boundary and initial conditions [24], [14], [15], and [20]. Using the method of integration along characteristics [33] these equations can be transformed into a pair of non-linear first-order differential delay equations [14], [15], [17]. The model consists of a proliferating phase where the cell population is denoted by $P(t)$ at time t, and a G_0 resting phase, with a population of cell $N(t)$. In the proliferating phase, cells are committed to undergo cell division a constant time τ after their entry. Note that the choice of τ as a constant is to simplify the problem, though some models with a non constant value of τ exist [1], [3]. The loss rate γ in the proliferating phase is due to apoptosis (programmed cell death). At the point of cytokinesis (cell division), a cell divides into two daughter cells which enter the resting phase. In this phase, cells can not divide but they have the choice of between three different fates. They may have one of three possible fates: differentiate at a constant rate δ, reenter the proliferating phase at a rate β, or simply remain in G_0. Note that the reentering rate β will be a nonlinear term in our equation and the focus of our study (see Figure (2.1) for an schematic illustration of the cell cycle).

The model, described by a coupled non-linear first order delay equations, takes the following 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 to proliferative phase feedback rate β is taken to be a Hill function of the form

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

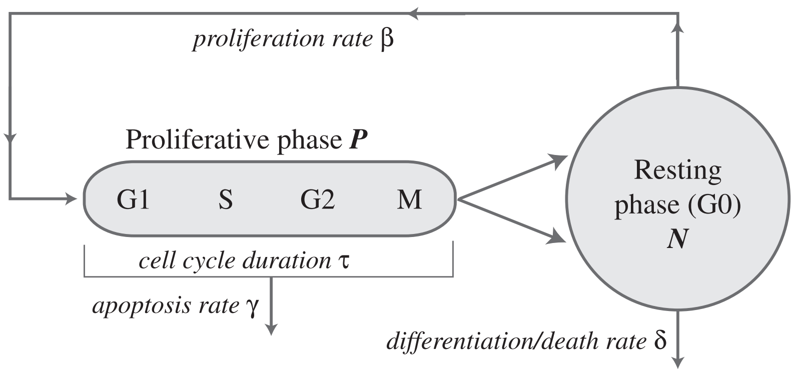

FIG. 2.1. *A schematic representation of the G_0 stem cell model. Proliferating phase cells (P) include those cells in G_1, S (DNA synthesis), G_2, and M (mitosis) while the resting phase (N) cells are in the G_0 phase. δ is the rate of differentiation into all the committed stem cell populations, and γ represents a loss of proliferating phase cells due to apoptosis. β is the rate of cell reentry from G_0 into the proliferative phase, and τ is the duration of the proliferative phase. See [14], [15], [17] for further details.*

In equation (2.2), the first term represents the loss of proliferating cells to cell division ($\beta(N)N$) and to differentiation (δN). The second term represents the production of proliferating stem cells, with the factor 2 accounting for the amplifying effect of cell division while $e^{-\gamma\tau}$ accounts for the attenuation due to apoptosis. Note that, we only need to understand the dynamics of the G_0 phase resting population (governed by equation (2.2)) since the proliferating phase dynamics (governed by equation (2.1)) are driven by the dynamics of the resting cells.

By introducing the dimensionless variable $x = N/\theta$, we can rewrite equation (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 state x_* of equation (2.3) are given by the solution of $dx/dt \equiv 0$. Then we have $x_* \equiv 0$, or

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

Here we require

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

so that $\beta_0 \dfrac{k-1}{\delta} > 1$ in (2.5).

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 Equation (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 equation (2.3) subject to the initial condition φ.

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

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

As in the paper by Pujo-Menjouet et al. [22], we introduce two constants by

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

Inserting the above step function $\beta(x)$ into equation (2.3), we have

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

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

For the equation (3.1), we choose the initial function $\varphi(t) \ge 1 + \eta$ for $t \in [-\tau, 0)$ and $\varphi(0) = 1 + \eta$ where η is a small positive constant chosen later. We should remark that if we choose $\varphi(t) \le 1 + \eta$ for $t \in [-\tau, 0)$, the results and the techniques to be obtained and developed are similar. By the continuity of the solution x, we have from equation (3.1) the existence of a 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 can 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 $[t_1, t_1 + \tau]$, the dynamics are given by

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

The solution is then given by $x(t) = e^{-\alpha(t - t_1)}$ for $t \in [t_1, t_1 + \tau]$ and satisfies $x(t_1 + \tau) = e^{-\alpha\tau}$ which is independent of the initial function $\varphi(t)$. In other words, the solution destroys all memory of the initial data.

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

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

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 periodic solution. In particular, if

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

then the solution may stay below the line of $x = 1$ so long that the analysis becomes very complicated. This is also undesirable biologically since the period will be extremely long. Note that for $t \in [t_1 + \tau, t_1 + 2\tau]$, $x(t-\tau) = e^{-\alpha(t-t_1-\tau)}$. Then, from (3.1), we have $\dfrac{dx}{dt} = -\alpha x + \Gamma x_\tau = -\alpha x + \Gamma e^{-\alpha\tau(t-t_1-\tau)}$ 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:

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

so that (3.5) holds when $x \leq 1$ (due to $x(t-\tau) \geq e^{-\alpha\tau}$), and also $x(t_1 + 2\tau) = e^{-\alpha\tau}(e^{-\alpha\tau} + \Gamma\tau) > 1$ by (3.6). [1]

Since $x(t)$ is increasing in $t \in [t_1 + \tau, t_1 + 2\tau]$, there exists a unique point $t_2 \in (t_1 + \tau, t_1 + 2\tau)$ so that $x(t_2) = 1$. Assume $t_2 = t_1 + \tau + u$, $u \in (0, \tau)$. Then from (3.6) we have

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

The above equation (3.8) is a transcendental equation and cannot be solved explicitly. But we can expand $e^{\alpha u}$ by Taylor's series, that is $1 + \alpha u + \dfrac{(\alpha u)^2}{2}$ and solve u by the approximated equation

$$1 + \alpha u + \frac{\alpha^2}{2}u^2 \approx e^{-\alpha\tau} + \Gamma u.$$

Next for $t \in [t_2, t_1 + 2\tau]$, the dynamics are

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

which gives

$$x(t) = e^{-\delta\tau(t-t_2)}\{1 - \frac{\Gamma}{\beta_0}e^{\alpha(t_1+\tau)-\delta t_2}\left(e^{-\beta_0 t} - e^{-\beta_0 t_2}\right)\}. \tag{3.9}$$

[1] Note that this condition allows us to get the shortest period length for the solution. In order to get longer periods, we should assume other conditions on Γ such that $x(t_1 + 2\tau) < 1$, thus the slope of the increasing part of the solution would be less steep.

Finally for $t \in [t_1 + 2\tau, t_2 + \tau]$,

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

that is

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

where

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

We now claim that

$$x(t) > 1, \; t \in (t_2, t_2 + \tau]. \tag{3.10}$$

Indeed, at the point t_2, $x(t_2) = 1$, $x(t_2 - \tau) \geq e^{-\alpha\tau}$. By (3.7) we have

$$x'(t_2) > -\delta x + \Gamma x_\tau > 0.$$

Suppose, y way of contradiction, that there exists a point $h \in (t_2, t_2 + \tau)$ such that $x(h) = 1$, $x'(h) \leq 0$ and $x(t) > 1$ for $t \in (t_2, h)$. Then using equation (3.1) we have by (3.7)

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

This is a contradiction and our claim is true.

After the time $t_2 + \tau$, both x_1 and x are greater than 1, and the solution satisfies

$$x' = -\delta x(t) \tag{3.11}$$

and hence is decreasing. Therefore, there exists a point, say $t = d$ so that $x(d) = 1$. Now we can use (3.10) and (3.11) to choose a small positive constant η such that at some point $T_x < d$

$$x(T_x) = 1 + \eta, \; x(T_x + s) > 1 + \eta, \; s \in [-\tau, 0). \tag{3.12}$$

Actually, this T_x is exactly the period of the solution $x(t)$. Summarizing the above analysis, we have the following result:

THEOREM 3.1. *Assume that x is the solution of (3.1) subject to the initial condition $\phi \geq 1 + \eta$ where η is a small positive constant defined in (3.12). Suppose that Γ satisfies (3.7). Then x is a periodic solution.*

4. Periodic solutions: general nonlinearity.

4.1. Perturbed delay equation. With the detailed analysis of the G_0 model when the Hill function reduces to the Heaviside step function, we can now consider the general nonlinearity from the viewpoint of regular perturbation. More precisely, we consider the perturbed problem

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

i.e., we return to the original problem with $\beta = \beta_0 \frac{1}{1+y^n}$. Denote by $\varepsilon = 1/n$, we can rewrite the Hill function as

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

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

LEMMA 4.1. *Assume that ε is sufficiently small. We have*

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

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

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

$$\beta_0 > \beta(y) > \beta_0(1-\varepsilon)\ , \ \text{ and } \ |y\beta(y) - \beta_0 y| < \beta_0\epsilon. \tag{4.2}$$

(b)Moreover,

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

and

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

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

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

and

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

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

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

and

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

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

$$\left|(y\beta(y))'\right| = \beta_0 \frac{\left|(\frac{1}{\varepsilon}-1)y^{1/\varepsilon}-1\right|}{(1+y^{1/\varepsilon})^2} \le \beta_0(\frac{1}{\varepsilon}-1)y^{-1/\varepsilon} < \beta_0\varepsilon.$$

Since the function

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

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

$$\left|(y\beta(y) - \beta_0 y)'\right| = \beta_0 \frac{(1+\frac{1}{\varepsilon})y^{1/\varepsilon} + \frac{1}{\varepsilon}y^{2/\varepsilon}}{1+y^{1/\varepsilon}} < \beta_0\varepsilon,$$

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

Returning to equation (4.1), we let the initial function $\varphi(t)$ be chosen in the following closed convex sets

$$A(\eta) = \{\varphi(t) \in C([0,1]) : 1+\eta \le \varphi(t) \text{ and } \varphi(0) = 1+\eta\},$$

where η is a small positive constant defined in the previous section. For given $\varphi(t)$ in $A(\eta)$, we can have a unique solution to equation (4.1). The relations

$$F_\beta(t,\varphi) = y_t,\ y_t = y(t+s),\ -\tau \le s \le 0,\ t \ge 0$$

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

We find that for the simpler equation (3.1), if $\varphi(t) \in A(\eta)$, then the solution will return to $A(\eta)$ after finite time. We like to know whether or not this situation still happens for equation (4.1). The study of this point becomes necessary and also important in order to build a returning map. Fortunately, we have

LEMMA 4.2. *Let $y(t)$ be the solution of equation (4.1) with any initial function $\varphi \in A(\eta)$. Then*

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

for $t \in [0, T_x]$ where T_x is the period of periodic solution $x(t)$, defined in Theorem 3.1, to equation (3.1).

Proof From (4.1) we know that the solution $y(t)$ is decreasing in t in the right neighborhood of the starting point $t=0$. We can further claim that there exist three points η_1, t_1^y, η_2, $\eta_1 < t_1^y < \eta_2$, so that

$$y(\eta_1) = \left(\frac{1}{\varepsilon}\right)^{2\varepsilon}, \;\; y(t_1^y) = 1, \; y(\eta_2) = \left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon}, \tag{4.3}$$

and in the interval $(0, \eta_2)$, the solution $y(t)$ is decreasing. Indeed, if $y(t) > \left(\frac{1}{\varepsilon}\right)^{2\varepsilon} > \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)}$, and $y(t-\tau) > \left(\frac{1}{\varepsilon}\right)^{2\varepsilon} > \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)}$, then by Lemma 4.1 we have

$$\beta(y)y < \beta_0\varepsilon, \;\; \beta(y_\tau)y_\tau < \beta_0\varepsilon$$

and it follows from equation (4.1) that

$$\begin{aligned} \frac{dy}{dt} &= -(\delta + \beta(y))y + k\beta(y_\tau)y_\tau, \\ &< -\frac{\delta}{2} \;\text{ as } \varepsilon \to 0, \end{aligned} \tag{4.4}$$

which means that $y(t)$ is decreasing and there exists a point η_1 such that $y(\eta_1) = (1/\varepsilon)^{2\varepsilon}$ and $1+\eta > y(t) > (1/\varepsilon)^{2\varepsilon}$, for $t \in (0, \eta_1)$. Similarly at the right neighborhood of η_1, say $(\eta_1, \eta_1 + \tau/2)$,we have $\beta(y_\tau)y_\tau = O(\varepsilon)$ and (4.4) still holds. This means the solution is still decreasing in t and there exist two points t_1^y, η_2, $\eta_1 < t_1^y < \eta_2$ so 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 know that

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

or equivalently

$$\eta_2 - \eta_1 \leq \frac{2}{\delta}(y(\eta_1) - y(\eta_2)) = O(-\varepsilon\log\varepsilon).$$

Therefore,

$$t_1^y - \eta_1 < \eta_2 - \eta_1 = O(-\varepsilon\log\varepsilon). \tag{4.5}$$

Now using again the equations (4.1) and (3.1) for $t \in [0, \eta_1]$, we have from Lemma 4.1

$$(x-y)' = -\delta(x-y) + O(\varepsilon),$$

which implies that

$$|x(t) - y(t)| = O(\varepsilon)$$

for $t \in [0, \eta_1]$. In particular at the point $t = \eta_1$,

$$x(\eta_1) = y(\eta_1) + O(\varepsilon) = \left(\frac{1}{\varepsilon}\right)^{\varepsilon/(1-\varepsilon)} + O(\varepsilon) = 1 + O(-\varepsilon \log \varepsilon).$$

It follows from (3.2) and (3.4) that t_1, defined in (3.3) satisfies

$$t_1 = \eta_1 + O(-\varepsilon \log \varepsilon),$$

and

$$t_1 = t_1^y + O(-\varepsilon \log \varepsilon).$$

For $t \in [\eta_1, \eta_2]$, since both the derivative of $x(t)$ and $y(t)$ are of the order of $O(1)$ and the length of the interval $[\eta_1, \eta_2]$ is of the order of $O(-\varepsilon \log \varepsilon)$, we can conclude that

$$y(t) = x(t) + O(-\varepsilon \log \varepsilon). \tag{4.6}$$

For $t \in [\eta_2, \tau + \eta_1]$, $y(t - \tau) > (1/\varepsilon)^{2\varepsilon}$. By Lemma 4.1, we still have

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

By equation (4.1) we know that the solution $y(t)$ will still be decreasing for $t \in [\eta_2, \tau + \eta_1]$. Note that $0 < y(t) < y(\eta_2) = \varepsilon^\varepsilon$, so that (4.2) in Lemma 4.1 holds. Thus we can derive from (4.1) that

$$y'(t) = -\alpha y(t) + O(\varepsilon), \tag{4.7}$$

for $t \in [\eta_2, \tau + \eta_1]$. Coupling this equation with (3.4) and using (4.6) at the point $t = \eta_2$ gives

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

for $t \in [\eta_2, \tau + \eta_1]$.

For $t \in [\tau + \eta_1, \tau + \eta_2]$, using again the fact that both the derivatives of $x(t)$ and $y(t)$ are bounded by $O(1)$ and the length of this interval is of order $O(-\varepsilon \log \varepsilon)$, we have

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

For $t \geq 1 + \eta_2$, the solution $y(t)$ begins to increase since Γ satisfies (3.7). By the similar argument used above, it follows that there exist three point $\eta_3, t_2^y, \eta_4, \eta_3 < t_2^y < \eta_4$ such that

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

and

$$\eta_3 = t_2^y + O(\varepsilon \log \varepsilon), \quad \eta_4 = t_2^y + O(\varepsilon \log \varepsilon), \tag{4.8}$$

and

$$t_2^y = t_2 + O(\varepsilon \log \varepsilon). \tag{4.9}$$

We can continue the process above and it is not difficult to find that $y(t)$ will satisfy

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

for $t \in [0, \eta_4]$.

By (3.7) and (4.1) we find that the solution $y(t)$ is increasing at the point $t = \eta_4$ and in the interval $[\eta_4, \tau + \eta_3]$, $y(t)$ and $x(t)$ satisfy

$$(x - y)' = -\delta(x - y) + O(\varepsilon),$$

and

$$(x - y)|_{\eta_4} = O(\varepsilon \log \varepsilon).$$

So we have

$$x - y = O(\varepsilon \log \varepsilon), \text{ for } t \in [\eta_4, \tau + \eta_3].$$

For $t \in [\tau + \eta_3, \tau + \eta_4]$, using the same argument as in the interval $[\tau + \eta_1, \tau + \eta_2]$, we have

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

Finally for $t \geq \tau + \eta_4$, the solution is decreasing and attains the value $1 + \eta$ at some point T_y. To be more specific, we have

$$y(t)' = -\delta y(t) + O(\varepsilon), \tag{4.11}$$

and

$$x(t) = -\delta x(t). \tag{4.12}$$

Using (4.10), (4.11) and (4.12) we can derive that

$$y(t) = x(t) + O(\varepsilon \log \varepsilon), \tag{4.13}$$

and

$$T_y = T_x + O(\varepsilon \log \varepsilon). \tag{4.14}$$

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

$$y(t) \geq 1 + \eta \text{ for } [T_y - \tau, T_y] \tag{4.15}$$

provided that ε is sufficiently small.□

REMARK 4.3. *By Lemma 4.2 and equation (4.1) we can have two positive constants M_1 and M_2 which are independent of ε, so that*

$$|y(t)| \leq M_1, \tag{4.16}$$

and

$$\left|\frac{dy}{dt}\right| \leq M_2. \tag{4.17}$$

Now we are ready to define a continuous returning map

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

where $q(\varphi) = T_y$. In order to verify that there exists a unique fixed point in $A(\eta)$ for this map R, we need to derive its Lipschitz constant estimation and show this map R is contractive, i.e., its Lipschitz constant is less than 1.

4.2. Lipschitz constant for the map R. Lipschitz constants of maps $T : D_T \to Y$, $D_T \subset X$, X and Y normed linear space, are given by

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

In the case when $D_T = X = \mathbf{R}$ and $\sigma = [x_1, x_2] \in \mathbf{R}$, and $f = T$ we set

$$L_{[x_1,x_2]}(f) = L(f|[x_1, x_2]).$$

In the case when $f = y\beta(y)$, we define the following four Lipschitz constants

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

Similarly for the function $f = y\beta(y) - \beta_0 y$, we also define the following Lipschitz constant for later use,

$$L_5 = L_{\left(0,\left(\frac{\varepsilon^2}{1+\varepsilon}\right)^{\varepsilon}\right)}(y\beta(y) - \beta_0 y).$$

THEOREM 4.4. *When ε is small, the Lipschitz constant for the map R satisfies*

$$\lim_{\varepsilon\to 0} L_R = 0 < 1$$

Proof Step 1. For $\phi, \bar{\phi}$ in $A(\eta)$. By a similar manner 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, respectively,

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

and

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

Let

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

and

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

Then by (4.5) we have

$$\eta_{\max} - \eta_{\min} = O(\varepsilon \log \varepsilon). \tag{4.18}$$

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

$$\frac{dy^{\phi}(t)}{dt} = -[\delta + \beta(y^{\phi}(t))]y^{\phi}(t) + k\beta(y^{\phi}(t-\tau))y^{\phi}(t-\tau), \tag{4.19}$$

and

$$\frac{dy^{\bar{\phi}}(t)}{dt} = -[\delta + \beta(y^{\bar{\phi}}(t))]y^{\bar{\phi}}(t) + k\beta(y^{\bar{\phi}}(t-\tau))y^{\bar{\phi}}(t-\tau). \tag{4.20}$$

Now we begin to estimate the difference between $y^{\phi}(t)$ and $y^{\bar{\phi}}(t)$. Coupling with (4.19) and (4.20) yields

$$\begin{aligned}(y^{\phi} - y^{\bar{\phi}})' = &-\delta(y^{\phi} - y^{\bar{\phi}}) \\ &-[\beta(y^{\phi})y^{\phi} - \beta(y^{\bar{\phi}})y^{\bar{\phi}}] \\ &+k[\beta(y^{\phi}_{\tau})y^{\phi}_{\tau} - \beta(y^{\bar{\phi}}_{\tau})y^{\bar{\phi}}_{\tau}].\end{aligned} \tag{4.21}$$

Substituting the following inequalities

$$|\beta(y^{\phi})y^{\phi} - \beta(y^{\bar{\phi}})y^{\bar{\phi}}| \le L_2|y^{\phi} - y^{\bar{\phi}}|,$$

and

$$|\beta(y^{\phi}_{\tau})y^{\phi}_{\tau} - \beta(y^{\bar{\phi}}_{\tau})y^{\bar{\phi}}_{\tau}| \le L_1||\phi - \bar{\phi}||$$

into (4.21), we have

$$(y^{\phi} - y^{\bar{\phi}})' \le (\delta + L_2)\,|y^{\phi} - y^{\bar{\phi}}| + kL_1||\phi - \bar{\phi}||. \tag{4.22}$$

Integrating (4.22) from 0 to t, gives

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

Similarly we have

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

Thus,

$$|y^{\phi} - y^{\bar{\phi}}| \leq \int_0^t \Big((\delta + L_2)\, |y^{\phi} - y^{\bar{\phi}}| + kL_1 ||\phi - \bar{\phi}|| \Big)\, ds. \tag{4.23}$$

Solving (4.23) (or by Gronwall inequality), we obtain

$$|y^{\phi} - y^{\bar{\phi}}| \leq C_1 ||\phi - \bar{\phi}||, \tag{4.24}$$

where

$$C_1 = \frac{e^{(\delta + L_2)\eta_{\min}} - 1}{\delta + L_2} kL_1. \tag{4.25}$$

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

$$|\beta(y^{\phi})y^{\phi} - \beta(y^{\bar{\phi}})y^{\bar{\phi}}| \leq L_3 |y^{\phi} - y^{\bar{\phi}}|,$$

and

$$|\beta(y^{\phi}_{\tau})y^{\phi}_{\tau} - \beta(y^{\bar{\phi}}_{\tau})y^{\bar{\phi}}_{\tau}| \leq L_1 ||\phi - \bar{\phi}||.$$

Thus from (4.19) and (4.20) we can obtain as before

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

Then by Gronwall inequality we have

$$|y^{\phi} - y^{\bar{\phi}}| \leq C_2 ||\phi - \bar{\phi}|| \tag{4.26}$$

where

$$C_2 = C_1 e^{(\delta + L_3)(\eta_{\max} - \eta_{\min})} + \frac{e^{\delta + L_3(\eta_{\max} - \eta_{\min})} - 1}{\delta + L_3} kL_1 > C_1. \tag{4.27}$$

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

$$|\beta(y^{\phi})y^{\phi} - \beta_0 y^{\phi} - (\beta(y^{\bar{\phi}})y^{\bar{\phi}} - \beta_0 y^{\bar{\phi}})| \leq L_5 |y^{\phi} - y^{\bar{\phi}}|$$

and

$$|\beta(y^{\phi}_{\tau})y^{\phi}_{\tau} - \beta(y^{\bar{\phi}}_{\tau})y^{\bar{\phi}}_{\tau}| \leq L_2 ||\phi - \bar{\phi}||.$$

It is thus easy to have

$$|y^{\phi}-y^{\bar{\phi}}| \leq \int_{\eta_{\max}}^{t} \Big((\alpha+L_5)|y^{\phi}-y^{\bar{\phi}}| + kL_2C_1||\phi-\bar{\phi}||\Big)\, ds + C_2||\phi-\bar{\phi}||,$$

and to conclude that (due to $1+\eta_{\min}-\eta_{\max}<\tau$)

$$|y^{\phi}-y^{\bar{\phi}}| \leq C_3||\phi-\bar{\phi}||, \tag{4.28}$$

where

$$C_3 = C_2 e^{\alpha\tau+\tau L_5} + \frac{e^{\alpha\tau+\tau L_5}-1}{\alpha+L_5} kL_2C_1 > C_2. \tag{4.29}$$

Step 4. When $t \geq 1+\eta_{\min}$, We note that from the proof of Lemma 4.2, there exist $\eta_3<\eta_4$, and $\bar{\eta}_3<\bar{\eta}_4$ so that

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

and

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

Let

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

Then by (4.8) we have

$$\eta_{\max}^4 - \eta_{\min}^3 = O(\varepsilon\log\varepsilon). \tag{4.30}$$

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

$$|y^{\phi}-y^{\bar{\phi}}| \leq \int_{\tau+\eta_{\min}}^{t} \Big((\alpha+L_5)|y^{\phi}-y^{\bar{\phi}}| + kL_3C_3||\phi-\bar{\phi}||\Big)\, ds + C_3||\phi-\bar{\phi}||,$$

and

$$|y^{\phi}-y^{\bar{\phi}}| \leq C_4||\phi-\bar{\phi}||, \tag{4.31}$$

where

$$C_4 = C_3 e^{(\alpha+L_5)(\eta_{\min}^3-\tau-\eta_{\min})} + \frac{e^{(\alpha+L_5)(\eta_{\min}^3-\tau-\eta_{\min})}-1}{\alpha-L_5} kL_3C_3 > C_3. \tag{4.32}$$

Step 5. For $t \in [\eta_{\min}^3, \eta_{\max}^4]$,

$$|y^{\phi}-y^{\bar{\phi}}| \leq \int_{\eta_{\min}^3}^{t} \Big((\delta+L_3)|y^{\phi}-y^{\bar{\phi}}| + kL_4C_4||\phi-\bar{\phi}||\Big)\, ds + C_4||\phi-\bar{\phi}||.$$

Thus,

$$|y^{\phi} - y^{\bar{\phi}}| \le C_5 ||\phi - \bar{\phi}|| \tag{4.33}$$

where

$$C_5 = C_4 \left(e^{\delta + L_3(\eta^4_{\max} - \eta^3_{\min})} + \frac{e^{\delta + L_3(\eta^4_{\max} - \eta^3_{\min})} - 1}{\delta + L_3} k L_4 \right).. \tag{4.34}$$

Step 6. For $t \in [\eta^4_{\max}, \tau + \eta^4_{\max}]$, we have

$$|y^{\phi} - y^{\bar{\phi}}| \le \int_{\eta_{\max}}^{t} \Big((\delta + L_2)|y^{\phi} - y^{\bar{\phi}}| + k L_3 C_5 ||\phi - \bar{\phi}|| \Big) \, ds + C_5 ||\phi - \bar{\phi}||$$

and

$$|y^{\phi} - y^{\bar{\phi}}| \le C_6 ||\phi - \bar{\phi}||, \tag{4.35}$$

where

$$C_6 = C_5 (e^{(\delta + L_2)\tau} + \frac{e^{(\delta + L_2)\tau} - 1}{\delta - L_2} k L_3). \tag{4.36}$$

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

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

For the later proof, we only consider the case $s < \bar{s}$, since the case when $s \ge \bar{s}$ can be similarly dealt with and the proof will be omitted. By Lemma 4.2 we know

$$y^{\phi}(t) = x(t) + O(\varepsilon \log \varepsilon), \; y^{\bar{\phi}}(t) = x(t) + O(\varepsilon \log \varepsilon).$$

By (4.8), (4.9) and (4.14) we can 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 function $x(t)$. Because the distant between $\tau + \eta^4_{\max}$ and s may be greater than τ. Thus we need split the interval $[\tau + \eta^4_{\max}, s]$ as $[\tau + \eta^4_{\max}, 2\tau + \eta^4_{\max}]$, $[2\tau + \eta^4_{\max}, 3\tau + \eta^4_{\max}], \cdots, [m\tau + \eta^4_{\max}, s]$ 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 estimate $|y^{\phi} - y^{\bar{\phi}}|$ interval by interval and finally to obtain

$$|y^{\phi} - y^{\bar{\phi}}| \le C_7 ||\phi - \bar{\phi}||, \tag{4.37}$$

with

$$C_7 = C_6 \left(e^{(\delta + L_2)\tau} + \frac{e^{(\delta + L_2)\tau} - 1}{\delta - L_2} k L_2 \right)^{T_x}. \tag{4.38}$$

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

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

from which and the equation (4.1) we know that $y^{\bar{\phi}}(t)$ is decreasing and

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

when ε is small. Applying the Mean-Value theorem to the function $y^{\bar{\phi}}(t)$ implies 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 (4.37),

$$\begin{aligned} |\bar{s} - s| &\leq \frac{2}{\delta(1+\eta)} |y^{\bar{\phi}}(\bar{s}) - y^{\bar{\phi}}(s)| = \frac{2}{\delta(1+\eta)} |y^{\phi}(s) - y^{\bar{\phi}}(s)|, \\ &\leq \frac{2C_7}{\delta(1+\eta)} ||\phi - \bar{\phi}||. \end{aligned} \tag{4.39}$$

Our ultimate goal is give the estimate of $|y^{\bar{\phi}}_{\bar{s}}(\theta) - y^{\phi}_s(\theta)|$ where $\theta \in [-\tau, 0]$. Indeed

$$|y^{\bar{\phi}}_{\bar{s}}(\theta) - y^{\phi}_s(\theta)| \leq |y^{\bar{\phi}}_{\bar{s}}(\theta) - y^{\bar{\phi}}_s(\theta)| + |y^{\bar{\phi}}_s(\theta) - y^{\phi}_s(\theta)|. \tag{4.40}$$

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 derivative of the function $y^{\bar{\phi}}(t)$, see remark 4.3. The second term of (4.40) is bounded by $C_7||\phi - \bar{\phi}||$. Thus from (4.40), we have

$$|y^{\bar{\phi}}_{\bar{s}}(\theta) - y^{\phi}_s(\theta)| \leq C_7(1 + \frac{2M_2}{\delta(1+\eta)})||\phi - \bar{\phi}||. \tag{4.41}$$

When $\varepsilon \to 0$, we have

$$L_1 = O(\frac{1}{\varepsilon(1+\eta)^{1/\varepsilon}}), \;\; L_2 = O(\varepsilon), \;\; L_3 = O(1/\varepsilon), \;\; L_4 = O(1), \;\; L_5 = O(\varepsilon).$$

Since L_1 is exponentially small as $\varepsilon \to 0$, we conclude from (4.25), (4.27), (4.29), (4.32), (4.34), (4.36) and (4.38) that L_R is exponentially small and satisfies

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

This completes our proof.□

Since $L_R < 1$, it means that the returning map R is contractive and there exists a unique fixed-point ϕ in $A(\eta)$ so that $R(\phi) = \phi$. Thus we find a slowly oscillating periodic solution $y(t, \phi)$ for the equation (4.1). This periodic solution is also globally attractive for any initial function φ in $A(\eta)$.

5. Full Asymptotic Expansion for the Periodic Solution. In the previous section we use fixed-point theory to prove that there exists a unique periodic solution in $A(\eta)$ for the equation (4.1) . Now we like to give a quantitative analysis to this solution. Since the map R is contractive with the Lipschitz constant L_R being exponentially small, it is possible to give a full asymptotic expansion for this particular solution.

If we take the initial function $\phi = 1 + \eta$, then we get a solution $y(t, 1 + \eta)$ which may not be periodic. But by Lemma 4.2, $y(t, 1+\eta) = x(t)+O(\varepsilon \log \varepsilon)$ when t is finite and there exists a $T_{1+\eta} > 0$ such that

$$y(T_{1+\eta}, 1 + \eta) = 1 + \eta,\ y(T_{1+\eta} + \theta, 1 + \eta) \geq 1 + \eta, \theta \in [-\tau, 0).$$

Then $y(\theta + T_{1+\eta}, 1 + \eta) \in A(\eta)$.

Assume that $y(t)$ is the periodic solution to (4.1) which can be extended to $(-\infty, +\infty)$ and satisfies $y(t) \in A(\eta)$ for $t \in [-\tau, 0]$. Suppose also that for $t \in [-\tau, 0]$, $y(t)$ has the following asymptotic formula

$$y(t) = \sum_{i=0}^{\infty} \phi_i(t) \tag{5.1}$$

where $\phi_0(t) = y(t + T_{1+\eta}, 1 + \eta)$ and $\phi_i(t, \varepsilon), i \geq 1$ will be determined later. Let $y_0(T_0 + \theta)$ denote the image of the returning map of R on ϕ_0, i.e.,

$$y_0(T_0 + \theta) = F_\beta(T_0, \phi_0),\ \theta \in [-\tau, 0]$$

where $T_0 > 0$ satisfies

$$y_0(T_0) = 1 + \eta,\ y_0(T_0 + \theta) \geq 1 + \eta,\ \theta \in [-\tau, 0).$$

similarly by induction set

$$\phi_1(\theta) = y_0(T_0 + \theta) - \phi_{0,}$$

$$y_{i-1}(T_{i-1} + \theta) = F_\beta(T_{i-1}, \sum_{j=0}^{i-1} \phi_j) = F_\beta(T_{i-1}, y_{i-2}),\ i \geq 2,$$

and

$$\phi_i(\theta) = y_{i-1}(\theta + T_{i-1}) - y_{i-2}(\theta + T_{i-2}),\ i \geq 2,$$

where for $i \geq 1$, $T_i > 0$ and also satisfies

$$y_i(T_i) = 1 + \eta,\ y_i(T_i + \theta) \geq 1 + \eta,\ \theta \in [-\tau, 0).$$

Using the result in (4.39) we can also have

$$|T_i - T_{i-1}| \leq (L_R)^{i-1} |T_1 - T_0|,$$

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 by Theorem 4.4 we have for $\theta \in [-\tau, 0]$,

$$\begin{aligned} |y_i(\theta + T_i) - y_{i-1}(\theta + T_{i-1})| &= |F(T_i, y_{i-1}) - F(T_{i-1}, y_{i-2})| \\ &\le L_R\, |y_{i-1}(\theta + T_{i-1}) - y_{i-2}(\theta + T_{i-2})| \\ &\le (L_R)^{i-1}\, |y_1(\theta + T_1) - y_0(\theta + T_0)| \\ &\le (L_R)^i |y_0(t, \phi_0) - \phi_0|. \end{aligned} \tag{5.2}$$

Then for $s \in [-\tau, 0]$, we conclude that

$$y_0(s + T_0) + \sum_{j=1}^{\infty} (y_j(s + T_j) - y_{j-1}(s + T_{j-1})) \tag{5.3}$$

is absolutely convergent and have the same value as the initial function $\sum_{i=0}^{\infty} \phi_i(s)$. Since L_R is exponentially small, It is easy to prove that the value of T_ε is dominated by T_0 and likewise the value of (5.3) is dominated by $y_0(s+T_0)$, each of which has the exponential error bound. For the leading term $y_0(t)$, obviously we have from Lemma 4.2 the rough estimates

$$y_0(t) = x(t) + O(\varepsilon \log \varepsilon),\ T_0 = T_x + O(\varepsilon \log \varepsilon).$$

Next we would like to give the refined estimate for $y_0(t)$ and T_0 by using this information and developing the idea of Lemma 4.2.

Like in Lemma 4.2, we shall split the interval $[0, T_0]$ and estimate $y_0(t)$ interval by interval. For illustration, we only need to show the first interval's estimate to the readers. Keep in mind that the initial data is taken as $y(t + T_{1+\eta}, 1 + \eta)$ which is greater than $1 + \eta$ when t lies in the interval $[-\tau, 0)$. Let η_1 and η_2 be still the value in Lemma 4.2 and $t_1^{y_0}$ satisfy $y_0(t_1^{y_0}) = 1$. We denote $y_0(t) = y_0(t)$. Integrating the equation (4.1) from 0 to t, $t \in [0, t_1^{y_0}]$, gives

$$\begin{aligned} y_0(t) - y_0(0) = -\delta \int_0^t y_0(t)dt - \int_0^t \beta(y_0) y_0(t)dt \\ +k \int_0^t \beta(y_0(t-\tau)) y_0(t-\tau)dt. \end{aligned} \tag{5.4}$$

It is obvious that the last term of the right hand side of (5.4) is exponentially small and can be viewed as $O(\varepsilon)$. Next we claim that

$$\int_0^t \beta(y_0) y_0(t)dt = O(\varepsilon). \tag{5.5}$$

To see this, we need to note that $y_0(t)$ is decreasing in $t \in [0, t_1^{y_0}]$ and dy_0/dt is the order of $O(1)$ or more precisely

$$-\alpha(1+\eta) \leq \frac{dy_0}{dt} = -[\beta(y_0)+\delta]y_0 + O(\varepsilon) \leq -\delta + O(\varepsilon). \tag{5.6}$$

Thus from (5.6) and the fact

$$\begin{aligned}\int_0^t \beta(y_0)y_0(t)\frac{dy_0}{dt}dt &\leq \int_0^{t_1^{y_0}} \beta(y_0)y_0(t)\frac{dy_0}{dt}dt,\\ &= \int_{1+\eta}^1 \frac{\beta_0 y}{1+y^{1/\varepsilon}}dy,\\ &= O(\varepsilon),\end{aligned}$$

we know that $\int_0^t \beta(y_0)y_0(t)dt$ is also the order of $O(\varepsilon)$ and the claim of (5.5) is true. It follows then from (5.4)

$$y_0(t) \ = -\delta\int_0^t y_0(t)dt + 1 + \eta + O(\varepsilon).$$

Solving this integral equation, we get

$$y_0(t) = (1+\eta+O(\varepsilon))e^{-\delta t},$$

which implies

$$y_0(t) = y_0(t,\varepsilon) = x(t) + O(\varepsilon),\ t \in [0, t_1^y]. \tag{5.7}$$

Using the same approaches above we can prove that in the whole interval $[0, T_0]$, (5.7) is still true. Furthermore, we can prove that

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

which completes our refined estimates.

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