

## RELAXATION OSCILLATIONS IN A CLASS OF DELAY DIFFERENTIAL EQUATIONS\*

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**Abstract.** We study a class of delay differential equations which have been used to model hematological stem cell regulation and dynamics. Under certain circumstances the model exhibits self-sustained oscillations, with periods which can be significantly longer than the basic cell cycle time. We show that the long periods in the oscillations occur when the cell generation rate is small, and we provide an asymptotic analysis of the model in this case. This analysis bears a close resemblance to the analysis of relaxation oscillators (such as the Van der Pol oscillator), except that in our case the slow manifold is infinite dimensional. Despite this, a fairly complete analysis of the problem is possible.

**Key words.** relaxation oscillations, delay differential equations, hematopoiesis, stem cells, chronic myelogenous leukaemia

**AMS subject classifications.** 34K99, 92A07, 34C15, 34E05

**PII.** S0036139901393512

**1. Introduction.** The understanding of periodic behavior in nonlinear ordinary differential equations is reasonably complete. Near Hopf bifurcation, periodic solutions are generically of small amplitude and can be analyzed using the methods of multiple scales. At more extreme parameter values, oscillations are often strongly nonlinear, and it is frequently the case that the dynamics are relaxational, in which case they can be understood through the existence of slow manifolds in phase space and the associated asymptotic analysis of the resulting relaxation oscillators. The classic example is the relaxation oscillation of the Van der Pol oscillator, whose analysis is ably expounded by Kevorkian and Cole (1981).

The situation is much less satisfactory for delay differential equations, which are frequently used to model populations, for example, in ecology (Gurney, Blythe, and Nisbet (1980)) or physiology (Mackey (1997)). One example is the delay recruitment equation

$$(1.1) \quad \varepsilon \dot{x} = -x + f(x_1),$$

where  $x_1 = x(t-1)$ . For unimodal  $f$  (i.e.,  $f(0) = 0$ ,  $(x-x^*)f'(x) < 0$  for some  $x^* > 0$ ), periodic oscillations can occur for sufficiently small  $\varepsilon$ . In some circumstances, a singular perturbation analysis of periodic solutions when  $\varepsilon \ll 1$  is possible (Chow and Mallet-Paret (1982); Chow, Lin, and Mallet-Paret (1989)), but the results have been limited in scope.

Although linear and weakly nonlinear stability methods are straightforward for delay differential equations, singular perturbation methods appear difficult to implement in general. Much of the work that has been done, such as Chow and Mallet-Paret's work cited above, is concerned with systems with large delay (thus (1.1) or

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\*Received by the editors August 6, 2001; accepted for publication (in revised form) March 7, 2002; published electronically September 12, 2002.

<http://www.siam.org/journals/siap/63-1/39351.html>

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its generalizations (Chow and Huang (1994); Hale and Huang (1996))). Artstein and Slemrod (2001) place their discussion of relaxation oscillations in the context of slow and fast manifolds familiar from ordinary differential equations and draw a distinction between systems where the delay is “fast” or “slow.” (In this context we will find that the delay in our system is fast.)

Actual constructive asymptotic methods are less common. Fowler (1982) analyzed the delayed logistic equation  $\varepsilon \dot{x} = x(1 - x_1)$ , and Bonilla and Liñan (1984) analyzed a more general system having distributed delay and with diffusion. In a sequence of papers, Lange and Miura (e.g., 1982, 1984) provided asymptotic analyses of models with delays and exhibited boundary layer behavior, although they were exclusively concerned with boundary value problems, and their systems were linear. More recently, Pieroux et al. (2000) analyzed a laser system when the delay was large but dependence on the delayed variable was weak, using multiple scale techniques. In this paper, we show how a constructive relaxational perturbation analysis can be carried out for a particular class of delay differential equations describing stem cell dynamics, when the net proliferation rate is small.

**2. A mathematical model of stem cell dynamics.** Hematological diseases are interesting and have attracted a significant amount of modeling attention because a number of them are periodic in nature (Haurie, Dale, and Mackey (1998)). Some of these diseases involve only one blood cell type and are due to the destabilization of peripheral control mechanisms, e.g., periodic auto-immune hemolytic anemia (Bélair, Mackey, and Mahaffy (1995); Mahaffy, Bélair, and Mackey (1998)) and cyclical thrombocytopenia (Swinburne and Mackey (2000); Santillan et al. (2000)). Typically, periodic hematological diseases of this type involve periodicities between two and four times the bone marrow production/maturation delay (which is different from the delay considered in this paper).

Other periodic hematological diseases involve oscillations in all of the blood cells (white cells, red blood cells, and platelets). Examples include cyclical neutropenia (Haurie, Dale, and Mackey (1999); Haurie et al. (1999); Haurie et al. (2000)) and periodic chronic myelogenous leukemia (Fortin and Mackey (1999)). These diseases involve very long period dynamics (on the order of weeks to months) and are thought to be due to a destabilization of the pluripotential stem cell (PPSC) compartment from which all of these mature blood cell types are derived.

In Figure 2.1 we have given a pictorial representation of the PPSC compartment and defined the important variables. The dynamics of this PPSC population are governed (Mackey (1978), (1997), (2001)) by the pair of coupled differential delay equations

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

for the dynamics of the proliferating phase cells and

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

for the nonproliferating ( $G_0$ ) phase cells. In these equations,  $\hat{t}$  is time,  $\tau$  is the time required for a cell to traverse the proliferative phase,  $N_\tau = N(\hat{t} - \tau)$ , and the resting to proliferative phase feedback rate  $\beta$  is taken to be a Hill function of the form

$$(2.3) \quad \beta(N) = \frac{\beta_0 \theta^n}{\theta^n + N^n}.$$

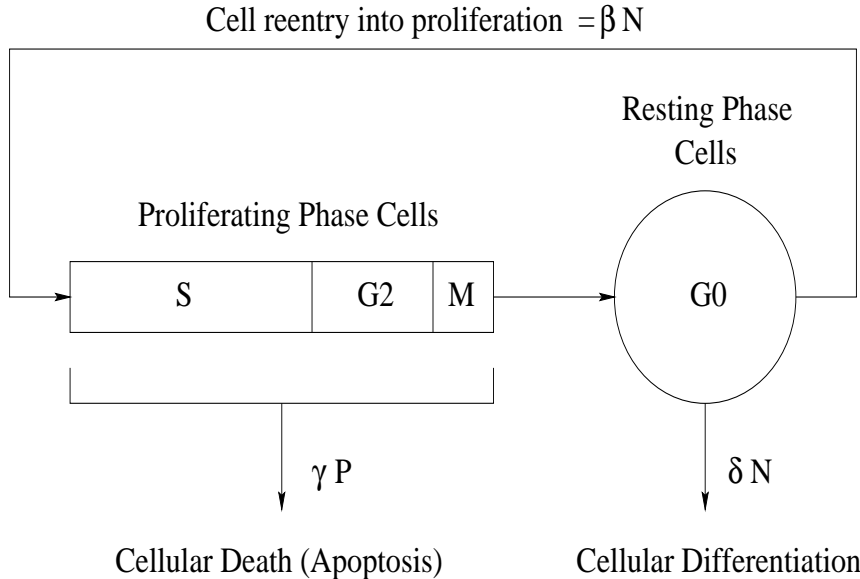


FIG. 2.1. A schematic representation of the  $G_0$  stem cell model. Proliferating phase cells ( $P$ ) include those cells in  $S$  (DNA synthesis),  $G_2$ , and  $M$  (mitosis) while the resting phase ( $N$ ) cells are in the  $G_0$  phase.  $\delta$  is the rate of differentiation into all of the committed stem cell populations, while  $\gamma$  represents a loss of proliferating phase cells due to apoptosis.  $\beta$  is the rate of cell reentry from  $G_0$  into the proliferative phase, and  $\tau$  is the duration of the proliferative phase. See Mackey (1978), (1979), (1997) for further details.

The origin of the terms in these equations is fairly obvious. For example, the first term of (2.2) represents the loss of proliferating cells to cell division ( $\beta(N)N$ ) and to differentiation ( $\delta N$ ). 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 (programmed cell death) at rate  $\gamma$ . It is clear that in investigating the dynamics of the PPSC we need only understand the dynamics of the  $G_0$  phase resting cell population since the proliferating phase dynamics are driven by the dynamics of  $N$ .

Typical values of the parameters for humans are given by Mackey (1978), (1997) as

$$(2.4) \quad \delta = 0.05 \text{ d}^{-1}, \quad \beta_0 = 1.77 \text{ d}^{-1}, \quad \tau = 2.2 \text{ d}, \quad n = 3.$$

(The value of  $\theta$  is  $1.62 \times 10^8 \text{ cells kg}^{-1}$ , but this is immaterial for dynamic considerations.) For values of  $\gamma$  in the range  $0.2 \text{ d}^{-1}$ , the consequent steady state is unstable and there is a periodic solution whose period  $P$  at the bifurcation ranges from 20–40 days. It is the observation that  $P \gg \tau$ , which arouses our curiosity, and which we wish to explain. (In differential delay equations, periodic oscillations have periods bounded below by  $2\tau$  and under certain circumstances the period may be in the range  $2\tau$  to  $4\tau$ .)

We rewrite (2.2) in a standard form as follows. First scale the nonproliferating phase cell numbers by  $\theta$  and the time by  $\tau$  so that

$$(2.5) \quad N \rightarrow \theta N, \quad \hat{t} = \tau t^*,$$

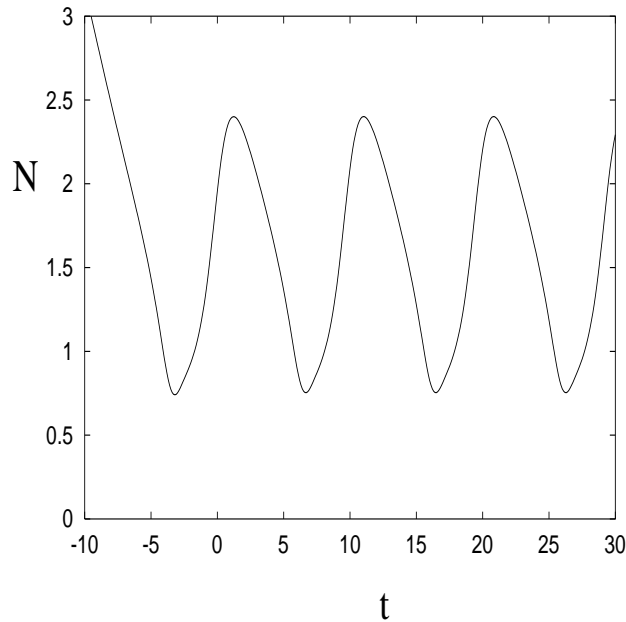


FIG. 2.2. Solution of (2.6) with  $\varepsilon = 0.11$ ,  $b = 3.9$ , and  $\mu = 1.2$ .

and (2.2) becomes

$$(2.6) \quad \dot{N} = g(N_1) - g(N) + \varepsilon[\mu g(N_1) - N],$$

where  $\dot{N} = dN/dt^*$ ,  $N_1 = N(t^* - 1)$ ,

$$(2.7) \quad g(N) = \frac{bN}{1 + N^n},$$

and the parameters are defined by

$$(2.8) \quad b = \beta_0\tau, \quad \varepsilon = \delta\tau, \quad \mu = \frac{2e^{-\gamma\tau} - 1}{\delta\tau}.$$

The biological interpretation of these is as follows:  $b$  represents the rate at which cells migrate round the loop in Figure 2.1,  $\varepsilon$  represents the rate of loss through differentiation, and  $\mu$  represents the net proliferation rate round the loop. The dimensionless time  $t^*$  is measured in units of the proliferative time spent in the loop. If we take  $\gamma \sim 0.2 \text{ d}^{-1}$ , then typical values of the parameters are

$$(2.9) \quad b \sim 3.9, \quad \mu \sim 2.6, \quad \varepsilon \sim 0.11.$$

On this basis, we suppose  $b, \mu = O(1)$ . The long periods are associated with the relatively small value of  $\varepsilon$ , and so the aim of our analysis is to solve (2.6) when  $\varepsilon \ll 1$ . Figure 2.2 shows the periodic behavior when  $\varepsilon = 0.11$ ,  $b = 3.9$ , and  $\mu = 1.2$  (the steady state is stable when  $\mu = 2.6$ ).

**3. Singular perturbation analysis.** The first order delay differential equation (2.6) is an infinite dimensional system. For example, defining the function

$$(3.1) \quad u_{t^*}(s) = N(t^* + s), \quad s \in [-1, 0],$$

we can consider (2.6) as a sequence of ordinary differential equations on the Banach space  $C[-1, 0]$  of continuous functions on  $[-1, 0]$ . Singular perturbation analysis is therefore not necessarily straightforward, but we shall see that a formal procedure is indeed possible.

The key observation for our investigation is that a solution of (2.6) can be slowly varying, on a slow time scale

$$(3.2) \quad t = \varepsilon t^*,$$

or on a rather loosely defined “slow manifold” on which  $N \approx N_1$ . In terms of  $t$ , which represents time measured in units of the slower differentiation time scale, we have  $N(t^* - 1) = N(t - \varepsilon)$ ; thus (2.6) is  $(N' = dN/dt)$

$$(3.3) \quad N' = \frac{g(N_\varepsilon) - g(N)}{\varepsilon} + \mu g(N_\varepsilon) - N.$$

Also, by expanding  $N_\varepsilon$  for small  $\varepsilon$ , we have

$$(3.4) \quad \begin{aligned} N_\varepsilon &= N - \varepsilon N' + \frac{1}{2}\varepsilon^2 N'' \dots, \\ g(N_\varepsilon) &= g(N) - [\varepsilon N' - \frac{1}{2}\varepsilon^2 N'' + \frac{1}{6}\varepsilon^3 N''' \dots]g'(N) + [\frac{1}{2}\varepsilon^2 N'^2 \dots]g''(N) + \dots; \end{aligned}$$

note that  $N' = dN/dt$ , while  $g'(N) = dg/dN$ . We thus have

$$(3.5) \quad [1 + g'(N)]N' = \mu g(N) - N + \varepsilon[-\mu g'N' + \frac{1}{2}N''g' + \frac{1}{2}N'^2g''] + \dots,$$

and successive terms in the expansion

$$(3.6) \quad N \sim N_0 + \varepsilon N_1 + \dots$$

satisfy the equations

$$(3.7) \quad N'_0 = \frac{\mu g(N_0) - N_0}{1 + g'(N_0)},$$

$$(3.8) \quad \begin{aligned} &[1 + g'(N_0)]N'_1 + g''(N_0)N'_0N_1 \\ &= \mu g'(N_0)N_1 - N_1 + [-\mu g'(N_0)N'_0 + \frac{1}{2}N''_0g'(N_0) + \frac{1}{2}N'^2_0g''(N_0)], \end{aligned}$$

and so on. Note particularly that in this slow region  $N_1$  denotes the second term in the expansion for  $N$  and does *not* represent  $N(t^* - 1)$ ; it will revert to the former meaning when we consider the dynamics in the fast “shock” layer (when the expansion will use  $u$  and  $v$  as first and second order terms). Equation (3.7) states that the rate of change of the resting stem cell population is due to net proliferation (the first term in the numerator) and loss by differentiation (the second). The effect of the delay in the proliferative cycle is to mediate the rate by the denominator. In our procedure we now begin to follow Kevorkian and Cole’s (1981) exposition (pp. 67 and the following ones) quite closely.

The function  $g = bN/(1 + N^n)$  is unimodal. If  $g' > -1$  everywhere, then  $N$  will evolve on the slow time scale to a steady state. Suppose now that

$$(3.9) \quad b > b_c = \frac{4n}{(n - 1)^2},$$

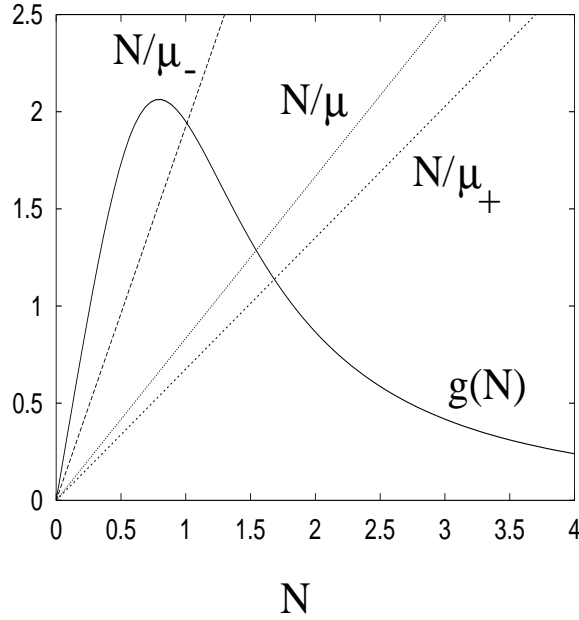


FIG. 3.1. Graphs of  $g(N)$  and  $N/\mu$  for  $b = 3.9$ ,  $n = 3$ , and  $\mu = 1.2$  in the range  $(\mu_-, \mu_+) = (0.52, 1.48)$ . Also shown are graphs of  $N/\mu_-$  and  $N/\mu_+$ .

which is the criterion for  $g'$  to reach  $-1$ . Then there are two values  $N_- < N_+$  at which  $g' = -1$ ; for (2.7), we have, explicitly,

$$(3.10) \quad N_{\pm}^n = \frac{1}{2}(n-1)[b \pm (b^2 - b_c b)^{1/2}] - 1.$$

If  $\mu b < 1$ ,  $N = 0$  is stable, by consideration of (3.7). If  $\mu b > 1$ , then there is a positive steady state  $N^*$  in which  $N^* = \mu g(N^*)$ . We define the two values of  $\mu$  where  $N^* = N_{\pm}$  as  $\mu_{\pm}$ ; thus,

$$(3.11) \quad \mu_{\pm} = \frac{N_{\pm}}{g(N_{\pm})}, \quad \mu_- < \mu_+.$$

Using (3.10), we have, explicitly,

$$(3.12) \quad \mu_{\pm} = \frac{1}{2}(n-1) \left[ 1 \pm \left( 1 - \frac{b_c}{b} \right)^{1/2} \right].$$

The situation which is of interest is when  $\mu_- < \mu < \mu_+$ , and this is depicted in Figure 3.1. In this situation, the graph of  $N'_0$  versus  $N_0$  is as shown in Figure 3.2, and it is apparent that the fixed point in  $(N_-, N_+)$  is unstable, because the slope of the graph at the fixed point (where  $N' = 0$ ) is positive. (Conversely, there is a stable fixed point when  $\mu$  is outside this range.)

Suppose that  $N > N_+$  initially. Then  $N_0$  decreases and reaches  $N_+$  at finite time. Define this time to be when  $t = 0$ ; then

$$(3.13) \quad \int_{N_+}^{N_0} \left\{ \frac{1 + g'(N)}{N - \mu g(N)} \right\} dN = -t.$$

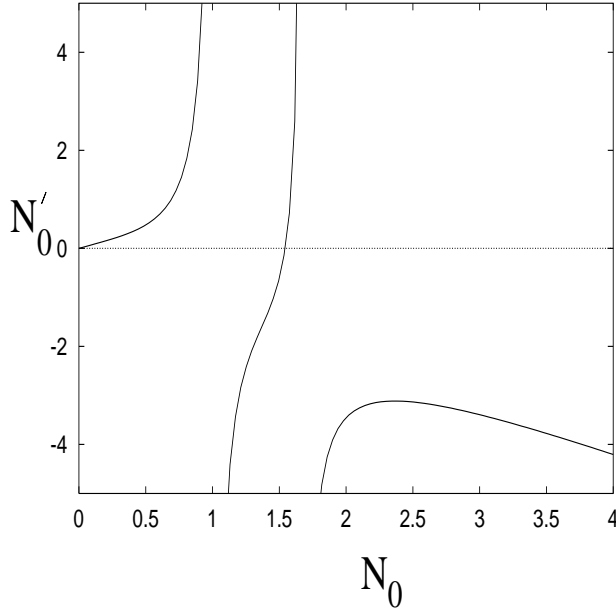


FIG. 3.2. Graph of  $N'_0(N_0)$  given by (3.7) when  $n = 3$ ,  $b = 3.9$ , and  $\mu = 1.2$ .

Since  $1 + g'(N_+) = 0$ , the first term in the expansion of the integral in (3.13) for small  $N_0 - N_+$  is quadratic, and from this we find, as  $-t \rightarrow 0+$ ,

$$(3.14) \quad N_0 \sim N_+ + q_1(-t)^{1/2} + q_2(-t) + O[(-t)^{3/2}].$$

Detailed expressions for the coefficients are given in the appendix.

Rearrangement of (3.8) using (3.7) allows  $N_1$  to be obtained in the form

$$(3.15) \quad N_1 = \left( \frac{N_0 - \mu g(N_0)}{1 + g'(N_0)} \right) \left[ A_1 - \frac{g'(N_0)}{2\{1 + g'(N_0)\}} + \int_{N_+}^{N_0} k(N) dN + h_+ \ln(N_0 - N_+) \right],$$

where  $h_+ = h(N_+)$ ,

$$(3.16) \quad h(N) = -\frac{g'(N)\{1 - \mu g'(N)\}(N - N_+)}{2\{N - \mu g(N)\}\{1 + g'(N)\}}$$

(with the singularity at  $N_+$  removed), and

$$(3.17) \quad k(N) = \frac{h(N) - h(N_+)}{N - N_+} - \frac{\mu g'(N)}{N - \mu g(N)}.$$

In particular,

$$(3.18) \quad h_+ = \frac{1 + \mu}{2g'_+(N_+ - \mu g_+)},$$

where  $g_+ = g(N_+)$ , etc. Higher order terms can be obtained in a similar way. Note that, since  $N_0 - N_+ \sim (-t)^{1/2}$  as  $-t \rightarrow 0$ , and  $g'(N_+) = -1$ , it follows that  $1 + g'(N_0) \sim (-t)^{1/2}$  as  $-t \rightarrow 0$ , and therefore (3.15) implies that  $N_1 = O(1/(-t))$  as  $-t \rightarrow 0+$ , and the validity of the expansion breaks down when  $(-t)^{1/2} \sim \varepsilon/(-t)$ , i.e., when  $-t \sim \varepsilon^{2/3}$ .

**3.1. Transition layer.** The solution becomes disordered as  $-t \rightarrow 0$ , and specifically when  $-t \sim \varepsilon^{2/3}$ . In this section we analyze this “transition” layer. In addition, we might anticipate the existence of a region in which  $N$  changes on the fast (delay) time scale  $t^*$ , and this will indeed turn out to be the case. However, it transpires that such a fast region cannot be matched directly to the slow outer region, and, just as for the Van der Pol oscillator, the inability to match slow and fast regions also suggests that there is a transition region which joins the two. In terms of the outer time scale  $t$ , we shall find that the slow solution is valid for  $-t \sim O(1)$ , the transition region for  $-t \sim O(\varepsilon^{2/3})$ , and the fast “shock” layer for  $-t \sim O(\varepsilon)$ . Indeed, the dynamics of these three regions are essentially the same as those of the corresponding regions in the analysis of the Van der Pol equations, and we follow the exposition in Kevorkian and Cole (1981) closely. In particular, consultation of this book is strongly recommended for those less familiar with the basic procedure of matched asymptotic expansions. (Note that there are some algebraic errors in Kevorkian and Cole’s exposition.)

A distinguished limit exists in which we put

$$(3.19) \quad t = \rho(\varepsilon) + \left( \frac{\varepsilon^{2/3}}{\Omega} \right) \tilde{t},$$

where we assume  $\tilde{t}$  is  $O(1)$ . The definition of  $\Omega$  is

$$(3.20) \quad \Omega = (g_+'' q_1)^{2/3},$$

and  $\rho(\varepsilon)$  is a (small) origin shift which is introduced to allow matching to be carried out. Since  $N - N_+ \sim (-t)^{1/2}$  as  $-t \rightarrow 0+$ , this requires  $N - N_+ \sim \varepsilon^{1/3}$ , and we define  $f$  via

$$(3.21) \quad N = N_+ + \left( \frac{\varepsilon^{1/3} \Omega}{g_+''} \right) f.$$

It is still appropriate to expand the delay term, and we find, from (3.3), that  $f(\tilde{t})$  satisfies

$$(3.22) \quad f'' + 2ff' + 1 = \varepsilon^{1/3} [-\kappa f + \frac{1}{3}\Omega f''' + \Omega(f'^2 + ff'') - \lambda f^2 f'] + O(\varepsilon^{2/3}),$$

where

$$(3.23) \quad \lambda = \frac{\Omega g_+'''}{g_+''^2}, \quad \kappa = \frac{2}{\Omega^2} (1 + \mu).$$

We expand  $f$  in powers of  $\varepsilon^{1/3}$ , thus

$$(3.24) \quad f \sim f_1 + \varepsilon^{1/3} f_2 + \dots;$$

then from (3.22) we find that

$$(3.25) \quad \begin{aligned} f_1'' + 2f_1 f_1' + 1 &= 0, \\ f_2'' + 2(f_1 f_2)' &= -\kappa f_1 + \frac{1}{3}\Omega f_1''' + \Omega(f_1 f_1')' - \lambda f_1^2 f_1', \end{aligned}$$

and so on. The first of these may be integrated to yield

$$(3.26) \quad f_1' + f_1^2 + \tilde{t} = 0,$$



where the constant of integration is absorbed into the time shift  $\rho(\varepsilon)$  in (3.19). The solution of the Riccati equation (3.26) is

$$(3.27) \quad f_1 = \frac{V'(\tilde{t})}{V(\tilde{t})},$$

where  $V$  satisfies the modified Airy equation

$$(3.28) \quad V'' + \tilde{t}V = 0.$$

The solutions of (3.28) are  $\text{Ai}(-\tilde{t})$  and  $\text{Bi}(-\tilde{t})$ , whose leading order behaviors as  $\tilde{t} \rightarrow -\infty$  are  $V \sim \exp[\pm \frac{2}{3}(-\tilde{t})^{3/2}]$  (minus for  $\text{Ai}$ ). Thus if  $V$  contains any  $\text{Bi}$ , it will dominate as  $\tilde{t} \rightarrow -\infty$ , and hence  $f_1 = V'(\tilde{t})/V(\tilde{t}) \sim -(-\tilde{t})^{1/2}$  in this limit. Therefore, in order to obtain  $f_1 \sim (-\tilde{t})^{1/2}$  as  $\tilde{t} \rightarrow -\infty$ , which is required for matching purposes, we must suppress the  $\text{Bi}$  component and choose

$$(3.29) \quad V(\tilde{t}) = 2\sqrt{\pi}\text{Ai}(-\tilde{t}),$$

where the premultiplicative constant is chosen for later algebraic convenience (it does not affect the definition of  $f_1$ ). Since  $f_1 \sim (-\tilde{t})^{1/2}$  as  $\tilde{t} \rightarrow -\infty$ ,  $f_1$  is monotonically decreasing for large  $-\tilde{t}$ , and hence from (3.26)  $f_1 > (-\tilde{t})^{1/2}$ . If  $f_1'$  first reaches zero for some value of  $\tilde{t} = \tilde{t}_c < 0$ , then at that point (3.26) implies that  $f_1 = (-\tilde{t})^{1/2}$  and also that (since  $f_1'$  is continuous and  $f_1 > (-\tilde{t})^{1/2}$  for  $\tilde{t} < \tilde{t}_c$ )  $f_1' < 0$ , which contradicts the assertion. Thus  $f_1' < 0$  for all  $\tilde{t} < 0$ , and (3.26) implies this directly for  $\tilde{t} > 0$ . Thus we find  $f_1$  is monotonically decreasing while it is finite, which is in the region  $\tilde{t} < \tilde{t}_0$ , where  $\tilde{t}_0 \approx 2.338$  is the first zero of  $\text{Ai}(-\tilde{t})$ . The solution will break down as  $\tilde{t} \rightarrow \tilde{t}_0$ , where it will match to an inner region, or shock layer, in which  $t^* = O(1)$  (with a suitably chosen origin for  $t^*$ ).

The first integral of (3.25)<sub>2</sub> is (using  $f_1 = V'/V$ )

$$(3.30) \quad f_2' + 2f_1f_2 = -\kappa \ln V + \frac{1}{3}\Omega f_1'' + \Omega f_1f_1' - \frac{1}{3}\lambda f_1^3 + C_2,$$

where  $C_2$  is constant. By differentiation of (3.26) we find that  $-C_2f_1'$  is a particular solution for (3.30) when only the  $C_2$  term is present on the right-hand side. Using  $f_1 = V'/V$ , we have

$$(3.31) \quad (V^2f_2)' = C_2V^2 - \kappa V^2 \ln V + \frac{1}{3}\Omega V^2 f_1'' + \Omega V^2 f_1f_1' - \frac{1}{3}\lambda V^2 f_1^3.$$

Next we make use of the following identities, which can be obtained by integrating by parts and using (3.27) and (3.28):

$$(3.32) \quad \begin{aligned} \int V^2 f_1 f_1' &= \frac{1}{2}V^2 f_1^2 - \int V^2 f_1^3, \\ \int V^2 f_1'' &= V^2 f_1' - V^2 f_1^2 + 2 \int V^2 f_1^3, \\ \int V^2 f_1^3 &= V'^2 \ln V + (V^2 \ln V - \frac{1}{2}V^2)\tilde{t} - \int (V^2 \ln V - \frac{1}{2}V^2). \end{aligned}$$

The comment after (3.30) implies that

$$(3.33) \quad \frac{1}{V^2} \int_{-\infty}^{\tilde{t}} V^2 d\tilde{t} = -f_1',$$

and use of (3.26) and integration by parts in (3.32) implies that

$$(3.34) \quad \frac{1}{V^2} \int V^2 f_1^3 = -f_1' \ln V - \frac{1}{V^2} \int V^2 \ln V + \frac{1}{2} f_1^2.$$

Hence we obtain the solution

$$(3.35) \quad \begin{aligned} f_2 = & f_1' [-C_2 + \frac{1}{3}\Omega + \frac{1}{3}(\Omega + \lambda) \ln V] - \frac{1}{6} \lambda f_1^2 \\ & + [\frac{1}{3}(\Omega + \lambda) - \kappa] \frac{1}{V^2} \int_{-\infty}^{\tilde{t}} V^2 \ln V \, d\tilde{t}, \end{aligned}$$

where we have set the integration constant  $D_2$  (in a term  $D_2/V^2$ ) to zero to prevent exponential growth as  $\tilde{t} \rightarrow -\infty$ .

**3.2. Matching.** In order to match the outer solution to the transition solution, we expand the latter for large  $-\tilde{t}$  and the former for small  $-t$ . Equation (3.14) gives the behavior of  $N_0$  for small  $(-t)$ , while if we expand (3.15) for  $N_0$  near  $N_+$ , and use (3.14), we find

$$(3.36) \quad N_1 \sim \frac{r_1}{(-t)} + \frac{r_{21}(A_1) + r_{22} \ln(-t)}{(-t)^{1/2}} + O(1),$$

where the constants  $r_1, r_{21}, r_{22}$  are given in the appendix;  $r_1$  and  $r_{22}$  are known, while  $r_{21}$  involves the unknown constant  $A_1$  in (3.15).

Next we need the behavior of  $f_1$  and  $f_2$  as  $\tilde{t} \rightarrow -\infty$ . The function  $V = 2\sqrt{\pi} \text{Ai}(-\tilde{t})$  has the following asymptotic behavior as  $\tilde{t} \rightarrow -\infty$ :

$$(3.37) \quad V \sim (-\tilde{t})^{-1/4} \exp[-\frac{2}{3}(-\tilde{t})^{3/2}] \left[ 1 - \frac{5}{48(-\tilde{t})^{3/2}} + \dots \right].$$

Since  $f_1 = V'/V$ , we have

$$(3.38) \quad f_1 \sim (-\tilde{t})^{1/2} + \frac{1}{4(-\tilde{t})} + O[(-\tilde{t})^{-5/2}],$$

and thence we find from (3.35) that

$$(3.39) \quad f_2 \sim s_1(-\tilde{t}) + \frac{s_{21}(C_2) + s_{22} \ln(-\tilde{t})}{(-\tilde{t})^{1/2}} + O\left[\frac{\ln(-\tilde{t})}{(-\tilde{t})^2}\right],$$

and the coefficients  $s_1, s_{22}$ , and  $s_{21}$  are given in the appendix. Again,  $s_1$  and  $s_{22}$  are known, and  $s_{21}$  involves the unknown constant  $C_2$  in (3.35).

We match in an intermediate region where

$$(3.40) \quad t = \eta t_\eta + \rho(\varepsilon), \quad \tilde{t} = \left(\frac{\Omega}{\varepsilon^{2/3}}\right) \eta t_\eta,$$

and we take  $\varepsilon^{2/3} \ll \eta \ll 1$  and also presume that  $\eta \gg \rho$ . Writing both expansions (3.6) and (3.24) in terms of  $t_\eta$ , the outer expansion is given by

$$(3.41) \quad \begin{aligned} N \sim & N_+ + q_1(-\eta t_\eta)^{1/2} - \frac{\rho q_1}{2(-\eta t_\eta)^{1/2}} \dots + q_2(-\eta t_\eta) + \dots \\ & + \frac{\varepsilon r_1}{(-\eta t_\eta)} \dots + \frac{\varepsilon[r_{21} + r_{22} \ln(-\eta t_\eta) \dots]}{(-\eta t_\eta)^{1/2}} \dots, \end{aligned}$$

while the transition expansion is

$$(3.42) \quad N \sim N_+ + q_1(-\eta t_\eta)^{1/2} + \frac{\varepsilon}{4g_+''(-\eta t_\eta)} \dots + \frac{s_1\Omega^2}{g_+''}(-\eta t_\eta) + \frac{\varepsilon\Omega^{1/2}}{g_+''} \frac{[s_{21} + s_{22}\{\ln(\Omega/\varepsilon^{2/3}) + \ln(-\eta t_\eta)\}]}{(-\eta t_\eta)^{1/2}} \dots,$$

and matching requires

$$(3.43) \quad \begin{aligned} r_1 &= \frac{1}{4g_+''}, & q_2 &= \frac{s_1\Omega^2}{g_+''}, & r_{22} &= \frac{\Omega^{1/2}}{g_+''}s_{22}, \\ r_{21} &= \frac{\Omega^{1/2}}{g_+''}[s_{21} + s_{22} \ln \Omega], \\ \rho &= \frac{4\Omega^{1/2}s_{22}}{3g_+''q_1} \varepsilon \ln \varepsilon. \end{aligned}$$

The first three of these are satisfied identically (see the appendix), while the fourth and fifth determine  $s_{21}$  and  $\rho$ , given  $r_{21}$  in the outer solution.

**3.3. Matching to the shock layer.** The transition solution governed by (3.22) breaks down as  $\tilde{t} \rightarrow \tilde{t}_0$ . Near  $\tilde{t}_0$ , we have that

$$(3.44) \quad V \approx -K(\tilde{t} - \tilde{t}_0) + \frac{1}{6}K\tilde{t}_0(\tilde{t} - \tilde{t}_0)^3 + O[(\tilde{t} - \tilde{t}_0)^4],$$

where  $K = 2\sqrt{\pi}\text{Ai}'(-\tilde{t}_0) \approx 2.486$ , and thus

$$(3.45) \quad f_1 \sim -\frac{1}{(\tilde{t}_0 - \tilde{t})} + \frac{1}{3}\tilde{t}_0(\tilde{t}_0 - \tilde{t}) \dots$$

$N - N_+$  becomes of  $O(1)$  when  $\tilde{t}_0 - \tilde{t} \sim \varepsilon^{1/3}$  (this follows from (3.45) together with (3.21)), and this suggests that we put

$$(3.46) \quad \tilde{t} = \tilde{t}_0 + \Omega\{\varepsilon^{1/3}t^* + \sigma(\varepsilon)\},$$

and we anticipate that  $\sigma \ll 1$ . In terms of  $t$ ,

$$(3.47) \quad t = \rho(\varepsilon) + \left(\frac{\varepsilon^{2/3}}{\Omega}\right)\tilde{t}_0 + \varepsilon^{2/3}\sigma(\varepsilon) + \varepsilon t^*,$$

so that in the transition layer  $N(t^*)$  satisfies (2.6), i.e.,

$$(3.48) \quad \frac{dN}{dt^*} = g(N_1) - g(N) + \varepsilon[\mu g(N_1) - N],$$

and  $N_1$  reverts here to its original meaning as  $N(t^* - 1)$ . The behavior of  $f_2$  as  $\tilde{t} \rightarrow \tilde{t}_0$  follows from (3.35), which implies

$$(3.49) \quad f_2 \sim -\frac{1}{3}(\Omega + \lambda) \frac{\ln(\tilde{t}_0 - \tilde{t})}{(\tilde{t}_0 - \tilde{t})^2} + \frac{C_3}{(\tilde{t}_0 - \tilde{t})^2},$$

where

$$(3.50) \quad C_3 = C_2 - \frac{1}{3}\Omega - \frac{1}{3}(\Omega + \lambda) \ln K - \frac{1}{6}\lambda + \left[\frac{1}{3}(\Omega + \lambda) - \kappa\right] \frac{I_0}{K^2},$$

$$(3.51) \quad I_0 = \int_{-\infty}^{\tilde{t}_0} V^2 \ln V \, dV.$$

If we expand  $N$  in a transition region where  $\varepsilon^{1/3}t^* = \eta t_\eta \ll 1$ , and we suppose  $\sigma \ll \eta$ , then from (3.45) and (3.49) we find that

$$(3.52) \quad N \sim N_+ + \frac{\varepsilon^{1/3}}{g_+''} \left[ \frac{1}{\eta t_\eta} \left\{ 1 - \frac{\sigma}{\eta t_\eta} \right\} - \frac{1}{3} \Omega^2 \tilde{t}_0 (\eta t_\eta + \sigma) \dots \right] \\ + \frac{\varepsilon^{2/3}}{\Omega g_+''} \frac{1}{(\eta t_\eta)^2} \left[ \{C_3 - \frac{1}{3}(\Omega + \lambda) \ln \Omega\} - \frac{1}{3}(\Omega + \lambda) \ln(-\eta t_\eta) \right] \dots$$

The presence of the term in  $\varepsilon^{2/3}$  formally requires that we expand (3.48) as

$$(3.53) \quad N \sim u + \varepsilon^{2/3}v + O(\varepsilon)$$

and that  $u, v$  satisfy

$$(3.54) \quad u' = g(u_1) - g(u), \\ v' = g'(u_1)v_1 - g'(u)v,$$

where the suffix 1 indicates a delayed argument.

Evidently,  $u \rightarrow N_+$  as  $t^* \rightarrow -\infty$ , and its asymptotic behavior can be determined by writing

$$(3.55) \quad u = N_+ + \phi$$

and expanding for small  $\phi$ , together with a Taylor expansion for  $\phi_1 \equiv \phi(t^* - 1)$  as  $\phi - \phi' + \dots$ . This leads (with the ansatz  $\phi \gg \phi' \gg \phi'' \dots$ ) to

$$(3.56) \quad 0 = [-\frac{1}{2}\phi'' - g_+''\phi\phi'] + [\frac{1}{6}\phi''' + \frac{1}{2}g_+''(\phi'^2 + \phi\phi'') - \frac{1}{2}g_+'''\phi^2\phi'] + \dots,$$

where the brackets enclose terms of similar order. Two terms of the solution of this as  $t^* \rightarrow -\infty$  yield

$$(3.57) \quad \phi \sim \frac{1}{g_+''t^*} + \frac{[E_1 - E_2 \ln(-t^*)]}{t^{*2}} + \dots,$$

where  $E_1$  is an arbitrary constant, and  $E_2$  is defined in the appendix. The equation for  $\phi$  is autonomous, and an arbitrary constant can be added to  $t^*$ . It is clear that this is equivalent to changing the value of  $E_1$ ; therefore the value of  $E_1$  fixes the phase of  $\phi$ .

The asymptotic behavior of  $v$  can then be found in a similar way, and we find that

$$(3.58) \quad 0 = [-\frac{1}{2}v'' - g_+''(\phi v)'] + [\frac{1}{6}v''' + \frac{1}{2}g_+''(v\phi)'' - \frac{1}{2}g_+'''\phi^2v'] + \dots,$$

whence

$$(3.59) \quad v \sim -E_3[t^* + g_+''E_2 \ln(-t^*) - E_4 + \dots],$$

where  $E_3$  is arbitrary and  $E_4$  is given in the appendix. As in the Van der Pol analysis,  $v$  has a ‘‘homogeneous’’ solution  $v = g'(u)u'$ , which is  $O(1/t^{*2})$  as  $t^* \rightarrow -\infty$ , and (3.59) comes from the ‘‘particular’’ solution of (3.54)<sub>2</sub>, which does not tend to zero at  $-\infty$ .

The behavior of  $N$  as  $t^* \rightarrow -\infty$  is thus

$$(3.60) \quad N \sim N_+ + \frac{1}{g_+''t^*} + \frac{[E_1 - E_2 \ln(-t^*)]}{t^{*2}} + \dots \\ - \varepsilon^{2/3}E_3[t^* + g_+''E_2 \ln(-t^*) - E_4],$$

and putting  $\varepsilon^{1/3}t^* = \eta t_\eta$  in the matching region gives

$$(3.61) \quad N \sim N_+ + \frac{\varepsilon^{1/3}}{g_+'' \eta t_\eta} + \frac{\varepsilon^{2/3}[E_1 + E_2 \ln \varepsilon^{1/3} - E_2 \ln(-\eta t_\eta)]}{(\eta t_\eta)^2} \dots \\ - \varepsilon^{1/3} E_3(\eta t_\eta) - \varepsilon^{2/3} E_3[g_+'' E_2 \ln(-\eta t_\eta) - g_+'' E_2 \ln \varepsilon^{1/3} - E_4] \dots$$

Terms in (3.52) can be matched to the corresponding terms in (3.61) if

$$(3.62) \quad \sigma = -\varepsilon^{1/3} \left\{ \frac{1}{3} g_+'' E_2 \ln \varepsilon - E_4 \right\}, \\ E_1 = \frac{C_3 - \frac{1}{3}(\Omega + \lambda) \ln \Omega}{\Omega g_+''} - \frac{E_4}{g_+''}, \\ E_3 = \frac{\Omega^2 \tilde{t}_0}{3g_+''}, \\ E_2 = \frac{\Omega + \lambda}{3\Omega g_+''};$$

these determine  $E_1$ ,  $E_3$ , and  $\sigma$ , while the equation for  $E_2$  is satisfied automatically.

**3.4. Shock layer.** To compute  $N$  for  $t^* = O(1)$ , we must solve for  $N = u + \varepsilon^{2/3}v$  the equations

$$(3.63) \quad u' = g(u_1) - g(u), \\ u \sim N_+ + \frac{1}{g_+'' t^*} + \frac{[E_1 - E_2 \ln(-t^*)]}{t^{*2}} + \dots \text{ as } t^* \rightarrow -\infty, \\ v' = g'(u_1)v_1 - g'(u)v, \\ v \sim -E_3[t^* + g_+'' E_2 \ln(-t^*) - E_4] \text{ as } t^* \rightarrow -\infty.$$

The solutions of these must be obtained numerically. Note that the value of  $E_1$  determines the origin of  $t^*$ , i.e., varying  $E_1$  in (3.63)<sub>2</sub> simply phase shifts the solution.

It is at this point that the solution method deviates significantly from the Van der Pol procedure. The Van der Pol shock layer equation admits a first integral, and the solution can be written as a quadrature. The important point, however, is the existence of this first integral. Remarkably, an analogous procedure can be followed for the delay equations (3.63).

First, numerical integration of (3.63) indicates that  $u$  tends to a constant as  $t^* \rightarrow \infty$ . This is shown in Figure 3.3. The phase of the solution depends on the location of the initial interval, as shown in Figure 3.4. For the purposes of our analysis, we need to know this constant, and it can be found as follows. A trivial integration of (3.63)<sub>1</sub> shows that

$$(3.64) \quad u(t^*) + \int_{t^*-1}^{t^*} g[u(s)] ds = N_+ + g_+$$

is constant, where the right-hand side is evaluated from the asymptotic expression for  $u$  as  $t^* \rightarrow -\infty$ . This immediately implies  $u$  is bounded (by  $N_+ + g_+ \pm \max g$ ) as  $t \rightarrow \infty$ , and if we suppose that  $u$  tends to a constant  $N_L$  (as in Figure 3.3), then the value of the constant is easily found from (3.64) to satisfy

$$(3.65) \quad N_L + g_L = N_+ + g_+,$$

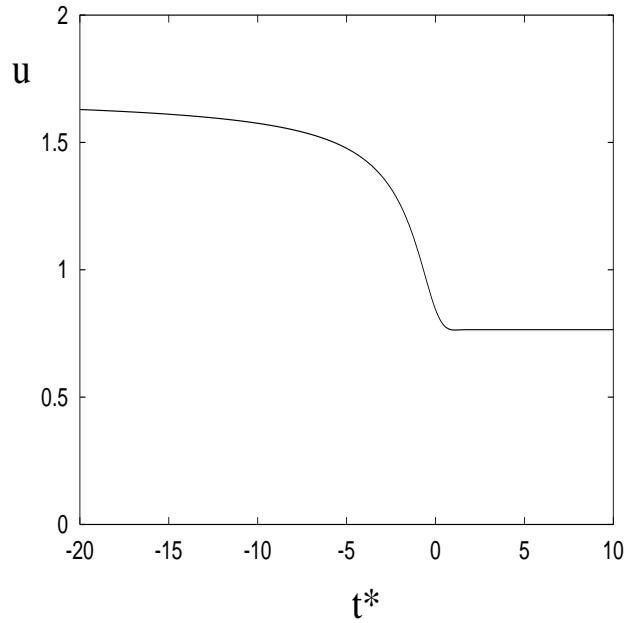


FIG. 3.3. The solution  $u_{\Delta}(t^*)$  of (3.63)<sub>1</sub> for  $u$  with the initial data taken from (3.63)<sub>2</sub> on the interval  $[-\Delta - 1, -\Delta]$ . The solution  $u_{20}(t^*)$  shown is obtained using  $E_1 = 0$  and  $\Delta = 20$ . The choice of  $\Delta$  affects the phase of the solution, as indicated in Figure 3.4. This phase shift does not affect the analysis since the solution tends to a constant exponentially, so that only exponentially small terms in the slow recovery phase are affected.

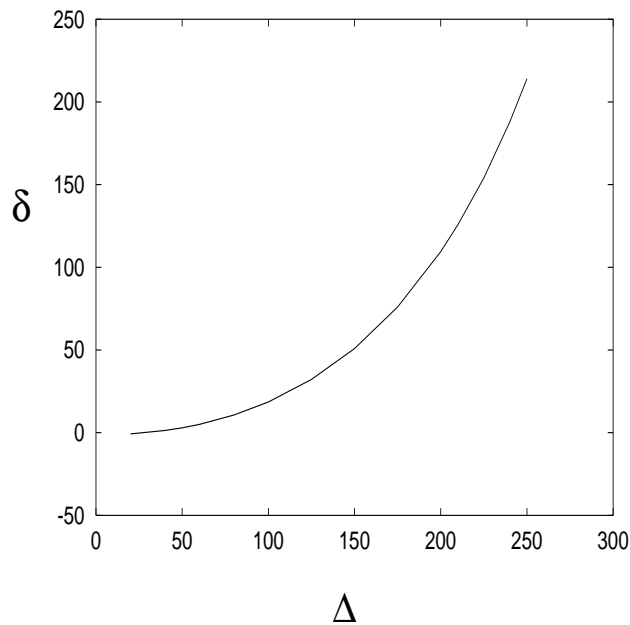


FIG. 3.4. The variation of the computed value  $\delta$  where  $u = 1$  (i.e., a measure of the phase of the solution of (3.63)<sub>1</sub>) as a function of the location  $\Delta$  of the initial interval  $[-\Delta - 1, -\Delta]$ .

where  $g_L = g(N_L)$ .

Next, we study the behavior of  $u$  near  $N_L$  by writing

$$(3.66) \quad u = N_L + U,$$

so that

$$(3.67) \quad U' \approx g'_L(U_1 - U),$$

where  $g'_L = g'(N_L)$ , and solutions are  $e^{-\lambda t^*}$  for a denumerable set  $\lambda_1, \lambda_2, \dots$  of exponents. It is straightforward to show that, if these are assigned in order of increasing real part, then  $\text{Re } \lambda_1 > 0$ , and  $\text{Im } \lambda_k \in ((2k-1)\pi, 2k\pi)$  if  $g'_L > 0$ ,  $\text{Im } \lambda_k \in (2(k-1)\pi, (2k-1)\pi)$  if  $-1 < g'_L < 0$  (we can assume  $g'_L > -1$ ) except that  $\text{Im } \lambda_1 = 0$ . In any event  $u = N_L$  is stable, and

$$(3.68) \quad u = N_L + O(e^{-\lambda_1 t^*}) \quad \text{as } t^* \rightarrow \infty.$$

Integration of (3.63)<sub>3</sub> with the matching condition (3.63)<sub>4</sub> now shows that

$$(3.69) \quad N(t) + \int_{t-1}^t g'[u(s)]v(s)ds = -E_3 \left[ \frac{3}{2} + g'_+ E_2 \right],$$

and therefore

$$(3.70) \quad v = -v_L + O(e^{-\lambda_1 t^*}) \quad \text{as } t^* \rightarrow \infty,$$

where

$$(3.71) \quad v_L = \frac{E_3 \left[ \frac{3}{2} + g'_+ E_2 \right]}{1 + g'_L}.$$

Thus as  $t^* \rightarrow \infty$ ,

$$(3.72) \quad N \sim N_L - \varepsilon^{2/3} v_L + O(\varepsilon, \text{TST}),$$

where TST denotes the transcendently small exponential terms.

**3.5. Recovery phase.** The second part of the oscillation resembles the first. There follows a slow recovery phase, terminating with transition and shock regions, and then the first slow phase is repeated. As Kevorkian and Cole (1981) point out, it is not worth the effort to compute the  $O(\varepsilon \ln \varepsilon)$  terms without also computing the  $O(\varepsilon)$  terms, which requires solving for further terms in the expansions. Having shown that the matching procedure does indeed work, we now abandon the  $O(\varepsilon \ln \varepsilon)$  terms, and thus we do not require all the detail presented previously. Since the details of the recovery phase are similar to those of the preceding (initiation) phase, we summarize the relevant results much more briefly.

In the recovery phase, we revert to the slow time defined by (3.47):

$$(3.73) \quad t = \alpha + \varepsilon t^*,$$

where

$$(3.74) \quad \alpha = \frac{\varepsilon^{2/3} \tilde{t}_0}{\Omega} + O(\varepsilon \ln \varepsilon),$$

bearing in mind the definitions of  $\rho$  and  $\sigma$ . As before,  $N$  satisfies (3.5), although the  $O(\varepsilon^{2/3})$  term in the shock layer requires a corresponding term in the expansion. However, it is convenient (since there is no forcing term at  $O(\varepsilon^{2/3})$ ) to lump this correction into the  $O(1)$  term, accommodating the  $O(\varepsilon^{2/3})$  correction by a further phase shift in the time origin. Specifically,

$$(3.75) \quad N \sim N_0 + \varepsilon N_1 + \dots,$$

and the solution for  $N_0$  can be written as

$$(3.76) \quad \int_{N_0}^{N_-} \left\{ \frac{1 + g'}{\mu g - N} \right\} dN = t_- - t.$$

Note that  $N_0 \rightarrow N_L$  as  $t \rightarrow \alpha$ , and (cf. Figure 3.2)  $N_L < N_-$ ; thus in the recovery phase  $1 + g' > 0$  and  $\mu g > N$ . In (3.70),  $t_-$  is the time when the second transition region occurs.

We match (3.76) to the preceding shock layer by writing  $N \sim N_0 \sim N_L - \varepsilon^{2/3} v_L$ ,  $t = \alpha + \varepsilon t^*$  in (3.76), and we find that matching requires that

$$(3.77) \quad t_- = \int_{N_L}^{N_-} \left\{ \frac{1 + g'(N)}{\mu g(N) - N} \right\} dN + \varepsilon^{2/3} \left[ \frac{\tilde{t}_0}{\Omega} + v_L \left\{ \frac{1 + g'_L}{\mu g_L - N_L} \right\} \right] + O(\varepsilon \ln \varepsilon).$$

As  $t \rightarrow t_-$ , (3.76) gives, analogously to (3.14),

$$(3.78) \quad N_0 \sim N_- - Q_1(t_- - t)^{1/2} + Q_2(t_- - t) + \dots,$$

and in the transition region at  $t = t_-$ , we get

$$(3.79) \quad \begin{aligned} N &= N_- + \frac{\varepsilon^{1/3} \omega}{g''_-} f, \\ t &= t_- + r(\varepsilon) + \frac{\varepsilon^{2/3}}{\omega} \tilde{t}, \end{aligned}$$

where

$$(3.80) \quad \omega = [-g''_- Q_1]^{2/3}$$

(note  $g''_- < 0$  and  $Q_1 > 0$ ).

This leads directly to (3.22), but with  $k, l, \omega$  replacing  $\kappa, \lambda, \Omega$ ;  $k$  and  $l$  are defined in the appendix as  $\kappa$  and  $\lambda$ , but with  $\omega, g''_-, g'''_+$  replacing  $\Omega, g''_+, g'''_+$ . Hence

$$(3.81) \quad f \sim \frac{-\text{Ai}'(-\tilde{t})}{\text{Ai}(-\tilde{t})} + O(\varepsilon^{1/3}),$$

and matching occurs automatically at leading order (and  $r = O(\varepsilon \ln \varepsilon)$ ).

The transition layer leads to a shock layer where we write, by analogy to (3.47),

$$(3.82) \quad t = t_- + \frac{\varepsilon^{2/3} \tilde{t}_0}{\omega} + [r(\varepsilon) + \varepsilon^{2/3} s(\varepsilon)] + \varepsilon t^*,$$

and  $r + \varepsilon^{2/3} s = O(\varepsilon \ln \varepsilon)$ . Now, notice that to obtain the  $O(\varepsilon^{2/3})$  shift in (3.77), we need to know  $v_L$ , and thus  $E_2$  and  $E_3$  in (3.71). Similarly, we find that, putting

$$(3.83) \quad N \sim u + \varepsilon^{2/3} v + O(\varepsilon)$$



in the recovery shock, then

$$(3.84) \quad \begin{aligned} u &\sim N_- + \frac{1}{g''_- t^*} + \frac{e_1 - e_2 \ln(-t^*)}{t^{*2}} + \dots, \\ v &\sim -e_3 [t^* + e_2 g''_- \ln(-t^*) - e_4 \dots] \end{aligned}$$

as  $t^* \rightarrow -\infty$ , and we will need  $e_2$  and  $e_3$ . Since the equation for  $f$  in the recovery transition region is of the same form as in the first transition region,  $e_2$  and  $e_3$  are found in the same way, and thus

$$(3.85) \quad e_2 = \frac{\omega + l}{3\omega g''_-}, \quad e_3 = \frac{\omega^2 \tilde{t}_0}{3g''_-}.$$

Finally, as  $t^* \rightarrow \infty$  in the recovery shock,

$$(3.86) \quad N \sim N_U - \varepsilon^{2/3} v_U + O(\varepsilon, \text{TST}),$$

where

$$(3.87) \quad \begin{aligned} N_U + g_U &= N_- + g_-, \\ v_U &= \frac{e_3 [\frac{3}{2} + g''_- e_2]}{1 + g'_U}. \end{aligned}$$

At this point, we reenter the first slow phase, and if the motion is periodic, with period  $P(\varepsilon)$ , then we should regain the slow phase solution (3.13) with  $t$  replaced by  $t_+$ , where

$$(3.88) \quad t_+ = t - P(\varepsilon);$$

thus

$$(3.89) \quad \int_{N_+}^N \left\{ \frac{1 + g'}{N - \mu g} \right\} dN \sim -t_+ = P(\varepsilon) - t,$$

and we match this directly to the recovery shock as  $t_+ \rightarrow 0$ . We have  $N \sim N_U - \varepsilon^{2/3} v_U$ ,  $t = t_- + \varepsilon^{2/3} \tilde{t}_0 / \omega + \varepsilon t^* + O(\varepsilon \ln \varepsilon)$ , and matching of the two expressions requires, using (3.77), that

$$(3.90) \quad \begin{aligned} P(\varepsilon) &= \int_{N_+}^{N_U} \left( \frac{1 + g'}{N - \mu g} \right) dN + \int_{N_L}^{N_-} \left( \frac{1 + g'}{\mu g - N} \right) dN \\ &\quad + \varepsilon^{2/3} \left[ \tilde{t}_0 \left( \frac{1}{\omega} + \frac{1}{\Omega} \right) + v_L \left( \frac{1 + g'_L}{\mu g_L - N_L} \right) - v_U \left( \frac{1 + g'_U}{N_U - \mu g_U} \right) \right] \\ &\quad + O(\varepsilon \ln \varepsilon), \end{aligned}$$

and this completes our analysis of the periodic solutions.

**4. Discussion.** The model we have sought to understand is (2.6):

$$(4.1) \quad \dot{N} = g(N_1) - g(N) + \varepsilon[\mu g(N_1) - N].$$

If written in terms of the slow time  $t = \varepsilon t^*$ , this is

$$(4.2) \quad \varepsilon N' = g(N_\varepsilon) - g(N) + \varepsilon[\mu g(N_\varepsilon) - N].$$

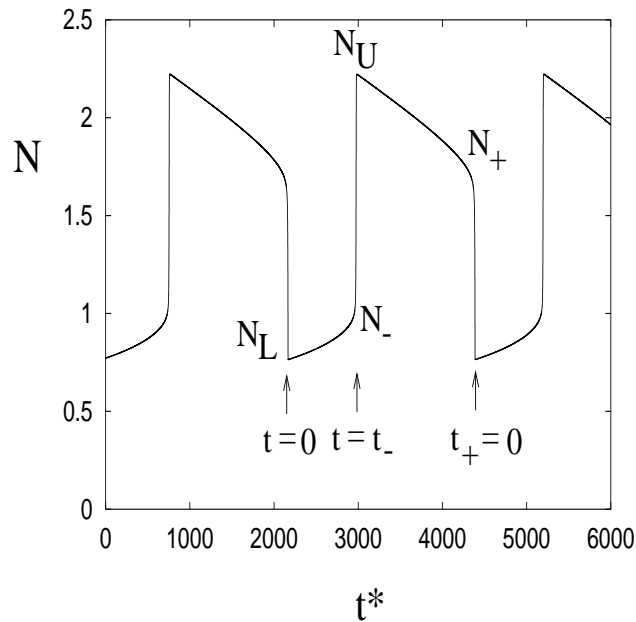


FIG. 4.1. Numerical solution for  $N(t^*)$  when  $b = 3.9$ ,  $\mu = 1.2$ ,  $n = 3$ , and  $\varepsilon = 0.0001$ . For a choice of origin for  $t$  at the minimum, the subsequent value  $t_-$  at the next transition is shown, and also shown is the phase resetting origin for  $t_+ = t + P$ .

The analysis applies generally for unimodal functions satisfying  $g'(N_{\pm}) = -1$ , and oscillations occur for  $\mu \in (\mu_-, \mu_+)$ , where

$$(4.3) \quad \mu_{\pm} = \frac{N_{\pm}}{g(N_{\pm})}.$$

As  $\varepsilon \rightarrow 0$ , we predict periodic solutions having periods (in  $t^*$ ) of  $P(\varepsilon)/\varepsilon$ , where  $P$  is given by (3.90). The maximum and minimum values are approximately

$$(4.4) \quad N_{\max} = N_U - \varepsilon^{2/3} v_U$$

and

$$(4.5) \quad N_{\min} = N_L - \varepsilon^{2/3} v_L,$$

respectively. Figure 4.1 shows an example of the solution at very low  $\varepsilon$ , while Table 4.1 and Figures 4.2–4.5 show how these predictions compare with numerical solutions, for the particular choice of  $g = bN/(1 + N^n)$ . It can be seen that the agreement improves, as expected, as  $\varepsilon$  becomes small.

In terms of the original dimensional quantities of the model, we see that the maximum and minimum values of  $N$  depend asymptotically entirely on the form of the function  $g(N)$ . The dimensional period is given to leading order by  $P_0\tau/\varepsilon$ , where

$$(4.6) \quad P_0 = \int_{N_+}^{N_U} \left( \frac{1 + g'}{N - \mu g} \right) dN + \int_{N_L}^{N_-} \left( \frac{1 + g'}{\mu g - N} \right) dN.$$

TABLE 4.1

Numerical and predicted values of  $N_{\max}$ ,  $N_{\min}$ , and period  $P$  given by (4.4), (4.5), and (3.90). Upper figures in each row are the values from numerical solutions; lower figures are analytical results. Parameter values used are  $n = 3$ ,  $b = 3.9$ , and  $\mu = 1.2$ . A fourth order Runge–Kutta method is used to solve the equation, and results vary somewhat with step size, as can be seen in Figures 4.4 and 4.5. All these results are using a step size of 0.01.

$\varepsilon$	Max	Min	$P/\varepsilon$	$P$
0.11	2.401	0.753	9.8	1.078
0.1	2.393	0.760	10.31	1.031
	3.546	0.578	16.14	1.614
0.05	2.342	0.778	15.03	0.7515
	3.060	0.645	21.91	1.095
0.02	2.300	0.776	26.17	0.5234
	2.681	0.698	34.58	0.692
0.005	2.260	0.765	69.11	0.34555
	2.410	0.736	80.47	0.402
0.001	2.237	0.762	260.14	0.26014
	2.293	0.753	277.12	0.277
0.0001	2.223	0.763	2220.9	0.2221
	2.245	0.759	2260.6	0.226
0.00002	2.220	0.763	10738.0	0.21476
	2.236	0.760	10841.6	0.217

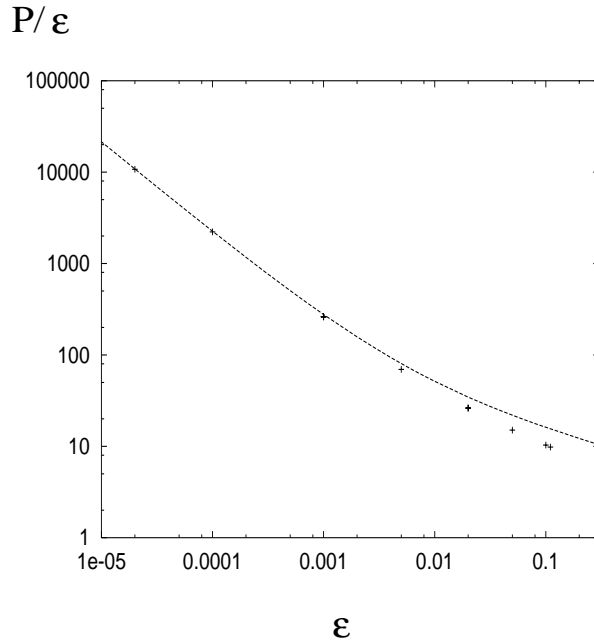


FIG. 4.2. Variation of the actual period (in  $t^*$ ) of the numerical solution (crosses) as a function of  $\varepsilon$ , together with the theoretical prediction (solid curve) from (3.90), for  $b = 3.9$ ,  $\mu = 1.2$ ,  $n = 3$ .

$P_0$  essentially depends only on the shape of  $g(N)$ , and thus the period is

$$(4.7) \quad P_{\text{dim}} = \frac{P_0}{\delta},$$

that is, it is controlled by the rate of differentiation. However, oscillations do not

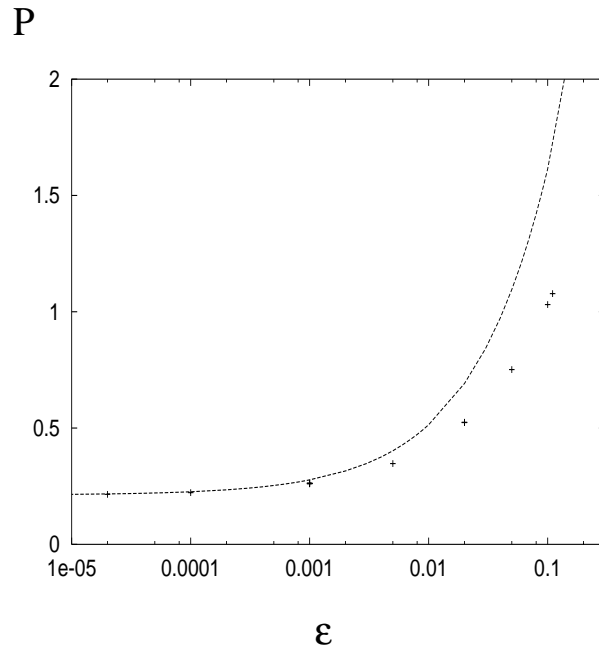


FIG. 4.3. As for Figure 4.2, but plotting the period in  $t$ ,  $P$ , versus  $\epsilon$ .

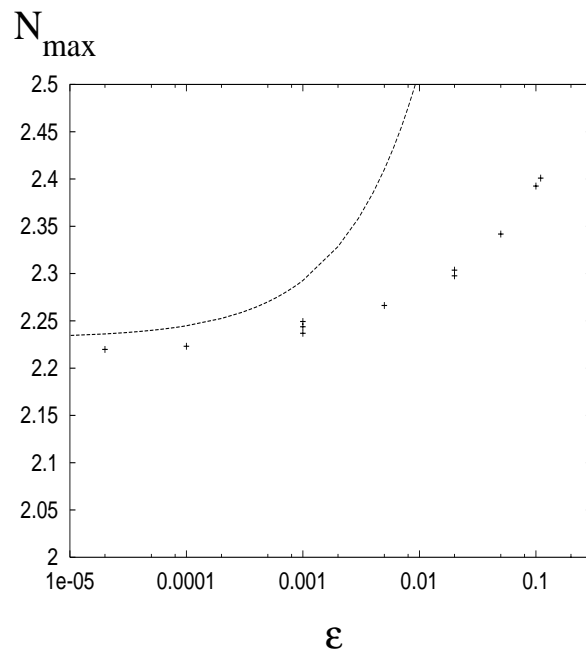


FIG. 4.4. Numerical values of  $N_{\max}$  (crosses) and predicted values (solid curve) from (4.4) as a function of  $\epsilon$  for  $b = 3.9$ ,  $\mu = 1.2$ ,  $n = 3$ . When more than one cross is plotted, as at  $\epsilon = 0.001$ , the different values come from the use of different step sizes in the integrator. Specifically, at  $\epsilon = 0.001$ , decreasing step sizes 0.01, 0.005, 0.001 gave increasing values of  $N_{\max}$ .

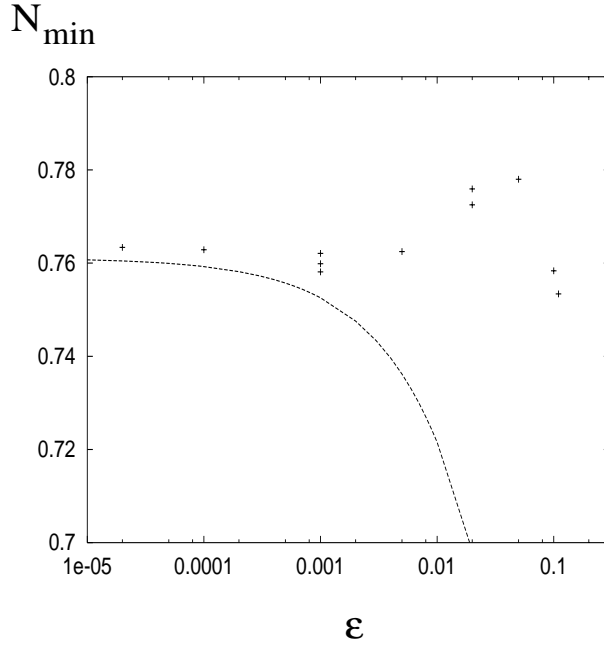


FIG. 4.5. Computed and predicted values for  $N_{\min}$ , similar to Figure 4.4. Here decreasing step size at  $\varepsilon = 0.001$  leads to decreasing  $N_{\min}$ .

occur at all unless  $\mu$  is a finite range of  $O(1)$ , and this requires that  $\gamma\tau$  is increased over normal values, which can be due either to an increased proliferation delay  $\tau$  or to an increased apoptotic rate  $\gamma$ .

It is difficult to give a useful characterization of the dimensional maximum and minimum values of  $N$ . These are simply  $N_{\dim}^{\max} \approx \theta N_U$  and  $N_{\dim}^{\min} \approx \theta N_L$ . The easiest interpretation of  $N_U$  and  $N_L$  is that shown graphically in Figure 4.6. We can get a crude idea of the magnitude of the maximum and minimum values, however, if we consider the specific proliferation rate  $\beta(N)$  to be adequately represented by the two quantities  $\beta_0$ , which is the maximum specific proliferation rate, and  $\theta$ , which gives an estimate of the value of  $N$  where the proliferation rate “turns off.” Our crude estimate idealizes  $\beta$  as being piecewise constant, with a switch off occurring at  $N = \theta$ , and will generally be reasonably accurate if the switch at  $N \approx \theta$  is sharp. Then we have the estimates

$$(4.8) \quad \begin{aligned} N_{\dim}^{\min} &\approx \frac{\theta}{1 + \beta_0\tau}, \\ N_{\dim}^{\max} &\approx (1 + \beta_0\tau)\theta, \end{aligned}$$

and these could in principle be used to constrain the appropriate form of  $\beta$  in the model. The amplitude of the oscillation is, very roughly,  $2\beta_0\tau\theta$ .

From a mathematical perspective, the most interesting feature of the analysis is that it is completely analogous to that of a second order relaxational differential equation. In fact, Figure 4.6 indicates the similarity which can be drawn between the present model and that of the simple system

$$(4.9) \quad \begin{aligned} \varepsilon N' &= v - g(N), \\ N' + v' &= \mu g(N) - N - \varepsilon\mu v'. \end{aligned}$$

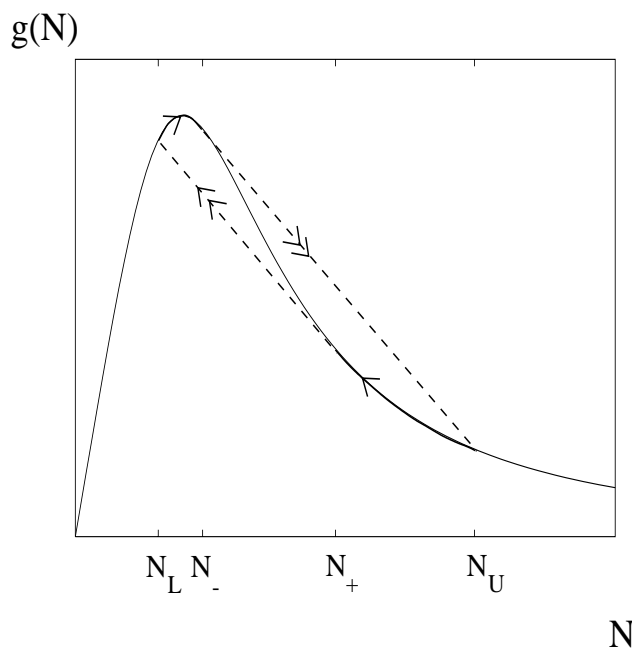


FIG. 4.6. Phase diagram of the relaxation oscillations of both (4.9) and (4.13).  $g(N)$  is plotted for  $b = 5$ ,  $n = 3$ .

In (4.9), the slow manifold is  $v = g(N)$ , and on this

$$(4.10) \quad N' \approx \frac{\mu g - N}{1 + g'}$$

just as for (4.2). For (4.9), there is a fast phase as  $N \rightarrow N_+$  or  $N \rightarrow N_-$ , and in the fast phases,  $N + v$  is approximately constant; since  $v \rightarrow g(N)$  at either end we have the same results

$$(4.11) \quad \begin{aligned} N_+ + g(N_+) &= N_L + g(N_L), \\ N_- + g(N_-) &= N_U + g(N_U), \end{aligned}$$

as for (4.2).

The analogy can be slightly tightened by defining the functions

$$(4.12) \quad \begin{aligned} v &= g(N_\varepsilon) + \varepsilon[\mu g(N_\varepsilon) - N], \\ \hat{v} &= \frac{g(N) - g(N_\varepsilon)}{\varepsilon}. \end{aligned}$$

Evidently  $\hat{v}$  is functionally dependent on  $v$ , and for slowly varying  $N$ , we have  $v \approx g(N)$ ,  $\hat{v} \approx [g(N)]'$ , i.e.,  $\hat{v} \approx v'$ ; clearly this is inappropriate when  $N$  is rapidly varying. The definitions (4.12) allow us to write (4.2) in the suggestive form

$$(4.13) \quad \begin{aligned} \varepsilon N' &= v - g(N), \\ N' + \hat{v} &= \mu g(N) - N - \varepsilon \mu \hat{v}, \end{aligned}$$

and we see that the functional equation reduces precisely to the second order system (4.9) under the identification  $\hat{v} = v'$ . What appears to be extraordinary is that the

infinite dimensional breakdown of this approximation in the fast shock layers does not affect the analytical description in any significant way.

Apart from the mathematical novelty of solving a delay differential equation, there are some physiological ramifications of our analysis. The model for stem cell proliferation in (2.2) is a reasonable synopsis of the process, but the rate function of progress through the cycle,  $\beta(N)$ , is not well constrained. Nor is it possible to access this function directly, since the stem cell population itself is hidden, and oscillations are manifested in the differentiated products, which are themselves dynamically controlled by peripheral controlling mechanisms. Therefore it is useful to be able to characterize the oscillations of the resting stem cell population for a variety of different progression functions  $\beta(N)$ , and our analysis allows us to do this. It will also allow us in future work to analyze how oscillations in the stem cell population propagate through the maturing cell types, so that in principle we can use resulting observed cell cycles as a constraint on the stem cell dynamics.

**Appendix.** In (3.14), we find  $q_1$  and  $q_2$ :

$$(A.1) \quad q_1 = \left[ \frac{2(N_+ - \mu g_+)}{g_+''} \right]^{1/2},$$

$$(A.2) \quad q_2 = \frac{1}{3} q_1^2 \left[ \left( \frac{1 + \mu}{N_+ - \mu g_+} \right) - \frac{g_+'''}{2g_+''} \right];$$

$h_+$  is defined in (3.18):

$$(A.3) \quad h_+ = \frac{1 + \mu}{2g_+''(N_+ - \mu g_+)};$$

$\Omega$  is defined in (3.20):

$$(A.4) \quad \Omega = q_1^{2/3} g_+''^{2/3};$$

$\kappa$  and  $\lambda$  are defined in (3.23):

$$(A.5) \quad \kappa = \frac{2}{\Omega^2}(1 + \mu),$$

$$(A.6) \quad \lambda = \frac{\Omega g_+'''}{g_+''^2};$$

$r_1$ ,  $r_{21}$ , and  $r_{22}$  are defined in (3.41):

$$(A.7) \quad r_1 = \frac{1}{4g_+''},$$

$$(A.8) \quad r_{21} = \frac{q_1}{2} \left[ A_1 + \frac{q_2}{2g_+''q_1^2} - \frac{1}{2} - \frac{g_+'''}{4g_+''^2} + h_+ \ln q_1 \right],$$

$$(A.9) \quad r_{22} = \frac{1}{4} q_1 h_+;$$

$s_1$ ,  $s_{21}$ , and  $s_{22}$  are defined in (3.42):

$$(A.10) \quad s_1 = \frac{1}{3} \kappa - \frac{1}{6} \lambda,$$

$$(A.11) \quad s_{21} = \frac{1}{2} C_2 - \frac{1}{4} \Omega - \frac{1}{6} \lambda + \frac{1}{12} \kappa,$$

$$(A.12) \quad s_{22} = \frac{1}{8} \kappa.$$

$E_2$  and  $E_4$  appear in (3.57) and (3.59):

$$(A.13) \quad E_2 = \frac{1}{3g_+''} \left( 1 + \frac{g_+'''}{g_+''^2} \right),$$

$$(A.14) \quad E_4 = \frac{1}{2}g_+''E_2 + \frac{g_+'''}{g_+''^2} + g_+''E_1.$$

In (3.78) we find  $Q_1$  and  $Q_2$ :

$$(A.15) \quad Q_1 = \left[ \frac{2(N_- - \mu g_-)}{g_-''} \right]^{1/2},$$

$$(A.16) \quad Q_2 = \frac{1}{3}Q_1^2 \left[ \left( \frac{1 + \mu}{N_- - \mu g_-} \right) - \frac{g_-'''}{2g_-''} \right],$$

and then  $\omega$ ,  $k$ , and  $l$  are introduced in (3.80) and are restated below:

$$(A.17) \quad \omega = (-Q_1 g_-'')^{2/3},$$

$$(A.18) \quad k = \frac{2}{\omega^2}(1 + \mu),$$

$$(A.19) \quad l = \frac{\omega g_-'''}{g_-''^2}.$$

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