

Insight into the Transfer Function, Gain, and Oscillation Onset for the Pupil Light Reflex Using Nonlinear Delay-Differential Equations

A. Longtin¹ and J. G. Milton²

¹ Department of Physics and ² Department of Physiology, McGill University, 3655 Drummond Street, Montreal, P.Q., Canada H3G 1Y6

Abstract. Analogies are drawn between a physiologically relevant nonlinear delay-differential equation (DDE) model for the pupil light reflex and servo control analytic approaches. This DDE is shown to be consistent with the measured open loop transfer function and hence physiological insight can be obtained into the gain of the reflex and its properties. A Hopf bifurcation analysis of the DDE shows that a limit cycle oscillation in pupil area occurs when the first mode of the characteristic equation becomes unstable. Its period agrees well with experimental measurements. Beyond the point of instability onset, more modes become unstable corresponding to multiple encirclings of $(-1, 0)$ on the Nyquist plot. These modes primarily influence the shape of the oscillation. Techniques from dynamical systems theory, e.g. bifurcation analysis, can augment servo control analytic methods for the study of oscillations produced by nonlinear neural feedback mechanisms.

1 Introduction

One of the most important mechanisms for regulating neural activity is feedback. An undeniable feature of human neural feedback mechanisms in health and disease is their propensity to generate oscillations and other complex dynamical behaviours, e.g. tremors and the electrical activity of the cortex (Mackey and Milton 1987). The pupil light reflex is a human neural feedback mechanism in which it is possible to study the occurrence of oscillations and their properties non-invasively (Stark 1984). It is well known that regular oscillations in pupil area occur under “high gain” conditions (Milton et al. 1988; Stark 1959, 1962; Stark and Cornsweet 1958; Stern 1944) and that the period of these oscillations can be estimated from the experimentally measured open-loop transfer function for this reflex (Stark and Cornsweet 1958). Moreover, it has

been demonstrated that the “linear” properties of this reflex determine the frequency of these oscillations, whereas the shape and amplitude depend on the “nonlinearities” (Stark 1962).

Interpretation of the above findings in a biological context requires that parameters such as the gain and open-loop transfer function be defined neuro-physiologically. Previous studies have examined the effect of the nonlinear characteristics of the iris musculature on the overall reflex gain and on pupillary phenomena such as hippus and the pupil size effect (Krenz and Stark 1984; Stark 1984; Usui and Stark 1982). However, little attention has been given to identifying the physiological parameters which determine the linear and nonlinear properties of the high gain oscillations.

In a previous study we showed that the oscillations in pupil area which occur under conditions of external piecewise constant feedback were well described by the solutions of a nonlinear delay-differential equation (Longtin and Milton 1988). Here we draw analogies between this delay-differential equation and servo control analytic theory. In this way we are able to obtain insight into the neuro-physiological properties of this reflex which determine the gain and open loop transfer function and which shape the high gain oscillations.

2 Background

The changes in pupil area, A , which occur under conditions of imposed piecewise constant feedback can be described by (Longtin and Milton 1988; Milton and Longtin in preparation)

$$\frac{dg}{dA} \frac{dA}{dt} + \alpha g(A) = F(A_\tau), \quad (1)$$

where α is the rate constant for pupillary movements, τ is the neural time delay, and $F(A_\tau)$ is a piecewise

constant function of A_τ . The function $F(A_\tau)$ takes on one of two values depending on whether pupil area is greater than or less than a threshold. The notation A_τ denotes pupil area at a time τ in the past, i.e. $A_\tau = A(t - \tau)$. The feedback function, $g(A)$, relates changes in iris muscle activity, x , to changes in A and takes into account the inverse relationship between x and A . In our previous studies $g(A)$ was taken to be a linear function. Note that in order to solve (1) it is necessary to specify A_τ as an initial function on the interval $(-\tau, 0)$.

The right hand side of (1) is a forcing term that represents the changes in the retinal light flux, $\phi(\phi = IA$, where I is the retinal illumination), due to changes in pupil area. For smooth negative feedback, (1) becomes (Longtin and Milton, in preparation)

$$\frac{dg}{dA} \frac{dA}{dt} + \alpha g(A) = \gamma \ln \left[\frac{\phi_\tau}{\phi} \right] = \gamma \ln \left[\frac{I_\tau A_\tau}{\hat{I} \hat{A}} \right], \quad (2)$$

where we have taken into account the logarithmic compression of light intensities at the retina (Cornsweet 1967), γ is the rate constant for the neural firing frequency and $\hat{\phi}$, \hat{I} , \hat{A} are the values of ϕ , I , A at threshold, i.e. the values below which there is no pupillary response.

Comparison of (2) to linear servo control theoretical descriptions of the pupil light reflex (Stark 1962, 1984) requires linearization of (2) about the equilibrium pupil area, A^* , corresponding to an incident illumination of I^* . The value of A^* is obtained from (2) by setting $dA/dt = 0$ and is the solution of the Eq.

$$\alpha g(A^*) = \gamma \ln \left[\frac{I^* A^*}{\hat{I} \hat{A}} \right] \quad (3)$$

and linearization of (2) about A^* leads to

$$\alpha^{-1} \frac{dA}{dt} + A = G \cdot [A_\tau - A^*] + A^*, \quad (4)$$

where

$$G \equiv \frac{\gamma}{\alpha \beta A^*} \quad (5)$$

and $\beta \equiv dg/dA$ evaluated at A^* . When $\beta < 0$, it follows that $G < 0$ which corresponds to negative feedback.

3 Transfer Function

In this section we show that (4) can be derived from the experimentally measured closed loop transfer function for the pupil light reflex, $H(s)$

$$H(s) = \frac{P(s)}{1 + P(s)}, \quad (6)$$

where the open-loop transfer function is

$$P(s) = \frac{G_0 \exp(-\tau s)}{(1 + ks)^3} \quad (7)$$

and where s is the Laplace variable and $\tau = 0.18$ s. While the 18 db/octave roll-off of the Bode amplitude plot suggested that the transfer function had three poles, they could not be determined individually and were all set equal to 10 s^{-1} by choosing the time constant $k = 0.1$ s (Stark 1959).

$G_0 = 0.16$ is the dimensionless open-loop gain. The open loop gain is normally equal to the product of the forward gain and the feedback gain. The latter corresponds to the coefficient of $P(s)$ in the denominator of (6) and is unity here. We have called G_0 in (7) the open-loop gain since it is numerically equal to the forward gain.

Based on small signal analysis, Stark (1959) has argued that the open-loop gain should be expressed as

$$G_0 \equiv \frac{I^* \Delta A}{A^* \Delta I} = \frac{\Delta A / A^*}{\Delta I / I^*}. \quad (8)$$

The numerator of (8) describes the change of flux due to pupil constriction in response to the change of flux due to the light increment in the denominator.¹ Since $I^* \Delta A < 0$ when $A^* \Delta I > 0$, G_0 is negative. However, G_0 has been defined to be positive (Stark 1959) and the negative sign is taken into account in writing the closed-loop transfer function for negative feedback $H(s)$ (6).

In order to compare (4) to the formulation of (6), it is necessary to rewrite (6) in the time domain to obtain

$$k^3 \frac{d^3 \phi}{dt^3} + 3k^2 \frac{d^2 \phi}{dt^2} + 3k \frac{d\phi}{dt} + \phi(t) = G_0 \cdot [F(t - \tau) - \phi(t - \tau)], \quad (9)$$

where $\phi = I^* \Delta A$ is the retinal light flux change due to pupil area change, $F = A^* \Delta I$ reflects the flux change due to the light change and A^* is the equilibrium pupil area in an ambient light level I^* . The forcing variable F and the state variable ϕ have the same units.² The equilibrium retinal flux for a constant forcing F is $\phi = G_0 F$ in open-loop, and is a factor $(1 + G_0)^{-1}$ smaller in closed-loop.

¹ Another way of seeing this is to write the total differential for the flux. Let $I = I^* + dI$, $A = A^* + dA$; then

$$d\phi \approx \phi(I, A) - \phi(I^*, A^*) = I^* dA + A^* dI + O(dI dA).$$

From (8) we see that the open-loop gain appears as the ratio of the two first order terms

² This can be made clearer by defining the gain as the relative area change over relative illuminance change and dividing (9) by the mean flux $\phi^* = I^* A^*$ to make all quantities dimensionless relative changes

If we identify, to first order, ϕ with $I^* \Delta A$ and F with $A^* \Delta I$, then (9) becomes

$$k^3 I^* \frac{d^3(\Delta A)}{dt^3} + 3k^2 I^* \frac{d^2(\Delta A)}{dt^2} + 3k I^* \frac{d(\Delta A)}{dt} + I^*(\Delta A) = \frac{I^*(\Delta A^*)}{A^*(\Delta I^*)} [A^*(\Delta I)_t - I^*(\Delta A)_t]. \quad (10)$$

Note that ΔI^* and ΔA^* are simply numbers that determine the numerical value of G_0 . Dividing by I^* , keeping only first order derivatives and defining $3k \equiv \alpha^{-1}$, we obtain

$$\alpha^{-1} \frac{d(\Delta A)}{dt} + \Delta A = \frac{\Delta A^*}{A^* \Delta I^*} [A^*(\Delta I)_t - I^*(\Delta A)_t]. \quad (11)$$

Next, define $\Delta A = A - A^*$, then

$$\alpha^{-1} \frac{dA}{dt} + A = A^* - \frac{(\Delta A^*) I^*}{A^*(\Delta I^*)} A_t + \frac{\Delta A^*}{\Delta I^*} (\Delta I)_t + \frac{\Delta A^*}{\Delta I^*} I^* \quad (12)$$

In obtaining (4), we assumed that everything was linearized about A^* which is the steady state response to I^* . In the transfer function approach, this means that the input is constant and equal to I^* . Therefore $(\Delta I)_t = I_t - I^* = 0$. Thus if we identify G_0 in (8) with $-G$ in (5), (12) becomes

$$\alpha^{-1} \frac{dA}{dt} + A = A^* + \frac{\gamma}{\alpha \beta A^*} A_t - \frac{\gamma}{\alpha \beta} = G \cdot [A_t - A^*] + A^* \quad (13)$$

which is exactly our (4).

4 Gain

The observations in Sect. 3 indicate that the gain, G , defined by (5) and the gain, G_0 , defined by (8) are related. The identification $G_0 \rightarrow -G$ is reasonable in view of the way we defined the signs of these two gains. Further, both determine the magnitude of the influence of a delayed variable on the instantaneous time evolution of this variable. It thus makes sense to identify the forward gain (or open loop gain as we have seen) in control systems theory with the coefficient of A_t in the delay-differential equation describing feedback operation.

An alternate way in which the association between G and G_0 can be explored is to use the fixed point condition given by (3). Equation (3) simply states that I^* can be considered an explicit function of A^*

$$I^* = \frac{\hat{\phi}}{A^*} \exp[\alpha \gamma^{-1} g(A^*)]. \quad (14)$$

We can then compute

$$\frac{dI^*}{dA^*} = -\frac{I^*}{A^*} + g'(A^*) I^* \alpha \gamma^{-1} \quad (15)$$

$$\frac{A^* dI^*}{I^* dA^*} = -1 + A^* \alpha g'(A^*) \gamma^{-1}. \quad (16)$$

Provided we identify $g'(A^*)$ with β and the left hand side with $-1/G_0$ (we put a negative sign here because G_0 is defined positive), we obtain

$$-\frac{1}{G_0} = -1 + \frac{1}{G} \quad \text{or} \quad G = \frac{G_0}{G_0 - 1}. \quad (17)$$

This calculation is justified as long as we are not too far from equilibrium where the fixed point condition holds. This means that A^* should not vary too much, i.e. $dA^*/dI^* \ll 1$, implying that (17) holds only for $G_0 \ll 1$. In this limit we do indeed recover our earlier relation: $G \approx -G_0 - G_0^2 \approx -G_0$.

5 Pupil Response to a Step Light Input

From the open loop transfer function given by (7), the predicted response of the pupil to a step light input, $U_3(t)$, is

$$U_3(t) = 1 - \exp\left(-\frac{t}{k}\right) \left[1 + \frac{t}{k} + \frac{t^2}{k}\right], \quad (18)$$

where we have neglected the time delay which would simply shift the response. On the other hand, the observations in Sect. 3 suggest that under certain conditions it is possible to approximate $U_3(t)$ by a first-order response, $U_1(t)$, i.e.

$$U_3(t) \sim U_1(t) = 1 - \exp\left(-\frac{t}{\delta}\right), \quad (19)$$

where δ is a time constant to be determined. We can compute δ in a way that will minimize the square deviation of these two positive definite functions, i.e.

$$\frac{d}{d\delta} \int_0^{\infty} |U_1(t) - U_3(t)|^2 dt = 0. \quad (20)$$

This problem leads, after a lengthy, but straightforward algebraic computation, to the problem of finding the roots of a fourth order polynomial in δ which can be solved numerically in terms of k . The physically meaningful root is $\delta = 0.311$ s which is roughly equal to $3k$ since $k = 0.1$ s.

As shown in Fig. 1 the first order impulse function using the above value of δ agrees with the third order step response. Interestingly the value of $\delta = 0.311$ s is roughly equal to $3k$, where $k = 0.1$ s is the value determined by Stark (1959). Thus this value of δ can be regarded as the value of α^{-1} in (4). It should be noted

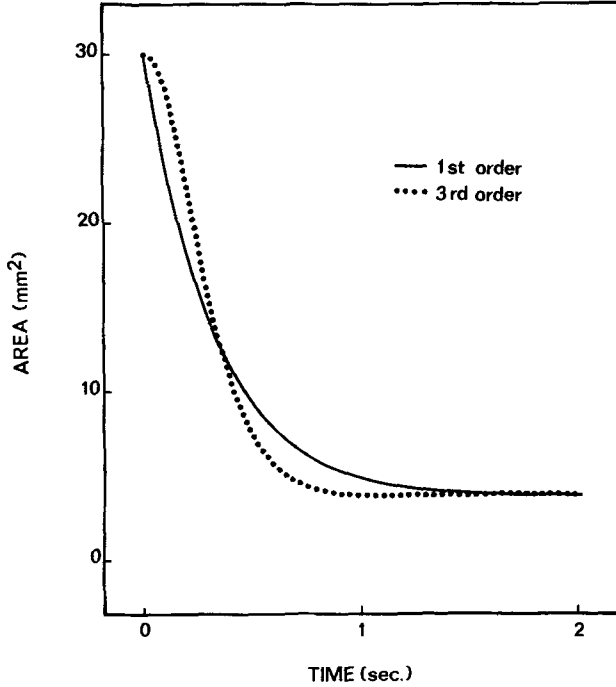


Fig. 1. Comparison of open loop step responses for iris activity for a third order model (7) with $k = 0.1$ s (dotted line) with a first order approximation with $\delta = 0.311$ s (solid line). We have neglected the time delay which would simply shift the responses. Ordinate is pupil area computed by subtracting iris activity from the maximal pupil area (Stark 1959) and has been arbitrarily illustrated by plotting $A(t) = 30 - 2U_3(t)$

that the slow onset of $U_3(t)$ may be at least partially incorporated into $U_1(t)$ as an additional contribution to the pure lag.

6 Conditions for Oscillation Onset

In linear control systems theory, the onset of oscillation is studied using the Nyquist criterion (Fig. 2). When the polar plot of the open loop transfer function (Nyquist plot) encircles the $(-1, 0)$ point in the complex plane, regenerative feedback occurs at a frequency for which $P(s) = -1$, corresponding to a pole in the closed-loop transfer function (see e.g. Pallu de la Barriere 1967). This criterion is also applicable when delays are present. Generally delays destabilize systems as do increases in gain. The presence of a delay causes a pure rotation of the polar plot, which may lead to an encircling of the $(-1, 0)$ point. That is why even a first order delay-differential equation can be made unstable by increasing the gain or the delay.

The conditions for instability and the frequency of the oscillation at the onset of instability can be directly determined from an analysis of (4). Define a small deviation in pupil area from A^* as $a(t)$, i.e. $a(t) = A(t) - A^*$. Then the characteristic equation can be

obtained by substituting $a(t) \sim \exp(\lambda t)$ into (4) and is

$$\lambda + \alpha + B \exp(-\lambda\tau) = 0, \quad (21)$$

where λ is typically a complex eigenvalue and $B \equiv -\alpha G$. Equation (21) has an infinite number of roots which we denote as $\lambda_i, \bar{\lambda}_i$, where $\bar{\lambda}_i$ is the complex conjugate of λ_i . A conjugate pair of roots, $(\sigma_i + i\omega_i, \sigma_i - i\omega_i)$, characterize a mode. In Fig. 3 we show the values of σ, ω for the two modes of (21) with the largest real parts as a function of B for $\alpha = 3.21 \text{ s}^{-1}$ and $\tau = 300 \text{ ms}$. For simplicity only the root with positive frequency has been shown.

The problem of looking for pure imaginary roots of the characteristic equation is the same as that of determining the condition for regenerative feedback. At the point of onset of instability, the frequency of the oscillation will be determined by the mode with the largest real part, σ_1 (Longtin and Milton, in preparation). Further, there is a supercritical Hopf bifurcation between a locally stable equilibrium and a locally stable periodic solution (limit cycle). The condition for the appearance of the limit cycle is

$$\omega_H \tau \geq \cos^{-1} \left(\frac{1}{G} \right), \quad (22)$$

where ω_H is the value of ω_1 when $\sigma_1 = 0, |G| < 1$ and $\omega_H^2 = \alpha^2(G^2 - 1)$ and the inverse cosine takes its value in the interval $[\frac{\pi}{2}, \pi]$ (Hayes 1950; Mackey 1979). Equality holds in (22) at the bifurcation point, where the period, T , is given exactly by

$$T = \frac{2\pi}{\omega_H}, \quad 2\tau < T < 4\tau. \quad (23)$$

Near the bifurcation point B_0 (or τ_0) the period is given approximately by (23) and the amplitude of the oscillation is proportional to the square root of the distance (in parameter space) from the bifurcation point, i.e.

$$\text{Amplitude} \propto \sqrt{B - B_0} \quad (\text{or } \sqrt{\tau - \tau_0}). \quad (24)$$

For an average measured value of $\tau \sim 300 \text{ ms}$ (Milton et al. 1988), the period predicted by (23) is in good agreement with that predicted from the Nyquist plot and that measured experimentally.

Equations (9) and (13) are of the same form. Thus, in the same way that (9) is associated with the third order open loop transfer function (7), it is possible to associate a first order open loop transfer function with (13), and hence to compute a Nyquist plot for (13). In Fig. 2a we compare the Nyquist plot calculated from our first order model (solid line) to the third order open loop transfer function measured experimentally (dotted line; Eq. 7) but using the average time delay we have measured for the pupil light reflex (0.3 s) (Milton

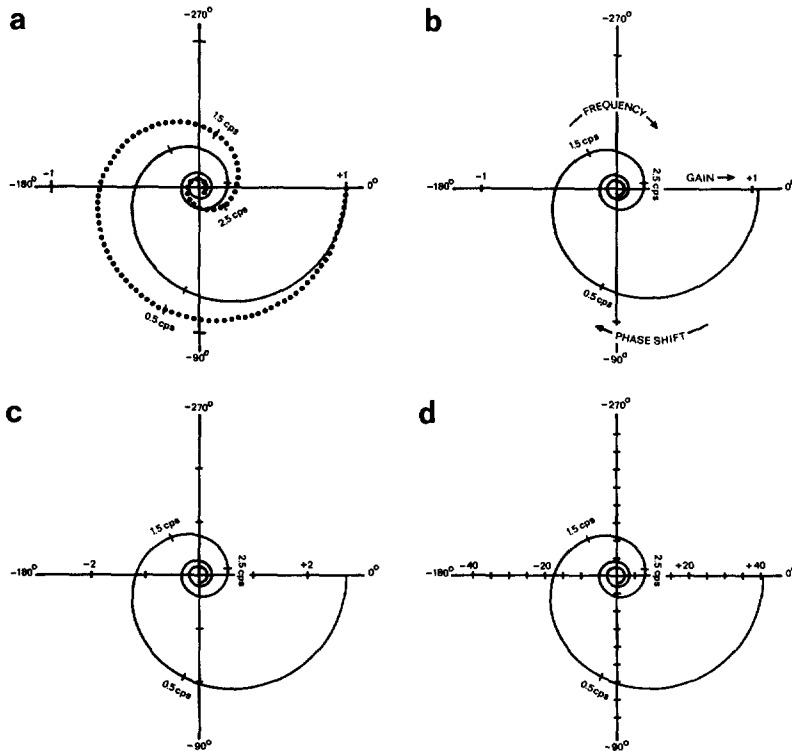


Fig. 2a-d. Polar plots of open loop transfer function (Nyquist plots) for the pupil light reflex. In **a** we compare the third-order open-loop transfer function (dotted line; 7) with $k=0.1$ s and $\tau=0.3$ s to a first-order open-loop transfer function with the same delay and time constant $\delta=0.311$ s (solid line; 19). The gain has been set to one in both cases. In **b-d** we show the effect of increasing n on the Nyquist plots calculated by use of the characteristic equation for (25) (obtained by first linearizing Eq. 25) for the same values of n shown in Fig. 4. The gain in **b-d**, which is proportional to n , is respectively, 3.36, 8.75, 130.3. There are seven encirclings of the $(-1, 0)$ point in **d**. The parameterization is only for positive frequencies (in cps)

et al. 1988). This time delay is longer than that estimated by Stark (1959) from the Bode phase plot (i.e. $\tau=0.18$ s), which is deduced from the phase of the transfer function at 4 Hz and the fact that the third order pole should contribute 270° at this frequency. Differences in τ of this magnitude can arise, for example, because of differences in retinal illumination used to measure the delay (Ellis 1981). It may also arise because the third order step response (Fig. 1) has a slow onset which may be included in our experimentally measured value of τ . As can be seen the predicted high gain oscillation frequency for the first and third order model are similar (respectively, 1.2 Hz and 0.8 Hz). Both of these frequencies are in good agreement with measurements of pupil cycling (Longtin and Milton 1988; Milton et al. 1988; Stark and Cornsweat 1958).

7 Gain Dependence of Oscillation Frequency

It should be noted that the condition for the appearance of undamped oscillatory solutions of (4), i.e. (22), will always be satisfied for sufficiently large τ and/or G . The effect of increasing G on the properties of the oscillations that occur can be studied by analyzing how the roots of (21) depend on the parameter B (proportional to the gain G). In Fig. 3, it is clear that when $\sigma_1 > 0$, $d\lambda_1/dB \approx d\sigma_1/dB$. Hence the frequency varies only slightly with the gain. This accounts for the

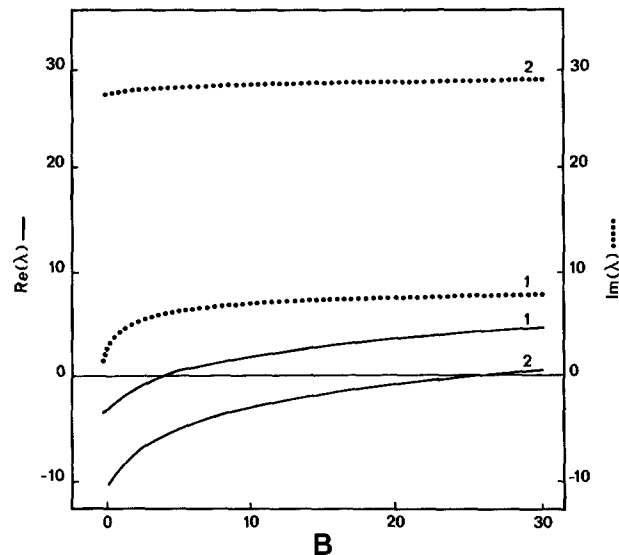


Fig. 3. Plot of the real (solid line) and imaginary (dotted lines) parts of the first two roots of the characteristic equation (21) as a function of B . Parameter values were $\alpha=3.21$ s $^{-1}$ and $\tau=0.3$ s. Only the roots with positive frequency have been plotted

accuracy of the period of the oscillation predicted by linear theory. Interestingly, the period of the first unstable mode in our first order approximation (Sect. 5) is $\sim 2\pi/6$ which is in good agreement with Stark and Cornsweat (1958) and with our measured lower limit (0.9–1.2 s).

8 Beyond the Point of Instability Onset

As G increases in value, more linear modes become unstable as more root pairs cross the imaginary axis into the right hand complex plane. In order to determine the extent to which these additional modes contribute to the frequency and/or shape of the oscillations, we considered the following specific example (Mackey 1979; Mackey and Glass 1977)

$$\frac{dA}{dt} + \alpha A = \frac{c\theta^n}{\theta^n + A^n}, \quad (25)$$

where c and θ are constants. This equation, a generalization of (1), describes first order dynamics for the pupil light reflex operating with smooth external negative feedback (Longtin and Milton, in preparation). The “gain”, which is proportional to the slope of the Hill function evaluated at $A \approx \theta$, increases as n increases. As shown in Fig. 4, regular oscillations in pupil area occur for sufficiently large n . A supercritical Hopf bifurcation occurs for n between 3 and 10. Although the shape of these oscillations change as a function of n , there is little change in the frequency (compare Fig. 4b with 4c). In addition, the more complex waveforms characteristic of the occurrence of higher order bifurcations are not seen.

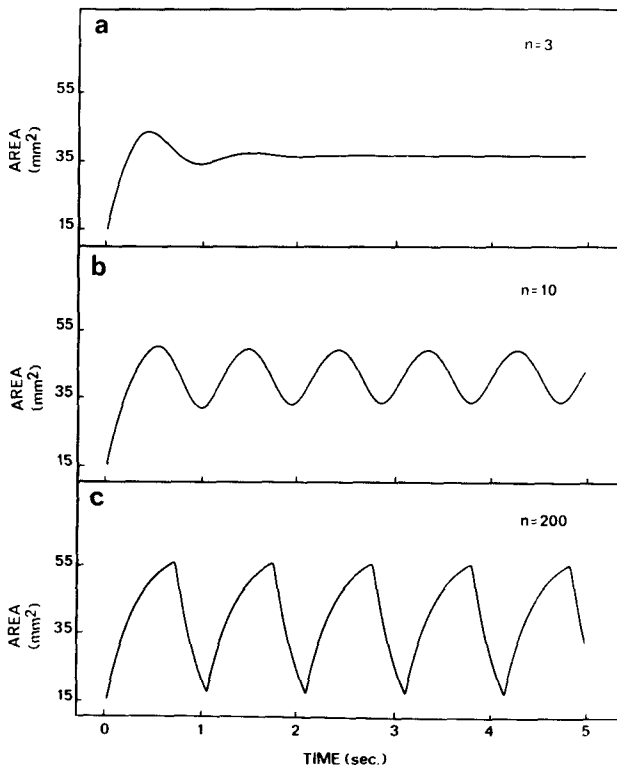


Fig. 4a-c. Solutions of (25) for increasing values of n . Initial condition for solution is: $A(t) = 15 \text{ mm}^2$, $t \in (-\tau, 0)$. Parameter values were: $\tau = 0.3 \text{ s}$; $\alpha = 3.21 \text{ mm}^2$; $\theta = 50 \text{ mm}^2$; $c = 200 \text{ mm}^2$

Figure 7b-d shows the Nyquist plots for (25) as n is increased. As n increases in value, more linear modes become unstable, corresponding to multiple encirclements of $(-1, 0)$ on the Nyquist plot (for example, there are seven encirclements in Fig. 7d). Numerical calculations demonstrated that as either n or τ is increased, the real parts of the eigenvalues increase monotonically, i.e. an unstable mode does not become stable again. Also, in the limit of very large delay, many modes tend to become unstable simultaneously. The modes that become unstable contribute to changing the shape of the oscillations (Fig. 4). The observation that increasing the number of unstable modes in a system can affect mainly the shape, and not the frequency of the oscillation has been reported previously (Nardone et al. 1986).

The above results on the migration of roots across the imaginary axis also hold for a third order system (data not shown). Indeed, we have numerically computed the loci of the first poles of $H(s)$ (6) for $\tau = 0.2 \text{ s}$, $k = 0.1 \text{ s}$ and G_0 between 0.16 and 10. The lowest frequency roots cross at $\omega_1 = 6.3$ and $\omega_2 = 28.6$ corresponding, respectively, to frequencies of 1.0 Hz and 4.55 Hz. These values are very close to those calculated from the characteristic equation of our first order approximation (Fig. 3).

9 Discussion

We have shown that direct analogies can be drawn between a delay-differential equation model for the pupil light reflex and previous servo control analytical studies. Since this delay-differential equation can be derived on the basis of neuro-physiological and anatomical considerations (Longtin and Milton, in preparation), this approach allows us to obtain insight into the properties of the reflex arc which determine, for example, its gain and transfer function. In particular, we are able to associate the gain, G_0 , defined empirically by Stark (1959, p. 1938) with three parameters (5): 1) the rate constant for the neural firing frequency (γ); 2) the steepness of the feedback function (β); and 3) the rate constant for pupillary movements (α). This association is further strengthened by the observation that both G (Longtin and Milton, in preparation) and G_0 (Usui and Stark 1982) attain their highest values at intermediate values of the steady state pupil area. This effect has been studied extensively and has been explained in terms of an “expansive range nonlinearity” operating at the neuromuscular level and related to the nonlinear length-tension diagrams of the iris muscles.

Oscillations in pupil area occur when the gain and/or delay become sufficiently large (22). The frequency of this oscillation predicted by linear servo

control theory and a bifurcation analysis of (4) are both in good agreement with that measured experimentally, i.e. ~ 1 Hz. The appearance of this oscillation is associated with the migration of a root of the characteristic equation of (4), i.e. (21), with the largest real part (λ_1) across the imaginary axis into the right hand complex plane. As we have shown, the success of linear systems analysis in predicting this frequency is related to the relative insensitivity of the imaginary part of λ_1 to changes in the gain.

As the gain increases beyond the point of instability onset, more modes become unstable. In his "clamped" pupil light reflex experiment, Stark (1962) observed a double oscillation. It was suggested that the second mode to cross the imaginary axis results in a 0.2 Hz component superimposed on the basic 1 Hz rhythm. In the language of nonlinear dynamics, this suggests that a bifurcation from a limit cycle to a 2-torus has occurred. However, we have shown that for a first order delay equation this root alters the shape of the oscillation but has relatively little effect on its period. Moreover, numerical simulations of the third order system indicate that the second mode would lie at a frequency of ~ 4.55 Hz and not at 0.2 Hz. This observation indicates that the 0.2 Hz oscillation observed experimentally for the clamped pupil light reflex (Stark 1962), in spontaneously recorded hippus (Bouma and Baghuis 1971) and in narcoleptics at sleep onset (Yoss et al. 1970) cannot be attributed to simple nonlinear negative feedback mechanisms of the type we have considered here.

An important nonlinearity in the pupil light reflex is the response asymmetry of the reflex to the onset and offset of light (Clynes 1968; Stark 1959). Although this asymmetry is most clearly manifested as a difference in the rates of pupil constriction and dilation (Longtin and Milton 1988; Milton and Longtin, in preparation), there is neurophysiological evidence that this asymmetry also occurs at the level of the output of the retina and midbrain as well (Arkin and Miller 1988; Nisida et al. 1959; Schiller 1984). Because of this response asymmetry it is not possible to derive an impulse response in the classical sense from the pupil's response to a single light pulse.

The role played by reflex asymmetry in shaping pupil dynamics is most clearly shown in the case of external piecewise constant feedback since in this case the light is either on or off (Longtin and Milton 1988; Milton and Longtin, in preparation). The transient behaviours of the pupil light reflex highlight the asymmetry. In Fig. 3 we showed that ω_1 is not strongly dependent on the gain (through the related parameter B). We have found that this is also true if α in (21) is varied instead of B in either of two ways: first, by keeping B constant in the same range as that used in

Fig. 3 and second by recomputing B for every value of α since α determines A^* and the parameter B contains $g'(A^*)$. Thus, if transients have died out, the waveforms should depend only on the imaginary part of the eigenvalues which vary only slightly with α . Asymmetry, which requires different values of α , would then be unnoticeable. This may explain the observation that transfer functions obtained under steady state conditions using low amplitude sinusoids predict so well the frequency of the high gain oscillations (Stark and Cornsweet 1958). Presumably there has been some kind of averaging of the asymmetric responses. We expect that a transfer function based on transients (e.g. one obtained by Fourier transforming the time derivative of the step response) may yield different results for light onset and offset.

Servo control analytical techniques, such as linear transfer functions, Volterra or Wiener kernel nonlinear response-fitting techniques, have been extensively used to provide descriptions of the response of the pupil to transient and steady state oscillatory light inputs and to identify nonlinearities in the reflex arc (Krenz and Stark 1984; Semmlow and Chen 1977; Stark 1959, 1984; Usui and Stark 1982). However, the description of the complex oscillatory phenomena produced by nonlinear neural control mechanisms (see, for example, Mackey and Milton 1987) requires that these techniques be augmented with methods from dynamical systems theory such as bifurcation analysis. The analogies between the bifurcation analysis of a nonlinear ordinary differential equation and servo control analytic techniques have been made previously (e.g. Allwright 1977; Mees and Allwright 1979). Here we have given a concrete example to illustrate that these analogies can also be effectively made for nonlinear delay-differential equations.

Acknowledgements. This research was partially supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) through Grant A-0091. AL was supported by an NSERC post-graduate scholarship. We thank Drs. J. Bélair, L. Glass, M. Guevara, and M. Mackey for their comments and assistance.

References

- Allwright DJ (1977) Harmonic balance and the Hopf bifurcation. *Math Proc Camb Phil Soc* 82:453-467
- Arkin MS, Miller RF (1988) Bipolar origin of synaptic inputs to sustained OFF-ganglion cells in the mudpuppy retina. *J Neurophys* 60:1122-1142
- Bouma H, Baghuis LCJ (1971) Hippus of the pupil: periods of slow oscillations of unknown origin. *Vision Res* 11:1345-1351
- Clynes M (1968) Unidirectional rate sensitivity: a biocybernetic law of reflex and humoral systems as physiologic channels of control and communication. *Ann NY Acad Sci* 92:949-969

- Cornsweet TN (1967) Visual perception. Academic Press, New York
- Ellis CJK (1981) The pupillary light reflex in normal subjects. *Br J Ophthalmol* 65:754–759
- Hayes ND (1950) Roots of the transcendental equation associated with a certain difference differential equation. *J Lond Math Soc* 25:226–232
- Krenz W, Stark L (1984) Neuronal population model for the pupil size effect. *Math Biosci* 68:247–265
- Longtin A, Milton JG (1988) Complex oscillations in the pupil light reflex with “mixed” and delayed feedback. *Math Biosci* 90:183–199
- Mackey MC (1979) Periodic auto-immune hemolytic anemia: An induced dynamical disease. *Bull Math Biol* 41:829–834
- Mackey MC, Glass L (1977) Oscillation and chaos in physiological control systems. *Science* 197:287–289
- Mackey MC, Milton JG (1987) Dynamical diseases. *Ann NY Acad Sci* 504:16–32
- Mees AI, Allwright DJ (1979) Using characteristic loci in the Hopf bifurcation. *Proc IEE* 126:628–632
- Milton JG, Longtin A, Kirkham TH, Francis GS (1988) Irregular pupil cycling as a characteristic abnormality in patients with demyelinating optic neuropathy. *Am J Ophthalmol* 105:402–407
- Nardone P, Mandel P, Kapral R (1986) Analysis of a delay-differential equation in optical bistability. *Phys Rev A* 33:2465–2471
- Nisida I, Okada H, Nakano O (1959) Electrical activity of the pretectal region of the cat to visual stimulus. *Yonago Acta Med* 4:7–18
- Pallu de la Barriere R (1967) Optimal control theory. Dover, New York
- Schiller PH (1984) The connections of the retinal ON and OFF pathways to the lateral geniculate nucleus of the monkey. *Vision Res* 24:923–932
- Semmlow J, Chen D (1977) A simulation model of the human pupil light reflex. *Math Biol* 33:5–24
- Stark L (1959) Stability, oscillations and noise in the human pupil servomechanism. *Proc IRE* 47:1925–1939
- Stark L (1962) Environmental clamping of biological systems: pupil servomechanism. *J Opt Soc Am* 52:925–930
- Stark L (1984) The pupil as a paradigm for neurological control systems. *IEEE Trans Biomed Eng* 31:919–924
- Stark L, Cornsweet TN (1958) Testing a servoanalytic hypothesis for pupil oscillations. *Science* 127:588
- Stern HJ (1944) A simple method for the early diagnosis of abnormality of the pupillary reaction. *Br J Ophthalmol* 28:275–276
- Usui S, Stark L (1982) A model for nonlinear stochastic behaviour of the pupil. *Biol Cybern* 45:13–22
- Yoss RE, Moyer NJ, Hollenhurst RW (1970) Hippus and other spontaneous rhythmic pupillary waves. *Am J Ophthalmol* 70:935–941

Received: November 15, 1988

Dr. John G. Milton
 Department of Physiology
 McGill University
 3655 Drummond Street
 Montreal, P.Q.
 Canada H3G 1Y6