MODELLING AUTONOMOUS OSCILLATIONS IN THE HUMAN PUPIL LIGHT REFLEX USING NON-LINEAR DELAY-DIFFERENTIAL EQUATIONS

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Neurophysiological and anatomical observations are used to derive a non-linear delay-differential equation for the pupil light reflex with negative feedback. As the gain or the time delay in the reflex is increased, a supercritical Hopf bifurcation occurs from a stable fixed point to a stable limit cycle oscillation in pupil area. A Hopf bifurcation analysis is used to determine the conditions for instability and the period and amplitude of these oscillations. The more complex waveforms typical of the occurrence of higher order bifurcations were not seen in numerical simulations of the model. This model provides a general framework to study the different types of dynamical behaviors which can be produced by the pupil light reflex, e.g. edge-light pupil cycling.

1. Introduction. An intriguing aspect of the nervous system in health and disease is the widespread occurrence of complex dynamical behaviors, e.g. tremors and the electrical activity of the cortex (see, for example, Mackey and Milton, 1987; Milton *et al.*, 1989). Recently there has been a great deal of speculation concerning the role of non-linear neural control mechanisms in generating some of these dynamical behaviors (Guevara *et al.*, 1983; King *et al.*, 1984; Mackey and an der Heiden, 1982). These proposals have been based on mathematical studies of physiologically realistic equations in which qualitative changes in dynamics ("bifurcations") occur as certain parameters are varied. The changes in dynamics produced by parameter variation range from stable equilibria to simple and complex periodic oscillations to aperiodic (chaotic in the current vernacular) fluctuations (Bai-Lin, 1984; Glass and Mackey, 1988). However, experimental verification of these predictions has been hindered by the paucity of suitable models in which it is possible to study the dynamics that arise by parameter variation.

A neural feedback control mechanism which is amenable to manipulation is the pupil light reflex. As shown in Table I, this reflex exhibits a wide range of dynamical behaviors, which are typically monitored by changes in pupil area. For example, irregular variations in pupil area ("hippus") occur spontaneously, whereas regular oscillations ("pupil cycling") can be induced by

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focusing a small light beam at the pupillary margin (Campbell and Whiteside, 1950; Stern 1944). The period (Martyn and Ewing, 1986; Miller and Thompson, 1978) and regularity (Milton et al. 1988; Ukai et al., 1980) of pupil cycling are altered by pathology within the pupil light reflex pathways.

An important feature of this reflex is the ease by which it can be manipulated and monitored non-invasively. In particular, it is possible to "clamp" this reflex (Longtin and Milton, 1988; Milton et al., 1988; Reulen et al., 1988; Stark, 1962). Clamping refers to an experimental technique in which the feedback loop of the reflex is first "opened" by focusing a small beam of light on the center of the pupil in order to circumvent the shading effect of the iris on the retina (Stark and Sherman, 1957). The feedback loop is then reclosed with an electronically constructed "area comparator" relating changes in pupil area to changes in light intensity. Thus a precisely specified feedback can be inserted into the reflex. In this manner Stark (1962) verified that pupil area oscillations could occur once the gain became sufficiently large. The "linear" properties of the reflex determined the frequency of these oscillations, whereas their shape and amplitude depended on the "non-linearities".

Recent studies have emphasized clamping the pupil light reflex with piecewise constant types of feedback (Longtin and Milton, 1988; Milton et al., 1988; 1989): the light is either on or off depending on the value of the pupil area relative to certain area thresholds. The main advantages of the use of piecewise constant feedback over smooth feedback are (1) the pupil area oscillations are much easier to control experimentally (Milton et al., 1988); (2) the properties of the oscillations are better understood analytically (an der Heiden and Mackey, 1982; Longtin and Milton, 1988; Milton et al., 1989). This approach has resulted in a new technique for detecting optic nerve pathology (Milton et al., 1988) and moreover allows certain non-linearities of the reflex to be isolated for detailed study (this paper). From the general point of view of non-linear dynamics, this experimental paradigm of neural control provides unique opportunities to verify theoretical predictions, to draw attention to unexplained phenomena, and to assess the role of superimposed random variations ("noise") in shaping the observed dynamics (Longtin and Milton, 1988; Milton et al., 1989). It can be anticipated that insights obtained from studies of the clamped pupil light reflex can be applied to other neural control mechanisms as well.

Despite the attractiveness of the study of the pupil light reflex as a non-linear dynamical system, we know of no previous attempts to model it from this point of view. Indeed previous investigators have focused on the modelling of, for example, the response of the pupil to transient and steady state oscillatory light inputs, and of various non-linearities in the reflex arc (Stark, 1959; 1962; 1984; Stark and Cornsweet, 1958; Semmlow and Chen, 1977). Here we use neurophysiological and anatomical considerations to derive a model for the pupil

TABLE I
Summary of Spontaneous Dynamical Behaviors Exhibited by the Pupil Light Reflex

Type of Dynamical Behavior	Description	Reference
Regular oscillations		
Simple waveforms	Edge-light pupil cycle time	Campbell and Whiteside (1950)
		Martyn and Ewing (1986)
		Miller and Thompson (1978)
		Stark and Cornsweet (1958)
		Stern (1944)
	Pupil cycling with external electronic feedback ("clamping")	
	(i) Continuous negative feedback	Reulen et al. (1988)
		Stark (1962)
	(ii) Piecewise constant negative feedback	Milton et al. (1988, 1989)
Complex waveforms	Hippus in narcoleptic patients	Yoss et al. (1970)
	Pupil cycling with external "mixed" and delayed feedback	Longtin and Milton (1988)
Irregular oscillations	Intermittent irregular pupil cycling in demyelinative optic neuropathy	Milton et al. (1988)
		Ukai et al. (1980)
Noise-like fluctuations	Hippus	Bouma and Baghuis (1971)
		Stark et al. (1958)

light reflex. A bifurcation analysis of the resulting non-linear delay-differential equation is used to characterize its dynamical behaviors and to examine the influence of parameter variations on them. This model provides a general framework in which it is possible to study the different types of behaviors produced by the pupil light reflex.

2. The Pupil Light Reflex. The pupil light reflex pathway is represented schematically in Fig. 1. Pupil size reflects a balance between constricting and dilating mechanisms (Miller, 1985). Pupil constriction is caused by contraction of the circularly arranged pupillary constrictor muscle which is innervated by parasympathetic fibers. The motor nucleus for this muscle is the Edinger–Westphal nucleus located in the oculomotor complex in the midbrain. There are two main neural mechanisms for pupil dilation (Loewenfeld, 1958): (1) a mechanism which involves contraction of the radially arranged pupillary dilator muscle innervated by sympathetic fibers (traditionally referred to as "active" reflex dilation); (2) a mechanism which operates by inhibition of the activity of the Edinger–Westphal nucleus (traditionally referred to as "passive" reflex dilation). Pupil cycling occurs even when the sympathetic supply to the iris is cut surgically (Milton *et al.*, 1988) or blocked pharmacologically (Martyn and Ewing, 1986). Thus during pupil cycling, dilation is primarily the result of (1) a decrease in the afferent activity and (2) increased inhibition of the activity of the Edinger–Westphal nucleus. The role of the sympathetic nervous system seems to be primarily one of determining the average pupil size.
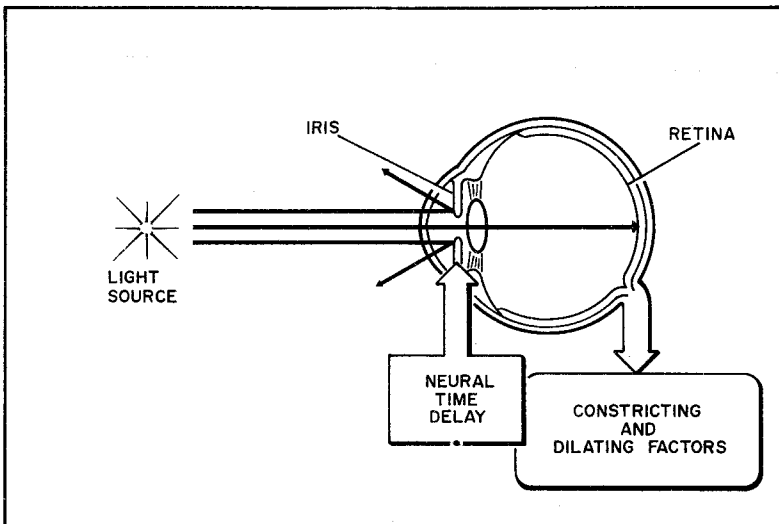

Figure 1. Simplified diagram of pupil light reflex. See text for explanation.

This reflex functions as a time-delayed negative feedback system (Stark, 1959; 1968; 1984). The time delay, or pupil latency time, is ~ 200–500 msec (Ellis, 1981; Milton *et al.*, 1988). This time delay is much longer than would be anticipated simply on the basis of neural conduction times. The part of the reflex in which this delay originates is presently controversial: some authors favor an origin in the midbrain (Smith *et al.*, 1970), others suggest that it arises at the level of the iris and its musculature (Ellis, 1981; Loewenfeld, 1966).

3. Model. The variable controlled by the pupil light reflex is the retinal light level (flux), ϕ (lumens), which is equal to the illuminance, I (lumens mm^{-2}), multiplied by the pupil area, A (mm^2) (Stark, 1959):

$$\phi = IA \tag{1}$$

The retinal light flux ϕ is transformed, after a time delay τ_r, into neural action potentials which travel along the optic nerve. We assume that it is the rate of these action potentials, i.e. $N(t)$ = number of action potentials per unit time, which is important for reflex dynamics and that $N(t)$ is related to ϕ by:

$$N(t) = \eta \ln\left[\frac{\phi(t - \tau_r)}{\bar{\phi}}\right] \tag{2}$$

where η is a rate constant, $\bar{\phi}$ is the threshold retinal light level (i.e. the light level below which there is no response), and the notation $\phi(t - \tau_r)$ indicates that this quantity depends on the retinal light flux at a time τ_r in the past. The logarithmic compression of light intensities at the retina has been discussed previously by Cornsweet (1967) and is referred to as the Weber–Fechner law (e.g. Webster, 1971).

The afferent neural action potential rate, $N(t)$, gives rise to an efferent neural signal, $E(t)$, which is produced by the Edinger–Westphal nucleus after a time delay, τ_t. This efferent neural activity, also measured as the number of action potentials per unit time, exits the midbrain via parasympathetic fibers. We assume that:

$$E(t) = \gamma' \ln\left[\frac{\phi(t - (\tau_r + \tau_t))}{\bar{\phi}}\right] \tag{3}$$

where γ' is a rate constant and τ_t is the midbrain time delay.

At the neuromuscular junction of the pupillary constrictor muscle, the neural action potentials result in the release of a chemical neurotransmitter (acetylcholine) which diffuses across the synaptic cleft, binds to specific receptors on the muscle membrane thus leading to the generation of muscle action potentials and initiating muscle contraction. These events require a time delay, τ_m. In this way the neural activity, $E(t)$, is transduced into tension in the

constrictor muscle; this tension then produces a resulting pupil area. We first define a relationship between $E(t)$ and iris muscle activity, x, and then between x and pupil area, A.

The iris muscle activity, x, is determined by a number of factors which may include Ca^{2+} concentration and diffusion, actin–myosin cross linking and the initial length and tension in the constrictor muscle. Since we are ultimately interested in pupil area, A, it is not necessary to exactly specify x. We take the relationship between $E(t)$ and x to be of the form (Partridge and Benton, 1981):

$$E(t) = M\left(x, \frac{dx}{dt}, \frac{d^2x}{dt^2}, \dots\right),$$

$$\simeq k\left(\frac{dx}{dt} + \alpha x\right), \tag{4}$$

where α is a rate constant and k is a proportionality factor which depends on the definition and units of x used in the model. The justification for the first order approximation to $M(x, dx/dt, d^2x/dt^2, \dots)$ is the success that the subsequent model has in predicting the experimentally observed oscillations in pupil area (Longtin and Milton, 1988; Milton et al., 1989).

By combining equations (3) and (4) we obtain the following non-linear delay-differential equation:

$$\frac{dx}{dt} + \alpha x = \gamma \ln\left[\frac{\phi(t-\tau)}{\bar{\phi}}\right], \tag{5}$$

where $\tau = \tau_r + \tau_t + \tau_m$ is the total time delay in the reflex arc and $\gamma \equiv \gamma'/k$.

Equation (5) is written in terms of muscle activity; however, experimentally it is pupil area that is more typically measured. In order to re-write (5) in terms of pupil area, A, it is necessary to have a function, $f(x)$, that relates muscle activity and pupil area, i.e.

$$A = f(x). \tag{6}$$

The function $f(x)$ must (1) meet the requirement that pupil area is positive and bounded by finite limits and (2) reflect the role played by elasto-mechanical properties of the iris in shaping pupil dynamics. In principle, $f(x)$ can be measured experimentally (Terdiman et al., 1971). Here we consider one possible choice of $f(x)$ which satisfies the above requirements, i.e. the Hill function (Fig. 2):

$$A = f(x) = \frac{\Lambda \theta^n}{\theta^n + x^n} + \Lambda', \tag{7}$$

where $\Lambda + \Lambda'$, Λ' are, respectively, the maximum and minimum pupil area

$(\Lambda + \Lambda' > \Lambda' > 0)$ and θ is the value of x for which pupil area is mid-range. A similar function, i.e. "S-shaped curve", has been proposed previously (Usui and Stark, 1978; 1982). We show in Section 5 that this choice of $f(x)$ also reflects the non-linear mechanical properties of the iris.
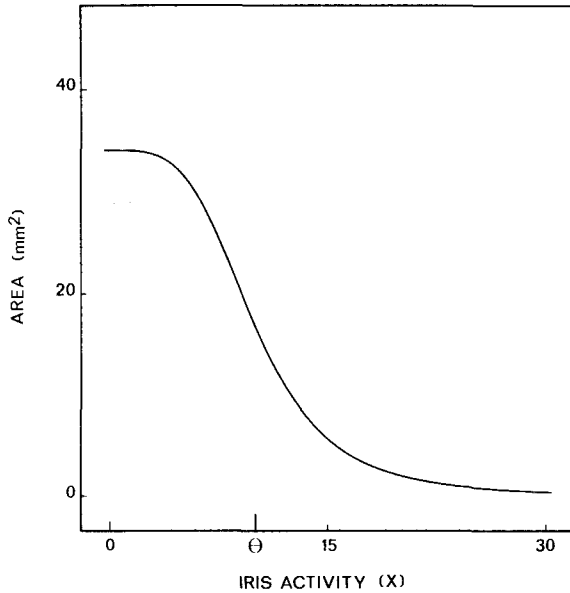

Figure 2. Plot of a Hill function (6) relating pupil area, A, to iris activity, x (solid line). Parameters are: $\Lambda = 30$ mm^2; $\Lambda' = 0$ mm^2; $\theta = 10$ mm^2; $n = 4$.

Using equation (7) we can re-write (5) in terms of pupil area, A, as:

$$\frac{dg}{dA}\frac{dA}{dt} + \alpha g(A) = \gamma \ln\left[\frac{\phi(t-\tau)}{\bar{I}\bar{A}}\right],$$

$$= \gamma \ln\left[\frac{I(t-\tau)A(t-\tau)}{\bar{I}\bar{A}}\right], \tag{8}$$

where $g(A) \equiv f^{-1}(A) = x$ (Fig. 3), and we have made use of (1). Note that to solve (8) it is necessary to specify the initial functions $I(t)$ and $A(t)$ on the interval $t \in (-\tau, 0)$.

4. *Stability Analysis.*   We now investigate how spontaneous oscillations in pupil area may develop under conditions of constant light illumination. As will become clear, the method of analysing (8) depends on the relative values of the pupillary rate constant for constriction (α_c) and dilation (α_d). In a few
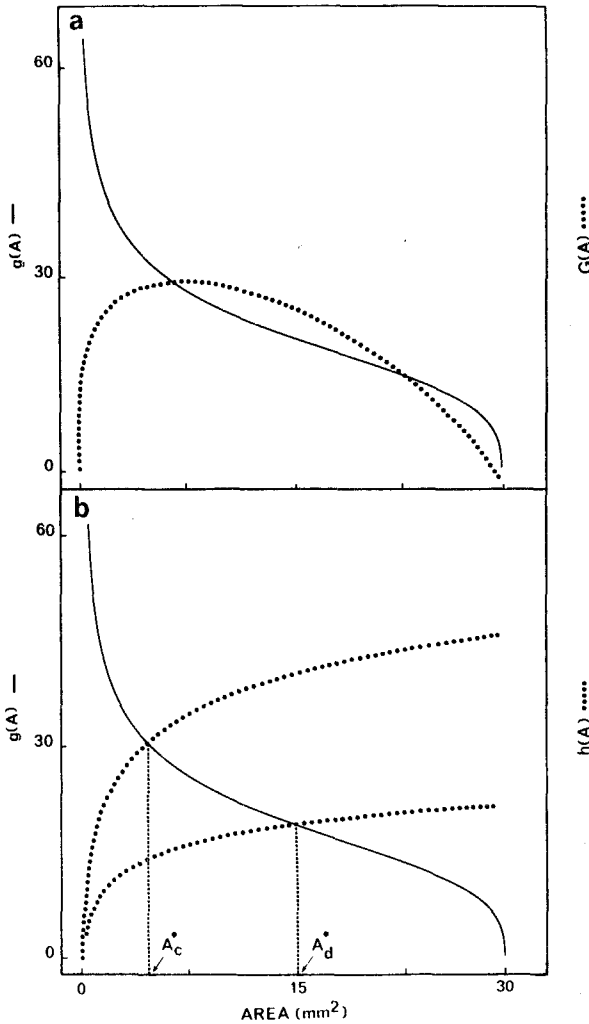
Figure 3. Plot of the inverse of the Hill function, $g(A)$, shown in Fig. 2 (i.e. $x = f^{-1}(A) \equiv g(A)$) as a function of pupil area, A. In (a) we compare $g(A)$ to the gain, G, which for $f(x)$ given by (7), can be written as:

$$G(A) = -\frac{n\gamma A}{\alpha \Lambda \theta} \left[\frac{\Lambda}{A} - 1 \right]^{(N-1)/N},$$

where $\Lambda' = 0$ mm^2. In (b) we show a graphical method for determining the fixed points of (9) when $\alpha_c > \alpha_d$. The fixed point A^* is given by the intersection of $g(A)$ (solid line) and the right hand side of (9) which we have defined as $h(A)$ (dotted line). Parameter values have been arbitrarily set to $\Lambda = 30$ mm^2, $\Lambda' = 0$ mm^2, $n = 4$, $\gamma = 5$ sec^{-1}, $I = 10$ lumens mm^{-2}, $\bar{\phi} = 1$ lumen.

individuals, $\alpha_c \approx \alpha_d$ (Lowenstein and Friedman, 1942); however, in the majority $\alpha_c > \alpha_d$ (Lowenstein and Friedman, 1942; Longtin and Milton, 1988). We refer to these cases as, respectively, a symmetric and an asymmetric pupil light reflex.

4.1. Symmetric pupil light reflex $(\alpha_c = \alpha_d)$.   The unique equilibrium pupil area, A^*, corresponding to an incident light illuminance, I^*, is defined by $dA/dt = 0$, and from (8) it is the solution of the equation (Fig. 3b):

$$\alpha g(A^*) = \gamma \ln\left[\frac{I^* A^*}{\bar{I}\bar{A}}\right]. \tag{9}$$

To determine the stability of this fixed point, it is necessary to linearize (8) about A^*. This is done in two steps. First, in equation (8), we expand $g(A)$ to first order around A^*, i.e.

$$g(A) \simeq g(A^*) + \beta(A - A^*), \tag{10}$$

where β is given by dA/dt evaluated at A^*. Substituting (10) into (8) we obtain:

$$\beta \frac{dA}{dt} + \alpha g(A^*) + \alpha\beta(A - A^*) = \gamma \ln\{A(t-\tau)\} + \gamma \ln\left[\frac{I^*}{\bar{I}\bar{A}}\right]. \tag{11}$$

Next we define the displacement of $A(t)$ from equilibrium as $a(t) = A(t) - A^*$. For small amplitude oscillations, $a/A \ll 1$ and hence we can expand the first term on the right hand side of equation (11):

$$\gamma \ln[A(t-\tau)] = \gamma \ln\left\{A^*\left[\frac{a(t-\tau)}{A^*} + 1\right]\right\}$$

$$\simeq \gamma \ln A^* + \frac{\gamma}{A^*} a(t-\tau). \tag{12}$$

Combining equations (11) and (12) and using equation (9) we obtain:

$$\frac{da}{dt} + \alpha a = \frac{\gamma}{\beta A^*} a(t-\tau), \tag{13}$$

which in terms of pupil area, $A = a + A^*$, yields:

$$\alpha^{-1} \frac{dA}{dt} + A = G \cdot [A(t-\tau) - A^*] + A^*, \tag{14}$$

where we have defined the dimensionless quantity, G, as:

$$G \equiv \frac{\gamma}{\alpha\beta A^*}. \tag{15}$$

Since $\beta < 0$, it follows that $G < 0$ which corresponds to negative feedback.

To examine the response of the pupil to small deviations in pupil area, A, from the equilibrium area A^* as described by equation (14), we make the usual ansatz that $A(t) \propto \exp(\lambda t)$. The characteristic equation is:

$$\lambda + \alpha + B \exp(-\lambda \tau) = 0, \tag{16}$$

where $\alpha > 0$ and $B \equiv -\alpha G > 0$. This quasi-polynomial has an infinite number of roots. We denote by $\lambda_1 = \sigma_1 \pm i\omega_1$ the root with the largest real part. The roots come in complex conjugate pairs since (16) is invariant under sign reversal of ω. We will focus only on the roots with positive frequency. It can be shown that (14) has a periodic solution when (Hayes, 1950; Mackey, 1978):

$$\omega_1 \tau = \cos^{-1}\left(\frac{1}{G}\right), \tag{17}$$

where $|G| < 1$, $\omega_1^2 = \alpha^2 (G^2 - 1)$ and the inverse cosine takes its value in the interval $[\pi/2, \pi]$. This is an implicit relation among the parameters of (14) that defines the condition $Re(\lambda_1) = \sigma_1 = 0$. The period, T, of this periodic solution is given by:

$$T = \frac{2\pi}{\omega_1}, \quad 2\tau < T < 4\tau. \tag{18}$$

Assume for now that the delay τ is the bifurcation parameter. Then, for α and B fixed, there will be a value of $\tau = \tau_0$ for which (17) will hold. By implicit differentiation of (16) with respect to τ, one obtains:

$$\left.\frac{dRe(\lambda)}{d\tau}\right|_{\substack{\tau=\tau_0 \\ \lambda=i\omega_1}} = \frac{\omega_1^2}{(1 + \alpha\tau_0)^2 + \omega_1^2 \tau_0^2} > 0. \tag{19}$$

Hence $Re(\lambda_1) > 0$ for $\tau > \tau_0$ which corresponds to local instability of the fixed point $A = A^*$ when the delay is increased past the critical value τ_0. This also implies that in (17) the right hand side is greater than the left hand side. Hence periodic solutions occur in (14) for $\tau \geqslant \tau_0$. Similarly, if B is the bifurcation parameter, then keeping α and τ fixed, we obtain:

$$\left.\frac{dRe(\lambda)}{dB}\right|_{\substack{B=B_0 \\ \lambda=i\omega_1}} = \frac{\alpha + \alpha^2 \tau}{B_0(1 + 2\alpha\tau + B_0^2 \tau^2)} > 0, \tag{20}$$

where B_0 is the value of B satisfying (17). Thus periodic solutions occur in (14) for $B \geqslant B_0$.

In general, a Hopf bifurcation from a stable equilibrium point to a stable limit cycle may be either subcritical ("hard" excitation) or supercritical ("soft" excitation) (Guckenheimer and Holmes, 1983). Classifying the Hopf bifurca-

tion for (8) is important since it allows a prediction of how the oscillation amplitude grows for values of τ (or B) beyond the point of oscillation onset, i.e. τ_0 (or B_0).

The fate of the periodic solution that existed for the linearized system at $\tau = \tau_0$ (or $B = B_0$) is determined by the non-linear terms that have been neglected in going from (8) to (13). A supercritical Hopf bifurcation will occur provided that certain non-degeneracy conditions are fulfilled by these non-linear terms (Stech, 1985). This means that as a complex conjugate pair of roots migrates across the imaginary axis (from left to right), the stable equilibrium becomes unstable and a stable limit cycle arises.

Verification of these nondegeneracy conditions is quite involved for functional differential equations such as (8). Instead, we have numerically verified (data not shown) that the bifurcation is supercritical by demonstrating that locally the amplitude of the oscillation grows as the square root of the distance (in parameter space) from the bifurcation point, i.e.

$$\text{Amplitude} \propto \sqrt{B - B_0} \text{ (or } \sqrt{\tau - \tau_0}). \tag{21}$$

Further, the analytical computation of higher order corrections to the period (17) and amplitude (21) using the Hopf analysis for functional differential equations (of delay type here) is also quite involved and is not carried out here (see Stech, 1985; Sirkus, 1975).

Other bifucations may occur as τ and B are increased further leading to other limit cycles, quasiperiodic motion and bounded aperiodic (chaotic) dynamics. This depends on the functional form of $g(A)$ in (8). For general $g(A)$, numerical integration is necessary to determine which type(s) of solution will be observed for a given choice of parameters and initial functions on $(-\tau, 0)$. For negative feedback, numerical calculations indicate that no other bifurcations occur after the Hopf bifurcation.

4.2. Asymmetric pupil light reflex ($\alpha_c > \alpha_d$).   In the derivation of our model, we have used the same dynamical variable x to describe constriction and dilation, even though each process involves different mechanisms which depend on different parameters (Arkin and Miller, 1988; Clarke and Ikeda, 1985; Nisida *et al.*, 1959; Schiller, 1984; Smith *et al.*, 1970). The observation that $\alpha_c > \alpha_d$ introduces an asymmetry into our model of the pupil light reflex. To account for this we replace α in (8) by:

$$\alpha' = \tfrac{1}{2}[\alpha_c + \alpha_d + (\alpha_d - \alpha_c)\text{sgn}\{\dot{A}\}], \tag{22}$$

where $\text{sgn}\{\dot{A}\}$ equals $+1$ if $\dot{A} \equiv dA/dt > 0$ and -1 otherwise. The stability analysis requires first solving (9) for A^* with $\alpha = \alpha'$. Since α can have one of two values, equation (9) will not yield a unique A^* for a given $g(A^*)$. Indeed the

graphical solution in Fig. 3b indicates two fixed points A_c^* and A_d^* corresponding, respectively, to α_c and α_d. The analytical methods for determining the stability of such an equation in which the fixed point depends on the sign of the derivative of the state variable have not, to our knowledge, been developed. We therefore explored the behavior of such an equation numerically.

Specifically, we simulated (8) with the asymmetry in α given by (22). We found that the solution depends on the initial condition (data not shown). The solution can go to one fixed point or the other, or oscillate around one fixed point, or the other. In addition for certain parameter values, we have an ill-defined problem: the initial value of α determines the fixed point and the sign of the derivative in the fourth order Runge–Kutta algorithm. However, based on this sign, α' takes on the other value and the system attempts to converge to the other fixed point. The solution thus oscillates between the two fixed points with the value of the derivative changing at every integration time step.

5. *Gain.* The parameter, G, can be formally identified with the gain, G_0, defined empirically from measurements of the response of the pupil to small amplitude sinusoidally modulated illumination (Longtin and Milton, 1989). Here we examine the dependence of G on the equilibrium pupil size, A^*.

It has been observed that the gain, G_0, attains its highest values at intermediate pupil sizes. This effect has been referred to as the "expansive range non-linearity" and has been interpreted as a reflection of the non-linear mechanical properties of the iris (Usui and Stark, 1978; 1982). Figure 3a plots G as a function of A^*. In preparing this plot we have kept the parameters α and γ constant. Normally, A^* will depend on the value of α and γ (9), but we assumed that A^* is in fact varying independently of them, e.g. being set by the accommodation level of the lens (Sun *et al.*, 1983). As can be seen, the gain G will have its largest values for intermediate values of A^*. Furthermore, these observations indicate that the relevant non-linear properties of the iris have been incorporated into the choice of the function $g(A)$ (see Section 7).

6. *External Piecewise Constant Negative Feedback.* In previous studies (Longtin and Milton, 1988; Milton *et al.*, 1989) we found empirically that under conditions of imposed piecewise constant negative feedback, the oscillations in pupil area could be described by the equation

$$\alpha^{-1} \frac{dA}{dt} + A = \begin{cases} A_{\text{off}}, & \text{if } A_\tau < A_{\text{ref}} \\ A_{\text{on}}, & \text{if } A_\tau > A_{\text{ref}}, \end{cases} \tag{23}$$

where the rate constant α differs for constriction (α_c) and dilation (α_d). When pupil area is greater than a threshold A_{ref}, pupil size decreases exponentially to a lower asymptotic area (A_{on}), whereas when $A < A_{\text{ref}}$, pupil size increases exponentially to a higher asymptotic area (A_{off}). This equation describes "high

gain" oscillations in pupil area since the gain is infinite when $A = A_{ref}$ (it is zero for all other values of A). The forcings, A_{on} and A_{off}, correspond physically to two different values of the flux (ϕ).

In the case of external piecewise constant negative feedback, the illumination is constructed electronically to be a Heaviside function of pupil area, $H(A)$, and hence:

$$\phi(t) = \phi_b H[A(t) - A_{ref}] + \phi_{off}, \tag{24}$$

where:

$$H[A(t) - A_{ref}] = \begin{cases} 1, & \text{if } A > A_{ref} \\ 0, & \text{if } A \leqslant A_{ref}, \end{cases} \tag{25}$$

and where ϕ_{off} is the retinal light flux due to background illumination when the light beam is off and ϕ_b is the retinal light flux produced by the narrow light beam. Thus the retinal light level changes because the illuminance is switched on or off, while the area is constant and equal to the sectional area of the narrow light beam. Under these conditions it follows from (8) that the changes in pupil area are described by:

$$\frac{dg}{dA} \frac{dA}{dt} + \alpha g(A) = \gamma \ln\left[\frac{\phi_{off}}{\bar{\phi}} + \frac{\phi_b}{\bar{\phi}} H(A_\tau - A_{ref})\right]. \tag{26}$$

It is important to note that the right hand side of (26) is known. The unknown properties of our model for the pupil light reflex, i.e. $g(A)$ and $M(x, dx/dt, d^2x/dt^2, \ldots)$ (4) are confined to the left hand side of (26). Thus the advantage of studying the dynamics produced by the pupil light reflex clamped with piecewise constant negative feedback is that it directly permits evaluation of plausible choices for $g(A)$ and $M(x, dx/dt, d^2x/dt^2, \ldots)$.

To illustrate the above procedure let $M(x, dx/dt, d^2x/dt^2, \ldots)$ be given by (4) and take $g(A)$ as a linear function of A, i.e.

$$g(A) = g(A^*) + \beta(A - A^*), \tag{27}$$

where $\beta = dg/dA|_{A*} < 0$ and $A^* \in [A_c^*, A_d^*]$ (Fig. 3). A reasonable choice for A^* would be a mid-range value. Then (26) becomes:

$$\alpha^{-1}\frac{dA}{dt} + A(t) = A_0 + \frac{\gamma}{\alpha\beta} \ln\left[\frac{\phi_{off}}{\bar{\phi}} + \frac{\phi_b}{\bar{\phi}} H(A_\tau - A_{ref})\right]. \tag{28}$$

This equation is of the same form as (23) where:

$$A_{off} = A_0 + \frac{\gamma}{\alpha_d\beta} \ln\left[\frac{\phi_{off}}{\bar{\phi}}\right], \tag{29}$$

$$A_{\text{on}} = A_0 + \frac{\gamma}{\alpha_c \beta} \ln\left[\frac{(\phi_{\text{off}} + \phi_{\text{b}})}{\bar{\phi}}\right], \tag{30}$$

and the pupil area, A_0, is the maximal pupil area corresponding to zero iris muscular activity and is given by $[g(A_0) = 0$ in (27)]:

$$A_0 = A^* - \beta^{-1} g(A^*). \tag{31}$$

Since $\beta < 0$, it follows that if $\alpha_c/\alpha_d < \ln[(\phi_{\text{off}} + \phi_{\text{b}})/\bar{\phi}]/\ln[\phi_{\text{off}}/\bar{\phi}]$ then $A_{\text{off}} > A_{\text{ref}} > A_{\text{on}}$. This latter condition is satisfied for the symmetric case and for the asymmetric case holds provided that ϕ_{b} is large enough.

It should be noted that the behavior of (23) cannot be determined using a Hopf bifurcation analysis since the feedback function is not differentiable. The solution of (23) [and (28)] can be determined analytically (an der Heiden and Mackey, 1982; Longtin and Milton, 1988; Milton *et al.*, 1989). Experimentally it is found that the period and amplitude of the observed pupil area oscillations agree to within 5–10% of these predicted (Longtin and Milton, 1988; Milton *et al.*, 1989). However, the predicted oscillations clearly have a slope discontinuity; this is not observed experimentally, We are presently evaluating alternative choices and $g(A)$ and $M(x, dx/dt, d^2x/dt^2, \ldots)$ in order to improve the agreement between theory and observation.

In principle, piecewise constant feedback can be used to evaluate $M(x, dx/dt, d^2x/dt^2, \ldots)$ without the necessity of determining $g(A)$. The gain is proportional to the slope of the Hill function (7) and can be made infinitely steep by letting $n \to \infty$. Substituting (7) into (5) and taking the limit we obtain:

$$\frac{dx}{dt} + \alpha x = \lim_{n \to \infty} \gamma \ln\left[\frac{I}{\bar{\phi}}\left\{\frac{\Lambda \theta^n}{\theta^n + x(t-\tau)^n} + \Lambda'\right\}\right],$$

$$= \gamma \ln\left[\frac{I\Lambda}{\bar{\phi}} H(x(t-\tau) - x_{\text{ref}}) + \frac{\Lambda' I}{\bar{\phi}}\right], \tag{32}$$

where $I = I(t-\tau)$, $H(x(t-\tau) - x_{\text{ref}})$ is a Heaviside function, and we have identified x_{ref} with the limit as $n \to \infty$ of the inflection point of (7), i.e.

$$x_{\text{ref}} \equiv \lim_{n \to \infty} [\theta^{(N-1)/(N+1)}] = \theta. \tag{33}$$

Equation (32) takes the same form as (23) (i.e. the flux can take on two values). However, given the difficulties in measuring (and for that matter defining) x, this approach is presently not useful practically.

7. Illustrative Example. To illustrate the dynamical behaviors which can be produced by this class of equations we studied the following example:

$$\frac{\mathrm{d}A}{\mathrm{d}t} + \alpha A = \frac{c\theta^n}{\theta^n + A(t-\tau)^n}, \tag{34}$$

where c is a constant. This equation can be regarded to be a generalization of (23) for smooth negative feedback.

Figure 4 shows the solutions of (34) as the steepness of the Hill function is increased by increasing the parameter n. For small n there is a damped oscillation in pupil area (Fig. 4a). For larger values of n, sustained regular oscillations in pupil area are obtained (Figs 4b–d). A supercritical Hopf bifurcation occurs between n equal to 3 and 10. Although the shape of these oscillations changes as n increases beyond 10, the more complex waveforms typical of the occurrence of higher order bifurcations are not seen.

8. *Discussion.* We have used neuro-physiological and anatomical consider-ations to derive a non-linear delay-differential equation describing the pupil light reflex. The main motivation behind this model was to develop a general framework to study the different types of dynamical behaviors produced by the pupil light reflex (Table I) and, in particular, to examine the oscillations that occur under conditions of "high gain" negative feedback, e.g. edge-light or electronic pupil cycling (Milton *et al.*, 1988; Stark, 1962; Stark and Cornsweet, 1958; Stern, 1944).

Three observations lend support to our model for the pupil light reflex. First, the predicted period of the oscillations in pupil area from (18) (i.e. 600–1200 msec for a measured delay of ~ 300 msec) agrees well with the observed period of edge-light pupil cycling (900 msec: Campbell and Whiteside, 1950; Miller and Thompson, 1978; Stern, 1944; Stark and Cornsweet, 1958). Second, for the special case of external piecewise constant feedback, our model reduces to the same form as an empirical model known to have solutions which are in good agreement with experimental observations for a variety of feedback. choices (Longtin and Milton, 1988; Milton *et al.*, 1989). Moreover we have shown that this experimental design permits certain non-linearities in the reflex to be isolated for more detailed study. Third, the dependence of the gain in our model on pupil size is consistent with the "expansive range non-linearity" studies by Usui and Stark (1978; 1982). Finally, in a separate study we have shown that our model is compatible with descriptions of the pupil light reflex based on experimentally measured transfer functions (Longtin and Milton, 1989).

Oscillations in pupil area occur whenever the time delay and/or the gain become sufficiently large (17). The gain is related to three parameters: (1) the rate constant for the neural firing frequency (γ); (2) the steepness of the feedback function (β); (3) the rate constant for pupillary movements (α). Stark (1959) has used empirical observations to argue that constriction gain is
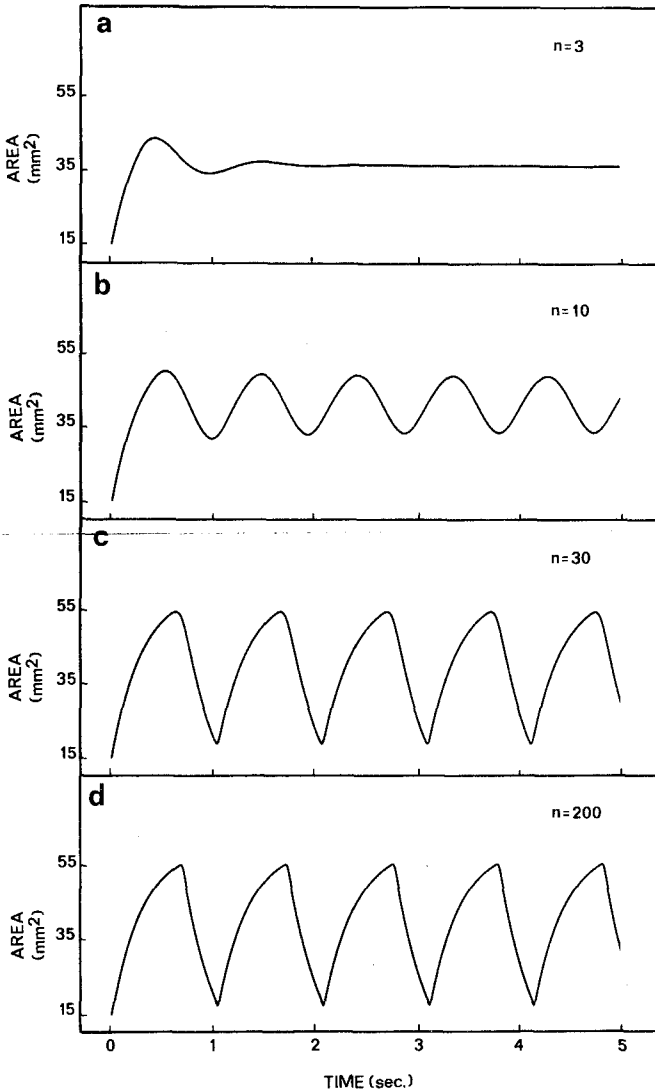
Figure 4. Solutions of (34) for increasing steepness of the feedback function. Value of n of the Hill function [right hand side of (34)] has been indicated on each curve. In going from $n = 3$ to 10, the system has undergone a supercritical Hopf bifurcation. Initial condition for each simulation was $A(t) = 15$ mm^2, $t \in (-\tau, 0)$. Parameter values were: $\tau = 300$ msec; $\alpha = 3.21$ sec^{-1}; $\theta = 50$ mm^2; $c = 200$ mm^2.

decreased by retinal light adaptation and is inversely proportional to the constriction rate constant. These features come out very naturally in our model. The conditions for the onset of an oscillation as well as the period and amplitude of the oscillations should be sensitive to pathological alterations in any one of these three parameters. A variety of abnormalities in pupil area

oscillations are indeed seen in patients with disease in the pupil light reflex pathways (Martyn and Ewing, 1986; Miller and Thompson, 1978; Milton *et al.*, 1988).

As the time delay and/or gain are increased beyond the point of oscillation onset the shape of the oscillation changes with little subsequent change in its frequency (Fig. 4). Near the bifurcation point, the oscillation amplitude is predicted to grow as the square root of these parameters beyond the point of instability onset. The more complex waveforms typically associated with the occurrence of higher-order bifurcations, i.e. period doubling bifurcations, or bifurcation from a limit cycle to a 2-torus, are not seen. This finding is consistent with previous studies of first order non-linear delay-differential equations with negative feedback (an der Heiden and Mackey, 1982); in particular, those which arise in the descriptions of the control of respiration (Glass and Mackey, 1979; Mackey and Glass, 1977), erythropoiesis (Mackey, 1979) and the commodity price market (Mackey, 1989). Thus noise-like fluctuations in pupil area ("pupillary hippus") cannot represent chaotic dynamics produced by a non-linear negative feedback mechanism of the type we have considered here. However, we cannot exclude the possibility that hippus represents a chaotic process somewhere in the reflex arc or that it is simply due to noise injected, for example, at the level of the Edinger-Westphal nucleus (Stanten and Stark, 1966; Stark *et al.*, 1957).

One non-linearity in the pupil light reflex that has received little attention in previous modelling studies is the response asymmetry of the pupil to the onset and offset of light. Although this asymmetry is most clearly manifested as a difference in the rates of pupil constriction and dilation (Longtin and Milton, 1988), it is likely that it also occurs at the level of the output of the retina and midbrain as well. Neuro-physiological evidence for the presence of distinct light-ON and light-OFF responses in the reflex arc has been obtained for retinal ganglion cells (Arkin and Miller, 1988; Schiller, 1984) and for neuronal populations in the midbrain (Clarke and Ikeda, 1985; Nisida *et al.*, 1959; Smith *et al.*, 1970). As the observations in Section 4.2 indicate the analysis of this situation certainly presents problems, except in the case of external piecewise constant feedback (Longtin and Milton, 1988; Milton *et al.*, 1989; Milton and Longtin, in preparation). Previous modellers have also been concerned with the problem of reflex asymmetry (Clynes, 1968; Stark, 1959). For example, Stark (1959) suggested that a steady-state oscillation occurs when the constriction and dilation gains are equal. Thus, after a transient, there is no net increase or decrease in area in each oscillation period. In our model this would imply that $\gamma_c/\alpha_c = \gamma_d/\alpha_d$, where γ_c and γ_d are the neural firing frequencies (3) for, respectively, constriction and dilation. However, this assumption is not sufficient by itself to uniquely determine the mean pupil area the system tends to (it likely will be a value between A_c^* and A_d^*). Determining whether the

stabilization of the limit cycle occurs through this precise compensation or through another mechanism will require experimental investigations.

In our model we neglected the possibility that time-dependent processes occur in the response of the retina, e.g. adaptation (Tranchina *et al.*, 1984). It may be possible that by including these influences in (8), e.g. by making γ a function of time, that we will be able to obtain insights into pupil phenomena, such as pupillary escape (Sun *et al.*, 1983). In addition, it may be possible to account for some of the complex dynamical behaviors shown in Table 1, e.g. spontaneous periodic oscillations in sleepy narcoleptics (Yoss *et al.*, 1970), as more physiological information is incorporated into the choices of $f(x)$ (7) and γ.

We expect that models based on non-linear dynamical systems approaches will come to play a greater role in the study of the properties of neural control mechanisms (Longtin and Milton, 1989; Mackey and Milton, 1987; Milton *et al.*, 1989). The advantage of these approaches is that the analysis is not restricted to the study of equilibria and their stability. By employing a combination of analytical and numerical techniques it should be possible to obtain insights into the nature of the complex dynamical behaviors produced by the nervous system in health and disease.

LITERATURE

an der Heiden, U. and M. C. Mackey. 1982. "The Dynamics of Production and Destruction: Analytic Insight into Complex Behaviour." *J. math. Biol.* **16**, 75–101.

Arkin, M. S. and R. F. Miller. 1988. "Bipolar Origin of Synaptic Inputs to Sustained OFF-Ganglion Cells in the Mudpuppy Retina." *J. Neurophys.* **60**, 1122–1142.

Bai-Lin, H. 1984. *Chaos.* New Jersey: World Scientific.

Bouma, H. and L. C. J. Baghuis. 1971. "Hippus of the Pupil: Periods of Slow Oscillations of Unknown Origin." *Vision Res.* **11**, 1345–1351.

Campbell, F. W. and T. C. D. Whiteside. 1950. "Induced Pupillary Oscillations." *Br. J. Ophthalmol.* **34**, 180–189.

Clarke, R. J. and H. Ikeda. 1985. "Luminance and Darkness Detectors in the Olivary and Posterior Pretectal Nuclei and their Relationship to the Pupillary Light Reflex in the Rat—I. Studies with Steady Luminance Levels." *Exp. Brain Res.* **57**, 224–232.

Clynes, M. 1968. "Unidirectional Rate Sensitivity: A Biocybernetic Law of Reflex and Humoral Systems as Physiologic Channels of Control and Communication." *Ann. N.Y. Acad. Sci.* **92**, 949–969.

Cornsweet, T. N. 1967. *Visual Perception.* New York: Academic Press.

Ellis, C. J. K. 1981. "The Pupillary Light Reflex in Normal Subjects." *Br. J. Ophthalmol.* **65**, 754–759.

Glass, L. and M. C. Mackey. 1979. "Pathological Conditions Resulting from Instabilities in Physiological Control Systems." *Ann. N.Y. Acad. Sci.* **316**, 214–235.

——— and ———. 1988. *From Clocks to Chaos: The Rhythms of Life*. New Jersey: Princeton University Press.

Guckenheimer, J. and P. Holmes. 1983. *Non-linear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*. New York: Springer-Verlag.

Guevara, M. R., L. Glass, M. C. Mackey and A. Shrier. 1983. "Chaos in neurobiology." *IEEE Trans. Syst. Man Cybern.* **SMC-13**, 790–798.

Hayes, N. D. 1950. "Roots of the Transcendental Equation Associated with a certain Difference Differential Equation." *J. Lond. math. Soc.* **25**, 226–232.

King, R., J. D. Barchas and B. A. Huberman. 1984. "Chaotic Behavior in Dopamine Neurodynamics." *Proc. natl Acad. Sci. U.S.A.* **81**, 1244–1247.

Loewenfeld, I. E. 1958. "Mechanisms of Reflex Dilation of the Pupil: Historical Review and Experimental Analysis." *Doc. Ophthalmol.* **12**, 185–448.

———. 1966. "Pupillary Movements Associated with Light and Near Vision: An Experimental Review of the Literature." In *Recent Developments in Vision Research*, M. Whitcomb (Ed.), N.R.C. Report No. 1272, pp. 17–105. Washington: National Research Council.

Longtin, A. and J. G. Milton. 1988. "Complex Oscillations in the Pupil Light Reflex with 'Mixed' and Delayed Feedback." *Math. Biosci.* **90**, 183–199.

——— and ———. 1989. "Insight into the Transfer Function, Gain, and Oscillation Onset for the Pupil Light Reflex using Non-Linear Delay-Differential Equations." *Biol. Cybern.*, **61**, 51–58.

Lowenstein, O. and E. D. Friedman. 1942. "Pupillographic Studies—I. Present State of Pupillography; its Method and Diagnostic Significance." *Arch. Ophthalmol.* **27**, 969–993.

Mackey, M. C. 1978. "A Unified Hypothesis for the Origin of Aplastic Anemia and Periodic Haematopoiesis." *Blood* **51**, 941–956.

———. 1979. "Periodic Auto-Immune Hemolytic Anemia: An Induced Dynamical Disease." *Bull. math. Biol.* **41**, 829–834.

———. 1988. "Commodity Price Fluctuations: Price Dependent Delays and Non-Linearities as Explanatory Factors." *J. econ. Theory*, in press.

——— and U. an der Heiden. 1982. "The Dynamics of Recurrent Inhibition." *J. Math. Biol.* **19**, 211–225.

——— and L. Glass. 1977. "Oscillation and Chaos in Physiological Control Systems." *Science* **197**, 287–289.

——— and J. G. Milton. 1987. "Dynamical Diseases." *Ann. N.Y. Acad. Sci.* **504**, 16–32.

Martyn, C. N. and D. L. Ewing. 1986. "Pupil Cycle Time. A Simple Way of Measuring an Autonomic Reflex." *J. Neurol. Neurosurg. Psychiat.* **49**, 771–774.

Miller, N. R. (Ed.). 1985. *Walsh and Hoyt's Clinical Neuro-Ophthalmology, Volume 2*. Baltimore, MD: Williams and Wilkins.

Miller, S. D. and H. S. Thompson. 1978. "Edge-Light Pupil Cycle Time." *Br. J. Ophthalmol.* **62**, 495–500.

Milton, J. G., A. Longtin, T. H. Kirkham and G. S. Francis. 1988. "Irregular Pupil Cycling as a Characteristic Abnormality in Patients with Demyelinative Optic Neuropathy." *Am. J. Ophthalmol.* **105**, 402–407.

———, ———, A. Beuter, M. C. Mackey and L. Glass. 1989. "Complex Dynamics and Bifurcations in neurology." *J. theor. Biol.*, **138**, 129–147.

Nisida, I., H. Okada and O. Nakano. 1959. "Electrical Activity of the Pretectal Region of the Cat to Visual Stimulus." *Yonago Acta Medica* **4**, 7–18.

Partridge, L. D. and L. A. Benton. 1981. "Muscle: The Motor". In *Handbook of Physiology, Motor Control*, V. Brooks (Ed.), Vol. 2, pp. 43–106. Washington: American Physiological Society.

Reulen, J. P. H., J. T. Marcus, M. J. van Gilst, D. Koops, J. E. Bos, G. Tiesinga, F. R. de Vries and K. Boshuizen. 1988. "Stimulation and Recording of Dynamic Pupillary Reflex: the IRIS Technique. Part 2." *Med. biol. Engng Comp.* **26**, 27–32.

Schiller, P. H. 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. and D. Chen. 1977. "A Simulation Model of the Human Pupil Light Reflex." *Math. Biol*. **33**, 5–24.

Sirkus, V. 1975. *Hopf Bifurcation for Delay-Differential Equations*. M. Sc. Thesis, McGill University, Montreal.

Smith, J. D., G. A. Masek, L. Y. Ichinose, T. Watanabe and L. Stark. 1970. "Single Neuron Activity in the Pupillary System." *Brain Res*. **24**, 219–234.

Stanten, S. F. and L. Stark. 1966. "A Statistical Analysis of Pupil Noise." *IEEE Trans. biomed. Engng* **13**, 140–152.

Stark, L. 1959. "Stability, Oscillations and Noise in the Human Pupil Servomechanism." *Proc. IRE* **47**, 1925–1939.

———. 1962. "Environmental Clamping of Biological Systems: Pupil Servomechanism." *J. Opt. Soc. Am*. **52**, 925–930.

———. 1984. "The Pupil as a Paradigm for Neurological Control Systems." *IEEE Trans. biomed. Engng* **31**, 919–924.

———, F. W. Campbell and J. Atwood. 1958. "Pupil Unrest: An Example of Noise in a Biological Servomechanism." *Nature* **182**, 857–858.

——— and T. N. Cornsweet. 1958. "Testing a Servoanalytic Hypothesis for Pupil Oscillations." *Science* **127**, 588.

——— and P. M. Sherman. 1957. "A Servoanalytic Study of Consensual Pupil Reflex to Light." *J. Neurophysiol*. **20**, 17–26.

Stech, H. W. 1985. "Hopf Bifurcation Calculations for Functional Differential Equations." *J. math. Anal. Appl*. **109**, 472–491.

Stern, H. J. 1944. "A Simple Method for the Early Diagnosis of Abnormality of the Pupillary Reaction." *Br. J. Ophthalmol*. **28**, 275–276.

Sun, F., W. C. Krenz and L. Stark. 1983. "A Systems Model for the Pupil Size Effect—I. Transient Data." *Biol. Cybern*. **48**, 101–108.

Terdiman, J., J. D. Smith and L. Stark. 1971. "Dynamic Analysis of the Pupil with Light and Electrical Stimulation." *IEEE Trans. Syst. Man Cybern*. **SMC-1**, 239–251.

Tranchina, D., J. Gordon and R. Shapley. 1984. "Retinal Light Adaptation—Evidence for a Feedback Mechanism." *Nature* **310**, 314–316.

Ukai, K., J. Higashi and S. Ishikawa. 1980. "Edge-Light Pupil Oscillation of Optic Neuritis." *Neuro-ophthalmology* **1**, 33–43.

Usui, S. and L. Stark. 1978. "Sensory and Motor Mechanisms Interact to Control Amplitude of Pupil Noise." *Vision Res*. **18**, 505–507.

——— and ———. 1982. "Model for Non-Linear Stochastic Behaviour of the Pupil." *Biol. Cybern*. **45**, 13–22.

Webster, J. G. 1971. "Pupillary Light Reflex: Development of Teaching Models." *IEEE Trans. biomed. Engng* **18**, 187–194.

Yoss, R. E., N. J. Moyer and R. W. Hollenhorst. 1970. "Hippus and Other Spontaneous Rhythmic Pupillary Waves." *Am. J. Ophthalmol*. **70**, 935–941.