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MASTER *MS*

NONLINEAR DYNAMICS OF NEURAL DELAYED FEEDBACK.

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ABSTRACT.

Neural delayed feedback is a property shared by many circuits in the central and peripheral nervous systems. The evolution of the neural activity in these circuits depends on their present state as well as on their past states, due to finite propagation time of neural activity along the feedback loop. These systems are often seen to undergo a change from a quiescent state characterized by low level fluctuations to a oscillatory state. We discuss the problem of analyzing this transition using techniques from nonlinear dynamics and stochastic processes. Our main goal is to characterize the nonlinearities which enable autonomous oscillations to occur and to uncover the properties of the noise sources these circuits interact with. The concepts are illustrated on the human pupil light reflex (PLR) which has been studied both theoretically and experimentally using this approach.

1 - INTRODUCTION.

Neural delayed feedback.

By neural delayed feedback system (NDFS), we mean an assembly of one or several populations of neurons forming a feedback loop, i.e. a path from the input of a neural system to its output and back to its input. In each of these populations, the evolution of neural activity at time t is a function of the input to **and** output of this population from the past all the way up to time t . This delayed action arises because of the finite velocity at which signals (graded potentials or action potentials) are transmitted between these neural populations. That mathematical models of the phenomena we will be discussing should take these delays into account is a consequence of the fact that the delays are of the same order of magnitude or larger than the response time of these systems (see Section 3).

In general there is a certain arbitrariness in designating a given neural activity as the input or output of a system. These are often chosen according to the experimentally measurable quantities. For example, the pupil light reflex controls the retinal light flux,

equal to the product of light intensity and pupil area (the pupil is the hole in the middle of the colored part of the eyeball formed by the iris muscles). An input to this system is a variation in retinal light flux, due e.g. to a variation in the ambient light intensity; the output response is also a variation in retinal flux due to a change in pupil area. This example illustrates that the "neural" feedback loop need not comprise only neurons, but can include muscle cells and receptor cells.

Two interesting questions about neural systems.

One of the most interesting questions in the study of human neural systems in particular, as well as of physiological systems in general, is the origin of the ongoing fluctuations in the time course of measurable quantities. There has been much speculation, in the wake of recent studies (see e.g. Ref.6) that this variability may be due in great part to deterministic chaos. The fact that certain low dimensional deterministic systems behave in many respects like probabilistic systems (e.g. they generate invariant densities) has provided investigators with a new paradigm with which to reinterpret mechanisms theretofore attributed to noise. Most studies^{2,6} involve either 1) modelling or 2) computation from time series of dynamical invariants such as the fractal dimension or Lyapunov spectrum. Determining whether aperiodic time series are the manifestation of a stochastic process (i.e. noise) or a deterministic process (chaos) is important theoretically, and each point of view suggests different kinds of experiments to further knowledge about the system under study.

Another equally important question is how oscillatory behavior either arises or is suppressed in neural systems. Oscillations in neural activity are ubiquitous within the central nervous system and between the peripheral and central nervous system (e.g. in reflexes). Oscillatory neural activity can be associated either with health or pathology. An epileptic seizure is a dramatic transition to a pathological oscillatory state¹⁹. The respiratory rhythm⁶, as well as oscillations in olfactory⁴ and visual⁷ cortex, seem to occur under normal healthy conditions. Much work has been invested in developing a theory for oscillation onset in neural systems^{1,9,11,13}. Two aspects of these phenomena have received little attention: 1) the very noisy background on which the oscillatory activity is superposed, and 2) propagation delays. While it is not necessarily useful to view all neural systems generating oscillations as delayed feedback systems, it is important to realize when delayed feedback is the key component leading to the oscillatory instability.

Nonlinear dynamics and neural modelling.

Nonlinear dynamics deals with the study of periodic and aperiodic oscillations. It has become clear in the last few decades that nonlinear dynamics is a useful tool to understand how neurophysiological systems undergo qualitative behavior changes as parameters are varied. Examples include single neuron dynamics^{1,10,23} and physiological control systems⁶. These studies involve building sound physiological models and identifying the proper bifurcation parameter (s) leading to the oscillatory state. Essential to these studies has been the availability of data for guiding mathematical modelling and for validating model predictions. We will see in Section 4 that nonlinear dynamics has to be augmented to include the effects of noise in order to understand oscillation onset in NDFS's.

The paradigm of neural delayed feedback systems.

In the case of human neural control systems, it is often very difficult to carry out experiments, and thus models are based on known anatomy, animal studies and/or hypothetical mechanisms. There is one system which is amenable to experimental investigation and whose study holds hope for uncovering more functional principles of neural control: the human pupil light reflex (PLR). This was one of the systems to which concepts from cybernetics were first applied in the 50's, especially in the work of Stark and his colleagues. The essential feature of this reflex is that its feedback loop can be opened by an optical trick (see Section 2). This makes it possible to induce and control oscillations in this reflex by artificially increasing its feedback gain. Among its many interesting dynamical behaviors, the PLR exhibits "hippus" which is an ongoing pupil area fluctuation that occurs even under constant lighting conditions and seems to be due to neural noise injected into the reflex arc^{15,17,24,28}. Of course, one of the main advantages of working with the human PLR is that the results are directly relevant for humans.

This paper deals with the properties of oscillatory NDFS's, and focusses in particular on the PLR. Section 2 describes experiments designed to induce oscillatory neural activity in the human PLR. Section 3 outlines a model used to study autonomous oscillations in the human PLR. We further describe the Hopf bifurcation in ordinary and delay-differential equations. Section 4 deals with the stochastic Hopf bifurcation in DDE's and the concept of physiological order parameter. Physiological irregularity is discussed in Section 5, and the paper ends with a conclusion and outlook on future investigations in Section 6.

2 - THE HUMAN PUPIL LIGHT REFLEX.

The human pupil light reflex is the involuntary response of the iris musculature to

variations in the light intensity impinging on the eye. Light enters the eye through the pupil and falls on the retina. The reflex tries to control the retinal light flux, equal to the product of light intensity and pupil area. It is a negative feedback control system: an increase in retinal light flux (due, e.g., to an increase in the ambient light intensity) is counteracted by a neural response which decreases the light flux (e.g., a decrease in pupil area).

This control loop can be opened using an optical trick first discussed by James Clerk Maxwell and popularized by Stark and Sherman²⁷. "Maxwellian view" involves shining a narrow beam of light down the center of the pupil, as in Fig.1a. The beam is so narrow that iris movements can not influence the retinal illumination, and thus the feedback loop is opened. It is possible to electronically close this loop with an analog signal proportional to pupil area provided, e.g., by a pupillometer^{17,22,26,27}. This signal can then be used to control the intensity of a light source in Maxwellian view. This procedure is termed "clamping" and allows the experimenter to substitute a different feedback in the place of the nonlinear feedback naturally present in the system. This involves designing an "area comparator" which electronically converts area values to light intensity values. The changes in retinal light flux are then due to changes in intensity, since the area of the light beam entering the pupil is fixed.

The data shown in Fig.2 was obtained by our collaborators at the Free University of Amsterdam using a reflectance type pupillometer^{17,22}. The area comparator is simply a linear amplifier relating pupil area to light intensity, as shown in Fig.1b. The (positive) gain of this amplifier is adjustable, and sets the slope in Fig.1b. From the point of view of pupil area A , the clamped reflex as a whole operates with the feedback of Fig.1c, where the forcing on the pupil area is plotted versus the area itself. The slope here is negative because an increase in area causes an increase in light intensity which forces the area to decrease. Also, the saturation of the feedback at high and low area values is a consequence of the nonlinearities in the reflex. Hence, from the point of view of pupil area, the area comparator of Fig.1b actually produces a negative feedback configuration.

Fig.2 shows experimental recordings of pupil area versus time at four different gain settings. All the data is obtained from the same healthy subject within a short time span in order to maximize stationarity. The baselines have been corrected for drift. While the mean amplitude of the oscillation increases with the gain, the period varies only mildly. Further, the signals are strongly aperiodic despite the presence of a dominant frequency.

From classical control systems theory based on linear transfer functions, one expects the system to begin oscillating as the gain is increased. While oscillations are definitely more prominent as the gain is increased, it is not clear at which point they appear (data at lower gain values than those shown substantiate this point). Pinpointing oscillation onset in this NDFS will be the focus of Section 4.

We must emphasize that the oscillations are not externally driven by some periodic modulation of the light intensity. Rather, the oscillations are autonomous in the sense that pupillary dynamics determine the retinal light flux. Once the system is set up in the high gain configuration along with a mean light beam intensity, the oscillations begin spontaneously.

3 - HOPF BIFURCATION IN NEURAL DELAYED FEEDBACK.

The Hopf bifurcation.

This section focusses on the Hopf bifurcation, i.e. the transition from a stable equilibrium (fixed point) to a stable oscillation (limit cycle), as a parameter is varied. This bifurcation is characterized by the crossing of a pair of roots of the characteristic equation, obtained from the linearization of the nonlinear equations of motion, into the right hand side of the complex plane. It is relatively straightforward to compute the condition for the roots to migrate across the imaginary axis and to verify the further condition that this crossing be non-tangential. However, this calculation only indicates how the fixed point goes unstable, but does not guarantee the existence of a stable limit cycle. This depends on whether the equations of motion satisfy certain non-degeneracy conditions⁸.

Hopf bifurcation analysis, although quite involved, can be used to compute the period and amplitude of the limit cycle oscillation. In practice, one often resorts to numerical simulation of the equations of motion to obtain this information, as well as to determine whether the bifurcation is super- or subcritical. The basic difference here is that in the former case, the amplitude of the oscillation is zero at the bifurcation point. In the latter case, the amplitude is finite and the limit cycle can only be reached through some perturbation from the fixed point (so-called "hard excitation")⁸.

The Hopf bifurcation theorem is essentially the same for a system of ordinary differential equations (ODE's) or delay-differential equations (DDE's). However, the analysis is much more complicated for DDE's because they are infinite dimensional systems evolving in a functional (Banach) space rather than the usual phase space spanned by the finite number of degrees of freedom of ODE's. This is a consequence of the fact that a family

of solutions to a DDE is parametrized not by a finite vector of initial conditions but by a function on the interval $(-\tau, 0)$, where τ is the delay. Further, the characteristic equation for linear DDE's is a transcendental function. This implies that it can not be solved analytically for its complex roots, and that it has an infinite number of roots.

Model for high gain oscillations in the PLR.

We now outline a mathematical model for nonlinear autonomous oscillations in the PLR which occur as the feedback gain is increased. Details can be found in Ref.16. Although the PLR is a spatially distributed system with thousands of parallel pathways, not much is known about the parameters characterizing the spatial features beyond the retina. What is known is where the neurons of one nucleus project to, and we have found that this is sufficient to explain the phenomena we are interested in. Thus our model is spatially homogeneous, and deals with one scalar variable, the pupil area $A(t)$. This area value is inversely proportional to the area of the iris muscles. The main iris muscle is a sphincter surrounding the pupillary margin. It reduces its diameter upon constriction, thereby stretching the iris tissues. Hence, iris area is proportional to the iris sphincter activity.

The retinal light flux is transduced into neural activity in the optic nerve (for simplicity, one can assume that stimulus strength is encoded in firing frequency of action potentials). This neural activity is processed by different brainstem nuclei and finally reaches the sphincter muscle. The result is that an increase in retinal light flux increases sphincter activity which decreases pupil area. The following model has been shown to predict the basic features of pupillary dynamics including oscillatory behavior¹⁶:

$$\frac{dg(A)}{dA} \frac{dA(t)}{dt} + \alpha g(A) = \gamma \ln \left[\frac{\phi(t - \tau)}{\bar{\phi}} \right] \quad (1)$$

where τ is the time delay between the falling of light on the retina and a change in pupil area. α is a rate constant for pupillary motion, $\phi(t)$ is the retinal light flux and $\bar{\phi}$ is the threshold flux below which no pupil response occurs. The function $g(A)$ (shaped like the inverse of a sigmoid) relates area to iris sphincter activity. The logarithm accounts for the compression of the light flux scale in the transduction process at the retina. A rate constant of 3 sec^{-1} and a delay of 300 msec are typical.

To induce pupillary oscillations as in Fig.2, the retarded flux is given by

$$\phi(t - \tau) = I(t - \tau) A_{beam} \quad (2)$$

$$= [I_m + I_{a.c.}(A(t - \tau))] A_{beam} \quad (3)$$

where A_{beam} is the area of the light beam used in Maxwellian view, $I(t)$ is the light intensity, I_m is the mean light intensity, and $I_{a.c.}$ is the functional dependence of light intensity on pupil area synthesized by the area comparator (see Fig.1b). Under these conditions, the delay also comprises the external electronic delay. Eq.(1) has a fixed point solution A^* given by the root of the transcendental equation obtained by setting the time derivative equal to zero. Eq.(1) undergoes a supercritical Hopf bifurcation when the delay is increased past a critical value. This is also the case when the slope of the nonlinearity $g(A)$ evaluated at the fixed point decreases below a critical value. This corresponds to increasing the feedback gain. The amplitude of the limit cycle is constrained by the neuromuscular nonlinearity and the logarithmic compression at the retina. Near the bifurcation, the amplitude is predicted to grow as the square root of the deviation of the parameter from its value at the bifurcation point, while the period varies slowly across the bifurcation.

4 - DEFINING OSCILLATION ONSET: PHYSIOLOGICAL ORDER PARAMETERS.

The limit cycles in Fig.2 are irregular. Quantitative analysis of the data shows¹⁷ that the amplitude does not grow as the square root of the distance from the bifurcation point, as the deterministic theory reviewed in Section 3 predicts. However, both the observed growth and the aperiodicity can be explained by hypothesizing that stochastic forces are also driving pupillary dynamics. Noise such as "hippus" can arise from the spontaneous activity of the neurons in the reflex arc, or from the activity of other neural pathways which impinge on those of the PLR but are not under experimental control. The power spectrum of hippus is approximately broad band up to a cutoff frequency of $\approx 1Hz$, which indicates that it is a colored noise. Its correlation time can be roughly estimated as the inverse of the spectrum bandwidth, i.e. $\approx 1sec$.

In a noisy system, one is confronted with the very basic problem of defining what is meant by oscillation onset. Defining a "statistical bifurcation point" can be done with some help from nonequilibrium statistical mechanics. The idea is to find a quantity that exhibits a qualitative change as the bifurcation parameter is swept, just as in the deterministic Hopf bifurcation case. The obvious measure of oscillation, i.e. the height of the main peak in the power spectrum, does not undergo such a qualitative change⁵. Any amount of noise will reveal this peak, even when the parameter is well below the bifurcation point (the peak is a "noisy precursor" of the Hopf bifurcation - see Ref.5). The peak simply grows as the parameter is swept across the deterministic bifurcation point. The autocorrelation

function does not exhibit any qualitative change either, as it is obtained from the Fourier transform of the power spectrum.

However, the probability $\rho(x)$ that a signal $x(t)$ takes on a value between x and $x + dx$ does undergo a qualitative change from a unimodal to a bimodal shape. The distance between the peaks, which serves as an “order parameter”, is a statistical measure of amplitude different from “the mean oscillation amplitude”; in fact, the order parameter can be zero even though the mean amplitude in the time series is not.

The probability densities for the area time series of Fig.2 are shown in Fig.3. Although one sees a widening of the density as the gain is increased, the order parameter is always zero. At the highest gain, however, one could argue that the order parameter is not zero, but it simply can not be resolved from the short time series available. This is supported by numerical experiments. The behavior of this order parameter has been computed in Ref. 17 by numerically integrating a simplified version of Eq.(1) having the same qualitative dynamics. The noise is modelled by an Ornstein-Uhlenbeck process which is an exponentially correlated colored noise (correlation time 1sec). At each parameter in a set spanning across the deterministic bifurcation, the density $\rho(A)$ is computed from the simulated time series $A(t)$ and the order parameter is computed. We find that it is very important to allow for transients to die out, especially near the bifurcation point where the exchange of stability occurs. At this point “critical slowing down” occurs, which means that perturbations away from the attractor decay more and more slowly as the bifurcation point is approached. In practice, the solution has to be integrated over thousands of periods in order to resolve the growth of the order parameter. Hence, the poor resolution in Fig.3 is not surprising, given the length of the available time series.

Another interesting result is that the peaks of $\rho(A)$ do not correspond to those of the deterministic case (i.e. the extrema of the oscillation); in fact, the order parameter is smaller than the deterministic amplitude. The parameter value at which the order parameter becomes non-zero, i.e. the point which we define as “oscillation onset”, is larger than the deterministic one. Noise postpones oscillation onset from a statistical point of view: on the limit cycle side of the bifurcation, the system spends more time near the unstable fixed point than in the absence of noise. This effect has been reported in ODE's and is called a “noise-induced transition”⁵. We have found this to occur with both additive and multiplicative noise.

Physiological order parameters have also been studied in the context of movement

coordination in Ref.9. Order parameters are very difficult to resolve on short experimental time series such as those shown in Fig.2. However, we believe that an understanding of their behavior is an essential backbone of any analysis. Further, measurements of order parameters may still be used to validate a model despite their large standard deviation. But other measures may be more useful for short neurological time series, such as the behavior of period, amplitude and phase of oscillations. In fact, it was shown in Ref.17 that the noise intensity at which the predicted and measured curves of "mean amplitude versus gain" have similar shapes also yields similar shapes for the predicted and observed curves of "mean period - " as well as "relative amplitude and period fluctuations versus gain". These last three curves further agree quantitatively with the data. While these quantities do not undergo qualitative changes, they are important characteristics of the oscillations and the proper prediction of their behavior serves as a strong test for the model.

5 - ORIGIN OF PHYSIOLOGICAL IRREGULARITY.

Although the mean behavior of NDFS's may be described by deterministic laws, upon closer scrutiny they are seen to generate aperiodic activities. For example, in the case of the PLR, hippus is always more or less manifest. This general observation raises the question of the origin and purpose of this irregularity. This has been a subject of great debate over the past few years (for a comprehensive review, see Ref.21). The debate has centered on whether chaos, noise or both underlie the irregularity. Thus the simpler view of simple dynamical motion with noise has received little attention. The reasons for this are varied, the major one being that fractal dimensions and other quantities can be cranked out of time series with relative ease, along with the immediate conclusion that the dynamics are principally chaotic. There are many problems with this view (for a review see Ref.19). It is safe to state in these cases that the steady state dynamics involve only a few degrees of freedom. But the presence of chaos will remain uncertain until one can rule out the other kinds of (maybe noisy) dynamics which can yield e.g. similar dimension values. It is known^{14,20} for example that the fractal dimension of attractors reconstructed from time series of colored type noises such as $1/f$ (one-over-f) are also finite (although it diverges to infinity in the white noise limit); thus results have to be interpreted with extreme care. Fractal dimension algorithms are now being extensively used because 1) often there is no adequate theory for the system under study, or 2) system parameters can not be varied to produce bifurcations leading to the chaotic state, or simply 3) they are readily available. More stringent and self-consistent tests for chaos, based on prediction of time series, are

being developed and hold hope for clarifying the source(s) of irregularity (for a review see Ref.3).

Without further belaboring the merits and pitfalls of these methods, we wish to emphasize that simple dynamics with noise should also be considered as a candidate for irregularity. This is especially true in the vicinity of bifurcation points where the dynamics are dominated by the noise, due to critical slowing down. It is possible that even in simple NDFS's there are a few feedback loops that interact together and with different noise sources (there are at least three pathways in the human PLR - see Ref.15), and hence that critical behavior could occur around more bifurcation points.

Previous studies^{24,25,28} have focussed on the dynamics of hippus in the steady state and during transient responses to light; they have concluded that hippus is probably noise. Longtin et al.¹⁷ have investigated hippus at oscillation onset by studying the critical behavior of a model DDE at a Hopf bifurcation; they have reached the same conclusion. This raises two questions. Is the noise really injected into the reflex arc with a 1 sec correlation time, or is it quasi-white but appears strongly colored because of the lowpass characteristics of this neuromuscular system, as suggested in Ref.24 ? This remains to be investigated. Also, what is the ultimate origin of hippus? Is it the trace of a chaotic process? Important clues may lie in the fact that the interaction of hippus with the dynamics of the reflex arc seems to be unidirectional, i.e. the dynamics of the arc are influenced by that of the noise, but not vice-versa.

Assessing stochastic components of any dynamics requires proper characterization of the noise, namely its density, spectrum and source. It is conceivable that characteristics of the noise itself may serve as bifurcation parameters in real NDFS's.

6 - CONCLUSION AND OUTLOOK.

NDFS's are inherently nonlinear, and under experimental control display a variety of dynamical behaviors. Stochastic components of NDFS's must be disentangled from deterministic ones in order to understand their behavior in the vicinity of bifurcation points. The special problem of oscillation onset leads one to define a physiological order parameter as the distance between the two peaks of the invariant density for the dynamics of the measured variable. While these peaks are extremely difficult to resolve on short time series, as is the case for the PLR experiments, it is nevertheless important to know this distance is less than the limit cycle amplitude in the absence of noise. This means noise postpones the oscillation onset by stabilizing the fixed point. That noise is responsible for

the observed aperiodicity can be proved by explaining the behavior of more easily measured quantities such as the the mean and standard deviation of the period and amplitude of the area fluctuations. In this way, hypotheses about stochastic inputs to a system can be validated.

Numerous avenues remain to be explored. One is to understand the influence of distributed delays (which result from a distribution of nerve axon diameters) and of the spatial extent of NDFS's on oscillation onset. It may be that critical behavior and growth of order parameters different from what is expected from a spatially homogeneous system can be a signature of interactions between parallel pathways comprising the neural system. Tests that differentiate between additive and multiplicative noise would also be quite useful, as our analysis of pupil dynamics can not resolve their effects. One needs a theory with which the mean and variance of the amplitude and period fluctuations can be analytically rather than numerically computed. Further, hardly anything is known about the behavior of stochastic DDE's (see however Ref.12, Chapter 4). A Fokker-Planck-type theory for "generalized delayed Langevin equations" would be more than welcome as it would allow densities and order parameters to be calculable at least in principle. It is expected that this knowledge will become important as more neural systems involving delays are investigated.

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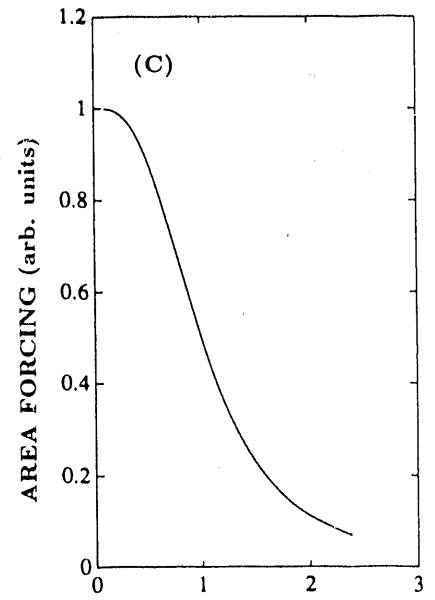
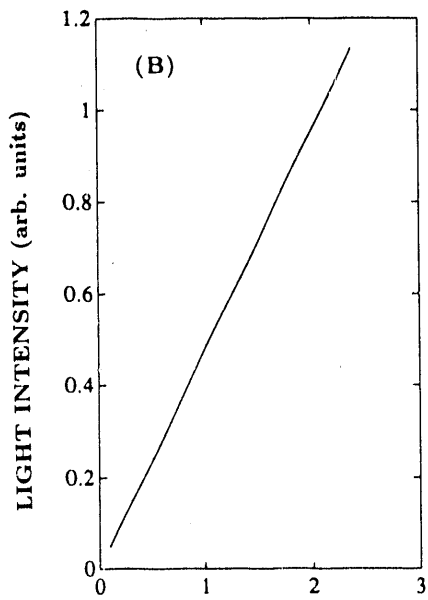
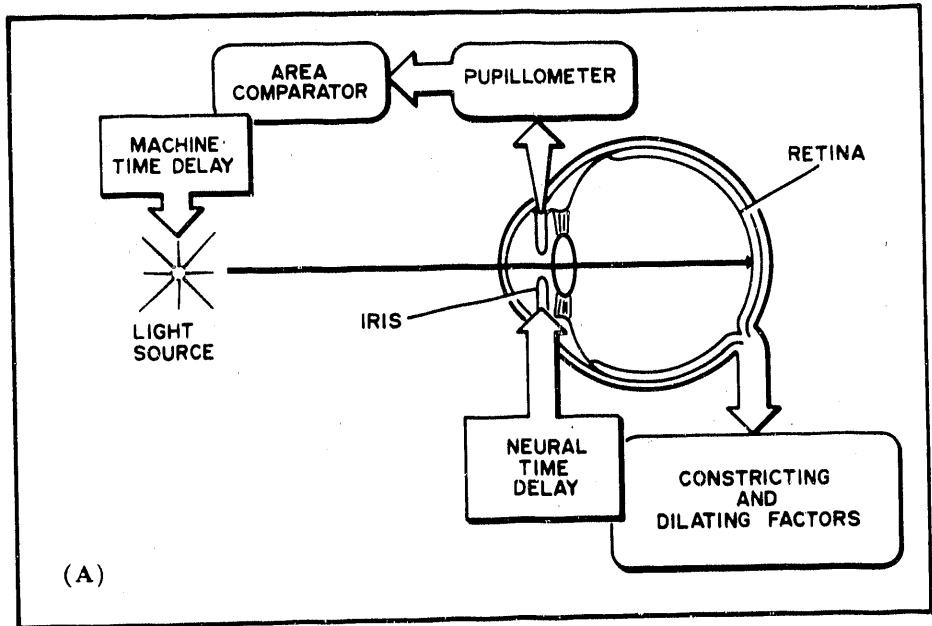
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FIGURE LEGENDS.

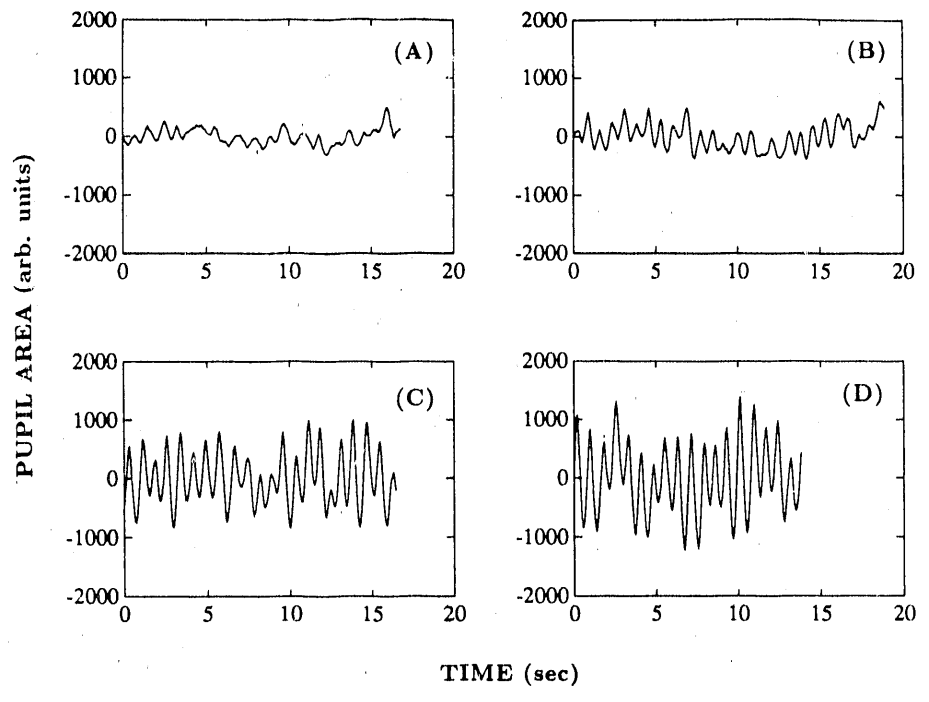
Figure 1. a) Schematic of clamped pupil light reflex. The narrow beam of light illuminates the retina in open-loop, i.e. the iris muscles can not block the beam even under maximal constriction. The area comparator is the electronically synthesized external feedback which relates light intensity to measured pupil area. b) Area comparator used here to produce oscillations. The gain is equal to the slope of this curve. c) Forcing on the pupil area as a function of pupil area. Because an increase in light intensity causes a decrease in pupil area, this area comparator actually produces a negative feedback configuration as in the unclamped pupil light reflex. The nonlinearities of the reflex are responsible for saturation at high and low area values.

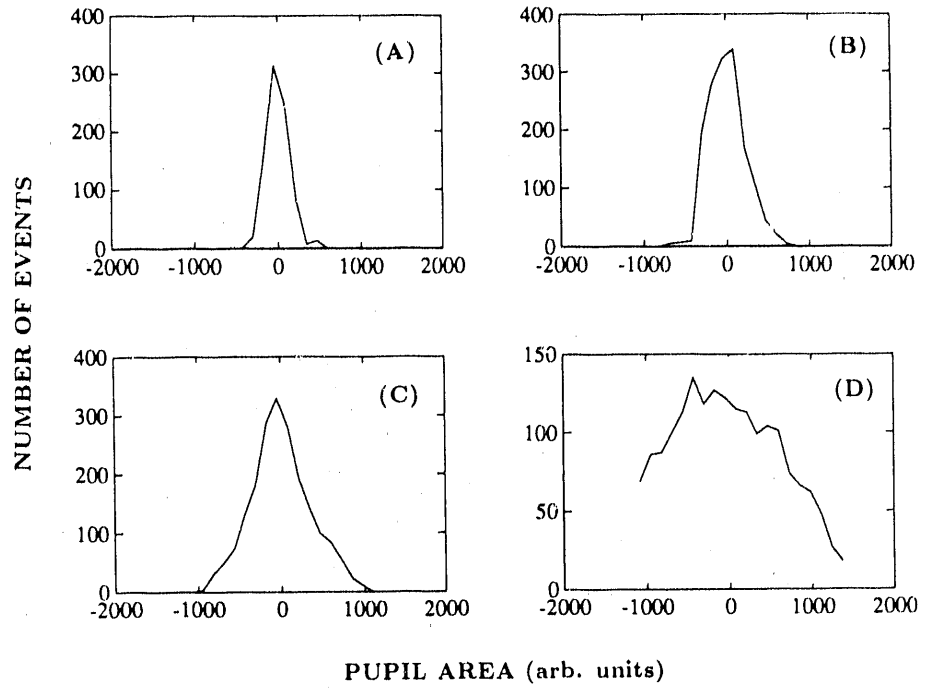
Figure 2. Pupil area as a function of time at four different gain settings: a) 1.41 ; b) 2.0 ; c) 2.82 ; d) 4.0 . Area is measured in arbitrary units (the same throughout the whole experiment) relative to the mean for a given record. The linear trend across one record has also been removed. The sampling rate is 50 Hz.

Figure 3. Area densities corresponding to the time series in Fig.2. The densities are 20 bin histograms of the area values spanning the range of values obtained with a 4.0 gain. The data in Fig.2 along with more data corresponding to total recording times of a) 16.78 ; b) 29.90 ; c) 39.60 and d) 35.96 sec has been used to construct the densities.



PUPIL AREA (arb. units)





END

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