allata are also a link in the humoral cycle initiating ovarian development in mosquitoes.

JOSEPH R. LARSEN
Division of Medical Entomology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland

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Testing a Servoanalytic Hypothesis for Pupil Oscillations

Oscillations are a common and important instance of the malfunctioning of a servomechanism. Oscillations are also a common pathological abnormality in a wide variety of neurological diseases and are manifested in such clinical signs as tremor, ataxia, clonus, and nystagmus. This report indicates how a biological system has been analyzed by linear servoanalytic methods and experimentally justifies this approach by quantitatively verifying a prediction.

The pupil response to light—an example of neurological servosystem—has been studied by means of servoanalytic concepts and techniques (*1*). A sinusoidally varying intensity of light was applied, and the pupil area was continuously recorded. When intensity increases, the pupil contracts. The resultant effect of light falling on the retina can be resolved into two factors: (i) an increase due to increase in applied intensity and (ii) a decrease due to contraction of the pupil. System gain is here defined as the ratio of (ii) to (i). An open-loop transfer function

$$G(s) = 0.16e^{-0.18s}/(1+0.1s)^3$$

was computed from data graphically displayed in Fig. 1. This, the Nyquist diagram, is a vector plot of the relationship between gain and phase shift at various frequencies. For example, at 1.2 cy/sec, the gain is 0.12, with a phase lag of 180°. This gain means that the pupil compensates for 12 percent of the change in applied light intensity.

If the gain were to be increased to 1.0 or more, the system would become unstable, and the pupil would oscillate at its natural frequency—that is, the frequency at which the phase lag is 180°. From the figure we see that this frequency is 1.2 cy/sec. Thus, from our servoanalysis of the normal, low-gain, stable pupil system, we are led to predict that a large increase in gain would produce sustained oscillations and that the frequency of these oscillations would be 1.2 cy/sec (72 cy/min). A test of the validity of the servoanalytic method would be the production of pupil oscillations in this manner and at the predicted frequency. Observations which comprise such a test are already available for evaluation.

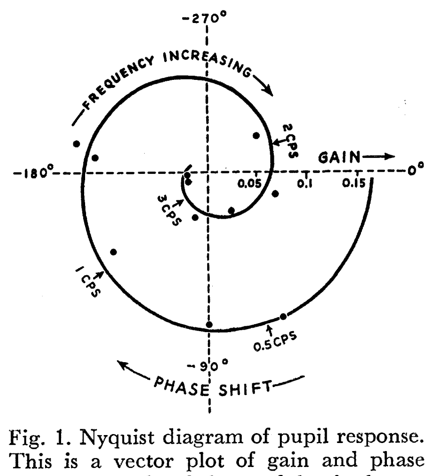

Fig. 1. Nyquist diagram of pupil response. This is a vector plot of gain and phase shift. The scale of the modulus is shown, and a few frequencies are indicated. The curve is derived from fitted lines from gain and phase frequency-response graphs, while the points are experimental.

Clinical studies have been reported in which sustained oscillations of the pupil have been produced and in which the frequency of the oscillations has been measured. Stern (*2*) pointed out that a series of oscillations of the pupil could be induced by imaging a small point of light just on the margin of the pupil. This causes the iris to contract, and all the light is cut off in the early phase of contraction. The iris therefore redilates, and full light intensity again enters the eye. The gain is thus increased to more than 1.0, and sustained oscillations result. Campbell and Whiteside (*3*) made a careful study of parameters affecting this induced pupil oscillation, using quantitative techniques on a group of normal subjects. A third report is that of Wybar (*4*), who studied a large number of normal subjects and also patients with multiple sclerosis (*5*). In Table 1 the frequencies of the sustained oscillation observed are summarized.

There is good agreement between the frequency of pupil oscillations observed in normal subjects and our prediction. Further experiments have been carried out by Stark and Baker (*6*) in which the transfer function of the pupil system has been altered by drugs. For example, when the 180°-phase cross-over frequency was changed from 1.5 to 0.9 cy/sec, the high-gain oscillation frequency shifted in a parallel fashion from 1.5 to 1.0 cy/sec (*6*).

Table 1. Observed frequencies of pupil oscillations (references in parentheses).

Group studied	Mean frequency (cy/min)
10 Normal subjects (*2*)	80
1 Normal subject (*3*)	71
37 Normal subjects (*3*)	69
34 Normal subjects (*4*)	62
Patients with multiple sclerosis: 70 pupils (*4*)	41
Predicted value (*1*)	72

The qualitative value of the servoanalytic approach is demonstrated by the clarification introduced through explanation of the nature of these pupil oscillations. The quantitative nature of the method is illustrated by the accuracy of the prediction (*7*).

LAWRENCE STARK
TOM N. CORNSWEET
Departments of Neurology and Psychology, Yale University, New Haven, Connecticut

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7. We gratefully acknowledge discussions with Peter Schultheiss, Philip Sherman, Fergus Campbell, and Gilbert Glaser. This work is being supported by the National Multiple Sclerosis Society, the National Science Foundation, the National Institute of Neurological Diseases and Blindness, and the George Knight Fund.

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Preparation of an Apoprotein from Ceruloplasmin by Reversible Dissociation of Copper

The blue copper-protein of plasma, ceruloplasmin, with a molecular weight of 151,000, contains eight atoms of copper per molecule (*1*). The physiologic significance of this protein, while not clear, has usually been implicitly associated with its oxidase activity (*2–5*). On the other hand, the possibility that reversible binding and release of copper by the protein may be the basis of its