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Modeling the pupil light reflex with differential delay equations

Nonlinear differential delay equations (DDE) with piecewise constant negative feedback (PCNF) arise in the description of the pupil cycling. Here we show that for certain parameter ranges a second-order DDE with PCNF exhibits multistability of periodic orbits, i.e. the co-existence of multiple stable limit cycles. It is suggested that multistability may be one source of the variability observed in pupil oscillation waveforms during pupil cycling.

1 Introduction

Complex dynamics occur ubiquitously in physiological systems in health and disease. Untangling the relative roles played by deterministic and stochastic processes in shaping these dynamics is a formidable task [1]. A case in point concerns the oscillations which occur in the pupil light reflex under "high gain conditions", i.e. so-called pupil cycling [2]. Clinically, pupil cycling is a valuable non-invasive method for localizing pathology within the reflex arc [2-3]. However, the considerable variability present in the pupillary waveforms, even during the same record, makes analysis difficult. Variability in dynamical systems typically arises from the influence of noisy perturbations (both additive and multiplicative). Here we draw attention to an additional source of variability in noisy dynamical systems with delayed feedback, such as the pupil light reflex. Namely there can be multistability, i.e. the co-existence of multiple stable limit cycles.

2 Pupil cycling

Pupil cycling is most easily done by clamping the pupil light reflex with PCNF, $f(A(t-\tau))$, i.e.

$$f(A(t-\tau)) = \begin{cases} a & \text{if } A(t-\tau) > \theta \\ b & \text{if } A(t-\tau) < \theta \end{cases} \tag{1}$$

where $A(t-\tau)$ is the pupil area at time $t-\tau$ in the past, τ is the time delay, a, b describe the retinal illumination ($a > b$), and θ is an area threshold [2-3]. In this technique the feedback loop is first "opened" and then reclosed using an electronic circuit which relates measured changes in pupil area to changes in retinal illumination. The advantage of this approach is that the feedback is exactly known and thus direct comparison between theory and experiment becomes possible.

Figure 1 shows a plot of pupil area, A, versus time for pupil cycling. There are fluctuations in the amplitude and period of the oscillation. Moreover the shape of the waveform varies between two different waveforms: some waveforms have a small kink on the dilating phase (labelled "a"), others do not ("b"). The observation of two different waveforms during pupil cycling suggests the possibility of a bistable dynamical system in which noisy perturbations cause switches between two different limit cycles.

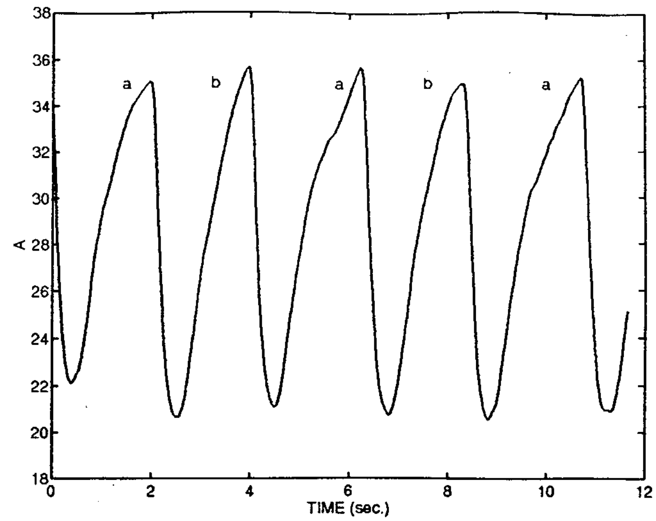

Figure 1: Plot of pupil area, A (mm^2), versus time under conditions of pupil cycling. $\theta = 34$ mm^2.

3 Multistability in second-order DDEs

Here we discuss the occurrence of multistability in second–order DDE with PCNF [4], i.e.

$$d^2A(t)/dt^2 + \beta dA(t)/dt + \alpha A(t) = f(A(t-\tau)) \tag{2}$$

where α, β are positive constants and f is given by (1). For a discussion of a first–order DDE model for pupil cycling the reader is referred to [2]. When the damping coefficient is zero, i.e. $\beta = 0$, substantial analytical insight and results can be obtained [5-7]. These results include the derivation

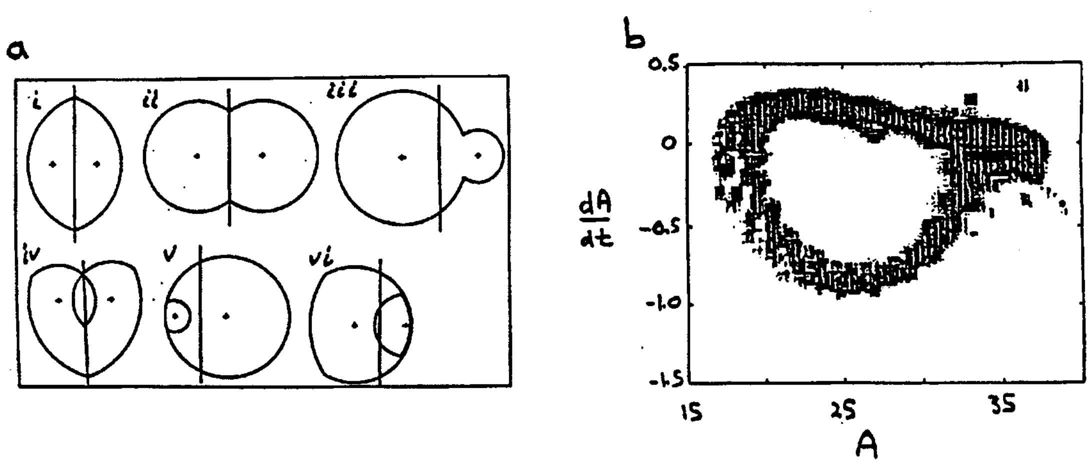

Figure 2: a) Six types of periodic solutions observed for (3) when $\theta = 0$. b) Plot of pupil velocity, dA/dt (mm^2 per digitization time step of ~ 17 msec) versus area, A (mm^2), for pupil cycling. $\theta = 34$ mm^2.

of a rich bifurcation scheme for many types of periodic orbits with infinitely many different minimal periods. Rescaling and shifting of coordinates and taking, without loss of generality, $\alpha = 1$, $a = .5$,

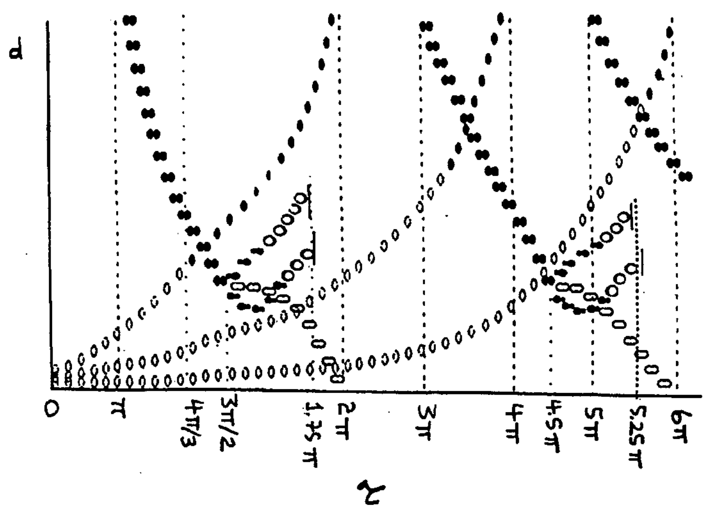

Figure 3: Bifurcation diagram for eq. (2) when $\theta = 0$. Horizontal axis is the bifurcation parameter, τ, and the vertical axis,d, gives the diameter of the periodic orbits. Filled symbols: stable solutions, hollow symbols: unstable solutions.

$b = -.5$, (2) can be written as

$$\begin{aligned} dx(t)/dt &= y(t) \\ dy(t)/dt &= f(x(t-\tau)) \end{aligned} \tag{3}$$

Solutions of (3) are piecewise composed of arcs of circles with centers either at $(x, y) = (-.5, 0)$ or $(x, y) = (.5, 0)$. It can be proven that there are at least six types of periodic orbits [5-6] (Fig. 2a). All of the periodic orbits, except one, are asymptotically orbitally stable in certain ranges of τ and θ [7]. Figure 2b shows a plot of dA/dt versus A for pupil cycling. There is qualitative agreement between the experimentally observed limit cycle (the "a" waveform predominated in this experiment) and the Type *iii* limit cycle shown in Fig. 2a.

We state the following two theorems (proved in [7]).

Theorem 1. *Let $\theta \in [0, .5]$, $n \in \mathbb{N}$ and $\tau \in (0, 2n\pi)$. Then there exists a periodic orbit (of Type i Fig. 2a) with minimal period $T = \frac{\tau}{n}$. The two arcs of the orbit have lengths $\frac{\tau}{2n} \pm \delta$, where* $\delta = \arcsin(2\theta \sin(\tau/2n))$.

Theorem 2. *Let $\theta \in [0, .5]$ and n be an odd integer. Then there is a number $\tau_L \in [1.74\pi, 1.75\pi]$ such that for each $\tau \in (n\pi, n\tau_L)$ there is a periodic orbit (of Type ii Fig. 2a for $\theta = 0$, otherwise of Type iii) with minimal period $T = 2\tau/n$. The two arcs of the orbit have lengths $\tau/n \pm \delta_L$, where* $\sin(\delta_L) = \sin(\frac{\tau}{n}) \left[2(\theta - 1/2)\cos(\tau/n) - \sqrt{1 - 4(\theta - 1/2)^2 \sin^2(\tau/n)}\right]$.

We do not state here the domains of existence for the other types of solutions. The bifurcation diagram when $\theta = 0$ is shown in Fig. 3. Each branch of this diagram is labeled by a symbol showing the phase plane representation (i.e. dx/dt versus x). As can be seen there are regions of τ (and in general θ) where multiple stable and qualitatively different limit cycles coexist (multistability). In particular, the type *iii* limit cycle (Fig. 2a) co-exists with other stable limit cycles, e.g. two when $\tau \in (3\pi/2, 1.75\pi)$. This observations supports the possibility that the changes in the shapes of the waveforms observed during pupil cycling reflect an underlying multistable dynamical system.

Numerical simulations of (2) when $\beta > 0$ indicate that these solutions (with some distortion) persist provided β is not too large. However in this case periodic solutions are only seen when $\tau > \pi$ (for smaller τ the solutions damp away).

4 Discussion

Here we have shown that multistability can arise in a second–order DDE with PCNF. Recently, multistability has also been reported to occur in a damped harmonic oscillator with delayed negative feedback [4]. In order to solve a DDE it is necessary to specify an initial function, $\phi(s)$ where $s \in [-\tau, 0]$. Different solutions correspond to different choices of $\phi(s)$; each solution type has its own basin of attraction in a functional space. Noisy perturbations alter $\phi(s)$ and as a consequence the dynamical system is moved between local basins of attractions. Consequently the observed dynamics reflect the relative times spent in each basin of attraction.

A vexing question is whether the variability seen during pupil cycling reflects a multistable dynamical system under the influence of noise. The fact that there is some qualitative agreement between the phase plane diagram for pupil cycling and one of the solutions of (3), which typically co–exists with at least one other stable limit cycle, is suggestive. We are presently undertaking experiments to determine whether other types of limit cycles can be recognized and whether suitable perturbations can be found to switch from one limit cycle to others.

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