TIME DELAYS AND THE COMPLEXITY OF PHYSIOLOGICAL DYNAMICS

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ABSTRACT

This paper examines the dynamics of physiological control mechanisms with negative and "mixed" feedback from the point of view of delay-differential equations (DDEs).

INTRODUCTION

Oscillations and other complex dynamical behaviors are ubiquitous features of physiological control mechanisms. However, the nature of the mechanisms which generate these behaviors are unknown. Consequently interest has focussed on the characterization of the dynamics which can be produced by known physiological control mechanisms (see also Layton, this session).

In many instances the dynamics of physiological variables, $x(t)$, can be modeled by DDEs of the form

$$\dot{x}(t) = F(x(t-\tau)) - c\,x \qquad (1)$$

where the feedback, $F(x(t-\tau))$, depends on the value of $x(t)$ at a time $t-\tau$ in the past, τ is the time delay and c is a positive constant. The formulation in terms of DDEs arises because an important intrinsic property of many physiological control mechanisms is the presence of time delays. The time delays arise, for example, because of non-zero conduction times in the nervous system and maturation times in replicating cellular populations.

Most commonly $F(x(t-\tau))$ is a monotone decreasing function of $x(t-\tau)$ ("negative feedback"), e.g.

$$F(x(t-\tau)) = b\theta^n/(\theta^n + x(t-\tau)^n)$$

where b, θ, n are positive constants. However, in some cases $F(x(t-\tau))$ is more complex and represents a mixture of positive and negative, i.e. "mixed", feedback, e.g.

$$F(x(t-\tau)) = bx(t-\tau)\theta^n/(\theta^n + x(t-\tau)^n)$$

Here we use results from analytical, numerical and experimental studies to compare the dynamics which can be produced by negative and mixed feedback mechanisms.

NEGATIVE FEEDBACK

Negative feedback mechanisms arise, for example, in the control of red blood cell populations [1], respiration [2], and simple neural networks [3]. Two types of stable solutions of (1) exist: i) a locally stable equilibrium point defined by $\dot{x} = 0$, and ii) a stable limit cycle oscillation. The oscillation period, T, is $2\tau < T < 4\tau$ and its onset coincides with a supercritical Hopf bifurcation. Numerical studies suggest that more complex oscillations, such as chaos, cannot be generated by feedback mechanisms of these types.

Experimentally it has been found that the properties of oscillations in the PLR [3-4], Cheyne-Stokes respiration [2] and autoimmune hemolytic anemia [1] are consistent with these predictions.

In the special case of piecewise constant negative feedback (PCNF), i.e.

$$F(x(t-\tau)) = a \text{ , if } x(t-\tau) < \theta$$
$$= 0 \text{ , if } x(t-\tau) > \theta$$

where a, θ are positive constants, it is possible to show that (1) has only one type of oscillatory solution [5]. In studies of the oscillations in pupil area which occur when the pupil light reflex (PLR) is electronically "clamped" with PCNF a quantitative agreement between prediction and observation is found [6].

"MIXED" FEEDBACK

Mixed feedback mechanisms arise in

descriptions of neural networks [7] and in the control of white blood cell populations [2]. It is well known from numerical studies that (1) with mixed feedback produces a richness of dynamics not seen with negative feedback [2]. These dynamics include simple and complex periodic oscillations and aperiodic fluctuations which exhibit a sensitive dependence to initial conditions ("chaotic" in the current vernacular). Better characterization of these dynamics has been made possible by the recent development of electronic analog circuits to integrate this equation (see Losson, this session).

The distribution of interspike intervals from a CA1 neuron was measured in a rat hippocampal slice. The distribution of interspike intervals produced by a mixed feedbak model of hippocampal recurrent inhibition [7] was in qualitative agreement.

As for negative feedback, it has been possible to obtain greater analytical insight for the case of piecewise constant mixed feedback (PCMF),i.e.

$$\begin{aligned} F(x(t-r)) &= 0 \text{ , if } x(t-r) < \theta_1 \\ &= a \text{ , if } \theta_1 < x(t-r) < \theta_2 \\ &= d \text{ , if } \theta_2 < x(t-r) \end{aligned}$$

where $\theta_2 > \theta_1 > 0$ and $a > d > 0$. It has been proved for constant initial conditions that there exist stable equilibria, stable and simple limit cycles, Li and Yorke type chaos, and mixing and exact motions for various parameter values [7]. Experiments in which the PLR is clamped with PCMF yield a variety of complex oscillations in pupil area which are not seen when the reflex is clamped with PCNF [8-9].

CONCLUSIONS

Our observations suggest that the type of dynamics generated by a physiological control mechanism depends on the type of feedback involved. Complex dynamics are more likely to be associated with mixed feedback mechanisms. However, irregular fluctuations are often measured in physiological variables thought to be controlled by negative feedback mechanisms, e.g. "hippus" in the PLR [10]. These fluctuations presumably reflect noise injected into the reflex arc (see Longtin, this session) and/or arise because multiple feedback loops are involved (see Beuter, this session). Thus it is important to develop methods to assess the relative roles of stochastic and deterministic mechanisms in shaping the observed dynamics (see papers by Longtin and by Rapp, this session). In this way it should be possible to develop novel diagnostic techniques (see [6,11] and Collura, this session) and, hopefully, effective therapuetic strategies based on manipulation of the properties of feedback [2,12].

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