Interval timing

J. E. R. Staddon* and J. J. Higa†

*Department of Psychology and Neuroscience, Duke University, Durham, North Carolina 27708, USA. email: staddon@psych.duke.edu. †Department of Psychology, SWR, Room 334, Texas Christian University, Box 298920, Fort Worth, Texas 76129, USA. email: J.Higa@tcu.edu

The review of timing behaviour by Buhusi and Meck¹ misrepresents current understanding both of pacemaker–accumulator (PA) timing models and of behavioural research on interval timing in general. The article is not as balanced as it should have been, and the authors should have pointed out that the strongest evidence against PA models has always been theoretical/conceptual, behavioural and, to some extent, pharmacological, rather than physiological.

The brain is sufficiently rich in processes to be at least compatible with a wide range of behavioural models. Therefore, existing physiological data do not clearly favour either PA models, or the coincidence-detection model Buhusi and Meck offer as an alternative, over other possibilities. We briefly review the theoretical, behavioural and pharmacological evidence that supports non-PA approaches to the interval timing problem.

PA models are far from ‘straightforward’, containing up to six free parameters and existing in at least two forms^{2,3}. A profound theoretical problem is that a Poisson-variable pacemaker implies a square root relation between the mean and standard deviation of clock ‘ticks.’ If the number of ticks determines a behavioural measure such as peak time, its coefficient of variation should decrease with its mean, rather than being constant, as is usual in timing experiments³ (PA theorists resolve this discrepancy not by abandoning the pacemaker assumption, as parsimony would require, but by adding *ad hoc* multiplicative variability).

Behavioural evidence also poses problems for the PA model. For example, linear representation of time is a key feature of a pacemaker-driven ‘clock’. An important proof for linear time has been the time-left experiment, in which animal subjects choose between a fixed delay for food and a delay that decreases with time. But the logic of the experiment has been questioned² and subsequent experiments have shown that delay-of-reinforcement effects and the animal’s selection of a time marker are dominant in this procedure^{4,5}.

Some drug effects are readily interpretable in clock terms. For example, a drug injection that causes an immediate leftward scalar shift in the time of peak response, followed by a slow recovery to the pre-drug position (and the reverse ‘rebound’ rightward shift followed by slow recovery, when drug injections cease) can be interpreted as an increase in clock speed. Methamphetamine has been reported to produce a leftward shift of this sort in peak-interval timing experiments with rats⁶ — suggesting that dopaminergic drugs increase clock speed and dopamine antagonists, such as haloperidol, decrease it¹.

Unfortunately, several studies have shown a wide range of other amphetamine effects: no effect on the position of the timing peak, but a marked effect on the variability of the timing distribution; no rebound effect (required by the clock interpretation); and mixed results, even including a rightward shift in the timing peak^{7,8}. One explicit test of the timing interpretation⁹ noted that the effects of amphetamine have long been considered an example of rate dependency — a long known and much analysed effect of many drugs that elevate low response rates and depress high rates¹⁰. Taken together, these studies suggest that the effects of amphetamine are not restricted to a specialized interval timing process.

So what is the correct timing model? Buhusi and Meck propose a coincidence-detection model which, in its final form, shares many of the properties of PA models¹¹. Any such process naturally gives rise to harmonics and free-running oscillations that are almost never observed in timing experiments. These can be eliminated, and the Weber law (scalar) property duplicated, only by the addition of several assumptions, most of which cannot be independently verified¹¹. Buhusi and Meck do not discuss cascade timing models, despite the fact that in numerous comparative tests they do better than PA models^{12,13}. The memory-derived multiple-timescale theory (MTS) has the advantage that it postulates no specialized timing process. It has been applied successfully to a wide variety of timing experiments. Most interestingly, the cascade of slower and slower exponential integrators hypothesized for purely theoretical reasons in MTS has been independently identified in habituation experiments using magnetic source brain imaging^{14,15,16}.

All existing models either do not address, or come into actual conflict with, the results of some behavioural experiments. None of these behavioural models is the last word. However, intimate connections to working

memory, and the cascade property, seem to be increasingly necessary features of any neural model for interval timing. Continued discussion of the protean PA model distracts attention from the many links between interval timing and basic memory and learning processes. It is to these, rather than a specialized 'internal clock' for which there is less and less evidence, that future neurophysiological research should be directed.

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