WHAT DO MATHEMATICAL MODELS TELL US ABOUT CIRCADIAN CLOCKS?

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The paper reviews a series of models for circadian clocks and discusses their conclusions and predictions. Attention is focused on Pittendrigh's empirical model, two mathematical models by the author and Winfree's work.

I. Introduction. This paper has as its goal to summarize the development of a class of models for circadian clocks without the use of mathematical formalism. Our first order of business is to clarify the term model since it has been used to mean different things by different people. Basically a model is a hypothesis about how a physical system works. In general it must have the following two essential properties: (1) It must summarize the available experimental evidence so that the description of the physical system through the model must be more concise than the description through a table of experimental results. (2) It must predict the behavior of the system under new circumstances. However it need not say anything about the “deep” structure of the system.

Strictly speaking this structure can never be known. In many cases it is customary to assume it to coincide with that of a very successful model but this is not really justified. For example the acceptance of the heliocentric over the geocentric model in physics is not due to any “real truth” but to the fact that the former gives a more compact description of the planetary system and has far more successful predictions than the latter. It is still theoretically possible that one day someone may come up with a superior geocentric model. This limitation of models has a certain implication for their value in the search for the circadian clock. It is highly unlikely that they will ever give any direct
evidence about the biological structure of the system. On the other hand they can be quite helpful in aiding the development of "structural" theories as we shall see in the sequel.

It is a good idea to distinguish between a model and its instances. We define the latter term to mean different formulations of a given model which provide both the same degree of "data compaction" and the same set of predictions. It should be emphasized that the common practice in the literature is to refer to such instances as models but I believe that this tends to confuse the issues involved.

The major emphasis in this paper will be on single unit models. The study of populations of such units will be the subject of a second paper. References to the literature are to those papers directly related to this one. Excellent sources for an overview of the field are the volumes of collected papers published after different symposia in the past (Aschoff, 1965; Menaker, 1971; Hastings and Schweiger, 1976). The last reference has the particularly attractive feature of containing "state of the art" group reports in addition to individual papers. There are also a number of sources treating the general subjects of circadian clocks and the mathematics of biological oscillators (Bunning, 1973; Pavlidis, 1973b).

II. Review of Models Dealing with Pulse Inputs. We will start our discussion with Pittendrigh's empirical model which was first proposed more than ten years ago (Pittendrigh, 1965) and is discussed in detail in (Pittendrigh, 1974, 1976). It was developed for the Drosophila pseudoobscura eclosion rhythm and its basic claim is that the 15 min high light intensity phase response curve (PRC) describes the behavior of the system for a combination of such pulses. Note that the model meets the criteria of both compaction (if one knows the effect of a single pulse then he also knows the effect of a combination thereof) and prediction (the behavior of the system under untried light pulse combinations is predicted). More specifically the model can be stated as following: The state of the system is described by its phase, i.e. subjective circadian time (abbreviated as CT). The change in the phase predicted by the PRC occurs "instantaneously". The observed transients are due to the secondary system driven by the circadian regulator (pacemaker). The major success of the model has been its precise quantitative prediction and subsequent experimental verification of the entrainment of the eclosion rhythm by brief (15 min) light pulses (ibid).

Operationally the model consists of the PRC, giving the phaseshift in terms of the current phase of the rhythm, and the relation:

\[ \text{new phase} = \text{old phase} + \text{phaseshift}. \]