MODE ANALYSIS OF PHYSIOLOGICAL OSCILLATORS INTERCOUPLED VIA PURE TIME DELAYS

D. A. LINKENS
Department of Control Engineering, University of Sheffield
University of Sheffield
Sheffield S1 3JD.

R. I. KITNEY
Engineering in Medicine Laboratory,
Department of Electrical Engineering,
Imperial College, London, U.K.

The study of bi-directionally coupled oscillators is relevant in biological modelling of such systems as gastro-intestinal electrical activity, cardiac pacemakers, cardiovascular and respiratory interactions and circadian rhythms. Interconnecting pathways in biological systems often exhibit pure time-delay characteristics. In this paper the multiple-mode limit-cycle behaviour of such systems is analysed using the method of harmonic balance. It is shown that the coupling time delay radically affects the number, frequency and amplitudes of entrained limit-cycles.

1. Introduction. For a long time the concept of biological oscillations being an integral part of the homeostatic mechanism was not considered sound. However, with the introduction of more quantitative methods of analysing physiological systems it has gradually become clearer that oscillations or fluctuations of one form or another are often inherent in biological systems. The best known rhythms of this type are of course circadian rhythms, although there is a wide range of so-called biological clocks which have been identified in the body. A good example of how a basic mechanism is modified to produce spontaneous oscillatory activity is the sino-atrial node of the heart. If the function of the SA node is considered from the starting point of normal propagation of action potential along an axon, then in the classic voltage clamp experiments undertaken by Hodgkin and Huxley (1952), it is clear that following the application of a current spike the threshold potential is achieved and an action potential is produced. In the case of the sino-atrial node, a number of workers have shown that the fundamental difference between depolarisation in these cells and the function of the nerve axon is that they have a leaky membrane which allows the conduction of sodium ions into the cell; this in turn leads to spontaneous depolarisation. Each sino-atrial cell can therefore be considered as an autonomous biological oscillator controlled by dynamics which can be closely approximated by
a modified version of the Hodgkin-Huxley model (Noble, 1974). The same example can also be used to illustrate another important feature of spontaneously oscillating physiological systems. The sino-atrial node comprises a colony of many thousands of cells which synchronously depolarise. The process which produces this phenomenon is called entrainment and is an important property of spontaneously oscillating physiological systems which interact. In the case of the colony of sino-atrial nodal cells the phenomenon has been described in detail by Winfree (1967). In the SA node the rate of depolarisation is varied by sympathetic and parasympathetic activity affecting the cell membrane conductances. This is an example of how a biological oscillator can be influenced by external factors. In more general physiological terms, the factors which influence a biological oscillator are often the output from another biological oscillator which is in turn oscillating spontaneously. It is this particular phenomenon which is analysed in some detail in this paper.

The area which formed the physiological motivation to this study is the effect of the respiratory system on heart rate. It has been known for a considerable period that the heart rate is affected by the respiratory system. This phenomenon has traditionally been referred to as sinus arrhythmia and more recently respiratory sinus arrhythmia. As has already been mentioned, fundamental heart rate is produced by the spontaneous depolarisation of SA nodal cells and can be viewed as a biological oscillator. Similarly, the basic pattern of respiration can also be seen as resulting from a biological oscillator. The model of the inspiratory switch-off mechanism has become known as the von Euler model and is described in Bradley et al. (1975). Figure 1 is a block diagram of the model, redrawn in a slightly modified form. In physiological terms the model comprises three neuronal pools, A, B and C. This entire process

![Diagram](image-url)