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The manipulation of calcium oscillations by harnessing self-organisation

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ABSTRACT

This paper investigates how self-organisation might be harnessed for the manipulation and control of calcium oscillations. Calcium signalling mechanisms are responsible for a number of important functions within biological systems, such as fertilization, secretion, contraction, neuronal signalling and learning. In this paper, calcium oscillations are investigated as a biological periodic process. Within biological systems such periodic behaviour is one of the outcomes from self-organisation. The understanding of periodic processes in living systems can enable more accurate diagnosis and physiologically suitable clinical therapies to be proposed, for diseases such as cancer, epilepsy, cardiac diseases and other dynamic diseases. In this paper these ideas are investigated by means of the calcium-induced calcium release (CICR) model and a number of representative simulations of intra and inter-cellular calcium oscillations are used to illustrate the manipulation and control of these oscillations in normal and pathological situations.

1. Introduction

Self-organisation is the spontaneous formation of spatial, temporal, spatio-temporal structures or functions in a system composed of few or many interacting components (Haken, 2008; Banzhaf, 2002). In biological systems, this outcome from self-organising processes can have features such as excitability, bistability, periodicity, chaos or spatio-temporal pattern formation (Walleczek, 2000). The work presented here focuses on a self-organised process that has periodicity. In living systems, periodic processes account for several functions. In humans, the cardiac and respiratory functions and the circadian rhythm of sleep and wakefulness are periodic processes essential to the maintenance of life. The nonlinear manipulation and control of these periodic processes in living systems can help in their understanding, enabling more accurate diagnosis and physiologically suitable clinical therapies to be proposed, for diseases such as cancer (Schreiber, 2005; Wissenbach et al., 2004), epilepsy (Larter et al., 2000), cardiac diseases (Winfree, 1987) and other dynamic diseases (Glass and Mackey, 1988).

Periodic phenomena can also be seen in physical (josephson junctions), chemical (chemical oscillating reactions such as the Belousov–Zhabotinsky reaction) and artificial (electronic oscillators) systems. All these rhythmic systems are nonlinear dynamical systems with limit cycle behaviour (Strogatz, 1994). They exhibit common characteristics, namely self-organisation and robustness, and their overall behaviour is not a result of the function of the single elements, but a consequence of the interaction between these elements.

The heart is an example of such rhythmic system. It is robust, considering the diversity of influences that act upon it (Sole and Goodwin, 2002) but also adaptable to changes in the person's psychological and emotional state, physical workload and chemical balance (Winfree, 1987). Cardiac muscle can be seen as an excitable media as the qualitative behaviour of cardiac cells can be modeled by the FitzHugh–Nagumo (FHN) model (Fitzhugh, 1961), which is a generic model for excitable media. In a previous work (Santini and Tyrrell, 2007) we used the FHN model to show numerical simulations of cardiac cells and to characterise synchronisation on a group of these cells. These results reproduced successfully the qualitative behaviour of the heart when contrasted to what is known about synchronisation and propagation of stimuli on cardiac cells. As robustness and adaptivity are desirable properties in artificial systems, we used the electronic equivalent of the FHN model to build an electronic circuit, also characterising synchronisation on this system.

The contribution of the work presented in this paper is the understanding of a system level behaviour as a self-organised process and the investigation of how this principle could be harnessed on the manipulation and control of the system's outcome.

The biological system investigated is (intra and inter-cellular) calcium oscillations. These oscillations are calcium signalling mechanisms, that are responsible for controlling numerous cellular

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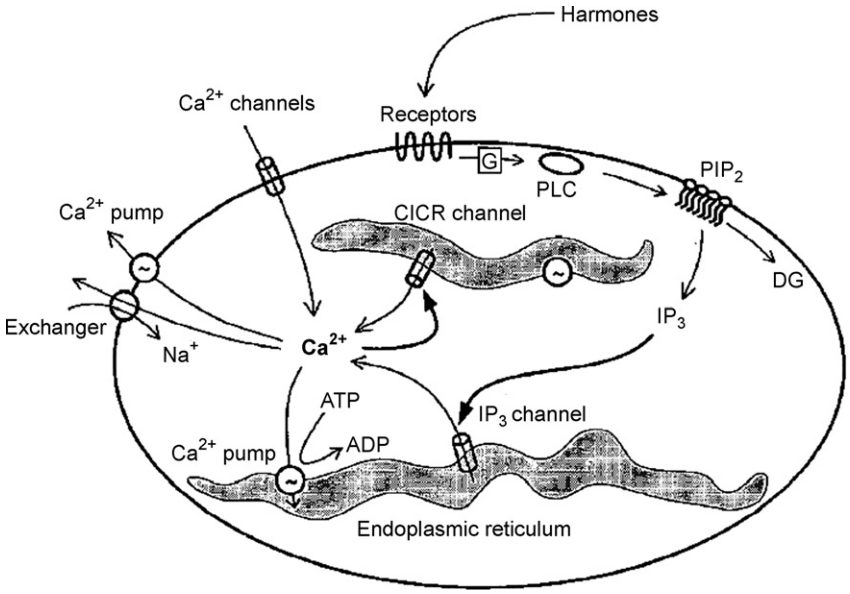

Fig. 1. Control of the cytosolic calcium level. Mitochondria are not shown because whether they have a physiologic role in regulating Ca_i is uncertain. The calcium-induced calcium release (CICR) store appears to be present in electrically excitable cells. The IP_3-sensitive store is present in nearly all mammalian cells studied thus far. From Meyer and Stryer (1991).

processes including fertilization, secretion, contraction, neuronal signalling and learning. Using the calcium-induced calcium release (CICR) model, numerical simulations of intra and inter-cellular calcium oscillations for some different situations, both normal and pathological, are presented. The aim is to investigate how to manipulate and control this biological system's periodic outcome, both to understand and to propose a physiologically suitable clinical therapy. To address this question, a method is proposed, based on the fact that this is a nonlinear system whose outcome (functionality) is a consequence of the interaction between its elements. Therefore, a designed rhythmic system is integrated into this system and set to interact with this system's elements. Due to the variables involved and the integration of the elements, a chemical oscillator is chosen. To theoretically evaluate this integration, a model for a chemical oscillator, the Brusselator, is used.

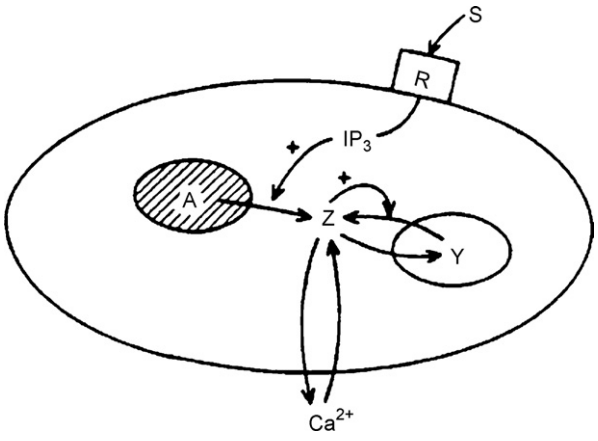

Fig. 2. Calcium-induced calcium release (CICR) model proposed by Dupont and Goldbeter in 1989. The stimulus (S) acting on a cell surface receptor (R) triggers the synthesis of $InsP_3$; the latter intracellular messenger elicits the release of Ca^{2+} from an $InsP_3$-sensitive store (A) at a rate proportional to the saturation function (β) of the $InsP_3$ receptor. Cytosolic Ca^{2+} (Z) is pumped into an $InsP_3$-insensitive intracellular store; Ca^{2+} in the latter store (Y) is released into the cytosol in a process activated by cytosolic Ca^{2+}. This feedback gives rise to Ca^{2+} oscillations. Other arrows refer to a possible leak of Y into Z, and to the exchange of Ca^{2+} between the cytosol and the extracellular medium. From Dupont and Goldbeter (1989).

This paper presents and discusses an approach based on the common properties of diverse rhythmic systems. (The CICR model used, for example, can be put into the form of a generalized FHN model (Keener and Sneyd, 2001).) Regarding the experimental feasibility of the theoretical study, throughout the paper several simplifications and abstractions are made. However, some of the issues that would have to be considered for an experimental test of the approach are considered.

This paper is organised as follows: in the next section some aspects of calcium signalling mechanisms are discussed. In Section 3 the CICR model is presented and some numerical simulation results of intra and inter-cellular calcium oscillations are shown. In Section 4, the designed rhythmic system, that integrated into the cell, is used to manipulate and control the biochemical rhythm, is briefly presented. In Section 5 some theoretical results of this integration are shown and discussed. In Section 6 the role of self-organisation is further investigated. Finally in Section 7 the paper is concluded. The results obtained are discussed, considering the abstractions made and the applicability of the approach to biological periodic system in general.

2. Calcium Signalling Mechanisms

Calcium signalling mechanisms are responsible for controlling numerous cellular processes, including fertilization, secretion, contraction, neuronal signalling and learning. The versatility and universality of this mechanism has already been reported in several books and reviews (Keener and Sneyd, 2001; Goldbeter, 1997; Berridge et al., 1998, 2000; Meyer and Stryer, 1991; Tsien and Tsien, 1990).

Calcium oscillations occur in a large number of cell types, either spontaneously or as a result of stimulation by an external signal such as hormone or neurotransmitter. Intracellular calcium oscillations correspond to calcium waves within the cytosol and intercellular oscillations correspond to the propagation of calcium waves between adjacent cells.