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High order sliding-mode dynamic control for chaotic intracellular calcium oscillations

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ABSTRACT

In this article the closed-loop stability conditions and the control design of a class of biological system that exhibit chaotic oscillations are addressed. It is proved that the biological system is minimum phase. A class of nonlinear dynamic feedback control is designed using sliding-mode control ideas, which can be used for regulation, tracking and synchronization tasks. Numerical experiments illustrate the satisfactory performance of the proposed control methodology.

1. Introduction

The ubiquity of oscillations in biological systems is well established. Oscillations are observed in all types of organisms from the simplest to the most complex. Periods can range from fractions of a second to months or years [1]. From time to time, it has been suggested that many biological oscillations are the result of the breakdown of effective self-regulation. In recent years, it has been argued that most periodic behavior is not pathological but rather constitutes the normal operation for these systems [1–5]. Biochemical oscillations are present because they confer positive functional advantages to the organism. The advantages fall into five general categories: temporal organization, spatial organization, prediction of repetitive events, efficiency and precision of control [5,6].

Examples of biochemical oscillations include the oscillation dynamics of the mRNA concentration, insulin-secreting cells of the pancreas, oscillations and waves in the concentration of free intracellular calcium Ca^{2+}, etc [1,4,6]. Indeed, over the last 15 years oscillations in intracellular Ca^{2+} have become a major example of oscillatory behavior at the cellular level. Intracellular Ca^{2+} is a messenger used to activate various cellular processes relaying information within cells to regulate their activity. For example, Ca^{2+} triggers life at fertilization, and controls the development and differentiation of cells into specialized types. It mediates the subsequent activity of these cells and, finally, is invariably involved in cell death. To coordinate all of these functions, Ca^{2+} signals need to be flexible yet precisely regulated. This incredible versatility arises through the use of a Ca^{2+} signaling "tool kit", whereby the ion can act in the various contexts of space, time and amplitude. It is widely believed that intercellular Ca^{2+} waves are a mechanism by which a group of cells can communicate with one another and coordinate a multicellular response to a local event [7–10]. Recently, it has been observed in a

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variety of systems that calcium signals can also propagate from one cell to another and thereby serve as a means of intercellular communication [11]. Experiments afford evidence for the existence of highly nonlinear behavior in systems with calcium signals, thereby requiring the developments of complex dynamic models accounting for these nonlinear properties [8,10].

The desire to understand the biophysical mechanisms of cellular dynamics has led to introduce feedback control laws in some biological systems. Indeed, by interpreting feedback biological mechanisms as a feedback controller, it can be show that (i) feedback mechanisms can lead to oscillatory phenomena, and (ii) adaptation mechanism is a consequence of robustness [12–16]. The aims of feedback control laws in biological systems are to cause excitation or suppression of oscillations, entrainment and synchronization, or transitions from chaotic to periodic oscillations and vice versa [17] using realistic control inputs. Departing from the above ideas, this paper explores links between feedback control schemes, with an external input, and intracellular calcium functions for coordination and control. By manipulation of an external input with a feedback control scheme, we show that (a) chaotic oscillations at the external input can suppress intracellular calcium oscillations, and (b) chaotic synchronization can be achieved between intracellular calcium oscillators with a simple function of influx of Ca^{2+}. From a general point of view external forcing of biological processes is important in many application areas ranging from bioengineering to biomedicine [17,18].

In this work, we introduce a versatile nonlinear feedback control scheme that can be used in the synchronization, suppression/regulation and tracking of the nonlinear behavior displayed by an intracellular Ca^{2+} model. For control and synchronization of simple to complex oscillations there are a lot of control approaches [19–23] that can be used in biological systems. However, in this paper we introduce a new sliding type control approach that has three nice features for biological applications: (i) robustness against model uncertainties, (ii) simplicity in the design, and (iii) switched type responses. The sliding-mode control schemes have shown several advantages as allowing the presence of matched model uncertainties and convergence speed over others existing techniques as Lyapunov-based techniques, feedback linearization and extended linearization [24–26]. On the other hand, standard sliding-mode controllers have the main drawback that the closed-loop trajectory, of the designed solution, is not robust even with respect to the matched disturbances on a time interval preceding the sliding motion. Indeed, the classical sliding-mode controllers are robust in the case of matched disturbances only the designed controller ensures the optimality only after the entrance point into the sliding mode [25]. To try to avoid the above disadvantage a relatively new kind of sliding-mode scheme has been proposed, the high-order sliding-mode technique. This control scheme considers a fractional power of the absolute value of the tracking error, coupled with the sign function; this structure provides several advantages as simplification of the control law, higher accuracy and chattering prevention [27, 28]. In this paper it is proposed a high order sliding-mode controller coupled with an integral action for the control and synchronization of intracellular calcium dynamics. The proposed control law is able to stimulate, via inflow of Ca^{2+}, the autonomous intracellular calcium behavior and compensates its nonlinear (chaotic) dynamic to force an imposed trajectory, for regulation, tracking and synchronization purposes.

2. Intracellular calcium model

The mechanisms underlying the spatial and temporal patterns of the global Ca^{2+} response have been investigated extensively in recent years [29–34]. The mechanism of Ca^{2+} oscillations and that of associated waves rests on the regulation of Ca^{2+} levels within the cell.

2.1. Mathematical model of intracellular calcium dynamics

A variety of models for Ca^{2+} oscillations and waves have been proposed [1,8,29]. Differing by the degree of detail with which the dynamics and control of the IP_3 (inocytol triphosphate.) receptor are treated, most of these models are based on Calcium-Induced Calcium-Release (CICR) as the main instability-generating mechanism. DuPont et al., [30] have developed some mathematical models; one of them is related with the activation and autophosphorylation of the multifunctional Ca^{2+}-calmodulin kinase II (CaMKII) by Ca^{2+} and calmodulin (CaM) are through to underlie its ability to decode Ca^{2+} oscillations and to control multiple cellular functions. Another simplified model, presented by Houart et al. [31], exhibits a diversity of calcium responses, notably steady states, spiking and bursting oscillations, multi-rhythmic and chaotic regimes. Furthermore, this model looks appropriate for control purposes; insofar as it is affine (linear) in the control input (input flow of Ca^{2+} from the extra cellular medium) and the controller design procedure can be simplified.

The model of Houart et al. [31] is an extension of the minimal model proposed by DuPont and Goldbeter [30] to account for the existence of simple Ca^{2+} oscillations in response to extra cellular stimulation. The original model only involves two variables, namely cytosolic and intravascular Ca^{2+}concentrations. The release of Ca^{2+} from the internal stores into the cytosol is activated by IP_3 and cytosolic Ca^{2+}, such as autocatalytic process of IP_3-sensitive CICR is at the core of the oscillatory mechanism. The extended model incorporates Ca^{2+} pumping into the stores, Ca^{2+} exchange with the external medium, as well as stimulus-activated Ca^{2+} entry [31]. Besides simple periodic behavior, this model for cytosolic Ca^{2+} oscillations in non-excitable cells shows complex oscillatory phenomena as bursting or chaos.

The model contains three variables, namely the concentrations of free Ca^{2+} in the cytosol (x_1) and in the internal pool (x_2), and the IP_3 concentration (x_3).