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Robust Control Approaches for Synchronization of Biochemical Oscillators

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1. Introduction

Synchronization is an important property in fundamental biological processes. Synchronization of biochemical oscillations confers positive functional advantages to the organism, including temporal organization, spatial organization, and efficiency for communication between cells (Berridge et al., 1998; Fall et al., 2002; Goldbeter, 2002; Keener & Sneyd, 1998). Indeed, the relevance of synchronization has been stressed frequently. For instance synchronized circadian rhythms may influence the pharmacology and the tolerability of anticancer drugs and/or their antitumor efficacy (Petty, 2004; Fu & Lee, 2003). In the heart, the impulses coming through the vagus nerve trigger the contraction of the heart only if they are properly synchronized (Keener & Sneyd, 1998; diBernardo et al., 1998). Synchronized behavior of calcium oscillators is believed that enables communication from one side of a cell to another, or between cells, and can serve to synchronize a global, multicellular, response to a local stimulus (Berridge et al., 1998; Perc & Marhl, 2004). Moreover, there are some evidences which support that coherent oscillations play an important role in sensory processing (Izhikevich, 2007).

Understanding both the processes that influence the synchronization of individual biochemical oscillators and how the behaviors of living cells arise out of the properties of coupled populations of biological oscillators are important goals in the study of biological systems, and a field of research with enormous practical application. For instance, elucidating how and why local biochemical oscillators separated by different distances fluctuate in synchrony and the study of conditions under which spatiotemporal patterns of biochemical oscillators can be generated and suppressed (Mikhailov & Hess, 1995; Wolkenhauer et al., 2003; Walleczek, 2003). Indeed, clarifying the mechanisms behind spatial synchrony represents a challenge for biologist and also could ultimately provide critical information to exploit the synchronized behavior in living organisms. For instance, the application of the knowledge of dynamical systems in biology and medicine is giving rise to new therapeutic approaches, such as the treatment of Parkinson's disease by means of neuronal desynchronization (Tass, 2002), or the indications for the development of new drugs based on the collective dynamical instabilities in living cells (Petty, 2004).

Different approaches have been used to synchronize individual biochemical oscillators (Afraimovich et al., 1997; Boccaletti et al., 2002; Canavier et al., 1999; Collins & Stewart, 1994; Goldbeter, 1996; Mirollo & Strogatz, 1990; Morgul & Solak, 1996; Nijmeijer & Mareels, 1997; Pikovsky et al., 1996; Zhou et al., 2008). Classical synchronization approaches includes different coupling approaches and the periodic modulation of an external forcing (periodical or noisy). Despite that synchronization of nonlinear oscillators has been addressed from control theory community, few papers have been addressed the control and synchronization problem of biochemical oscillators. In particular, from control theory perspective, there are basically two ways that are used for synchronization of nonlinear systems. The first is related with observer based synchronization which is applied for coupling identical systems (*i.e.*, same structure and order) and different initial conditions (Alvarez-Ramirez et al., 2002; Nijmeijer & Mareels, 1997; Morgul & Solak, 1996). In these cases, identical synchronization is reached which implies the coincidence of the states of the coupled systems. The second approach from control theory is the application of control laws allows to achieve the synchronization between nonlinear oscillators, with different structure and order, where the variable states of the slave system are forced to follow the trajectories of the master system, such that this approach can be seen as a tracking problem (Fradkov & Pogromsky, 1998; Alvarez-Ramirez et al., 2001). For control designs the presence of disturbances, dynamic uncertainties, and nonlinearities in biochemical models pose great challenges. In particular, biochemical systems have a high degree of uncertainties.

Relevant contributions using control and system theory approaches are the following. Sontag (2004) has been establishes global asymptotic stability results using small gain theorems for a class of biochemical systems. Kimura and Nishigaki (2005) have been established an analogy of circadian rhythm with the PLL framework. Iglesias (2003) has been addressed the feedback mechanism in chemotaxis using control theory concepts. Steeling et al. (2004) have been introduced a robustness analysis and a model predictive control approach for circadian oscillations. Takeuchi *et al.* (2006) have been also addressed the generation and suppression of circadian oscillations with control theory tools. We have previously showed that both modeling error compensation approach and high-order sliding mode control approach can be used to robust synchronize intracellular calcium oscillators and excitable media (Puebla, 2005, Puebla et al., 2009; Puebla et al., 2010; Aguilar-Lopez et al., 2010).

In this chapter we extend the application of robust controllers for the synchronization of three benchmark models of biochemical oscillators: (i) Goodwin model of genetic oscillations (Goodwin, 1965), (ii) FitzHugh-Nagumo model of neurons (FitzHugh, 1961); and (iii) a model of circadian rhythms in Drosphila (Goldbeter, 1996). We introduce three robust control approaches for the synchronization of biochemical oscillators: (i) A modeling error compensation approach (Alvarez-Ramirez, 1999), (ii) integral sliding mode control (Levant, 2001), and (iii) geometric linearizing control (Alvarez-Ramirez, 1999; Hangos et al., 2004). The proposed controllers have two nice features for biological applications: (*i*) robustness against model uncertainties, and (*ii*) simplicity in the resulting controller. We show how a certain class of cellular processes can be dynamically synchronized by appropriate input signals.

This chapter is organized as follows: In Section 2, for the sake of clarity in presentation, we briefly provide some issues on the phenomenology, modeling and nonlinear dynamics in cellular systems. In Section 3 we review classical synchronization approaches of biochemical oscillations that have been reported in the literature. In Section 4 we present the synchronization problem addressed in this chapter and the robust control approaches for the synchronization of biochemical oscillations. Three numerical benchmark examples in Section

5 shows the implementation of the proposed feedback control approaches. Finally, in Section 6 we close this chapter with some concluding remarks.

2. Modeling of biochemical oscillators

In this section we define the class of biochemical oscillators that we are studying. First, we briefly discuss the phenomenology of biological mechanism underlying in biochemical systems. Next we present some ideas of the modeling of biochemical systems. Finally, we introduce the class of biochemical systems under consideration in this chapter.

2.1 Biological mechanisms

The processes that underlie cellular behavior are organized in complexly coupled biochemical reaction networks, where feedforward and feedback information flows provide the links between the different levels in the hierarchy of cell biochemical network organization (Arkin & Ross, 1994; Goldbeter, 1996; Glass & Mackey, 1988). Theoretical models of biochemical reaction networks have been proposed that simulate, for example, cellular dynamics of Ca oscillations, interactions between different cell signaling pathways, genetic regulatory circuits, cellular control networks for DNA replication and cellular division (Segel, 1980; Goldbeter, 1996; Keener & Sneyd, 1998; Smolen et al., 2003).

Cells are equipped with exquisite sensing systems which allow them to be continuously aware of the conditions in their environment and react appropriately to these conditions. The basic elements of a cellular signaling system are a sensor protein, made of a receptor domain and a transmitter domain, and a response regulator, consisting of a receiver domain and a regulator domain (Keener & Sneyd, 1998; Blumenfeld & Tikhonov, 1994). Stimulation of the sensor (normally bound to the cell membrane) leads to activation of the transmitter, which produces an intracellular signal. This signal is processed by a cascade of molecules and finally arrives at the receiver, which in turn activates the regulator. Regulators produce a response by modulating gene expression or enzyme activities. The key components in this transfer of information are proteins, which form networks and are able to perform computational tasks (Goldbeter, 1996; Glass & Mackey, 1998; Fall et al., 2002). Proteins can change their state by interaction with other proteins or by biochemical modifications (such as phosphorylations) catalyzed by other proteins. Another common mechanism is the release of small molecules called second messengers, which diffuse in the cell and activate other proteins (Berridge, 1998; Keener & Sneyd, 1998).

2.2 Modeling of cellular processes

In contrast to the high complexity of the cell, simple mathematical models have been developed, mostly based on experimental observations describing phenomena like limitation, activation, inhibition, saturation, multiple substrate uptake, bottlenecks and multiplicity of metabolic steady states (De Jong, 2002; Fall et al., 2002; Goldbeter, 2002; Segel, 1980). Mathematical models of the intracellular complexity of cellular systems are often based on systems of nonlinear ordinary differential equations (ODEs). These models are usually valid for a limited, but often sufficiently large range of operating conditions. Of course, the level of complexity of the mathematical description depends on the application. When the problem is taken with all its complexity, for instance, if we require that the model accounts for spatial inhomogeneity, diffusion processes and transport delay, then we deal with partial differential

equations and time delay (De Jong, 2002; Smolen et al., 2003; Asthagiri & Lauffenburger, 2001). In this chapter, we restrict ourselves to the simpler case of ODEs.

In cells, most biochemical reactions of interest are catalyzed by enzymes, and a variety of mathematical descriptions have been developed for these reactions. Many enzymatic reactions have complex kinetic mechanisms, and specialized equations are needed to describe their rates in detail. Two typical rate models are the Michelis-Menten kinetics and the allosteric Hill function (Keener & Sneyd, 1998; Segel, 1980).

1. Michaelis-Menten model: This kinetic model is relevant to situations where there is no intermediate or product inhibition, and there is no allostericity or cooperativity. The kinetic model is defined by,

$$\mu_{\max} \frac{S}{k_s + S} \tag{1}$$

$\mu_{\max}$ is the maximal growth rate and k_s the half-saturation constant.

2. Allosteric interactions: Binding of small molecules can alter an enzyme's conformation and alter the rate of the reaction catalyzed by the enzyme. Allosteric interactions can therefore mediate feedback and feedforward interactions within a biochemical pathway, as well as crosstalk between pathways. In models of enzyme regulation, allosteric interactions are commonly represented by Hill functions. These are saturable functions of the concentration of the effector molecule. With the concentration of effector denoted by L, if L activates an enzyme, the enzyme activity is taken as proportional to the following increasing function of the n-th power of L:

$$\frac{L^n}{L^n + K_H^n} \tag{2}$$

The parameter n is called the Hill coefficient. Greater values of n correspond to steeper sigmoids, that is, to a narrowing of the range of L over which the enzyme activity is significantly above 0 and also significantly below 1. If L inhibits an enzyme, the enzyme activity is taken as proportional to a decreasing function of L:

$$\frac{K_H^n}{L^n + K_H^n} \tag{3}$$

2.3 Nonlinear dynamics in cellular systems

Nonlinear phenomena including multiple steady states, periodic or chaotic temporal evolution and self-organization can be supported by the dynamical cellular system since functional kinetics are nonlinear in the descriptive variables and the system is maintained far from equilibrium. The variety of functional dynamics is a consequence of the nonlinearities inherent in multiple modes of biochemical regulation, such as cooperativity and kinetics at the levels of gene expression, protein synthesis, enzyme activity, receptor function, and transport processes (Keener & Sneyd, 1998; Blumenfeld & Tikhonov, 1994; Goldbeter, 2002; Glass, 2001).

1. Simple oscillations: Oscillations occur at every level of a biological organization, with periods ranging from milliseconds (neurons) to seconds (cardiac cells), minutes (oscillatory enzymes), hours (pulsatile hormone secretion), days (circadian rhythms), weeks (ovarian cycle) and even to years (predator-prey interactions in ecology). Oscillatory behavior

often originates at the cellular level from regulatory feedback loops which involve many parameters and interacting variables. More generally, oscillations in reaction rates and concentrations commonly rely, on negative feedback to sustain oscillations. Oscillations have been observed in the metabolic flux through glycolysis and also in the rates of secretion of hormones such as insulin (Goldbeter, 2002; Glass, 2001).

2. Bursting and chaos: Bursting represents one type of complex oscillations that is particularly common in neurobiology. An active phase of spike generation is followed by a quiescent phase, after which a new active phase begins. Chaos is a common mode of complex oscillatory behavior that has been studied intensively in physical, chemical and biological systems. It has been discussed the existence of two main routes to complex oscillatory phenomena. The first relies on forcing a system that displays simple periodic oscillations by a periodic input. In an appropriate range of input frequency and amplitude, one can often observe the transition from simple to complex oscillatory behavior such as bursting and chaos. For other frequencies and amplitudes of the forcing, entrainment or quasi-periodic oscillations occur. In the second route complex oscillatory phenomena may arise through the interplay between several instability-generating mechanisms, each of which is capable of producing sustained oscillations (Goldbeter, 2002; Glass, 2001).

Oscillatory dynamic is not the only possible outcome of nonlinear equations. Indeed, nonlinear systems are in general classified within three categories: bistable, excitable, and oscillatory. Bistable systems are characterized by the existence of two different stable states. Excitable systems posses a unique stable fixed point; however, if they are affected by a perturbation which overcomes a certain threshold amplitude, they are able to perform an excursion in the phase space before returning to the stable fixed point. That is, they do not relax immediately to the stationary state, but keep the excitation for a finite time (Ferrel, 2002; Fall et al., 2002; Mikhailov & Hess, 1995).

2.4 The class of biochemical oscillators

As the basic single biochemical oscillator we consider single-input nonlinear systems in the form,

$$\frac{dy}{dt} = f_1(y, z) + g(y, z)u \tag{4}$$
$$\frac{dz}{dt} = f_2(y, z)$$

where $f_1(y, z) \in \mathbb{R}$, $f_2(y, z) \in \mathbb{R}^{n-1}$, and $g(y, z) \in \mathbb{R}$, are smooth functions of their arguments, $y \in \mathbb{R}$, is the measured output of the system, $z \in \mathbb{R}^{n-1}$, is the internal state, and u can be manipulated for synchronization purposes.

Suppose that there are N subsystems in a lattice y_i, $i = 1, ..., N$, and, in the absence of coupling, the dynamics of y_i is given by the biochemical oscillator (4). That is, the dynamics of y_i satisfies,

$$\frac{dy_i}{dt} = f_{1,i}(y_i, z_i) + g_i(y_i, z_i)u_i, \ i = 1, ..., N \tag{5}$$
$$\frac{dz_i}{dt} = f_{2,i}(y_i, z_i)$$

Its not hard to see that several published models of biochemical oscillators can be described by model (5) (Keener & Sneyd, 1998; Goldbeter, 2002; Tyson et al., 2003; De Jong, 2002).

3. Synchronization of biochemical oscillations

Classical theory of synchronization distinguishes between forced synchronization by an external periodic driving force and synchronization via the coupling between oscillators. In both cases manifestations of synchronization are the same. In this section we briefly review both external forcing and coupling based synchronization approaches proposed in the literature for biochemical oscillations.

3.1 Synchronization of biochemical oscillations via coupling

Consider that the N subsystems are coupled,

$$\frac{dy_i}{dt} = \mathcal{C}_i(y) + f_{1,i}(y_i, z_i) + g_i(y_i, z_i)u_i, \ i = 1, ..., N \tag{6}$$
$$\frac{dz_i}{dt} = f_{2,i}(y_i, z_i)$$

where $y = [y_1, ..., y_N]^T$ and $\mathcal{C}(y)$ is a coupling function.

3.1.1 Diffusive coupling

Consider that the coupling function $\mathcal{C}(y)$ is described via a local diffusive (nearest neighborhood) coupling, such that,

$$\mathcal{C}(y) = \sigma(y_{i-1} - 2y_i + y_{i+1}) \tag{7}$$

where σ is the coupling strength. This case is quite interesting since it can be seen as a lattice approximation to reaction-diffusion systems,

$$\frac{\partial^2 y}{\partial t^2} = \sigma \frac{\partial^2 y}{\partial \xi^2} + f(y, z) + g(y, z)u \tag{8}$$

where $u = [u_1, ..., u_N]^T \in \mathbb{R}^N$ and ξ is the spatial coordinate.

Local coupling provides the system with the notion of vicinity and distance. This is, each element directly interacts only with its neighbors, which then transmit the interaction to their own neighbors. Thus, a localized perturbation spreads through the system affecting first its close proximity and later reaching the farther parts of the system. This is a crucial property of reaction-diffusion systems.

Diffusive coupling via gap junctions is considered as the natural form of coupling in many cellular processes (di Bernando et al., 1998; Fall et al., 2002; Glass, 2001; Mirollo & Strogatz, 1990). Gap junctions are composed of arrays of small channels that permit small molecules to shuttle from one cell to another and thus directly link the interior of adjacent cells. Importantly, gap junctions allow electrical and metabolic coupling among cells because signals initiated in one cell can readily propagate to neighboring cells (Keener & Sneyd, 1998; Izhikevich, 2007). Thus, gap junctions between cells and electrical coupling can be considered as a particular form of diffusive coupling.

In the domain of biological systems, nonlocal coupling can be present as well. Coupling is nonlocal if diffusion is such that the substance released by one cell can reach and affect not only its neighbors, but even cells which are located far away from it.

3.1.2 Random coupling

In random coupling the coupling function is described as follows,

$$\mathcal{C}(y) = \sigma A y \tag{9}$$

where the elements A_{kl} of the matrix A are either 0 or 1 and are assigned in a random way. This is,

$$A_{kl} = \begin{cases} 0 \text{ if } r_{kl} < r_{\min} \\ 1 \text{ if } r_{kl} \geq r_{\min} \end{cases} \tag{10}$$

where $r_{kl} \in [0,1]$ is a uniformly distributed random number and the threshold $r_{\min} \in (0,1)$. This coupling structure resembles that of neural networks (Izhikevich, 2007).

3.1.3 Kuramoto coupling

A successful approach to the problem of synchronization consists of modeling each member of the population as a phase oscillator. Kuramoto analyzed a model of phase oscillators running at arbitrary intrinsic frequencies, and coupled through the sine of their phase differences (Kuramoto, 1984). The Kuramoto model is simple enough to be mathematically tractable, yet sufficiently complex to be non-trivial. The model is rich enough to display a large variety of synchronization patterns and sufficiently flexible to be adapted to many different contexts. The Kuramoto model consists of a population of N coupled phase oscillators, $\theta_i(t)$, having natural frequencies ω_i distributed with a given probability density $g(\omega)$, and whose dynamics is governed by,

$$\frac{d\theta_i}{dt} = \omega_i + \sum_{j=1}^{N} K_{ij} \sin(\theta_j - \theta_i), \quad i = 1, ..., N \tag{11}$$

where K_{ij} is the coupling matrix. When the coupling is sufficiently weak, the oscillators run incoherently whereas beyond a certain threshold collective synchronization emerges spontaneously. Many different models for the coupling matrix K_{ij} have been considered such as nearest-neighbor coupling, hierarchical coupling, random long-range coupling, or even state dependent interactions (Kuramoto, 1984).

3.2 Applications

Classical synchronization approaches have been applied successfully for the synchronization of biochemical oscillators. Winfree (2002) has suggested that such critical perturbations applied at the appropriate phase of a limit cycle should stop the clock, at least transiently, if the perturbation brings the oscillator back into the vicinity of the steady state. Ueda *et al* (2002) studied a model for circadian rhythms in Drosophila. As a single cell oscillator, they used a more detailed model incorporating 10 variables. They then apply a local coupling through each possible variable, and show that for some of them, synchronization occurs. Interestingly, they assessed the effect of fluctuations in parameter values and show that the coupled system is relatively robust to noise. Another theoretical model of coupled circadian oscillators through local coupling has been proposed by Kunz and Achermann (2003). Using

the van der Pol model, they described possible spatial effects, including wave propagation and pattern formation. Gonze *et al* (2005) proved that a mean field approach can be an effective way to couple a population of circadian oscillators, where the global coupling drives oscillators, which would be damped under a constant forcing.

Gap junctions are tacitly postulated as a sufficient means of intercellular communication for synchronizing Ca^{2+} transients (Berridge, 1998; Perc & Marhl, 2004). Ca^{2+} ions may pass through gap junction channels to the neighboring cell by passive diffusion. Recently, it has been shown that individual hepatocytes can have very different intrinsic oscillation frequencies but become phase-locked when coupled by gap junctions (Hofer, 2003; Tang & Othmer, 1995). It is shown that junctional calcium fluxes are effective in synchronizing calcium oscillations in coupled hepatocytes. Many neuronal and non-neuronal systems exhibit synchronized oscillatory behavior in networks of electrically coupled cells (Fall et al., 2002). Experimental findings have revealed that in some of these systems electrical coupling is essential for the generation of oscillations and not only for their modulation (FitzHugh, 1961; Winfree, 2001; Izhikevich, 2007).

3.3 Synchronization of biochemical oscillations via an external forcing

The intrinsic nonlinearity of living systems is of great significance to scientists who study the response of cells, tissues and whole organisms to natural or artificial stimuli. External or artificial stimuli of biological systems by time variation of appropriate control parameters is of great importance from a general point of view. Forced or tuned oscillators are not only considered to be important in cellular rhythms, but also in technical applications involving biochemical reaction systems external control may be of great benefit for improving performance criteria of bioengineering processes (Greenman et al., 2004).

External modulated forcing has been applied for synchronization purposes in some contributions. For example a population of chaotic amoebae was subjected to a small-amplitude periodic forcing, which appeared to be sufficient to transform chaotic behavior into periodic (Goldbeter, 1996). In many organisms, the source of external forcing has been identified to be a variation of the light due to night and day cycles. Indeed, the molecular basis of the effect of light on different circadian biochemical networks has been unraveled (Gonze & Goldbeter, 2000; Jewett et al., 1991). The question on whether such external forcing is enough to induce the synchronization between circadian cells usually observed in experiments, or if coupling between the cells is needed, is still open.

4. Robust control approaches for synchronization of biochemical oscillators

In this section the synchronization problem framed as a tracking feedback control problem is presented. Three robust control approaches are then briefly described: (i) the modeling error compensation, (ii) the sliding mode control, and (iii) geometric linearizing control.

4.1 Synchronization problem

The synchronization problem consists of making two or more systems oscillate in a synchronized way. This synchronization problem is cast as a control problem where the control objective is tracking with respect to a desired single synchronization signal $y_{ref}(t)$ via manipulation of an external input u.

The synchronization problem description is completed by the following assumptions:

A1 The measurement of the variable to be synchronized y, is available for synchronization design purposes.

A2 Nonlinear functions $f_{1,j}(x_i)$ and $g_{1,j}(x_i)$ are uncertain, and can be available rough estimates of these terms.

The following comments are in order:

- $A1$ is a reasonable assumption. For instance, in neurons the measurement of the membrane potential is standard. Free intracellular calcium (Ca^{2+}) can be also measured using florescence techniques. Even in the absence of such measurements, a state estimator can be designed. On the other hand, cell must have some internal mechanism to knows perfectly its behavior. Indeed, it has been reported elsewhere that Ca^{2+} acts as an intracellular messenger, relaying information within cells to regulate their activity, such that should be exist some internal mechanism in the cells to knows its behavior (Berridge, 1998).

- $A2$ considers that functions $f_{1,j}(x_i)$ and $g_{1,j}(x_i)$ can contain uncertain parameters, or in the worst case the whole terms are unknown. Indeed, parameters in biochemical systems have some degree of uncertainties, as these parameter values commonly are estimated from experimental data, which contain errors due to both the estimation procedure adopted to fit data and the experimental errors of the data themselves (De Jong, 2002; Keener & Sneyd, 1998). From a practical viewpoint, the assumption of model uncertainties in our control methodology allows to design a controller that uses only the minimum system information in order to control the calcium nonlinear dynamics and the resulting control can be easily interpreted from a biological viewpoint and implemented.

- The use of an external input as the manipulable variable is realistic. Indeed, several experimental studies have shown that the synchronization of individual biochemical oscillators depends on external stimulus properties (FitzHugh, 1961; Glass, 2001; Gonze & Goldbeter, 2000; Jewett et al., 1991; Marhl & Schuster, 2003; Izhikevich, 2007). An external electrical stimuli can be modeled including an applied current in the current balance equation. Chemical stimuli can be modeled either by varying concentrations of relevant agents or by varying parameters which are believed to be correlated to the stimulating chemical.

The proposed feedback and synchronization arrangements are shown in Fig. 1. A sensor measures a time-varying output from the cell, $y(t)$, and feeds it to a controller. The controller produces a signal, $u(t)$, which drives an actuator to produce a time-varying input to individual biochemical oscillators to get the desired synchronized dynamic behavior. On the other hand, a reference or master oscillator provides the desired reference to individual or slave oscillators, that will be driven by individual external inputs to follow the desired reference behavior.

4.2 Modeling error compensation approach

Sun et al. (1994) proposed a robust controller design method for single-input/single-output (SISO) minimum-phase linear systems. The design approach consists of a modeling error compensator (MEC). The central idea is to compensate the error due to uncertainty by determining the modeling error via plant input and output signals and use this information in the design. In addition to a nominal feedback, another feedback loop is introduced using the modeling error and this feedback action is explicitly proportional to the parametric error which is the source of uncertainty. The MEC approach was extended for a class of
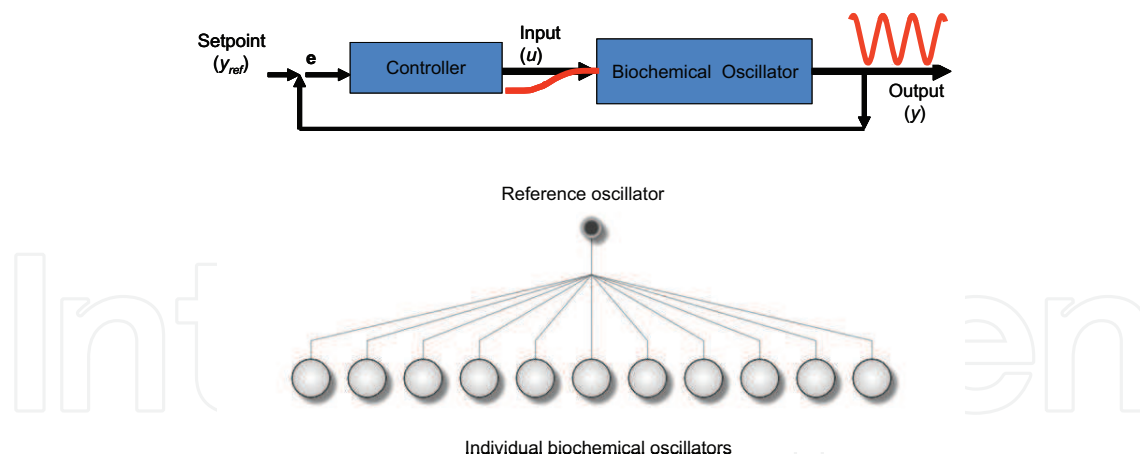
Fig. 1. Feedback and synchronization system.

linear time-varying and nonlinear linearizable lumped parameter systems with uncertain and unknown terms by Alvarez-Ramirez (1999), where instead of designing a robust state feedback to dominate the uncertain term, the uncertain term is viewed as an extra state that is estimated using a high-gain observer. The estimation of the uncertain term gives the control system some degree of adaptability. The extension of the MEC approach to distributed parameter systems has been applied by Puebla (2005) and Puebla et al. (2009, 2010) for a class of biological distributed parameter systems. The underlying idea behind MEC control designs is to lump the input-output uncertainties into a term, which is estimated and compensated via a suitable algorithm.

Consider the class of biochemical oscillators described in Section 2:

$$\frac{dy_i}{dt} = f_{1,i}(y_i, z_i) + g_i(y_i, z_i)u_i, \ i = 1, ..., N \tag{12}$$
$$\frac{dz_i}{dt} = f_{2,i}(y_i, z_i)$$

Let $e_i = y_i - y_{ref}$ be the tracking error, and define the modeling error function η_i as,

$$\eta_i = (\widetilde{f}_{1,i} - f_{1,i}) + (\widetilde{g}_i - g_i)u_i \tag{13}$$

where $\widetilde{f}_{1,i}$ and $\widetilde{g}_i$ are rough estimates of uncertain functions $f_{1,i}$ and g_i respectively. System (12) can be written as,

$$\overset{\bullet}{e}_i = \eta_i - \widetilde{f}_{1,i} - \widetilde{g}_i u - \overset{\bullet}{y}_{ref} \tag{14}$$

where $\overset{\bullet}{y}_{ref}$ is the first derivative of y_{ref}. Consider the inverse dynamics control law,

$$u_i = \widetilde{g}_i^{-1}(\eta_i - \widetilde{f}_{1,i} - \overset{\bullet}{y}_{ref} + \tau_c^{-1}e_i) \tag{15}$$

where $\tau_c > 0$ is a closed-loop time constant. Under the inverse-dynamics control law (15), the closed-loop system dynamics is $de_i/dt = -\tau_c^{-1}e_i$, so that the error dynamic behavior is given as $e(t) = e(0)\exp(-t/\tau_c)$. In this way, the asymptotic convergence $e(t) \to 0$, and so $y \to y_{ref}$, is guaranteed.

In order to implement the control input an estimate of the real uncertain term is computed using a high-gain reduced-order observer,

$$\dot{\widetilde{\eta}}_i = \tau_e^{-1}(\eta_i - \widetilde{\eta}_i) \tag{16}$$

where $\tau_e > 0$ is the estimation time constant. After some direct algebraic manipulations the reduced order observer (16) can be written as,

$$\dot{w}_i = \widetilde{f}_{1,i} + \widetilde{g}_i u_i + \dot{y}_{ref} - \widetilde{\eta}_i \tag{17}$$
$$\widetilde{\eta}_i = \tau_e^{-1}(w_i + e_i)$$

The final form of the controller is given by the feedback function (18) and the modeling error estimator (17),

$$u_i = \widetilde{g}_i^{-1}(\widetilde{\eta}_i - \widetilde{f}_{1,i} - \dot{y}_{ref} + \tau_c^{-1}e_i) \tag{18}$$

the resulting feedback controlled depends only on the measure y and the estimated values of uncertain terms $\widetilde{f}_{1,i}$ and $\widetilde{g}_i$. Notice that in a worst-case design, one can choose $\widetilde{f}_{1,i} = 0$.

The above model-based control approach has only two control design parameters, *i.e.*, τ_c and τ_e. The closed-loop parameter τ_c can be chosen as the inverse of the dominant frequency of the open-loop dynamics. On the other hand, the estimation parameter $\tau_e > 0$, which determines the smoothness of the modeling error can be chosen as $\tau_e < \frac{1}{2}\tau_c$. On the other hand, system (12) is of relative grade one. However, straight extensions of the MEC control design to both autonomous third and second order systems can be found in Puebla *et al.* (2003), and Alvarez-Ramirez, respectively.

4.3 Sliding mode control approaches

Sliding mode control techniques have long been recognized as a powerful robust control method (Hangos et al., 2004; Levant, 2001; Sira-Ramirez, 2002). Sliding-mode control schemes, have shown several advantages like allowing the presence of matched model uncertainties and convergence speed over others existing techniques as Lyapunov-based techniques, feedback linearization and extended linearization, however standard sliding-mode controllers have some drawbacks: 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, 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. To try to avoid the above a relatively new kind of sliding-mode structures have been proposed as the named high-order sliding-mode technique, these techniques consider 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 (Hangos et al., 2004; Levant, 2001; Sira-Ramirez, 2002). In this section we present some ideas of the integral high order sliding mode control (IHOSMC).

Sliding mode control design consists of two phases. In the first phase the sliding surface is to be reached (reaching mode), while in the second the system is controlled to move along the sliding surface (sliding mode). In fact, these two phases can be designed independently from each other. Reaching the sliding surface can be realized by appropriate switching elements (Hangos et al., 2004).

Defining

$$\sigma(e) = e_i = y_i - y_{ref}$$

as the sliding surface, we have that the continuous part of the sliding mode controller is given by,

$$u_{eq,i} = -g_i^{-1}(f_{1,i} - \dot{y}_{ref})$$

such that,

$$\dot{\sigma}(e) = 0$$

where $\dot{y}_{ref}$ is the time-derivative of the desired trajectory signal. Once on the surface, the dynamic response of the system is governed by $de_i/dt = 0$. To force the system trajectory to converge to the sliding surface in the presence of both model uncertainties and disturbances, with chattering minimization and finite-time convergence, the sliding trajectory is proposed as (Levant, 2001; Aguilar-Lopez et al., 2010),

$$u_{eq,i} = -g_i^{-1}[\delta_1 e_i + \delta_2 \int_0^t \left\{ sign(e_i) |e_i|^{1/p} \right\} d\tau] \tag{19}$$

where δ_1 and δ_2 are control design parameters. The final IHOSMC is given by,

$$u_i = -g_i^{-1}(f_{1,i} - \dot{y}_{ref} + \delta_1 e_i + \delta_2 \int_0^t \left\{ sign(e_i) |e_i|^{1/p} \right\} d\tau) \tag{20}$$

The synthesis of the above control law requires accurate knowledge of both $f_{1,i}$ and dy_{ref}/dt to be realizable. To enhance the robust performance of the above control laws, the uncertain terms is lumped in single terms and compensated with a reduced-order observer. However, by exploiting the properties of the sliding part of the sliding-mode type controllers to compensates uncertain nonlinear terms, the knowledge of the nonlinear term $f_{1,i}$ can be avoided.

Summarizing, the IHOSMC is composed by a proportional action, which has stabilizing effects on the control performance, and a high order sliding surface, which compensates the uncertain nonlinear terms to provide robustness to the closed-loop system. This behavior is exhibited because, once on the sliding surface, system trajectories remain on that surface, so the sliding condition is taken and make the surface and invariant set. This implies that some disturbances or dynamic uncertainties can be compensated while still keeping the surface an invariant set.

4.4 Robust geometric linearizing control

Differential geometry is an essential tool for the study of the structural properties of nonlinear control systems. Differential geometric techniques of nonlinear control include static and dynamic feedback linearization, input-output linearization, nonlinear state observers and disturbance decoupling (Hangos et al., 2004). In exact linearization the main idea is to apply a suitable nonlinear coordinate transformation to a nonlinear system in order to obtain a linear one in the new co-ordinates and between the original output and the newly introduced transformed input. The coordinates transformation must be supplemented by a static nonlinear feedback to achieve linearization. After linearization any controller design method can be used to stabilize the system or modify its dynamic properties.

Exact linearization via state feedback is a limited technique for control of nonlinear systems because it is only applicable for systems satisfying a relative degree condition. Indeed, the relative degree of the system needs to be equal to the number of state variables, i.e. $r = n$. Therefore the exact linearization may not be applicable or may not be feasible in practical cases. Input–output linearization is an alternative way of achieving linear behavior of a system by nonlinear coordinate transformation (Hangos et al., 2004).

A main drawback in the use of differential geometric control techniques is that depends on the exact cancelation of the nonlinear dynamics in order to obtain an input-output linear dynamic behavior. As a consequence, the perfect knowledge of the system is required. Robustness of geometric differential approaches has received attention in the literature. In this section we describe a robust geometric input-output linearizing control, where the presence of modeling errors, unmeasured disturbances and parametric uncertainties are considered in the controller design.

Consider the class of biochemical oscillators described in Section 2 with $y_i = h_i(y_i, z_i)$. An input-output linearizing controller u_i is given by,

$$
\begin{aligned}
u_i &= \frac{1}{\mathcal{L}_g \mathcal{L}_f^{r-1} h_i(y_i, z_i)} (-\mathcal{L}_f^r h_i(y_i, z_i) + v_i) \\
&= \alpha_i(y_i, z_i) + \beta_i(y_i, z_i) v_i \\
\alpha_i(y_i, z_i) &= \frac{-\mathcal{L}_f^r h_i(y_i, z_i)}{\mathcal{L}_g \mathcal{L}_f^{r-1} h_i(y_i, z_i)} \\
\beta_i(y_i, z_i) &= \frac{1}{\mathcal{L}_g \mathcal{L}_f^{r-1} h_i(y_i, z_i)}
\end{aligned}
\tag{21}
$$

where $\mathcal{L}_g$ and $\mathcal{L}_f$ are the lie derivatives of g_i and $f_{1,i}$ respectively, and v_i is a new external input.

Under the input-output linearizing controller we have,

$$
\frac{dy_i}{dt} = f_{1,i}(y_i, z_i) + g_i(y_i, z_i)\alpha_i(y_i, z_i) + \beta_i(y_i, z_i)v_i, \ i = 1, ..., N
\tag{22}
$$

$$
\frac{dz_i}{dt} = f_{2,i}(y_i, z_i)
\tag{23}
$$

The linearizing input-output controller decomposes the system into two parts: (i) a linear subsystem of order r which is influenced by the chosen input u_i (22), and (ii) a nonlinear subsystem described by the zero dynamics. Thus the main applicability condition of input–output linearization is to have a stable zero dynamics in a wide domain of the state-space, or even better, a globally stable zero dynamics (Hangos et al., 2004).

If exact cancelation of nonlinear terms is achieved then the closed-loop system is given by,

$$
\frac{dy_i}{dt} = v_i
\tag{24}
$$

$$
\frac{dz_i}{dt} = f_{2,i}(y_i, z_i)
$$

It is relatively simple to device a feedback control law for v_i, which stabilizes the output of the system, y_i, to the desired reference, y_{ref}. A valid choice of the new control input is a simple linear input, $v_i = -\tau_c^{-1}(y_i - y_{ref}) + \dot{y}_{ref}$, that guarantees the stability of the overall system provided that the zero dynamics is stable, i.e.,

$$\frac{de_i}{dt} = -e_i \tag{25}$$

where τ_c is controller design parameter, $e_i = y_i - y_{ref}$, is the tracking error.

The linearizing input-output controller needs accurate knowledge of the nonlinear dynamics of the system, hence, turns to be inapplicable if the model for the process includes uncertainties. This fact is behind the motivation to provide robustness properties of the above linearizing input-output controller. In order to provide robustness against inexact model cancelations of nonlinear terms, unmodeled dynamics, and external perturbation we proceed as in the approach of modeling error compensation approach (Alvarez-Ramirez, 1999). Consider system (22) subject to model uncertainties η_i,

$$\frac{dy_i}{dt} = \tilde{f}_{1,i}(y_i, z_i) + \tilde{g}_i(y_i, z_i)\alpha_i(y_i, z_i) + \beta_i(y_i, z_i)v_i + \eta_i, \ i = 1, ..., N \tag{26}$$

where η_i is defined as,

$$\eta_i = (f_{1,i}(y_i, z_i) - \tilde{f}_{1,i}(y_i, z_i)) + (g_i(y_i, z_i) - \tilde{g}_i(y_i, z_i))\alpha_i(y_i, z_i) \tag{27}$$

where $\tilde{f}_{1,i}$ and $\tilde{g}_i$ are rough estimates of terms $f_{1,i}$ and g_i all the uncertain terms associated to the biochemical system model are lumped. The uncertain function η_i can be estimated using a state observer (Alvarez-Ramirez, 1999). We introduce a reduced order observer given by (16) to this end. After some direct algebraic manipulations we get the robust linearizing input-output controller as,

$$\frac{dw_i}{dt} = -\tilde{f}_{1,i}(y_i, z_i) - \tilde{g}_i(y_i, z_i)\alpha_i(y_i, z_i) - \beta_i(y_i, z_i)v_i - \bar{\eta}_i, \ i = 1, ..., N \tag{28}$$

$$\bar{\eta}_i = \tau_e^{-1}(w_i + y_i)$$

$$v_i = -\beta_i(y_i, z_i)^{-1}[\bar{\eta}_i - \tau_c^{-1}e_i]$$

$$u_i = -\alpha_i(y_i, z_i) + \beta_i(y_i, z_i)v_i$$

Comparing the above robust linearizing input-output controllers with the controller derived via a MEC approach we can exploit the tunning guidelines of the MEC approach to provide some guidelines for the tunning of controller parameters τ_c and τ_e (Alvarez-Ramirez, 1999).

5. Applications

In this section we consider three examples of the implementation of the proposed synchronization approach with the robust feedback control approaches presented in the above section. The examples are: (i) the Goodwin model, (ii) a Fitz-Hugh-Nagumo neuron model, and (iii) circadian rhythms in Drosphila.

5.1 Goodwin model for genetic oscillators

Synchronization of coupled genetic oscillators has important biological implications and potential engineering applications from both theoretical and experimental viewpoints, and it is also essential for the understanding of the rhythmic phenomena of living organisms at both molecular and cellular levels. The Goodwin model (Goodwin, 1965) is a benchmark model of genetic oscillations that contains three simple biochemical components (nuclear messenger, cytoplasmic messenger, and repressor). In the original model, a clock gene mRNA produces a clock protein, which activates a transcriptional inhibitor, which inhibits the transcription of the clock gene, thus forming a negative feedback loop.

Using the notation previously introduced, we consider the following external forcing modification of the Goodwin model that consists of the following set of three ordinary differential equations (Goodwin, 1965; Keener & Sneyd, 1998),

$$\frac{dy}{dt} = \frac{c_1}{1 + z_2^p} - c_2 y + u \tag{29}$$

$$\frac{dz_1}{dt} = c_3 y - c_4 z_1$$

$$\frac{dz_2}{dt} = c_5 z_1 - c_6 z_2$$

where y, z_1 and z_2 represent respectively the concentrations of the mRNA, the enzyme and the product of the reaction of the enzyme and a substrate, assumed to be available at a constant level. All c_i are constant positive parameters. The creation of y is inhibited by the product z_2 and is degraded according to first-order kinetics, while z_1 and z_2 are created and degraded by first-order kinetics. We also assumed that u is a plausible manipulated variable.

The synchronization objective is to synchronize an ensemble of two independent genetic oscillators, to the dynamics generated by a reference Goodwin genetic oscillator, via an external forcing u to the mRNA concentration y. Figure 2 shows the synchronization performance for the three proposed robust control approaches: MEC control, IHOSMC, and the GLC, in the upper, middle and bottom parts of Figure 2 respectively. It can be seen from Figure 2 that the synchronization objective is achieved for all robust control approaches. MEC approach uses less control effort than IHOSMC and GLC. The control input for the IHOSMC displays a switching type behavior typical of SMC approaches. The modulation of external inputs depends on the measured state such that a feedback mechanism is established and modifies the natural dynamic behavior of the controlled biochemical oscillators.

5.2 FitzHugh-Nagumo model of neurons

The central nervous system can display a wide spectrum of spatially synchronized, rhythmic oscillatory patterns of activity with frequencies in the range from 0.5Hz (rhythm), 20Hz (rhythm), to 30-80 Hz (rhythm) and even higher up to 200Hz (Izhikevich, 2007). In the past decade it has been shown that synchronized activity and temporal correlation are fundamental tools for encoding and exchanging information for neuronal information processing in the brain (Izhikevich, 2007). In particular, it has been suggested that clusters of cells organize spontaneously into flexible groups of neurons with similar firing rates, but with a different temporal correlation structure.
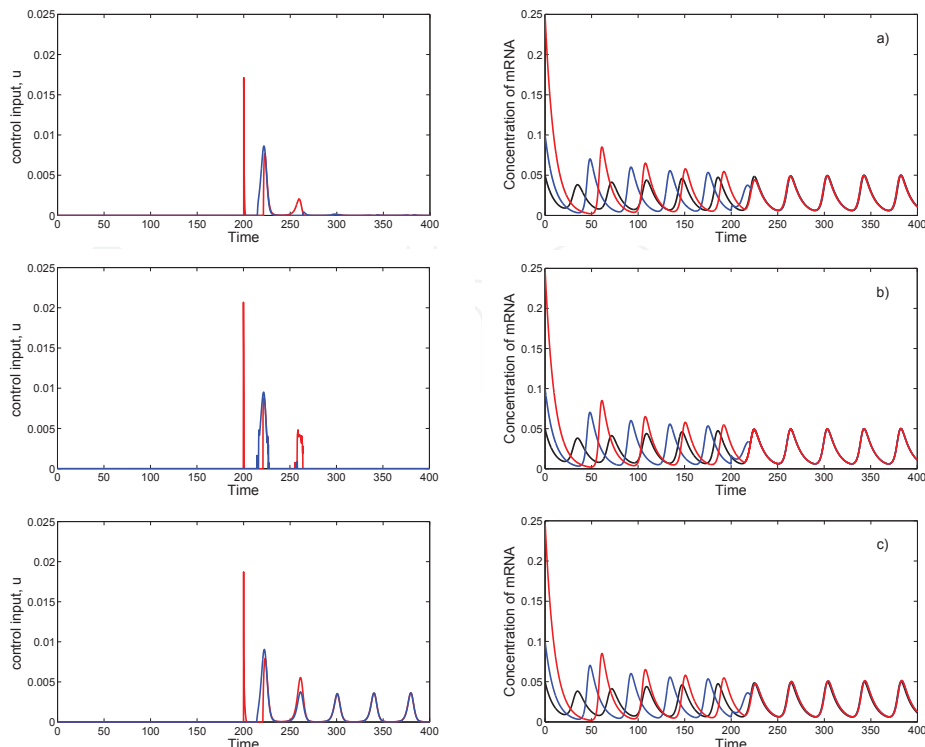
Fig. 2. Synchronization of Goodwin model for genetic oscillators via (a) MEC, (b) IHOSMC and (c) GLC

A benchmark model of neural activity was proposed by FitzHugh and Nagumo (FHN) as a mathematical representation of the firing behavior of neuron (FitzHugh, 1961). The neural FHN model is an excitable media (Keener & Sneyd, 1998). Excitable media are systems that sit at a steady state and are stable to small disturbances. If, however, they receive a disturbance (such as a sudden increase in the concentration of the feedback species) above some critical or threshold value, then they respond with an excitation event (which corresponds to the reaction front). The FHN model and its modifications served well as simple but reasonable models of excitation propagation in nerve, heart muscle and other biological excitable media (Izhikevich, 2007).

The FHN neuron model with external current u studied in this paper is described by the following set of two ordinary differential equations,

$$\frac{dy}{dt} = -y(y - c_1)(y - 1) - z + I_0 + I\cos(c_4 t) + u \tag{30}$$
$$\frac{dz}{dt} = \beta(c_5 y - z)$$

where y is the potential difference across the membrane, z is a recovery variable which measures the state of excitability of the cell. Parameters c_i are positive constants, I_0 stands for the ionic current inside the cell, I is the amplitude of the external current.

We apply a control approach by injecting the external signal at each individual oscillator in order to track the desired synchronized signal. In this case, the desired synchronized signal is a periodic signal. Figures 3 and 4 shows the synchronization performance for the MEC approach
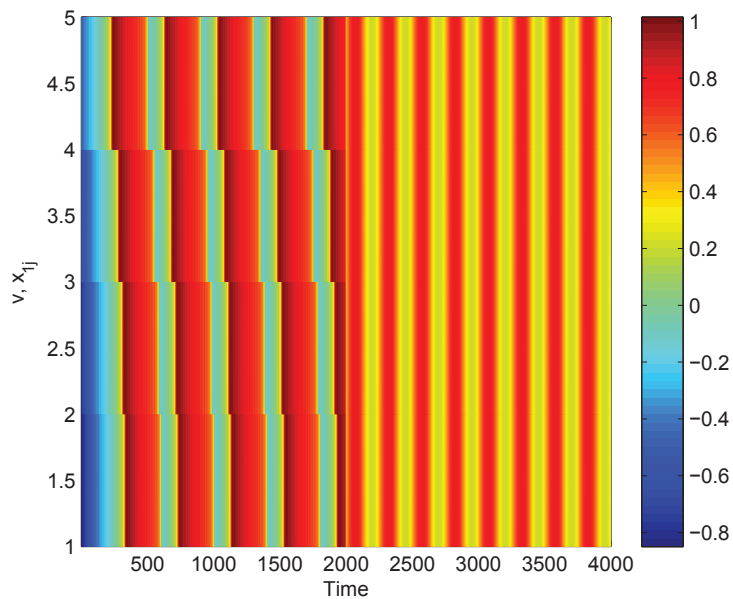
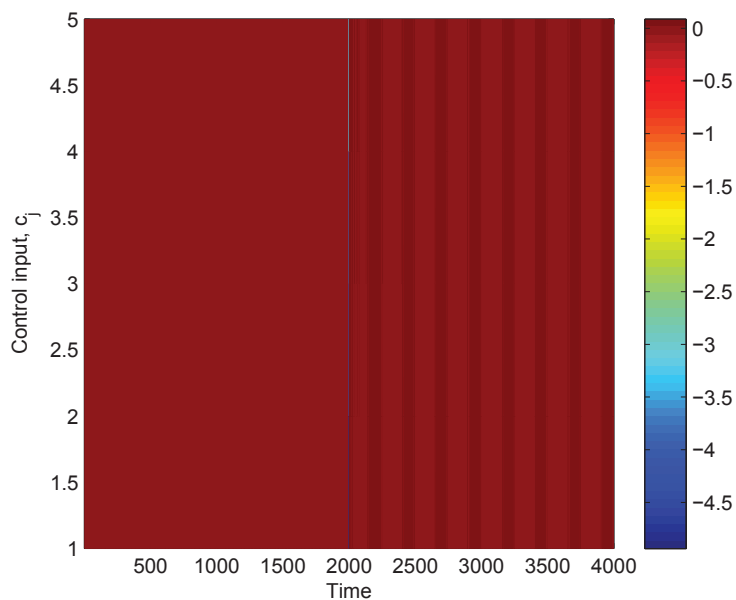Fig. 3. Synchronization of 5 individual oscillators for FHN model of neurons.

Fig. 4. Corresponding control input for Figure 3.

for an ensemble of 5 individual oscillators. It can be seen that, after a short transient, the array of FHN neurons synchronizes about the desired periodical dynamical behavior. Figure 4 shows that by using periodic applied current we can force the periodicity of the synchronized neurons. The applied input depends on the current state of the neuron which receives the external impulse.

5.3 Circadian rhythms in Drosphila

The biological functions of most living organisms are organized along an approximate 24-h time cycle or circadian rhythm (Goldbeter, 1996). Circadian rhythms, are endogenous because they can occur in constant environmental conditions, e.g. constant darkness. Circadian rhythm can also be entrained by external forcing of modified light-darkness cycles or phase-shifted when exposed to light pulses (Goldbeter, 1996; Fu & Lee, 2003; Jewett et al., 1991).

Circadian rhythms are centrally regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus. Most neurons in the SCN become active during the day and are believed to comprise the biological clock. Dispersed SCN cells exhibit sustained circadian oscillations with periods ranging from 20 to 28 hours, but on the tissue level, SCN neurons display a significant degree of synchrony. Over time, the development of a circadian rhythm might impart larger benefits to the organism. In cyanobacteria, for example, matching of the free-running period to the light-dark cycle time provides a selective advantage, which is presumably the basis for its evolution (Ouyang et al., 1998). In Arabidopsis, matching between the circadian period and the light-dark cycle results in plants that fix carbon at a higher rate and grow and survive better than those that lack such a match (Dodd et al., 2005).

Concerning the modeling of this phenomenon, it has to be stressed that the mechanism can be considerably different for the different living beings in which it has been studied, ranging from unicellular organisms to mammalians, going through fungi and flies. Some of the most recent models have a high degree of complexity and involve up to 16 differential equations. However, it seems to be accepted that the central mechanism causing oscillations is represented by a negative feedback exerted by a protein on the expression of its corresponding gene.

We consider as the single biochemical oscillator a simple five-variable model proposed for circadian rhythms for the central clock of fruit fly Drosophila (Gonze & Goldbeter, 2000),

$$\frac{dy}{dt} = u\frac{K_I^n}{K_I^n + z_4^n} - v_m\frac{y}{K_m + y}$$

$$\frac{dz_1}{dt} = k_s y - V_1\frac{z_1}{K_1 + z_1} + V_2\frac{z_2}{K_2 + z_2}$$

$$\frac{dz_2}{dt} = V_1\frac{z_1}{K_1 + z_1} - V_2\frac{z_2}{K_2 + z_2} - V_3\frac{z_2}{K_3 + z_2} + V_4\frac{z_3}{K_4 + z_4}$$

$$\frac{dz_3}{dt} = V_3\frac{z_2}{K_3 + z_2} - V_4\frac{z_3}{K_4 + z_4} - k_1 z_3 + k_2 z_4 - v_d\frac{z_3}{K_d + z_3}$$

$$\frac{dz_4}{dt} = k_1 z_3 - k_2 z_4$$

where y, z_1, z_2, z_3 and z_4 denote, respectively, the concentrations of mRNA, PER protein, mono- and di-phosphorylated forms of PER protein, and the amount of phosphorylated protein located in the cells. Once in the nucleus, PER protein down-regulates mRNA translation, leading to the observed oscillating behavior. The manipulated variable u denotes the maximal speed of transcription of y. It seems that progresses in gene manipulation techniques make it reasonable to think of modifying of this parameter. Definition of other parameters can be found in Goldbeter, (1996). Kinetic parameters can differ from one oscillator to the other and thus holds variability in individual circadian oscillators.
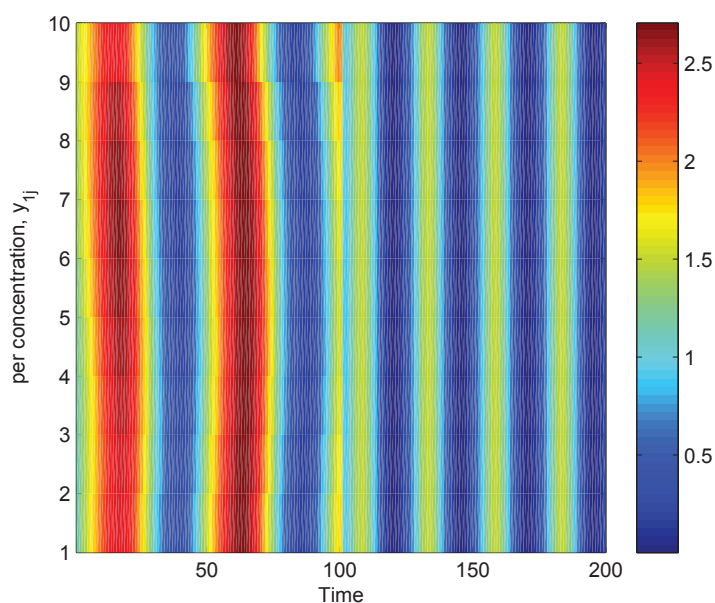
Fig. 5. Synchronization of the circadian rhythms in Drosphila using a periodic modulation of the external input.

The synchronization objective is fix a nominal 24-h period of the circadian oscillations for an ensemble of individual circadian oscillators. In this case we have implemented the GLC. Figures 5 and 6 shows that by using a periodic modulation of the external input, we can force the circadian periodicity. As was stated above, synchronization of circadian rhythms has been achieved via the periodic modulation of a light sensitive parameter. In this case, the parameter modulation requires the periodic manipulation of the maxima speed of transcription of mRNA, which should be addressed using gene manipulation techniques, and is beyond of the scope of this contribution.

6. Conclusions and perspectives

In this chapter we have discussed the synchronization problem of biochemical oscillators and we have addressed this problem via three robust feedback control approaches. In this section we provide some concluding remarks and a perspective on the synchronization of biochemical systems.

6.1 Concluding remarks

One interesting phenomenon in biological systems is the collective rhythm of all dynamic cells. Synchronization occurs in many populations of biological oscillators. From the general synchronization point of view, synchronization approaches can be classified into two general groups: (i) natural coupling (self-synchronization), and (ii) artificial coupling forced via periodic modulation or explicit feedback control approaches. Classical methods are determined by an interplay of time scales by phase locking or, respectively, natural frequency entrainment or due to suppression of inherent frequencies. Artificial coupling where an external input can be manipulated can be looked as control synthesis issue and studied within the control theory framework developed in this work.
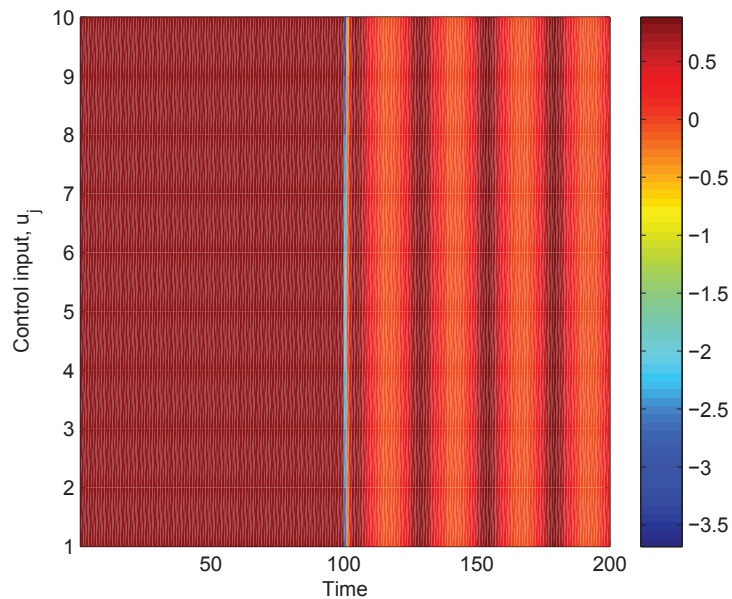
Fig. 6. Corresponding control input for Figure 5.

In this chapter we have shown that external stimulation with robust feedback control can effectively synchronize populations of individual oscillators. We have introduced three robust feedback control approaches: (i) the MEC approach, that leads to simple practical control design with good robustness and performance capabilities, (ii) sliding mode control approach that leads to a simple design with the feature of switching type action that can be appropriate for biochemical systems, and (iii) a robust geometric linearizing input-output control, that can be useful to establish a relation between neural processing behavior in cells and the mathematical formalism of geometric differential methods. Numerical simulations results indicate good tracking performance of the proposed robust control approaches. The three robust control schemes are based on a minimum information from the cell model (output), not on the precise details of the model (*e.g.*, kinetic parameters). Thus, our control scheme is likely to be effective in the more complicated models of cell dynamics.

From a general point of view external forcing of cellular processes is important in many application areas ranging from bioengineering to biomedicine. At the level of biology the problem is to supply an input to the cell such that the biochemical processes of the cell achieve specified control objectives. At the level of control theory the biological problem amounts to the construction of a control law such the control objectives are achieved. In this way, the results in this work must be seen as a first approach to addressing the systematic design of control systems in cellular processes.

6.2 Perspectives

Feedback control and synchronization for cells is in its infancy, with numerous challenges and opportunities ahead. For instance, an implicit assumption of the control frameworks discussed in this article is that the control law is implemented without regard the actuator and sensor constraints for cells. Besides, we have considered cellular systems described by ordinary differential systems, without delays. Delays are however known to be involved in biological systems, because for example mRNA synthesis and transport (in eukaryotic cells)

are certainly not instantaneous. Systems with delays are however most difficult to analyze and control, because they are differential systems of infinite dimensions, to which mathematical tools are more involved.

Feedback control theory in combination with biological knowledge can lead to a better understand of the complex dynamics of cellular processes. Indeed, the design of closed-loop system in biological systems is a first step to gain insights of the suppression and generation of oscillatory behavior, and the closed-loop response can resembles the features of the behavior of biological processes. Current work is in progress in order to study various synchronization mechanisms by investigating the effects of various biologically plausible couplings and several kinds of noise from the viewpoint of feedback control theory.

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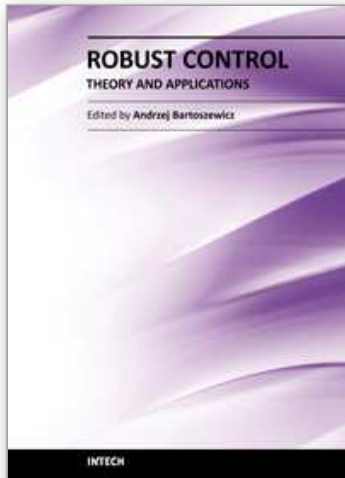
Robust Control, Theory and Applications

Edited by Prof. Andrzej Bartoszewicz

The main objective of this monograph is to present a broad range of well worked out, recent theoretical and application studies in the field of robust control system analysis and design. The contributions presented here include but are not limited to robust PID, H-infinity, sliding mode, fault tolerant, fuzzy and QFT based control systems. They advance the current progress in the field, and motivate and encourage new ideas and solutions in the robust control area.

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