Introduction

Theory of hybrid dynamical systems and its applications to biological and medical systems

BY KAZUYUKI AIHARA* AND HIDEYUKI SUZUKI

Institute of Industrial Science, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan

In this introductory article, we survey the contents of this Theme Issue. This Theme Issue deals with a fertile region of hybrid dynamical systems that are characterized by the coexistence of continuous and discrete dynamics. It is now well known that there exist many hybrid dynamical systems with discontinuities such as impact, switching, friction and sliding. The first aim of this Issue is to discuss recent developments in understanding nonlinear dynamics of hybrid dynamical systems in the two main theoretical fields of dynamical systems theory and control systems theory. A combined study of the hybrid systems dynamics in the two theoretical fields might contribute to a more comprehensive understanding of hybrid dynamical systems. In addition, mathematical modelling by hybrid dynamical systems is particularly important for understanding the nonlinear dynamics of biological and medical systems as they have many discontinuities such as threshold-triggered firing in neurons, on–off switching of gene expression by a transcription factor, division in cells and certain types of chronotherapy for prostate cancer. Hence, the second aim is to discuss recent applications of hybrid dynamical systems in biology and medicine. Thus, this Issue is not only general to serve as a survey of recent progress in hybrid systems theory but also specific to introduce interesting and stimulating applications of hybrid systems in biology and medicine. As the introduction to the topics in this Theme Issue, we provide a brief history of nonlinear dynamics and mathematical modelling, different mathematical models of hybrid dynamical systems, the relationship between dynamical systems theory and control systems theory, examples of complex behaviour in a simple neuron model and its variants, applications of hybrid dynamical systems in biology and medicine as a road map of articles in this Theme Issue and future directions of hybrid systems modelling.

Keywords: hybrid dynamical systems; mathematical modelling; biological systems; medical systems; nonlinear dynamics; control

1. Nonlinear dynamics and mathematical modelling

The history of natural science can be traced back to Isaac Newton in the seventeenth century. He formulated equations relating force and motion and co-invented calculus. This seminal work inaugurated the field of dynamical systems theory.

*Author for correspondence (aihara@sat.t.u-tokyo.ac.jp).

One contribution of 12 to a Theme Issue ‘Theory of hybrid dynamical systems and its applications to biological and medical systems’.

This journal is © 2010 The Royal Society
systems. His laws of force and motion are also the origin of mathematical modelling of dynamical phenomena in this world. Because calculus generally hates discontinuities and instabilities, most classical studies of dynamical systems and mathematical modelling concentrated on solutions that were smooth and stable. The universe was thus conceived of as a precision machine with smoothness and stability; based on the initial conditions, one could accurately predict future behaviour such as that of planets orbiting the Sun or that of a pendulum clock. However, in the 1960s and 1970s, ‘catastrophe theory’ (Thom 1975) and ‘chaos theory’ (Li & Yorke 1975; May 1976) were formulated as special branches of dynamical systems theory; these branches deal with nonlinear phenomena with discontinuities or abrupt changes in behaviour and with instabilities or unstable and unpredictable dynamics, respectively.

Catastrophe theory was subsequently applied to many real-world phenomena in different disciplines, including biological and even social sciences. This very popular approach, however, unfortunately turned out to be superficial, because it was applied with oversimplified generality instead of being based on sound characterization of each specific phenomenon (Kolata 1977; Zahler & Sussmann 1977); see also Scheffer et al. (2009) for recent progress on tipping points and critical transitions.

Catastrophe theory can be included in the more general theory of bifurcations, which describes how a variation in some parameter values results in a sudden change in the qualitative structure of the solutions to dynamical systems. In fact, catastrophe theory is related to the essence of bifurcations specific to dynamical systems with potential. Presently, there are several advanced theorems on bifurcations, some of which can explain even the emergence of chaos through a universal route with successive period-doubling bifurcations (Feigenbaum 1978).

Chaos is a mathematical term that describes complex behaviour in deterministic dynamical systems, which has short-term predictability but is nevertheless unstable and unpredictable in the long term. Extensive studies on chaos in the 1980s clarified that chaos is ubiquitous not only in mathematical models but also in real-world systems.

Thus, with the advent of the catastrophe and chaos theory, it was found that the behaviour of nature is beyond smooth and stable.

This Theme Issue deals with another fertile region of dynamical systems that are widely related to discontinuities and instabilities, namely hybrid dynamical systems (Witsenhausen 1966; Filippov 1988; Guckenheimer & Johnson 1995; Branicky et al. 1998; Matveev & Savkin 2000; van der Schaft & Schumacher 2000; Leine & Nijmeijer 2004; Haddad et al. 2006; Awrejcewicz & Holicke 2007; Zavalishchin & Sesekin 2007; Acary & Brogliato 2008; di Bernardo et al. 2008; Goebel et al. 2009; Lunze & Lamnabhi-Lagarrigue 2009); see also the Proceedings of the International Hybrid Systems Workshops, International Conferences on Hybrid Systems and the ACM International Conference on Hybrid Systems as well as references in the review articles by di Bernardo & Hogan (2010) and Heemels et al. (2010) in this Theme Issue. Generally speaking, hybrid dynamical systems are characterized by the coexistence of continuous and discrete dynamics.

It is now well known that, among natural and engineering systems, there exist several hybrid dynamical systems with discontinuities that do not arise from elementary bifurcations accounted for by the catastrophe theory. Examples of such discontinuous systems include impact, switching, friction and sliding;

Phil. Trans. R. Soc. A (2010)
these systems can be mathematically described as hybrid dynamical systems with continuous and discrete variables. Since such discontinuities are found everywhere, modelling of hybrid dynamical systems is applicable to almost all research areas in life science and other disciplines as well as in physical science. Moreover, the nonlinear dynamics of hybrid dynamical systems is considerably richer and more complicated than that of the usual smooth dynamical systems, generating even special bifurcations, as shown in this Theme Issue.

However, such intriguing nonlinear dynamics has been studied separately in two main theoretical fields, namely dynamical systems theory and control systems theory, as discussed in §3. The first aim of this Theme Issue is to discuss recent developments in understanding nonlinear dynamics of hybrid dynamical systems in the respective theoretical fields through the review articles by di Bernardo & Hogan (2010) and Heemels et al. (2010)

A combined study of the hybrid systems dynamics in the two theoretical fields might contribute to a more comprehensive understanding of the complex nonlinear dynamics in hybrid dynamical systems. Computer science and software engineering are also important fields, especially for considering discrete aspects in hybrid dynamical systems (e.g. Lunze & Lamnabhi-Lagarrigue 2009).

In addition, mathematical modelling by hybrid dynamical systems is particularly important for understanding the nonlinear dynamics of biological and medical systems as they have many discontinuities. Typical examples of such discontinuities are threshold-triggered firing in neurons (Izhikevich 2010), on–off switching of gene expression by a transcription factor (Imura et al. 2010; Perkins et al. 2010; Singh & Hespanha 2010), division in cells (Chen et al. 2004; Battogtokh et al. 2006; Osborne et al. 2010) and certain types of chronotherapy for prostate cancer (Guo et al. 2008; Ideta et al. 2008; Shimada & Aihara 2008; Tanaka et al. 2008, 2010; Hirata et al. 2010; Suzuki et al. 2010). Hence, the second aim of this Theme Issue is to discuss recent studies which apply hybrid dynamical systems to the fields of biology and medicine, through the nine articles with a variety of topics; this should stimulate applications of hybrid systems modelling to other research areas as well.

Thus, this Issue is not only general to serve as a survey of progress in hybrid systems theory from the perspectives of the two theoretical fields of dynamical systems and control systems, but also specific to introduce interesting and stimulating applications of hybrid systems in biology and medicine.

A potential scientific and social impact of this issue is the expansion of the scope of mathematical modelling from conventional smooth dynamical systems to hybrid dynamical systems with analogue and digital variables. Dynamical systems theory has been providing the basic methodology of science since the seminal work of Isaac Newton. Although dynamical systems theory usually only considers smooth systems with continuous variables, important real-world systems of many fields in general and biological and medical systems in particular can be described by hybrid dynamical systems with both continuous and discrete variables.

The topics of this Theme Issue are cross-disciplinary in two senses. First, as already explained, this issue aims to cover two theoretical fields on hybrid systems dynamics; namely, dynamical systems theory in mathematics and control systems theory in engineering and technology. Second, the application fields of

*Phil. Trans. R. Soc. A* (2010)
hybrid systems theory are truly cross-disciplinary as they deal with many systems in science, engineering, economics and so on. Although this Theme Issue will focus on the applications of hybrid dynamical systems to biological and medical sciences, we hope that the theory and application examples provided in this Issue encourage similar studies in many other disciplines.

2. Mathematical models of hybrid dynamical systems

Although hybrid dynamical systems are ubiquitous, they have not yet been formulated by a common mathematical description owing to their great diversity. One of the well-organized general formulations from the viewpoint of deterministic dynamics is summarized as follows (Branicky et al. 1998; Imura & Azuma 2007; di Bernardo et al. 2008; Lunze & Lamnabhi-Lagarrigue 2009):

\[
\frac{dx(t)}{dt} = F_i(t)(x(t), u(t), \mu), \quad (2.1)
\]

\[
i(t) = G(i(t_-), x(t_-), u(t), \mu), \quad (2.2)
\]

\[
x(t) = R(i(t_-), x(t_-), u(t), \mu), \quad (2.3)
\]

\[
y(t) = O(i(t), x(t), u(t), \mu), \quad (2.4)
\]

where \(x(t) \in \mathbb{R}^n\) is the continuous state at time \(t \in \mathbb{R}\); \(i(t) \in \{1, \ldots, N\}\) is the discrete state at time \(t\); \(F_i(t)\) is the vector-valued smooth function specified by \(i(t)\); \(u(t) \in \mathbb{R}^m\) is the external input; \(\mu \in \mathbb{R}^l\) is the system (bifurcation) parameters; \(G\) is a map of discrete-state transitions from \(i(t_-)\) to \(i(t)\) with \(i(t_-) \equiv \lim_{\tau \to t-0} i(\tau)\); \(R\) is a reset map of continuous states accompanying a discrete-state transition; \(y(t) \in \mathbb{R}^k\) is the output; and \(O\) is the output function.

If \(F_i(t), G, R\) and \(O\) in equations (2.1)–(2.4) do not depend on external input \(u(t)\), then the hybrid system is autonomous; otherwise, it is non-autonomous. An important class of autonomous hybrid dynamical systems is a piecewise smooth hybrid system (di Bernardo et al. 2008; di Bernardo & Hogan 2010), defined as follows (figure 1):

\[
\frac{dx}{dt} = F_i(x, \mu) \quad \text{for} \quad x \in S_i \quad (2.5)
\]

and

\[
x \mapsto R_{ji}(x, \mu) \quad \text{if} \quad x \in \Sigma_{ji} \equiv \overline{S_j} \cap \overline{S_i}, \quad (2.6)
\]

where \(F_i\) is a smooth vector field specified by \(i\). Each region \(S_i \subset \mathbb{R}^n\) has a non-empty interior. \(R_{ji}\) is a reset map on the intersection \(\Sigma_{ji}\). A typical example of the reset map is the discontinuous change in velocity \(v\) of a bouncing ball on impact from \(v\) to \(-rv\) with a restitution coefficient \(r\) \((0 \leq r \leq 1)\). The degree of smoothness on a discontinuous (switching) boundary \(\Sigma_{ji}\) is defined as zero if there is a jump of the system state \(x\) itself like this bouncing ball (see di Bernardo et al. (2008) and di Bernardo & Hogan (2010) in this issue for the definition of the degree of smoothness).
Figure 1. Schematic of a piecewise smooth hybrid system where each arrow shows a discrete transition accompanied by a reset map of the continuous state.

When the reset map is the identity map $R_{ji}(x) = x$, the hybrid system (2.5) and (2.6) is called 'a piecewise smooth flow' or 'a piecewise smooth ordinary differential equation (ODE)', defined as follows:

$$\frac{dx}{dt} = F_i(x, \mu) \quad \text{for} \quad x \in S_i. \quad (2.7)$$

Examples of a one-dimensional piecewise smooth ODE with the degrees of smoothness 1 and 2 at the origin are, respectively, given as follows:

$$\frac{dx}{dt} = -\text{sgn}(x) \quad (2.8)$$

and

$$\frac{dx}{dt} = |x|, \quad (2.9)$$

where $\text{sgn}(x) = 1$ for $x \geq 0$, and $\text{sgn}(x) = -1$ otherwise.

If each $F_i$ is affine, then equation (2.7) is simplified into a continuous-time piecewise affine system as follows:

$$\frac{dx}{dt} = A_i x + b_i \quad \text{for} \quad x \in S_i, \quad (2.10)$$

where $A_i \in \mathbb{R}^{n \times n}$ and $b_i \in \mathbb{R}^n$. 

Phil. Trans. R. Soc. A (2010)
The discrete-time version of the continuous-time piecewise smooth system (2.7) is widely used in discrete-time/sampled-data control, which is represented by a piecewise smooth map, or a discrete-time piecewise smooth system as follows (di Bernardo et al. 2008):

\[ x(t + 1) = F_i(x(t), \mu) \quad \text{for} \ x(t) \in S_i, \]  

(2.11)

where \( t = 0, 1, 2, \ldots \). Moreover, if each mapping \( F_i \) is affine, then equation (2.11) is simplified into a piecewise affine map, or a discrete-time piecewise affine system as follows:

\[ x(t + 1) = A_i x(t) + b_i \quad \text{for} \ x(t) \in S_i. \]  

(2.12)

Although equation (2.12) looks quite simple, its behaviour can be very complicated even for \( n = 1 \). An example of such complex behaviour in simple hybrid dynamical systems will be introduced in §4.

### 3. Dynamical systems theory and control systems theory

In this section, we explain a short history of the branching between dynamical systems theory and control systems theory and the importance of their combined study.

Newton’s formulation of the equations for laws of force and motion as well as of differential and integral calculus, followed by the great contributions of Jules Henri Poincaré and other pioneers, led to the establishment of dynamical systems theory, which is the basis of mathematical modelling today. The Industrial Revolution triggered by James Watt’s steam engines, on the other hand, posed a nuisance problem for the stability of governors. James Clark Maxwell mathematically solved this problem and created the field of control systems theory. Although dynamical systems theory and control systems theory treat similar dynamical problems, they saw almost independent developments during the twentieth century, except for some excellent work such as L. S. Pontryagin’s maximum principle (Pontryagin et al. 1962) and R. E. Kalman’s analysis on random behaviour in nonlinear sampled-data control systems (Kalman 1956); Kalman showed that a simple one-dimensional piecewise affine map (2.12) as a model of a nonlinear sampled-data feedback control system is equivalent to a typical chaotic map, now termed the tent map.

These independent developments of dynamical systems theory and control systems theory seem to have been caused by their different characteristics. First of all, while there are no control inputs in celestial mechanics, which is the origin of dynamical systems theory, control systems theory makes complete use of control inputs. Although chaotic dynamics is immanent even in the classical three-body problem of the celestial mechanics, control systems theory is primarily focused on the realization of stable linear dynamics rather than unstable nonlinear dynamics like chaos. Thus, dynamical systems theory and control systems theory are typically characterized by possibly unstable nonlinear dynamics without control inputs and stable linear dynamics with control inputs, respectively.
Since dynamical systems theory and control systems theory have seen considerable advancements in complementary directions, their combination can lead to a powerful methodology. The following are just a few examples of important research subjects (Aihara 2010):

— stabilization and bifurcation control of limit cycles and strange attractors in nonlinear dynamical systems; a pioneering work is the OGY control (Ott et al. 1990);
— construction of mathematical models directly from observed data according to embedding theorems (Takens 1984; Sauer et al. 1991; Stark 1999), estimation of parameter values in obtained models by system identification and data assimilation and application of such models to model-based prediction and model predictive control;
— a combination of bifurcation theory on stability regions of attractors in parameter space and robust-control theory on stability with respect to variation in nominal models and noise; and
— control of mathematical models described by hybrid partial differential equations, delay-differential equations and other complex dynamical systems.

In this Theme Issue, the recent progress of research on hybrid dynamical systems theory and that on hybrid control systems theory, especially discontinuity-induced bifurcations of piecewise smooth dynamical systems and stability analysis and controller synthesis for hybrid dynamical systems, are reviewed by di Bernardo & Hogan (2010) and Heemels et al. (2010), respectively. Since hybrid dynamical systems are ubiquitous and involve very rich nonlinear phenomena, these developments are quite important in terms of applications as well as theory.

4. Complex behaviour in a simple neuron model and its variants

To demonstrate the applications of hybrid dynamical systems to mathematical modelling of biological and medical systems, we introduce here a simple hybrid neuron model that shows complicated behaviour in spite of its simplicity.

Neurons are fundamental elements of the brain. Information in the brain is believed to be transmitted by spikes, or action potentials, which are generated by neurons. Since the genesis of action potentials is a discontinuous event that is triggered at the threshold, the process has been modelled by hybrid dynamical systems.

Caianiello’s neuronic equation, which is a generalized version of the first neuron model for artificial neural networks proposed by McCulloch & Pitts (1943), is given as follows (Caianiello 1961):

$$y_i(t + 1) = H \left[ \sum_{j=1}^{N} \sum_{d=0}^{t} w_{ij}^{(d)} y_j(t-d) - \theta \right],$$  \hspace{1cm} (4.1)

where, for the $i$th constituent neuron of a neural network, $y_i(t + 1)$ is the output with alternative discrete values of 0 (resting) and 1 (firing); $t$ is a discrete time step ($t = 0, 1, 2, \ldots$); $N$ is the number of constituent neurons and $H$ is the
Heaviside output function where $H(x) = 1$ for $x \geq 0$ and $H(x) = 0$ otherwise. $w_{ij}^{(d)}$ with $i \neq j$ represents the post-synaptic effect of a spike from the $j$th neuron after $d$ time-unit delay, and $w_{ii}^{(d)}$ represents the memory effect such as refractoriness on the $i$th neuron that is caused by the firing of the $i$th neuron itself before $d$ time units. $\theta$ is the threshold for firing.

Nagumo & Sato (1972) analysed the responses of a neuron to a single input line by considering the accumulation of refractory effects owing to a sequence of past firing. The refractory effects are assumed to exponentially decay with time and be linearly superimposed. This property is described by the term $\alpha \sum_{d=0}^{t} k^d y(t - d)$, where $\alpha$ is a scaling factor; $k$ is the decay factor with $0 \leq k \leq 1$; and $y(t)$ is the output of this neuron at time $t$. The refractory effect at time $t$ owing to the past firing $d$ time units ago is given by $\alpha k^d y(t - d)$. This formulation corresponds to setting $w_{ii}^{(d)} = -\alpha k^d$ in Caianiello’s neuronic equation (4.1). Thus, Nagumo & Sato (1972) studied neuronal responses with the refractoriness to steady stimulation by the following equation:

$$y(t + 1) = H \left[ A - \alpha \sum_{d=0}^{t} k^d y(t - d) - \theta \right], \quad (4.2)$$

where $A$ is the constant strength of the input.

By defining the internal state $x(t + 1)$ by $x(t + 1) = A - \alpha \sum_{d=0}^{t} k^d y(t - d) - \theta$, the dynamics of equation (4.2) is transformed to

$$x(t + 1) = F(x(t)) = kx(t) - \alpha H[x(t)] + a, \quad (4.3)$$

where $a = (1 - k)(A - \theta)$ is the bias including both the threshold and the constant input strength, and output $y(t)$ is obtained by $y(t) = H[x(t)]$ with the Heaviside function $H$. Equation (4.3) can be rewritten as follows:

$$x(t + 1) = kx(t) - \alpha + a, \quad \text{if} \quad x(t) \geq 0 \quad (4.4)$$

and

$$x(t + 1) = kx(t) + a, \quad \text{if} \quad x(t) < 0. \quad (4.5)$$

Equations (4.4) and (4.5) are a typical example of a one-dimensional piecewise affine map or a discrete-time piecewise affine system (see equation (2.12) and the review article by Heemels et al. (2010) in this issue).

Figure 2 shows examples of periodic responses of the Nagumo–Sato model. It is shown that almost all the responses of the Nagumo–Sato model are periodic (Nagumo & Sato 1972).

Let us define the average firing rate $\rho$ and the Lyapunov exponent $\lambda$ for the Nagumo–Sato model as follows:

$$\rho = \lim_{n \to \infty} \frac{1}{n} \sum_{t=0}^{n-1} y(t) \quad (4.6)$$

and

$$\lambda = \lim_{n \to \infty} \frac{1}{n} \sum_{t=0}^{n-1} \ln \left| \frac{d F(x(t))}{dx(t)} \right|. \quad (4.7)$$
An example of the bifurcation structure of the Nagumo–Sato model with increasing the value of $a$ is shown in figure 3. When the Lyapunov exponent $\lambda$ is negative, the response of the neuron is stably periodic. As illustrated in figures 2 and 3c, the Nagumo–Sato model has only periodic attractors for almost all parameter values. Figure 3b illustrates that the global property of the average firing rates forms a complete devil’s staircase (Jensen et al. 1983; Bak 1986). The complete devil’s staircase is a non-constant but continuous and monotonously non-decreasing singular function, which has an infinite number of steps corresponding to all rational numbers in $[0,1]$, and has the zero derivative almost everywhere. It should also be noted that the discontinuity of the Nagumo–Sato model owing to the Heaviside function produces chaotic solutions only on a self-similar Cantor set of parameter values with zero Lebesgue measure (Nagumo & Sato 1972; Tsuda 1981; Hata 1982, 1998).

Figure 4 shows the corresponding periodic responses of the membrane potential in a squid giant axon that is in the resting state and stimulated by periodic pulses with a constant amplitude. The model of equations (4.4) and (4.5) and its variants (Aihara et al. 1990) reproduce these responses of squid giant axons well, including even chaotic responses (Aihara & Matsumoto 1986; Matsumoto et al. 1987; Mees et al. 1992; Aihara 2002; Suzuki & Aihara 2008).

Next, we show that this complex dynamics of the Nagumo–Sato model also arises from a simple hybrid control system. Let us consider a one-dimensional continuous-time piecewise affine system that switches the following two linear systems:

\[
\frac{dx}{dt} = -\frac{1}{\tau} (x - s_1), \quad \text{if } x \geq h \quad (\text{system 1})
\]

(4.8)

and

\[
\frac{dx}{dt} = -\frac{1}{\tau} (x - s_0), \quad \text{if } x < h \quad (\text{system 0}),
\]

(4.9)
Figure 3. Response characteristics of (a) the bifurcation diagram, (b) the average firing rate $\rho$, and (c) the Lyapunov exponent $\lambda$ in the Nagumo–Sato model where $k = 0.85$ and $\alpha = 1$.

Figure 4. (a) 1/3-periodic and (b) 2/3-periodic responses of the membrane potential in a squid giant axon that is in the resting state and stimulated by periodic pulses with a pulse width of 0.5 ms and a pulse interval of 5.0 ms; pulse amplitude $A = (a) 7.6 \mu$A (1.297 times the threshold current) and (b) 18.4 $\mu$A (3.14 times the threshold current); upper, the stimulation; lower, the response of the membrane potential.
where \( x \in \mathbb{R} \) denotes the continuous state of the system to be controlled, \( \tau \) is a time constant and \( s_1 \) and \( s_0 \) are stable equilibriums of the two systems, where \( s_1 < s_0 \). Given a preset value \( h \) between \( s_1 \) and \( s_0 \), we consider sampled-data on–off control of the system. Assuming that the value of \( x \) is sampled only at uniform intervals of 1 unit time, the system dynamics can be described by a piecewise affine map or a discrete-time piecewise affine system as follows:

\[
x(t+1) = \begin{cases} 
  kx(t) + (1-k)s_1, & \text{if } x(t) \geq h, \\
  kx(t) + (1-k)s_0, & \text{if } x(t) < h,
\end{cases}
\]

(4.10)

where \( k = \exp(-1/\tau) \). The dynamics of this system is equivalent to that of the Nagumo–Sato model in equations (4.4) and (4.5). Since systems 1 and 0 correspond to the firing and resting states in the Nagumo–Sato model, respectively, the average firing rate \( \rho \) can be regarded as the rate at which system 1 is chosen. Furthermore, the bias parameter \( a \) in the Nagumo–Sato model corresponds to the preset value \( h \) in this switching system by the relations \( a = (1-k)(s_0 - h) \) and \( a = (1-k)(s_0 - s_1) \). Therefore, the devil’s staircase in figure 3b can also be regarded as a graph of the rate of system 1 as a function of the preset value \( h \). In this control system, it is natural to consider hysteresis, as in familiar on–off control systems such as thermostats. With such hysteresis, the system dynamics is equivalent to that of the Nagumo–Sato model with a positive self-recurrent connection.

Similarly, a rotation on a circle, which can be obtained as the limit case of \( k \to 1 \) in the Nagumo–Sato model, also arises in a simple hybrid control system. Now, we consider a continuous-time piecewise affine system composed of the following two systems:

\[
\frac{dx}{dt} = r - R, \quad \text{if } x \geq h \quad \text{(system 1)}
\]

(4.11)

and

\[
\frac{dx}{dt} = r, \quad \text{if } x < h \quad \text{(system 0)},
\]

(4.12)

where both \( r \) and \( R \) are constants satisfying \( 0 < r < R \). Considering sampled-data on–off control in a similar way, we obtain the following piecewise affine map:

\[
x(t+1) = \begin{cases} 
  x(t) + r - R, & \text{if } x(t) \geq h, \\
  x(t) + r, & \text{if } x(t) < h.
\end{cases}
\]

(4.13)

This is equivalent to a rotation map or the limit case of \( k \to 1 \) in the Nagumo–Sato model. The sequence of 1 (system 1) or 0 (system 0) chosen at each time step is called a rotation sequence. The ratio of 1s in the sequence converges to \( r/R \) as the length of the sequence tends to infinity. In the field of machine learning, this system appears as a one-dimensional case of a herding system that deterministically yields a sequence of data samples satisfying some predefined statistics (Welling 2009). In the field of signal processing, this system with a time-varying \( r \) is called a \( \Sigma-\Delta \) modulator, which is an AD converter widely used in the industry because of its stability and noise-shaping property (Inose et al. 1962; Gray 1987). Error-diffusion dithering, which is an algorithm commonly used in digital halftoning of images, is also a variant of the \( \Sigma-\Delta \) modulator (Adler et al. 2003). Introducing hysteresis in this control system produces more
complex dynamics (Suzuki & Aihara 2005), which can be reduced to a double rotation as follows (Suzuki et al. 2005):

\[
x(t + 1) = \begin{cases} 
  \{x(t) + \alpha\}, & \text{if } x \geq h, \\
  \{x(t) + \beta\}, & \text{if } x < h,
\end{cases}
\]  

(4.14)

where \( x \in [0,1) \), \( \{ \cdot \} \) is defined by \( \{ x \} = x - \lfloor x \rfloor \) and \( (\alpha, \beta, h) \in [0,1) \times [0,1) \times [0,1) \).

Double rotations form a subclass of interval translation mappings (Boshernitzan & Kornfeld 1995), or, more generally, piecewise isometries (Goetz 2000). Piecewise isometries arise in various models in engineering and exhibit complex dynamics because of their discontinuities (Deane 2006). For example, the complex behaviour of partial-discharge phenomena in the field of high-voltage engineering is explained by a simple model that can be reduced to a double rotation (Suzuki et al. 2004).

The two abovementioned switching control systems can be regarded as the simplest examples of piecewise affine maps. Owing to their simplicity, these hybrid systems and their variants can be found in various research fields (Suzuki & Aihara 2008). In this sense, these hybrid dynamical systems are ubiquitous in mathematical models of different systems in the real world. It should be stressed here that even the simple piecewise affine maps used in sampled-data control can generate considerably complicated behaviour. It should also be noted, on the other hand, that continuous-time hybrid systems produce different types of challenging behaviour such as sliding modes and the Zeno behaviour (di Bernardo et al. 2008; Lunze & Lamnabhi-Lagarrigue 2009).

5. Hybrid dynamical systems in biology and medicine

Here, we briefly introduce the contents of the nine articles on applications of hybrid dynamical systems to biology and medicine in this Theme Issue as a ‘road map’.

These articles are mainly categorized into three topics: (i) biochemical and gene regulatory networks, (ii) cancer and its treatment, and (iii) neurons, neural systems and neuromechanics.

The first topics of biochemical and gene regulatory networks are discussed in three articles by Perkins et al. (2010), Imura et al. (2010) and Singh & Hespanha (2010).

Gene expression is switched on and off by proteins called transcription factors. Perkins et al. (2010) analyse robust dynamics of gene regulatory networks by hybrid models with logical functions representing genes and real variables describing controlling transcription factor protein molecules. This formulation successfully relates the underlying logical structure of gene regulatory networks to robust dynamics. They also apply their modelling to interesting data on the cell cycle in yeast, which are provided by John Tyson.

Imura et al. (2010) discuss piecewise affine systems approaches to modelling, analysing and synthesizing biological networks such as gene regulatory networks. They further examine the control of a quorum-sensing system in the pathogen 

\textit{Pseudomonas aeruginosa}, which is a major opportunistic human pathogen living in various environments. Since the copy numbers of proteins and mRNAs

\textit{Phil. Trans. R. Soc. A} (2010)
are usually low in a cell, they are subject to large stochastic fluctuations. A convenient framework of stochastic hybrid systems modelling for such biochemical processes is provided by Singh & Hespanha (2010). In addition, they demonstrate recently developed techniques for fast computations of statistical moments of the population count and review different examples of systems that can be modelled by stochastic hybrid systems (see also Chen et al. (2010) for related topics).

The second topic of cancer and its treatment are considered in three articles by Osborne et al. (2010), Tanaka et al. (2010) and Suzuki et al. (2010)

Osborne et al. (2010) focus on cancer dynamics of a colorectal crypt in colorectal cancer. Since cancer originates from a mutation initially creating a single abnormal cell, there exists a problem of small numbers of cells, which is different from that of small copy numbers of proteins and mRNAs discussed in Singh & Hespanha (2010). Owing to the small numbers of cells, they study cell-based ‘hybrid’ models in which cells are considered as discrete, with dynamical changes such as division, proliferation and movement encoded either through rules or as the result of dynamics occurring on other scales. They also compare and contrast two different cell-based models with a homogenized continuum model.

When the number of cancer cells increases with the tumour growth, another hybrid model can be used by describing cells as discrete in some parts and as a continuum in others (see also Anderson & Quaranta 2008). Hybrid dynamical systems are usually described with continuous and discrete-state variables. Representations of time and space, however, are also quite important; the above modelling brings hybrid properties of space into sharp relief. The hybrid properties of time have also been discussed in previous studies (Ye et al. 1998; Chen & Aihara 2001; Dai 2008; Michel et al. 2008). Thus, the mathematical modelling of hybrid dynamical systems should also be considered from the perspective of time and space; that is, the continuous and discrete structure of time and space.

Tanaka et al. (2010) and Suzuki et al. (2010) focus on the hybrid systems modelling of prostate cancer and its treatment. Since prostate tumour growth is sensitive to the male sexual hormone or androgen, at least in its early state, hormone therapy is quite effective. In particular, intermittent hormone therapy (Bruchovsky et al. 1990; Akakura et al. 1993), which switches the treatment of hormone therapy on and off based on the observation of the serum prostate-specific antigen (PSA) level, has been recently studied using mathematical models (Guo et al. 2008; Ideta et al. 2008; Shimada & Aihara 2008; Tanaka et al. 2008; Tao et al. 2009; Hirata et al. 2010). These mathematical models of intermittent hormone therapy are hybrid dynamical systems with peculiar bifurcation structures. Tanaka et al. (2008), Guo et al. (2008) and Tao et al. (2009) extended the models to hybrid partial differential equations.

Tanaka et al. (2010) further extend the deterministic hybrid models to the stochastic one. Suzuki et al. (2010) propose optimal control of intermittent hormone therapy on the basis of piecewise affine systems modelling. Both these articles involve analysis of real clinical time-series data of PSA to validate their models. These studies on hybrid systems modelling of intermittent hormone therapy for prostate cancer are now giving rise to an entirely new type of personalized therapy for prostate cancer. The methodology is based on a tailor-made mathematical model (Hirata et al. 2010) obtained only from the PSA
time-series data of each patient, which can be easily monitored by means of the usual blood test. This type of mathematical model-based personalized therapy can be generalized to other diseases if some efficient biomarkers and drugs are available.

The third set of topics of neurons, neural systems and neuromechanics is taken up by Izhikevich (2010), Cao & Ibarz (2010) and Proctor et al. (2010).

The firing of neurons can be described as discontinuity with a threshold as discussed in §4. The simplest continuous-time model of such firing is the following leaky integrate-and-fire model:

$$C \frac{dv}{dt} = g(E - v) + I, \quad \text{if } v \geq v_{\text{threshold}}, \quad \text{then } v \leftarrow c, \quad (5.1)$$

where $v$ is the membrane potential of the neuron; $C$ is the membrane capacitance; $g$ is the leak conductance; $E$ is the reversal potential; $I$ is the input current; $v_{\text{threshold}}$ is the threshold potential for firing; and $c$ is the reset potential. Izhikevich (2010) presents his famous hybrid systems models of neurons that combine a continuous spike-generation mechanism and a discontinuous after-spike reset of state variables. The models can excellently reproduce the response properties in different kinds of real neurons (see also Izhikevich 2007). He also introduces related hardware implementation and the hybrid numerical method.

Cao & Ibarz (2010) and Proctor et al. (2010) propose models of neural and neuromechanical systems. Neurons in the brain are connected by chemical and electrical synapses. While the latter is represented as continuous and smooth interactions, the former provides a connection scheme with switching dynamics depending on spikes generated by neuronal firing. Cao & Ibarz (2010) examine discrete-time hybrid neural networks with not only chemical but also electrical synapses. As an example of a hybrid systems approach to higher brain functions, Sato et al. (2007) formulated Bayesian inference with continuous and binary variables, the latter of which represents whether or not visual and auditory stimuli originate from the same source. Such a hybrid formulation will probably be effective in studying the binding problem in the brain (Fujii et al. 1996).

Locomotion also offers interesting examples of hybrid dynamical systems with piecewise holonomic constraints (e.g. owing to intermittent foot contacts in walking and running). Rather than using conventional spiking neuron models, Proctor et al. (2010) develop a phase-reduced model of the neural pattern generator, subject to sensory spikes, and emitting spikes to control a hybrid model of muscles and leg contacts. In spite of many simplifications, the model captures key features of the overall system dynamics quite well, including gait characteristics and responses to impulsive perturbations.

6. Discussion and conclusions

Two review articles in this Theme Issue survey the recent developments in hybrid dynamical systems theory from the viewpoints of both dynamical systems theory and control systems theory, while nine articles introduce contemporary applications of hybrid dynamical systems in biology and medicine.

Phil. Trans. R. Soc. A (2010)
The topics of hybrid dynamical systems in these articles are also related to a variety of applications in other fields. In particular, there are many interesting studies on such applications in engineering systems (Blazejczyk-Okolewska et al. 1999; Wiercigroch & de Kraker 2000; Savkin & Evans 2002; Awrejcewicz & Lamarque 2003; Tse 2003; Zhusubaliyev & Mosekilde 2003; Sobhani-Tehrani & Khorasani 2009; Leonov et al. 2010). A famous example of hybrid dynamical systems in electronic circuits is Chua’s double-scroll system, which is described as follows (Chua et al. 1986; Awrejcewicz & Lamarque 2003):

\[
\frac{dx}{dt} = \alpha(y - h(x)), \quad (6.1)
\]
\[
\frac{dy}{dt} = x - y + z \quad (6.2)
\]
\[
\frac{dz}{dt} = -\beta y, \quad (6.3)
\]

where \(x, y,\) and \(z\) are continuous state variables, \(\alpha\) and \(\beta\) are positive parameters and \(h(x)\) is a piecewise smooth function of \(x\). The cover image of this Theme Issue is composed of some strange attractors obtained from equations (6.1)–(6.3) with \(h(x)\) that is more complicated than the original.

Figure 5 shows another chaotic circuit with hysteresis, some attractors of which are shown in figure 6. The dynamics of this circuit is represented as follows (Hamada et al. 2007):

\[
\frac{d}{dt} \begin{pmatrix} C_1 v_1 \\ C_2 v_2 \end{pmatrix} = \begin{pmatrix} g_{m1} - g_{m1} & -g_{m1} + g_{m1} \\ g_{m2} + g_{m2} - g_{m2} & 0 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \end{pmatrix} - \begin{pmatrix} H_1(v_1 - v_2) \\ H_2(v_1) \end{pmatrix}, \quad (6.4)
\]

where \(C_1, C_2\) and \(g_m\)’s are positive parameters. \(H_1\) and \(H_2\) are the following hysteresis elements:

\[
H_i(v) = \begin{cases} 
-I_i + I_i, & \text{if } v_i \leq E_i, \\
I_i + I_i, & \text{if } v_i \geq -E_i,
\end{cases} \quad i = 1, 2, \quad (6.5)
\]

where \(I_i, I_i\) and \(E_i\) are positive parameters.
These analogue circuits of hybrid dynamical systems enable new nonlinear techniques of electronics and possible components of future computers. Computers are indispensable for today’s highly informationalized society. The term ‘computers’ is now synonymous with digital computers, but their implication was very different only 60–70 years ago when analogue computers, now obsolete, were competing with digital computers for the leading position in research and development of electronic computers. Digital computers finally superseded analogue computers because of their firm mathematical basis of the Turing machine, universal programmability, higher computational accuracy and greater memory capacity. Further, their continual remarkable developments are being made, mainly supported by the astonishing evolution of electronic digital hardware.

At present, however, the hardware-based evolution of digital computers, as has taken place in the past, is gradually slowing down. First, the conventional hardware technology seems to be approaching its fundamental limit. Second, the power of the digital computation is fundamentally limited not only by the computational complexity such as the non-deterministic polynomial (NP)-complete and NP-hard problems, but also by the undecidability problem inherent
in the Turing machines. Third, uncertain and imprecise data in the real world are a hindrance to the development of usable intelligent systems based on digital computers with strict logical computation.

To cope with these problems of present digital computers, the possibilities of creating new types of computing methods and machines have been explored. Examples include (i) soft computing with fuzzy logic, neurocomputing, genetic algorithm, evolutionary computing and probabilistic reasoning (Zadeh 1996; Liu & Miyamoto 2000), (ii) exotic computing machines (Casti 1997) such as cellular automata (Wolfram 2002), quantum computers (Deutsch 1985; Bernstein & Vazirani 1997) and the Blum–Shub–Smale model (Blum et al. 1997), (iii) Moore’s generalized shift (Moore 1990, 1991), and continuous-time analogue computation (Moore 1996), (iv) Siegelmann’s analogue neural networks (Siegelmann 1999) and our chaotic neural networks (Aihara et al. 1990; Aihara 2002), and (v) a new generation of analogue computing with neural, fuzzy and chaos computing models (Aihara 1993, 2002; Aihara & Katayama 1995). Some of these new computing models and all the others can be accurately implemented and simulated at least approximately by digital computers, respectively. It should be noted, however, that digital computation of even simple chaotic dynamics, for example, suffers from fundamental difficulties related to the computation of unstable dynamics accompanied by complexity of real numbers (Aihara 2002).

While hybrid computers with digital and analogue systems were intensively studied much earlier in the 1960s and 1970s (Bekey & Karplus 1968), the possibility of creating a new generation of hybrid computing has recently been explored using analogue computation with chaotic neuro-dynamics and digital computation through algorithm (Aihara 2003; Horio & Aihara 2008); see also Branicky (1995) and Bournez & Cosnard (1996) for the computational power of hybrid systems.

As the brain is an extremely complex hybrid system with hierarchical analogue and digital properties (Aihara 1993) such as digital on/off gating and an analogue opening time of ionic channels in nerve membranes, analogue dynamics for the generation of spikes (Hodgkin & Huxley 1952), digital propagation of spikes along axons according to the all-or-nothing law, analogue post-synaptic potentials and analogue neural coding with ‘digital’ spikes such as firing rates, interspike intervals and spike timing, we might learn much from the brain for possible hybrid computing systems.

In conclusion, it is desirable to combine dynamical systems theory and control systems theory for comprehensive mathematical modelling of nonlinear dynamics in complex hybrid systems in general and its transdisciplinary applications in science and technology, including further applications in biology and medicine as well as hybrid computing systems (Horio & Aihara 2008). This Theme Issue is the first step towards fulfilling such a purpose (Aihara 2010).

I would like to acknowledge all the authors of the articles involved in this Theme Issue for their immensely beneficial contributions, Suzanne Abbott for her kind collaboration, and M. di Bernardo, M. Heemels, Y. Hirata, Y. Horio, J. Imura and A. Mees for their valuable comments. I also thank Keiko Kimoto and Munehisa Sekikawa for creating the beautiful cover image of this issue. This research is partially supported by the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST). Certain portions of §1 in this article are used from Aihara (2003).
References


Aihara, K. 2003 ERATO. Aihara Complexity Modelling Project of JST (Japan Science and Technology Agency). See http://www.sat.t.u-tokyo.ac.jp/jst/.


Introduction


Introduction


