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Dissipative structures and biological rhythms

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Sustained oscillations abound in biological systems. They occur at all levels of biological organization over a wide range of periods, from a fraction of a second to years, and with a variety of underlying mechanisms. They control major physiological functions, and their dysfunction is associated with a variety of physiological disorders. The goal of this review is (i) to give an overview of the main rhythms observed at the cellular and supracellular levels, (ii) to briefly describe how the study of biological rhythms unfolded in the course of time, in parallel with studies on chemical oscillations, (iii) to present the major roles of biological rhythms in the control of physiological functions, and (iv) the pathologies associated with the alteration, disappearance, or spurious occurrence of biological rhythms. Two tables present the main examples of cellular and supracellular rhythms ordered according to their period, and their role in physiology and pathophysiology. Among the rhythms discussed are neural and cardiac rhythms, metabolic oscillations such as those occurring in glycolysis in yeast, intracellular Ca^{++} oscillations, cyclic AMP oscillations in *Dictyostelium* amoebae, the segmentation clock that controls somitogenesis, pulsatile hormone secretion, circadian rhythms which occur in all eukaryotes and some bacteria with a period close to 24 h, the oscillatory dynamics of the enzymatic network driving the cell cycle, and oscillations in transcription factors such as NF-KB and tumor suppressors such as p53. Ilya Prigogine's concept of dissipative structures applies to temporal oscillations and allows us to unify within a common framework the various rhythms observed at different levels of biological organization, regardless of their period and underlying mechanism. *Published by AIP Publishing.* [http://dx.doi.org/10.1063/1.4990783]

Five decades have passed since Ilya Prigogine introduced the concept of dissipative structures to unify various modes of self-organization in time and space which arise beyond a critical point of instability in open systems far from equilibrium. This review aims at showing how widespread dissipative structures are in biological systems, with emphasis on biological rhythms, which correspond to temporal organization. Illustrations of spatial and spatiotemporal dissipative structures pertain mostly to developmental biology. Numerous examples of bistability and other modes of coexistence between multiple attractors have been invoked in a variety of biological contexts, mainly for cell fate determination in the course of differentiation. Strinkingly abundant are cellular and supracellular biological rhythms, which can be viewed as temporal dissipative structures. After a brief description of the unfolding of studies on biological rhythms at the cellular and molecular levels, the focus turns to the key roles played by these rhythms in physiology. Dysfunction of many biological rhythms is associated with a wide range of physiological disorders. Prigogine's concept of dissipative structures exquisitely applies to temporal oscillations and allows us to unify within a common theoretical framework the various rhythms observed at different levels of biological organization, regardless of their period and underlying mechanism.

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I. FROM CHEMICAL OSCILLATIONS TO BIOLOGICAL RHYTHMS

Time and self-organization always occupied a central position in Ilya Prigogine's work devoted to the Thermodynamics of irreversible processes (Prigogine, 1967). It is perhaps not surprising that the two research topics combined when he started his investigations on the origin of order in chemical systems by studying the conditions in which sustained oscillations occur in time (Prigogine and Balescu, 1956). Prigogine and Balescu used the Lotka-Volterra model to show that periodic behavior becomes possible once the system is governed by nonlinear kinetics and operates at a sufficient distance from thermodynamic equilibrium.

While oscillations represent a phenomenon of self-organization in time, in the following decade, building on the seminal work of Turing (1952), Prigogine extended his analysis to processes of self-organization in space. To stress the fact that such processes of self-organization occur in open systems and require the dissipation of energy, he proposed to refer to them as dissipative structures, so as to distinguish them from equlibrium structures. The conditions for the existence of dissipative structures are particularly well established in living systems, which are open and operate far from thermodynamic equilibrium. Moreover, living systems are generally, if not always, governed by nonlinear evolution equations. Besides cooperativity at the level of allosteric enzymes, receptors, transcription factor binding to gene promoters, and ion channels, a major source of nonlinearity is

provided by the multiple modes of regulation, mediated by feedback processes, which developed at the cellular and supracellular levels in the course of evolution to optimize the operation and survival capability of biological systems. That Prigogine attributed a key importance to self-organization in biological systems is well reflected by the title "*Structure, dissipation and life*" that he gave to one of his first contributions (Prigogine, 1969) where he introduced the concept of dissipative structures.

Dissipative structures form far from equilibrium when a steady state becomes unstable at a critical bifurcation point. Sustained oscillations in time represent temporal dissipative structures—the occurrence of oscillatory behavior is indeed one of the clearest manifestations of nonequilibrium instability. Besides oscillations and stationary spatial structures, often referred to as *Turing patterns*, spatiotemporal structures in the form of propagating waves may also develop. Moreover, because of the nonlinearity of the evolution equations, multiple attractors may sometimes coexist, which situation corresponds to the appearance of a form of functional order. Thus, bistability is associated with the coexistence of two stable steady states, each of which can be reached from different sets of initial conditions, which define their basins of attraction. The phenomenon is referred to as tristability when three stable steady states coexist. Other modes of coexistence may involve an even larger number of attractors, or one steady state and one periodic attractor (*hard excitation*), and two or three periodic attractors (*birhythmicity* or *trirhythmicity*). Besides periodic oscillatory behavior, aperiodic oscillations in the form of chaos corresponding to the evolution to a *strange attractor* may also be observed, which may sometimes coexist with a periodic attractor or a stable steady state.

Given the rich repertoire of dissipative structures and the ubiquitousness of nonlinearity at the cellular and supracellular levels, it seems befitting to examine in this article celebrating the memory of Ilya Prigogine how relevant is the concept of dissipative structure for understanding the dynamical bases of self-organization in biological systems, and to see how and where it has been applied to illuminate the dynamics of life processes in the five decades since it was initially proposed. This brief review will focus primarily on biological rhythms, which can be viewed as temporal dissipative structures, and which play key roles at all levels of biological organization.

II. SPATIAL AND SPATIOTEMPORAL DISSIPATIVE STRUCTURES

In the five decades since the initial intial studies of Prigogine and coworkers on dissipative structures, numerous applications to biological processes have been proposed. Thus, aggregation of social amoebae in response to a chemotactic factor emitted by the cells has been viewed as an instability of the homogeneous steady-state distribution of cells, leading to the formation of a spatial structure (Keller and Segel, 1970 and Nanjundiah, 1973). Spatial dissipative structures have been invoked in the origin of patterns in developing embryos, particularly in the emergence of body segments associated with the formation of band patterns of gene expression in *Drosophila*. However, extensive genetic and modeling studies have shown that the mechanism for the formation of the spatial pattern is based on gradients in maternal proteins acting on a cascade of regulatory genes forming a segmentation network, which involves gap, pair-rule, and segment-polarity genes (see Jaeger *et al.*, 2012, for a recent review). Spatial dissipative structures involving instability with respect to diffusion, i.e., Turing patterns, have been implicated in the formation of pigment stripe or dot patterns in fish skin (Nakamasu *et al.*, 2009; Watanabe and Kondo, 2015; and Bullara and De Decker, 2015), or scale patterns in lizards (Manukyan *et al.*, 2017). Another example of Turing pattern is provided by the formation of fingers in the course of development (Sheth *et al.*, 2012; Raspopovic *et al.*, 2014; Marcon *et al.*, 2016). At a more macroscopic level, arid vegetation patterns known as "tiger bush" have been shown mathematically to belong to the class of spatial dissipative structures (Lefever and Lejeune, 1997 and Bordeu *et al.*, 2016). Additional examples of biological pattern formation are discussed in the books of Meinhardt (1982), Murray (1989), and Camazine *et al.* (2003). The latter includes examples of patterns arising from interactions in insect societies.

Possibly more common are the examples of spatiotemporal dissipative structures that combine self-organization in time and space, as observed in a variety of biological phenomena ranging from the propagation of nerve impulses, the propagation of electrical excitation in the heart both in physiological and pathogical conditions (which lead, in the latter case, to cardiac fibrillation), intracellular and intercellular Ca^{++} waves, and the spiral and concentric patterns of slime aggregation associated with waves of cyclic AMP in *Dictyostelium discoideum* amoebae (Lauzeral *et al.*, 1997). Spatial patterns may also originate from the combination of a clock and a moving wavefront involving the transition between two stable steady states (Cooke and Zeeman, 1976). One of the best examples of such a spatial pattern originating from a combination of oscillations, diffusion, and bistability is provided by the periodic formation of somites in vertebrate embryos (Cooke and Zeeman, 1976 and Pourquié, 2003).

III. MULTIPLE ATTRACTORS: BISTABILITY

Multiple steady states abound in biological systems, although they have been observed in theoretical models more often than in experiments, probably because it is more straightforward to obtain evidence of bistability by constructing bifurcation diagrams when analyzing a model mathematically. To demonstrate the coexistence of multiple stable attractors experimentally, one way is to observe the existence of hysteresis: by successively increasing and decreasing the value of a control parameter, in a certain range of this parameter the system is then capable of evolving to either one of two stable steady states, depending on the initial conditions. An alternative procedure is to induce the transition to another steady state by means of a suprathreshold change in the level of one of the variables of the system. However, it is cumbersome to use any of these two

methods systematically for demonstrating bistability, because if a system operates in a stable steady state, one is not incited, without specific reasons, to test whether another stable steady state may exist in the same set of experimental conditions. The situation is different for oscillatory behavior, which is observed, when it occurs, without the need for probing the response of the system to a change in a control parameter or to suprathreshold perturbations.

Observing bistability in theoretical models is relatively easier than in experiments, because it is the custom to construct bifurcation diagrams showing how the steady state(s) of a system changes as a function of a control parameter. In the case of bistability, the bifurcation diagram takes the form of an S-shaped curve, which, in a certain range bounded by two critical values of the control parameter, admits three steady states, two of which are stable, whereas the intermediate steady state is unstable. While the latter state can readily be determined numerically in a model, it is not amenable to experimental observation.

Theoretical examples of bistability have accumulated at an increasing pace in the last few decades, in a wide variety of biological contexts ranging from enzyme to gene regulation, from prebiotic evolution to developmental biology, and from immunology to pathophysiology, including diabetes as well as prion and Alzheimer diseases. One of the first mentions of bistability in a biological context was given by Delbrück (1949) nearly 70 years ago, who alluded in a discussion remark in a volume of conference proceedings to the role of multiple steady states in genetic networks controlling cell differentiation. Cell differentiation is the field *par excellence* in which the occurrence of multiple attractors has been invoked as a mechanism underlying cell fate specification. As conjectured by René Thomas (Thomas and d'Ari, 1990 and Thomas and Kaufman, 2001), multistationarity requires the presence of positive circuits in the underlying regulatory network. Such positive circuits are extremely common in genetic regulatory networks and involve direct positive feedback or mutual inhibition. Cell fate specification often involves a succession of binary choices between two stable steady states, due to mutual inhibition of two transcription factors, as discussed in detail by Zhou and Huang (2011). Theoretical models suggest that cell fate specification may sometimes involve more than two stable steady states (Tian *et al.*, 2013; Bessonnard *et al.*, 2014; and De Mot *et al.* 2016).

Mutual inhibition as a source of bistability is a recurrent regulatory motif in biological systems. It illustrates how the same regulatory structure produces similar dynamical phenomena at markedly different levels of biological organization. Thus, two mutually inhibiting repressors have been shown experimentally to produce bistability in a synthetic genetic network referred to as *toggle switch* (Gardner *et al.*, 2000). As indicated above, theoretical models suggest that cell fate specification is often based on the mutual inhibition of two transcription factors, which type of regulation has been repeatedly documented experimentally. Mutual inhibition producing bistability is also encountered in ecology, where the competition of two animal populations for the same resource can either lead to coexistence of the two populations or to elimination of one or the other population, depending on the initial conditions. Such a problem has long been examined mathematically, and represents, since the contributions by Volterra, a classical problem in theoretical ecology (Pianka, 1976). Between genetic networks and interacting animal populations, mutual inhibition has been invoked as a source of bistability at many other levels of biological organization. Thus two putative, mutually inhibiting neural circuits have been implicated theoretically in the mechanism underlying REM-nonREM transitions during sleep (Lu *et al.*, 2006) as well as transitions between phases of mania and depression in bipolar disorders (Goldbeter, 2011).

In the cell cycle (see Sec. IV), positive feedback in the regulation of cyclin-dependent kinases (Cdks) has been shown theoretically and experimentally to lead to bistable transitions (Sha *et al.*, 2003 and Pomerening *et al.*, 2003). The Cdk network that governs the progression through the successive phases of the cell cycle thus potentially contains multiple sources of bistability, which contribute to render the transition from one to the next phase of the cycle irreversible (Novak *et al.*, 2007).

The coexistence of multiple attractors is not limited to the case where the system can evolve toward either one of two stable steady states, separated by an unstable state. Multiple attractors may also involve the coexistence between a stable steady state and a stable oscillatory regime (hard excitation), or the coexistence between two stable oscillatory regimes, periodic or chaotic (birhythmicity) (Decroly and Goldbeter, 1982). The multiplicity can also involve more than two attractors: cases of tristability or trirhythmicity have thus been described, primarily in theoretical models. The coexistence between two or more stable rhythms has been reported in a chemical system (Alamgir and Epstein, 1983) but remains to be observed experimentally in a biological context.

IV. THE UNFOLDING OF STUDIES ON BIOLOGICAL RHYTHMS

The interest of Ilya Prigogine for oscillatory phenomena first materialized in an article published in 1956 with Radu Balescu on the thermodynamic analysis of oscillations in a chemical system obeying Lotka-Volterra kinetic equations. These equations were proposed by Lotka (1920) in a theoretical study devoted to chemical oscillations, and by Volterra (1926) in a model proposed for predator-prey oscillations in an ecological system. In the following decade, Prigogine's interests moved to spatial and temporal dissipative structures. With René Lefever he focused on a model chemical reaction system displaying the capability of self-organization in space (Prigogine and Lefever, 1968), in the form of stable patterns, referred to as dissipative structures. This model, which Tyson (1973) later referred to as the *Brusselator*, was also shown to display sustained oscillations (Lefever *et al.*, 1967). The Brusselator became a most useful model for studying various modes of nonequilibrtium self-organization (Nicolis and Prigogine, 1977).

Oscillations in chemical systems were known since the XIXth century, particularly in electrochemistry. The interest in periodic chemical reactions began to surge at the end of the 1960s (see Tyson *et al.*, 2008, for a review of developments in the study of oscillations and bistability). A graph published by Burger and Bujdoso (1985) shows the number of articles published yearly about chemical oscillations from 1910 to 1985. The steep surge that occurred at the end of the 1960s was due to a number of reasons. First, the Belousov-Zhabotinsky reaction provided a prototypic example of a periodic chemical recation that could be readily reproduced and studied in the laboratory; its complex kinetic mechanism was fully brought to light in the following decade (Noyes *et al.*, 1972). Second, the discovery of glycolytic oscillations in yeast cells and extracts around 1965 (Chance *et al.*, 1964; for other early references see Hess and Boiteux, 1971; Goldbeter and Caplan, 1976; and Goldbeter, 1996) provided another example of oscillatory behavior, this time in a biochemical rather than purely chemical system. Third, the thermodynamic and nonlinear kinetic framework developed at the same time by Prigogine and coworkers significantly contributed to put chemical and biochemical oscillations into focus, and to transform them into an exciting, new topic of research. In subsequent years, the field of chemical oscillations developed rapidly, and new families of oscillatory chemical reactions were identified. Nevertheless, over the years, it became increasingly clear that biological systems represent the domain of largest abundance of periodic behavior.

Rhythmic phenomena occur at all levels of biological organization, with periods that cover more than ten orders of magnitude (see Table I). Most of these rhythms occur at the cellular level (for more detailed accounts and additional references see Goldbeter, 1996, 2002, 2007; Maroto and Monk, 2008; and Goldbeter *et al.*, 2012). New examples of biological rhythms continue to be uncovered, while artificial oscillatory networks based on gene regulation are being synthetized. The main reason why rhythmic behavior is so frequently encountered in biological systems is related to the existence of feedback processes, which control the dynamics of organisms at the cellular and supracellular levels. Oscillations are clearly a systemic property, associated with regulatory interactions between the constitutive elements of biological systems, which may range from metabolic and genetic networks to cell and animal populations. Rhythmic phenomena therefore represent a prototypic field of research in Systems Biology. In line with the development of Systems Biology, rhythms have been approached, from the very beginning, both from an experimental and a modeling perspective (Winfree, 1981; Glass and Mackey, 1988; and Goldbeter, 1996, 2010).

In hindsight, it was for long apparent that rhythmic phenomena abound in biological systems. This is due to the fact that many of these rhythms are readily perceptible and belong to our daily human experience. Rhythms in the electrical activity of cardiac muscle and neurons are known experimentally for more than one hundred years, but the development of studies on their ionic mechanism dates back to the 1950s. As recalled in Sec. V below, the main

TABLE I. Main biological rhythms at the cellular or supracellular levels. The rhythms are presented in the order of increasing period.

Biological rhythm	Period
Cellular rhythms	
Neural rhythms	0.01 s–10 s
Individual neurons	
Bursting neurons (e.g., R15 in *Aplysia*)	
Neural networks	
Central pattern generators	
Muscle cells	0.01 s to s
Cardiac cells	1 s
Oscillatory peroxidase reaction	30 s
Min protein oscillations in *E. coli* bacteria	100 s
Glycolytic oscillations	
Individual yeast cells	10–30 s
Yeast cell extracts	5–8 min
Cardiac cells	1.5 min
Skeletal muscle extracts	20 min
Pancreatic β-cells	5–10 min
Ca^{++} oscillations and waves	s to min
Periodic reversal of direction in swarming *Myxococcus* bacteria (the *Frizzilator*)	2–50 min
Nucleocytoplasmic oscillations of transcription factors in yeast	
Msn2	min
Crz1	min
Oscillations and waves of cyclic AMP in *Dictyostelium* amoebae	5-10 min
Segmentation clock in somitogenesis	
Zebrafish	30 min
Chicken	90 min
Mouse	2 h
NF-KB transcription factor oscillations	100 min
P53 tumor suppressor oscillations	3–4 h
Pulsatile hormone secretion	
Insulin	10 min
GnRH, LH, FSH	1 h
Growth hormone	3–5 h
Yeast respiratory oscillations	5 h
Synthetic oscillators	
Repressilator (first example)	3–4 h
Others	Tunable period (h)
Cyclin-dependent kinase (Cdk) oscillations driving the cell cycle	
Amphibian embryos (first 12 cycles)	30 min
Yeast	8 h
Mammalian cells	15 h–30 h
Circadian oscillations	
Cyanobacteria	Close to 21 h
Neurospora	Close to 22 h
Plants	Close to 24 h
Drosophila	Close to 24 h
Mammals	Close to 24 h
Supracellular rhythms	
Ovarian cycle	28 days (in human female)
Predator-prey oscillations	
Microorganisms	hours
Animal populations	years
Epidemies	
Influenza	1 year

TABLE I. (*Continued*.)

Biological rhythm	Period
Measles	2 or more years
Annual rhythms	1 year
Flowering	
Animal reproduction	
Migrations	
Periodic cicadas	13 or 17 years

physiological functions, e.g., generation of the heartbeat and the respiratory rhythm, are rhythmic. The brain is a rhythmic organ, producing oscillations over a wide range of frequencies (Buzsaki, 2006). The electrocardiogram (ECG) and the electroencephalogram (EEG) are used for nearly hundred years to probe the periodic activity of the heart and of the brain. Much as excitability, rhythmic electrical behavior is an intrinsic property of neurons. This led the French neurophysiologist Fessard to publish a book in 1936 entitled "Propriétés rythmiques de la matière vivante" ("*Rhythmic properties of living matter*") which, in spite of its general title, was restricted to neuronal oscillations (Fessard, 1936). However, the title of this book points to a reality that extends well beyond the oscillations of the membrane potential in nerves cells. Muscle cells share with neurons the capability of displaying oscillatory behavior (Takaki *et al*., 2010).

The periodic behavior of individual neurons generally takes the form of trains of action potentials occurring either spontaneously or as a result of external stimulation. More complex oscillatory behavior was later observed in individual neurons of molluscs such as *Aplysia* (Arvanitaki and Cardot, 1941). In particular, the neuron R15 of *Aplysia* provided the prototype of bursting oscillatory behavior, in which silent phases separate active phases during which a train of rapid action potentials occur (Adams and Benson, 1985). Such bursting oscillatory behavior also characterizes the electrical activity of insulin-secreting pancreatic β-cells, and was studied in detail in mathematical models for neuronal activity (Rinzel, 1987) and for a multiply regulated biochemical system (Decroly and Goldbeter, 1987).

Oscillations can also arise from the interactions between cells coupled within neural networks. Some major physiological functions, such as respiration, feeding, and the coordination of body movements, originate from the periodic operation of neural networks, named "central pattern generators" (Grillner and Wallén, 1985). Oscillations can also be produced in individual neurons embedded within circuits in which oscillations originate from cellular interactions (Selverston and Moulins, 1985 and Marder *et al*., 2015).

The experimental observation of neuronal oscillations preceded the elucidation by Hodgkin and Huxley of the ionic bases of the action potential in electrically excitable cells. It is noteworthy that the series of papers that they published in 1952 included a mathematical analysis (Hodgkin and Huxley, 1952) that is still being used today for modeling the dynamics of neurons and other electrically excitable cells. Similar equations were later used to describe the ionic mechanisms that underlie the periodic generation of action potentials in cardiac tissue, and to develop large-scale computational models with the goal of building a "virtual heart" (Noble, 2010).

If we look at the progress of research on biological rhythms, it is convenient to consider its unfolding decade by decade, by listing major developments. Besides the important class of cellular rhythms associated with the periodic generation of action potentials in electrically excitable cells such as neurons and cardiac myocytes, a variety of rhythms of nonelectrical nature have been observed, mostly at the cellular level. As mentioned above, an important example of cellular rhythm discovered in the 1960s was that of glycolytic oscillations which occur in yeast cells and extracts (Hess and Boiteux, 1971), and were later observed in pancreatic β cells (Chou *et al*., 1992). These oscillations originate from the regulation of key glycolytic enzymes such as phosphofructokinase (PFK) (Hess and Boiteux, 1971; Goldbeter and Caplan, 1976; Goldbeter, 1996; and Madsen *et al*., 2005). Glycolytic oscillations continue to be studied, both experimentally and theoretically, in individual yeast cells (Gustavsson *et al*., 2012) and yeast cell populations (Weber *et al*., 2012). Models for glycolytic oscillations evolved in two directions: initially, minimal models centered on the regulation of PFK, namely, its activation by a reaction product (Sel'kov, 1968), and took into account its allosteric properties (Goldbeter and Lefever, 1972; Goldbeter and Nicolis, 1976; and Goldbeter, 1996); subsequently, more comprehensive models for the glycolytic pathway were proposed (Hynne *et al*., 2001 and Du Preez *et al*., 2012). Recent studies further corroborate the conclusion that glycolytic oscillations originate from the self-activation of the allosteric PFK enzyme (Gustavsson *et al*., 2014), as considered in early minimal models for the phenomenon.

Glycolytic oscillations also provided an example in yeast extracts of entrainment and subharmonic entrainment of a sustained oscillator by periodic forcing (Boiteux *et al*., 1975), and of control of oscillations by quorum sensing in a yeast cell population (De Monte *et al*., 2007). Another example of oscillatory enzyme reaction was provided by peroxidase (Nakamura *et al*., 1969), which later served as a case study of chaotic behavior in a biochemical system (Larter *et al*., 1993).

After the observation of glycolytic oscillations, the next decade saw the discovery (Gerisch and Wick, 1975) of oscillations of cyclic AMP (cAMP), which underlie the wavelike aggregation of *Dictyostelium* amoebae after starvation (Gerisch, 1968 and Alcantara and Monk, 1974). These oscillations are due to the regulation of cAMP synthesis, which, in this species of slime mold, is subjected to mixed positive and negative feedback of extracellular as well as intracellular nature (Martiel and Goldbeter, 1987 and Maeda *et al*., 2004). The pulsatile formation of multicellular aggregates through a chemotactic response to pulses of cyclic AMP emitted by cells behaving as aggregation centres represents one of the most remarkable examples of spatiotemporal organization and pulsatile signaling in intercellular communication (Alcantara and Monk, 1974; Lauzeral *et al*., 1997; and Goldbeter, 2006a).

From mid-1980s to the 1990s, oscillations of intracellular Ca^{++}, and later intracellular and intercellular Ca^{++} waves were observed in a variety of cell types, either spontaneously or upon stimulation by hormones or neurotransmitters (Berridge and Galione, 1988; Berridge, 2009; Dupont, 2014; and Dupont *et al*., 2010, 2016). By their ubiquity and the importance of their physiological functions, oscillations in cytosolic Ca^{++} represent one of the most important examples of cellular rhythm. These oscillations result from the complex interplay of activatory and inhibitory processes that regulate both Ca^{++} release from the endoplasmic reticulum (ER) and Ca^{++} entry from the extracellular medium. Release from the intracellular stores is brought about by an increase in the concentration of inositol 1,4,5-trisphosphate (IP_3), the messenger synthesized in response to hormonal stimulation. IP_3 receptors are located in the membrane of the ER and release Ca^{++} upon ligand binding. As this receptor is activated and inhibited by Ca^{++} itself, oscillations can develop (Berridge, 2009 and Dupont *et al*., 2010). As in the case of glycolytic oscillations, which are observed in yeast extracts in a range bounded by two critical values of the substrate injection rate, Ca^{++} oscillations occur in a range bounded by two critical values of the external stimulation (Rooney *et al*., 1989). A minimal model for Ca^{++} oscillations based on Ca^{++}-induced Ca^{++} release (Goldbeter *et al*., 1990) accounts for this observation.

Much as cAMP signals and Ca^{++} oscillations, most hormones were found to be encoded in terms of the frequency of their pulsatile secretion (Leng, 1988), as exemplified by the case of gonadropin-releasing hormone (GnRH) released by the hypothalamus as a 5-min pulse every hour (Karsch, 1987), and by insulin which is secreted by pancreatic β-cells with a periodicity of about 10 min (Lang *et al*., 1979).

Biological rhythms which persist in constant environmental conditions with a period of about 24 h have been investigated for centuries—the first written description of such rhythms and of their "endogenous" nature was given in 1729 by d'Ortous de Mairan, who observed that the periodic movements of the leaves of a plant persist in continuous darkness. These oscillations, now known as *circadian rhythms*, allow nearly all eukaryotic and some prokaryotic organisms to adapt to the natural periodicity of the light-dark cycle, which characterizes our terrestrial environment. Circadian clocks remain the prototype of biological clocks (Bünning, 1964), even though they represent but one, admittedly important class of biological rhythms, as made clear in Table I. Circadian rhythms –the term was coined at the turn of the 1960s—entered the field of genetic studies through the seminal work of Konopka and Benzer (1971) in *Drosophila*; their molecular bases have largely been clarified since the 1990s (Hardin *et al*., 1990). Several recent reviews have summarized the rich flow of information collected during the last two decades in experiments on the regulatory network that controls circadian rhythms in *Drosophila*, *Neurospora*, plants, cyanobacteria, and mammals (Dunlap *et al*., 2007; Ukai and Ueda, 2010; Dibner *et al*., 2010; Zhang and Kay, 2010; Baker *et al*., 2012; and Mohawk *et al*., 2012). This network involves a dozen genes, which may differ according to the organism. The mechanism of circadian rhythmicity is based on transcriptional regulation involving the interplay of positive and negative feedback loops. Models based on transcriptional regulation have been proposed for circadian rhythms in various organisms (Goldbeter, 1995; Leloup *et al*., 1999; Leloup and Goldbeter, 2003; Forger and Peskin, 2003; Mirsky *et al*., 2009; Pokhilko *et al*., 2012; and De Caluwé *et al*., 2016). The models show that rhythmic behavior occurs in precise conditions, beyond critical values of control parameters. In the concentration space, these sustained oscillations correspond to the evolution to a limit cycle.

Light controls circadian rhythms in ways that differ according to the organism. Thus, in *Drosophila*, the rate of degradation of TIM, a clock protein, increases in the light phase. In mammals, light enhances the expression of *Per* genes, which play a key role in the indirect negative feedback that lies at the core of the circadian oscillatory mechanism. Phase shifts induced by light pulses as well as the entrainment of the oscillations by light-dark cycles can be modeled through modulation of light-controlled parameters. Such simulations help to understand the nature of phase response curves, to identify the conditions in which entrainment occurs, and to clarify the dynamics of resychronization after jet lags. The circadian pacemaker in mammals is located in the suprachiasmatic nuclei (SCN) within the hypothalamus, but circadian clocks operate in a number of peripheral tissues (Dibner *et al*., 2010 and Mohawk *et al*., 2012). Circadian oscillations already occur in isolated SCN neurons; the intercellular coupling that results in their synchronization has been modeled theoretically (Gonze *et al*., 2005 and To *et al*., 2007).

In some organisms, e.g., cyanobacteria, circadian rhythms may also originate from a non-transcriptional regulatory mechanism. Thus, in *Synechococcus*, as shown *in vitro* (Nakajima *et al*., 2005), the mechanism responsible for circadian oscillations relies on a cascade of phosphorylations of the KaiC protein. The Kai oscillator is nevertheless coupled to a mechanism based on transcriptional regulation (Kitayama *et al*., 2008).

In view of its major role in development and in the pathological consequences of its deregulation, cell division is a key process in cell biology. Experimental progress in the mechanism driving the cell division cycle was first made on early cell cycles in amphibian embryos, which are driven by the periodic activation of a *mitosis promoting factor*, MPF, which was shown to be a complex between a cyclin protein and a kinase, cdc2 (Murray and Hunt, 1993). These early cell cycles occur with a period of 30 min, and are driven by cyclin synthesis (Murray and Kirschner, 1989). The kinase cdc2 is activated through dephosphorylation by phosphatase Cdc25 once the cyclin level exceeds a threshold. The periodicity of MPF activation relies on a negative feedback loop, as Cdc2 activation leads to cyclin degradation (Félix *et al*., 1990). Early models for the embryonic cell cycles showed that sustained oscillations indeed occur as a result of such negative autoregulation in a phosphorylation-dephosphorylation cascade (Goldbeter, 1991, 1996). Positive feedback also occurs in this system, because the kinase Cdc2 activates phosphatase Cdc25 and inhibits its inhibitory kinase Wee1. Models incorporating

such positive feedback loops were proposed by Novak and Tyson (1993) for the embryonic cell cycles. They stressed the role of positive feedback in allowing for the coexistence between two distinct, stable levels of activity of Cdc2. Experimental studies based on theoretical models demonstrated in frog egg extracts the occurrence of bistability and of the associated phenomenon of hysteresis in which Cdc2 periodically undergoes abrupt transitions between a low and a high state of activity, driven by variations in the level of cyclin due to alternating phases of accumulation and Cdc2-induced degradation (Sha *et al.*, 2003 and Pomerening *et al.*, 2003).

Yeast was the other organism of choice for which major advances were made on characterizing the biochemical mechanisms governing the transitions between the successive phases of the cell cycle (Murray and Hunt, 1993 and Nurse, 2002). The dynamics of the yeast cell cycle in terms of cyclin-dependent kinase (Cdk) regulation through kinases and phosphatases continues to be the topic of numerous experimental studies (Domingo-Sananes *et al.*, 2011). A comprehensive computational model for the ordering of cell cycle events in budding yeast under control of cell mass accounts for the phenotype of a large number of cell cycle mutants (Chen *et al.*, 2004).

In mammals, a network of cyclin-dependent kinases controls the transitions between the successive phases G1, S (DNA replication), G2, and M (mitosis) of the cell cycle. The Cdks are controlled through phosphorylation-dephosphorylation, through cyclin synthesis and degradation, and also through association with protein inhibitors such as p21 (Morgan, 2006). A detailed model for the Cdk network shows that in the presence of sufficient amounts of growth factor the Cdk network is capable of temporal self-organization in the form of sustained oscillations (Gérard and Goldbeter, 2009). The transition from cell quiescence to cell proliferation can be viewed as the switch from a stable to an unstable steady state of the Cdk network. Beyond this critical point of instability, instead of reaching a stable steady level in the course of time, the various cyclin/Cdk complexes undergo sustained oscillations, which correspond to the ordered, sequential activation of the various cyclin/Cdk complexes that control the successive phases of the cell cycle.

Less complex models that retain the core regulatory structure of the Cdk network show a similar capability of temporal self-organization in the form of sustained oscillations (Gérard and Goldbeter, 2011). In view of its complexity, it is not surprising that the Cdk network contains several circuits that are capable, each on its own, of producing oscillations (Gérard and Goldbeter, 2009, 2010). Because of their tight coupling through regulatory interactions, these oscillators are synchronized so that one peak of cyclin B/Cdk1 generally occurs per peak of cyclin E/Cdk2 and cyclin A/Cdk2 over one cell cycle. If the coupling between the oscillatory circuits weakens, however, internal synchronization may break down, leading, for example, to oscillations in Cdk2 but not in Cdk1. Such a situation corresponds to endoreplication in which multiple rounds of DNA replication occur in the absence of mitosis (Gérard and Goldbeter, 2009).

A flurry of advances on cellular rhythms have been made in the last two decades with the rapid development of Systems Biology. One of the most remarkable developments pertains to the segmentation clock that controls the periodic formation of somites in vertebrate embryos. This clock controls the oscillatory expression of specific genes involved in somitogenesis with a period of the order of 30 min in zebrafish to 1.5–2 h in mouse and chicken embryos (Giudicelli *et al.*, 2007; Pourquié, 2011; and Oates *et al.*, 2012). Because the clock results in the formation of a spatial pattern, this oscillatory system provides an exquisite example of spatiotemporal organization at the supracellular level (Pourquié, 2003 and Oates *et al.*, 2012). The existence of a clock was predicted by the analysis of a theoretical model (Cooke and Zeeman, 1976) and subsequently confirmed experimentally (Palmeirim *et al.*, 1997). The Notch, FGF and Wnt signaling pathways are involved in the mechanism of the segmentation clock (Aulehla and Pourquié, 2008). A model for this cellular rhythm based on the cross-talk between these three signaling pathways has been proposed (Goldbeter and Pourquié, 2008) and later extended and incorporated into a model for the segmentation process (Hester *et al.*, 2011). Bistability responsible for sharp developmental transitions was part of the initial "clock and wavefront" model proposed by Cooke and Zeeman (1976). The mutual inhibition of the transcription factors FGF and retinoic acid, which participate in the control of somitogenesis, could be involved in generating bistable transitions (Goldbeter *et al.*, 2007).

Two other significant findings made since the year 2000 are the oscillatory synthesis of the tumor suppressor p53 and the transcription factor NF-κB with a periodicity of a few hours. Since the crossed regulatory interactions between p53 and its inhibitor Mdm2 were predicted to give rise to oscillations (Lev Bar-Or *et al.*, 2000), numerous experimental (Geva-Zatorsky *et al.*, 2006) and theoretical (Ciliberto *et al.*, 2005 and Ouattara *et al.*, 2010) studies have been devoted to the mechanism of p53 oscillations and to their role in the response to DNA damage. The dynamics of p53 pulses has been determined in single cells as well as in cell populations. As in other instances, e.g., GnRH pulsatile secretion (Pohl *et al.*, 1983), where the dynamic pattern of the signal rather than its sole level carries information, the temporal profile of p53 has been shown to govern the cellular response (Zhang *et al.*, 2009).

A similar situation is encountered for NF-κB, which plays a key role in inflammation. Since the discovery of NF-κB oscillations of a period of the order of 100 min, several mathematical models have been proposed for the phenomenon (Nelson *et al.*, 2004 and Krishna *et al.*, 2006). The mechanism of oscillations in NF-κB triggered by TNFα stimulation involves the regulatory interactions with its inhibitor I-κB: when NF-κB is released from I-κB in the cytosol, it is translocated into the nucleus. The regulation by NF-κB of I-κB transcription represents a delayed negative feedback loop that drives oscillations in NF-κB translocation. Here again the temporal profile of NF-κB controls the cellular response: the timing and specificity of NF-κB-dependent transcription

are governed by the frequency of TNFα pulses (Ashall *et al.*, 2009).

On a shorter time scale, oscillations in nucleocytoplasmic shuttling of transcription factors have been observed in yeast. Thus, in yeast cells subjected to stress, the factor Msn2 shows coordinated movements in and out of the nucleus with a period of the order of 6 min (Jacquet *et al.*, 2003 and Bodvard *et al.*, 2011). Experimental evidence supported by a modeling approach indicates that the phenomenon originates from periodic activation of Msn2 by PKA, driven by cAMP oscillations (Garmendia-Torres *et al.*, 2007) that are reminiscent of those observed due to a similar mechanism in *Dictyostelium* cells (Maeda *et al.*, 2004). Periodic nuclear translocation, playing a role in gene regulation, has been observed in yeast for another transcription factor, Crz1 (Cai *et al.*, 2008).

Other cellular oscillations have been characterized. Thus, oscillations in the expression of genes of the Notch signaling pathway, such as *Hes1*, have been observed in cell cultures. These oscillations, related to those observed in the segmentation clock, are based on negative feedback on transcription (Hirata *et al.*, 2002) and have been modeled in terms of a negative feedback loop incorporating a delay (Momiji and Monk, 2008), as proposed for the segmentation clock in zebrafish (Lewis, 2003). In *Escherichia coli*, rapid pole to pole oscillations of the Min proteins with a period of about 100 s ensure that division is restricted to the middle of the cell (Raskin and de Boer, 1999). In *Myxococcus* bacteria, a biochemical oscillator involving the Frz protein (and modeled as the *Frizzilator*) governs the spontaneous reversal of direction in swarming with a period of minutes (Igoshin *et al.*, 2004).

In 2000, the construction of the first synthetic oscillator signaled the entry into the new era of artificial cellular rhythms. This oscillator, known as the *Repressilator*, expressed in *E. coli*, consists of a set of three repressors coupled cyclically (Elowitz and Leibler, 2000). This regulatory structure is reminiscent of recurrent cyclic inhibition, which was shown to produce sustained oscillations in neural networks (Kling and Szekely, 1968). This first success was followed by the development of a variety of synthetic oscillatory networks expressed in bacteria or mammalian cells, mostly based on genetic regulation. These synthetic networks display oscillations with tunable frequencies covering a wide range, from tens of minutes up to 24 h (Stricker *et al.*, 2008 and Tigges *et al.*, 2009). An artificial clock was shown to rescue circadian rhythmicity in clock-defective mice (D'Alessandro *et al.*, 2015). Coupling the oscillatory network to a mechanism of quorum sensing allows the synchronization of oscillations in bacterial populations, which can take the form of propagating waves (Mondragón-Palomino *et al.*, 2011).

All biological rhythms mentioned so far originate at the cellular level or in networks of interconnected cells, as is the case for neural networks that operate as central pattern generators. Rhythms do also occur at the supracellular level, with longer periods. Among the few examples listed at the bottom of Table I are the ovarian cycle, which controls ovulation, predator-prey oscillations in ecological systems—which were likely the first among biological rhythms to be described mathematically (Volterra, 1926)—, epidemies which recur with periods of one up to a few years (Grenfell *et al.*, 2001), annual rhythms which allow many insect, plant, and animal species to adapt to the other natural periodicity of the environment, and finally some long-period rhythms such as those which characterize the emergence of somes species of cicadas every 13 or 17 years. Many annual rhythms appear to be driven by internal clocks entrained by seasonal periodicities, whereas the ovarian cycle and the life cycle of periodic cicadas provide examples of cyclical processes which involve the passage through a discontinuity—degeneration of the corpus luteum in the case of the ovulatory cycle, and death of an organism marking the end of a life cycle. In contrast, most cellular rhythms listed in Table I belong to the class of continuous or quasi-discontinuous (relaxation) oscillations of the limit cycle type, which occur once a critical point of instability corresponding to a bifurcation is crossed in parameter space.

V. RHYTHMS IN PHYSIOLOGY AND PATHOPHYSIOLOGY

Biological rhythms govern many key functions in mammalian—including human—physiology. Some major examples are listed in the upper part of Table II. Many involve rhythms of electrical nature, which underlie the operation of repetitive machines responsible for the periodic contraction of the heart or the respiratory rhythm. Central pattern generators are neural networks that coordinate rhythmic body movements (Grillner and Wallén, 1985 and Selverston and Moulins, 1985). Neuronal oscillations further underlie sensory perception (Melloni *et al.*, 2007) and likely human consciousness (Llinás *et al.*, 1998).

Rhythms of electrical nature produced by interstitial Cajal cells are responsible for periodic intestinal contractions: these cells act as pacemakers in the gastrointestinal tract (Sanders *et al.*, 2006). Another set of physiological rhythms involve Ca^{++} oscillations in reproductive processes where they play roles at various levels, inducing egg development after fertilization (Nomikos *et al.*, 2013) and triggering uterine contractions at the onset of delivery (Wray, 2007).

The circadian clock located in the suprachiasmatic nuclei of the hypothalamus controls the sleep-wake cycle. Within sleep, the alternation of REM-non REM sleep phases is controlled by a neuronal oscillation of 90 min period (Hobson *et al.*, 1975 and Lu *et al.*, 2006). Besides sleep, the circadian clock controls other aspects of human physiology, such as metabolism (Eckel-Mahan and Sassone-Corsi, 2013) and the nutrition cycle, as well as the immune response and cell proliferation. Many hormones display circadian rhythmicity and thereby contribute to adapt our organism to the natural alternation of day and night. In addition, most hormones are encoded in pulses whose frequency determines their physiological efficiency. As stressed by Knobil (1981), the temporal pattern of hormones is as important, if not more, than their absolute level in the blood. The best example is provided by the pulsatile secretion of GnRH by the

TABLE II. Examples of rhythmic behavior in physiology (upper part) and pathophysiology (lower part). Pathologies result either from an alteration or absence of a rhythm occurring in physiological conditions, or from the appearance of rhythmic or chaotic behavior in a normally nonoscillating system.

Physiological rhythm
Neuronal oscillations in cognitive or sensory processes
Neuronal control of movements: central pattern generators
Periodic contraction of the heart
Respiratory rhythm
Periodic intestinal contractions (generated by interstitial Cajal cells)
90-min cycles of alternating REM-nonREM phases in sleep
Sleep-wake cycle (controlled by the circadian clock)
Nutrition cycle (controlled by the circadian clock)
Cell division
Hormonal rhythms and pulsatile hormone secretion (e.g., GnRH, growth hormone, insulin)
Ovulation
Fertilization-induced Ca^{++} oscillations trigger the onset of egg development
Uterine contractions (triggered by Ca^{++} oscillations)
Seasonal rhythms (flowering, animal reproduction, migrations)
Some physiological disorders associated with biological rhythms
Cardiac arrhythmias and fibrillation
Large-amplitude neuronal oscillations in epileptic seizures
Breathing pattern disorders (e.g., Cheyne-Stokes respiration)
Sleep disorders linked to the circadian clock (familial advanced or delayed sleep phase syndromes, jet lag, 12 h-phase shift of melatonin circadian rhythm in Smith-Magenis syndrome)
Scoliosis originating from alterations of the segmentation clock controlling somitogenesis
Morphogenetic defects associated with abnormal Ca^{++} oscillations (Noonan syndrome)
Deafness associated with impaired Ca^{++} wave propagation in cochlear cells
Premature puberty (premature onset of pulsatile GnRH secretion)
Female infertility due to lack of ovulation resulting from abnormal GnRH pulsatile secretion
Male infertility due to lack of sperm-induced Ca^{++} oscillations in fertilized egg
Premature birth (premature onset of uterine contractions triggered by Ca^{++} oscillations)
Intestinal disorders associated with alteration or lack of periodic contractions
Muscular tremor (e.g., in Parkinson's disease)
Periodic haematological diseases (chronic myolegenous leukemia, cyclic thrombocytopenia, cyclic neutropenia)
Bipolar disorders: spontaneous alternation of phases of mania and depression

hypothalamus: only when this hormone is released in the form of one pulse per hour can it induce the secretion of the hormones LH and FSH by the pituitary and thereby lead to ovulation (Pohl *et al.*, 1983).

Circadian rhythms have marked effects on the action of drugs. Thus, pharmacological dose-response curves depend on the time of the day at which they are established. That the action of drugs often varies according to the time of their administration stems from the fact that many enzyme activities display circadian variations. Circadian rhythms therefore possess important therapeutic implications, which have been explored, in particular, for the chronophamacology of anticancer drugs (Lévi and Schibler, 2007).

It is often when a physiological function goes awry that the role played by biological rhythms comes to light. In the lower part of Table II are listed pathologies which result either from an alteration or the absence of a rhythm occurring in physiological conditions, or from the appearance of rhythmic behavior in a normally nonoscillating system. All physiological rhythms can be perturbed and can thereby lead to physiological disorders characterized by syndromes or more severe pathologies. Numerous types of cardiac arrhythmias fill the pages of textbooks in cardiology; ventricular or atrial fibrillation represents the most prominent disorders of the heart rhythm. In regard to brain rhythms, diseases associated with altered oscillatory behavior are exemplified by epileptic seizures. On the other hand, the implication of abnormal brain oscillations has been invoked in schizophrenia (Uhlhaas and Singer, 2010). Alterations of the respiratory rhythm are also known, an example being the Cheyne-Stokes mode of breathing (Naughton, 1998).

Disorders linked to alterations of the circadian clock primarily pertain to the sleep-wake cycle (Richardson and Malin, 1996). Thus, the familial advanced sleep phase syndrome (FASPS) and the familial delayed sleep phase syndrome (FDSPS) denote conditions in which the onset of sleep is, respectively, advanced or delayed by several hours, while the duration of sleep remains normal. Remarkably, genetic studies in families have shown that FASPS and FADPS are due to mutations affecting the PER2 (Toh *et al.*, 2001) and CRY1 (Patke *et al.*, 2017) circadian clock genes, respectively. These mutations slightly modify the autonomous period of the circadian clock and thereby change its phase upon entrainment by the light-dark cycle. This in turn shifts the phase of the sleep-wake cycle, leading to its advance or delay by several hours. The phase of the circadian clock is modified in other disorders such as the Smith-Magenis syndrome (De Leersnyder, 2013). The absence of entrainment of the circadian clock by the light-dark cycle (Leloup and Goldbeter, 2008) leads to the relatively rare, non-24 h sleep-wake cycle syndrome, in which the clock freeruns with a drifting phase, even though the affected person is not blind (Richardson and Malin, 1996).

Another, well-known manifestation of the circadian clock is the jet lag associated with long-distance flights, although this transient disorder is by no means pathological. Theoretical studies (Leloup and Goldbeter, 2013) corroborated by experimental and other modeling observations (Kori *et al.*, 2017) nevertheless point to conditions in which recovery from jet lag could be significantly delayed or, conversely, accelerated.

In another context, it appears that a robust, unperturbed circadian clock provides protection against cancer. Experimental studies in mice have indeed shown that circadian clock mutations (Fu *et al.*, 2002) or perturbation of the clock by chronic jet lag (Filipski *et al.*, 2004) favor tumor development.

Alteration or the absence of hormone pulsatile release can have marked physiological consequences. A case in point is the absence of GnRH pulsatile release, which is associated with infertility. Implantation of a pump injecting GnRH at the physiological frequency of one pulse per hour

restores normal patterns of LH and FSH secretion and thereby ovulation (Leyendecker *et al*., 1980). The frequency encoding of pulsatile hormone secretion also applies to other hormones such as the growth hormone (GH), which is most efficient in inducing growth when applied in pulses at the physiological frequency (Hindmarsh *et al*., 1990). What is the basis for the enhanced efficacy of pulsatile versus constant hormone stimulation? Constant stimulation leads to receptor desensitization or down-regulation, which is avoided by pulsatile stimulation at the optimal frequency (Li and Goldbeter, 1989).

Another case of infertility, this time in male patients, has been associated with the absence of Ca^{++} oscillations triggered in the egg upon fertilization. This absence is due to a mutation of the sperm enzyme phospholipase C zeta (PLCζ) (Kashir *et al*., 2012), which is injected into the egg at fertilization and normally elicits the initial release of Ca^{++} from intracellular stores that triggers the onset of Ca^{++} oscillations (Nomikos *et al*., 2013). Other disorders involve Ca^{++} signaling. Thus, failure of intercellular Ca^{++} wave propagation in cochlear cells has been implicated in some cases of deafness (Beltramello *et al*., 2005). Conversely, a gain-of-function mutation of a phosphatase results in the spontaneous onset or increase in the frequency of Ca^{++} oscillations in fibroblasts and cardiac myocytes, and thereby alters the pattern of activation of the transcription factor NFAT. This disruption of Ca^{++} oscillatory control of NFAT has been associated with congenital heart defects in the Noonan syndrome, a human developmental disorder (Uhlén *et al*., 2006). Another developmental process that can be affected by perturbation of a cellular rhythm is somitogenesis, given that alterations in the segmentation clock may result in scoliosis (Pourquié, 2011).

Sometimes the physiological disorder arises from the spurious occurrence of oscillations in a physiological system that normally operates in a nonoscillatory state, or from the transition from periodic behavior to chaos. Mackey and Glass (1977) designate such pathological situations as dynamical diseases. Examples of dynamical diseases include a variety of hematopoietic disorders, such as chronic myolegenous leukemia, cyclic thrombocytopenia, and cyclic neutropenia. Such periodic hematological diseases have been modeled mathematically (Foley and Mackey, 2009). This analysis points to delays between different stages of cell maturation as a key factor in the onset of periodic or chaotic behavior.

Another disease involving the appearance of a rhythm that does not exist in physiological conditions is the cyclical alternation between phases of mania and depression. This manic-depressive illness, initially referred to as "folie circulaire" ("circular folly") by Falret (1854), and currently known as a manifestation of bipolar disorders (Soares and Young, 2007), has been modeled in terms of bistability and oscillations, based on regulatory interactions between putative neural circuits controlling the two poles of the disease (Goldbeter, 2011, 2013).

In the context of cell division, yet another example pertains to the transition between cell cycle arrest and cell proliferation. This transition can be viewed as a switch, beyond a critical point of instability, between a stable steady state and a state associated with self-sustained oscillations of the limit cycle type in the activity of the cyclin-dependent kinases that control the ordered progression along the successive phases of the cell cycle (Gérard and Goldbeter, 2009, 2014). Abnormal cell proliferation leading to cancer might originate from changes in some parameter values leading to the spurious transition between cell cycle arrest and cell proliferation (Gérard and Goldbeter, 2014, 2016).

VI. BIOLOGICAL RHYTHMS AS TEMPORAL DISSIPATIVE STRUCTURES

The interest of Ilya Prigogine for self-organization phenomena began with a study of thermodynamic conditions for the occurrence of oscillations in chemical systems (Prigogine and Balescu, 1956). Prigogine subsequently turned his attention to the conditions for self-organization in space, which leads to the establishment of stationary spatial patterns, as envisioned by Turing (1952) in the context of morphogenesis, or of spatiotemporal patterns in the form of propagating concentration waves. Nonlinearity of evolution equations and a critical distance from thermodynamic equilibrium were found to be required for the occurrence of dissipative structures beyond a critical point of instability in open chemical, physical, or biological systems (Prigogine, 1969). The coexistence of multiple steady states represents another common manifestation of nonlinearity in open systems operating far from equilibrium. The discovery of sustained oscillations and spatial chemical patterns in the Belousov-Zhabotinsky reaction lent support to such theoretical predictions, and provided some of the first examples of dissipative structures in chemistry. At the same time, around 1965, the discovery of glycolytic oscillations in yeast extracts corroborated the occurrence of dissipative structures in biological systems.

Some five decades since the initial work of Prigogine on dissipative structures, the present, special issue of *Chaos* provides a good opportunity to assess how his ideas on self-organization in time and space have resonated with developments in the field of self-organisation, more specifically in the life sciences. In Sec. II, we briefly considered how spatial dissipative structures, also known as Turing patterns, were used to account for the emergence of spatial patterns in developmental biology. Several examples were given, ranging from slime mold aggregation to skin patterns in fish, and finger formation. Spatiotemporal patterns in the form of concentric or spiral propagating waves are commonly observed, from the cellular to the tissue and organ levels, and to that of animal populations. Besides wavelike aggregation of *Dictyostelium* amoebae and spirals of electrical activity in the heart, a striking example is the segmentation clock that controls periodic somite formation in vertebrate embryos.

Numerous examples, mostly theoretical, but also experimental, have illustrated how widespread is the coexistence between multiple attractors in biological systems. As discussed in Sec. III, bistability, i.e., the coexistence between two stable steady states separated by an unstable state, has been repeatedly invoked in instances ranging from the control

of gene expression to enzyme regulation, and from interacting animal populations to the dynamics of the immune response. One major field where bistable transitions appear to be ubiquitous is that of cell fate determination in the course of development. Bistability, and even tristability likely lie at the very core of such developmental decisions, as a result of cross-regulatory interactions between transcription factors.

Oscillations represent a major field of application for temporal self-organization. Looking for applications in the life sciences, one can only be struck by the abundance of rhythms in biological systems. Rhythms occur at all levels of biological organization, from cellular to multicellular, and from tissues and organs to animal populations, over a wide range of periods and with markedly different mechanisms. The main part of this paper was devoted in Sec. IV to an overview of biological rhythms, and a discussion of how their study unfolded in the last five decades. The major biological rhythms were classified according to their period in Table I. In Sec. V, we saw that biological rhythms control all major physiological functions, while their dysfunction is associated with a wide range of physiological disorders. The major roles of biological rhythms in physiological and pathological conditions are summarized in Table II.

Since the impetus given by Ilya Prigogine to the study of oscillatory phenomena and other processes of self-organization in chemical and biochemical systems, a unified view of biological rhythms has emerged, in spite of the diversity in their period and underlying mechanism. In each case, oscillations denote the occurrence of an instability in a system operating far from equilibrium. Cells are open systems that exchange matter and energy with their environment. By doing so they generally reach a stable steady state. However, once the system operates sufficiently far from equilibrium and when its kinetics acquire a nonlinear nature, the steady state may become unstable (Nicolis and Prigogine, 1977). When the steady state becomes unstable, the system moves away from it and may either evolve to another, stable steady state (in the case of bistability) or it may undergo sustained oscillations around the unstable steady state. In the phase or concentration space, these sustained oscillations correspond to the evolution to a closed, limit cycle trajectory. Such evolution is conserved, regardless of the number of variables. Mathematical models for oscillatory dynamics generally contain a minimum number of variables, ideally two, which facilitates the analysis of limit cycle behavior in a two-variable phase plane. A similar evolution to a closed, limit cycle trajectory was nevertheless observed in a detailed model for the mammalian cell cycle containing 39 variables (Gérard and Goldbeter, 2009), or even more (Gérard and Goldbeter, 2012a), and in a skeleton version of this model containing only 5 variables (Gérard and Goldbeter, 2011).

Feedback processes and cooperativity are two main sources of nonlinearity that favor the occurrence of instabilities in biological systems. The cellular regulations that form the core of the oscillatory mechanism may take multiple forms, and sometimes several of these cooperate to give rise to the instability that paves the way for rhythmic behavior. Thus, positive or negative feedback associated with the voltage-dependent activity of ion channels in the membrane of electrically excitable cells underlies the periodic generation of action potentials in neurons and cardiac myocytes. Feedback loops in the regulation of enzyme or receptor activity by allosteric transitions or by covalent modification, e.g., phosphorylation-dephosphorylation, participate in the mechanism of cyclic AMP oscillations in the slime mold *Dictyostelium discoideum*, in the mechanism of glycolytic oscillations in yeast, and in the oscillatory dynamics of the network of cyclin-dependent kinases driving the cell cycle. The regulation of gene expression, asssociated with mechanisms of post-translational control, forms the core of the circadian clock network. Regulation of intracellular transport between the cytosol and the endoplasmic reticulum or the nucleus is involved in the onset of Ca^{++} oscillations in a variety of cell types and in periodic nucleo-cytoplasmic shuttling of the transcription factor Msn2 in yeast.

Many cellular rhythms possess a mechanism that awaits to be fully characterized. Among these are the detailed molecular mechanisms responsible for the periodic operation of the segmentation clock in somitogenesis and for the pulsatile release of GnRH by the hypothalamus in the control of reproduction.

In certain cells, several rhythms of different periods originating from mechanisms based on distinct modes of cell regulation may coexist. A case in point is that of pancreatic β cells in which membrane potential bursting oscillations as well as glycolytic and Ca^{++} oscillations with periods of several minutes have been observed in relation to pulsatile insulin release (Bertram *et al.*, 2004). These cells are further controlled by the circadian clock which coordinates insulin secretion with the sleep-wake cycle.

Cells displaying a given cellular rhythm can synchronize through intercellular communication, as exemplified by the case of circadian rhythms or by the case of glycolytic oscillations in yeast cells (Richard *et al.*, 1996 and De Monte *et al.*, 2007). Within a cell, distinct rhythms may also be coupled. Thus, in the segmentation clock, oscillations occur in the FGF, Wnt, and Notch signaling pathways and synchronize as a result of cross-talk between these three pathways (Aulehla and Pourquié, 2008 and Goldbeter and Pourquié, 2008). Another example is provided by the cell cycle driven by the Cdk network, which appears to involve several, tightly coupled oscillatory circuits involving different Cdks or different negative feedback loops (Gérard and Goldbeter, 2009). In these cases, however, the oscillatory circuits are part of the same physiological oscillator, namely, the segmentation or cell cycle clocks.

Different cellular clocks may also be coupled, as exemplified by the coupling of the cell cycle to the circadian clock. In mammalian cells, one mode of coupling occurs through control of the expression of the cell cycle kinase Wee1, a Cdk inhibitor, by the circadian clock protein BMAL1 (Matsuo *et al.*, 2003). Incorporating such coupling into the model for the mammalian cell cycle shows that the latter can be entrained by the circadian clock over a large domain of the intrinsic period of the cell cycle (Gérard and Goldbeter, 2009, 2012b). Experimental evidence suggests

(Feillet *et al.*, 2014) that the coupling between the circadian clock and the cell cycle is bidirectional.

The author would like to conclude this paper devoted to Ilya Prigogine's intellectual legacy in the field of dissipative structures in biology by two personal reminiscences (for additional ones, see Goldbeter, 2003). The first was my encounter with him as a 3rd-year undergraduate student in Chemistry at the Université Libre de Bruxelles (ULB), a few months after May 1968. I had successfully passed my examination for the course of Quantum Mechanics, which was given at the time by Claude George, a co-worker of Prigogine. At the end of the examination Claude George asked me where I was going to do my Master thesis the following year. When I answered that I was considering doing work on enzyme regulation, he suggested that I see Ilya Prigogine who, according to what he said, was interested in biology. I went to see Prigogine, with a female student of the same class. Prigogine generously devoted half an hour to us, explaining with his formidable enthusiasm and unique charisma all the scientific questions he was attracted to at the time. At the end he offered (to my companion student!) a copy of his book "Introduction to Thermodynamics of Irreversible Processes." I decided to do my MSc thesis in his group, with the intention of switching to a biochemistry group thereafter to engage in research on cell regulation, but I was hooked: I did my PhD in Prigogine's group at ULB and never ceased working in the field of modeling cellular rhythms and their underlying regulatory mechanisms. For this, I remain grateful to Claude George, and to Ilya Prigogine for his generosity in transmitting his enthusiasm for scientific research and sharing with two young students his vision of the world. I remember vividly every minute of this first encounter. Months later Prigogine also showed his generosity by including my results in an article he was writing for *Nature* at the time (Prigogine *et al.*, 1969).

The second reminiscence pertains to a discussion with Ilya Prigogine a dozen years later. I was accompanying him to a conference in Vienna. In the plane, he asked me what I was working on at the time. I had just been modeling the dynamics of a family system in terms of bifurcations—the paper (Elkaïm *et al.*, 1987) appeared some years later [for a subsequent venture into modeling oscillations with a psychological component, see Goldbeter (2006b)]. This working example was the fruit of a collaboration with my wife Edith, a clinical psychologist, and a psychiatrist friend, Mony Elkaïm, both specialized in systemic family therapy. When I explained to Prigogine that the model, based on a videotaped session of the family with the therapist (M.E.), predicted oscillatory dynamics beyond a bifurcation point, he immediately incited me to speak about this work at the conference. I chose to speak on a more « classical » topic but will never forget how open Prigogine was to new ideas and to venturing into uncharted territories.

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