Chapter 11
Noise-Induced Phenomena and Complex Rhythms: A Test Scenario for Plant Systems Biology

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Abstract Combining the unravelling of the molecular bases of functions in time and of organization in space in biology, on the one hand, with nonlinear dynamics as part of theoretical physics, on the other, is promising great progress in basic understanding of nonlinear spatial pattern formation from huge amounts of data becoming available in systems biology. In this chapter, this will be assessed in terms of the "tripod" (1) experimentation, (2) modelling and (3) theory.

1. Empirical case studies of rhythmicity are derived from three areas of study, (i) Crassulacean acid metabolism, (ii) stomatal pore regulation by guard cells and (iii) plant memory. Biorhythmicity is underlying the former two, whose spatiotemporal dynamics can be documented by, among other techniques, chlorophyll fluorescence imaging. The third one, plant memory, is intimately related to rhythmicity and the biological clock with its set points and phase regulation. All three case studies reveal nonlinear performance with synchronization/desynchronization leading to modelling and theoretical concepts.
2. In modelling, maximal models, providing perfectionist "photographic" imaging of nature, are distinguished from minimal models singling out essential domains in the parameter space of systems, with heuristic aims. The latter are explored in approaches based on experiment/theory feedback.
3. Theoretical assessment dwells on the method of cellular automata, which are frameworks for simulating spatiotemporal patterns arising from local interactions. The theoretical concepts developed are based on the examination of stochasticity with the order-generating effects of noise in stochastic resonance

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and coherence resonance, where intermediate noise intensity generates quasi-rhythmic behaviour of systems from arrhythmicity.

This merges into a new path towards systems biology, where extensive data currently provided by analytical progress are integrated into the concept of universal dynamic principles. We illustrate this new path by using simple models of synchronization, this being one concept which systems biology can then exploit for the construction of more advanced models.

11.1 Introduction

Among the most conspicuous scientific success stories of the last few decades are, on the one hand, the unravelling of the molecular bases of functions in time and of organization in space in biology and, on the other, the study of nonlinear dynamics as part of theoretical physics. Completely new dynamical phenomena have initially been derived from theoretical constructs and then demonstrated experimentally in nature. Most prominent among these ideas is the functional role of noise, in particular stochastic resonance as a new view towards optimization (Gammaitoni et al. 1998; Moss 2000), and self-organized criticality resulting from long-term evolution as a unifying concept in ecosystem dynamics (Bak et al. 1988; Solé et al. 1996).

In this vein, existing empirical observations of organization over time in space (e.g. in developmental biology) or over a space in time (e.g. in biorhythms) strongly profit from subsequent theoretical analysis of the underlying mechanisms of self-organization. Indeed, both aspects of fundamental research are needed because, as Gierer (1998) writes, to understand the system properties of the living world, one needs experimental observations and data, an appropriate abstract perception of the experienced reality and—last but not least—suitable mathematical concepts. However, even though many branches of the life sciences have quickly grasped the intriguing ideas of nonlinear dynamics and have by now exploited these for more than 20 years, in some fields the use of such methods is still regarded as a somewhat exotic and, certainly, non-standard way of looking at a system. This may be due to the non-trivial mathematical tools involved.

Systems composed of modules can develop characteristics which the components themselves do not have. Integration of modules in networks with nonlinearity leads to the emergence of completely novel properties (Lüttge 2012). To grasp these emergent properties is the task of nonlinear system theories. The most interesting processes in the living world, and among them, developmental pattern formation, can be understood only with a combination of mathematical and system-theoretical approaches (Gierer 1998). Systems biology attempts to incorporate this systemic view into its modelling and data analysis endeavours. In its simplest form, systems biology is the systemic contextualization of large numbers of individual observations (see, e.g. Smith and Hütt 2010; Hütt 2014). At the core of systems-thinking in biology is the concept of networks (Barabási and Oltvai 2004; Gallos et al. 2007).

How does network architecture help analyse and understand rhythmic phenomena? It is well established now that the synchronizability of a network depends strongly on its architecture (see, e.g. Arenas et al. 2008). Furthermore, dynamical processes on networks can also have a pattern-like organization (Müller-Linow et al. 2008; Hütt et al. 2014). Such network equivalents of classical spatiotemporal patterns include waves organized around highly connected components ("hubs") and synchronized patches coinciding with the network's topological modules. Lastly, regulatory components in networks (like feedback loops) can specifically encode certain dynamical functions (Alon 2007).

On these grounds, we need to ask which experimental observations could be subjected to an extended analysis, using theoretical approaches. Beforehand, however, we have to know about these approaches. Apart from extending knowledge in the realm of nonlinear dynamics, the theoretical research efforts of the last decade have also made these approaches much more applicable. In many areas, promising theoretical results have helped starting joint projects between biology and physics. Here, we illustrate one way in which the technology of nonlinear dynamics, if applied, may lead to an important breakthrough in plant biology.

We will describe some of the general concepts and explicit methods which serve as tools for the formulation of mathematical models for biology and for the analysis of experimental data. The first focus of this chapter is on the mathematical description of plant metabolism, which helps understand oscillatory phenomena in plants. Under certain conditions, such systems can produce spatial patterns, which change with time. Spatiotemporal dynamics is, therefore, the second key topic of our chapter. Our third centre of interest is a concept which has implications for both the nonlinearities of the systems at hand and the capacity of the systems to produce patterns: *noise*. In all these cases, we will show how abstract theoretical concepts are linked with explicit biological observations, and how the notion of noise-induced behaviour can help understand biological systems.

The vivid dialogue between theory and experiment is essential to these examples. As plant physiologists, we will rarely, if ever, be able to actually apply the theoretical methods and, as theorists, we cannot design and execute experimental approaches—evidently, mutual learning of a communal language is vital. In the following, this will be identified as the most difficult but most important ingredient of nonlinear dynamics applications to biology, which will always remain an interdisciplinary endeavour. We shall organize this in seven sections of this chapter. We will begin with explaining aims and approaches of modelling (Sect. 11.2), followed by the two case studies of systems-theory-modelling of Crassulacean acid metabolism (Sect. 11.3) and stomatal patterns (Sect. 11.4). Then, we shall consider the role of rhythmicity for fitness (Sect. 11.5), the functions of biological clocks in plant memory (Sect. 11.6) and a third case study of systems-theory-modelling with a conceptual model of plant memory (Sect. 11.7). Finally, we shall advance at integrating the empirical and theoretical considerations in an attempt of finding a new path towards systems biology (Sect. 11.8).

11.2 Aims and Approaches of Modelling

What are the major objectives behind modelling? We consider there are three important aims: (1) to depict reality, (2) to understand reality and (3) to make predictions. The former two need models of opposing nature with respect to their significance for experimental work:

1. The development of a *maximal model* as close to reality as possible, providing a perfectionist "photographic" image of nature and enabling fine-tuned simulations, which can be regarded as a true alternative to experiments,
2. the design of a *minimal model*, which accounts only for the most important properties of the system and attempts to enhance the experiment's efficiency by singling out domains in the parameter space of the system, where knowledge of the system's dynamical behaviour is essential for the understanding of the system itself.

Interesting accounts of the aims of maximal models are given, for example, in Kohl et al. (2000). Conversely, in this review we focus mostly on minimal models. A minimal model (or skeleton model) is a mathematical model description which approximates a biological system by taking into account only the *relevant* mechanisms for an observed dynamical behaviour.

The question is then no longer *how close does one get to the dynamics of the original biological system?* but rather *what ingredients are really necessary for the model to reproduce the essential traits of the system's dynamics?*

A standard form of mathematical model is given by ordinary differential equations.[1] In such equations, the change of a dynamic variable with time is again a function of the variable itself. Properties of the system are then expressed in terms of the functional link between the variable (i.e. the state of the system at time t) and the temporal change (i.e. the time derivative of the dynamic variable). The general form of such a (one-dimensional) ordinary differential equation is given by

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x) \tag{11.1}$$

[1]Although ordinary differential equations are a frequent approach to modelling, a wide variety of other descriptions exists. One passes to partial differential equations when, in addition to changes in time, the spatial behaviour is taken into account. When a focus is on the influence of fluctuations on the dynamics, stochastic differential equations are analysed. Often, formulations which are discrete in space or time are selected due to their smaller computational demands and the capacity to incorporate local rules, which are not easily accommodated in the form of differential equations. Finite difference equations for the purely temporal case and cellular automata in the case of spatiotemporal patterns are examples of such formulations. We will briefly discuss cellular automata within the context of stomatal dynamics (Sect. 11.4).

Given an initial value $x(0)$, the function yields the change dx/dt from this point on, leading to a new value of x a little later and, thus, to a new function value $f(x)$ which, in turn, determines a new change dx/dt. In this way, the differential equation, Eq. (11.1), *encodes* the function $x(t)$. This function $x(t)$ is the solution of the differential equation. One can couple such simple cases of (one-dimensional) differential equations to form more complex models. In all such cases, the terms on the right-hand side of such equations can be interpreted as specific sources of change of the system's dynamic variables.

The theory of self-organization is an important theoretical building block of our understanding of complex systems. Elements interact locally and thus, on the system-wide level, produce coherent collective behaviour. Such collective system states are "emergent", i.e. they occur spontaneously when critical parameter values (e.g. in the interaction strength) are reached.

The internal parameters of the system affecting collective behaviour are called control parameters. Quantities capturing the collective behaviour are called order parameters. Mathematically speaking, it is a remarkable feature of self-organized processes that systems consisting of a multitude of components (large number of degrees of freedom) "synchronize" to comparatively few collective states (few possible values of an order parameter). Self-organization is an important property of diverse natural processes. The most striking examples are forms of synchronization (Strogatz 2004), human mobility patterns (Helbing et al. 1997, 2000) and aspects of neuronal activity (Deco et al. 2011).

In the case of coupled phase oscillators, the control parameter is the coupling strength and the order parameter is the clustering of phases on the circle (see below Fig. 11.7 and the discussion around Figs. 11.7, 11.8 and 11.9).

11.3 Case Study I of Systems-Theory-Modelling—Crassulacean Acid Metabolism (CAM)

In order to illustrate these ideas, we will describe an explicit case study, namely the cycle of CAM and its circadian endogenous oscillations. CAM is a modification of C_3-photosynthesis in which, under normal ambient conditions, CO_2 is fixed nocturnally via phospho*enol*pyruvate carboxylase (PEPC). This leads to the formation of malic acid (or its anion malate), which is transported across the tonoplast membrane for storage in the central cell sap vacuole, remobilized during the following daylight period, decarboxylated, and the CO_2 regained assimilated in the light via ribulose-bis-phosphate carboxylase/oxygenase (RubisCO), as in normal C_3-photosynthesis. CAM provides an excellent model system for the interdisciplinary study of circadian rhythmicity, as it displays a variety of dynamical phenomena which are of interest from the viewpoint of nonlinear dynamics. The most important dynamical event is the switching from vacuolar malate loading to vacuolar malate remobilization.

In the diurnal cycle under normal conditions, a conventional explanation of this switching would be feasible on the basis of equilibrium thermodynamics: the equilibrium of nocturnal malate loading is disturbed by fundamental changes of external conditions with the onset of the light period, due to irradiance and associated change of temperature, so that the switching to malate unloading has a ready explanation—as does, vice versa, the switching to loading again. In addition to light, temperature is an important control parameter in the regulation of these dynamics, as it affects the fluidity of the tonoplast lipoprotein membrane and, hence, malate permeability (Kluge et al. 1991; Kliemchen et al. 1993; Lüttge 2000). However, the fact that CAM is also free running as an endogenous rhythm with circadian oscillations of CO_2 exchange (J_{CO2}) and malate levels, due to switches between vacuolar loading and unloading in continuous light and under strictly constant conditions (Lüttge 2000), clearly points to the nonlinear dynamics of CAM.

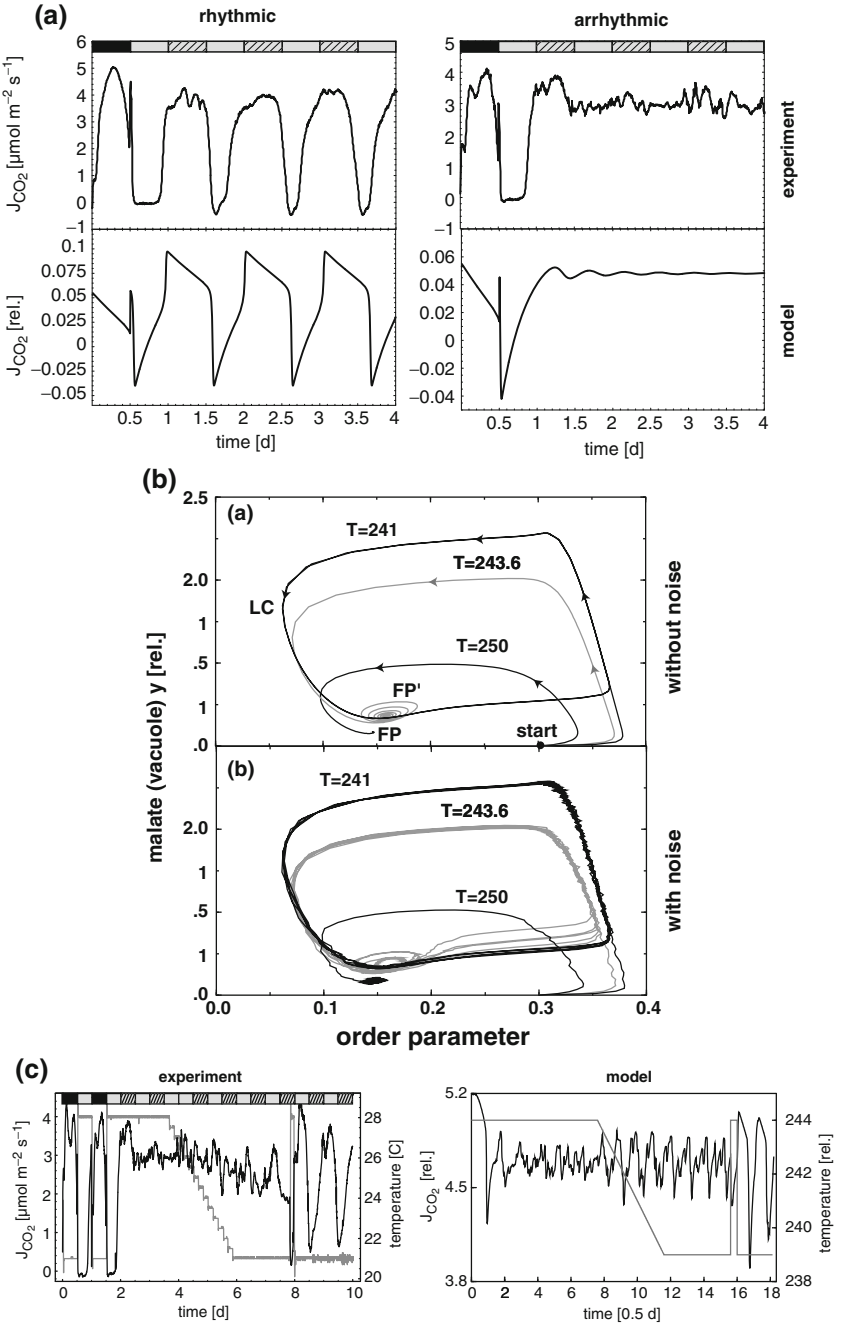
Biorhythm research is dominated by the quest for the biological clock or circadian oscillator on a genetic basis (for a review of the plant biological literature, see Lüttge 2003a). Some central oscillator genes or master genes have been identified. Although we must keep in mind that, in *Drosophila*, both the circadian rhythm of eclosion and locomotor activity and the very short ultradian rhythm of the male courtship song seem to be governed by the same PER gene (Dunlap 1993), it is highly debatable whether there is one central gene oscillator at the very top of the hierarchy of biological clock systems. The complexity must be larger, and major current progress at the molecular level clearly shows that we are dealing with genetic networks and multiple oscillator systems, rather than with one central oscillator (Lüttge 2003a). Well-known central clock genes of higher plants, such as *TOC1* (*timing of CAB—chlorophyll a/b binding protein—expression*), *CCA1* (*circadian clock associated*) and *LHY* (*late elongated hypocotyl*), are rhythmically expressed in CAM plants and, most interestingly, in one species, *Mesembryanthemum crystallinum* L., which can switch from C_3-photosynthesis to CAM, the phases of these oscillating genes are offset against each other in both modes of photosynthesis (Boxall et al. 2005). Moreover, a gene encoding PEPC-kinase, which modulates PEPC activity, a key function in CAM, is known to be a clock-controlled gene (CCG), i.e. subject to downstream control. However, the transcription of this apparent key gene is under metabolic control of malate, the product of PEPC activity (Borland et al. 1999), i.e. subject to upstream control. This is an example of the general principle of nonlinear interplay between the clock and metabolism, where in feedback loops the circadian clock controls metabolism and is itself controlled by metabolites (Müller 2014). Thus, although there is evidence of a *TOC1/CCA1/LHY*-oscillator to control oscillations in the CAM pathway (Hartwell 2005), it is seen that the gene hierarchies simultaneously work top–down (downstream regulation) and bottom-up (upstream regulation) in integrated network-type relations. Moreover, CAM is also an example where functioning of a biophysical circadian oscillator downstream of the direct involvement of genetic control can be demonstrated. Its dependence on malate levels makes its regulation subject to biophysical compartmentation between cytoplasm and vacuole, i.e. dependent on

vacuolar loading/unloading via the tonoplast membrane (Lüttge 2000; Nimmo 2000). At the bottom level, a direct involvement of CCGs appears to be excluded and the primary oscillator of the CAM cycle is based on post-translational functions.

Therefore, application of nonlinear dynamics tools was an important choice for advancing our understanding of the CAM oscillator. Over one and a half decade, a close collaboration has been established between plant physiologists and theoretical physicists, resulting in the development of dynamical minimal models (Lüttge and Beck 1992; Blasius et al. 1997, 1998, 1999; Lüttge 2000) as well as in several general contributions to nonlinear dynamics (e.g. Hütt and Neff 2001; Busch et al. 2001). Studies with the CAM plant *Kalanchoë daigremontiana* Hamet et Perrier de la Bâthie have revealed that, above a certain threshold temperature, J_{CO2} changes from rhythmic to arrhythmic behaviour and that this is reversible when temperature is lowered again (Lüttge and Beck 1992). It has been shown that these findings are well reproduced by minimal models of six, four (for which mathematical details are summarized in, e.g. Lüttge 2000) or even only three coupled nonlinear differential equations with temperature, light intensity and external CO_2 concentration as external parameters (Fig. 11.1a).

Due to the combination of a highly controllable experimental set-up and a consistent theoretical representation, we may regard the endogenous circadian CAM rhythm of *K. daigremontiana* as a very suitable model system for the study of the biological clock. We show here how the vivid exchange of concepts and ideas between model and experiment can lead to a completely new view of the functioning of this biological rhythm: the biological clock as a spatiotemporal phenomenon. One crucial tool in our interpretation of CAM dynamics is a mathematical model (Lüttge and Beck 1992; Blasius et al. 1997) which has been formulated on physiological grounds. The dynamics of six metabolite pools (malate in the cytoplasm, malate in the vacuole, internal CO_2-concentration, glucose-6-phosphate, phospho*enol*pyrovate (PEP) and starch) are determined by fluxes between these pools, which depend on three external control parameters (light, temperature, external CO_2 concentration). A wide variety of earlier experimental results for the CAM plant have been reproduced by this model and refinements thereof. Examples are shown in Fig. 11.1. Some of the refinements are worth mentioning, as they have immediate implications for a physiological understanding of CAM dynamics and, in addition, illustrate the idea of a *minimal* model:

1. Mathematical considerations regarding the different time constants of the processes involved enabled the elimination of three of the metabolite pools in the glycolytic pathway, namely starch, glucose-6-phosphate and PEP, showing that observations can be explained by the interacting dynamics of internal CO_2 and cytoplasmic and vacuolar malate alone (cf. Blasius et al. 1999 for details).
2. The thermodynamical properties of the tonoplast membrane during CAM have been analysed independently (Neff et al. 1998). It could be shown that, in the model, the average lipid area density serves as a control parameter, with lipid


(a)
rhythmic
arrhythmic
experiment
model
J_{CO_2} [µmol m^{-2} s^{-1}]
J_{CO_2} [rel.]
time [d]
(b)
(a)
(b)
T=241
T=243.6
T=250
LC
FP'
FP
start
without noise
with noise
malate (vacuole) y [rel.]
order parameter
(c)
experiment
model
J_{CO_2} [µmol m^{-2} s^{-1}]
temperature [C]
J_{CO_2} [rel.]
temperature [rel.]
time [d]
time [0.5 d]

◀ **Fig. 11.1** Typical simulation results obtained with the CAM models summarized in Lüttge (2000). For comparison, the corresponding experimental findings are also shown. **a** The elementary model consisting of six metabolite pools (as described in the text) schematically reproduces the rhythmic (below the upper temperature threshold) and the arrhythmic (above the upper temperature threshold) gas exchange patterns. **b** The same behaviour is displayed for the refined model without (*a*) and with noise (*b*), illustrating the dynamical properties of the model more clearly. A phase diagram shows the relation between two of the dynamical variables, namely the vacuolar malate content *y* and the lipid order parameter of the tonoplast. In such a phase diagram, time is a parameter along the curves (trajectories), as indicated by the *arrows*. In (*a*), the trajectories for three different temperatures are given. One sees a limit cycle (LC) at the lowest temperature and a rapid convergence into a fixed point (FP) at the highest temperature. At an intermediate value of temperature, the system slowly spirals into the fixed point which is now slightly shifted (to FP′), as the equilibrium states themselves depend on temperature. When noise is included in the theoretical description (*b*), the behaviour of the former two trajectories remains qualitatively the same. The intermediate case, however, displays a completely different form of dynamics, as now the spiralling process is interrupted frequently by stochastic kicks onto the nearby limit cycle, which the system leaves after a full oscillation to again approach the fixed point. The advanced version of the model is now capable of producing realistic time series even for rather complex experimental protocols. An example of this is given in (**c**). Here, a slow change from a temperature associated with arrhythmic behaviour to a temperature in the rhythmic regime (i.e. weak dynamics of signal input) is applied with the astonishing effect of observing an arrhythmic gas exchange pattern even in a temperature domain of usually rhythmic behaviour, which is restored after a sudden temperature pulse (i.e. strong dynamics of signal input). Due to the new ingredient of noise-induced desynchronization, the model is capable of reproducing this phenomenon. Model parameters (as well as the temperature in (**b**) are shown in relative units (adapted from Hütt and Lüttge 2002)

order undergoing a phase transition when this parameter is varied. The lipid order parameter thus has the role of a fourth dynamical variable in the three-pool model. The model is capable of accounting for the existence of a rhythmic and an arrhythmic domain, where the former is represented in terms of a limit cycle, whereas the latter is described by a fixed point of the system of differential equations (cf. Fig. 11.1b).

At this stage, the model can be thought of as a single circadian oscillator which, depending on external conditions, is either in a stationary state (fixed point) or in an oscillatory state (limit cycle). However, the idea of a single oscillator is quite contrary to the picture one gets experimentally. Here, one may expect the leaf to consist of different domains or patches which, under certain conditions, may behave as independent oscillators—in other words, each leaf cell performing CAM may contain an autonomous copy of the oscillator (Rascher et al. 2001). For the theoretical description, this means that one has to consider an ensemble of identical, independent or weakly coupled oscillators, rather than a single oscillator.

3. The next refinement is closely related to this major step taken from a purely temporal to a spatiotemporal dynamics. It concerns the inclusion of stochastic processes and dynamics at a small timescale, which formally enter the description as *noise*.

Unveiling the effect of noise in a (nonlinear) system can substantially contribute to the understanding of the processes within the system. Noise is a ubiquitous phenomenon and, in most cases, a disturbance to the measuring process. From the viewpoint of nonlinear dynamics, however, it may very well influence a system's dynamics in a more sophisticated way than only by overshadowing it. It is possible that some biological process (e.g. the detection of a signal) functions in an optimal way only at some intermediate noise level present in the system (Douglass et al. 1993; Bezrukov and Vodyanoy 1995; Gammaitoni et al. 1998; Anishchenko et al. 1999; Moss 2000). With lower or higher noise intensity, the efficiency of the process would decrease. A schematic example of such a *stochastic resonance* is given in Fig. 11.2a. This phenomenon is possible only in a nonlinear system (in our schematic example of Fig. 11.2a, the threshold serves as nonlinearity). This is by now theoretically well understood and has been observed, together with the related effect of coherence resonance (Pikovsky and Kurths 1997), in a variety of natural and model systems (Longtin et al. 1991; Moss et al. 1994; Bezrukov and Vodyanoy 1995; Lee et al. 1998; Beck et al. 2001). For circadian oscillations in plants, it was suggested that the desynchronization between noisy oscillations in single cells contributes to the observed damped oscillations at the level of the cell population (Guerriero et al. 2012).

Let us return to the CAM model. As soon as noise is included in the theoretical description, the arrhythmic gas exchange pattern is reproduced realistically and more complex scenarios, such as a slow (rather than abrupt) temperature variation, are simulated by the model, yielding high agreement with experimental data (Fig. 11.1c).

Two important new features enter the system due to the presence of noise. First, it is possible for the oscillators to loose synchronization: when several identical noisy CAM oscillators are used in the simulation (with the net CO_2 exchange being the average for this ensemble), and if no external *zeitgeber* is present, then the oscillators will desynchronize as time evolves. Second, spontaneous, noise-induced transitions from the fixed point to the limit cycle become possible (Fig. 11.1b). Indeed, these transitions display the highest correlation with the internal frequency of the CAM oscillator at intermediate noise strength. This phenomenon, named coherence resonance (Pikovsky and Kurths 1997), is similar to the stochastic resonance mentioned above (see also Fig. 11.2b).

Triggered by the theoretical suggestion of a loss of synchronization of distinct leaf areas, the experimental study of CAM dynamics has been advanced to the point where spatial and temporal variations over a given leaf can be investigated using the non-invasive technique of photographic chlorophyll fluorescence imaging to depict the synchronization and desynchronization of photosynthetic activity in leaf patches (Rascher et al. 2001; Rascher and Lüttge 2002). Internal CO_2 and its lateral diffusion within the leaf airspaces have been identified as an essential signalling element for synchronization (Duarte et al. 2005; Lüttge and Hütt 2006).

At the level of data analysis, graph variants of neighbourhood-based spatio-temporal analysis tools (see Hütt and Neff 2001; Hütt and Lüttge 2002) have been formulated and extended to a method for estimating connectivity from the time

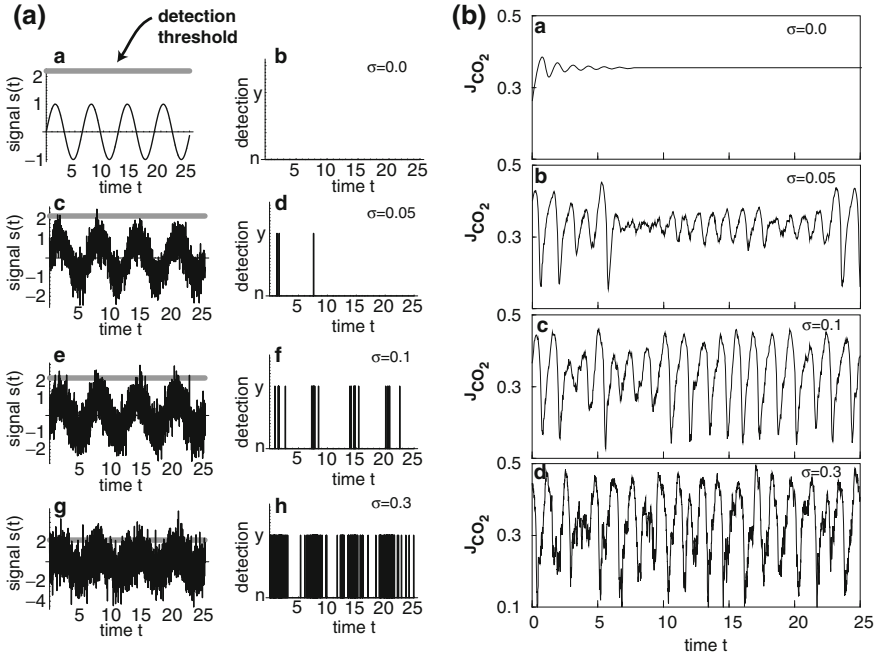


Fig. 11.2 **a** Schematic example of a system displaying stochastic resonance. A signal $s(t)$, consisting of a sine wave and additive noise, enters some detection mechanism with a threshold (*a*, *c*, *e* and *g* for different noise intensities σ). At each point in time, the signal is translated into yes (*y*) or no (*n*), depending on whether the signal reaches above the threshold or not (*b*, *d*, *f* and h). One sees that the sequence of maxima present in the pure signal (i.e. without noise, as seen in *a*) is best reproduced by this device at an intermediate noise intensity. In a natural system, the more frequent case is that a (almost) pure signal enters a system with a noisy threshold. Mathematically, these two cases are equivalent. **b** The CAM model, which is illustrated in Fig. 11.1, shows a similar behaviour with respect to recovering the circadian oscillation in the noisy fixed point. Data in *a* were schematic representation of the system without noise ($\sigma = 0$) reaching the fixed point. Data in *b*, *c* and *d* were obtained by numerical simulation with increasing noise intensities (σ of 0.05–0.3). At a medium noise intensity (*c*), the circadian rhythm is optimally recovered (coherence resonance). At higher (*d*) and lower (*b*) noise intensity, the CO_2 gas exchange curve J_{CO2} shows a much more irregular pattern (adapted from Hütt and Lüttge 2002)

series of oscillators on a graph (Hütt and Lüttge 2005a). Additionally, the impact of graph theory and network dynamics on plant physiology has been reviewed from a similar perspective (Hütt and Lüttge 2005b).

In CAM, the major interrelated subsystems are (1) malate compartmentation, (2) stomatal movements regulating CO_2 uptake and (3) CO_2 assimilation via Rubisco (Bohn et al. 2003). The overwhelming complexity here is illustrated by observations that the vacuolar malate accumulation/remobilization oscillator discussed above, i.e. subsystem 1, appears to be only part of the whole story. In *K. daigremontiana*, endogenous circadian malate oscillations are highly dampened within three to four circadian periods, without any dampening of the overt output

rhythm of net CO_2 exchange (Wyka and Lüttge 2003; Wyka et al. 2004). This implies that a delicate, fine-tuned internal regulation of oscillator and output networks must lead to takeover of subsystems 2 and/or 3, without any disturbance of the output itself and perhaps under the control of a genetic *TOC1/CCA1/LHY*-oscillator.

11.4 Case Study II of Systems-Theory-Modelling—Stomatal Patterns

Stomatal patterns in leaves are determined by a variety of external and internal control parameters interacting in signalling networks. This makes up the complexity of stomatal rhythms. The ultimate pacemaker of guard cell movements for stomatal opening and closing, however, appears to be CO_2 (Raschke 1965; Lüttge and Hütt 2006). Although a CO_2 sensor or receptor has not been definitely identified as yet, it is clear that increased and decreased internal CO_2 concentrations affect stomatal closing and opening, respectively. Spatiotemporal patterns of stomatal opening/closing states are then dependent on the homobaric or heterobaric nature of leaves (Neger 1918; Terashima 1992). Homobaric leaves have no conspicuous anatomical constraints for internal CO_2 diffusion, so that internal partial pressures of CO_2 are homogenous (homobaric) and, consequently, stomatal states are also largely homogenous over the leaves. Heterobaric leaves have anatomical vein arrangements hindering gas diffusion, which leads to the well-known spatiotemporal phenomenon of stomatal patchiness (Beyschlag and Eckstein 1997; Haefner et al. 1997). Under particular conditions, and rather than anatomical features, it is physiological constraints which may lead to physiological homobary (Duarte et al. 2005; Lüttge and Hütt 2006).

Ever since the discovery of stomata as elements of an oscillatory CO_2 regulation system (Raschke 1965), stomata have been a key example of cybernetics in plants. Ultradian oscillations of stomatal aperture and conductivity for water vapour have been reported over decades (Barrs 1971; Teoh and Palmer 1971; Cowan 1972a, b; Kaiser and Kappen 2001; Roelfsema and Hedrich 2002). Primary external signals or control parameters are blue and red light, hydraulic effects and leaf internal airspace CO_2 (Willmer 1988), affecting a highly complex internal regulation network. Cytoplasmic Ca^{2+} levels play a key role as a central node in this network (McAinsh et al. 1997), and a plasma membrane Ca^{2+} channel may be an important oscillator in the system (McAinsh et al. 1995). Interrelated subsystems involved are stomatal guard cell movements as such and photosynthesis. Due to the intimate interaction of photosynthetic metabolism and gas exchange, it is difficult and often impossible to distinguish between oscillations of stomata and photosynthesis. Oscillations of stomata and photosynthetic output parameters begin after abrupt changes in external parameters such as light, CO_2, O_2, H_2O and temperature (Walker 1992; Giersch 1994). However, there are also spontaneous stomatal

oscillations (Raschke 1975). Giersch (1994) considered the various possible metabolic control points and discussed two different mathematical minimal or "skeleton" models simulating oscillations. One model is based on a "two-kinase hypothesis" (see also Giersch et al. 1991), with phosphoglycerate and phosphoribulose kinases, and the other is based on a "coupling hypothesis", with the interdependence of photosynthetic electron flow and photophosphorylation. Evidence is in favour of the former hypothesis.

In spite of its intrinsic lack of quantitative comparison with a precise mathematical model, from our point of view the study by Peak et al. (2004) constitutes a huge progress in conceptually understanding the spatiotemporal behaviour of stomatal guard cells. By observing that stomata basically have to compute an opening state optimal at the global (leaf-wide) level using only local (cell–cell) communication, the authors compare stomatal dynamics with a model system from complexity theory, namely cellular automata (CA).

Let us look at this type of modelling in more detail. A cellular automaton is a framework for simulating spatiotemporal patterns arising from local interactions. Figure 11.3 summarizes this concept. In the case of one spatial dimension (1D CA), one has a chain of elements, each of which can be in a particular state in a state space Σ. Update rules translate neighbourhood constellations at time t into the state of the central element at the next time step $t + 1$ (see Fig. 11.3a). By consecutively applying the update rules, one can simulate the time evolution of such a chain of elements corresponding to this particular selection of update rules. A strength of cellular automata lies in the simplicity of both the concept and the state space of a specific model, which usually contains only few distinct states. Consequently, the idea of cellular automata is not to describe a biological phenomenon as accurately as possible but rather to grasp the essence of a system in terms of few degrees of freedom. In this sense, cellular automata represent an extreme case of minimal model for biological situations.

As this brief summary of cellular automata already shows, this model operates in a discrete space, at a discrete time, and in a finite and discrete state space. Figure 11.3b gives an example of a simple cellular automaton. This example considers three-element neighbourhoods ($N = 3$) and a binary (two-element) state space ($K = 2$), e.g. containing only 0 and 1. In this case, $2^3 = 8$ neighbourhood constellations have to be specified. The example given in Fig. 11.3b leads to a steady-state pattern, after a short transient.

This general framework of cellular automata has received much scientific attention as a laboratory for studying complex systems (see, e.g. Wolfram 2002). Moreover, specific cellular automata have proven useful as minimal models for aspects of biological pattern formation ranging from simplest Turing patterns to the characteristic spiral wave patterns observed in excitable media. Even against this wide background, however, it is not readily understood how this CA-type of model could mimic the behaviour of stomatal dynamics. The interesting approach by Peak et al. (2004) has been to analyse the statistical features of a rather famous cellular automaton designed to perform a specific computational task, and compare these

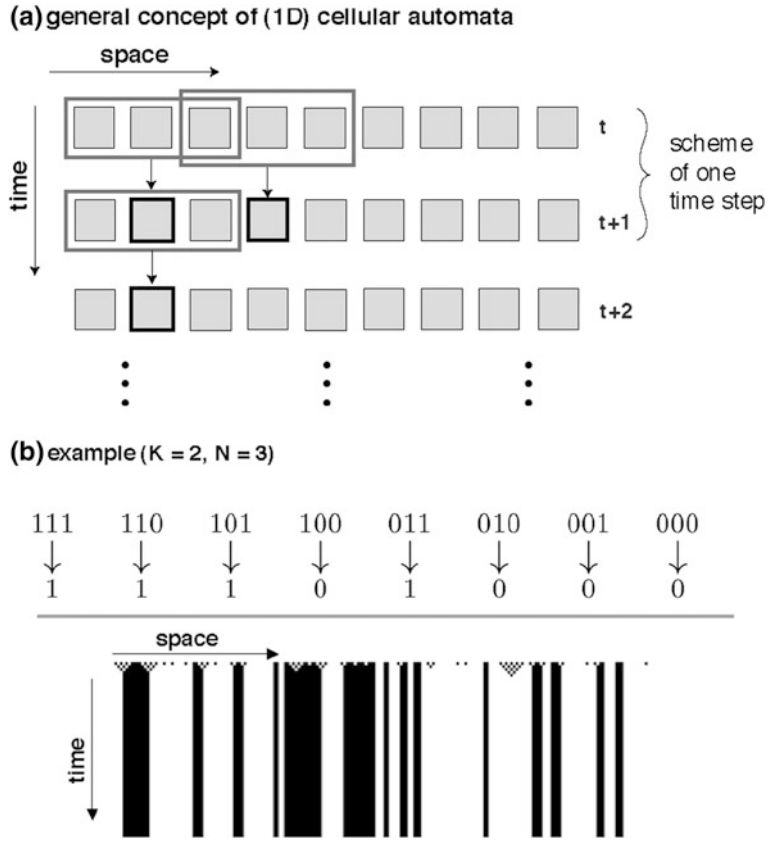


Fig. 11.3 Concept of cellular automata (CA) illustrated for one spatial dimension (**a**) and an example of a CA simulation for a binary state space and a three-element neighbourhood (**b**). For this selection of update rules, one obtains fixed-point dynamics after a short transient (adapted from Lüttge and Hütt 2006)

features with the computational task they record in stomatal spatiotemporal dynamics.

The cellular automaton they consider is a so-called *density classifier*. In its simplest form, the computational task of density classification starts from a random distribution of 0*s* and 1*s* and then uses local rules to determine the state with the highest global density. Note that, with the help of an external agent, this would be a trivial computational task requiring only to count, e.g. the number of 1*s* in the initial state. With no external agent and using only local interactions between the elements, the computation of the state with the highest initial density is far from trivial. This situation has been studied extensively in complexity theory (see, e.g. Mitchell et al. 1994; Crutchfield and Mitchell 1995; Wolfram 2002). A simple example of such a density classification is the *majority rule*, where the update rule maps an

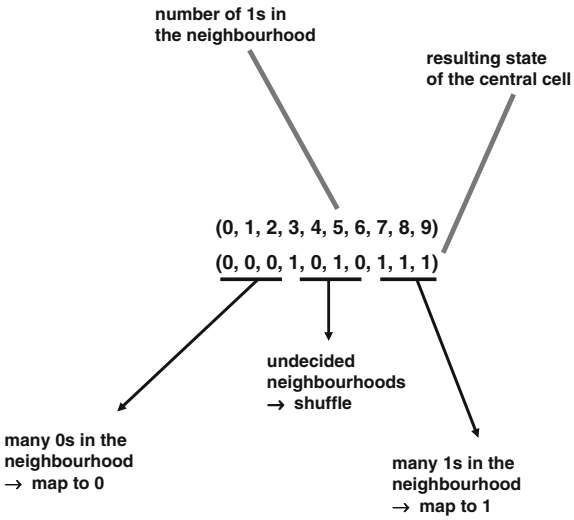


Fig. 11.4 Summary of the update rule for a totalistic CA suitable for density classification. The *upper line* of digits in parentheses gives the number of 1*s* in a spatial (nine-element) neighbourhood, whereas the *lower line* lists the corresponding state of the central cell in the next time step (adapted from Lüttge and Hütt 2006)

element to the state which holds the majority in the neighbourhood under consideration. In order to advance one step closer to the biological phenomenon, we consider the case of two spatial dimensions. Figure 11.4 summarizes the update rule, which retains some features of the majority rule with the additional condition of shuffling undecided neighbourhoods. Here, the update rule operates on the number of 1*s* in the nine-element neighbourhood for this automaton in two spatial dimensions. Update rules involving only the number of, e.g. 1*s*, rather than their distribution in the neighbourhood, are called *totalistic cellular automata* in CA theory. Figure 11.5 shows spatial snapshots at different time points starting from an initial density of 1*s*, p_1, close to 0.5. The corresponding time course of the density is displayed in the bottom part of Fig. 11.5. The capacity of this automaton to classify initial densities by converging to a specific state is summarized in Fig. 11.6. Here, densities $\rho(t)$ for different initial densities, p_1, are compared. It is seen that whereas highly biased densities are rapidly classified by this automaton, the difficult cases, where $p_1 \approx 0.5$, can lead to long transients (and also to an occasional misclassification). Peak et al. (2004) evaluate such cellular automata in terms of the event-size distributions and other statistical parameters and compare these quantities with the stomatal patterns. Both in theory and experiment, they focus on the long transients.

This approach is conceptually different from the usual framework of theoretical biology, where specific mathematical models are formulated and then analysed with methods of nonlinear dynamics. Here, the mathematical description focuses on analogies. A quantitative analysis then relies on comparing statistical properties of the real-life data with those from the theoretical counterpart. For stomatal dynamics,

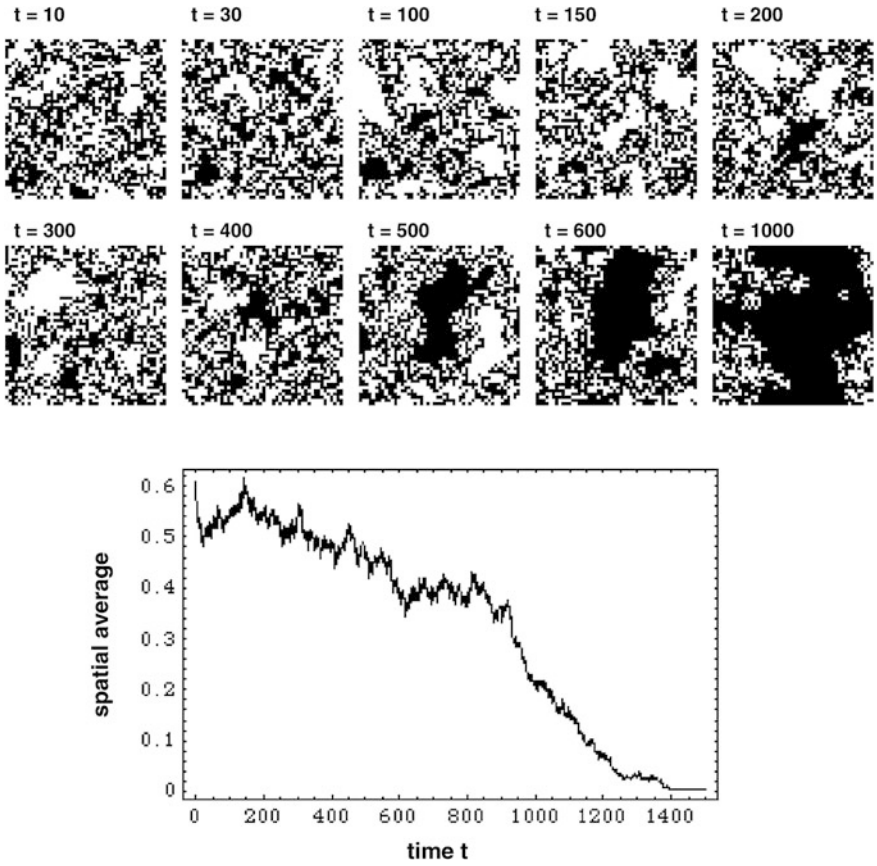


Fig. 11.5 Spatial snapshots of the CA in Fig. 11.4 at different time points (*top*) and time course of the density $r(t)$ of $1s$ (i.e. of the spatial average over the lattice at each time point; adapted from Lüttge and Hütt 2006)

Peak et al. (2004) analyse event sizes, the scaling of transients and the distribution of interpeak intervals in the average opening state (see also West et al. 2005). Such "complex systems that perform tasks" (Mott and Peak 2006) have a multitude of additional applications across many scientific disciplines (see Moreira et al. (2004) for a more stylized example).

One can view this study as an example of a new trend in theoretical biology on its way to an understanding at a system-wide level: ever larger systems and, on the other hand, an increasing importance of stochastic contributions (usually coming from few-molecule configurations beyond the usual average concentrations and far beyond the molecular level) require models with abstract, discrete dynamics and the use of stochastic processes to implement the effect of stochasticity at this abstract level (see also Bornholdt 2005).

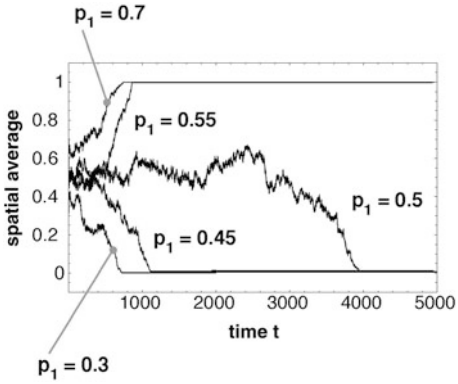


Fig. 11.6 Density $r(t)$ as a function of time t for different values of the initial density of 1s, p_1. The cellular automaton is the same as in Figs. 11.4 and 11.5 (adapted from Lüttge and Hütt 2006)

11.5 Rhythmicity and Fitness

The biological clock communicates alertness to organisms ensuring their punctual performance under rhythmically changing external conditions. This particularly relates to the fluctuations of day/night conditions. That this is a major function for providing fitness somewhat is common-place wisdom also repeated time and again in the scientific literature. However, we must check, what is the solid evidence for this (Sect. 11.5.2)? Moreover, we must ask, what is fitness? Is it success of reproduction for selection in the vein of the evolutionary theory of Charles Darwin and Alfred Russel Wallace? Is it sustaining of ecophysiological performance with adaptive responses to variable spatiotemporal environmental stress? Is it competitiveness given by productivity of biomass and hence growth? If we consider fitness in a broad sense comprising a variety of these aspects, we shall see that indeed rhythmicity does support it. Thus, correlations between rhythmicity and fitness are given not only under the direct action of the circadian biological clock (Sect. 11.5.2) but also with ultradian (Sect. 11.5.1) and annual or phenological oscillations (Sect. 11.5.3).

11.5.1 Ultradian Rhythms

Ultradian rhythms lie below a lot of biophysical, biochemical and physiological functions as listed and reviewed by Lüttge and Hütt (2004), namely

- biophysical functions of membranes,
- biochemical functions of isolated enzymes and metabolic networks,
- cell growth and development (e.g. pollen tubes),
- movements of stomatal guard cells and photosynthesis,

- circumnutation of shoots and tendrils,
- leaf movements and
- cell elongation and extension growth.

We can see that ultradian rhythmicity supports robustness of a plethora of essential functions and therefore sustains performance as a basis of fitness.

Among the ultradian cellular oscillators, Berridge and Rapp (1979) distinguish two types, (1) cytoplasmic oscillators, in which the periodic phenomena are generated by an instability in metabolic pathways and (2) membrane oscillators, generating rhythms of membrane potential. Oscillations of membrane functions and biochemical reactions in the cells never occur in isolation. The discovery and understanding of ultradian oscillations of glycolysis goes back to the work of Britton Chance (Ghosh and Chance 1964; Chance et al. 1964; Betz and Chance 1965) and has received interest over decades (e.g. Goldbeter and Lefever 1972; Berridge and Rapp 1979; Olsen and Degn 1985; Rapp 1986; Goldbeter 1996). These oscillations involve ultradian rhythms of the redox state of the pyridine nucleotide system (Betz and Chance 1965). More recent work with yeast cells by the group of David Lloyd shows that the complete redox poise of the cells is affected where H_2S has signalling functions (Lloyd and Murray 2006; Lloyd 2008). Hence, this group speaks of an "ultradian clock" (Lloyd and Kippert 1993). The redox poise is considered as an overarching aspect. Koukkari et al. (1997) have searched among ultradian rhythms for a "biological hour". Among ultradian oscillations in bacteria, amoebae, yeast, higher plants and mammals they found periods ranging from 30 to 240 min averaging 95 min. However, for the redox poise the Lloyd group notes a period length of 40 min which they think is the basic period of the ultradian clock. With the central importance of the redox poise in cell biology, we may ask if one can construct circadian rhythms from ultradian rhythms (Lüttge and Hütt 2004). Indeed, the Lloyd group argues that interference of many fast ultradian oscillations can produce robust circadian oscillations: the period length of 40 min is contained exactly 36 times in the natural diurnal 24-h rhythm. The large number of known ultradian rhythms provides a huge experimental data basis for system analysis to unravel governing principles of nonlinear dynamics. This is generic, and it may be one of the reasons for the great success of studies of model systems such as glycolysis and also the oscillations of cyclic adenosine monophosphate (cAMP) secretion regulating the attraction and pattern formation of amoebae of the slime mould *Dictyostelium* (e.g. Berridge and Rapp 1979; Lüttge and Hütt 2009).

A concrete hint for the interaction of rhythmicity and fitness is the general role of oscillations in encoding information and signalling in transduction chains or networks (McAinsh et al. 1995; Berridge et al. 1998; Shabala et al. 2001). In an ecophysiological context of fitness, it is noteworthy that natural light fluctuations in Tasmania due to cloud dynamics showed frequency peaks corresponding to periods of 3, 6 and 14 min in the same range as those of ultradian oscillations of photosynthesis (Shabala et al. 1997).

11.5.2 Circadian Rhythms

With the first case study of systems-theory-modelling above, CAM was introduced as an example of free running circadian rhythms in plants (Sect. 11.3). The molecular structure of the clock of higher plants is studied in the greatest detail in *Arabidopsis thaliana* (Nakamichi 2011). The master genes CCA1/LHY and TOC1 (see Sect. 11.3) are expressed in the morning and evening, respectively. However, master genes per se do not make up an all governing central oscillator. In a non-linear network fashion, a large number of rhythmic functions of genes and biochemical/biophysical processes are involved. There are further morning and evening elements which function as transcription factors (Harmer and Kay 2005; Kikis et al. 2005; McClung 2006; Nakamichi 2011). These genes determine the phase of the clock. Downstream a vast number of other genes are controlled by the clock, the so-called clock-controlled genes (CCGs). In the cyanobacterium *Synechococcus elongatus*, almost all genes and, in the angiosperm *Arabidopsis thaliana* (L.) Heynh., very many genes are CCGs (Liu et al. 1995; Michael and McClung 2003). Almost all functions of life appear to be subject to circadian regulation. The plant circadian clock regulates virtually every plant biological process and most prominently hormonal and stress response pathways (McClung and Gutiérrez 2010).

That this provides fitness primarily comes from a generally accepted logical contention of common sense. In support of the argument, mostly the paper of Dodd et al. (2005) is cited in the scientific literature. The most solid evidence has been obtained in experiments with period-length mutants. The rationale was that mutants with different period lengths should perform best and have competitive advantage over other mutants when the period length of an external light/dark rhythm is close to or identical to their endogenous period length. S.S. Golden and collaborators used period-length mutants of the cyanobacterium *Synechococcus elongatus* PCC7942. They grew mutants having different circadian periods of their endogenous clocks in co-culture and subjected these cultures to different external light–dark rhythms. The mutants having the correct endogenous period, i.e. closest to the imposed external light–dark rhythm, out-competed the others during growth. Under constant environmental conditions, this competitive advantage disappeared. Evidently, the endogenous circadian rhythm of the cyanobacteria provided them competitive fitness under external fluctuations of dark and light periods (Ouyang et al. 1998; Johnson and Golden 1999; Woelfle et al. 2004). Yerushalmi et al. (2011) crossed *Arabidopsis thaliana* mutants with different circadian period lengths and subjected the F2 and F3 generations to altered light/dark cycle periods. They found that under such environmental pressure selection occurred favouring the plants which had an endogenous circadian rhythm that resonated with the environmental one. Thus, this suggests that endogenous rhythmicity matching environmental rhythmicity can confer fitness to the plants and provide a selective advantage (Green et al. 2002; Hotta et al. 2007; Yerushalmi and Green 2009; Yerushalmi et al. 2011). Nevertheless, matching of internal circadian periods with

periods of external rhythmicity is not sufficient for guaranteeing positive clock effects on growth and competitiveness. This is due to the complex nonlinear network dynamics involved, where metabolomics controlled by gene expression exert feedback by controlling transcription (Sect. 11.3; Müller et al. 2014). As a result of a detailed systems-level analysis of circadian rhythms, it was shown that 12-h rhythms can be linked to physical binding properties of transcription factors in the presence of a circadian clock (Westermark and Herzel 2013).

Summarizing, circadian rhythmicity can therefore be viewed as a phenomenon organized across several system scales. On the cellular level, rhythms can be associated with feedback loops in the underlying regulatory networks. Due to this deep relationship between the architectural ("hardware") properties of the regulatory networks and the dynamics (i.e. the diverse types of rhythmic behaviour), cellular rhythms have, over the last few years, become an important topic in systems biology (see, e.g. Goldbeter et al. 2012). In the last few years, the relevance of transcriptional regulation for circadian oscillations has been re-evaluated. In particular, it was shown that non-transcriptional mechanisms are sufficient to sustain circadian timekeeping in eukaryotes (O'Neill et al. 2011). Circadian rhythms can thus be regarded as a multilevel phenomenon that cannot be related to a single layer of cellular organization.

Additionally, it is well established by now that circadian rhythms in plants can have a complex underlying spatiotemporal organization, leading to propagating waves along leaves, coordinating photosynthetic activity (Rascher et al. 2001). The stomatal cells of plants respond with complex patterns (termed "stomatal patchiness") to changes in the environment, which effectively implement a density classification algorithm (Peak et al. 2004).

11.5.3 Annual Rhythmicity of Phenological Patterns

The clearest evidence for the absolute necessity of the biological clock for plant fitness comes from phenological patterns which are subject to annual rhythmicity. Among the most important examples of phenological phenomena are plant growth and development, flowering and seed production, initiation of frost hardiness and preparation for leaf shedding of deciduous woody plants (Lüttge and Hertel 2009). These processes are subject to regulation by day-length or photoperiod. Their appropriate annual periodicity is directly related to the various aspects of fitness. It requires measurement of day-length, and this is mediated via the biological clock, whose phase adjustment is an essential mechanism in photoperiod perception (Frankhauser and Staiger 2002; Roden et al. 2002; Love et al. 2004; Ogudi et al. 2004; Fujiwara et al. 2008; Niwa et al. 2009; Ibáñez et al. 2010). The genetic basis of phase information is revealed by the identification of phase information genes (Michael and McClung 2002; Salomé et al. 2002), phase mutants (Onai et al. 2004) and genetically encoded phase variations in populations (Darrah et al. 2006).

11.6 Biological Clocks and Plant Memory

Plants are sensitive to many different stimuli (such as wind, rain, touch, drought, cold shock, heat shock, wounding and attack by fungi, bacteria or viruses). They are even sensitive to low-intensity 0.9 and 105 GHz electromagnetic radiation (Tafforeau et al. 2002, 2004; Roux et al. 2006; Vian et al. 2006). When they have perceived a stimulus, plants generate a final response consisting sometimes of a macroscopic movement and most usually of growth and/or metabolic modifications. Upon perception of a stimulus, in most cases the plant reacts almost immediately by Ca^{2+} invasion of the cytosol in the cells in the stimulated area (Knight et al. 1991). The intermediate steps between Ca^{2+} invasion of the cytosol and the final response are still not completely unravelled, but they implicate the modification (especially the phosphorylation) of some existing proteins, the activation/inactivation of ionic channels and changes in genome expression.

Quite often, the final response is stereotyped and follows the perception of the stimulus almost immediately (with only the delay for the intermediate steps to take place). This may be termed a "direct" response. However, it has been recognised since the beginning of the 1980s (Thellier et al. 1982), and often confirmed afterwards, that cases exist in which a "memory" is also involved. More precisely, it has appeared (Trewavas 2003) that in plants we may distinguish memory function with capacities of priming and store/recall [STO/RCL] memories (Thellier 2011; Thellier and Lüttge 2013; Thellier et al. 2013). Stimulating the priming memory changes the way the plant transduces one or several subsequent stimuli, with the effect of "familiarization" ignoring subsequent harmless stimuli or, conversely, with "sensitization" producing increasingly violent responses to harmful stimuli. The memory with STO/RCL functions is more sophisticated: it involves (i) storage of information as a consequence of the perception of a first stimulus and (ii) recall of that information at a later time, allowing the plant to make use of that information in the control of its growth and metabolism. To some extent, the STO/RCL function of plant memory resembles the store/evocation function of animal and human memory.

The characteristics of the STO/RCL memory were studied mainly in three different systems (I–III):

- In system I, seedlings of *Bidens pilosa* L. were grown under conditions of low light and deficient mineral nutrition (Thellier et al. 1982; Desbiez et al. 1984, 1991a, b). When the terminal bud of the seedlings was removed by decapitation at the onset of daylight, there was outgrowth of both lateral buds in the axils of the cotyledons. Preferentially, one of the two buds was taking the lead, but symmetry was given in that it was impossible to predict which one it was. If one of the cotyledons was stimulated mechanically or chemically, this broke the symmetry and there was preferential outgrowth of the bud in the axil of the opposite cotyledon. To obtain this effect, decapitation could be done up to 2 weeks after cotyledon stimulation (Fig. 11.7). This proves that there is memory, which in fact has separate functions of signal storage (cotyledon

stimulation) and recall (asymmetric bud outgrowth), respectively. Whether STO (pricking stimulus) was stimulated before or after RCL (decapitation) made no difference, which shows that the STO and RCL boxes work independently of each other. When a dissymmetrical stimulus (pricks administered to a single cotyledon of each plant) was combined with one or several symmetrical stimuli (same number of pricks administered simultaneously to both cotyledons), it was possible to repeatedly recall the stored information.

- In system II, the inhibition of hypocotyl elongation of *B. pilosa* was studied (Desbiez et al. 1987) shortly after seed germination (Fig. 11.8). The stimulus was pricking (STO-function). However, the reaction of hypocotyl elongation only occurred when the seedlings were in water and not in nutrient solution. When the seedlings were in water, there was an immediate effect of the stimulus. When the stimulus (STO) occurred on day 6 and without effect with the seedlings in nutrient solution, a transfer two days later on day 8 elicited an immediate effect (RCL on).
- In system III, the production of epidermal meristems in hypocotyls of flax seedlings was studied (Verdus et al. 1997, 2007, 2012) shortly after seed germination (Fig. 11.9). Here, the stimulus (STO) was manipulation by transfer to a new nutrient medium and the recall function was activated by transient removal of calcium (RCL). The 1st control was an immediate reaction (RCL on) upon a stimulus (STO) and after 2 days in the absence of Ca^{2+}. The 2nd control was giving only the stimulus (STO) when there was no reaction. The 3rd control was transient removal of Ca^{2+} only with no stimulus and naturally again no reaction. The 1st interesting response was after giving the stimulus (STO) followed 4 or 8 days later by transient removal of Ca^{2+} (RCL on) then eliciting the reaction. This shows the existence of memory. Again (see system I), repeated recall is possible as shown by sequences of transient Ca^{2+} removal (RCL on) followed

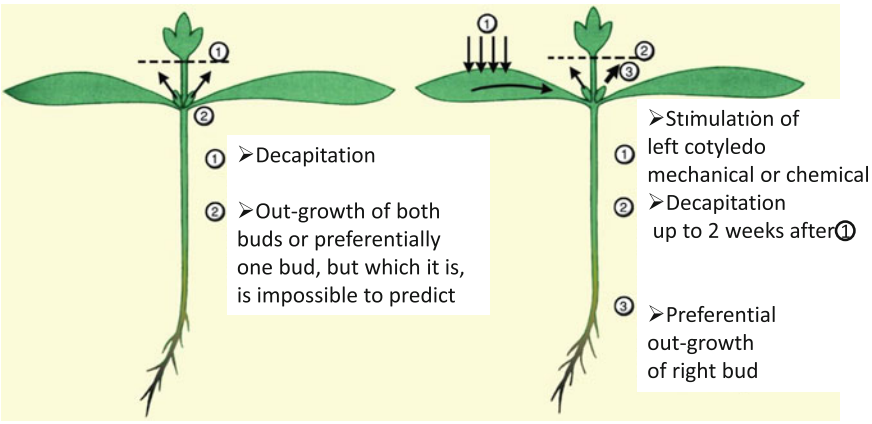


Fig. 11.7 Storage of information breaking the symmetry of lateral bud outgrowth in the axils of cotyledons of *Bidens pilosa* (L.) seedlings and its recall after decapitation

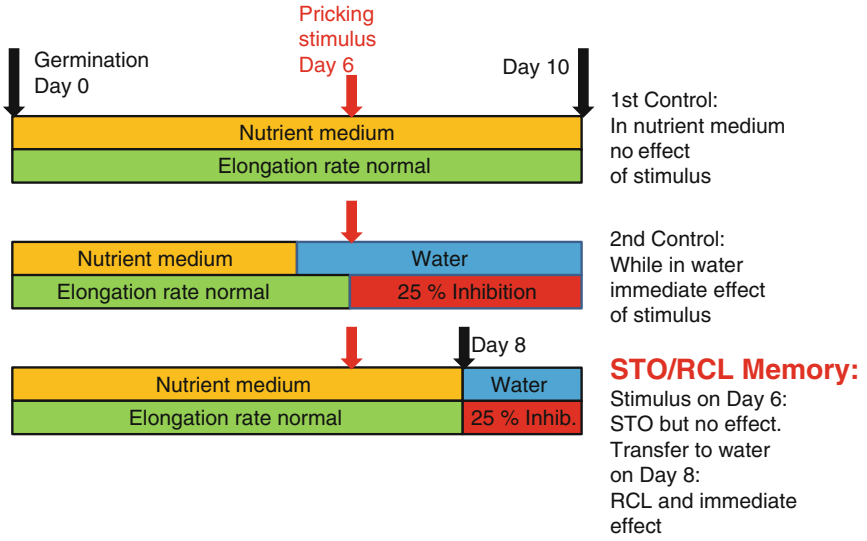


Fig. 11.8 Store/recall (STO/RCL) functions revealed by inhibition of hypocotyl elongation in *Bidens pilosa* (L.)

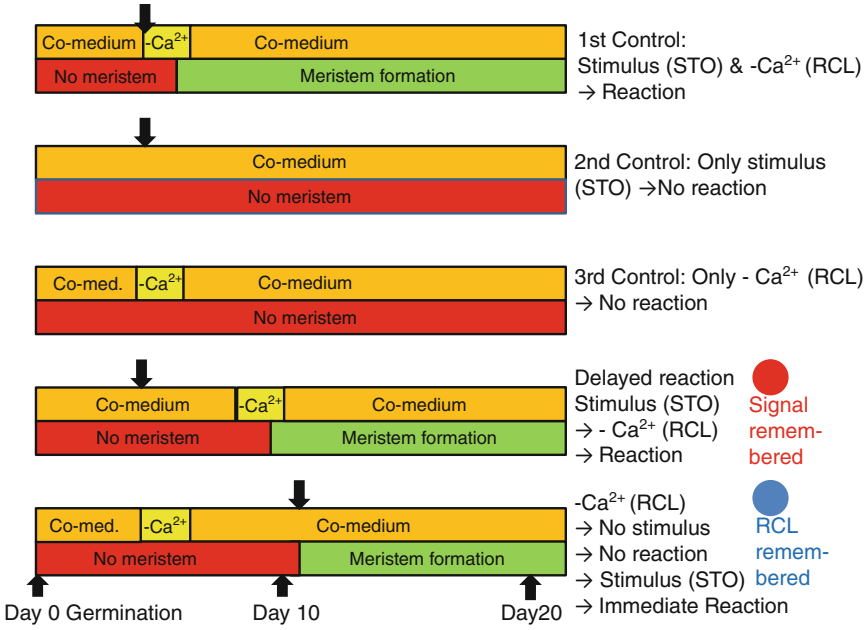


Fig. 11.9 Independent operation of store (STO) and recall (RCL) boxes shown by epidermal meristem formation in hypocotyls of flax seedlings. *Black arrows pointing downwards* stimulus by transfer to new culture medium of the seedlings. Co = control medium

by transient Ca^{2+} excess (RCL off) followed by transient Ca^{2+} removal (again RCL on). The 2nd interesting response was transiently removing Ca^{2+} (RCL on) without stimulus, and hence without response followed later by a stimulus (STO) eliciting an immediate reaction. This shows that the recall function was remembered. Again (see system I and Fig. 11.7), these experiments show that the STO and RCL boxes work independently of each other.

From the compilation of data as indicated above (Thellier and Lüttge 2013) or found in the literature, one may select a few interesting characteristics of the STO/RCL memories.

- The shape, amplitude and duration of the Ca^{2+} wave invading the cytosol immediately after stimulus perception have been found to be specific of the perceived stimulus [e.g. touch, cold shock or drought] (Dolmetsch et al. 1997; Knight et al. 1998; McAinsh and Hetherington 1998). Some of the early protein modifications (e.g. phosphorylation) and changes in genome expression are also specific of the perceived stimulus (Tafforeau et al. 2006). However, at a longer-term, it becomes impossible to find a memorized trace of the perceived stimulus. The only information that can eventually be recalled (even when recalled repetitively) is a sort of instruction controlling the final response (breaking of the symmetry of bud growth in system I, inhibition of hypocotyl growth in system II and production of epidermal meristems in system III) to be done in reaction to the perceived stimulus. Hence, it seems that the early reactions of the plant would orient the plant towards a response appropriate to the perceived stimulus. Briefly, by contrast to animals and humans that memorize facts and events, plants memorize the response to be done to stimulation.
- It has been observed with system III that the combination of several different stimuli changes the final response. This means that a STO/RCL memory can elaborate an integrated, updated response to the variety of stimuli and their fluctuations that are perceived in the course of time. This has definitely a better ecological value than memorizing the stimuli themselves and their fluctuations.
- The logic of the three types of final responses that a plant can make to stimulation then begins to get clearer. Direct, stereotyped responses are appropriate to react to rare or unknown stimuli. Responses involving priming memory permit the plant to economize producing defence substances against innocuous stimuli (familiarization) or increase the rapidity and efficacy of their reaction to harmful attacks (sensitization). Responses involving STO/RCL memory are particularly useful for acclimatizing the plant to the environmental conditions existing at the place where it has rooted. Moreover, the RCL function can serve to synchronize the use of stored information with the progress of other processes or reactions within the plant.

The functioning of plant STO/RCL memory is apparently associated with plant rhythmicity.

- With system I, the combination of an asymmetrical pricking stimulus with appropriate stimuli after varied intervals of time tends to turn the RCL box “on”

when this interval of time (h) is in the range of 0.5–2, 7–10 or 1 > 14, while it tends to turn the RCL box "off" when it is in the range of 2–4 or 10–14. The functioning of the RCL box thus is associated with an ultradian rhythm reset by the asymmetrical pricking treatment (Fig. 11.10).

- Again with system I, it was stated above that using seedlings that were asymmetrically stimulated (e.g. by pricking only one of the plant cotyledons) then decapitated sometime later at the onset of daylight, there was preferential outgrowth of the bud in the axil of the opposite cotyledon. This means that information subsequent to the asymmetrical stimulus was stored (box STO) in the plant and that, under these conditions of plant decapitation, the RCL box was "on". Now, when plant decapitation was carried out in the middle of the day both buds had equal chances to be the first to start growing, meaning that the RCL box was then switched "off" (Desbiez et al. 1986, 1991b; Thellier et al. 2013). Moreover, when decapitation was carried out at the end of the day, the RCL box tended to reopen (M. O. Desbiez, personal communication of preliminary results). The RCL box thus is clearly connected to the circadian rhythm.
- With system III (Verdus et al. 1997), when using plants all subjected to transient Ca^{2+} depletion, a very significant increase of the production of meristems has been observed to take place in the period of April to June whether these plants were stimulated or non-stimulated; however, the number of meristems produced in the stimulated plants remained at least 5 to 10 times larger in the stimulated than in the non-stimulated plants. By contrast, when using plants non-subjected to transient Ca^{2+} depletion, the number of meristems produced was always close to zero, whether the plants were stimulated or not and whatever the period of the year. It may thus be inferred that the functioning of the RCL box is somehow linked with an annual rhythm of the plants.

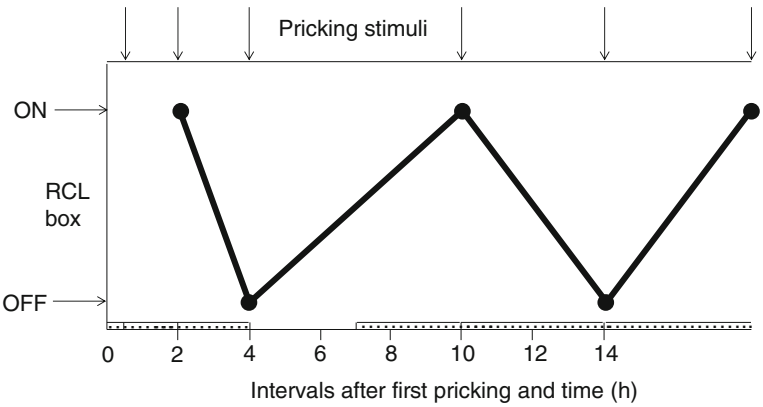


Fig. 11.10 Ultradian rhythm of switching the RCL box on and off, respectively, when pricking stimuli (*arrows* at the *upper* abscissa) are given after different time intervals (*dotted lines* at the *lower* abscissa)

In conclusion, the switching on/off (and inversely) of the RCL box thus appears to be intimately linked with all the types of rhythms of the plants. This reinforces the idea that the RCL box of the STO/RCL types of plant memory plays a part in the synchronization of the response to stimuli with the ultradian, circadian and seasonal evolutions of the metabolism and growth of the plant.

11.7 Case Study III of Systems-Theory-Modelling—Towards a Conceptual Model of Plant Memory

The data above suggest connecting memory to the biological clocks in the plants. However, basically a clock allows measuring the flow of time, but as such this is not memory. A clock becomes part of the structure and function of memory if it contains set points. An alarm clock set on a specific point in time is a reminder: it causes us to remember. An essential aspect is resetting of the clock. We experience this with our own endogenous biological clock after jetlag. We may change existing and introduce new set points of the memory and reminder functions of the clock. Resetting in general terms is the basis of new entrainment when phases of environmental rhythms have changed. Therefore, phase information genes (see Sect. 11.5.3) may constitute an important link between biological clock and memory, which are both basic building blocks in systems biology. Currently, this does not appear to be studied, but it should be a fascinating theme for future research deepening our understanding of biological systems.

We may now endeavour to draw a hypothetical, minimal model, which we may term a conceptual model, of plant memory (Thellier et al. 2013; Thellier and Lüttge 2013). Certainly, we expect that STO and RCL functions must have genetic bases, and we hypothesize the existence of STO and RCL genes. Proteome changes, i.e. up-regulation and down-regulation of the expression of genes for some proteins, and transient protein phosphorylation shortly after a stimulus are related to the STO/RCL memory (Henry-Vian et al. 1995; Tafforeau et al. 2006; Thellier 2011; Thellier et al. 2013). Studies of substrate induction of biochemical reactions in organisms led to the regulator–operator theory of gene regulation of François Jacob and Jacques Monod (Nobel Prize in 1965). Addition of the β-galactoside lactose to the prokaryotic cells of the bacterium *Escherichia coli* induced β-galactoside uptake and metabolism by inactivating a repressor. The induction was still effective, i.e. remembered, sometime after removal of the substrate until turnover produced an active repressor again and the induction was then forgotten. Glucose uptake by the eukaryotic algal cells of *Chlorella* is another example of substrate induction stable or memorized for more than 10 h after substrate removal (Tanner et al. 1970).

The genetically best studied genetic basis of memory functions is that of the epigenetic memory (Thellier and Lüttge 2013). Molecular epigenetics is a system of reading the genetic information of DNA. The molecular mechanism of epigenetic regulation is based on modifications of structure and conformation properties of

DNA and nucleosomal histones in the chromatin and changed acetylation/methylation equilibria (Zhang and Reinberg 2011; Yaish et al. 2011). Methylation leads to silencing of the genes (Chinnusamy and Zhu 2009). It controls biological functions of genes (Zhang et al. 2006). Epigenetic modifications are not associated with changes in DNA sequences. They can be triggered by the input of environmental cues, and they can be stable during cycles of mitosis and even meiosis. This means that there is epigenetic memory even through generations (Bird 2002; Hauser et al. 2011; Bilichak et al. 2012). From this, a minimal model of epigenetic memory can be derived as shown in Fig. 11.11 (Thellier and Lüttge 2013). Stimuli and environmental cues via various signals lead to modification of histones and chromatin and changed methylation/demethylation states. The methylation/demethylation state is then transmitted during mitotic or meiotic cell divisions. Alternatively, the histone/chromatin conformation is transmitted which then is followed by changed methylation/demethylation equilibria.

It is one of the basic approaches of systems biology to integrate modules into networks to study the emergent properties and to produce models for simulations (Lüttge 2012). With the modules of plant memory described above, a hypothetical minimal model can be built (Thellier and Lüttge 2013; Fig. 11.12). Separate STO and RCL genes are responsible for the separate functions of the STO/RCL memory. Stimuli and environmental cues via various signals and effectors, via the biological clock or via the epigenetic memory, unlock locked genes of the priming or the STO/RCL memory. Ca^{2+} waves (Berridge et al. 1998) derived from a

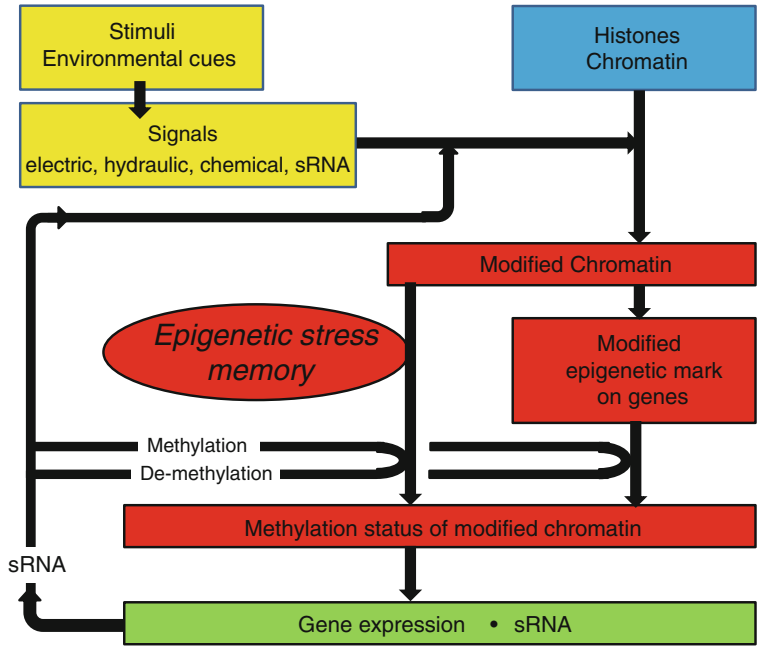


Fig. 11.11 Minimal model of the epigenetic stress memory

threshold-dependent Ca^{2+} condensation/decondensation on fixed negative charges and not obeying the mass-action law may be involved in activating the RCL-genes (Verdus et al. 2007; Ripoll et al. 2009; Thellier and Lüttge 2013; Thellier et al. 2013). The RCL-gene products affect the activation of the STO-genes. The STO-gene products are steering the processes of life such as those described above, i.e. growth (e.g. hypocotyl elongation, bud outgrowth), development (e.g. meristem formation) and differentiation.

The diverse observations on plant memory discussed in the previous section could in principle serve as a starting point for a mathematical model incorporating the notion of plant memory. Starting from the conceptual model of plant memory, it is interesting to try to elaborate a more mathematical model to become able to make quantitative predictions that can be tested experimentally. Several approaches have already been followed (Kergosien et al. 1979; Desbiez et al. 1994; Demongeot et al. 2000, 2006; Thellier et al. 2004). However, two challenges are the existence of multiple timescales and the requirement to go beyond a single type of biological processes (e.g. by including epigenetic signals, in addition to standard signal transduction and transcriptional regulation). Here, the diverse theoretical literature on modelling memory phenomena (Henke 2010), and multiscale phenomena (Twycross et al. 2010), as well as the progress in understanding epigenetic signals (Bonasio et al. 2010), might provide some guidelines in this direction.

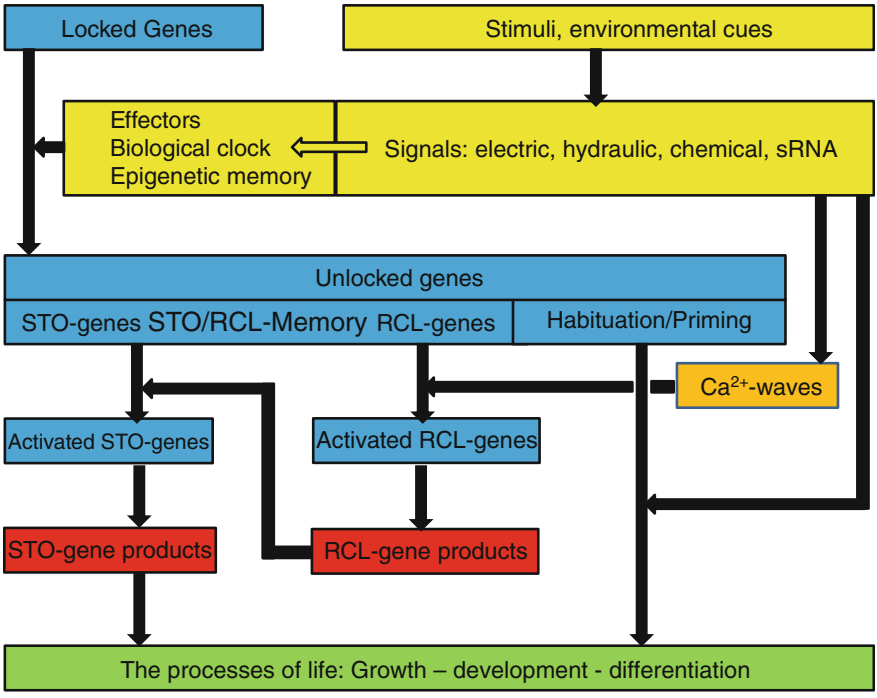


Fig. 11.12 Minimal model of the habituation/priming and store/recall (STO/RCL) memories of plants

11.8 A Path Towards Systems Biology

Systems biology has diverse subfoci, e.g. the formulation of minimal models (strongly influenced by statistical physics, theoretical biology and nonlinear dynamics), the development of detailed process ("in silico") models (inspired by engineering) and the integration and interpretation of high-throughput (multi-"omics") data (at the interface to bioinformatics). In plant biology, the systems view has by now established itself as an important research focus (see, e.g. Liu et al. 2010; Lucas et al. 2011; McClung and Gutiérrez 2010; Collakova et al. 2012; Bassel et al. 2012). Recently, this trend has been emphasized by two striking developments in the systems biology of *Arabidopsis thaliana*: the formulation of a compartmentalized metabolic model (Mintz-Oron et al. 2012) and the publication of a multiscale digital model capable of reproducing the effects of environmental regulators on *Arabidopsis* growth (Chew et al. 2014). Genome-scale metabolic models in plant science have also been reviewed in Collakova et al. (2012). In Liu et al. (2010) some recent progress in modelling of metabolism, growth, signalling and circadian rhythms in plant cells is summarized. How interaction networks can facilitate a systems-level view on many organizational scales in plant science is described in Lucas et al. (2011).

What are the origins of the high complexity of biorhythmicity when viewing it as an inherent property of systems? First, there are a variety of external control parameters, which may interact among each other. Second, the external control parameters feed in their signals via receptors into complex input networks with primary and secondary messengers. Third, the oscillators themselves are networks composed of a hierarchy of clock elements constituting the knots of molecular, biochemical, biophysical and physiological components interconnected by the edges of the networks. Fourth, the output pathways again are networks of feedback-regulated reaction systems, i.e. subsystems of the output machinery. Fifth, even the overt output oscillations may feedback information into the entire system (Lüttge 2003b; Lüttge and Hütt 2004). This forcefully underlines the strong nonlinearity as well as the entry of noise as a factor establishing ordered responses in biorhythmic phenomena, which can be grasped only by approaches incorporating all three legs of the magic tripod, viz. experimentation, theory and modelling—where our metaphor by no means implies witchcraft!

By adding to the standard approaches of theoretical biology, particularly the construction of minimal models, biology is currently at the threshold of addressing functional issues by means of integrative approaches at a system-wide level. Systems biology is emerging from genome sequencing. Initially, this aims at collecting data on cells ("cellome") and organisms (Raikhel and Coruzzi 2003) with "accurate measurements of thousands of molecules from complex biological samples" (Sweetlove et al. 2003). The conceptual idea behind this is comprehensive modelling, i.e. "the complete mathematical description of a model plant species" (Sweetlove et al. 2003)—in our view, this would be called a maximal model (Sect. 11.2). Subsequently, however, a key ingredient in the transition to systems

biology becomes integration of data on the spatial and temporal organization of biological units at very different scales. Beyond the existence of a particular gene in the genome, such a *systems biology* approach draws attention to several questions—under which external conditions is this gene expressed, which other genes regulate its expression, which external control parameters (e.g. temperature and resources) characterize the external conditions, and many other aspects.

Our understanding of circadian rhythms is a good example of such a transition towards an integrative approach. The process of integrating system-wide information from several scales is the core competence of systems biology. In terms of a slightly narrower definition based on (computational) systems biology, one needs to understand the step from laboratory experiments (either for living organisms, in vivo; or for subsystems—e.g. cell cultures, in vitro) to computer simulations (here, the term in silico seems now widely accepted) in order to understand system properties. In this approach, one assumes that a (mathematical) model representation of the system exists which is close to reality. Therefore, such systems biology approaches deviate from the minimal model concept, which attempts to grasp the essential systemic ingredients (for a particular set of phenomena; e.g. rhythmicity) with the smallest mathematical effort (or, more precisely, with the least complex model).

The task of systems biology—exploiting all empirical data to yield in silico simulations of the system—is tremendously difficult. On the one hand, this comes from the high complexity inherent in real biological systems. On the other hand, this task is complicated enormously by the sheer complexity of even very simple mathematical description. From our point of view, the general aims of systems biology can, therefore, only be accomplished by exploiting universal dynamic principles. These may provide a framework within which systems biology approaches can be incorporated. Indeed, to a certain extent they represent, in a very condensed form, a wealth of information on dynamic systems. In order to appreciate both the complexity of a systems biology approach as well as the potential patterning of realistic descriptions by universal dynamic principles, we will briefly discuss the minimal modelling of rhythmic phenomena as well as an example of such a universal dynamic principle relevant to rhythmicity, namely the emergence of spontaneous synchronization at an increasing coupling of dynamic elements.

This impressive example of a universal dynamic principle which may provide fundamental guidelines for a path towards systems biology has been discovered by Winfree (1967) and incorporated into a minimal model by Kuramoto (1984). As a collective dynamic phenomenon, synchronization has many facets in nature. Fireflies synchronize their flashing, leading to the dramatic visual perception of rhythmically flickering trees, and crickets synchronize their sound, just as concert visitors synchronize their applause. In epilepsy, a synchronous firing of many neurons is an essential part of the pathological dynamic state. Many forms of spatiotemporal pattern formation in biology require a (spatially organized) synchronization of functional units, e.g. to establish spiral waves and other forms of propagating patterns.

Discussing synchronization/desynchronization, we may distinguish between qualitatively different types of rhythmic output, which may be due to qualitatively different underlying oscillators, and qualitatively identical rhythmic output based on multiple copies of (qualitatively) the same oscillator. There are many examples of different types of rhythms expressed even within the same cells, and in both prokaryotic and eukaryotic unicellular organisms (Lüttge 2003a). Generally, these rhythms are not synchronized. Synchronization of multiple copies of functionally identical units is an important problem for theoretical analysis of nonlinear dynamics of spatiotemporal pattern formation. In plant biology, examples of timescales in synchronization/desynchronization range from rather short periods to those as long as, e.g. 30–40 years for the flowering of bamboo plants. For the shorter timescales, again we may return to stomata. Synchronization/desynchronization, of course, is involved in stomatal non-patchiness/patchiness (see Sect. 11.3 above). Individual oscillators or leaf patches also play a role in whether or not overall gas exchange of a leaf is seen to oscillate. Cardon et al. (1994) have demonstrated patchy distribution of stomatal oscillations in sunflower using chlorophyll fluorescence imaging and gas exchange techniques. Siebke and Weis (1995a, b) also used chlorophyll fluorescence imaging. With the assimilation images obtained, they observed that rapid changes in gas composition initiated synchronous oscillations in net gas exchange (H_2O and CO_2) which changed into non-synchronous oscillations due to slight local variations in the period. Obviously, oscillations in net gas exchange eventually disappeared but assimilation persisted, oscillating non-homogenously and non-synchronously over areas, patches or spots of the leaves (Siebke and Weis 1995a). Gas diffusion within the leaf may play a role in this respect (see Sect. 11.3; Cardon et al. 1994; Siebke and Weis 1995a), but minor vein distribution and its mediation of transport processes (e.g. sugar export) also appears to be involved (Siebke and Weis 1995b). Leaf cells of the CAM plant *Kalanchoë daigremontiana* oscillating in phase at high internal CO_2 levels desynchronize when internal CO_2 levels decrease (Rascher et al. 2001). When oscillations are desynchronized above an upper temperature threshold and leaves show overt arrhythmicity abrupt but not gradual reduction of temperature below the threshold triggers synchronization and overt rhythmicity (Rascher et al. 1998, see also above Sect. 11.3).

Still, how unavoidable is synchronization? How does it depend on external influences on the system? Do forms of partial synchronization exist, where only a subset of dynamic elements is synchronized? If so, which properties qualify an element to be part of the synchronous group? In order to understand the phenomenon of synchronization, we will look at it from a more formal perspective. Figure 11.13 shows the "generator" of our periodic signal, which will be the focus of our discussion. A point moves with uniform (angular) velocity along a circle of radius r in one plane. The position of the point can best be described in polar coordinates (ϕ, r). In terms of differential equations, one can summarize the dynamics simply by

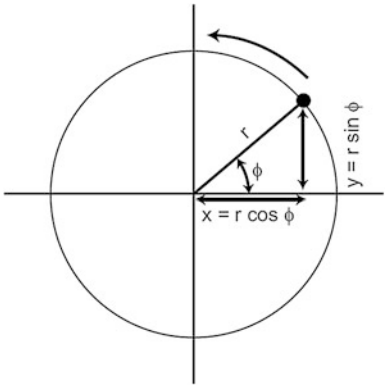


Fig. 11.13 Concept of a phase oscillator: schematic representation of a uniformly rotating point on a circle, together with the position given in Cartesian coordinates (x, y) and polar coordinates (r, ϕ; adapted from Hütt and Dehnert 2006)

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \text{const} = \omega \tag{11.2}$$

This simple system is called a phase oscillator. Here, the parameter ω is the eigenfrequency of this oscillator. A highly non-trivial level is reached when several such units are coupled. A frequent form of coupling is given by the sine of phase differences. For two such oscillators with eigenfrequencies ω_1 and ω_2, one has

$$\frac{\mathrm{d}\phi_1}{\mathrm{d}t} = \omega_1 + \varepsilon \sin(\phi_2 - \phi_1), \quad \frac{\mathrm{d}\phi_2}{\mathrm{d}t} = \omega_2 + \varepsilon \sin(\phi_1 - \phi_2) \tag{11.3}$$

The parameter ε is the coupling strength. One can now study the synchronization of the two oscillators as a function of ε and of the two eigenfrequencies ω_1 and ω_2. Figure 11.14 shows the phase *difference* $\Delta\phi = \phi_1 - \phi_2$ at fixed eigenfrequencies for increasing coupling. One can see that, at low coupling, the phases are independent, leading to a continuous change in $\Delta\phi$. At higher coupling, a significant crosstalk between the two phases appears. Over rather long time intervals, the phase difference is constant. For two oscillators with different eigenfrequencies to have a constant phase difference over time, they must adjust their respective frequencies to a common frequency (i.e. they must "synchronize"). Beyond Fig. 11.14, one can visualize this process by analysing the *effective* frequencies (i.e. the frequencies the coupled oscillators actually have) as a function of coupling strength. These effective frequencies Ω_1 and Ω_2 are given by the average phase change in a certain time interval. Figure 11.15a shows these effective frequencies Ω_1 and Ω_2 as a function of ε. At zero coupling, these effective frequencies coincide with the eigenfrequencies ω_1 and ω_2 from Eq. (11.3), as should be the case. At higher coupling, one observes the gradual adjustment of the two frequencies towards each other and, ultimately, the onset of synchronization.

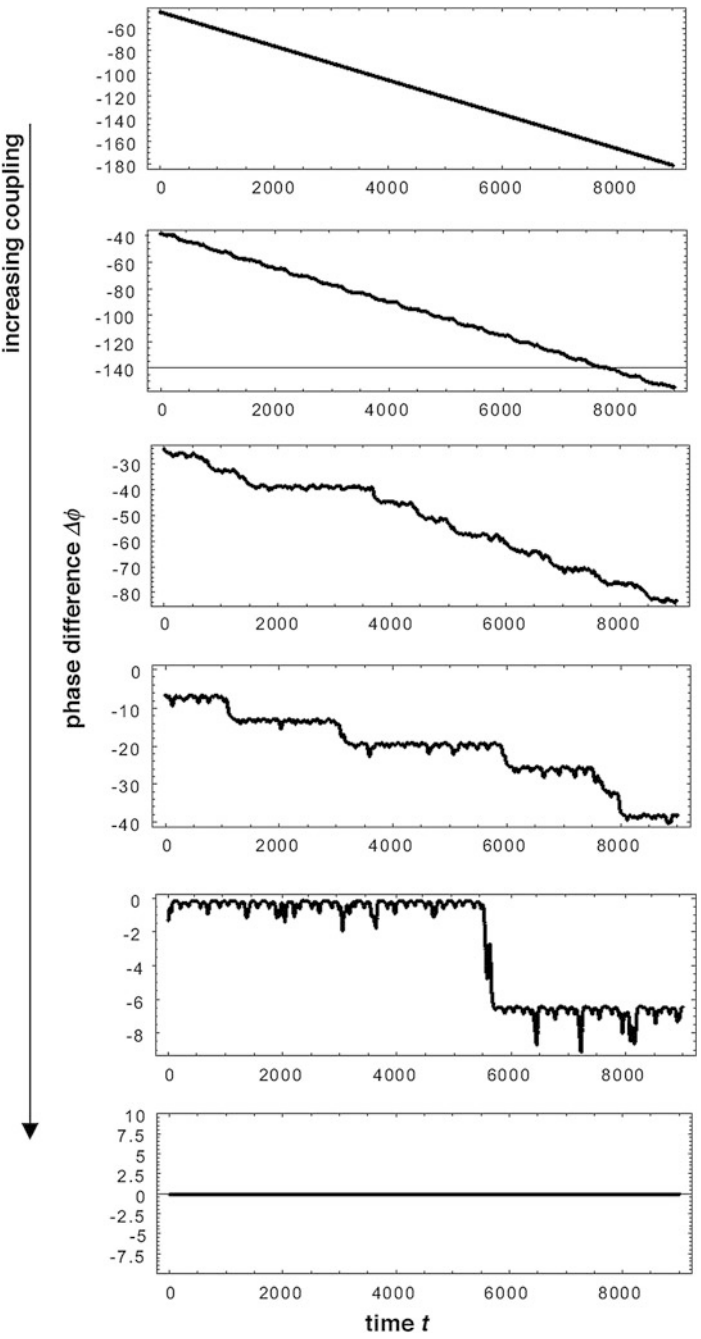


Fig. 11.14 Phase difference $\Delta\phi$ as a function of time t at different values of the coupling strength ε for a system of two coupled phase oscillators. The eigenfrequencies are $\omega_1 = -0.7$ and $\omega_2 = -0.4$. Coupling strength ε has been increased from $\varepsilon = 0$ (*top*) to $\varepsilon = 1.0$ (*bottom*) in steps of 0.2 (adapted from Hütt and Dehnert 2006)

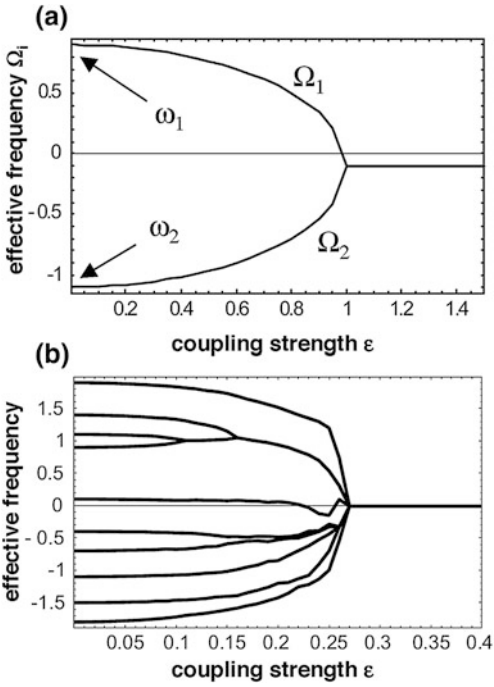


Fig. 11.15 **a** Effective frequencies Ω_1 and Ω_2 as a function of the coupling strength ε for the system of two coupled phase oscillators from Fig. 11.14. **b** Same as (**a**) but for ten coupled phase oscillators (adapted from Hütt and Dehnert 2006)

In a similar form, we can now discuss a larger set of phase oscillators. In Fig. 11.15b, the effective frequencies for a group of ten such oscillators are shown as a function of the coupling strength ε. A route towards complete synchronization paved by a stepwise synchronization of oscillators with similar eigenfrequencies is clearly seen. At a certain critical value of ε, all oscillators synchronize. This spontaneous onset of synchronization, when passing a critical coupling, is a minimal model of virtually any synchronization phenomenon in nature. At this point, the concept of universal dynamic principles discussed above becomes clear: a wide variety of individual phenomena is explained by a single principle. Furthermore, by having a universal description for the basic phenomenon of synchronization, it is now possible to identify additional effects in the individual systems beyond the basic phenomenon. An excellent non-mathematical introduction to synchronization is the book by Strogatz (2004). Systems biology can exploit such universal dynamic principles as backbones for the construction of more detailed and sophisticated models.

11.9 Conclusions

Among the three empirical examples chosen in our test scenario for plant systems biology two are directly displaying rhythmicity, namely CAM and stomatal patterns, while the third is intimately coupled with rhythmicity, namely memory. The concept of systems biology first emerged from technical advances which allowed analysing completely or almost completely all genes (genomics), all transcripts (transcriptomics), all metabolites (metabolomics), etc. of living systems. It then soon turned out that it was insufficient to know all those building blocks and that for understanding systems in addition all functions needed to be assessed. Progressively, this is still seen to be unsatisfactory because building-blocks and functions are nested in networks which always show nonlinear behaviour. This is particularly obvious where rhythmicity is involved, such as the ultradian, circadian and annual oscillations borne out by the case studies considered in this chapter. Such oscillations are intrinsically nonlinear phenomena. This requires searching for a new path towards systems biology where the three legs of the tripod—experimentation, modelling, theory—interact intimately and where coupling and synchronization of phase oscillators within networks allow to understand why the nonlinear functions of the biological systems with their enormous complexity are sustained.

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