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Time to grow: circadian regulation of growth and metabolism in photosynthetic organisms

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Circadian clocks are molecular devices that help adjust organisms to periodic environmental changes. Although formally described as self-sustaining oscillators that are synchronized by external cues and produce defined outputs, it is increasingly clear that physiological processes not only are regulated by, but also regulate the function of the clock. We discuss three recent examples of the intimate relationships between the function of the clock, growth and metabolism in photosynthetic organisms: the daily tracking of sun by sunflowers, the fine computations plants and cyanobacteria perform to manage carbon reserves and prevent starvation, and the changes in clock parameters that went along with domestication of tomato.

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Introduction

The course of Earth around its axis and around the sun exposes the surface of the planet to repetitive changes in light quality and quantity, temperature and water availability. The whole of the biosphere responds with rhythms in biological activity driven, in many organisms, by a molecular pacemaker called the circadian clock. The clock is entrained by environmental signals, yet is able to synchronize physiological and behavioural processes in the absence of external stimuli. Circadian clocks are built upon a group of proteins that are sequentially expressed in response to a setting condition, and mutually control their abundance and activity through transcriptional, translational and post-translational effects generating self-sustained periods of nearly 24 hours. This gear controls the expression of a significant portion of the genomes, allowing organisms to anticipate daily changes and to gauge the agreement between the predicted internal state and the actual environment [1]. Although external cues act as informative inputs, the ability to respond to a same stimulus varies according to the state of the oscillator, a phenomenon called 'gating'; inversely, internal signals reflecting the metabolic or developmental status impinge on the pulse of the oscillators.

In photosynthetic organisms, most physiological and developmental processes are associated with light:dark cycles. An impressive corpus of studies has delineated the plant circadian system as a quite complex genetic regulatory network based fundamentally on sequential, negative feedback loops. We refer to some recent revisions that describe the circuitry of the plant central oscillator [2–4]. Whereas many of the initial findings on clock-related processes stemmed from studies on defective seasonal reckoning in the form of flowering-time mutants, it is increasingly clear that the internal clock controls multitude of developmental processes along the life of plants. We summarize recent findings that exemplify the intimate relationships between the function of the clock, metabolism and growth.

Never doubt that the sun doth move

The daily folding of leaflets in legumes was probably the first attested rhythmic process in plants. Theophrastus (IVC BC) refers to the tamarind and its 'sleeping' leaves [5]; more than 2000 years later, Darwin's list of plants with sleep movements included many legumes [6]. However, these movements do not reflect irreversible growth but reversible changes of turgor in specialized cells [7]. In contrast, daily solar tracking (heliotropism) by sunflower (*Helianthus annuus*) apices is intimately associated with unidirectional growth, to the point that tracking movements cease as growth comes to an end when the inflorescences mature. Young sunflower apices point east in the morning, track westward sun movements during the day and regain an eastward orientation during the night. This behaviour depends on a directionally changing light source, but an internal time-keeping mechanism has been long suspected [8,9].

A recent report [10••] convincingly shows that the clock is involved in this behaviour. Solar tracking persists in constant conditions with a period of approximately 24 hours and is severely impaired when plants entrained in 24-hour cycles are transferred to extended day lengths, both hallmarks of clock-driven mechanisms. Heliotropism is caused by alternating growth patterns of both sides of the stems: the eastern side elongates during the day, whereas the western side elongates at night. Stems of sunflower plants under a fixed light source elongate only at night at about the same timing and rate as the western side, suggesting that the diurnal eastern growth is a specialized feature driven by an environmental stimulus but also muted by the clock at night. The expression of clock-related genes is the same in both sides of the stems, but homologs of auxin induced genes involved in phototropic responses in *Arabidopsis thaliana* are differentially expressed; this swaying growth pattern thus depends on an alternating hormonal input or sensitivity, probably driven by the clock (Figure 1a).

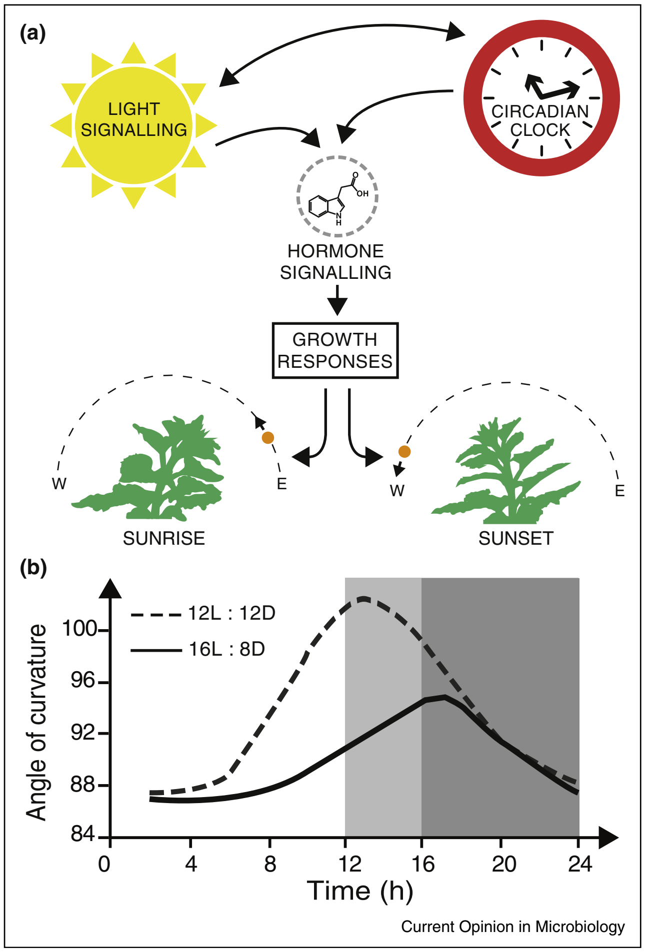
Differential growth appears to have several adaptive consequences. Interference with the plant's ability to track the sun leads to lower biomass production [10••], possibly because heliotropism reduces internal shading and may therefore optimize overall photosynthetic efficiency [8]. Also, mature inflorescences facing east heat up more rapidly in the morning, which makes them more appealing for pollinators and probably keeps them drier, preventing the attack of fungi and accelerating the maturation of seeds. However, mature apices are no longer heliotropic. Do young apices track the sun as a precondition to orient mature inflorescences eastwards, instead of using a (clock-gated) phototropic response that makes them face the rising sun?

In field-grown plants under different photoperiods the rate of stem curvature seems to depend on day length (Figure 1b). Given an apparently constant nighttime reorientation rate, this appears to be necessary to return on time to the initial position at dawn. In other words, sunflower apices appear to be able to compute day length and adjust growth rates to precisely reset their orientation according to the presumed time to sunrise. Although seasonal changes in growth patterns may be accounted for by several environmental factors (such as water availability, to which solar tracking in sunflowers is sensitive [8], or differences in light angle and fluence), this behaviour seems to be an aspect of a fundamental property of the clock: to keep track of the length of the day to fine tune the rates of physiological processes. In the next section we discuss two examples of this feature.

Hoy comamos y bebamos … que mañana ayunaremos[2]

Growth of photosynthetic organisms relies ultimately on carbon fixed in the light. Management of reserves is of paramount importance, since short spells of carbon depletion lead to growth inhibition [11,12]. Plants deploy thrifty strategies to prevent starvation during predictable light:dark cycles and when faced to stochastic changes in light supply. Plants linearly accumulate starch during the day and use it up almost completely during the night until dawn. Strikingly, plants are able to immediately reduce the rate of starch degradation when exposed to an early dusk, but exhaust their lot before time in face of a belated dawn [13,14] (Figure 2a). The internal timer thus keeps a record of the expected time until dawn and adjusts metabolic rates accordingly. In fact, mutants with shortened clock periods consume their reserves before dawn when exposed to 24-hour cycles, showing that the internal time, not the external conditions, sets the pace of starch metabolism [14]. Probably as a consequence of this

Figure 1



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Sun tracking by sunflowers as a concerted interplay between the environment and the clock. **(a)** Differential growth of the east and west sides of the stems during the day and night is driven by environmental cues and the clock. **(b)** Daily deflection (in angles) of developing apices in field-grown sunflowers in fall (12 hours light:12 hours darkness, dotted line) and summer (16 hours light:8 hours darkness, full line). In both cases, organ position is precisely reset before dawn. Adapted from data reported by [10••].

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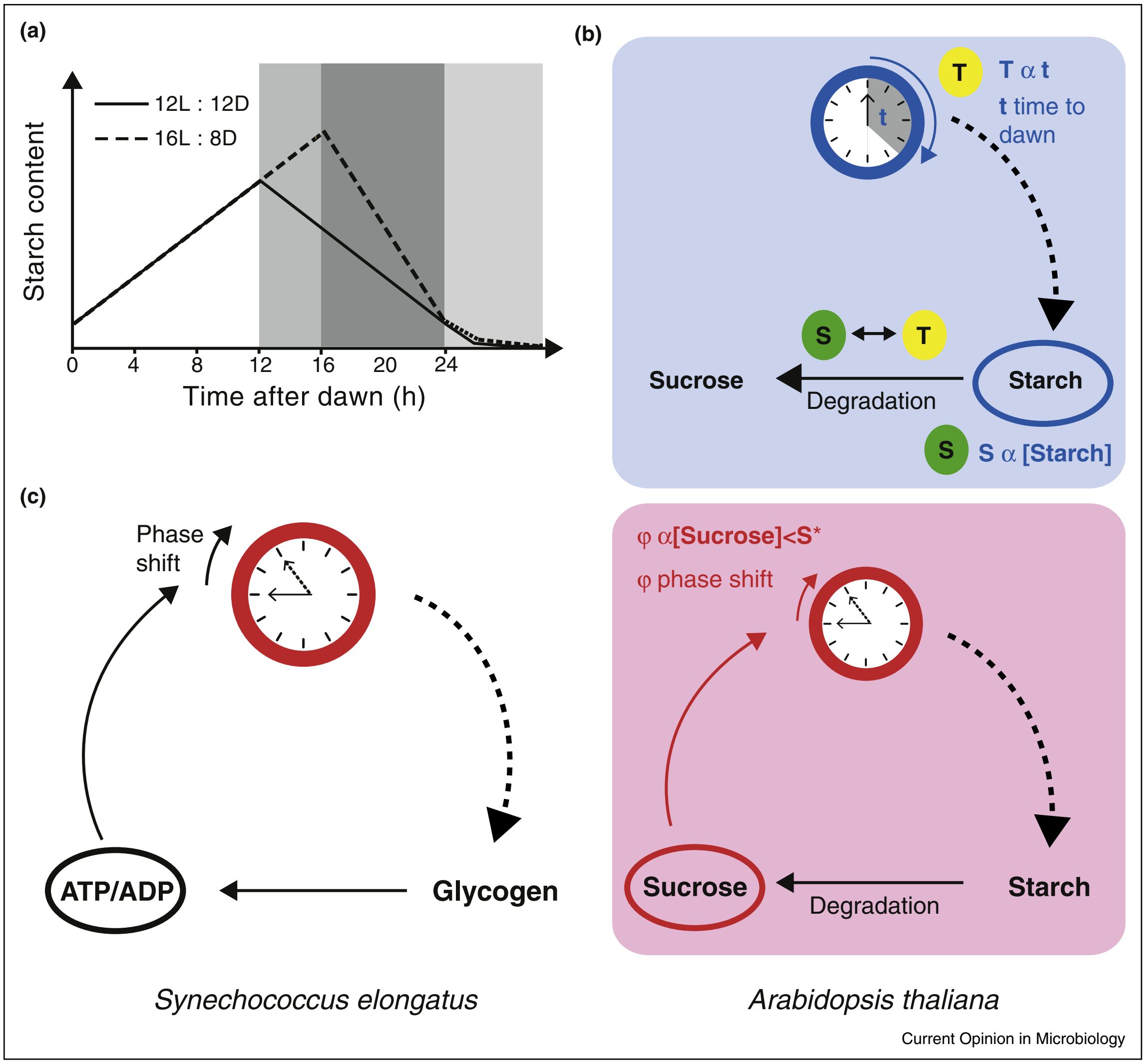
[2] 'Let's eat and drink today… for tomorrow we shall fast', Juan del Enzina (1468–1529), Cancionero de Palacio.

Figure 2



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Control of carbon metabolism by the clock in photosynthetic organisms. **(a)** Rates of starch degradation in Arabidopsis can immediately adjust to an early dusk (a change from 16 hours light:8 hours darkness to 12 hours light:12 hours darkness, shaded areas), so that starch reserves are nearly exhausted by the time of the predicted dawn (24 hours). A late dawn (shaded area beyond 24 hours) exposes plants to a period of unexpected starvation. Adapted from [47]. **(b)** Schematic representation of the two main models that have been suggested to account for linear rates in carbon allocation in Arabidopsis. In one of them (upper part, blue outlines), starch degradation rates are defined by the interplay between two molecular entities (S and T) whose abundance are proportional to the amount of starch and the estimated time to dawn (t), respectively. In the other (lower part, red outlines), sucrose availability is monitored and clock parameters modified accordingly when sucrose levels fall short of a starvation threshold S*. Adapted from [18,20,48]. Black arrows indicate that the clock regulates photosynthate partitioning and starch degradation. (c) Schematic representation of the interplay between clock and metabolism in *Synechococcus elongatus*. Dotted arrow indicates the circadian regulation of glycogen accumulation.

strategy, Arabidopsis mutants with shortened or extended periods perform better, in terms of biomass and offspring, when the external day length matches their internal predictions [14–16].

How do plants factor in the amount of starch available and the predicted time to dawn? Two main models have been put forward (Figure 2b). One of them assumes that plants sense the amounts of starch and the time until dawn and dynamically define a constant degradation rate through two hypothetical chemical entities that may interact on the surface of the starch grain [17•,18]. A complementary model introduces two components responsible for starch degradation in the night and synthesis in the day, regulated both by light and the clock [19]. The other hypothesis states that it is the amount of available sucrose that is sensed so as to prevent starvation. In this case, the starch degradation rate depends on phase shifts of the clock that adjust in real time to the availability of sucrose [20]. This idea, in turn, relies on the observation that the

Arabidopsis clock can be entrained, in constant darkness or when photosynthesis is prevented, by the exogenous supply of sucrose, and that sucrose induces phase and period shifts in outputs of the clock [21•]. However, the nature of these sensing mechanisms remains elusive: although the transcription of many genes related to starch metabolism strongly cycles during the day and may be good candidates for clock-controlled processes, their respective enzymes appear to be exceedingly stable [for example [22]]. A genetic screen aimed at identifying mutants that exhaust prematurely their starch reserves (*esv*, for 'early starvation') is producing its first fruits. *ESV1* codes for a chloroplastic protein of unknown function bound to starch granules, that appears to make starch more degradable [23].

Studies on a simpler biological model are providing independent insights into the connections between clock and metabolism. The central oscillator in the cyanobacterium *Synechoccocus elongatus* is made up of just three proteins; the pulse of the clock is sustained by a diel cycle of reversible auto-phosphorylation of the central oscillator protein, KaiC, coupled to a transcriptional-translational feedback circuit [24,25]. As in Arabidopsis [15,16], cyanobacterial strains with a functional clock outperform those with defective clocks in alternating light:dark conditions, and the competitive advantage is maximal when their internal rhythms resonate with the environment [26,27].

Cyanobacteria accumulate glycogen as a consequence of CO2 fixation during the day and use it up during the night; glycogen abundance oscillates in constant light and becomes arrhythmic in clock-defective mutants [28]. Although glycogen cycles under light:dark conditions in clock mutants, its accumulation kinetics is different from the wild-type, as happens with several circadian outputs in Arabidopsis clock mutants grown in illumination cycles [29]. As it appears, one of the main metabolic roles of the clock in *Synechococcus* is to set a nearly linear rate of glycogen accumulation during the day, driving the expression of the enzymes of the reductive branch of the pentose phosphate pathway (the Calvin-Benson cycle) at dawn and of the oxidative branch after dusk [30•]. Most experiments in cyanobacteria are performed in 12-hour light:12-hour darkness cycles; it would be interesting to check whether glycogen metabolism rates adjust to different photoperiods, as they do in Arabidopsis.

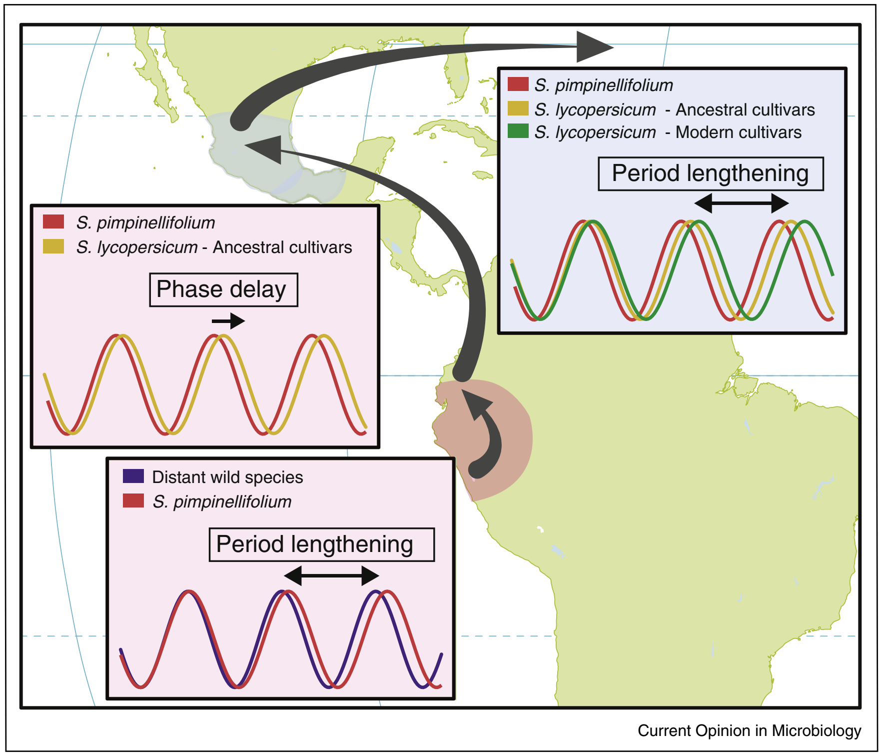
Most physiological processes in cyanobacteria arrest in the dark, correlating with a sharp decline in the concentration of ATP. Dark pulses during the subjective day delay the phase of the clock, whereas pulses during the subjective night barely have any effect [31], indicating a clock-gated process. A drop in the ATP/ADP ratio affects the phosphorylation kinetics of KaiC [32]. In fact, an engineered *Synechococcus* strain that grows heterotrophically when supplied with sugars demonstrated that rhythmic glucose feeding, through its effect on ATP concentrations, can entrain the clock independently of light [33••] (Figure 2c). Phase resetting by darkness is probably a consequence of the mismatch between the metabolic prediction by the clock and the actual metabolic status of the cell. Indeed, darkness imposes a heavy toll on cells caught in a growth-prone phase of their day, to the point of completely arresting growth, probably due to a failure in managing reserves in the absence of light [34]. The ability to accurately foresee the deprivations of night, rather than protecting from the dazzling sunlight, may be one of the major functions of circadian clocks in photosynthetic organisms. Studies on unicellular models highlight the intimate connections between the clock and metabolism: bidirectional feedback loops tune metabolism to the environmental cues, and metabolic states produce shifts in the function of the clock [35].

You may delay, but time will not

In the past 12000 years, the adoption of agriculture led to a worldwide experiment of genetic selection and niche construction. Along latitudinal clines, humans deftly selected plant variants whose life cycle matched seasonal changes in day length and temperature; in fact, clock-associated genes that modify photoperiod sensitivity have been recurrently targeted in most crop species [we refer to recent reviews on the subject [36•,37•]]. These gene variants modify outputs of the clock but not significantly the period of the oscillator itself, even if mutations in their orthologs in Arabidopsis cause rhythmic perturbations. This shouldn't be surprising: these variants have been selected because they do not impair, but instead enhance, growth and yield. A recent report shows, however, that at least in one crop species changes in the period and phase of the clock may have been selected for during domestication [38••].

The history of tomato cultivation remains obscure because of the dearth of archeological remains. Nonetheless, extensive genomic analyses have delineated a plausible history [39,40]. The closest wild relative, *Solanum pimpinellifolium*, grows in Northern Peru and in Ecuador. Although proofs of tomato cultivation by original cultures in South America are lacking, local varieties in the valleys of Ecuador (*Solanum lycopersicum* var. *cerasiforme*) display a high degree of heterozygosity and population structure, suggesting a long-term management [40]. Modern-day cultivars, however, descend from tomatoes that were grown in central Mexico when the Spaniards arrived in the XVI century. Genetic evidence shows that migration from South America to Mesoamerica was accompanied by a population bottleneck that caused a drop in heterozygosity [39]. Tomato thus appears to have been first subject to a certain degree of selection in equatorial western South America, and underwent further rounds of selection for plumper fruits in Central America, giving

Figure 3



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Clock parameters and domestication in tomato (*Solanum lycopersicum*). Arrows indicate the expansion of tomato culture from its centre of origin in Northern Peru and Ecuador to Mesoamerica in precolumbian times and, since the XVI century, to Europe. The area that hosts wild tomato populations (in particular, those of the presumed immediate ancestor *Solanum pimpinellifolium*) and locally grown cultivated varieties, where changes in clock parameters can already be detected, is shown in pink; in blue, the area in Mesoamerica whence modern cultivars derive from.

rise to the modern species (*Solanum lycopersicum* var. *lycopersicum*) (Figure 3).

In tomato, the regular movement of leaves under constant conditions, one of the preferred experimental outputs of the clock, is delayed both in phase and period (~3.5 and ~3 hours respectively) compared to its wild relatives [38••]. This phenotype extends to the expression of central oscillator genes, indicating the clock itself runs at a slower pace. The comparison of clock parameters between modern cultivars, landraces from South and Central America, *S. pimpinellifolium* and sympatric but more distantly related wild species revealed a three-step process that parallels the outlined domestication pathway: a first delay in the period of the immediate ancestor *S. pimpinellifolium*, followed by a phase shift in local South American varieties and finally a further period delay in local Mesoamerican and modern varieties. Two main genetic determinants underlie this behaviour, and one of them was identified as a mis-sense mutation in a homolog of Arabidopsis *EID1*, a gene that negatively regulates phytochrome signalling [41]. A significant loss in genetic diversity around this locus in cultivated varieties suggests that the domesticated variant has been selected by ancient farmers to alter light input to the central oscillator.

From its cradle near the equator, tomato ended up being cultivated at ~15–20° N in central Mexico and afterwards mainly in the Mediterranean basin (35–45° N) before modern breeding took off in the XIX century. It is assumed that a delayed oscillator may have been adaptive in the longer days tomatoes found in its northbound travels. Ancestral American tomato varieties are short-day plants, that is, they flower when nights extend beyond a certain critical length, but most modern cultivars flower independently of the photoperiod. A positive correlation between period length and latitude (particularly at high latitudes) has been observed in Arabidopsis [42]. In long-day conditions, the domesticated variant of *EID1* induces an end-of-the-day shift in the transcription pattern of a light-harvesting chlorophyll binding protein and in a homolog of Arabidopsis *GIGANTEA* (*GI*), a master clock gene that modulates a wealth of input and output pathways to the central oscillator [43]. In fact, *GI* has been ascribed a role as part of the metabolic sensors of the clock [44]. A delayed clock may, then, not only impact on flowering but probably has more general effects on metabolic adjustment.

Clock parameters show evidence of changes in the ancestor of cultivated tomato, compared to related wild species that thrive at about the same latitude [38••]. *S. pimpinellifolium* grows in finely grained landscapes, ranging from coastal deserts to humid, high-altitude valleys. Is there a relationship between local conditions and changes in period? Tomato's growth habit differs from most other model crop species: the apical meristem is terminated after a few leaves, and growth resumes from lateral meristems, producing 'sympodial units' consisting of typically 3 leaves and an inflorescence. Growth and termination therefore need to be assessed on a daily basis throughout the life of the plant [45,46]. Although assigning an adaptive explanation to the deceleration of the clock is not straightforward with the evidence available — the identification of the other genetic determinant of longer periods should shed more light on this issue — it is worth considering that shifts in the pace of the clock may have been selected to optimize growth and yield under specific conditions, a process that probably is being explored by tomato wild ancestors.

Circadian rhythms in sessile photosynthetic organisms can be considered a type of behaviour and, as such, are exquisitely sensitive to both external and internal signals. The cases discussed show that, invaluable as model systems and controlled conditions are to tackle difficult questions, the study of different species opens up new perspectives, and that mechanistic hypotheses on such broad categories as growth and fitness must take into consideration life strategies and ecological and evolutionary constraints.

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