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# Circadian gating: concepts, processes, and opportunities

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Circadian clocks provide a biological measure of time that coordinates metabolism, physiology and behaviour with 24 h cycles in the environment. Circadian systems have a variety of characteristic properties, such as entrainment to environmental cues, a self-sustaining rhythm of about 24 h and temperature compensation of the circadian rhythm. In this perspective, we discuss the process of circadian gating, which refers to the restriction of a biological event to particular times of day by the circadian clock. We introduce principles and processes associated with circadian gating in a variety of organisms, including some associated mechanisms. We highlight socioeconomic opportunities presented by the investigation of circadian gating, using selected examples from circadian medicine and agricultural crop production to illustrate its importance.

This article is part of the Theo Murphy meeting issue 'Circadian rhythms in infection and immunity'.

## 1. Introduction

The rotation of the Earth on its axis leads to predictable 24 h fluctuations in environmental conditions, including 24 h cycles of light, temperature and humidity. The selection pressures arising from these 24 h fluctuations have led to the evolution of circadian clocks, which are found across the kingdoms of life. Circadian clocks produce a cellular measure of the time of day, which aligns biological processes with the 24 h cycle of day and night (figure 1*a*). This is thought to increase the fitness of a range of organisms [1]. Circadian clocks are underpinned by a biological oscillator (the circadian oscillator), which is entrained to environmental cues to maintain an appropriate phase relationship between the circadian clock and the daily environmental cycle (figure 1*a*). The phase refers to the positioning of an oscillation in relation to a reference point; for example, whether a rhythm peaks at dawn (figure 1*a*) or 6 h after dawn. In most organisms, the circadian oscillator includes transcription–translation feedback loops that operate with a period of about 24 h, which causes time-of-day-specific expression of many genes and proteins (figure 1*b*). This means that the estimate of the time of day derived from the circadian clock is communicated to a variety of biological processes, establishing their circadian regulation (figure 1*b*).

Circadian clocks have a variety of properties that are necessary to establish appropriate phase relationships between clock-controlled physiology and the environment [2]. Important properties of the clock include a free-running (self-sustaining) rhythm with a period of approximately 24 h (figure 1*c*), entrainment of the clock to environmental cues, temperature compensation of the rhythm such that its period is relatively stable across a physiological temperature range and modulation of the circadian period by the intensity of light (so-called 'Aschoff's rule') [2,3]. Here, we consider a further property of circadian systems, known as circadian gating. This is the process whereby the circadian clock restricts processes or environmental responses to certain

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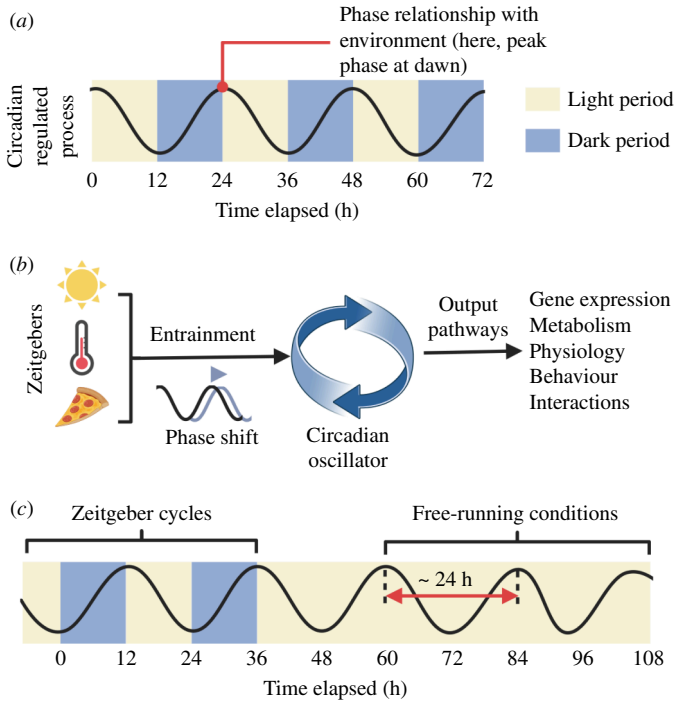


**Figure 1.** Key features of circadian rhythms. (*a*) Under 24 h environmental cycles, the circadian clock establishes a phase relationship between circadian-regulated biological processes and the 24 h fluctuating environment. (*b*) Conceptual organization of circadian systems. The circadian clock is entrained to 24 h fluctuations in environmental stimuli (known as zeitgebers) that lead to the entrainment of the circadian clock by adjusting its phase. Zeitgebers are graphically depicted as a sun (representing light), thermometer (representing temperature) and a pizza slice (representing nutrients or feeding conditions). The estimate of the time of day produced by the circadian oscillator is communicated through output pathways to circadian-regulated aspects of molecular biology, metabolism, physiology and behaviour. (*c*) Under free-running conditions (which might be continuous darkness or continuous light, depending on the study organism), the circadian clock and circadian-regulated physiology and behaviour possess a free-running rhythm that has a period of about 24 h.

times of day. Gating is an important feature of circadian rhythms because it determines how organisms respond to their fluctuating environments and is one process that ensures an appropriate temporal alignment between many biological processes and environmental conditions. While understanding the processes of circadian gating is valuable to appreciating how organisms respond to an increasingly unpredictable climate, it can also determine the times when organisms have the greatest sensitivity to interventions such as therapeutic treatments. Therefore, the processes that underlie circadian gating provide opportunities to make use of circadian rhythms for socioeconomic benefit.

## 2. Principles of circadian gating

The concept of circadian gating refers to the restriction of a biological process to certain times of day by the circadian clock. The concept is used in relation to several types of processes, with some variation in interpretation depending on the experimental system, types of physiology or behaviour under investigation. Some of the first investigations of circadian gating concerned the emergence of adult Drosophila flies (eclosion) from the pupal case. Under 24 h cycles of light and dark, eclosion is prevented during the periods of day when the temperature in nature would be greatest, with a 24 h cycle of eclosion being maintained under conditions of constant darkness [4]. This daily cycle is divided into periods when eclosion is 'allowed' or 'forbidden', which was subsequently described as a circadian gate of this developmental process [4,5]. In a similar manner, the cell division cycle of the unicellular eukaryotes *Euglena gracilis* and *Chlamydomonas reinhardtii* [6,7], and the cyanobacterium *Synechococcus elongatus* PCC7942 [8], separates into periods of the 24 h cycle when cell division is either permitted or prevented [8]. In the case of *S. elongatus*, this appears to arise from circadian control of the rate of the cell cycle [9]. However, the circadian gating of cell division does not seem to be universal because there is little evidence for this in *Saccharomyces cerevisiae* [10]. In these cases of circadian gating, the likelihood that an event such as eclosion or cell division occurs at any particular time of day is defined by the circadian clock (figure 2*a*).

Another form of circadian gating relates to the effect of entrainment cues (zeitgebers) upon the circadian clock. In this case, there is a circadian rhythm in the response of the oscillator to a zeitgeber (figure 2*b*), such that the zeitgeber produces a different magnitude of phase shift depending on its time of application (figure 2*c*). Examples of this occur in a variety of organisms. For example, in the circadian clock model fungus *Neurospora crassa*, the photoreceptor VIVID (VVD) participates in a mechanism that gates an entraining light input to the clock [11]. VVD is rapidly light-induced, with the magnitude of this induction being regulated by the clock. VVD influences the circadian phase of both *vvd* and *frq* transcripts by physically repressing the white collar complex of the *N. crassa* clock [12]. Furthermore, a VVD mutant substantially alters the phase response of entrainment to light of the *N. crassa* clock [11]. This positions VVD within a clock-gated light input module that participates in circadian entrainment. Similarly, in the model plant *Arabidopsis thaliana* (Arabidopsis), the proteins EARLY FLOWERING3 (ELF3) and

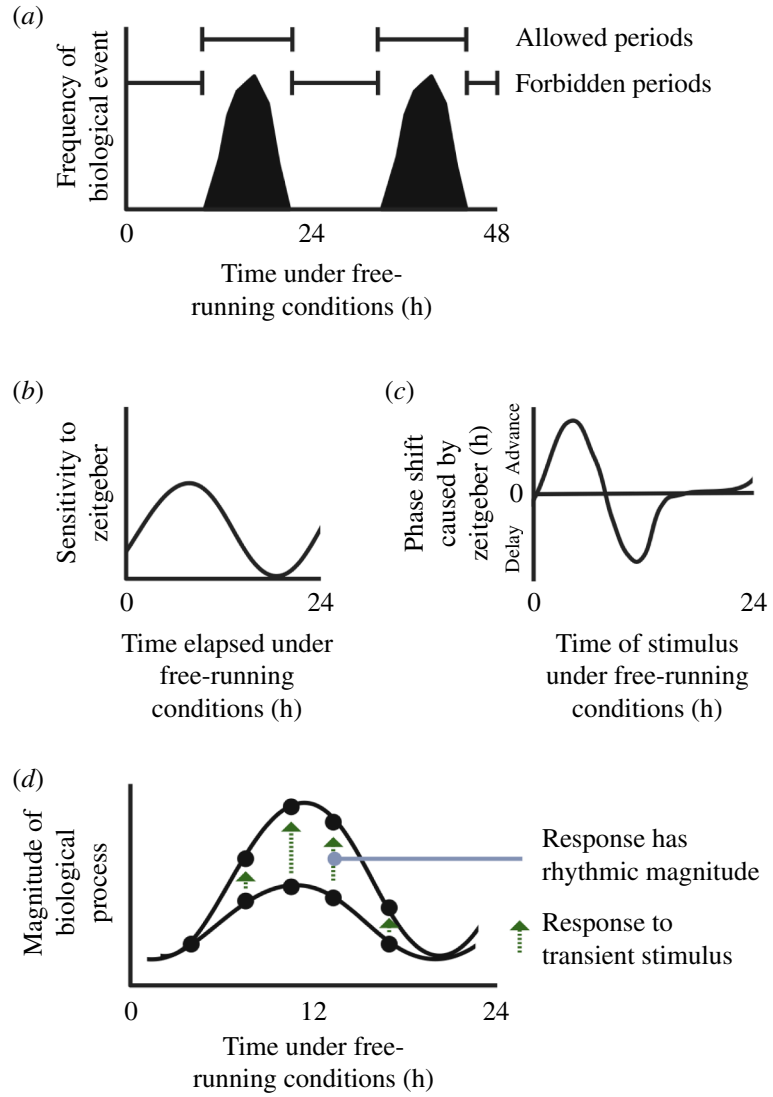


**Figure 2.** There are several manifestations of circadian gating. (*a*) The circadian clock controls a biological process so that it occurs at only certain times within the 24 h cycle. These have been described as time periods when the clock allows or forbids a process [4]. (*b, c*) Circadian gating acts upon the entrainment of many circadian clocks, such that there is an oscillation in sensitivity to the zeitgeber (*b*), which interacts with clock dynamics (it can, for instance, signal the clock to go faster or slower at different times of day) to produce a 24 h fluctuation in the magnitude of the phase shift of the circadian oscillator that is caused by the zeitgeber (*c*). (*d*) The circadian clock regulates the magnitude of a stimulus-induced response, such that the same stimulus applied at different times over the 24 h cycle leads to response of different magnitudes.

FAR-RED ELONGATED HYPOCOTYLS3 (FHY3) participate in the gating of light inputs to the circadian clock [13,14]. ELF3 is required for formation of the repressive evening complex (EC) of the circadian oscillator [15,16], and mutation of ELF3 leads to loss of circadian gating of light-responsive gene promoters and also disrupted entrainment of the circadian oscillator to light [13,17].

Circadian gating also acts within output pathways from the circadian oscillator (figure 1*b*). In this gating mode, the circadian oscillator causes a 24 h cycle in the magnitude of the response of a biological process to a stimulus (figure 2*d*). An example of this is the release of glucocorticoids and related molecules from the adrenal glands of rodents [18]. This glucocorticoid release occurs in response to adrenocorticotropin hormone (ACTH), which stimulates glucocorticoid production from the adrenal cortex [19]. There is a circadian fluctuation in the amount of glucocorticoid released in response to a given dose of ACTH [18]. This is abolished in the *Per1*/*Cry1* double mutant that lacks circadian rhythms in the adrenal gland, indicating that the clock underlies this rhythmic responsiveness to ACTH [18]. Another excellent example is the response of macrophages to lipopolysaccharide (LPS), a highly inflammatory molecule found on the outer membrane of gram-negative bacteria. When challenged with LPS, there is a circadian fluctuation in the production of proinflammatory cytokines such as interleukin (IL)-6, IL-12(p40), and chemokines including CCL2, CCL5 and CXCL1, with a greater response to LPS at subjective dusk, compared with the response to LPS at subjective dawn, when under free-running conditions [20,21]. This occurs through a mechanism involving the repressor REV-ERBα, which negatively regulates expression of the clock gene *Bmal1* [21]. Another example is the involvement of circadian regulation in the timing of mammalian ovulation, which incorporates multiple layers of circadian regulation involving the superchiasmatic nucleus and peripheral oscillators [22]. A surge of luteinizing hormone (LH) triggers ovulation, and it was found that the ovarian circadian clock modulates the frequency of ovulation in response to LH [23]. Injection of rats with an LH treatment during the night or subjective night causes a greater number of oocytes to be released compared with LH treatment during the day [23].

There is also widespread circadian gating of responses to environmental stimuli in plants [24]. In the model plant Arabidopsis, an example of this type of gating concerns the responses to cold temperature of a set of genes associated with the development of freezing tolerance (cold acclimation). Temperate plants use low non-freezing temperatures as a source of environmental information to trigger the development of freezing tolerance, through the expression of genes in the *C-REPEAT/DRE BINDING FACTOR* (*CBF*) family. The CBFs are transcriptional regulators of genes that underlie cold acclimation. There is circadian gating of the responses to cold of transcripts encoding CBF1–3; this is thought to be mediated by direct regulation of *CBF* gene promoters by the clock proteins CCA1 and LHY, which work in conjunction with cold-responsive translocation of the clock proteins REVEILLE4 (RVE4) and RVE8 into the nucleus to directly activate *CBF* expression [25–27]. Several genes in the circadian clock-associated *NIGHT LIGHT-INDUCIBLE AND CLOCK-REGULATED GENE* (*LNK*) family are also implicated in the circadian gating of the cold response of the *CBF* genes [28]. This picture is complicated by cold-responsive proteins and post-transcriptional processes feeding back to regulate the expression of circadian clock components [29–31]. While the circadian gating of CBF expression in plants in response to cold has been documented extensively, there is less evidence to explain why this regulation might be adaptive. Constitutive overexpression of CBFs not only increases stress tolerance but also impairs growth and development in Arabidopsis, barley and wheat [32–35], suggesting that CBF expression must be tuned precisely to avoid yield penalties. Perhaps the circadian gating of CBF expression allows this fine-tuning, to balance energy allocation within the plant between processes linked to cold acclimation and those required for growth. In general, we reason that circadian gating of responses to environmental cues represents a form of signal integration, whereby circadian timing cues are combined with other types of information to elicit a response that is appropriate for the time of day.

## 3. New concepts within circadian gating

In addition to the process of circadian gating having several general manifestations (figure 2), there are distinctions in the nature of the temporal restriction that is caused by the circadian clock. In the first case, which we term *discrete gating*, the circadian clock restricts a cellular process to specific time window(s) over the 24 h cycle (figure 3*a*). This can take the form of a developmental process (such as Drosophila eclosion [5]; figure 2*a*), or a response to an environmental stimulus. In the second case, the circadian clock leads to a modulation of the sensitivity of a process to an environmental cue, which we term *continuous gating* (figure 3*b*). Continuous gating is distinct from discrete gating (figure 3*a*) in that there is no complete deactivation of the process at certain times in the 24 h cycle. During continuous gating, the gate stays open but controls the flow of information. A good example of this is the circadian modulation of the magnitude of corticosterone release from the adrenal cortex in response to ACTH [18]. We speculate that continuous gating may be particularly important for surveillance of the environment and modulation of environmental stress responses.

## 4. The concept of circadian gating applied to biomedicine

The reader is referred to excellent reviews on the importance of circadian programs in human health and disease treatment (including [36–39]). Here, we provide some selected examples of aspects of circadian medicine for which circadian gating appears particularly relevant. One interesting area relates to rhythmic sensitivity to pharmacological agents (chronopharmacology) [40,41]. A broad range of organisms exhibit 24 h fluctuations in chemical sensitivity; an informative historical summary is provided by [42]. Many drugs with short half-lives have targets with circadian-regulated transcripts, suggesting that there is considerable scope to optimize drug delivery to maximize efficacy (figure 4*a*) [43]. For example, a recent study screened a variety of chemotherapy molecules for time-of-day efficacy in a cell culture model and found that several cell cycle inhibitors have rhythmic responses [44]. An affiliated constraint for in-hospital drug delivery is that doses are often delivered to patients at times most compatible with their preparation and distribution to patients, rather than at the time of optimum effectiveness [45].

Another area with interesting developments is the extent and mechanisms of the circadian regulation of adaptive immunity and vaccination responsiveness (figure 4*a*). A recent study identified an *in vivo* circadian fluctuation in the magnitude of activation of $CD8^+$ T lymphocytes in response to a peptide antigen, with this rhythm arising from the $CD8^+$ T-cell-specific circadian oscillator [46]. In dendritic cells, the cell-intrinsic circadian oscillator drives daily rhythms in antigen processing, which is necessary to present antigens to naive T cells [47]. Furthermore, dendritic cells exhibit 24 h rhythms in their migration to lymph nodes, which is the site of antigen presentation [48]. Thus, the magnitude of vaccine responsiveness *in vivo* is subject to overlapping regulatory layers of circadian control. Regardless, circadian regulation of vaccine responsiveness has been reported by several studies [49,50]. One such study inoculated mice with a commercial vaccine (HAVRIX, hepatitis A [HAV]) at two different times of day. This identified a difference in anti-HAV titre that depended upon the time of day of the vaccination that occurred several weeks previously [48]. This difference was abolished in mice that had T-cell-specific *Bmal1* deficiency ($Bmal1^{flox/flox}$, $Cd4^{Cre}$), demonstrating regulation from the circadian oscillator [48].

An exciting emerging area concerns the relatively recent discovery of circadian clocks in non-photosynthetic bacteria. Circadian rhythms have been identified in gut isolates of *Klebsiella aerogenes* [51,52] and the soil bacterium *Bacillus subtilis* [53–55], with little known about their molecular mechanisms. With greater future knowledge of the breadth of bacterial species that harbour circadian clocks (perhaps including pathogenic bacteria), it might be possible to target antibiotics to times in the 24 h cycle with greatest bacterial susceptibility to the antibiotic (figure 4*b*) [54] and thereby improve patient outcomes. In the case of *B. subtilis*, circadian rhythms have been detected only when biofilm forms [53], so understanding the relationship between circadian clocks, biofilm and pathogenesis also presents an interesting area for the future.

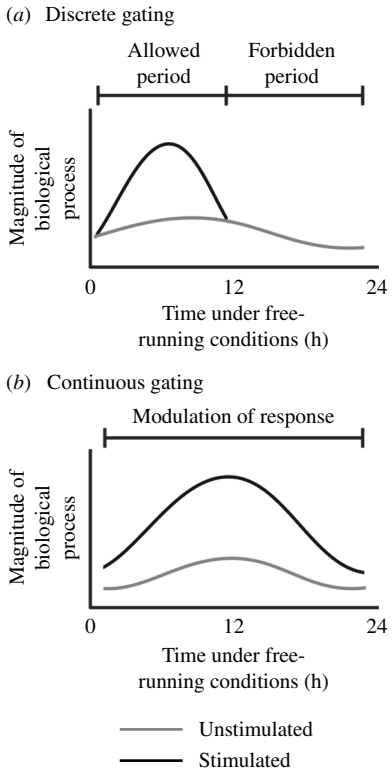


**Figure 3.** Discrete and continuous gating. (*a*) During discrete gating, a response to a stimulus or a biological process is restricted by the circadian clock to occur only at certain times in the 24 h cycle. These have been described as 'allowed' and 'forbidden' windows of time during the 24 h cycle [4,5]. (*b*) During continuous gating, there is a modulation over the 24 h cycle of a biological process or a response to a stimulus. In this case, the circadian clock determines the magnitude of the response, rather than acting as a switch that determines whether the response can occur.

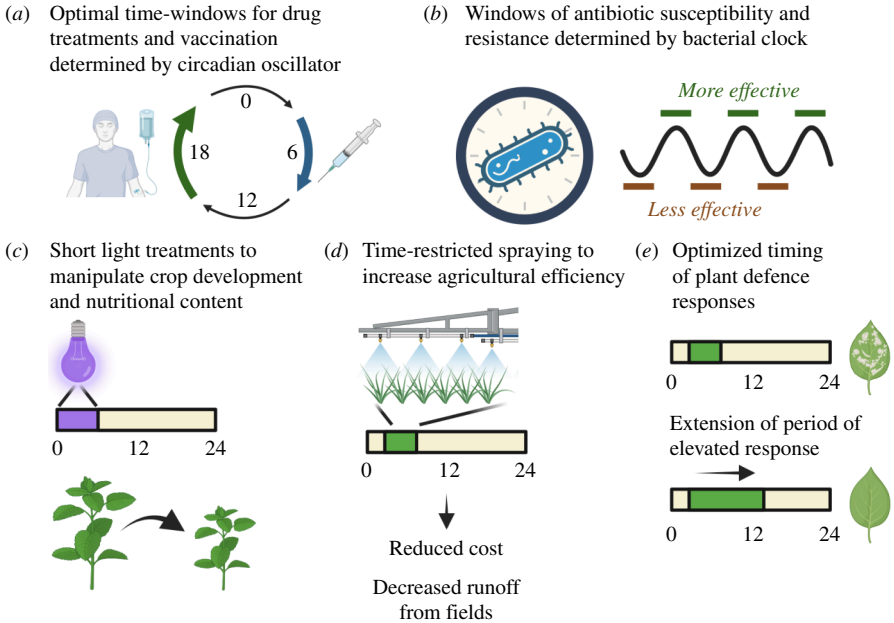


**Figure 4.** Opportunities presented by circadian gating. (*a*) In biomedicine, there are optimum times in the 24 h cycle for drug administration that maximizes efficacy and reduces toxicity, and 24 h oscillations in adaptive immune responses. (*b*) Discovery of circadian clocks in non-photosynthetic bacteria opens possibilities that antibiotic treatments might be aligned with times of greatest bacterial susceptibility. In agriculture, (*c*) temporal windows of sensitivity of development and metabolism to specific light wavelengths could allow crop optimization in controlled environment horticulture; (*d*) 24 h fluctuations in agrochemical efficacy could benefit agricultural economics and environmental protection; (*e*) circadian gating of plant pathogen defence responses presents opportunities to tune plant immunity through gene editing. In this example, extension of the period over which the plant has a greater pathogen response (green box) might adapt the defence response to new latitudes or to the effects of climate change upon pathogen dynamics.

## 5. Applications of circadian gating within agricultural food production

The pervasiveness of circadian gating of the responses of plants to environmental stimuli opens opportunities to use knowledge of circadian gating to enhance and customize crop performance. A good example of this is the effect of light conditions

upon plant development. Within indoor farming environments such as glasshouses or 'vertical farms', the light environment normally lacks the UV-B part of the spectrum (280–315 nm) owing to the transmission spectrum of glasshouse construction materials and the spectrum of artificial horticultural lighting. However, low-dose UV-B is a regulator of plant development that suppresses growth, and its presence leads to more compact plants that have greater concentrations of flavonoid antioxidants, enhancing both the crop aesthetics and health benefits for consumers [56,57]. In Arabidopsis, the circadian clock gates responses of certain genes to short UV-B treatments, including genes associated with antioxidant flavonoid synthesis, redox scavenging and development [58]. This opens the possibility that short low-dose UV-B treatments, applied at times of greatest sensitivity in the 24 h cycle, might be used to manipulate the development and metabolism of horticultural crops for socioeconomic benefit (figure 4*c*). Because UV-B is harmful to humans, circadian gating could be exploited to allow application of short UV-B treatments at times when staff are not present in the growing environment, yet the UV-B treatment remains effective.

A further example concerns the role of circadian clocks in plant responses to agrochemicals. In a proof-of-concept study using Arabidopsis as a model, the authors identified circadian gating of the effectiveness of a widely used active ingredient of herbicides (glyphosate), upon both plant growth and cell death markers [59]. It was also reported that there was a circadian rhythm in the effective dose of glyphosate under laboratory conditions, with this oscillation abolished in Arabidopsis plants, where arrhythmia was induced by overexpression of clock components [59]. A limitation of this study is that it occurred under controlled experimental conditions and predominantly with a model plant species, so whether the findings scale to field (farm) conditions remains to be determined. There are 24 h fluctuations in glyphosate sensitivity of field-grown weed species [60], but it is not clear whether this is caused by circadian regulation. The demonstration that the circadian clock can regulate herbicide efficacy [59] opens the possibility of rhythmic responses of plants to other herbicides, and to other types of agrochemicals (figure 4*d*). There is such extensive circadian and diel regulation of transcript levels [61,62], protein phosphorylation [63,64] and metabolism [65] in plants (including crops [66,67]) that further agrochemicals might encounter rhythmic targets in a manner that is similar, in principle, to chronopharmacology in biomedicine (figure 4*d*). It is also possible that the extension of chemical genetics from the discovery of circadian clock components [68–70] to the development of new agrochemicals could create opportunities to transiently manipulate the clock to optimize crop performance during conditions such as environmental stress.

There is evidence that the circadian clock can gate pathogen defence responses in plants (figure 4*e*). For example, in wild-type plants, infection with the oomycete pathogen *Hyaloperonospora arabidopsidis* at dawn causes fewer lesions on leaves relative to infection at dusk [71,72], with this dawn–dusk fluctuation being absent in a mutant of the plant circadian clock gene *CCA1* [71]. This suggests that the clock might gate a defence response to this pathogen. Since the *cca1* single mutant does not cause arrhythmia [73,74], there is some difficulty within this study in separating the role of CCA1 as a general transcriptional regulator from rhythmicity *per se* within the defence response. A component of the EC of the Arabidopsis circadian clock (LUX ARRHYTHMO) also participates in the development of systemic acquired resistance to *Pseudomonas syringae* [75]. There is a clear circadian rhythm in the level of infection susceptibility of Arabidopsis to *P. syringae*, which is absent from arrhythmic plants [76]. This might be caused by clock control of callose deposition responses in response to pathogen perception, which prevents some pathogens from spreading between cells [76–78].

These examples concern aspects of plant biology that are relevant to agriculture but derive from laboratory-based experimental research with model systems, rather than investigation of circadian gating in crops or under field conditions. Although circadian gating of environmental responses occurs in crop species [79] and has been inferred in field-grown rice and Arabidopsis using statistical modelling [80,81], there is much to be done to translate fundamental discoveries in plant circadian biology into practical applications for socioeconomic benefit [82].

## 6. Conclusions

Circadian gating is a widespread phenomenon that influences the responses of organisms to their fluctuating environments. By restricting processes or responses to certain times of day, circadian gating can clearly be harnessed for societal benefit in a variety of ways. There are cases where insights into circadian gating gained under controlled, laboratory conditions will benefit from investigation under more natural conditions (e.g. the clinic and in nature) to capitalize upon their benefits.

Ethics. This work did not require ethical approval from a human subject or animal welfare committee.

Data accessibility. This article has no additional data.

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. P.P.: conceptualization, visualization, writing—original draft, writing—review and editing; J.M.K.: writing—original draft, writing—review and editing; A.N.D.: conceptualization, funding acquisition, project administration, visualization, writing—original draft, writing —review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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