

## Original Research Article

# Mathematical insights into the role of dopamine signaling in circadian entrainment

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## ABSTRACT

The circadian clock in the mammalian brain comprises interlocked molecular feedback loops that have downstream effects on important physiological functions such as the sleep-wake cycle and hormone regulation. Experiments have shown that the circadian clock also modulates the synthesis and breakdown of the neurotransmitter dopamine. Imbalances in dopamine are linked to a host of neurological conditions including Parkinson's disease, attention-deficit/hyperactivity disorder, and mood disorders, and these conditions are often accompanied by circadian disruptions. We have previously created a mathematical model using nonlinear ordinary differential equations to describe the influences of the circadian clock on dopamine at the molecular level. Recent experiments suggest that dopamine reciprocally influences the circadian clock. Dopamine receptor D1 (DRD1) signaling has been shown to aid in the entrainment of the clock to the 24-hour light-dark cycle, but the underlying mechanisms are not well understood. In this paper, we use our mathematical model to support the experimental hypothesis that DRD1 signaling promotes circadian entrainment by modulating the clock's response to light. We model the effects of a phase advance or delay, as well as the therapeutic potential of a REV-ERB agonist. In addition to phase shifts, we study the influences of photoperiod, or day length, in the mathematical model, connect our findings with the experimental and clinical literature, and determine the parameter that affects the critical photoperiod that signals seasonal changes to physiology.

## 1. Introduction

The circadian clock in the suprachiasmatic nucleus (SCN) maintains highly robust rhythms synchronized to the 24-hour light-dark cycle and entrainable to external cues even in constant darkness. The SCN modulates circadian rhythms in important biological processes such as metabolism and behavior, and in turn receives critical timekeeping information from other areas of the brain. In particular, experiments [1] have shown that dopaminergic projections from the ventral tegmental area (VTA) to the SCN influence circadian rhythms. Dopamine (DA) is an important neurotransmitter involved in learning, motivation, and reward [2,3] and has been linked to a host of neurological conditions. Parkinson's disease is characterized by the death of DA-producing cells in the substantia nigra pars compacta (SNc) [4–6]. Imbalances in DA are also associated with schizophrenia, addiction, and attention-deficit/hyperactivity disorder (ADHD) [7]. Interestingly, people with DA-related conditions often experience circadian disruptions as well, suggesting that DA and circadian rhythms are intertwined. Parkinson's disease is associated with disrupted rhythms at both the molecular and behavioral levels [8]. Adults with ADHD are not only affected

by impaired sleep, but also demonstrate irregular patterns in important clock genes [9]. Depression, anxiety, and schizophrenia are all associated with disrupted circadian rhythms [10]. And, restless legs syndrome (RLS) is characterized by increased circadian variation in DA metabolites [11].

Animal studies [12] have demonstrated that DA varies with 24-hour rhythmicity and experimentalists [13–15] have proposed mechanisms by which clock proteins influence key dopaminergic enzymes, tyrosine hydroxylase (TH) and monoamine oxidase (MAO). We have previously created mathematical models of the molecular clock and its influences on the dopaminergic system [16,17]. The models describe interlocked feedback loops consisting of Brain and Muscle ARNT-Like 1 (Bmal1), the heterodimer BMAL1-CLOCK, Period (Per) and Cry genes and proteins, and orphan nuclear receptors REV-ERBs and retinoic acid-related orphan receptors (RORs). BMAL1-CLOCK complexes promote the transcription of Per and Cry, which encode proteins that inhibit their own transcription. In addition, REV-ERBs and RORs compete for binding to the Bmal1 promoter, with REV-ERBs inhibiting and RORs activating Bmal1 transcription. Experimentalists proposed that REV-ERBs and RORs coordinately modulate TH and BMAL1-CLOCK

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activates MAO. Our model [16] demonstrated that these mechanisms are enough to explain the diurnal variation in DA measured in [12]. We simplified the mathematical model to focus on the key dynamical aspects of circadian rhythms, including robust limit cycle oscillations and the synchronization of the intrinsic clock to external light-dark signaling [17]. For a schematic diagram of the reduced mathematical model see Fig. 1.

There is some experimental evidence that DA reciprocally influences the circadian clock. The neurotoxin 6-hydroxydopamine (6-OHDA) which is used to deplete DA in animal models of Parkinson’s disease has been shown to alter locomotor activity and clock gene expression in the rat dorsal striatum [18] and rat forebrain [19]. In mice with methamphetamine-induced elevations in DA levels, circadian rhythms of neural activity in the striatum were observable even in the absence of the SCN [20]. Cocaine affects the dopaminergic system as well, and cocaine-seeking behavior in mice is known to vary diurnally [21]. In mouse experiments, cocaine administration significantly alters circadian gene expression [22]. In addition, methylphenidate and atomoxetine which are used in the treatment of ADHD both affect clock gene expression throughout different regions of the mouse brain [23]. However, the underlying mechanisms for the influences of DA on the circadian clock are not well understood, and there are different ideas in the experimental literature about the role of DA in the SCN. Several studies [18,19] have shown that destroying DA-producing cells in rats has no effect on PER expression in the SCN, while other studies [24,25] have observed alterations in clock gene expression in the SCN of Parkinsonian animal models. In this paper, we use mathematical modeling to investigate a potential pathway for dopaminergic modulation of circadian rhythms in the SCN and provide evidence that clock-related consequences of DA depletion depend on light.

Grippeo et al. [1] showed that dopaminergic input from the VTA to the SCN influences the ability of the clock to entrain to the 24-hour light-dark cycle. A lack of D1 dopamine receptor (DRD1) signaling results in slow re-entrainment of mouse locomotor activity to a shifted light-dark schedule compared to wild-type mice [1], and stimulating either DRD1-expressing neurons in the SCN or DA neurons in the VTA accelerates the rate of re-entrainment [1]. Grippeo et al. [1] have hypothesized that DRD1 signaling sets the gain on light input into the clock circuitry. In Section 3.1, we provide strong evidence in support of this hypothesis. The model behavior in response to a 6-hour phase advance or delay corresponds well with what is known in the experimental literature [1,26] and can be used to explore clock-dopamine interactions as well as the effects of phase shifts due to east–west travel. In Section 3.2, we use the mathematical model to explore different outcomes of reduced DA and DRD1 signaling and propose therapeutic targets.

Another natural question related to light-dark perturbations is the influence of photoperiod, or day length, on the molecular clock. Amazingly, we see seasonal changes in the circadian clock machinery across different species, from plants and insects [27,28] to mammals [29, 30]. Previous computational studies have investigated the influence of day length on intercellular networks, with long photoperiods causing a wide dispersion of circadian rhythms across individual cells [31–33]. Because SCN cells synchronize with each other, this phenomenon results in low-amplitude rhythms at the network level [31–33]. In Section 3.3, we use mathematical modeling to investigate the effects of day length on the molecular clock and compare our results with experimental findings. In addition, a leading theory on photoperiodic encoding – how seasonal responses are determined – is the existence of a “coincidence timer” that tracks whether light/dark coincidences with a specific circadian time [30,34] and our model results support this idea. Finally, we identify the parameter in our model that determines the value of the “critical photoperiod”, the daylength above or below which a seasonal physiological response occurs.

## 2. Methods

We make a modification to our previous model of circadian rhythms [17] to consider the effects of DA and DRD1 signaling on clock gene expression. The mathematical model in this paper consists of 8 variables describing clock gene and protein interactions in a single SCN cell; see Fig. 1 for a schematic diagram with descriptions of model variables. Our simplified models used in [17] and in this paper do not include separate CRY dynamics. The transport of proteins between the nucleus and cytoplasm is also not explicitly modeled.

In [17], we showed how disrupted clock behaviors including aperiodicity, decoupling, and quasiperiodicity in the model affect TH, MAO, and extracellular DA. In this paper, we adjust the differential equation for unphosphorylated PER ( $P_1$ ), since it is known that light promotes the transcription of Per genes [35–37] and DRD1 is thought to influence the molecular clock through this pathway [1]. The variable  $P_1$  is represented by the circle in Fig. 1 with arrows pointing in from BMAL1-CLOCK and light input with DRD1 signaling.

The production rate of  $P_1$  depends on BMAL1-CLOCK ( $BC$ ) and the repressor  $P_4$ . The function

$$f(P, I, D) = \frac{1}{2} \left( P - I - D + \sqrt{(P - I - D)^2 + 4DP} \right) \tag{1}$$

describes the concentration of a protein  $P$  that is sequestered by an inhibitor  $I$  where  $D$  is the dissociation rate. Eq. (1) can be derived using the law of mass action [38,39] and has been used effectively in circadian models by Kim and Forger [40–42]. As in [17] we simplify Eq. (1) by taking  $D \rightarrow 0$ , so the inhibition by protein sequestration is modeled by the function

$$f_0(P, I) = \frac{P - I + |P - I|}{2} = \begin{cases} P - I & P > I \\ 0 & P \leq I. \end{cases} \tag{2}$$

In Eq. (3),  $f_0(BC, P_4)$  describes the concentration of available  $BC$  after sequestration by the repressor  $P_4$ . This term represents repressor binding to BMAL1-CLOCK in the nucleus to inhibit BMAL1-CLOCK activity. The production rate of  $P_1$  additionally depends on light which is modeled as a function of time  $L(t)$  in the model. The differential equation for  $P_1$  is

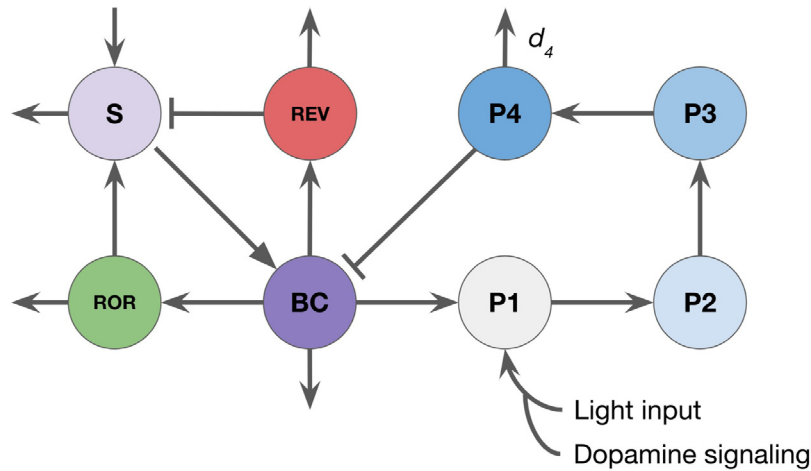
$$\frac{d}{dt} P_1 = r_1 L(t) f_0(BC, P_4) - r_2 P_1, \tag{3}$$

where  $L(t)$  is a square wave function given by

$$L(t) = \begin{cases} 1 + 0.3a & t \bmod 24 < 12 \\ 0.7 & \text{otherwise.} \end{cases} \tag{4}$$

The production rate of  $P_1$  is elevated when lights are on for the first 12 h and reduced when lights are off for the next 12 h of each day. We chose a square wave form for light signaling since many experiments create light versus dark conditions by switching lights on or off. The amplitude of light variation is 0.3 as in our previous model [17]. The parameter  $a$  is new and models a potential mechanism of DRD1 signaling in the SCN. We take  $a = 1$  to indicate normal DRD1 signaling. Experimentalists have shown that DA stimulates Per transcription in vitro [43] and in the rat dorsal striatum [18]. Grippeo et al. [1] have hypothesized that DA is involved in mediating light signaling in the SCN. In Section 3.1, we compare the effects of varying  $a$  in the model with the effects of varying the production rate directly via the parameter  $r_1$ . Our findings support the idea that DRD1 signaling sets the gain on light as opposed to influencing Per transcription independently.

In Section 3.2, we additionally show that reduced DRD1 signaling,  $a = 0.1$ , creates sensitivity of the model behavior to a 6-hour phase delay in the light-dark schedule. We model the therapeutic effects of a REV-ERB agonist which suppresses BMAL1 expression [44]. As in [16], the REV-ERB agonist is a separate variable that decays exponentially to a negligible amount within 24 h based on experimental observations [44]. All model equations for the 8 variables depicted in Fig. 1 are available in [17] and the equation for the REV-ERB agonist is available



**Fig. 1.** Schematic diagram of the mathematical model. The mathematical model contains 8 variables represented by circles in the schematic diagram. BMAL1-CLOCK activates the transcription of the Per gene. Outside of the nucleus, PER undergoes multiple phosphorylation steps, then re-enters the nucleus and inhibits BMAL1-CLOCK through protein sequestration. BMAL1-CLOCK also promotes the transcription of Rev-erb and Ror genes. REV-ERB inhibits and ROR activates the transcription of the Bmal1 gene. In the model, light promotes Per transcription and DRD1 signaling modulates this effect. Variable names: *BC*, the activator complex BMAL1-CLOCK;  $\{P_i\}_{i=1}^4$ , PER phosphorylation states with  $P_4$  representing inhibitory protein; *S*, a precursor to *BC*; *REV*, REV-ERBs that inhibit *S*; *ROR*, RORs that activate *S*.

in [16]. All model equations are additionally reproduced below along with their corresponding parameter values, with adjustments made only to the equation for  $P_1$  (see Eqs. (3)–(4)) from the equations in [17]. Numerical solutions to the model equations were computed using a MATLAB differential equations solver, ode45.

The equations for phosphorylated PER ( $\{P_i\}_{i=2}^4$ ) are

$$\frac{d}{dt}P_2 = r_2P_1 - r_3P_2, \tag{5}$$

$$\frac{d}{dt}P_3 = r_3P_2 - r_4P_3, \tag{6}$$

$$\frac{d}{dt}P_4 = r_4P_3 - d_4P_4. \tag{7}$$

The equations for BMAL1-CLOCK (*BC*), REV-ERBs (*REV*), RORs (*ROR*), and a precursor to BMAL1-CLOCK (*S*) are

$$\frac{d}{dt}BC = \beta_{bc}S - d_{bc}BC, \tag{8}$$

$$\frac{d}{dt}REV = r_{rev}f_0(BC, P_4) - d_{rev}REV, \tag{9}$$

$$\frac{d}{dt}ROR = r_{ror}f_0(BC, P_4) - d_{ror}ROR, \tag{10}$$

$$\frac{d}{dt}S = \beta + \alpha f_0(S, REV + Ag)ROR - d_sS. \tag{11}$$

*S* is a precursor to BMAL1-CLOCK that can be interpreted as Bmal1 gene expression. *REV* and *ROR* competitively modulate *S*.

In this paper, we additionally model the effects of a REV-ERB agonist, *Ag*, which has the same inhibitory effects as *REV*. Thus, the rate of increase of the concentration of *S* is represented by the term  $\alpha f_0(S, REV + Ag)ROR$  in Eq. (11). Since the considered agonist decays exponentially to a negligible amount in 24 h [44] and a drug is considered negligible after 5 half-lives [45], we estimate the half-life of *Ag* to be 4.8 h so that *Ag* undergoes 5 half-lives in 24 h. The differential equation for the REV-ERB agonist (*Ag*) is

$$\frac{d}{dt}Ag = -\frac{\ln(2)}{4.8}Ag. \tag{12}$$

In the nominal model, *Ag* is 0 so that it does not influence the system. Model parameter values are provided in Table 1. All values were kept the same as in our simplified model [17].

In Section 3.1, we quantify entrainment time for different phase shifting experiments. After a phase shift, the model curves take some time to recover and the difference between a variable and its entrained state can be observed as damped oscillations converging to zero as the solutions become re-entrained to the light-dark cycle. We fit a function of the form  $h(t) = e^{-kt} \cos(\omega t + \phi)$  to these damped oscillations where  $1/k$  is a measurement of entrainment time.

**Table 1**

Parameter values used in the mathematical model. The parameter values used are the same as in our previous model [17].

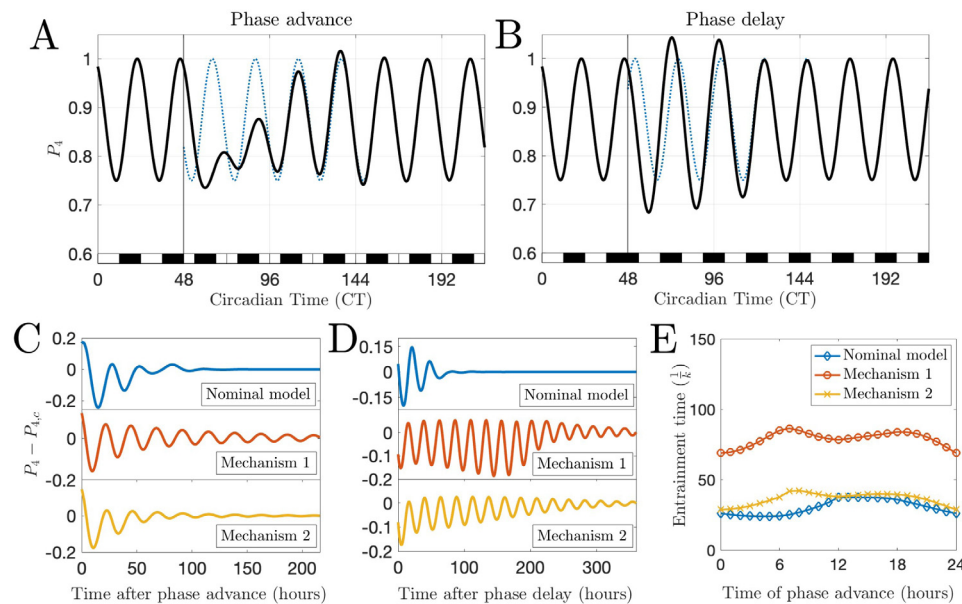
Parameter	Value
<i>a</i>	1
<i>r</i> <sub>1</sub>	0.5
<i>r</i> <sub>2</sub>	0.2
<i>r</i> <sub>3</sub>	0.2
<i>r</i> <sub>4</sub>	0.2
<i>d</i> <sub>4</sub>	0.2
$\beta_{bc}$	0.5
<i>d</i> <sub>bc</sub>	0.3
$\beta$	0.5
$\alpha$	0.5
<i>d</i> <sub>s</sub>	0.5
<i>r</i> <sub>rev</sub>	0.3
<i>d</i> <sub>rev</sub>	0.2
<i>r</i> <sub>ror</sub>	0.3
<i>d</i> <sub>ror</sub>	0.2

### 3. Results

#### 3.1. DRD1 signaling and phase shifts

Grippo et al. [1] show that a lack of D1 dopamine receptor (DRD1) signaling results in slow re-entrainment of mouse locomotor activity to a shifted light-dark cycle; see Fig. 3 in [1]. Previous studies [18,43] also suggest that dopamine and dopamine receptor signaling stimulate Per transcription. Experimentalists [1] have hypothesized that DRD1 signaling sets the gain on light input into the clock circuitry, but these influences are not well understood. In our mathematical model, we studied the effects of different mechanisms affecting Per transcription on circadian entrainment after a 6-hour light-dark phase advance or delay as in [1]. In the nominal model (with unperturbed parameters), clock rhythms re-entrain more quickly after a phase delay than a phase advance, and this is consistent with the experimental literature [26]; see Fig. 2A–B. In humans, it is known that the effects of jet lag are more severe in an advanced time zone than in a delayed time zone [46]. Advancing the light-dark schedule also seems to have long-term health consequences, with aged mice facing a higher mortality rate after chronic phase advances than after chronic phase delays [47].

To investigate the hypothesis that DRD1 signaling does not independently influence Per transcription but rather sets the gain on light, we have created a new parameter *a* in Eq. (4) which scales the percent



**Fig. 2.** Model response to 6-hour phase shifts. We shift the light-dark cycle in the mathematical model 6 h forward (phase advance) and backward (phase delay), representing east–west travel. Model concentrations of the repressor  $P_4$  in both cases are plotted in panels A and B (solid curves). The vertical line in each panel indicates the time of phase shift. For comparison, the dotted curves show what the model behavior would look like when already entrained to the shifted light-dark cycle. Consistent with experimental observations [26], the model behavior re-entrains to the shifted light-dark cycle more quickly after a phase delay than a phase advance (panels A-B). In panels C and D, we compare the rate of entrainment of this “nominal model” (with unperturbed parameters) with the rate of entrainment of the model with two potential mechanisms for reduced DRD1 signaling: weakening the influence of light ( $a = 0.1$ ) on Per transcription (Mechanism 1) or directly reducing Per transcription from  $r_1 = 0.5$  to  $r_1 = 0.395$  (Mechanism 2). Panels C and D show the difference between  $P_4$  and its entrained concentration,  $P_{4,c}$ , in the corresponding panel above. As the clock resynchronizes with the light-dark cycle, the curves in panels C and D converge to 0. Reduced DRD1 signaling has been shown to slow down the rate of entrainment after both a phase advance and a phase delay [1]. The model behavior with reduced light gain (Mechanism 1) corresponds to slower entrainment than in the nominal model for both phase shifts, while the model behavior for reduced Per transcription (Mechanism 2) shows a similar entrainment rate as in the nominal model after a phase advance; see panel C. Panel E shows how the entrainment time depends on the time of phase advance. We find that the Mechanism 1 model consistently has a slower entrainment rate than both the nominal model and Mechanism 2 model regardless of when during the light-dark cycle the phase is advanced (panel E) or delayed (not graphed). These results support the experimental hypothesis [1] that DRD1 signaling does not directly influence Per transcription but rather sets the gain on light.

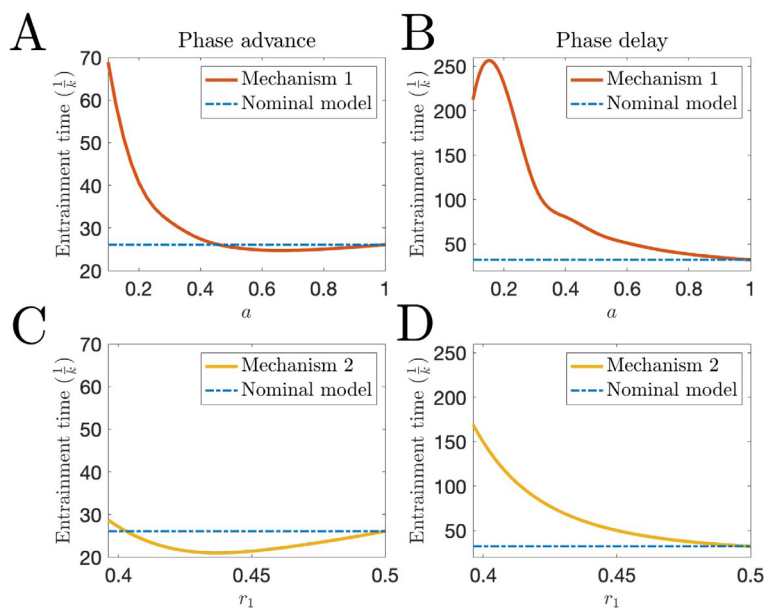
increase in Per transcription rate during the light phase. When  $a = 0.1$ , the clock behavior takes significantly longer to become re-entrained to the light-dark cycle after a phase shift; see Mechanism 1 in Fig. 2C-D. This result is consistent with the experimental findings in [1] that compare the behavior of DRD1 null mice to wild-type mice. On the other hand, if we instead reduce the Per transcription rate  $r_1$  by a factor of 0.79 (equivalent to the effect of  $a = 0.1$  during the light phase) regardless of photic input, the model behaves differently. After a phase advance, a reduced  $r_1$  results in a similar rate of re-entrainment to the nominal model unlike in the DRD1 experiments [1]; see Mechanism 2 in Fig. 2C. The difference between the two mechanisms is that Mechanism 1 affects the production rate of  $P_1$  only during the light phase, while Mechanism 2 affects the production rate of  $P_1$  during both the light and dark phases. These results support the hypothesis that the effect of DRD1 signaling on entrainment requires photic input, and does not simply modulate Per transcription on its own. The model with Mechanism 1 takes the longest to re-entrain regardless of when during the light-dark cycle the phase is advanced; see Fig. 2E. In the nominal model, entrainment time is reduced when the cycle is advanced during the light phase and increased when the cycle is advanced during the dark phase. For a phase delay, we again observe that the Mechanism 1 model takes the longest to re-entrain across different phases. However, we omit the graph because Fig. 2E sufficiently supports Mechanism 1.

The entrainment time is sensitive to reduced values of  $a$  (Mechanism 1) both after a 6-hour phase advance and after a 6-hour phase delay; see Fig. 3A-B. We also find that the entrainment time is robust to reduced values of  $r_1$  (Mechanism 2) after a phase advance, but sensitive to reduced  $r_1$  after a phase delay; see Fig. 3C-D.

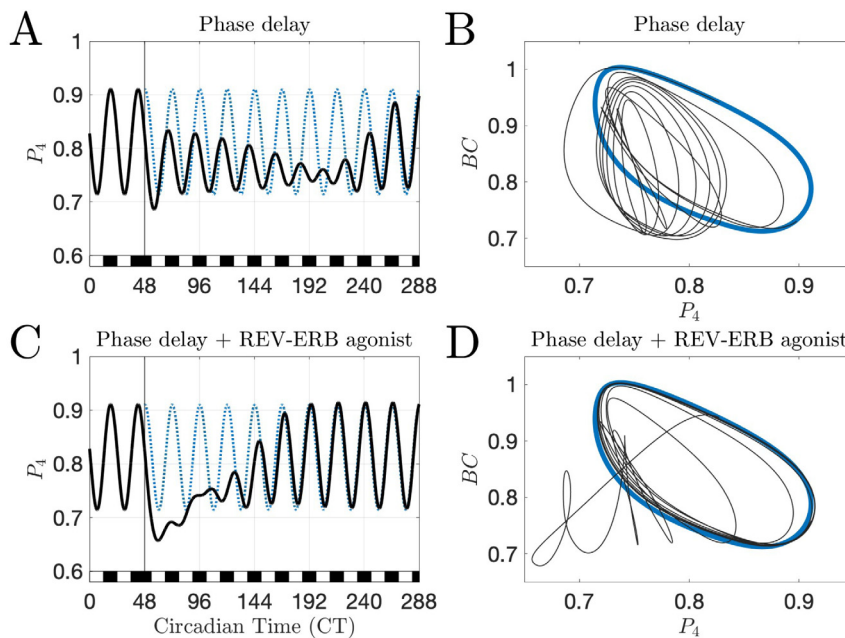
### 3.2. Therapeutic role of REV-ERB agonists

There are competing ideas in the experimental literature about whether or not DA affects the amplitude of circadian rhythms in the SCN. In some mouse models of Parkinson’s disease, the loss of DA neurons in the midbrain progressively reduced the amplitude of locomotor rhythms but did not affect the rhythms of two hormones, melatonin and cortisol, which are controlled by the SCN [48]. In other mouse models of Parkinson’s disease, the amplitudes of Per and Bmal1 gene expression levels in the SCN were significantly diminished [25]. Our mathematical model considers only the effects of DRD1 signaling on the molecular clock’s response to light. Nevertheless, we find that the model with reduced DRD1 signaling can produce both healthy and transient low-amplitude rhythms depending on the clock’s phase relative to the light-dark cycle. In Fig. 4, we show that reduced DRD1 signaling creates sensitivity in the model behavior. After a 6-hour light-dark phase delay, the model behavior takes more than 10 days to become re-entrained to the light-dark cycle; see Fig. 4A-B. In this case,  $P_4$  displays transient low-amplitude behavior, which eventually resynchronizes with the shifted light-dark cycle. Long-term suppression of clock amplitude is not only observable in mouse models of Parkinson’s disease [25,48] and in clinical studies of adults with ADHD [9] and depression [49], but it can also be created experimentally by light perturbations [50]. In addition, disrupted DA is known to reduce PER levels [19] and our model is consistent with this finding as the maximum daily concentration of  $P_4$  with reduced DRD1 signaling is 90% of its peak concentration in the nominal model.

With the reduced light gain in Fig. 4, a 6-hour phase delay causes significant disruptions in the amplitude and phase of  $P_4$ . We show that



**Fig. 3.** Entrainment times for varying  $a$  and  $r_1$ . The entrainment time after a 6-hour phase advance or delay is sensitive to variations in the parameter  $a$ , which corresponds to Mechanism 1 (panels A-B). The dashed lines in all four panels indicate  $1/k$  in the nominal model, which is 26 for a 6-hour phase advance and 32 for a 6-hour phase delay. Panels C and D show the entrainment times for values of  $r_1$  that correspond to the values of  $a$  in Panels A and B, as described in Section 3.1. Variations in  $r_1$  correspond to Mechanism 2 and have a relatively small influence on entrainment time.



**Fig. 4.** A REV-ERB agonist protects the clock after a 6-hour phase delay. The behavior of the model with reduced DRD1 signaling ( $a = 0.1$ ) is more sensitive to clock perturbations. In all panels, we have set  $a = 0.1$  which corresponds to low light gain due to reduced DRD1 signaling. The Circadian Time (CT) of light-dark phase shifts is indicated by vertical black lines in panels A and C. The solid black curves show the concentrations of the repressor  $P_4$  relative to its peak value in the nominal model, and the dotted curves starting at CT 48 show model behavior if already entrained to the shifted light-dark schedule. After a 6-hour phase day, the clock takes more than 10 days to become re-entrained to the shifted light-dark schedule (panel A). Interestingly, treatment with a REV-ERB agonist at the time of phase delay (panel C) promotes quicker re-entrainment than without treatment (panel A). Two-dimensional projected model trajectories for the two groups are additionally plotted in panels B and D, where the closed curve indicates the stable limit cycle solution and the transient curves correspond to the model behaviors after a phase delay without any treatment (panel B) and phase delay with the REV-ERB agonist treatment (panel D).

healthy, entrained behaviors can be restored quickly with a REV-ERB agonist administered at the same time as the light-dark phase delay; see Fig. 4C-D. Experimentalists [44] have identified REV-ERB agonists

that delay the phase of circadian rhythms, and we have previously modeled the phase shifting effects in the SCN [16]. In our model, the REV-ERB agonist inhibits Bmal1 expression and decays to a negligible

amount in 24 h as in [16]. In Fig. 4C, the REV-ERB agonist creates a temporary phase delay that aids in re-entrainment to the shifted light-dark schedule. These model results support experimental studies [44, 51] that identify REV-ERBs as potential therapeutic targets for sleep disorders and jet lag.

### 3.3. Effects of photoperiod

The relative lengths of day and night have a profound effect on the physiology of many animals. In mammals, hibernation is triggered by daylength as is the development of secondary sex characters such as antlers in deer [27,52]. In birds, mating, migration and plumage changes are induced by daylength [27]. In many insects, daylength can induce an overwintering diapause, long-distance migration, as well as the development of distinctive alternative seasonal morphs [28,53–55].

Previous studies have investigated the influence of day length on networks of synchronized SCN cells, where long photoperiods result in a wide dispersion of single-cell rhythms that create low-amplitude rhythms in the overall cell population [31–33]. In this paper, we use our mathematical model to study photoperiodic encoding at the single-cell level to better understand the effects of light on the underlying molecular clock machinery. We computed model time courses for the repressor  $P_4$  and activator  $BC$  over 3 days with a 16:8 light-dark schedule versus an 8:16 light-dark schedule; see Fig. 5. The amplitude of  $P_4$  is larger with the 8 h photoperiod (dashed curves in Figs. 5A and 5B). Regardless of photoperiod, the phase of the model curves stays fixed relative to the onset of darkness. A widely accepted theory of photoperiodic encoding is a “coincidence timing” mechanism which determines seasonal physiology based on whether light/dark coincides with a specific circadian time [30,34]. Our model supports coincidence timing as a mechanism for seasonal encoding. With a 16:8 light-dark cycle the peak of  $P_4$  occurs during the light phase, and with an 8:16 light-dark cycle the peak of  $P_4$  occurs during the dark phase; see Fig. 5A.

As mentioned earlier, the amplitude of  $P_4$  in our single-cell model is slightly larger during the 8:16 light-dark schedule than during the 16:8 light-dark schedule. This qualitative behavior is consistent with experimental findings that short versus long day lengths result in larger amplitudes of clock gene expression [56,57]. However, the difference in  $P_4$  amplitudes for the two light-dark schedules is relatively small. We computed the peak-to-trough amplitude of  $P_4$  (relative to its peak concentration) for photoperiods between 0 and 24; see Fig. 6. The amplitude for an 8 h photoperiod is around 0.26 of the peak  $P_4$  concentration, and this value decreases to 0.25 for a 12 h photoperiod and 0.24 for a 16 h photoperiod. In our model, the amplitudes of  $P_4$  and  $BC$  are quite homeostatic for day lengths between 6 and 18 h, while the model behaviors are oscillatory but aperiodic for day lengths outside of those values. These bifurcation points are indicated by vertical lines in Fig. 6. Such “quasiperiodic” behaviors were previously studied in [17] and resulted from desynchrony between the intrinsic clock and the light-dark cycle. Experimentalists have also observed a homeostatic plateau in seasonal responses in several species of insects at different latitudes, with instability for daylengths that are too short or too long [28]. The length of this homeostatic plateau is determined genetically and varies with the latitude to which a population is adapted. In our mathematical model, adjusting  $d_4$ , the degradation rate of  $P_4$ , controls the range of daylengths with homeostatic amplitude.

## 4. Discussion

We investigated the influence of dopamine signaling on the amount of time it takes for the molecular clock to become re-synchronized with the 24 h light-dark cycle after the cycle has been shifted 6 h forward or backward. In particular, activity of the dopamine receptor DRD1 has been shown to improve re-synchronization, but the mechanisms have not been well understood. The findings in our mathematical

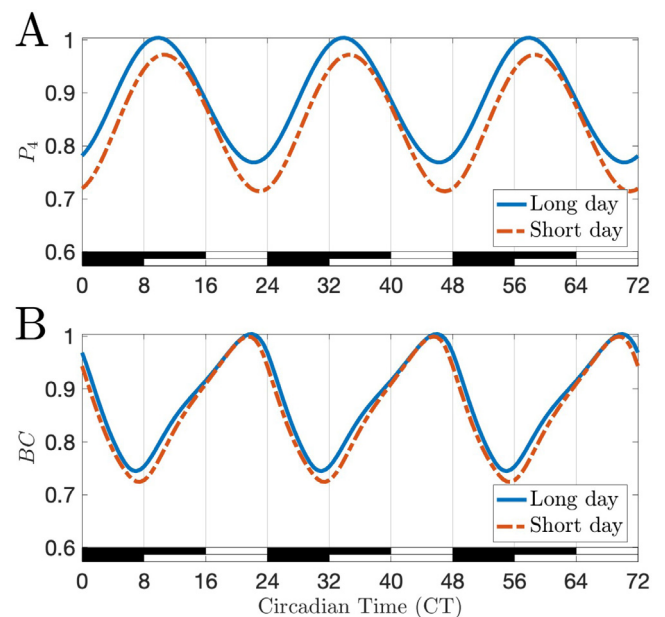
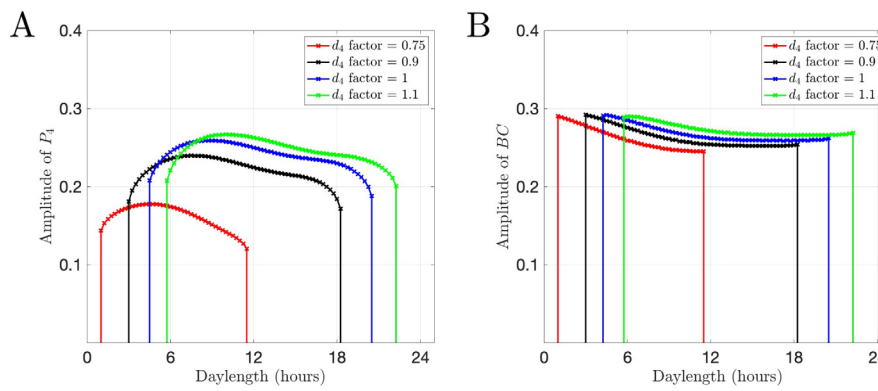


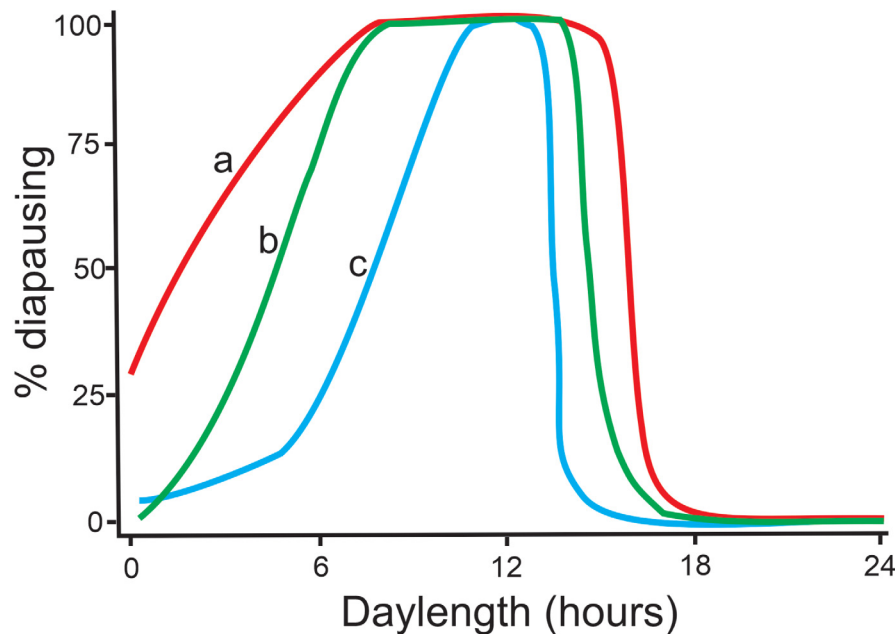
Fig. 5. Effects of long (16:8 light-dark) and short (8:16 light-dark) day lengths on model behavior. We computed model predictions for the repressor  $P_4$  (panel A) and activator  $BC$  (panel B) with a long, 16 h photoperiod (solid curve) versus a short, 8 h photoperiod (dashed curve). All solutions are plotted relative to peak concentrations during the 12:12 light-dark cycle. The amplitude of  $P_4$  is increased by about 0.02 with the short photoperiod and the peak concentration is reduced by about 0.03. The phase of the model curves remains nearly fixed relative to the onset of darkness. This finding is consistent with the idea of a “coincidence timing” mechanism for photoperiodic encoding that depends on whether some specific, crucial time period coincides with light or darkness.

model support experimentalists’ [1] hypothesis that DRD1 signaling modulates light gain, allowing for quicker entrainment of circadian rhythms in the SCN to photic input. The interactions between DA and circadian rhythms have large health impacts. Drugs like modafinil and armodafinil that increase dopamine levels have been shown to alleviate jet lag and shift-work sleep disorder [58–60]. Neurological conditions including Parkinson’s disease, ADHD, and depression that involve DA imbalances are linked to circadian disruption [8–10]. Our study provides strong support that DA signaling improves the entrainability of the circadian clock to the 24 h light-dark cycle by modulating light gain. This mathematical model can be used to investigate how dopamine signaling modulates the clock’s response to light-dark information in the SCN. There are several other proposed avenues for the influence of DA on circadian rhythms throughout other areas of the brain. DA depletion alters clock gene expression in the striatum and forebrain as well as locomotor activity [18,19]. Extending our mathematical model to understand network-level interactions between dopamine and circadian rhythms will be the subject of future work.

Jet lag commonly occurs after an abrupt time zone change due to east–west travel. Symptoms become alleviated as the internal clock readjusts to the light-dark cycle over time and exogenous treatments including melatonin pills help to accelerate adjustment by shifting the clock’s phase [58]. Another suggested therapy is the use of REV-ERB agonists that advance the clock’s phase [44] and our model shows that they may indeed be beneficial during a phase delay, especially for those more sensitive to the shift (Fig. 4). Physiological responses to phase shifts and their severity vary widely from individual to individual and depend on light, social, and other environmental cues [58]. There is also evidence that readjustment becomes more difficult with age [61]. Melatonin has the potential to shift the clock forward or backward depending on the circadian time but taking it at the wrong time can lead to longer readjustment times [58]. We have shown in our previous paper [16] how crucial the timing of REV-ERB agonists is as



**Fig. 6.** Amplitude versus daylength in the mathematical model. The amplitudes of model variables  $P_4$  and  $BC$  were computed for varying daylengths in the nominal model (curve iii) as well as for adjusted  $d_4$ , the degradation rate of  $P_4$  (curves i–ii, iv). The peak-to-trough amplitudes of the repressor  $P_4$  (panel A) and activator  $BC$  (panel B) are homeostatic to daylengths varying from about 6 to 18 h, with a slight downward trend as daylength is increased. When daylength is too short (4 h) or too long (21 h), the model predicts oscillatory but aperiodic behaviors where peak-to-trough amplitudes are inconsistent. Vertical lines indicate these bifurcation points. Though not graphed, for daylengths of 0 (constant darkness) and 24 (constant light), the solutions are periodic again.



**Fig. 7.** Photoperiodic response of three insects with different critical photoperiods. In all cases diapause is inhibited at both long and short daylengths. a, *Acronycta rumicis*. b, *Pieris brassicae*. c, *Laspeyresia molesta*. (After Danilevskii [28]).

well. We find that the model's response to REV-ERB agonists after a phase delay varies across Circadian Time, and this is a phenomenon we will explore in future work. Mathematical modeling has previously been used to design therapeutic strategies for jet lag based on timed light exposure [62,63]. We can further explore how these light-based interventions interact with exogenous treatments using melatonin or REV-ERB ligands.

Photoperiodic responses are typically referenced to the “critical photoperiod”, the daylength above, or below, which a particular developmental or physiological response is manifest. For instance, short-day plants flower, and insects enter an overwintering diapause, when daylengths in the autumn decline below this critical value. The particular value of the critical photoperiod is determined genetically and varies with species, and within a species varies with the latitude to which a population is adapted. Danilevskii [28] illustrates photoperiodic response curves for the induction of diapause in several species of insects occurring at different latitudes (e.g. Fig. 7). These curves have two interesting properties in that there is a middle region of

photoperiods where diapause is induced (100% diapause), but diapause fails to be induced at both shorter and longer photoperiods. Danilevskii [28] notes that the left side of the curve (Fig. 7) has no physiological significance and is probably an artifact of the underlying clock mechanism, but that the exact position of the right-hand drop-off of the curve is an adaptation and represents the critical photoperiod. It is interesting to note that our model likewise shows a relatively constant and homeostatic plateau at intermediate photoperiods, with instability at both shorter and longer photoperiods (Fig. 6). The position of the right-hand transition to instability can be controlled by the value of the  $d_4$  factor (Fig. 6), which suggests that the degradation rate of PER or of PER-CRY may be involved in setting the critical photoperiod.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

“The MATLAB code for the mathematical model used in this paper is available in Mendeley Data (<https://data.mendeley.com/datasets/2k92d4526y/1>)”.

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