A Coupled Oscillatory Model Mimicking Avian Circadian Regulatory Systems

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Abstract. Much evidence indicates that the pineal gland and the suprachiasmatic nucleus (SCN) are the primary pacemakers in the house sparrow, *Passer domesticus*. The interactions between the pineal and SCN predicted by the neuroendocrine loop model indicates that uncoupling would cause the two oscillators to damp out in constant darkness. Based upon the original neuroendocrine loop model, a mathematical framework of the house sparrow circadian regulatory organization that incorporates damping and co-inhibitory coupling has been formulated. The proposed model clearly indicates that two coupled oscillators must be 180° out of the phase for sustaining oscillations. From damping coefficients, which can be determined from experimental data, other parameters such as external stimuli (interaction coefficient) and characteristic frequencies can then be computed. Based upon earlier studies and simulations, we conclude that the sparrow pineal gland dampens more rapidly than does the SCN, suggesting that the SCN are probably more important in sparrows than previously thought. The model also provides the explanations of endogenous circadian period (τ) alteration. Finally, we extend this model to other avian and to mammalian circadian systems. We suggest that avian and mammalian circadian systems may differ in damping coefficients of pineal glands and the degree of SCN dominance.

Key words: Circadian pacemaker, coupled oscillators with damping, Eskin's knee, pineal gland, visual suprachiasmatic nuclei (vSCN)

Introduction

Circadian rhythms in the house sparrow, *Passer domesticus*, are regulated primarily by two coupled circadian pacemakers: the pineal gland and the suprachiasmatic nuclei (SCN) of the hypothalamus. These two pacemakers are thought being coupled via neuronal and hormonal pathways [1]. Although the eyes and deep brain extraocular photoreceptors may also contain pacemakers involved in the entrainment of circadian rhythms, these factors play relatively little role in constant darkness (DD).

Several lines of evidence indicate that the pineal gland regulates the circadian rhythms of the house sparrow. First, pinealectomy (PINX) abolishes perch-hopping activity [2] and body temperature rhythms [3] in DD. Second, transplantation of pineal tissue into the anterior chamber of the eyes of arrhythmic, PINX sparrows restores circadian activity rhythms with the phase of the donor bird [4, 5]. Third, melatonin release from sparrow and chick pineal glands *in vitro* exhibits circadian variations with a peak during the night but dampens out in DD or constant red light within a few cycles [6–8]. The damping of melatonin rhythm can be reversed by norepinephrine (NE) infusion or light-dark cycle (LD) alternations *in vitro* [8] and *in vivo* [9]. These data indicate that the avian pineal gland is a vital circadian oscillator, which requires environmental (light) or neural (NE) input to fully oscillate.

Any circadian pacemaker must have two basic properties, autonomous oscillation and regulating the rhythmicity. Avian pineal gland satisfies these two regiments. Pineal melatonin shows circadian rhythm *in vitro*. Constant melatonin release from surgically implanted silastic or beeswax capsules either shortens free-running period or abolishes circadian rhythms in the house sparrow [10] and the Java sparrow [11]. Periodic melatonin administration synchronizes both locomotor activity and metabolism in certain brain areas including the presumed SCN homolog, the visual suprachiasmatic nuclei (vSCN) in PINX house sparrows [12] [13], supporting the view that pineal melatonin regulates the rhythmicity.

The case for the second pacemaker residing in the vSCN follows a similar vein. First, the sparrow vSCN is retinorecipient and shares many immunocytochemical characteristics with the mammalian SCN [14]. Second, surgical destruction of a hypothalamic area, which includes the vSCN and adjacent hypothalamic tissue, abolishes circadian patterns of locomotor activity in house sparrows [15]. In addition, lesions restricted to the vSCN abolish the circadian pattern of norepinephrine turnover in the chick pineal gland [16]. Third, the sparrow vSCN are metabolically active during the subjective day [17]. This rhythm persists for at least 10 days in DD *in vivo* [18]. Finally and significantly, the vSCN of Japanese quail, *Coturnix coturnix japonica*, express circadian patterns of spontaneous electrical activity *in vitro* with high levels of activity during the subjective day [19].

Several biological models for avian circadian rhythms have been established previously. Menaker and colleagues [2, 20] proposed that the avian circadian system is an hierarchical structure in which the pineal, as a master pacemaker, regulates secondary oscillators downstream. This model was subsequently modified by Gwinner [21] to include weak couplings among the multiple sub-oscillators. However, recent studies have indicated that 1) the pineal gland itself is a damped oscillator [13, 18], and 2) pineal oscillation is influenced by the vSCN [16], suggesting that the pineal gland is not a master pacemaker but rather a co-dominant oscillator with the vSCN.

Recently, Gwinner [22] has proposed the model called ‘internal resonance model’. In this model, the avian pineal pacemaker is proposed to couple with an ‘extra-

pineal pacemaker system' (EPPS), which includes SCN or analogous structures, the retinae and perhaps some unidentified pacemakers. Resonance amplifies oscillator amplitudes. The term 'internal resonance' used here needs a bit clarification. In general, for small damping, when the frequency of the driving force approximately equals the natural frequency of the system, the amplitude of non-transient solution peaks, which is known as a resonance [23]. In addition, the phase difference between the driving force and the oscillator being driven is near 90° . Empirically, the phases between the pineal and SCN have been found 180° out of phase [1]. Because the delay effect of driving force, which is originated from one system empowers on the companion system, that makes the 90° phase difference with the system being driven. For different usages of resonance concepts, see Arrowsmith and Place [24], Nicolis [25], and Verhulst [26].

The neuroendocrine loop model [1, 18] proposes that the avian circadian system is composed of at least two populations of damped circadian oscillators, the pineal gland active during subjective night, and the vSCN active during subjective day. These two populations of damped oscillators maintain a rhythmic stability through mutual inhibition such that the pineal gland synthesizes and secretes melatonin during night. At this time, melatonin inhibits vSCN activity, while vSCN is electrically and metabolically active during the day inhibits melatonin synthesis *via* multiple synaptic circuits including superior cervical ganglions (SCG) and SCG efferent sympathetic nerve to the pineal gland. Under normal circumstances *in vivo*, the rhythmic input of melatonin synchronizes the vSCN activity by inhibiting their activity and neural output. Evidence in favor of this aspect of the model includes the fact that the vSCN contain specific high affinity [125 I]iodomelatonin (IMEL) binding and the administration of exogenous melatonin inhibits vSCN 2DG uptake [13] [27]. Norepnerphrine, secreted by sympathetic nerves, binds α_2 receptors and inhibits melatonin synthesis [8, 9, 28–30]. The experimental data indicate that once the coupling among the vSCN and pineal gland is destroyed (SCN lesion, PINX, superior cervical ganglionectomy, etc.), vSCN and the pineal gland damp out under constant environmental conditions.

Coupled Oscillatory Model

To further explore the neuroendocrine loop model, we have formulated a simple mathematical framework of this model based on the evidence of mutually inhibitory and 180° out of phase coupled oscillators. A mutually impelled oscillatory system can be depicted as a set of time-delayed second-order differential equations:

$$\frac{d^2x_1(t)}{dt^2} = -\omega_1^2(x_1(t) - \beta_1 \frac{dx_1(t)}{dt} + \gamma_{12}x_2(t - \tau_1)), \quad (1a)$$

and

$$\frac{d^2x_2(t)}{dt^2} = -\omega_2^2(x_2(t) - \beta_2 \frac{dx_2(t)}{dt} + \gamma_{21}x_1(t - \tau_2)), \quad (1b)$$

where x_j 's are the displacements with subscripts $j = 1$ and 2 referring to the two oscillators, ω_j 's and β_j 's are their respective characteristic frequencies and damping coefficients, γ_{ji} 's are the coupling coefficients – the endogenous prodding factors, and τ_j 's are the time lag of the stimuli to their respective displacements x_j . This time delayed formulation is based on the functional differential equations [31–33]. Equation (1) provides the rates of change of the system that depend not only at the time of consideration but also upon its past track and has been increasingly used in neurobiology [34].

There are two possible coupling mechanisms available: amplitude and rate. The choice between the two depends on the relative phase between the driving force and the displacement for a given oscillator. The driving force of an oscillator originates from its companion counter part and thus is ingrained with a time lag for transmitting the thrust. One of the most effective modes is when the driving force leading the corresponding displacement by a phase slightly less than $\pi/2$ [35]. The amplitude coupling yields such a phase difference while the same cannot be claimed in the rate coupling. For this reason we chose the amplitude coupling.

From the standard procedure for solving systems of linear differential equations, an acceptable solution set for Equation (1) can be expressed as:

$$x_1 = A_1 e^{i\Omega t}, \quad (2a)$$

$$x_2 = -A_2 e^{i\Omega t}, \quad (2b)$$

where A_j 's are the amplitudes and Ω is the circadian frequency. The complete out of phase nature of Equation (2) reflects the fact that SCN is active during the day and pineal produces melatonin at night in the neuroendocrine loop model. Substituting Equation (2) into Equation (1) and equating the real and imaginary parts, the following relationships can be established:

$$A_j = \frac{\gamma_{ji} A_i}{\sqrt{(\Omega^2 - \omega_j^2)^2 + \Omega^2 \beta_j^2}}, \quad (3)$$

and

$$\tau_j = \frac{1}{\Omega} \tan^{-1} \frac{\Omega \beta_i}{\Omega^2 - \omega_i^2}. \quad (4)$$

Equation (3) implies that the amplitude of oscillator j , A_j , is a function of the thrust from its companion oscillator i , $\gamma_{ji} A_i$. For a given thrust $\gamma_{ji} A_i$, the maximum amplitude of A_j occurs when Ω is so adjusted that the denominator is a minimum, i.e.,

$$\Omega^2 = \omega_j^2 - \frac{\beta_j^2}{2}. \quad (5)$$

Substituting this relationship into Equation (4), one obtains:

$$\tau_j = -\frac{1}{\Omega} \tan^{-1} \frac{2\Omega}{\beta_i}. \quad (6)$$

The negative sign in Equation (6) denotes that the stimuli are in fact leading their respective displacements. The product $\Omega\tau_j$ in Equation (6) represents the phase-angle δ_j that the displacement x_j is lagging (for $\delta_j < 0$) the external thrust, which conforms to the theory of forced oscillation with damping [35]. In other words, the periodical stimulation is lagging the displacement of its origin x_i by a phase angle of $\pi + \delta_j$. Using Equation (5), the amplitude ratio can be obtained from Equation (3):

$$\frac{A_j}{A_i} = \frac{\gamma_{ji}}{\beta_j \sqrt{\Omega^2 + \frac{\beta_j^2}{4}}} = \frac{\beta_i \sqrt{\Omega^2 + \frac{\beta_i^2}{4}}}{\gamma_{ij}} = \sqrt{\frac{\beta_i \gamma_{ji}}{\beta_j \gamma_{ij}}} \left(\frac{\Omega^2 + \frac{\beta_i^2}{4}}{\Omega^2 + \frac{\beta_j^2}{4}} \right)^{1/4}. \quad (7)$$

As the primarily function of resistance in any system is to sustain the stability, a damping factor needs not be excessively large, i.e., $\beta_j < \omega_j$ in Equation (5). This implies that the optimal mode occurs when the circadian frequency Ω is slightly less than the characteristic frequencies ω_j and the magnitude of the phase angle δ_j is slightly less than $\pi/2$ (additional discussions are given in the Appendix). By multiplying two amplitudes $A_i A_j$ in Equation (3), we obtain the following constraint:

$$\gamma_{ij} \gamma_{ji} = \beta_i \beta_j \Omega^2 \sqrt{1 + \frac{\beta_i^2}{4\Omega^2}} \sqrt{1 + \frac{\beta_j^2}{4\Omega^2}}, \quad (8)$$

which can be used for substantiating parameter estimations.

Decoupling and Parameter Estimation

Decoupling of this mutually impelled oscillatory system is equivalent to set $\gamma_{ij} = 0$ in Equation (1), i.e.

$$\frac{d^2 x_1}{dt^2} = -\omega_1^2 x_1 - \beta_1 \frac{dx_1}{dt}, \quad (9a)$$

and

$$\frac{d^2 x_2}{dt^2} = -\omega_2^2 x_2 - \beta_2 \frac{dx_2}{dt}. \quad (9b)$$

The solution of Equation (9) is

$$x_j = (-1)^{j-1} A_j e^{-\beta_j(t-t_0)/2} e^{i\Omega_j^* t}, \quad (10)$$

where t_0 is the time at which the decoupling occurs and

$$\Omega_j^{*2} = \omega_j^2 - \frac{\beta_j^2}{4}. \quad (11)$$

denotes the frequency of oscillator j after decoupling. By comparing with Equation (5), we obtain

$$\Omega_j^{*2} = \Omega^2 + \frac{\beta_j^2}{4}, \quad (12)$$

which implies that upon decoupling, the frequency of each oscillator would increase slightly.

Because of damping, the amplitude of a free vibration decays exponentially, i.e.,

$$A_j(t) = A_j e^{-\beta_j(t-t_o)/2} \text{ for } t > t_o, \quad (13)$$

where A_j is the amplitude prior to decoupling. As both A_j and $A_j(t)$ are measurable, Equation (13) can be used to evaluate the damping factor β_j , i.e.,

$$\beta_j = -\frac{2}{t-t_o} \ln \frac{A_j(t)}{A_j}. \quad (14)$$

Once β_j is determined, the value of ω_j can be estimated by Equation (5). Values for coupling parameter γ_{ji} can then be estimated from Equation (3), which may be approximated by the fact that $\beta_j \ll \omega_j$, or

$$\gamma_{ji} \approx \frac{A_j}{A_i} \beta_j \Omega. \quad (15)$$

Equation (8) can then be used to corroborate these parametric values.

The analysis described above indicates that the structure of this type of coupled oscillatory system, such as pineal and SCN, is amazingly effective. These two biochemical oscillators are tightly coupled and completely out of phase. In addition, the relationship given by Equation (14) provides a convenient means to evaluate a vital parameter, the damping factor β , from which all other relevant parameters such as ω and γ can be estimated.

Discussion

The damping parameter β_{SCN} was estimated to be about 0.0176 hr^{-1} by removing the pineal gland (6 pinealectomized sparrows were used). Recent studies by Murakami *et al.* [6] show that melatonin release from cultured sparrow pineal gland exhibits damping effect. Our estimation on β_{pineal} from Murakami *et al.* [6] is about 0.044 hr^{-1} , which is higher than β_{SCN} . As $\Omega = 2\pi/24 = 0.2618 \text{ hr}^{-1}$, the ratio β_{SCN}/Ω is equal to 0.067, which is indeed quite small. A neural coupled oscillatory system such as pineal and SCN can in fact be sustained by a very small stimulants.

From Equation (12), the difference between Ω_j^* and Ω can be approximated by

$$\Omega_j^* - \Omega = \frac{\Omega_j^{*2} - \Omega^2}{\Omega_j^* + \Omega} \approx \frac{1}{8} \frac{\beta_j^2}{\Omega}. \quad (17)$$

This result indicates that the frequency is slightly increased in a decoupled phase; in other words, the endogenous circadian period (τ) is shortened. The frequency increment is directly proportional to the damping coefficient squared. Earlier studies on house sparrows [36] and European starlings [21] support this conclusion. In constant darkness (DD), however, the τ value of sparrow has been observed to lengthen [37]. Our interpretation is that couplings among vSCN and pineal gland are strengthened by Zeitgeber (e.g. L:D cycle). In DD, the coupling strength is gradually decreased. Since the frequency is directly proportional to the coupling strength (Equation (15)), a gradual weakened coupling would cause a gradual slashed frequency or a lengthened τ .

Although several mathematical models of circadian rhythms have been proposed in recent years [38–43], these models are either general [38, 40] or concerned only with mammalian circadian systems [44–46]. Based upon the experimental data from house sparrows, Richie and Womack [47] developed a model of weakly coupled dual oscillators. This is the first model concerning with the avian circadian system. The model interprets the entrainment, the phase response curve (PRC) and τ instability (shorten upon decoupling and lengthen in DD) in house sparrows. However, the model differs from the neuroendocrine loop model in the following aspects: (1) the oscillators in the former are not damped, (2) their oscillators are co-excited, while co-inhibition is presumed in the neuroendocrine loop model, and (3) the oscillators are structured as a weakly coupled pair without a phase delay, whereas a phase delay is incorporated in the formulation of the neuroendocrine loop model that gives rise to an appearance of a strongly-coupled system.

Enright [39, 48] proposed an in-phase, mutually excited and un-damped oscillator model, in which, a master damped oscillator is coupled with multiple-oscillators via resonance. The mathematical simulation of that model revealed that as long as cycle-to-cycle damping factor is not excessively large, the system would reach stability promptly. The difference between the Enright model and the proposed model is in the postulations. The Enright model presumes that the circadian system is composed of in-phase, un-damped, co-excitable oscillators, while the proposed neuroendocrine loop model assumes that the circadian system consists of damped, co-inhibitory oscillators resulting a phase difference of 180° .

These two earlier mathematical models of avian circadian systems have a common premise that the oscillators are coupled by in phase mutual excitation. This presumption does not seem to be plausible. Many subsequent studies indicate that the SCN and the pineal gland inhibit each other.

The τ values of house sparrows spontaneously change in DD. Upon placing in DD, most birds initially exhibit free-running periods shorter than 24 hrs then spontaneously lengthen to approximately 24.5 hrs. This change is frequently termed ‘Eskin’s knee’ [37]. It is suggested that the values of τ change in sparrows are the result of a gradual reduction in couplings between the SCN and the pineal gland from LD to DD. Based on the relationship: $\gamma_{ij}\gamma_{ji} \approx \beta_i\beta_j\Omega^2$, a reduction in coupling strength gives rise to a lengthened τ . Richie and Womack [47] explained

the spontaneous change of tau by proposing that the two un-damped oscillators are weakly coupled, and that these coupled oscillators yield two characteristic frequencies. Although at present, we cannot be certain to which account is plausible, experimental results on house sparrows seem to support our rationalization. If our interpretation is correct, one would expect only a single 'knee' bend in DD, while in Richie and Womack's model would consist of multiple-knee bends. No multiple-knee patterns have been observed support our model.

Aschoff's rule (nocturnal animals have a tendency to show an increase in Circadian period (tau) under constant light condition (LL) while diurnal animals have a tendency to show a decrease in tau under LL condition) may also be interpreted as the coupling strength changes. Strong coupling shortens the circadian period while weak coupling lengthens the tau. In addition, the splitting is probably resulted from a weak coupling. Splitting is a phenomenon that within a normal cycle two weak sub-cycles are observed. For instance, in DD, the weakened coupling of diurnal animal results lengthened taus, and occasionally splittings are also observed [49, 50]. Similarly, the coupling is increased and taus are shortened when nocturnal animals are placed in DD. It has been noticed that splittings are always associated with lengthened tau values in both nocturnal and diurnal animals [51].

The importance of pineal gland has been shown to be different among avian species. Pinealectomy has variable effects on different species of birds, from no effect on Japanese quail [52] and chicks [53], to tau alteration in pigeons [54] and European starling, about half of the starlings exhibit arrhythmicity [21] and to complete arrhythmicity in the house sparrows [2], Java sparrows [11] and the white-crowned sparrows [36]. *In vitro* studies indicate that melatonin release from the pineal glands of both pigeons and house sparrows damp in DD and quail pineal melatonin shows no oscillation in DD [55]. These data are consistent with behavior studies. The SCN, on the other hand, are found to be crucial for the generation of avian circadian rhythms [11, 15, 56]. These studies indicate that the functionally conserved SCN are coupled with the functionally variable pineal gland in birds.

Since $\gamma_{ij}\gamma_{ji} \approx \beta_i\beta_j\Omega^2 = \text{constant}$ at the steady state, it suggests that if the coupling of SCN on pineal gland is strong, then the coupling of pineal gland on SCN must be weak. This result can be extended to the point that as the dependence of pineal gland on SCN increases, the pineal would damp more rapidly (Equation (15)), which seems to be the case. For instance, in house sparrows, PINX causes activities to damp to arrhythmicity in 7–9 days in DD while SCN lesion renders activity arrhythmic within 1–2 cycles of DD [15], suggesting that the coupling of SCN on pineal is stronger than that of pineal on SCN. In mammals, the dependence of pineal gland on SCN and SCN dominance are even more amplified.

In mammals, SCN is the dominant pacemakers. Mammalian SCN is capable of retaining circadian release of vasopressin for a long time *in vitro* [55]. The incapability of rat pineal gland to maintain N-Acetyl-transferase (NAT, the limiting enzyme for melatonin synthesis) rhythm without SCN [57] indicates that the mammalian SCN is the dominant oscillator and the pineal rhythm is entirely

conferred by SCN. These results are consistent with the analysis given above, i.e., the mammalian pineal gland is characterized by a significant damping while it is insignificant in the mammalian SCN.

Summary

The proposed model provides:

- (1) a direct determination of the damping coefficient from raw data, which can then be used to estimate all other parameters,
- (2) a verification for the stability of co-inhibitory oscillators can only be accomplished by out-of-phase oscillations,
- (3) SCN is the dominant pacemakers in birds and the mammalian SCN characterized by the least damping rate among the known animal circadian oscillators,
- (4) an explanation of tau instability in sparrows and tau shortening upon decoupling.

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Appendix

Equation (2) depicts that at $t = 0$, $x_1 = A_1$ and $x_2 = -A_2$ while the driving force on displacement x_j that originated from the component i is $f_{i \rightarrow j} = \gamma_{ji} A_i e^{-i\Delta_j}$, where $\Delta_i = \pi + \delta_j$, note that $\delta_j < 0$. This implies that the driving force of component j is leading the corresponding displacement by a phase angle slightly less than 90° while it is lagging its source displacement by slightly over 90° . As $\beta_{SCN}/\Omega = 0.067$, which implies that $\delta_{SCN} = 1.5372$, or the stimulus from the SCN is leading the pineal gland oscillation by 5.87 hours and lagging behind the oscillation of the SCN by 6.13 hours.

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