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Impacts of aging on the entrainment capability of the mammalian circadian system

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The circadian system of mammals is composed of a hierarchical network of oscillators, including a core clock and peripheral clocks. The core clock receives an external photic signal and transmits it to the peripheral clocks, which, in turn, feed back to the core clock. Aging affects various functions of organisms including the circadian system. Entrainment displays the adaptability of the circadian system to changes in the external environment. However, there is currently no systematic study on the effects of aging on the entrainment capability. To explore the influencing mechanism, we develop a mathematical model of two populations of Goodwin oscillators, which represent the core clock and peripheral clocks. Based on numerical simulations, we conduct a detailed study on the impact of three aging-related factors on the entrainment capability represented by the entrainment range, entrainment time, and entrainment phase. The results indicate that the decrease in the sensitivity of suprachiasmatic nucleus (SCN) to light and the coupling strength from the SCN to the peripheral clocks due to aging increase the phase difference between the core and peripheral clocks, narrow the entrainment range, and prolong the entrainment time. A reduction in the coupling strength within the SCN has little effect on the three aspects mentioned above but increases the entrainment phase. Overall, aging reduces the circadian system's adaptability to the external environment, and the increased entrainment phase may lead to corresponding sleep problems. We also show that modulating the internal coupling strength in the peripheral clocks can mitigate aging effects; this provides an idea for using peripheral clocks to adjust the core clock, while also revealing new insights into the interaction between aging and the elasticity of the circadian system. This mechanism provides theoretical support for treating or alleviating circadian system disorders or sleep problems caused by aging.

Keywords: circadian system, peripheral clocks, entrainment range, aging

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1. Introduction

Mammals possess endogenous circadian clocks with a period of approximately 24 hours, which coordinates physiological and behavioral rhythms. In mammals, the core circadian clock is located in the suprachiasmatic nucleus (SCN)[1] and coordinates peripheral clocks in nearly every tissue of the body.[2,3] The core clock primarily reacts to the external light–dark (LD) cycle,[2,3] and the peripheral clocks react to feed-fast cycles.[4,5] The core clock in the SCN sends signals to synchronize the peripheral clocks through the secretion of melatonin. Specifically, the SCN, as a central pacemaker in mammals, regulates the synchronization of the peripheral clocks throughout the body through a bidirectional feedback loop involving neural and hormonal signals. The SCN transmits time cues to the peripheral clocks via sympathetic nervous signals and hormones like melatonin, which regulate the expression of clock genes (e.g., Per, Bmal1) in peripheral tissues such as the liver, heart and adipose tissue, ensuring their synchronization with the central clock. Furthermore, the SCN's influence on the peripheral clocks is not limited to neural signals and hormones; it also strengthens rhythm synchronization by regulating metabolic activities in peripheral tissues. In turn, peripheral clocks provide feedback to the SCN, with the products of clock gene expression (e.g., PER and CRY proteins) influencing SCN activity through humoral signals, including metabolic products and hormones. For example, metabolic products or hormones from peripheral clocks can feed back onto the SCN, adjusting its melatonin secretion and the synthesis of other rhythmic factors, thereby regulating the SCN's rhythm. This feedback mechanism allows peripheral tissues to modulate SCN rhythmicity, ensuring precise synchronization and adaptability to environmental changes. Thus, the bidirectional feedback loop between the SCN and the peripheral clocks ensures coordinated circadian rhythms, maintaining physiological homeostasis across the organism.[6,7]

Entrainment is a key property of the circadian system, which reflects the adaptability of the circadian clock to external environmental changes. The entrainment capability includes but is not limited to the entrainment range, entrainment time, and entrainment phase. The core clock in the SCN can be entrained not only to the natural 24 h LD cycle but also to the artificial photoperiod of non-24 h cycles. Nowadays,

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most people work indoors for long periods of time and are exposed to various non-24 h artificial LD cycles. Entrainment time refers to the time required for the circadian system to synchronize with a LD cycle. Entrainment phase means the phase difference between the circadian oscillator and the LD cycle, which can be used to reflect people's sleep. Entrainment range is defined as the range between the lowest and highest periods of the external LD cycle which can entrain the circadian system.[8] There is considerable differences between different species. For instance, humans have an entrainment range from 20.5 h to 29 h; the Nile grass rat has an entrainment range from 22.5 h to 25.5 h.[9] Abrupt changes in the external LD cycle typically lead to circadian misalignment, resulting in various diseases including cardiovascular diseases, obesity, and cancer.[10–12] Therefore, further research on the entrainment capability can offer targeted insights for the treatment of such diseases caused by circadian clock disorders. Previous studies have shown the influence of the collective behavior of VL and DM within the SCN on the entrainment range.[13–15]

Aging affects most physiological processes in our bodies to some extent. Increasing evidence in recent years suggests that the aging process also influences the circadian system.[16] The circadian output of the core clock in the SCN weakens,[17,18] and the sympathetic input of peripheral clocks from the core clock in the SCN attenuates as aging.[19] This means that aging weakens the core clock's ability to drive the peripheral clocks. Additionally, it has been observed that the signal transduction of synaptic terminals and neurotransmitter gamma aminobutyric acid decreases with aging, which means that the coupling strength within the SCN weakens.[20,21] Furthermore, the aging of eyes also leads to a reduction in the amount of light reaching the SCN,[22] which means there is a decreased sensitivity of the SCN to light with aging. These findings clearly indicate that aging leads to an increased susceptibility of the circadian system to disruption. We wonder how aging affects the entrainment capability of the circadian system. To our knowledge, there is currently no systematic research work that examines this aspect.

Research on the entrainment mainly focuses on the core clock, aiming to capture the collective behavior of the entire SCN neurons, but neglecting the influence of the peripheral clocks. However, peripheral clocks also affect the overall circadian system,[23] and adjusting the feed-fast cycle responded to by the peripheral clocks is an effective intervention to accelerate circadian re-entrainment.[24] Therefore, it is necessary to consider both the core clock in the SCN and also peripheral clocks simultaneously for a deeper understanding of the circadian system.

Over the years, numerous mathematical models describing the circadian clocks have been developed,[25,26] with the majority of studies concentrating on the core clock. The Goodwin oscillator is a typical model for simulating the dynamics of neurons in the SCN,[27] which continues to be widely utilized to describe the core circadian oscillator[28] or the synchronization and entrainment of coupled circadian oscillators.[27,29] To investigate the impact of aging on the entrainment capability, we have built a novel model based on two populations of coupled Goodwin oscillators showing the interactions between the core clock in the SCN and peripheral clocks. Based on the biological basis of the impact of aging on the circadian rhythm system mentioned earlier, three age-related changes are considered:[24] (i) a decreased sensitivity of the circadian system to light; (ii) a reduction in the internal coupling strength of the SCN; and (iii) a lowered coupling strength from the SCN to the peripheral clocks. We explore the effects of aging on the entrainment range, entrainment time and entrainment phase. Based on the findings, we propose potential simple intervention strategies to mitigate the changes in the circadian system entrainment caused by aging.

The rest of this article is organized as follows. Section 2 presents the detailed mathematical model. Section 3 shows the numerical simulation and analysis. The conclusion and discussion are presented in Section 4.

2. Description of the mathematical model and method

The model is composed of two populations of coupled Goodwin oscillators, where one population represents the core clock in the SCN, entrained by the LD cycle, and the other population represents the peripheral clocks. The SCN transmits a photic signal to the peripheral clocks through the secretion of melatonin, thereby regulating the peripheral circadian clocks. Simultaneously, the core clock also receives feedback signals from the peripheral clocks.

The Goodwin oscillator contains three variables, describing a negative transcription–translation feedback loop.[30] The clock gene mRNA (X) produces the clock protein (Y), which activates a transcription inhibitor (Z), and in turn inhibits the transcription of the clock gene. Neurons synthesize a neuropeptide neurotransmitter denoted by F, which is induced by the activation of the clock gene (X). The coupling among the neurons depends on the concentration of the neurotransmitter in the extracellular medium. Under the fast transmission hypothesis, the extracellular concentration is assumed to equilibrate to the average cellular neurotransmitter concentration, which is referred to as the mean field, denoted by $\bar{F}$.

The core clock in the SCN with internal coupling and external coupling with the peripheral clocks is described as fol-

lows:

$$\begin{cases} \dot{X}_i = v_x \dfrac{K_1^4}{K_1^4 + Z_i^4} - \delta_x \dfrac{X_i}{K_x + X_i} + v_{Fx} \dfrac{g_F \bar{F}}{K_{Fd} + g_F \bar{F}} + L(t), \\ \dot{Y}_i = v_y X_i - \delta_y \dfrac{Y_i}{K_y + Y_i}, \\ \dot{Z}_i = v_z Y_i - \delta_z \dfrac{Z_i}{K_z + Z_i}, \quad i = 1, 2, \ldots, N_F, \\ \dot{F}_i = v_F X_i - \delta_F \dfrac{F_i}{K_F + F_i} - K\left(\bar{f} - \bar{F}\right), \\ \bar{F} = \dfrac{1}{N_F} \sum_{i=1}^{N_F} F_i, \end{cases} \tag{1}$$

where $i = 1, 2, \ldots, N_F$ and N_F represents the number of neurons in the SCN. v_x, v_y, v_z, v_F, and v_{Fx} are parameters reflecting the synthesis rate of various substances, respectively. δ_x, δ_y δ_z, and δ_F are parameters reflecting the decay rate of various substances, respectively. K_x, K_y, K_z, K_F, K_{Fd} and K_1 are Michaelis constants. g_F denotes the internal coupling strength among neurons within the SCN. K represents the coupling strength from the peripheral clocks to the core clock, and $L(t)$ denotes the external LD cycle

$$L(t) = L_0 \sin\left(\frac{2\pi t}{T_{\mathrm{LD}}}\right), \tag{2}$$

where L_0 and T_{LD} represent the intensity and period of the external LD cycle.

The peripheral clocks are described as follows:

$$\begin{cases} \dot{x}_i = v_a \dfrac{K_2^4}{K_2^4 + z_i^4} - \delta_a \dfrac{x_i}{K_a + x_i} + v_{fx} \dfrac{g_f \bar{f}}{K_{fd} + g_f \bar{f}}, \\ \dot{y}_i = v_b x_i - \delta_b \dfrac{y_i}{K_b + y_i}, \\ \dot{z}_i = v_c y_i - \delta_c \dfrac{z_i}{K_c + z_i}, \quad i = 1, 2, \ldots, N_f, \\ \dot{f}_i = v_f x_i - \delta_f \dfrac{f_i}{K_f + f_i} - k\left(\bar{F} - \bar{f}\right), \\ \bar{f} = \dfrac{1}{N_f} \sum_{i=1}^{N_f} f_i, \end{cases} \tag{3}$$

where $i = 1, 2, \ldots, N_f$ and N_f is the number of peripheral clocks. The meanings of each parameter refer to the explanation of the parameters of Eq. (1). Specifically, f is a substance that couples peripheral clocks and the coupling strength is g_f. k is the coupling strength from the core clock to the peripheral clocks.

The SCN regulates the peripheral clocks through sympathetic nervous signals and hormones such as melatonin; this influences the coupling substance f (the internal coupling substance of the peripheral clocks), thereby modulating the synchronization between the peripheral clocks and the SCN. Conversely, the peripheral clocks regulate the SCN by influencing F (the internal coupling substance of the SCN) through humoral signals, including metabolic products and hormones. The SCN transmits driving signals to the peripheral clocks by the term $k\left(\bar{F} - \bar{f}\right)$ indicated in Eq. (3), adjusting their activities and reflecting SCN control over the peripheral clocks. Similarly, the peripheral clocks provide feedback to the SCN by the term $K\left(\bar{f} - \bar{F}\right)$ shown in Eq. (1), modulating the SCN activity and ensuring synchronization between both systems.

This article mainly studies the overall properties of the rhythm system under the influence of aging, so we have established a generalized model without distinguishing between the central clock and peripheral clock from the perspective of molecular regulation. We use the same coupling mode as the central clock to mention different types of feedback loops in the peripheral clock, such as hormones and metabolism. The difference between them is that the coupling strength from the core clock to the peripheral clocks is much greater than that from the peripheral clocks to the core clock. That is to say $K \ll k$ in the model.

To study the entrainment range of the SCN, the period of the external LD cycle T_{LD} is set from 0 h to 50 h, at intervals of 0.001 h. If the period of the external LD cycle T_{LD} and those of oscillators in the SCN T_i satisfy $\sqrt{\frac{1}{N_F}\sum_{i=1}^{N_F}(T_{\mathrm{LD}} - T_i)^2} < \delta$, where $\delta = 1 \times 10^{-5}$ h, the SCN is entrained to the external LD cycle. For simplicity, the entrainment range is often represented by either the upper limit (ULE) or the lower limit of the entrainment range (LLE), assuming that both the upper and lower limits are symmetrically distant from the free-running period. In this paper, the LLE is utilized to represent the entrainment range, defined as the minimum period of the external LD cycle to which the system can be entrained.[31] A smaller LLE value indicates a larger entrainment range, and vice versa.

The parameter values are shown in Table 1. We scale the time by 1.26 times to achieve a 24 h free-running period for the circadian system. k, g_F, and L_0 are three factors related to aging. In the following numerical simulations, the Runge–Kutta method is applied, with a time step set to 0.01 h. The initial values of variables are randomly chosen from 0 to 1. Simulations are conducted with the total number of the oscillators in the SCN and peripheral clocks $N = 2000$, $N = 40$ and $N = 10$, respectively. The results of these three cases are similar. In this study, we present our numerical simulations of the case $N = 10$.

Table 1. Nominal parameter values for the model.

Parameters	Values
$v_x, v_a, v_y, v_b, v_z, v_c$	0.7
$\delta_x, \delta_a, \delta_y, \delta_b, \delta_z, \delta_c, v_F, v_f$	0.3
v_{Fx}, v_{fx}	0.4
$K_1, K_2, K_x, K_a, K_y, K_b, K_z, K_c, K_F, K_f, \delta_F, \delta_f, K_{Fd}, K_{fd}$	1.0
n	4
L_0	0.1
g_F, g_f	0.5
K	0.0005
k	0.11

3. Simulation results

3.1. Fundamental properties of the model

For a mathematical model of the circadian system, it is necessary to first verify whether dynamic behavior aligns with experimental observations. To observe the dynamic behavior of the individual oscillators, we disregard the external light input by setting the light intensity $L_0 = 0$. The temporal evolutions of the clock gene X_i and the x_i of the core and peripheral clocks are illustrated in Figs. 1(a) and 1(b), respectively. It is observed that the oscillators within the SCN oscillate freely and do not reach synchronization, with a free-running period of approximately 24 h under the continuous darkness condition; the peripheral clocks also have similar results. This finding is consistent with the experimental results.[32,33] The average values of X_i and x_i, denoted as $\bar{X}$ and $\bar{x}$, which stand for the system outputs, are depicted in Fig. 1(c). We can see that compared to $\bar{x}$, $\bar{X}$ has a phase delay of approximately 5 h; this is consistent with the experiment finding that the peak of the PER2 in the SCN and in the peripheral tissues of mice has a difference ranging from 3 h to 9 h in mice.[34]

Let us examine how aging affects the phase difference between $\bar{X}$ and $\bar{x}$, as shown in Figs. 1(d)–1(f). It is worth noting that aging means a decrease in the parameter values of L_0, k and g_F. It can be observed that the phase difference undergoes certain changes with the variation of aging factors L_0 and k, while g_F has almost no effect on the phase difference. The trends in the influence of L_0 and k on the phase difference are similar. The smaller the value of L_0 or k, the greater the phase difference. At the beginning of aging, the impact of L_0 degeneration is greater than that of k degeneration. However, as these factors continue to decrease, the impact of k degradation gradually increases, but the phase difference does not strictly monotonically increase with the decrease of k. In short, aging increases the phase difference between the core clock and peripheral clocks, making synchronization between the two more difficult.

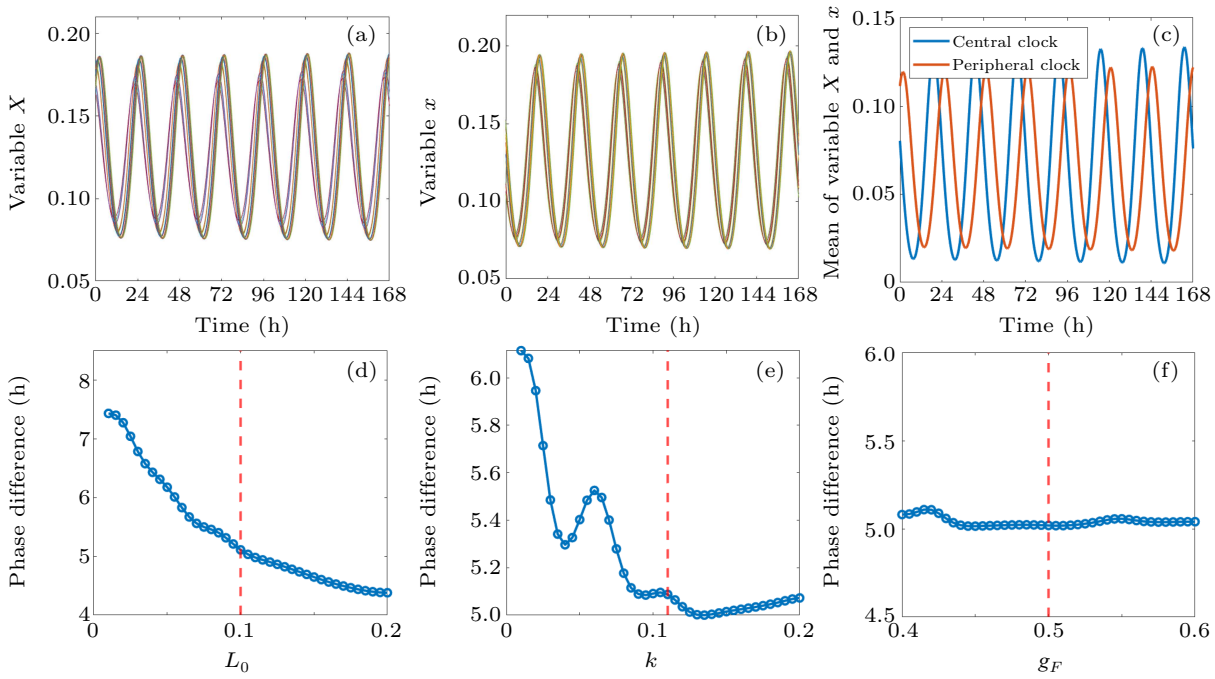


Fig. 1. Fundamental properties of the model without the external LD cycle. (a) The time course of variable X in the SCN. (b) The time course of variable x in the peripheral clocks. (c) The circadian output of the core clock $\bar{X}$ and peripheral clocks $\bar{x}$. (d)–(f) The effect of three aging factors L_0, k and g_F on the phase difference between the oscillators in the core clock $\bar{X}$ and peripheral clocks $\bar{x}$. The red dashed line represents the initial values of the corresponding parameter.

3.2. The impact of a single aging factor on the entrainment range

It is well known that entrainment is the process of aligning the phase of circadian oscillators with the LD cycle. When the SCN receives light information transmitted by the RHT, it conveys the LD cycle signal to the peripheral clocks through mechanisms such as sympathetic nervous signals and the secretion of melatonin. In turn, the peripheral clocks send feedback signals to the SCN, facilitating the phase adjustment of both the core and peripheral clocks to the external LD cycle, thereby achieving entrainment. In this study, we simulate the impact of aging on the entrainment range by altering the parameter values. To simplify the description of the aging effects, the parameters are multiplied by a constant factor C_L, where $C_L \in [0, 1]$ in the model to simulate the weakening of the coupling strength from the core clock to the peripheral clocks (k), the decrease in the internal coupling strength within the SCN (g_F), and the reduction in light sensitivity (L_0) due to ag-

ing. This paper mainly investigates the impact of aging on the entrainment ability. Therefore, all parameters for these numerical simulations are considered reasonable as long as they allow the model to oscillate normally and demonstrate the main characteristics of circadian systems. The LLE is utilized to represent the entrainment range of the circadian system.

Figures 2(a)–2(c) illustrate the impact of three aging-related factors (k, L_0, g_F) on the entrainment range. In the initial state without aging, it is observed that the LLE value for all factors stabilizes around 22.5, indicating that with an endogenous period of 24 h, the entrainment range spans from 22.5 h to 25.5 h. Figures 2(a) and 2(b) demonstrate that the LLE increases with the decrease of the L_0 and k values, implying that the decrease in L_0 and k values due to aging leads to a reduction in the entrainment range. Figure 2(c) indicates that the internal coupling strength within the SCN (g_F) has almost no effect on the entrainment range, with the LLE remaining stable at 22.5 h.

Aging reduces the entrainment range, making it harder for the circadian system to synchronize with the external environment. We explore whether adjusting the parameters of the peripheral clocks can help alleviate the effects of aging. The effects of g_f and K on the entrainment range are shown in Figs. 2(d) and 2(e). There is a positive correlation between g_f and the entrainment range, and K has almost no impact on the entrainment range. Figures 2(f) and 2(g) further demonstrate that a smaller g_f value corresponds to a larger entrainment range. This suggests that reducing the internal coupling strength of the peripheral clocks can effectively alleviate the impact of aging on the circadian system.

Our results suggest that aging weakens the coupling between the core clock and the peripheral clocks, leading to a reduction in the entrainment range. Additionally, the decrease in light sensitivity and coupling strength due to aging impairs the circadian system's ability to respond to environmental cues, especially light cycles, therefore reducing its overall adaptability. Furthermore, our study shows that adjusting the coupling strength in the peripheral clocks can help mitigate the effects of aging on the circadian system. This indicates that peripheral clocks may play a compensatory role in maintaining synchronization and adaptability when the core clock is compromised.

In fact, as a complex living system, the effects of aging on various factors are inevitably occurring simultaneously. Single factor analysis aims to examine what effects each factor under the influence of aging has on the entrainment ability of the circadian system. This also provides a theoretical reference for intervening in rhythm disorders caused by aging. For example, as the impact of reduced light sensitivity is significant, we can use light exploration or strong light therapy for treatment, which is currently used in clinical practice to regulate sleep or jet lag.

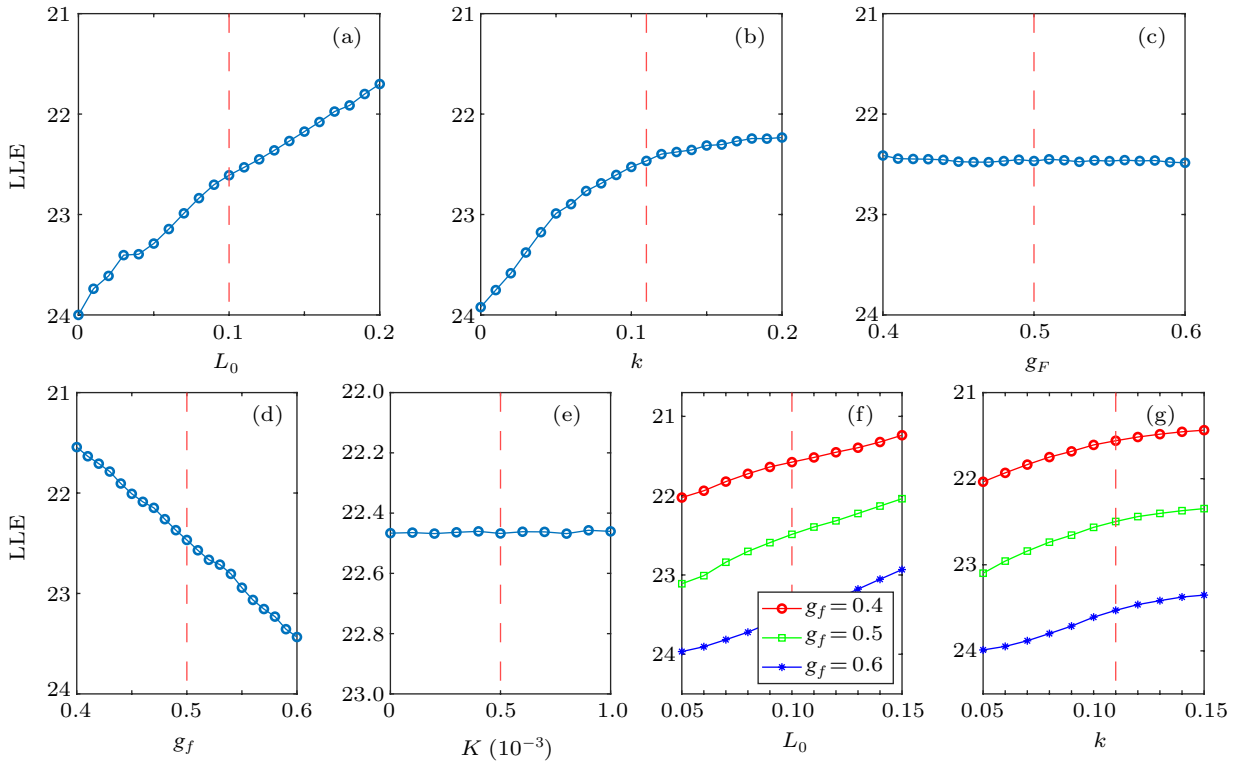


Fig. 2. Effect of the key parameters on the entrainment range. Panels (a)–(e) display the impact of the varying parameter values of k, L_0, g_f, g_F and K on the LLE, respectively. Panels (f) and (g) illustrate that lowering the value of g_f mitigates the effects of aging factors on the LLE. The red dashed lines represent the initial values of the corresponding parameters.

3.3. The impact of multiple aging factors on the entrainment range

In reality, normal aging results in a noticeable decline in various bodily functions. Here we simulate the comprehensive impact of simultaneous aging of multiple factors on the entrainment range. A parameter x aging $y\%$ means $\text{Value}_{x_\text{end}} = \text{Value}_{x_\text{init}} \times (1 - y\%)$, where x denotes an aging factor; $y\%$ represents the degree of aging; $\text{Value}_{x_\text{end}}$ is the value of x after aging, and $\text{Value}_{x_\text{init}}$ is the initial value of x representing the youthful state.

As previous studies have shown, aging factors L_0 and k have significant impacts on the entrainment range. Here we consider the combined effects of these two aging factors. We conduct research on three types of aging: (q_1) normal aging refers to the same degree of aging of L_0 and k; (q_2) the aging of photosensitivity is faster, that is, the degree of aging of L_0 is greater; (q_3) coupling strength from the core clock to peripheral clocks aging is faster, that is, the degree of aging of k is greater. The corresponding degrees of aging are (q_1) L_0 and k aging 25%; (q_2) L_0 aging 30%, k aging 25%; and (q_3) L_0 aging 25%, k aging 30%, respectively. (q_1) may be due to damage to the photosensitive element, while (q_2) may be due to weakened sympathetic nervous signals or impaired melatonin secretion ability during the aging process. Consider the impact of these three aging modes on the entrainment range at different aging starting points, which represent different youthful states. Let $\text{Value}_{x_\text{init}} = \text{Value}_{x_\text{default}} \times (1 + C)$, where $\text{Value}_{x_\text{default}}$ is the value in Table 1 and C is a constant.

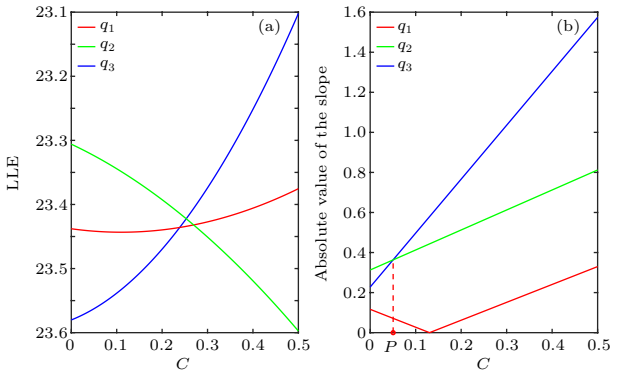


Fig. 3. Effect of different aging modes on the entrainment range. (a) The variation of the LLE with the initial state under different aging modes. (b) The speed of variation in the LLE with the initial state under different aging modes. The blue line represents the aging mode of 30% aging of k combined with a 25% aging of L_0; the red line represents a 25% aging of both k and L_0, and the green line represents a 25% aging of k combined with a 30% aging of L_0.

Figure 3(a) shows the variation of the entrainment range with C and figure 3(b) gives the slope plots representing the change rate of the curves in Fig. 3(a). The slope of the (q_1) curve gradually becomes steeper, evidently surpassing the (q_2) curve. Therefore, there exists a critical P as shown in Fig. 3(b). When $C < P$, the aging of k predominates; when $C > P$, the aging of L_0 is more pronounced. The LLE of the (q_1) curve stabilizes at around 23.4 h, showing a significant increase compared to the youthful state LLE of 22.5 h, and is also larger than the LLE of 22.8 h when aged by a single aging factor of 25%, as shown in Fig. 2. This indicates that the simultaneous aging of multiple factors leads to a more substantial reduction in the entrainment range compared to the aging of a single factor. Specifically, when both L_0 and k undergo aging, the entrainment range decreases significantly. Adjusting the values of k and L_0 to specific levels in a youthful state can alleviate the impact of damage to photosensitive components or melatonin secretion on the entrainment range after aging.

3.4. The impact of aging on the entrainment time

The core clock and peripheral clocks oscillate with the endogenous period 24 h under continuous darkness conditions. An external LD cycle with a certain period is added at a certain circadian time. The time interval from the time at which the LD cycle is added to that at which the circadian system is entrained to the LD cycle is defined as the entrainment time. It reflects the system's adaptability to the external environment. We wonder how aging affects the entrainment time.

The endogenous period of the circadian clock system is 24 h. The period of the external LD cycle is set to $T_{+\Delta T} = 24 + \Delta T$ or $T_{-\Delta T} = 24 - \Delta T$, $0 \le \Delta T \le 1$. The entrainment time is calculated under different conditions, as shown in Fig. 4. We can see that the entrainment time increases with the increase of ΔT, which means that the greater the difference between the period of the LD cycle and 24 h, the longer the entrainment time. Figures 4(a) and 4(b) show that the entrainment time increases with the decrease of L_0 and k. That is to say, it increases with aging. The impact of g_F on the entrainment time is not significant, as indicated by Fig. 4(c). It can also be noticed that the entrainment time of the circadian system to the external LD cycle with symmetrical periods of $24 + \Delta T$ and $24 - \Delta T$ with the same ΔT is almost the same. Comparing Figs. 4(a) and 4(b), under the same degree of aging in L_0 and k (the aging rate here is 20%), L_0 aging has a greater impact on the entrainment time. In short, aging makes it more difficult for the circadian system to synchronize with the external LD cycle. This result is consistent with the experimental findings that at the behavioral level, compared to young people, elderly people need more time to reach re-entrainment when facing jet lag.[35,36]

Similar to before, we explore whether adjusting the parameters of the peripheral clocks can help alleviate the effects of aging on the entrainment time. The effects of g_f and K on the entrainment time are shown in Figs. 4(d) and 4(e). There

is a positive correlation between g_f and the entrainment time, and K has almost no impact on the entrainment range. Therefore, reducing the value of g_f can also mitigate the effect of aging on the increasing entrainment time.

3.5. The impact of aging on the entrainment phase

When the phase difference between the circadian oscillator and the LD cycle is stable over time, the circadian clock is entrained to the LD cycle. At this point,

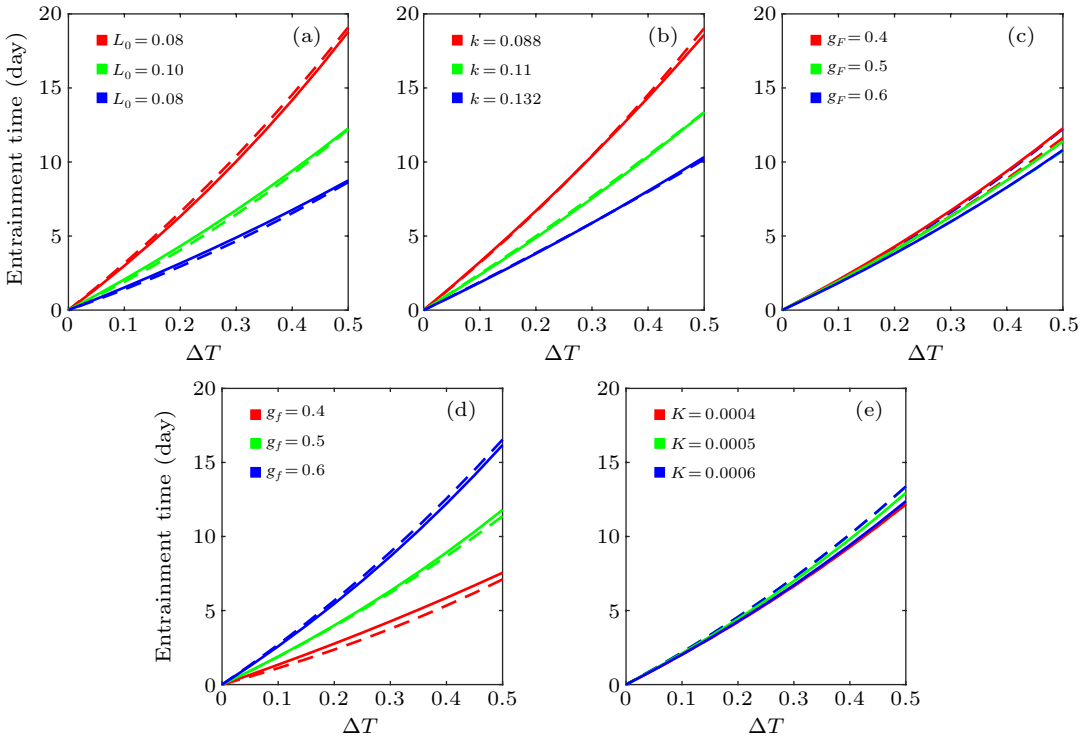


Fig. 4. Effect of the key parameters on the entrainment time. The variation of the entrainment time with the absolute value of the difference between the LD cycle and the intrinsic cycle (ΔT) at different L_0 (a), k (b), g_F (c), g_f (d) and K (e) are shown. The dashed lines indicate the LD cycle with a period of $T_{-\Delta T} = 24 - \Delta T$, and the solid lines represent the LD cycle with a period of $T_{+\Delta T} = 24 + \Delta T$.

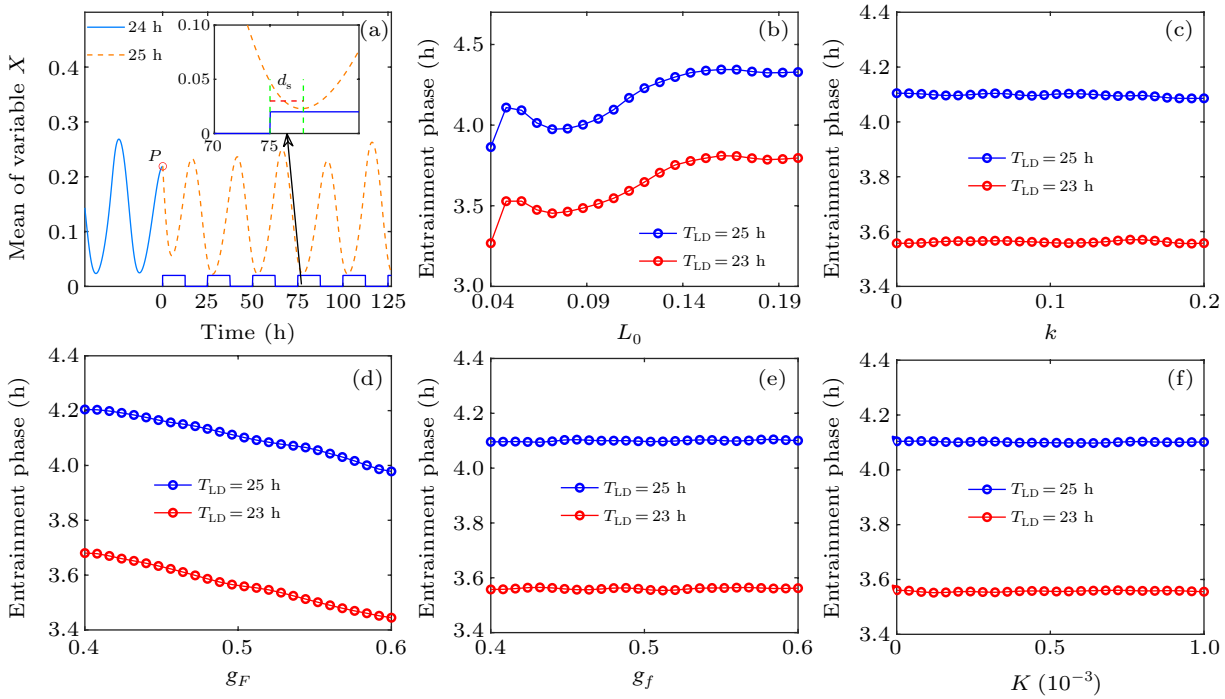


Fig. 5. Effect of the key parameters on the entrainment phase. (a) The time course curve of the core clock. The blue line represents the circadian system oscillating freely under continuous darkness, and the red line reveals that the curve is entrained to the LD cycle added at point P. The jagged line shows the LD cycle (11.5:11.5). The variation of the entrainment phase with L_0 (b), k (c), g_F (d), g_f (e) and K (f) are shown, where the periods of the LD cycle are 25 h and 23 h.

the phase difference is called the entrainment phase, denoted as d_s. However, the entrainment phase may not necessarily be zero. In Fig. 5(a), before point P, the circadian oscillator vibrates freely with its internal period of 24 h under continuous darkness. At point P, the LD cycle with a period of 23 h is added, and after several days the circadian oscillator has entrainment with the LD cycle. Here, the entrainment phase d_s does not equal zero. We wonder how aging affects the entrainment phase.

From Figs. 5(b)–5(d), we can see that the changes in L_0 and k have almost no effect on the entrainment phase d_s, and as g_F decreases, d_s increases. It is worth noting that aging means that L_0, k and g_F all decrease. Therefore, overall, aging leads to an increase in the entrainment phase, which is related to sleep problems in the elderly. For example, most elderly people have a sleep pattern of going to bed early and waking up early.[37] The effects of the parameters of the peripheral clocks g_f and K on the entrainment phase are shown in Figs. 5(e) and 5(f). We find that g_f and K have almost no impact on the entrainment phase. Therefore, the effect of aging on the increasing entrainment phase cannot be mitigated by adjusting the parameter values related to the peripheral clocks.

4. Discussion and conclusion

The mammalian circadian system is a hierarchical network of oscillators composed of a core clock and peripheral clocks. The core clock coordinates the peripheral clocks, which, in turn, feed back to the core clock, resulting in mutual coupling. Entrainment is a key property of the circadian system, which indicates the adaptability to changes of the external environment. Aging affects most physiological processes including the circadian system, and makes the circadian system more susceptible to interference.

The relationship between the circadian systems in the context of aging has not been fully studied, and it is difficult to assume that age-related changes only affect one aspect of the circadian system.[38] We discuss the complexity of this issue, particularly how aging affects the synchronization between the core clock and peripheral clocks and also its impact on overall adaptability. Our study provides preliminary insights into this question by analyzing the dynamic changes of both the core and peripheral clocks. Studies have found that older animals require longer periods of time to respond to the phase reversal of the LD cycle compared to younger counterparts.[39] This raises a question about whether aging changes the adaptability of the circadian system to environmental signals, especially the LD cycle. However, there is still a lack of a systematic understanding of the effect of aging on the entrainment of the circadian system. To study this question, we construct a mathematical model consisting of two populations of coupled Goodwin oscillators which describe the core clock and peripheral clocks. We study the adaptability of the circadian system to the external environment, which is weakened by aging. That is to say, aging reduces the entrainment ability between the circadian system and the LD cycle, which answers the previous question. In fact, the impact of aging on the function of the circadian system is quite complex, and the feedback loop of target organs or physiological behaviors can enable the function of the SCN to better adapt or adjust to environmental and physiological challenges.[40] This raises the question of whether peripheral clocks can compensate for the decline of core clocks caused by aging. Our research provides a positive answer to this question.

All in all, in this paper, three age-related factors of the circadian system are considered. With numerical simulation, we get the following meaningful results.

(i) Aging increases the phase difference between the core clock and the peripheral clocks, indicating that it is more difficult for the core clock and peripheral clocks to achieve synchronization. This is mainly reflected in the decrease of the sensitivity to external light and the weakening of the coupling strength from the core clock to the peripheral clocks caused by aging, which increases the phase difference.

(ii) Aging decreases the entrainment range and increases the entrainment time and the entrainment phase, making the circadian system less likely to synchronize with the external environment. Specifically, the decrease of the sensitivity to external light and the weakening of the coupling strength from the core clock to peripheral clocks increases the LLE and the entrainment time. In contrast, the decreasing internal coupling strength among neurons within the SCN increases the entrainment phase.

(iii) On the one hand, the numerical simulation results provide us with an idea to improve the entrainment capability. For example, increasing the intensity of illumination can help achieve synchronization with the external LD cycle. On the other hand, we also want to see if it is possible to offset the effects of aging by adjusting the parameter values of the peripheral clocks. Through numerical simulation, we find that reducing the coupling strength among the peripheral clocks can increase the entrainment range and reduce the entrainment time. However, changes in the peripheral clocks' coefficient cannot improve the sleep-related entrainment phase caused by aging. Perhaps we need to explore improvement methods from other perspectives.

These results demonstrate from a mathematical perspective the mechanism by which aging affects circadian systems, which offers a theoretical reference for biological work. The

developed mathematical model is meaningful and can be utilized to investigate other biological issues related to aging. The results and analytical framework proposed here offer insights for a better understanding of the relationship between aging and the entrainment of the circadian system.

Actually, the mathematical model proposed in this paper can also be considered from the perspective of complex networks.[41] The coupled neurons within the SCN and the coupled peripheral clocks each form a complex network. The interaction between these two parts can be viewed as the interaction between two motifs. From the perspective of complex networks, different coupling modes among neurons in the SCN or peripheral clocks can be considered for a more in-depth analysis. In order to have a clearer understanding of the effects of aging, we have only considered one coupling method, which is complete coupling. In fact, the coupling among neurons in the SCN or peripheral clocks is quite complex and may even change with age. It is also a future research direction to study the mutual regulation between the core clock and peripheral clocks with different coupling modes with the help of complex networks.

As described in this paper, the core clock primarily responds to the LD cycle. However, research has found that peripheral clocks respond to the feed-fast cycle.[4,5]

Nowadays, the irregular work patterns of night shifts and shift work disrupt the normal regulation of the circadian system, further leading to disorders. The irregular dietary patterns that come with it are associated with increased disease risk, while a regular dietary schedule can help maintain a strong circadian rhythm and prevent disease.[42] Time-restricted feeding (TRF) as a dietary intervention strategy is expected to alleviate circadian clock disorders and the related health risks associated with shift work.[43] Therefore, we will explore what kind of dietary patterns are more conducive to the entrainment of the circadian system to the external environment. Specifically, TRF will be incorporated into the model presented here. Similar to the LD cycle which is added to the part of the core clock, TRF described by a periodic function is added to the part of the peripheral clocks. This periodic function includes the feeding period, feeding time, and feeding duration, which are noted by some parameters. The expanded model makes it possible to explore how TRF might contribute to circadian synchronization and health outcomes, offering new insights into the potential therapeutic use of TRF in improving circadian-related diseases. Besides dietary patterns, including additional biological factors like sleep/wake cycles[44] or light exposure could also help make the model more comprehensive and applicable to real-world scenarios.

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