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Critical time delay of the pineal melatonin rhythm in humans due to weak electromagnetic exposure

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Electromagnetic fields (EMFs) can increase free radicals, activate the stress response and alter enzyme reactions. Intracellular signalling is mediated by free radicals and enzyme kinetics is affected by radical pair recombination rates. The magnetic field component of an external EMF can delay the "recombination rate" of free radical pairs. Magnetic fields thus increase radical life-times in biological systems. Although measured in nanoseconds, this extra time increases the potential to do more damage. Melatonin regulates the body's sleep-wake cycle or circadian rhythm. The World Health Organization (WHO) has confirmed that prolonged alterations in sleep patterns suppress the body's ability to make melatonin. Considerable cancer rates have been attributed to the reduction of melatonin production as a result of jet lag and night shift work. In this study, changes in circadian rhythm and melatonin concentration are observed due to the external perturbation of chemical reaction rates. We further analyze the pineal melatonin rhythm and investigate the critical time delay or maturation time of radical pair recombination rates, exploring the impact of the mRNA degradation rate on the critical time delay. The results show that significant melatonin interruption and changes to the circadian rhythm occur due to the perturbation of chemical reaction rates, as also reported in previous studies. The results also show the influence of the mRNA degradation rate on the circadian rhythm's critical time delay or maturation time. The results support the hypothesis that exposure to weak EMFs via melatonin disruption can adversely affect human health.

Keywords Melatonin level, Circadian rhythm, Pineal melatonin model, Electromagnetic fields, Health effects.

All living beings have an inner "body clock" that measures seasonal and daily (circadian) rhythms[1]. This circadian rhythm is crucial in determining the sleeping and feeding patterns of all animals, including human beings and has an approximately 24 h day-night cycle when not disturbed[2,3]. Studies have shown that deliberately disturbing humans' circadian rhythm can lead to severe health problems[4]. Since 1960, magnetic fields have been known as the synchronizers for circadian clocks[5], although how circadian clocks perceive and process magnetic information is still a mystery. It is assumed that the circadian rhythm can be disrupted by weak magnetic fields, thus can cause adverse biological effects[4].

Melatonin (5-methoxy-N-acetyltryptamine) is a hormone produced by the body's pineal gland, which controls the body's sleep-wake cycle or circadian rhythm[6]. This is regulated by the suprachiasmatic nucleus (SCN)[7,8], which is activated by the darkness and depressed by the light. Within the last decade, several studies have revealed that melatonin is a naturally occurring free radical scavenger and an inducer of antioxidant enzymes[9]. Melatonin promptly crosses the blood-brain-barrier into the brain, due to its permeability[10]. Consequently, it is found in the central nervous system at significantly higher levels than in the blood[9]. By measuring melatonin level, one can assess the development of the body clock in infants and this is a useful indicator of the sleep-wake rhythm development[11].

Melatonin is excited by low wavelength blue light (420-440 nm) exposure[2], although the necessary illuminance fluctuates from species to species. In addition to light intensity, wavelength (or color) of light is an important factor for resetting the clock[2,12]. Another recent study[11] has shown that salivary melatonin concentration in infants decreases between 6:00 am and 10.00 pm. Higher levels of melatonin concentration in the morning may possibly indicate an immature sleep-wake rhythm. Plasma melatonin levels in adults start to decrease after 6.00 am due to exposure to morning light, reaching their lowest level at 10.00 am and again starts increasing after 9.00 pm and peaks between 2.00 am and 6.00 am[13].

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The blood and urinary melatonin levels can be used to assess melatonin levels in the body, considered as a biomarker of circadian dysregulation[14]. Furthermore, recent studies have shown that disruption of melatonin due to exposure to weak EMFs could lead to long-term health effects in humans[15]. Exposure to electric and magnetic fields by transportation[16], production and distribution of electricity (50 Hz in Australia and Europe and 60 Hz in North America) is everywhere, especially in industrialized countries. International Commission on Non-Ionizing Radiation Protection (ICNIRP) limits are designed as guidelines to protect from low-frequency EMFs against nerve stimulation and from microwaves against body heating[17].

According to the World Health Organization (WHO), prolonged alterations in sleep patterns suppress the body's ability to make melatonin[18]. Considerable cancer rates have been detected due to the reduction of melatonin production as a result of jet lag and night shift work[19]. Melatonin reduction has also been suggested to be responsible for substantial increase in the incidence of breast cancer in industrialized countries in recent decades[20-22]. The Danish government even paid compensation to women who had developed breast cancer after long periods of working through the night. A higher cancer incidence has also been reported in people living and/or working in surroundings exposed to higher than normal artificial magnetic fields associated with a reduction of nocturnal melatonin[23]. It has also been hypothesized that the decrease of melatonin levels with age adds to the aging process[1]. The reduced production of night-time melatonin due to exposure to light at night from household as well as street lighting and magnetic fields associated with the electricity supply may also have an adverse effect on human health[15]. The exposure to constant light may lead to the quick development of mammary gland tumors, as shown in animal experiments on rats[24].

A study suggests that there may be a cumulative effect of magnetic field exposure on the stability of individual melatonin measurements over time[25]. The hypothesis of melatonin interruption in studies on the human population could also be due to factors other than the field intensity level, such as transients or switching or due to the field type (electric rather than magnetic field)[14]. The magnetic field disruption of melatonin is reported in human populations frequently exposed to both electric and magnetic fields related to electricity distribution[14]. The night-time melatonin output is found to be unchanged by mobile phone handset emissions, but there could be an effect on melatonin onset time[26]. A study involving electric utility workers has shown that certain electromagnetic field (EMF) environments have a greater effect on melatonin levels[27] and this is confirmed with a series of animal studies[28]. Volunteers exposed to non-acute and chronic exposures of magnetic fields have been shown the disruption of the nocturnal production of pineal melatonin[14].

In this paper, we have proposed a mathematical model for pineal melatonin rhythm and circadian rhythm changes, due to melatonin interruption. The critical time delay or maturation time and its consequences have also been analyzed.

Materials and Methods

Analyzing pineal melatonin model

The pineal melatonin model has been discussed in[3,29,30]. In both humans and rats, melatonin is produced corresponding to the sequence of tryptophan →serotonin →N-acetyl serotonin → melatonin[30]. The change in rate of a chemical reaction because of the involvement of a substance can join in multiple chemical transformations. The serotonin to melatonin conversion in the pineal gland involves basic enzymes, which catalyze reactions. The chemical bonds in the molecules are changed due to changes in the enzyme. The biochemical reaction is connected with a rate law and kinetic parameters[29]. This reaction involves many processes, like food digesting and sending nerve signals. The function of catalysis is to increase the rate of chemical reactions, although it is chemically unchanged at the end of the reaction[31].

The enzymes are proteins that enhance the rates of chemical reactions[29] in living organisms. Consider a biochemical reaction scheme in which an enzyme (***E***) binds to its substrate (***S***) to form the enzyme-substrate complex (***ES***). Then ***ES*** irreversibly breakdowns to form the product (***P***) of the reaction and release the enzyme (***E***). This mechanism can be written as follows[29]:

$$\boldsymbol{E} + \boldsymbol{S} \leftrightarrow \boldsymbol{ES} \text{ - Disassociation constant } = \frac{\boldsymbol{k}_{-1}}{\boldsymbol{k}_1}$$

$$\boldsymbol{ES} \rightarrow \boldsymbol{E} + \boldsymbol{P} \text{ - Rate constant } = \boldsymbol{k}_3$$

$$\boldsymbol{E} + \boldsymbol{S} \rightarrow \boldsymbol{M} \textit{ or } (\boldsymbol{ES}) \text{ - Disassociation constant } = \frac{\boldsymbol{k}_{-2}}{\boldsymbol{k}_2}$$

$$\boldsymbol{M} \rightarrow \boldsymbol{E} + \boldsymbol{P} \text{ - Rate constant } = \boldsymbol{k}_4.$$

Consider a biochemical network that involves a set of rate equations, which is a non-linear function of concentration of the chemical species X and the kinetic parameters. If we consider X number of elements with x concentration and time t and kinetic parameters p, in general, the reaction network can be written as[29],

$$\frac{dx_i}{dt} = f(x;p) = f_i(x_1, x_2, ..., x_n; p_1, p_2, ..., p_n),$$

where i = 1,2,….,n. At the steady-state, the solution of kinetic equations satisfies $f(x;p) = f_i(x_1, x_2, ..., x_n; p_1, p_2, ..., p_n) = 0$.

Although there could be many steady-state solutions due to nonlinear behavior, in this work, we consider only the solutions that satisfy $x_i \geq 0, \forall i$. Now, the rate of the reaction can be written as

$$v = \frac{d[P]}{dt} = -\frac{d[M]}{dt} = \frac{[E]\left(\frac{[M]}{K_{m1}}\right)\left(k_3 + k_4\left(\frac{[M]}{K_{m2}}\right)\right)}{1 + \left(\frac{[M]}{K_{m1}}\right) + \left(\frac{[M]^2}{K_{m1}K_{m2}}\right)}$$

where $K_{m1} = \frac{k_{-1} + k_3}{k_1}$ is the Michaelis-Menten constant for the interaction of the enzyme with the 1st substrate to bind and $K_{m2} = \frac{k_{-2} + k_4}{k_2}$ is inversely proportional to the correspondence of the enzyme for the 2nd substrate to bind[29].

Biochemical oscillator of living organisms

Biochemical and biophysical rhythms are ever-present characteristics of living organisms from rapid oscillations of membrane potential in nerve cells to slow cycles of ovulation in mammals[29]. The biochemical oscillator based on negative feedback was discovered by Goodwin[32]. By following his mechanism[29], the circadian behavior of intracellular circadian oscillator can be defined in kinetic equations as follows:

$$\frac{d[X_1]}{dt} = \frac{v_0}{1 + \left(\frac{[X_3]}{K_m}\right)^p} - k_1[X_1] \quad \ldots(1)$$

$$\frac{d[X_2]}{dt} = v_1[X_1] - k_2[X_2] \quad \ldots(2)$$

$$\frac{d[X_3]}{dt} = v_2[X_2] - k_3[X_3] \quad \ldots(3)$$

where $[X_1]$, $[X_2]$ and $[X_3]$ and are concentrations of mRNA, protein and end product, respectively; v_0, v_1 and v_2 are the rates of transcription, translation and catalysis, respectively, k_1, k_2 and k_3 and are rate constants for the degradation of each component, $\frac{1}{K_m}$ is the binding constant of the end product to the transcription factor and p is a measure of end product repression. Bliss and his co-workers[33] slightly modified Goodwin's Eqs (1)-(3) to account for the time delay during the transcription and the translation with mRNA and protein processing in the nucleus and cytoplasm. There are also delays in the feedback term due to: (*i*) the movement of end product into the nucleus, (*ii*) binding with transcription factors, and (*iii*) interaction with gene to affect its rate of transcription[29]. Considering the above, the delayed differential equation for negative feedback is given by:

$$\frac{d[M]}{dt} = \frac{r_M}{1 + \left(\frac{[P]}{k}\right)} - q_M[M] \quad \ldots(4)$$

$$\frac{d[P]}{dt} = r_P M(t - \quad) \quad - q_p[P] \quad \ldots(5)$$

where $[M]$ and $[P]$ are the concentrations of mRNA and protein, r_M and r_P are mRNA and protein production rate constants, q_M and q_P are mRNA and protein degradation rate constants, is Hill coefficient, is non-linearity in protein synthesis cascade, k is a scaling constant and is duration of protein synthesis cascade[29]. Circadian rhythmis a function of 7 parameters [Circadian rhythm = f(r_M, r_P, q_M, q_P, , ,], thus we can not observe all the parameters simultaneously.

Pineal melatonin rhythm and critical time delay

The pineal melatonin rhythm is driven by the circadian clock and entrained to (on average 24.6 h) day-night cycle. During the constant dim light,

human is on average 24.3 h or less[34], hence the clock needs to be phase advanced by 0.3 h or less on average each day. The delay-differential equation $\frac{dx}{dt} = \left[\frac{1}{1+x(t-\ )}\right] - q_M x$ needs to be solved for the case of discrete time lag. As described in[29], demonstrating periodic solutions at a Hopf bifurcation, numerically, we must require that b = - cos( ) and = - sin( ) where $= \frac{x^{-1}}{(1+x\ )^2}$ and is the oscillatory frequency. Using these equations, the critical time delay or maturation time $_c$ is given by:

$$_c(q_M) = \frac{\frac{1}{180}\left[\cos^{-1}\left(\frac{^{-q}M(1+x\ )^2}{x^{-1}}\right)\right]}{\left[\left(\frac{x^{-1}}{(1+x\ )^2}\right)^2 - q_M{}^2\right]} . \qquad (6)$$

We can investigate the impact of different parameters on critical time delay or maturation time, $_c$ by analyzing Eq. (6).

Results and Discussion

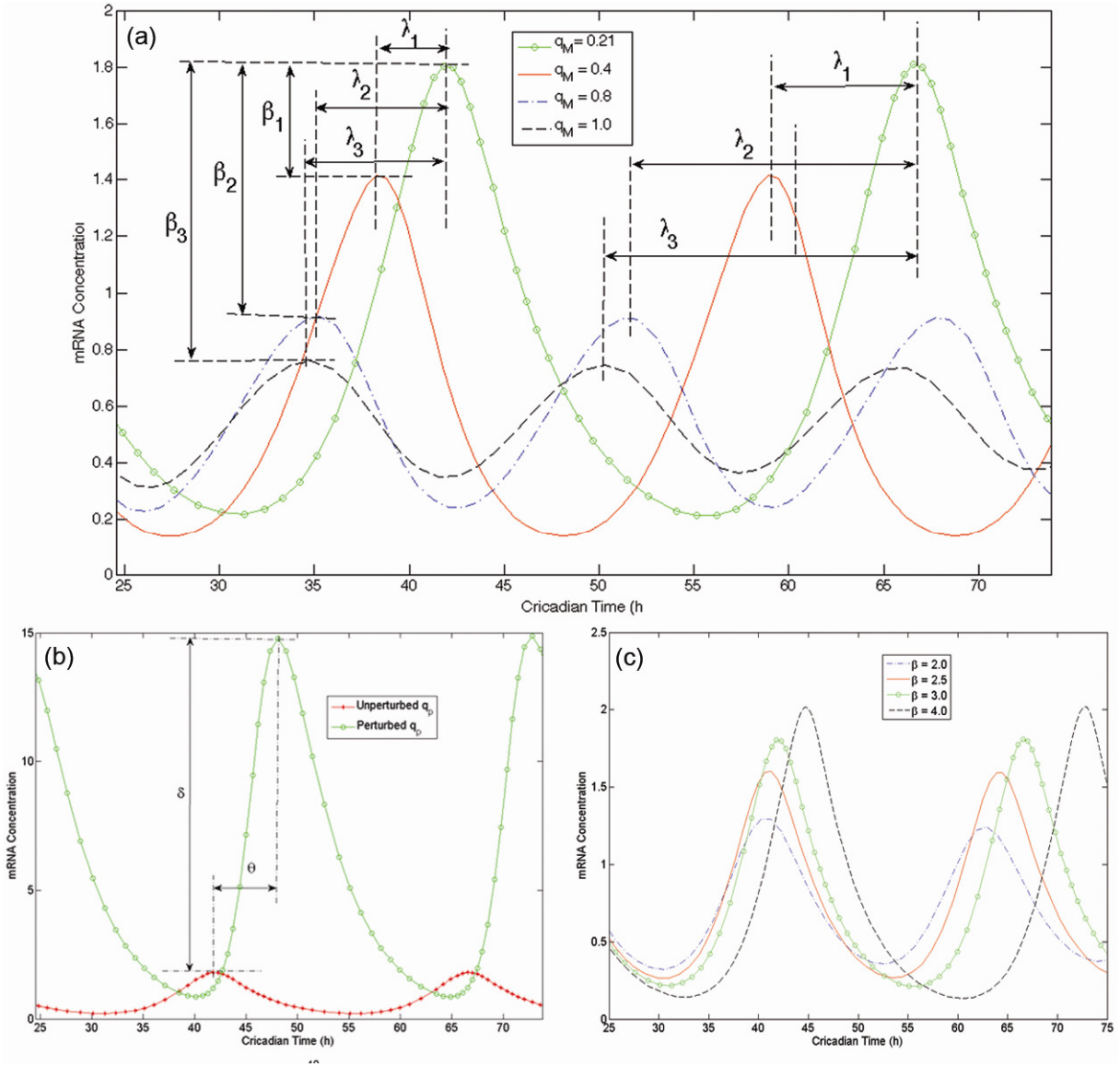
The results have been obtained using the delay differential equation with *dde*23 function in MATLAB. The model is defined by seven parameters and those values are, as in[35]: protein production rate r_P = 1.0 h^{-1}; mRNA production rate r_M = 1.0 h^{-1}; protein degradation rate q_P = 0.21 h^{-1}; mRNA degradation rate q_M = 0.21 h^{-1}; delay = 4 h; Hill coefficient = 2 and non-linearity in protein synthesis =3. In this work, we change one parameter out of seven at a given time, while keeping the other parameters constant to investigate the system, similar to the approach taken in[35]. Figure 1 shows the influence of parameters q_M, q_P, r_M, r_P and to mRNA concentration or entrainment with a period of 24.6-73.8 h (*i*) a free-running oscillator (unperturbed model) using Eqs (4) and (5) and to (*ii*) an external periodic stimulation (perturbed model). Oscillations are obtained with mRNA concentration and circadian rhythm changes over different mRNA degradation rates q_M.

We observe that mRNA concentration decreased significantly with increasing q_M in both unperturbed (Fig. 1a) and perturbed models. The difference in mRNA concentration (values) and circadian time shift (values) are shown in Table 1 with reference to q_M = 0.21. We observe that mRNA concentration increases with the increasing q_P, however, this variation is not significant after q_P = 1 h^{-1} in unperturbed models. In spite of this, in perturbed models, similar to the effect of q_M, significant changes to the peak concentrations of mRNA are observed due to protein degradation rate q_P. The difference in (or between) mRNA concentration (values) and circadian time shift (values), as marked in Fig. 1b is shown in Table 2 with reference to q_P = 0.21.

No remarkable changes in circadian rhythm or lagging time between the peak concentrations of mRNA due to variation of mRNA production rate r_M are observed, although changes are noted with mRNA concentration in the perturbed model. The consistent results are observed in the repeated analysis in unperturbed model. Additionally, no significant changes are observed in the circadian rhythm or mRNA concentration due to variation of protein production rate r_P in the perturbed model. There are only slight changes in the circadian rhythm in both unperturbed (Fig. 1c) and perturbed models (Fig. 1d). Significant changes to the peak concentrations of mRNA are also observed in both perturbed and unperturbed models (Fig. 2). Figure 3 shows the dependency of $_c$ on q_M for given values of . The maximum and minimum values for the mRNA concentration and circadian rhythm shift in the perturbed and unperturbed models are given in Table 2. Our repeated analysis for longer period of circadian rhythms has shown the consistent results.

Table 1—Circadian and melatonin values for q_P = 0.21 (unperturbed)

Circadian rhythm peak no.	q_M = 0.4		q_M = 0.8		q_M = 1.0	
	1	1	2	2	3	3
1	0.20	6.89	1.90	11.78	2.30	12.52
2	-3.89	7.60	-7.65	12.58	-6.59	13.38
3	-7.96	7.68	-15.55	12.65	-16.48	13.51
4	-12.05	7.69	-22.88	12.71	-25.20	13.56
5	-16.20	7.69	-32.23	12.71	-34.57	13.57
6	-20.20	7.69	-40.50	12.71	-43.70	13.58
7	-24.30	7.68	-47.80	12.71	-52.90	13.59
8	-28.40	7.68	-57.10	12.71	-63.10	13.59
9	-34.50	7.70	-65.40	12.67	-72.30	13.60
10	- 36.50	7.69	-73.10	12.66	-81.30	13.59
11	-40.60	7.69	-81.80	12.66	-90.80	13.59
12	-44.60	7.69	-90.30	12.67	-100.20	13.59



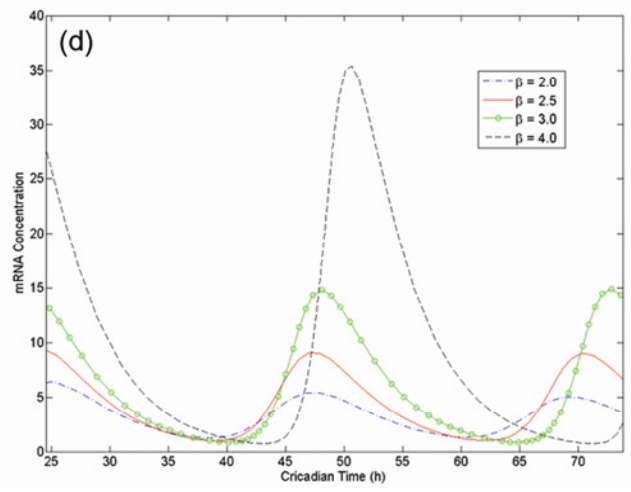


Fig. 1—Entrainment of a free-running oscillator to an external periodic stimulation with a period of 24.6 – 73.8 ***h***.[(**a**) Circadian and melatonin analysis - Unperturbed - Entrainment of a free-running oscillator to an external periodic stimulation of the mRNA degradation rate $\boldsymbol{q}_M$ Here $\boldsymbol{r}_M = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{r}_P = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_P = 0.21\ \boldsymbol{h}^{-1}$, = 2, **= *3***, ***k* =** 1.Other parameter values are as indicated; (**b**) Circadian and melatonin analysis - Perturbed and unperturbed of the protein degradation rate when $\boldsymbol{q}_P = 0.21$ Here $\boldsymbol{r}_M = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{r}_P = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_P = 0.21\ \boldsymbol{h}^{-1}$, = 2, **= *3***, ***k* =** 1. Other parameter values are as indicated; (**c**) Circadian and melatonin analysis - Unperturbed - Entrainment of a free-running oscillator to an external periodic stimulation of the non-linearity in protein synthesis . Here $\boldsymbol{r}_M = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{r}_P = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_P = 0.21\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_P = 0.21\ \boldsymbol{h}^{-1}$, = 2, ***k* =** 1. Other parameter values are as indicated; (**d**) Circadian and melatonin analysis - Perturbed - Entrainment of a free-running oscillator to an external periodic stimulation of the nonlinearity in protein synthesis Here $\boldsymbol{r}_P = 1\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_M = 0.21\ \boldsymbol{h}^{-1}$, $\boldsymbol{q}_P = 0.21\ \boldsymbol{h}^{-1}$, = 2, **= *3***, ***k* =** 1. Other parameter values are as indicated.

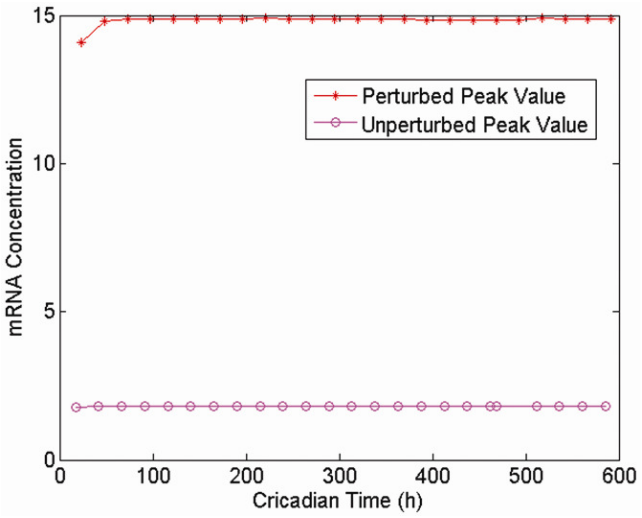


Fig. 2—Circadian and melatonin analysis–Perturbed and unperturbed peak values when q_P = 0.21 [Here r_P = 1 h^{-1}, q_M = 0.21 h^{-1}, q_P = 0.21 h^{-1}, = 2, = 3, k = 1]

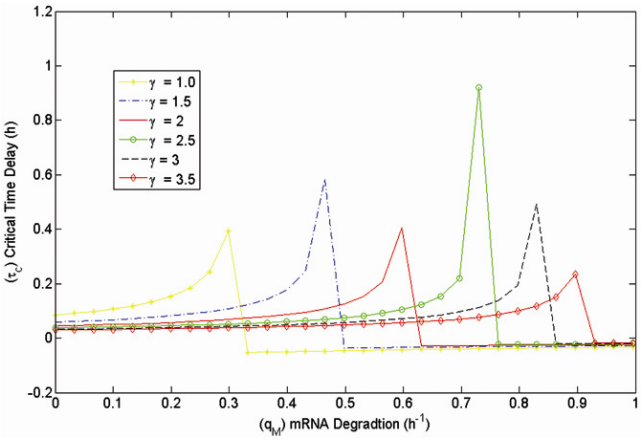


Fig. 3—Influence of the mRNA degradation rate constant q_M on the critical time delay or maturation time $_c$ for a given [The critical time delay or maturation time is plotted against the value of mRNA degradation rate constant by using Eq. x = 0.76. Here and other parameter values are as indicated]

The feasible values of the parameters are used, as in[35] to study circadian oscillations and melatonin changes due to external perturbation of chemical reaction rates. Our results also show that both the duration of melatonin and secretion are strongly regulated by the circadian system, as reported in literature[36]. Our results verify the conclusion in literature that significant melatonin interruption and changes of circadian rhythm occur due to perturbation of chemical reaction rates. Thus, our results predict that considerable melatonin interruption from exposure to weak EMFs will have impact on human health. Earlier, studies have suggested that circadian rhythms can be influenced, due to radical pair reactions that take place in the living organism[37,38]. As a consequence, the biological effects can be directly, due to magnetic fields when the circadian rhythms are influenced by the radical pair mechanism[37,38]. However, additional experimental work is required to further study the long-term effects of EMFs on melatonin interruption.

Table 2—Circadian and melatonin values for q_P = 0.21 (Perturbed and unperturbed)

Circadian rhythm peak no.		
1	5.78	12.23
2	6.32	12.99
3	6.29	13.07
4	6.30	13.08
5	6.30	13.08
6	6.30	13.08
7	6.30	13.07
8	6.30	13.07
9	6.30	13.09
10	6.30	13.08
11	6.30	13.08
12	6.30	13.08

Conclusion

It is observed that significant melatonin interruption and changes of circadian rhythm occur due to the perturbation of chemical reaction rates, which has also been proposed in literature. In addition, the results show the influence of mRNA degradation rate on critical time delay or maturation time of circadian rhythms. The results also support the hypothesis that long-term adverse health effects might be due to exposure to weak EMFs via melatonin interruption. However, further research could be conducted on the long-term effects of EMFs that can change human melatonin levels, as well as on the therapeutic advantage of melatonin in circadian rhythm-related sleep disorders.

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