DISCRETE DELAY MODEL FOR THE MAMMALIAN CIRCADIAN CLOCK

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A circadian rhythm is an oscillation with a period of approximately 24 hr, which exhibits entrainment to environmental light dark (LD) cycles and shifting of phase by light stimulation. Even though many theoretical models with ordinary differential equation (ODE) have been proposed based on the biochemical mechanisms for circadian rhythms [1], relatively few studies have been carried out with delay differential equations (DDE) [2, 3, 4, 5]. Delayed feedbacks are common and occur naturally in many biological systems and in particular, the regulatory networks of circadian rhythms.

Here, we propose a delay model for the circadian rhythm of the mammals [6] with three dynamical variables that has three delayed positive and negative feedback loops. The delayed positive feedback loops modelled by Michaelis-Menten kinetics that describes saturation behavior. The delayed negative feedback loops are modelled with Hill's type of equation that describes a switch like behavior. The form of interlocked positive and negative feedback loop is modelled along the same lines as that of Smolen *et al.* [5]. In formulating the present model, BMAL1 (B), PER-CRY (P) complex and REV-ERBα (R) protein concentrations are considered as the dynamical variables. The biological circuit is shown in Figure-1. The transcriptional activators CLOCK and BMAL1 form a heterodimer which positively regulates *Per, Cry* and *Rev-Erb*α genes. PER-CRY complex is taken as another dynamical variable because PER and CRY expressions are positively coregulated by BMAL1-CLOCK. Their phases are also similar and they both negatively regulate BMAL1 and CLOCK activity. REV-ERBα, the negative regulator of BMAL1 is taken as the third dynamical variable. Thus broadly, there are three negative and positive feedback loops, with BMAL1-CLOCK acting as positive limb and PER-CRY acting as negative limb. The following are the corresponding delay differential equations:

$$\frac{dB}{dt} = \frac{v_1 k_1^{n1}}{k_1^{n1} + R(t-\delta_3)^{n1}} + \frac{v_2 P_f(t-\delta_2)}{k_2 + P_f(t-\delta_2)} - k_3 B \tag{1}$$

$$\frac{dP}{dt} = \frac{v_3 k_5^{n2}}{k_5^{n2} + P_f(t-\delta_2)^{n2}} + \frac{v_4 B(t-\delta_1)}{k_4 + B(t-\delta_1)} - k_6 P \tag{2}$$

$$\frac{dR}{dt} = \frac{v_5 k_7^{n3}}{k_7^{n3} + P_f(t-\delta_2)^{n3}} + \frac{v_6 B(t-\delta_1)}{k_8 + B(t-\delta_1)} - k_9 R \tag{3}$$

Here, P_f is the free PER-CRY complex (P_f = P - B) and $P_f = 0$ if P < B, to account for the interlocked feedback loops between BMAL1 and PER-CRY complex proteins. $v_{1,2,3,4,5,6}$ are the rates at which the proteins are synthesized and the production rate v_3 of PER-CRY complex increases in the light phase. The other parameters are the Michaelis constants $k_{1,2,4,5,7,8}$, the Hill's coefficients, $n_{1,2,3}$ characterizing the degree

of co-operativity of the repression processes; $k_{3,6,9}$ are the first order degradation constants of B, P and R respectively. In the model, the overall time delay for the positive and negative feedback is approximately one circadian cycle. Delayed BMAL1 activation (13hrs) of PER-CRY complex and REV-ERBα constitutes half of the circadian cycle. Delayed activation and suppression of BMAL1 and REV-ERBα respectively by PER-CRY complex and its own suppression (6hr) constitutes one quarter of the cycle. Repression of BMAL1 by REV-ERBα is assumed to be 6hr, which is another quarter of the circadian cycle. In totality, half of the circadian cycle amounts to delay in positive feedback loop (BMAL1 activation) and the other half is the negative feed back loop (PER-CRY and REV-ERBα put together). The interplay of delayed positive and negative feedback loops contribute to one circadian cycle (Figure-2).

There are also other features exhibited by the model. The model shows entrainment to both shorter and

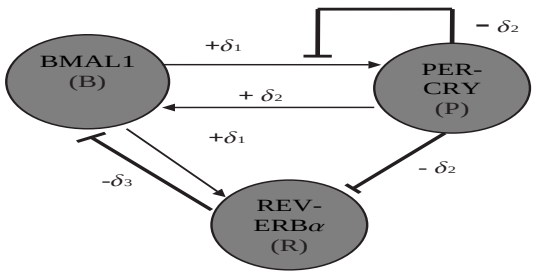

Figure 1: *Schematic representation of the present model for the mammalian rhythm. δ_1 is the delay in the positive feedback from B to initiate the synthesis of PER-CRY protein. The delay δ_1 is also the delayed positive feedback from B to initiate the synthesis of REV-ERBα protein. δ_2 is the delay for to activate and suppress BMAL1 and REV-ERBα protein, respectively. δ_3 is the time delay for REV-ERBα protein to suppress the production of BMAL1.*

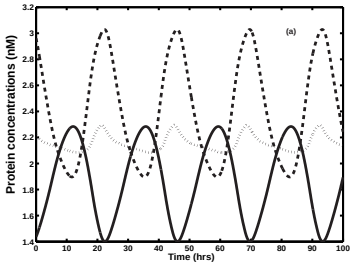

Figure 2: *Sustained oscillations generated by the model. The BMAL1 protein (in black continuous line) is approximately anti phase to proteins PER-CRY protein (black dotted lines) and REV-ERBα (black dashed dotted lines). The time series have been obtained by numerical integration of delay equations 1, 2 and 3 under constant darkness (DD) for the standard parameter set v_s= 4nMh^{-1}, v_d=0.97nMh^{-1}, v_p=1.0nMh^{-1}, v_m=0.7nMh^{-1}, v_r=0.1nMh^{-1}, v_c =1.0nMh^{-1},k_1=0.5nM ,k_2 =2.0nM,k_3 =0.21h^{-1}, k_4 =0.9nM, k_5=0.6nM, k_6 =0.45h^{-1}, k_7 =0.1nM, k_8 =0.1nM , k_9 =0.45h^{-1}, n1=n2=n3=2.0, δ_1=13 hr, δ_2=6 hr, δ_3=6 hr*

longer LD cycles. In all the LD cycles, the oscillator is entrained to 24 hr rhythm for the standard parameter set. When delay δ_2 is varied under LD cycles, the model exhibits phase advance, phase delay and lack of

entrainment, which are linked to physiological disorders. Apart from limit cycle, quasiperiodic and chaotic oscillations are also observed when the delay δ_2 is varied under the influence of constant periodic 12:12 LD cycles. Periodic forcing is known to bring about rich dynamical phenomena [7] and in our model constant periodic forcing with delay brings about a rich bifurcation diagram (Figure-3). The observed complex phenomena such as quasiperiodic and chaotic oscillations are linked to non 24hr sleep-wake syndrome and occurrence of cancer incidence, which may be a direct consequence of improper delayed circadian regulation due to *Per* gene mutation. The effects of mutant phenotype on the circadian period are well simulated by changing the parameters and time delay. The model also uncovers the possible existence of multiple oscillatory networks.

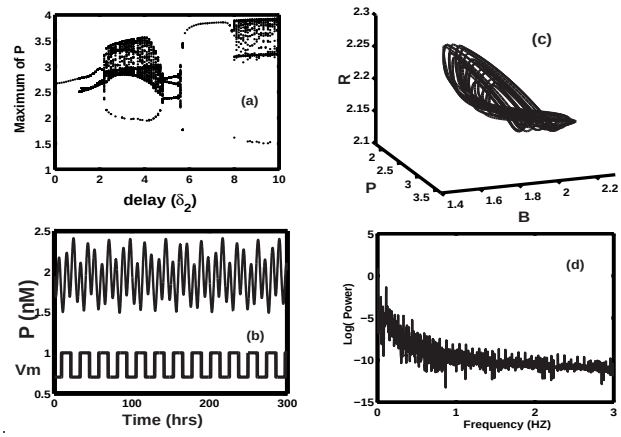

Figure 3: *(a) Bifurcation diagram obtained for the constant LD cycle with delay δ_2 as the parameter. The 12:12 LD cycle simulated with v_m taken a square wave function that is changed from the basal value of 0.7 to 1. (b) Chaotic time series of dynamical variable P, with 12:12 LD cycle for delay δ_2 = 3hrs, (c) the chaotic attractor and (d) the power spectrum. P is the dynamical variable, namely PER-CRY complex. All the other parameters are kept constant with delay δ_1 taken as 12hrs*

References

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