Ionic Mechanisms for Intrinsic Slow Oscillations in Thalamic Relay Neurons

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ABSTRACT The oscillatory properties of single thalamocortical neurons were investigated by using a Hodgkin-Huxley-like model that included Ca\(^{2+}\) diffusion, the low-threshold Ca\(^{2+}\) current (\(I_{h}\)) and the hyperpolarization-activated inward current (\(I_{h}\)).

\(I_{h}\) was modeled by double activation kinetics regulated by intracellular Ca\(^{2+}\). The model exhibited waxing and waning oscillations consisting of 1–25-s bursts of slow oscillations (3.5–4 Hz) separated by long silent periods (4–20 s). During the oscillatory phase, the entry of Ca\(^{2+}\) progressively shifted the activation function of \(I_{h}\), terminating the oscillations. A similar type of waxing and waning oscillation was also observed, in the absence of Ca\(^{2+}\) regulation of \(I_{h}\), from the combination of \(I_{f}\), \(I_{h}\), and a slow K\(^{+}\) current. Singular approximation showed that for both models, the activation variables of \(I_{h}\) controlled the dynamics of thalamocortical cells. Dynamical analysis of the system in a phase plane diagram showed that waxing and waning oscillations arose when \(I_{h}\) entrained the system alternately between stationary and oscillating branches.

INTRODUCTION

The thalamus is central to the generation of oscillatory activity during slow wave sleep. Two types of rhythmical activities of the electroencephalogram have been characterized, spindle waves (7–14 Hz) and delta waves (0.5–4 Hz). Spindle waves depend on both intrinsic and network mechanisms in the thalamus (Steriade and Deschenes, 1984; Steriade and waxing and waning of in vivo spindles, they have been called “spindle-like oscillation” (Leresche et al., 1990, 1991). However, in vivo spindles occur at a higher intraburst frequency (7–14 Hz) and depend on interactions with neurons of the thalamic reticular nucleus (Steriade and Deschenes, 1984; Steriade et al., 1985, 1987, 1990), so they are quite different.
based on voltage-clamp data of $I_T$ and $I_h$. Special emphasis is given to uncovering the role of $I_h$ in organizing the transitions between multiple oscillatory and resting states of the TC cell.

**MATERIALS AND METHODS**

Our single compartment model of a TC cell used a Hodgkin-Huxley-type scheme (Hodgkin and Huxley, 1952) for the ionic currents. The equation describing the derivative of the membrane potential $V$ was:

**TABLE 1 Activation functions and time constants for the voltage-dependent currents $I_T$, $I_h$, and $I_{K2}$.**

<table>
<thead>
<tr>
<th>Current</th>
<th>Variable</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_T$</td>
<td>$m$</td>
<td>$m_v(V) = 1/(1 + \exp(-(V + 65)/7.8))$</td>
</tr>
<tr>
<td></td>
<td>$\tau_m(V)$</td>
<td>$0.15m_v(V)(1.7 + \exp(-(V + 30.8)/13.5))$</td>
</tr>
<tr>
<td>$h$</td>
<td>$\alpha_h(V)$</td>
<td>$\exp(-(V + 162.3)/17.8)/0.26$</td>
</tr>
<tr>
<td></td>
<td>$K(V)$</td>
<td>$\sqrt{0.25 + \exp((V + 85.5)/6.3)} - 0.5$</td>
</tr>
<tr>
<td>$d$</td>
<td>$\alpha_d(V)$</td>
<td>$1/[\tau_d(V)K(V) + 1]$</td>
</tr>
<tr>
<td></td>
<td>$\tau_d(V)$</td>
<td>$62.4/[1 + \exp((V + 39.4)/30)]$</td>
</tr>
</tbody>
</table>
posed by McCormick (1992), is the regulation of $I_{K}$ by binding of intra-
cellular Ca$^{2+}$, as found in whole cell voltage-clamp studies of $I_{K}$ in sino-
atrial node cells (Hagiwara and Irisawa, 1989). Evidence for the control of
the voltage-dependent properties of $I_{K}$ by intracellular Ca$^{2+}$ were also
obtained in cat neocortical neurons (Schwindt et al., 1992). As the Ca$^{2+}$
dependence of $I_{K}$ has not yet been studied in TC cells, it was assumed to be
similar to that of sino-atrial node cells.

The activation curve of $I_{K}$ in sino-atrial node cells shifts toward more
positive potentials as the intracellular Ca$^{2+}$ concentration ($[Ca]_{i}$) is in-
creased (Hagiwara and Irisawa, 1989). Calmodulin and protein kinase C
were not involved in the Ca$^{2+}$ modulation of $I_{K}$, suggesting that Ca$^{2+}$ ions
directly affected $I_{K}$ channels (Hagiwara and Irisawa, 1989). There is also an
increase in the conductance of $I_{K}$ following the binding of Ca$^{2+}$. We have
developed a kinetic model for intracellular calcium (Ca$^{2+}$) binding to the
open channels of $I_{K}$ that is consistent with these data. The open state gates
$S_{open}$ and $F_{open}$ were assumed to have $n$ binding sites for Ca$^{2+}$, which, when
occupied, lead to the open forms $S_{bound}$ and $F_{bound}$ according to:

$$S_{open} + nCa^{2+} \rightleftharpoons S_{bound}$$

$$F_{open} + nCa^{2+} \rightleftharpoons F_{bound}$$

where $k_1$ and $k_2$ are the forward and backward rate constants for Ca$^{2+}$
binding.

If $S_1$ and $F_1$ represent the fraction of gates bound to calcium, then, com-
bining Eqs. 3 and 5, one obtains the following kinetic equations for $I_{K}$:

$$I_{K} = \frac{g_{K}(S_1 + S_2)(F_1 + F_2)(V - E_k)}{S_1}$$

$$S_1 = \frac{\alpha_1(V)S_0 - \beta_1(V)S_1 + k_2[S_2 - CS_1]}{F_1 = \frac{\alpha_2(V)F_0 - \beta_2(V)F_1 + k_2[F_2 - CS_1]}{S_2 = -k_1[S_2 - CS_1]}$$

where $S_0 = 1 - S_1 - S_2$, $F_0 = 1 - F_1 - F_2$, $C = ([Ca]_i/[Ca]_{o})^n$, and $\alpha_1$, $\beta_1$, $\alpha_2$, and $\beta_2$ were obtained from $H$ and $\tau_s$ as before. The number of binding sites was $n = 2$ in all of our simulations. We assumed $k_1 = k_2$, Ca$^{2+}$ is the critical value of [Ca]$_i$ at which Ca$^{2+}$ binding on $I_{K}$

channels is half-activated (if [Ca]$_i$ < [Ca]$_{crit}$, the effect of Ca$^{2+}$ is negligible; see Results for the estimation of this parameter from voltage-clamp data). $k_2 = 5 \times 10^{-11}$ m$^{-1}$ s$^{-1}$ is the inverse of the time constant of Ca$^{2+}$ binding on $I_{K}$ channels. These values were chosen to match the slow time course with which $I_{K}$ is modulated by intracellular Ca$^{2+}$.

**Influx and efflux of Ca$^{2+}$**

The dynamics of intracellular Ca$^{2+}$ were determined by two contributions:

(i) **Influx of Ca$^{2+}$ due to $I_{f}$**

Ca$^{2+}$ ions enter through $I_{f}$ channels and diffuse into the interior of the cell. Only the Ca$^{2+}$ concentration in a thin shell beneath the membrane was modeled. The influx of Ca$^{2+}$ into such a thin shell followed:

$$[Ca]_i = \frac{k}{2Fd}I_{f}$$

where $F = 96,489$ C mol$^{-1}$ is the Faraday constant, $d = 1$ $\mu$m is the depth of the shell beneath the membrane, and the unit conversion constant is $k = 0.1$ for $I_{f}$ in $\mu$A/cm$^2$ and [Ca]$_i$ in millimolar.

(ii) **Efflux of Ca$^{2+}$ due to an active pump**

In a thin shell beneath the membrane, Ca$^{2+}$ retrieval usually consists of a
combination of several processes, such as binding to Ca$^{2+}$ buffers, calcium
efflux due to Ca$^{2+}$ ATPase pump activity and diffusion to neighboring shells. Only the Ca$^{2+}$ pump was modeled here. We adopted the following kinetic scheme:

$$Ca^{2+} + P \rightleftharpoons CaP \rightleftharpoons P + Ca^{2+}.$$  

where $P$ represents the Ca$^{2+}$ pump, CaP is an intermediate state, Ca$^{2+}$ is the
extracellular Ca$^{2+}$ concentration, and $c_1$, $c_2$, and $c_3$ are rate constants. Ca$^{2+}$ ions have a high affinity for the pump $P$, whereas extrusion of Ca$^{2+}$ follows a slower process (Blaustein, 1988). Therefore, $c_3$ is low compared to $c_1$ and $c_2$, and the Michaelis-Menten approximation can be used for describing the kinetics of the pump. According to such a scheme, the kinetic equation for the Ca$^{2+}$ pump is:

$$[Ca]_i = \frac{-K_{P}[Ca]}{[Ca]_o + K_{P}}.$$ 

where $K_{P} = 10^{-4}$ mM s$^{-1}$ is the product of $c_3$ with the total concentration of $P$, and $K_{P} = c_3/c_1 = 10^{-4}$ mM is the dissociation constant, which can be interpreted here as the value of [Ca]$_i$ at which the pump is half-activated (if [Ca]$_i$ $\ll$ $K_{P}$ then the efflux is negligible).

The parameters of the pump were adjusted in order to have a fast Ca$^{2+}$
removal, based on an estimation made from the time course of the spike after hyperpolarization in TC cells (McCormick and Huguenard, 1992). Slow Ca$^{2+}$
handling is unlikely since Ca$^{2+}$-dependent channels would detect a slow
Ca$^{2+}$ accumulation in TC cells.

The extracellular Ca$^{2+}$ concentration was $[Ca]_o = 2$ mM as found in vivo. The change of [Ca]$_i$ due to the binding of Ca$^{2+}$ to $I_{K}$ channels was negligible and was neglected, as was the contribution of Ca$^{2+}$ efflux to the net Ca$^{2+}$ current in Eq. 7.

The Ca$^{2+}$ reversal potential strongly depends on the intracellular Ca$^{2+}$
concentration, and was calculated according to the Nernst relation:

$$E_{Ca} = \frac{RT}{2F} \log \left[ \frac{[Ca]_{o}}{[Ca]_{i}} \right].$$

where $R = 8.31$ J mol$^{-1}$ K$^{-1}$, $T = 300^\circ$ K, and the constant for unit conversion is $k = 1000$ for $E_{Ca}$, in mV. For $[Ca]_o = 2.4 \times 10^{-4}$ mM, which is an average value at rest in the simulations presented here, $E_{Ca}$ was approximately 120 mV.

**Slow K$^+$ current $I_{K2}$**

A plausible ionic mechanism for the generation of waxing and waning
oscillations depends on the interaction between three ionic currents, namely $I_{f}$, $I_{K}$, and a slow outward current. Different types of K$^+$ currents have been recently identified in TC cells (Busud et al., 1992; Huguenard and Prince, 1991; McCormick, 1991). Among these, a slowly inactivating K$^+$ current activated by depolarization was characterized and termed $I_{K2}$ by Huguenard and Prince (1991). They reported that this current inactivates very slowly with two time constants (around 250 ms and 3 s). A very similar current was found in TC cells in the lateral geniculate nucleus (McCormick, 1991). A kinetic model for this current was proposed by Huguenard and McCormick (1992):

$$I_{K2} = \frac{g_{K2}m_{2}(0.6d + 0.4d_{f})(V - E_k)}{2Fd}$$

$$m_2 = \frac{1}{\tau_{m2}(V)(m_2 - m_{2(max)})}$$

$$h_1 = \frac{1}{\tau_{h1}(V)(h_1 - h_{2(max)})}$$

$$h_2 = \frac{1}{\tau_{h2}(V)(h_2 - h_{2(max)})}$$

where $g_{K2}$ is the maximum value of $I_{K2}$ conductance and $E_{K} = -90$ mV is the
reversal potential for K$^+$ ions. The activation function and the time
constant of the activation variables $m_2$, $h_1$, and $h_2$ are given in Table 1.
Estimation of the values of parameters

Conductances values and reversal potentials for the above currents were estimated from published values provided by measurements in vitro. How: \( \text{Ne}^+ \uptau \text{K}^+ \)
states in a continuum and that the transition from slow oscillations to waxing and waning type of rhythmicity could be achieved by enhancement of \( I_h \). The same sequence of oscillations was observed here as \( I_h \) was enhanced in the model (Fig. 3). Other properties of in vitro waxing and waning oscillations include a characteristic hyperpolarization during the silent phase and their transformation into slow oscillations by a depolarizing current step. These properties were also present in our model (Fig. 4, A and B).

The transition from waxing and waning oscillation to slow oscillations from a depolarizing current step was not observed for all values of \( g_h \). For some values of \( g_h \), the opposite was observed: waxing and waning oscillations were trans-depolarization that was most clearly seen by averaging the membrane potential (Fig. 4 C).

The time courses of the different variables of the model during a waxing and waning sequence are displayed in Fig. 5. The membrane hyperpolarized slowly during the silent phase until \( I_T \) deinactivated and the oscillations began. During the burst of slow oscillations, \( Ca^{2+} \) entered transiently at the peak of each spike and bound progressively to \( I_h \) channels (reflected in the slow increase of \( S_h \) and \( F_h \)). \( Ca^{2+} \) binding to \( I_h \) channels shifted the \( I_h \) activation curve, producing a gradual depolarization during the oscillatory phase (Fig. 4 C). This depolarization prevented \( I_T \) from activating and damped the slow oscillations. During the ensuing silent
FIGURE 3 Resting states and slow oscillations in the presence of \( I_h \) and \( \text{Ca}^{2+} \)-dependent \( I_h \), obtained at four values of the maximal conductance of \( I_h \). (A) Hyperpolarized resting state close to \(-84 \text{ mV} \) for \( \bar{g}_h = 0 \). (B) Slow oscillations of about 3.5 Hz for \( \bar{g}_h = 0.01 \text{ mS/cm}^2 \). (C) Waxing and waning oscillations of about 4-8 Hz for \( \bar{g}_h = 0.04 \text{ mS/cm}^2 \). (D) Depolarized resting state around \(-58 \text{ mV} \) for \( \bar{g}_h = 0.11 \text{ mS/cm}^2 \). The maximum conductance of \( I_h \) was kept fixed at \( \bar{g}_{C_{\text{a}}} = 1.75 \text{ mS/cm}^2 \).

cation occurred around \( \bar{g}_h = 0.02 \text{ mS/cm}^2 \) from slow oscillations to a state where the slow oscillations were interrupted by short silent phases (Fig. 6 B). As \( \bar{g}_h \) increased, the length of the silent phase increased and the bursts became shorter (Fig. 6, C and D). The frequency inside the oscillatory phase was always comparable to that of the slow oscillations.

The duration of the silent phase and the oscillatory phase as a function of \( \bar{g}_h \) are reported in Fig. 7 A. The silent phase ranged from 4 to 20 s and decreased with \( \bar{g}_h \). The oscillatory phase became shorter with increase of \( \bar{g}_h \). In the limit, as \( \bar{g}_h \) decreased to 0.02 mS/cm², the duration of oscillatory phase tended to infinity. The opposite occurred as the depolarized state was approached, with oscillatory phase reducing to a minimum length before disappearing (sometimes a low amplitude periodic oscillation was seen in a very narrow range of \( \bar{g}_h \) before the depolarized state appeared). The period of the slow oscillation decreased with \( \bar{g}_h \) (indicated by S in Fig. 7 A), which is consistent with the slowing down of the slow oscillation observed after progressive blockage of \( I_h \) channels by cesium (McCormick and Pape, 1990a).

The length of the silent phase and of the oscillatory phase were directly proportional to the time constant of intracellular \( \text{Ca}^{2+} \) binding to \( I_h \) channels, \( k_2^{-1} \) (Fig. 7 B). This is

FIGURE 4 Properties of \( \text{Ca}^{2+} \)-dependent waxing and waning oscillations. (A) Transformation of waxing and waning oscillations into slow oscillations by application of a depolarizing current step of 0.05 \( \mu \text{A/cm}^2 \) (arrow). \( \bar{g}_h = 0.04 \text{ mS/cm}^2 \). (B) Waxing and waning oscillations at high amplification showing the slow hyperpolarization of the membrane during the silent phase. \( \bar{g}_h = 0.04 \text{ mS/cm}^2 \). (C) Average membrane potential showing a progressive depolarization during the oscillatory phase. Each point was obtained by averaging the membrane potential over a period of 500 ms. \( \bar{g}_h = 0.025 \text{ mS/cm}^2 \).
consistent with the assumption that the binding of Ca^{2+} is critical for the onset and termination of the oscillatory phase. The silent phase, which depends on the return of \( S_2 \) and \( F_2 \) to their resting values, is expected to be proportional to \( k_1^{-1} \). The length of the oscillatory phase, which depends on the rate of rise of \( S_2 \) and \( F_2 \), is also expected to be proportional to \( k_2^{-1} \).

during each cycle of the oscillatory phase. The resulting depolarization inactivates \( I_T \) and the oscillations damp.

Compared with the Ca^{2+}-dependent waxing and waning oscillations, the slow depolarization of the membrane during the oscillatory phase in the \( I_{K2} \)-dependent model is provided by a more pronounced \( I_h \) activation (\( S_1 \) reaches its maximal value during the oscillatory phase) and inactivation of \( I_{K2} \). Progressive deactivation of \( I_h \) then hyperpolarizes the membrane.

Waxing and waning oscillations were never observed
that wax and wane, usually result from several oscillatory or stationary states. In this section, the dynamical states underlying waxing and waning oscillations are studied using a than $S_2$. As before, Eq. 6 was used for Ca$^{2+}$-dependent waxing and waning oscillations, except that $S_2$ was assigned a constant value. In Fig. 5 A, since the variable $S_2$ oscillates
FIGURE 7 The period of Ca\(^{2+}\)-dependent waxing and waning oscillations depends on the maximal conductance of \(I_h\) and the time constant of Ca\(^{2+}\) binding to \(I_h\) channels. The length of the silent phase (SP) and the length of the oscillatory phase (OP) are shown as a function of these two parameters. (A) Period as a function of the maximal conductance of \(I_h\) (\(g_h\)). The range of values of \(g_h\) corresponding to slow oscillations (period labeled by S), waxing and waning oscillations and depolarized resting state are also indicated. (B) Period as a function of the time constant (\(k_2^{-1}\)) of intracellular Ca\(^{2+}\) binding on \(I_h\) channels. The inverse of the rate \(k_2\) is the time constant for Ca\(^{2+}\) binding.

FIGURE 8 Properties of \(I_{k_{Ca}}\)-dependent waxing and waning oscillations. (A) Transformation of waxing and waning oscillations into slow oscillations by applying a depolarizing current step of 0.24 \(\mu\)A/cm\(^2\) (arrow). (B) Waxing and waning oscillations at high amplification shows the slow hyperpolarization of the membrane during the silent phase. \(g_h = 0.4\) mS/cm\(^2\); \(g_{Ca} = 1.75\) mS/cm\(^2\).

The stable limit cycle coexisted with the stable stationary state (Fig. 10 B). The state of the system within this interval of \(S_2\) depended on its previous history.

Thus, in a waxing and waning sequence, \(S_2\) oscillates between values which drive the system alternately between stable stationary states and slow oscillations. As shown by Fig. 10 B, the waxing and waning oscillations are driven around a hysteresis loop by the slow oscillations of \(S_2\), as depicted by dotted arrows: as \(S_2\) decreases during the silent phase, the membrane potential hyperpolarizes slowly and follows the stable stationary state branch (arrow 1). As the critical point is reached, the stationary state loses its stability and the system jumps to the oscillating branch (arrow 2). \(S_2\) then starts to increase and follows the oscillating branch, while the amplitude of the oscillations decreases (arrow 3). The limit cycle oscillations lose stability and the system jumps back to the stationary branch (arrow 4). The oscillations damp and the silent phase starts again.

The trajectory of a simulated waxing and waning oscillation plotted in a \(V/S_2\) diagram, shown in Fig. 10 D, alternates between an oscillating and a stationary branch in a manner very similar to that in Fig. 10 B. The position of the oscillating and stationary branches seems to be slightly different from the solutions displayed in Fig. 10 B, but the structure remains the same. Waxing and waning oscillations with a longer oscillatory phase (see Fig. 6) correspond to a very similar trajectory, with an increased number of loops near the end of the oscillatory branch.

The same subcritical Hopf structure is still present for slow oscillations, but the successive loops do not leave the oscillatory branch and the oscillation does not wax and wane. A strong current pulse should, however, be able to make the trajectory jump from the oscillatory branch to the stationary branch. This prediction is borne out in Fig. 11, where a strong depolarizing current step induced a sudden transition to a silent phase during the slow oscillation (indicated by arrows 2 and 3 in Fig. 11 B) and the system returned back to the oscillatory branch (arrow 4) along a single hysteresis loop. Steps applied to \(S_2\) resulted in the same type of behavior.
FIGURE 10 Singual approximation applied to the Ca\[^{2+}\] -dependent model of waxing and waning oscillations. (A) For extreme values of the slow variable $S_2$, treated as a parameter, the system exhibited either slow oscillations ($S_2 = 0.09$) or a stable stationary state ($S_2 = 0.65$). Other parameters are the same as in Fig. 3 C. (B) Bifurcation diagram of the system as a function of $S_2$. During the slow oscillations of $S_2$, the system alternated between a slow oscillatory state and a resting state, tracing a hysteresis loop as shown in the diagram. The order of events underlying the waxing and waning sequence are indicated by dotted arrows. Dashed lines represent unstable states (USS, unstable stationary state; ULC, unstable limit cycle), and continuous lines represent stable states (SSS, stable stationary state; SLC, stable limit cycle). (C) Corresponding sequence of events in a single cycle of the waxing and waning oscillations. (D) Trajectories of waxing and waning oscillations in the V/$S_2$ diagram. Here the full system was simulated without considering $S_2$ as a parameter. Dashed lines represent the presumed position of oscillatory and stationary branches and dotted arrows depict the same sequence of events as in B.

Irisawa, 1989) and neocortical neurons (Schwindt et al., 1992). These data suggest that intracellular Ca\[^{2+}\] ions directly affect $I_h$ channels and shift the activation function toward more depolarized potentials. We assumed that the Ca\[^{2+}\] dependence of $I_h$ is caused by direct binding of Ca\[^{2+}\] ions on the open form of $I_h$ channels (for a different model of this shift in the context of TC cells, see Toth and Crunelli (1992b)). Our model accounts for the positive shift of the activation function of $I_h$ with increased intracellular Ca\[^{2+}\], but not for the substantial increase of conductance. It should be possible to verify the predicted logarithmic shift (Eq. 12) from whole cell patch-clamp experiments. function of $I_h$ by a few millivolts (McCormick and Pape, 1990b). We did not include this shift in our simulations.

We also found intermediate patterns of oscillations which were not reported experimentally. Close to the transition between slow oscillations and waxing and waning oscillations there were long oscillatory phases and short silent phases. TC cells in vitro show a variety of patterns of waxing and waning oscillations with silent and oscillatory phases of different lengths. The range of patterns found in the model for different values of the parameters suggests that the variability observed in vitro might arise from a heterogeneity of the conductance values among neurons.
Ca\textsuperscript{2+}-dependent waxing and waning oscillations were also observed in the presence of fast Na\textsuperscript{+} and K\textsuperscript{+} currents re-

Current pulse of 200 ms can force the TC cell out of the oscillatory phase for a period of about 15 s before the cells revert back to slow oscillations. However, weaker current pulses do not produce such an interruption but only affect the phase of the slow oscillations (not shown). This prediction of the model could be tested experimentally.

The role of $I_h$

Soltész et al. (1991) suggested that slow oscillations and waxing and waning rhythmicity observed in vitro correspond to two different equilibria between $I_f$ and $I_h$. The results presented here are consistent with this hypothesis.

The pattern of oscillations depended on the value of the maximal conductance of $I_h$ and slowly varying this parameter
tonic firing, slow oscillations, and waxing and waning oscillations in TC cells. Experiments can be designed to test which of the two proposed mechanisms is responsible for the oscillations. The higher frequency of the $I_{K_{C}}$-dependent model makes it less plausible than the $Ca^{2+}$-dependent model. The $I_{K_{C}}$-dependent model predicts that the waxing and waning oscillations should not survive blockage of all voltage-dependent $K^+$ currents (but not the leak $K^+$ currents, needed to maintain the level of membrane potential). The $Ca^{2+}$-dependent model could be tested by altering the intracellular $Ca^{2+}$ levels while monitoring the period of waxing and waning oscillations. The $Ca^{2+}$-dependent model predicts that this period should be sensitive to intracellular $Ca^{2+}$.

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