CA^{2+} DYNAMICS, CA^{2+} WAVES AND THE TOPOGRAPHY OF THE CA^{2+} CONTROL SYSTEM

Leighton T. Izu
University of California, Davis, USA

Tamás Bányász
University of Debrecen, Hungary

Ye Chen-Izu
University of California, Davis, USA

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Contents

Summary

All of life's responses to the environment are ultimately determined by cellular responses to external signals. These external signals, whether they be light, chemicals, or touch do not directly affect the cell's internal biochemical machinery but instead generate an intermediary signal—a second messenger—that carries the information into the cell. Perhaps the most widely used second messenger is the calcium ion. This article traces the information flow from the external signal through the calcium second messenger system and onto the receiver of the calcium signal. The information contained in the external signal is encoded into rapid changes in the calcium concentration. The information, now encoded in the fluctuating calcium concentration, propagates by diffusion into the cell. However, the physical constraints of diffusion preclude sending the signal more than about a micrometer so a number of mechanisms have evolved to permit calcium signaling in large cells. One mechanism is to change the shape of the cell, another is to use calcium waves. Both mechanisms are discussed here. The mechanism that can generate calcium waves can also generate calcium oscillations. Information in the external signal can be encoded in the frequency of the calcium oscillations. A mathematical model of a calcium oscillator that alters its frequency in response to the magnitude of the external signal is presented. Finally, we present two examples of biochemical systems that can decode the information encoded in the frequency of the calcium oscillations.

1. Introduction

Cells respond to their environment. The external signals cells respond to are diverse. They include foods, toxins, touch, pressure, gravity, light, electric fields, salinity, hormones, pheromones, and much more. Many external signals do not directly enter the cell. Instead the external signal, or primary message, is received by a sensor residing at the cell membrane, which is made of lipids that encloses the cell as a protective pocket. Figure 1 shows a schematic of the cellular signaling system.

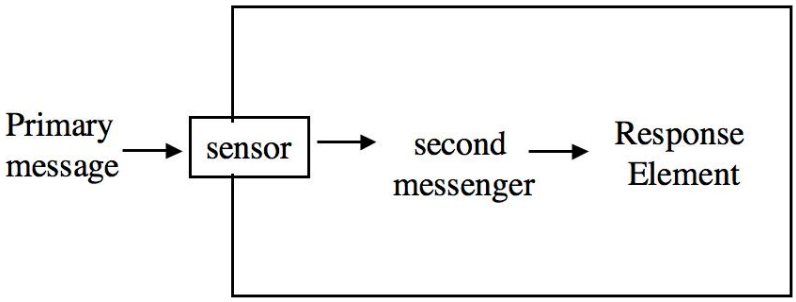

Figure 1. Schematic of second messenger signaling system.

When the sensor receives the primary message it *transduces* this information, that is, it encodes the information in a different physical form. This new form is called the *second messenger*. It is the second messenger that carries the information into the cell. We are all familiar with signal transduction. Consider the telephone. When we speak, the speech information is carried through the air as pressure variations (the primary signal).

The microphone in the mouthpiece transduces the pressure variation into a corresponding voltage signal. It is the voltage signal that sent through the phone line to the receiver, the person on the other end of the line.

In contrast to the wide diversity of primary signals, the number of second messengers is small. Currently, the known second messengers include nitric oxide (NO), inositol 1,4,5-trisphosphate (IP_3), cyclic AMP (cAMP), diacylglycerol, and the calcium ion (Ca^{2+}). The use of a small number of second messengers is not unique to cells. We see the same limited number of "second messengers" in electronic systems. Although there are an enormous variety of sensors (motion sensors for automatic switch, light sensors for dawn-and dusk lighting, voltage sensors in cardiac defibrillators, magnetic sensors, pH sensors, touch sensors, the sensor outputs are usually limited to changes in electric current, voltage, resistance, capacitance, and inductance.

Returning to our telephone analogy, you can send virtually an infinite number of different messages and how the listener responds to your message depends on what the message is and who the listener is. Likewise, the cell type and the primary message determine the cellular response to the external information. The *response element* (RE) is the molecule or molecules that receive the second messenger and somehow decodes the information carried by the second messenger. Some cellular responses include contraction of a muscle cell, change in the direction of ciliary beating to effect escape or approach in *Paramecium*, release of neurotransmitters in neurons, and release of saliva from salivary glands.

In this article we will focus on one important and ubiquitous second messenger, the Ca^{2+} ion. Our task here is somewhat like that of a telephone company. We won't care about the content of the conversation but we are interested in how the conversation is encoded, transmitted, and decoded. We will explore the following questions: How is the Ca^{2+} signal generated? How is information in the primary signal encoded in the Ca^{2+} signal? How is this information transmitted within the cell? What are the physical constraints on the transmission and how do cells circumvent these constraints? And, finally, how is the Ca^{2+} signal decoded?

2. The Minimal Ca^{2+} Signal Generating System

Cells contain certain concentration of free ions (not bound to proteins). Table 1 lists the concentrations of important free ions inside (intracellular) and outside (extracellular) of the cell, as well as the ratio of the extracellular to intracellular concentration.

Ca^{2+} stands out as exceptional in having such a low intracellular concentration and high concentration ratio. The cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) is between 50—150 nM while the extracellular Ca^{2+} concentration is around 1—2 mM in mammalian blood and about 10 mM in squid. Why is $[Ca^{2+}]_i$ so low? Kretsinger (1977) suggests that $[Ca^{2+}]_i$ must be low enough to prevent Ca^{2+} from reacting with phosphates, such as ATP, and forming calcium phosphate precipitate. Rasmussen (1981) presents another possible explanation for why Ca^{2+} is so low. He proposed that early life evolved in an ocean that was low in Ca^{2+} and as Ca^{2+} rose due to weathering of rocks, Nature could have either

replaced the metabolic machinery accustomed to the low Ca^{2+} or evolve machinery to keep the cytoplasmic Ca^{2+} low. Whatever the reason, all modern organisms have the machinery to maintain a resting intracellular Ca^{2+} concentration of about 100 nM.

Sensor	K_d (μM)
Calmodulin (N-lobe)	3.1
Calmodulin (C-lobe)	24
Calcineurin B	0.5
Troponin C	0.5
Ryanodine receptor	15
Synaptotagmin	10—50

Table 1 Intracellular and extracellular concentration of major ions and their ratios (extracellular/intracellular). Data from Alberts, et al., 2002.

The 10,000-fold concentration gradient (1 mM/100 nM) between the extracellular and intracellular Ca^{2+} concentrations and the electrical potential gradient (-80 mV inside the cell) provide a large electrochemical driving force for Ca^{2+} entry into the cell. Because of this large driving force, Ca^{2+} leakage into the cell is inevitable and if left unchecked will eventually cause the intracellular Ca^{2+} concentration to rise to a level that renders the metabolic machinery dysfunctional and ultimately kill the cell.

Compensating for this leakage and to maintain the Ca^{2+} concentration, $[Ca^{2+}]_i$, at about 100 nM are ATP-dependent Ca^{2+} pumps, Ca^{2+} exchangers, and Ca^{2+} buffers. The operation of the pumps and exchangers require the expenditure of free energy to move the Ca^{2+} out of the cell against its electrochemical gradient. The cell must also expend energy in making these pumps, exchangers, and buffers, which are large proteins. Having invested into the making of these proteins and expending energy in moving Ca^{2+} out of the cell, Nature has turned this leakage problem into the most diverse and flexible signaling system by adding one additional component: the Ca^{2+} channel.

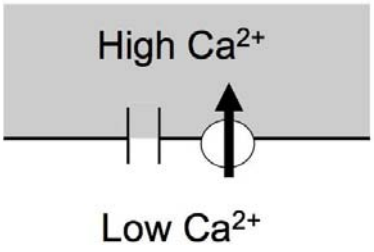

Figure 2. Minimal Ca^{2+} signal generating system. Gray represents region of high Ca^{2+} concentration while white represents low Ca^{2+} concentration. The horizontal line is the membrane, the pair of parallel vertical lines is the Ca^{2+} channel, and the circle and arrow pair represents the Ca^{2+} pump and Ca^{2+} exchanger.

The Ca^{2+} channel provides a controlled conduit for Ca^{2+} entry into the cell. There are different types of Ca^{2+} channels. The Ca^{2+} channels are usually closed in resting cells but open in response to electric fields, mechanical stretch, or ligands. Upon opening of

the channel, extracellular Ca^{2+} flows down its electrochemical gradient and enters the cell. In this way, the Ca^{2+} channel transduces the external signal—the electric field, mechanical stretch, or ligand—into an intracellular Ca^{2+} signal. Figure 2 shows the *minimal Ca^{2+} signal generating system* consisting of the Ca^{2+} channel, pumps and exchangers.

3. Ca^{2+} Signals are Transient

Figure 3 shows the Ca^{2+} concentration in the cytosol of tobacco plant seedlings in response to puffs of air of increasing force delivered at the times indicated by the arrowheads. When the force of the puff is very small (first arrow), there is no detectable change in the cytosolic Ca^{2+} concentration indicated by the aequorin luminescence (a Ca^{2+} indicator). When the force becomes sufficiently strong, the Ca^{2+} concentration rapidly rises. However, the rise in Ca^{2+} is not sustained but decays back to the basal level. The transient Ca^{2+} rise in Figure 3 is typical of Ca^{2+} signals. The Ca^{2+} concentration rises only transiently in response to an external signal. Similar transient Ca^{2+} signals are observed in plant cells in response to a change in direction of gravitational field, in root hairs responding to rhizobium nodulation signals, in eggs activated by sperm, in endothelial cells responding to histamine, and in skeletal and cardiac muscle cells in response to electrical stimulus.

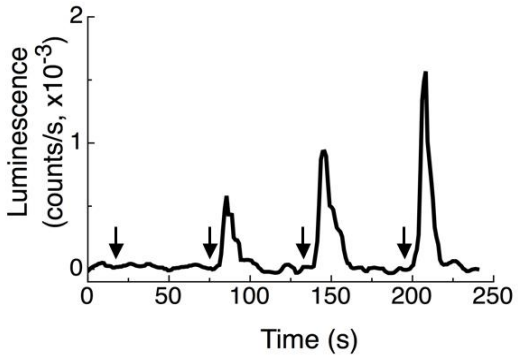

Figure 3. Ca^{2+} transients in response to air puffs (at arrows) in tobacco seedlings. Data redrawn from Haley et al. (1992) (Copyright 1992, National Academy of Sciences, U.S.A.)

The Ca^{2+} increase is transient because the Ca^{2+} channel will close within milliseconds even though the external signal remains present. When the channel closes the flow of Ca^{2+} is staunched and the Ca^{2+} that had entered the cell binds to the Ca^{2+} buffers and is soon removed from the cell by the pumps and exchangers thereby bringing $[Ca^{2+}]_i$ back to the resting level of ~100 nM.

4. Ca^{2+} Carries Information via Diffusion

When the Ca^{2+} channel opens the Ca^{2+} rushes in causing the Ca^{2+} concentration around the mouth of the channel to rapidly increase to 10—100 μM, much higher than the concentration in surrounding regions that are at the resting level of ~100 nM. Because of this concentration gradient, Ca^{2+} diffuses away from the Ca^{2+} channel. Information

about the external signal is carried away from the membrane into the cell with this diffusional flow of Ca^{2+}.

The analogy drawn between Ca^{2+} signaling and the phone company begins to break down here. Electromagnetic waves travel at a constant speed (the speed of light, *c*). Imagine sending a Morse code message to a friend. If your friend is a distance L from you then he will receive the message at time L/c. If your friend moves to a distance $2L$, he will have to wait twice as long $2L/c$ to receive the message.

Information transmission by diffusion is not so simple. Information flow slows down as the distance between the source and receiver increases and the magnitude of the signal also decreases with distance. These are fundamental constraints of diffusion and the Ca^{2+} signaling system must be structured to circumvent these constraints.

4.1 Range and Time Scale of Ca^{2+} Signaling

Diffusion of a substance in an isotropic medium is described by the diffusion equation

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2} + \frac{\partial^2 C}{\partial z^2}\right), \qquad (1)$$

where C is the concentration, t is time, $x, y,$ and z are the spatial coordinates, and D is the diffusion coefficient. We will use equation (1) to calculate the concentration of Ca^{2+} at any point in space and time. This equation is incomplete as it ignores the chemical reaction with the buffers; this is a more serious problem. There are no analytic solutions to the diffusion problem when chemical reactions are involved, except for the simple, special case of where the reaction is an isomerization.

However, under certain conditions that occur frequently in cells the diffusion equation with chemical reactions converges to the form given by (1), albeit with a modified diffusion coefficient *D.* When the buffer reaction is fast relative to diffusion (in a manner that is made precise in Wagner & Keizer, 1994) then we can still use equation (1) provided D is replaced by the apparent diffusion coefficient D_{app} (Wagner & Keizer, 1994)

$$D_{\text{app}} = D(C) = \frac{D}{1 + \dfrac{K_{\text{d}} B_{\text{T}}}{(K_{\text{d}} + C)^2}}. \qquad (2)$$

In this equation, K_{d} is the dissociation constant of the buffer and B_{T} is the total concentration of buffer binding sites. Notice that $D_{\text{app}} \le D$ and that as $C \to \infty, D_{\text{app}} \to D$. This inequality and limit has a simple physical meaning. When the Ca^{2+} concentration is low, there are many free Ca^{2+} binding sites so when a diffusing Ca^{2+} ion comes upon the binding site it becomes trapped, slowing the diffusion of Ca^{2+}.

Conversely, when the Ca^{2+} concentration becomes very high ($C \gg K_d$) most of the binding sites are already saturated with Ca^{2+} so a diffusing Ca^{2+} ion will not be impeded and it diffuses as if the buffer were absent. (This is not quite true since a buffer molecule fully bound with Ca^{2+} still provides a physical barrier to the diffusing ion.)

Even using approximation (2), equation (1) is too hard to solve. We make one more approximation. We will use the value of D_{app} at one particular Ca^{2+} concentration, the resting concentration of 100 nM. This allows us to determine the order of magnitude for the range and speed of Ca^{2+} signaling.

Let a Ca^{2+} channel carry a Ca^{2+} current i and let it be open for time T. For the Ca^{2+} channel known as the L-type Ca^{2+} channel found in many cells including muscle cells, neurons, and bacterial cells, i is about 0.2 pA (a picoamp is 10^{-12} amperes) and T is about 0.5 ms. The flow of Ca^{2+} through this channel, J, is related to i by $J = i/(2F)$, where F is the Faraday constant (96,485 coulombs/mol) and 2 is the charge of Ca^{2+}. The total number of moles of Ca^{2+} passing through the channel during the opening is $M = J \cdot T$. If we imagine that this many moles of Ca^{2+} ions were instantly deposited then the Ca^{2+} concentration at any point in space and time is given by (see Crank, 1975)

$$C(r,t) = \frac{M}{8(\pi D_{app} t)^{3/2}} \exp\left(-\frac{r^2}{4D_{app}t}\right). \qquad (3)$$

This solution assumes isotropic diffusion and absence of diffusion barriers. In this situation Ca^{2+} spreads out spherically with the radius of the sphere given by $r^2 = x^2 + y^2 + z^2$ and equation (1) can be simplified to $\partial C / \partial t = D_{app}\left(\partial^2 C / \partial r^2 + (2/r)\,\partial C / \partial r\right)$.

4.1.1. Time Scale of Diffusion

Unlike an electromagnetic wave, there is no unique "speed" of diffusion. Nevertheless we can define a characteristic time scale for diffusion as follows. Suppose that an intracellular Ca^{2+} sensor becomes activated when the Ca^{2+} concentration exceeds a threshold $\tilde{c}$. If the sensor is a distance r from the Ca^{2+} channel then this threshold concentration will be reached at time $\tilde{t}$ obtained by solving

$$C(r,\tilde{t}) - \tilde{c} = 0. \qquad (4)$$

To solve (4) let $z = \tilde{t}^{-1/2}$ and define

$$\beta = \frac{M}{8(\pi D_{app})^{3/2}} \text{ and } \gamma^2 = \frac{r^2}{4D_{app}} \qquad (5)$$

then (4) becomes

$$\beta z^3 e^{-\gamma^2 z^2} - \tilde{c} = 0. \qquad (6)$$

Equation (6) can be solved for z and from which we get $\tilde{t}$. Actually, there are two solutions $\tilde{t}_0$ and $\tilde{t}_{-1}$

$$\tilde{t}_{0,-1} = \frac{4\gamma^2}{-6W\left[\frac{2}{3}\left(-\frac{\gamma^3\tilde{c}}{\beta}\right)^{2/3}\right]}. \qquad (7)$$

This solution looks complicated but it can give important insights so it is worthwhile to understand its meaning. W is called the Lambert W function, which solves $W(x)e^{W(x)} = x$. Lambert W makes its appearance in diffusion problems (as we have here), in time delay problems (such as the delay between turning the hot water faucet and getting hot water out of the shower head), and in determining the optimal firing angle of a projectile when air resistance is present. (See (Corless, et al., 1993 for properties and applications of the Lambert W function.) W is real only when $x \geq -1/e$ and is double valued on $x \in (-1/e, 0)$. The solution $\tilde{t}_0$ is on the branch that extends from $[-1, \infty]$ and $\tilde{t}_{-1}$ is on the branch that extends from $(-\infty, -1]$.

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Biography Sketches

Leighton T. Izu received his BA in mathematics and psychology at the University of Hawaii at Manoa in 1979 and his PhD in biophysics from the State University of New York at Buffalo in 1990. His dissertation under the guidance of Professor Robert A. Spangler was on bifurcations in reaction-diffusion equations with nonlinear boundary conditions, which include models for Ca^{2+} oscillations in heart cells.
He is currently associate professor in Pharmacology at the University of California at Davis. His long-term interest is to understand how systems suddenly change their behavior. Of particular interest is in understanding the origin of cardiac arrhythmias. To this end, he and his collaborators combine large-scale simulations, high-speed confocal microscopy to measure Ca^{2+} dynamics, and electrophysiological methods to measure cell membrane currents and voltages.
Dr. Izu is a member of the Biophysical Society and the American Heart Association.

Tamás Bányász M.D., Ph.D. is associate professor at University of Debrecen. He received his M.D. and Ph.D. degrees from University of Debrecen. He is a professor of physiology at Department of Physiology with teaching and research activity. As a visiting researcher he spent several years at different laboratories (University of Oklahoma, Università di Milano-Bicocca and University of Kentucky).
His research interests include several aspects of cardiac arrhythmia including cardiac pharmacology and arrhythmogenesis with special interest in roles of ionic currents and intracellular calcium homeostasis. He has developed a particular expertise in action potential clamp technique. His current research focuses on the role of calmodulin kinase II in the mechanisms of cardiac arrhythmias and different cardiomyopathies. He has authored more than 60 research articles in peer-reviewed journals.

Ye Chen-Izu was born in 1963 at Nanjing, China. Her educational background includes Bachelor of Science degree in physics (B.S., 1985) from the National University of Defense Sciences and Technology, Changsha, China; Master of Science degree in bioengineering (M.S., 1988) from the Tsinghua University, Beijing, China; and Doctor of Philosophy degree in biophysics (Ph.D., 1994) from the State University of New York at Buffalo, New York, United States of America.
During 1995-1999, she conducted scientific research as Staff Fellow in the Laboratory of Cardiovascular Sciences, the National Institute on Aging, USA. During 1999-2004, she further pursued research on heart diseases in the Cardiology Division at the University of Maryland, Baltimore. In 2005, she was appointed Assistant Professor in the Department of Internal Medicine, University of Kentucky. Starting in 2009, she accepted a joint appointment as Assistant Professor in the Department of Pharmacology, Department of Medicine, and Departments of Biomedical Engineering at the University of California, Davis, California, USA. She uses interdisciplinary approach to study the mechanisms of heart diseases. In particular, she has studied the calcium signaling system in the cardiac muscle, including the L-type Calcium Channel, the intracellular calcium channel – Ryanodine Receptors, and remodeling of the calcium signaling system during heart disease development. Her current research focuses on hypertension-induced cardiac hypertrophy, arrhythmias, and heart failure. She employs various biophysical techniques such as electrophysiology, fluorescence imaging, and confocal microscopy to study the molecular and cellular mechanisms governing the cardiac muscle excitation-contraction and heart disease development.
Dr. Ye Chen-Izu is a member of professional scientific societies including Biophysical Society, American Heart Association/American Stroke Association, International Society for Heart Research, Federation of American Societies for Experimental Biology, and American Association for the Advancement of Science.