MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **1**, Number **1**, June **2004**

http://math.asu.edu/~mbe/

pp. **147–159**

# BIOLOGICAL COMPUTING WITH DIFFUSION AND EXCITABLE CALCIUM STORES

H.G.E. Hentschel

Department of Physics, Emory University
Atlanta GA 30322

Alan Fine

Department of Physiology and Biophysics
Dalhousie University, Halifax NS, Canada

C.S.Pencea

Department of Physics, Emory University
Atlanta GA 30322

(Communicated by Stefano Boccaletti)

Abstract. Intracellular signaling often employs excitable stores of calcium coupled by diffusion. We investigate the ability of various geometric configurations of such excitable stores to generate a complete set of logic gates for computation. We also describe how the mechanism of excitable calcium-induced calcium release can be used for constructing coincidence detectors for biological signals.

1. **Introduction.** Diffusion is a dissipative process generally associated with an increase of entropy and thus with loss of information. Nevertheless, in some cases diffusion does play an important role in the formation and evolution of complex spatial patterns. Examples in continuous systems include reaction-diffusion processes and the dynamics of excitable media, both of which can produce chemical waves and spiral patterns [1, 2, 3]. In biological systems, one very important class of excitable mechanisms is based on calcium-induced calcium release (CICR). Such mechanisms are known to be generically involved in biological signaling. Thus calcium is known to affect a variety of cell processes, from fertilization and proliferation to the death of the cell [4, 5, 6]. In neurons, calcium influences the information processing of neuronal signals (see fig. 1) as well as long-term potentiation (LTP), the underlying mechanism believed to be responsible for short-term memory [7].

Using CICR from localized stores coupled by diffusion [8, 9, 10, 11], calcium oscillations can be triggered by chemical, electrical, or even mechanical stimuli. Stores or pools of calcium exist inside the cell, and this bound calcium can be released if the free local cytosolic calcium concentrations rises above a critical threshold. Positive feedback can then lead to calcium oscillations and propagation. The diffusion of calcium is of course crucial in transforming these temporal calcium oscillations into spatial calcium waves, and they show many similarities to the excitable chemical

2000 *Mathematics Subject Classification.* 92C05, 92C55.

*Key words and phrases.* Computation, Diffusion, Calcium-Induced Calcium Release, Logic Gates, Biological Signaling.

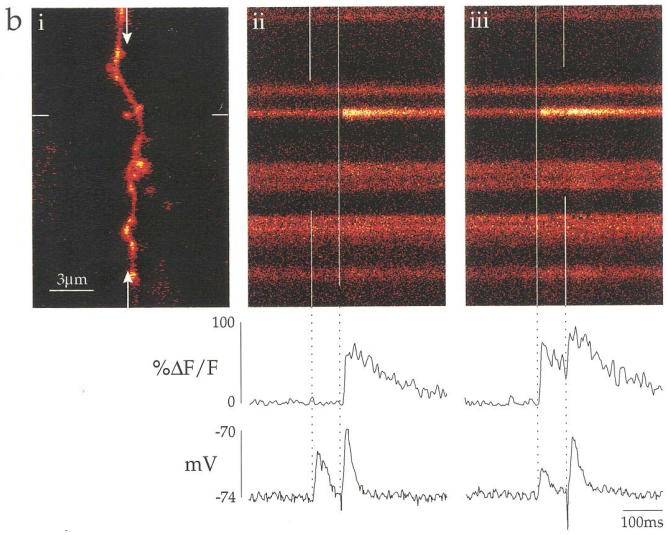


FIGURE 1. Release of calcium from internal stores contributes to calcium transients within individual dendritic spines evoked by afferent stimulation. (i) The postsynaptic spine stimulated lies at the targeted point; (ii) A calcium transient is evoked after two presynaptic stimuli have been applied – time is plotted along the x-axis while the y-axis is the one-dimensional spatial cut shown in (i); (iii) After application of ryanodine (20 $\mu M$) to suppress calcium-induced calcium release, identical stimuli fail to evoke postsynaptic calcium transients. The traces show the evoked postsynaptic calcium fluorescence changes within the spine, expressed as $\%\Delta F/F$.

waves discovered by Belousov and Zhabotinsky [12], though the nonlinear mechanisms involved are different: the increasing cytosolic calcium concentration does not trigger a chemical reaction but instead triggers the release of calcium from the filled stores, interacting with the cytosolic calcium wave front.

The dynamics of this excitable process can be understood as follows [8, 9, 10, 11]: The fixed point of the dynamics corresponds to a situation in which a relatively large amount of calcium is bound inside the store and a small concentration of free cytosolic calcium exists near the store. In this dynamical equilibrium, the Michaelis-Menten flux for CICR is balanced by the flux into the store from the cytosol. The usual perturbation of this equilibrium is due to an external increase of the free calcium concentration near the store. For a small increase in the concentration, the surplus is absorbed into the store. When the free calcium concentration is raised above a threshold value, however, the store evolves along an excitation trajectory whose beginning corresponds to a strong release of calcium from the store into the cytosol. The release of calcium from intracellular stores as a result of the increase of the free calcium concentration is known as CICR.

This excitable dynamics of calcium stores makes calcium a second messenger between extracellular stimuli and intracellular events: An extracellular stimulus can increase locally the cell membrane permeability to calcium ions. Extracellular calcium ions enter the cell and diffuse, causing CICR from excitable calcium stores

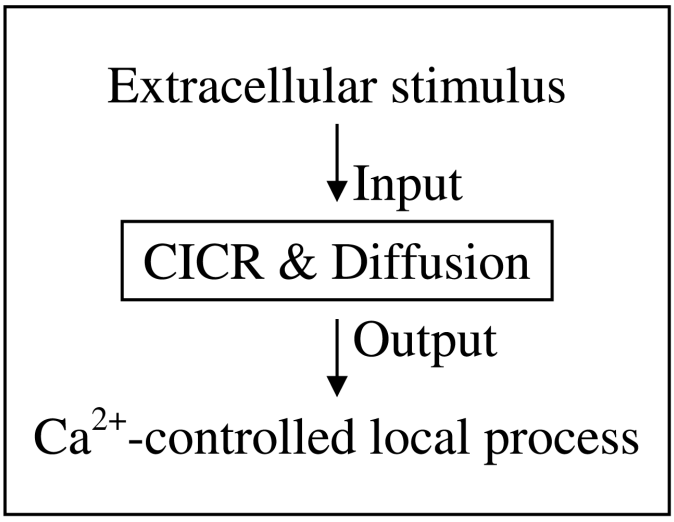


FIGURE 2. A schematic diagram of calcium as a second messenger between an extracellular signal and intracellular processing.

that exist near the membrane in the process. The surplus of calcium diffuses to further nearby stores, triggering them to release even more calcium via CICR. The result of this avalanche process is the calcium signal, a wave of calcium concentration that propagates inside a domain whose skeleton is the cluster formed by the stores triggered to release calcium. Eventually, the calcium signal propagates to some specific region of the cell, where it affects a particular intracellular process in a manner consistent with the initial stimulus. Such mechanisms are often geometrically localized. Thus, most calcium puffs that originate within a 2-3 $\mu m$ peri-nuclear zone propagate inside the nucleus, while remote puffs that originate far from the nucleus do not significantly influence the nuclear calcium concentration [13]. Figure 2 emphasizes in a schematic fashion the central role played by calcium stores as a medium for transmitting the information from the stimulus through intracellular processing until it is finally decoded into some output task.

The dynamics of this process have been studied in great detail by several groups [8, 9, 10, 11, 14, 15], though usually the distribution of such calcium stores is treated in a continuum manner. The idea in the continuum approach is to define a smooth local concentration of stored calcium whose temporal and spatial variation can be described by a partial differential equation. Such an approach may model the endoplasmic reticulum, smoothly filling a cytosolic domain, and the local release of stored calcium at a rate $k$ coupled to diffusion $D$ can lead to waves traveling with velocities $v \sim \sqrt{Dk}$ [8]. But what happens when the stores are well separated and the release time for the calcium $\tau \sim 1/k$ is much shorter than the propagation time $\tau_{prop} \sim r^2/D$ between stores, where $r$ is a typical distance between discrete stores?

In this special case, where the calcium (or other excitable medium) is well localized in stores, these regions can be regarded as the nodes of an excitable chemical network in which the role of diffusion is to provide the coupling between the localized excitable nodes [16]. Such chemical networks are capable of performing computational tasks, and in this paper we investigate the specific spatial and threshold conditions under which logic gates can be formed, providing the basic building

blocks of a computational network. We will also identify key configurations for coincidence detection–a very basic and important computational task required in intracellular signal processing.

2. **Previous Approaches to Excitable Computation.** Computation with excitable calcium is perhaps most ubiquitous in models of neuronal computation [17, 18, 19]. Thus, Shepherd and Brayton [17] used a compartmental representation of the dendritic spine system and the Hodgkin-Huxley equations for nerve impulse generation to investigate the effect of increasing the membrane conductance in either one or both of two spines across a synaptic cleft on a dendrite. Other spines located at few micrometers along the dendrites were used to determine the spread of the response. The behavior of this model can emulate $AND$, $OR$, or $AND$-$NOT$ logic gates, according to the type and amplitude of the initial stimulation, and also to the geometry (diameter) of the input spines.

More recently Adamatzky [19] investigated the computational properties of a lattice of excitable systems coupled by nearest-neighbor interactions, which can also emulate the behavior of various logic gates. In his model, a two dimensional lattice site gets excited at time $t+1$ if exactly 2 of its eight nearest and next nearest neighbors are excited at time $t$ (4 of the 26 neighbors in three dimensions); after being excited (at time $t+1$) the lattice site undergoes successive transitions to a refractory state (at $t+2$) and then to the rest state (at $t+3$). The propagation mechanism used in [19] causes specific particles ("bullets" consisting of a small number of sites in the excited and refractory states) to propagate across the lattice. Such particles can collide, resulting in the spreading of other particles moving at different angles across the lattice. The collision centers behave like logic gates whose inputs are the colliding bullets and whose outputs are the particles that emerge after the collision.

Tóth and Showalter [18] have shown that the interaction of excitable chemical waves that propagate through capillary tubes can also be the underlying mechanism that emulates logic gate behavior. Specifically Tóth and Showalter [18] studied the propagation of such waves through various capillary geometries. The excitable chemical reaction, used in. [18] involves an activatory component with fast dynamics and an inhibitory component whose dynamics is slow. The role of the capillary tubes in emulating logic gate-like behaviors is then to confine the excitation and to conduct it toward regions where waves arriving through different tubes can interact. Once it reaches the end of a capillary tube, the excitation wave explodes in the open space only if the diameter of the tube is greater than a critical value. Otherwise the diffusion will spread the excess of the fast-varying chemical component, whose production and diffusion are causing the wave propagation, more rapidly than it is produced by the excitable chemical reaction, and the excitable behavior, which requires a threshold concentration of the fast-varying chemical component, is stopped. It is possible, however, to have two capillary tubes, with radii slightly under the critical value, ending very close to each other. In this case, the cumulative effect of chemical waves arriving simultaneously through the two channels can be strong enough to trigger the propagation of the wave in the open space. This is a realization of an $AND$ gate, which can also act as a coincidence detector because propagation will only occur if the relative delay between the two signals is small enough. $NOT$ and $XNOR$ gates can also be obtained by perturbing the necessary coincidence in a clock-driven $AND$ gate by transverse input signals [18].

The same reaction-diffusion framework allows the construction of an excitable diode–a configuration displaying unidirectional conductivity of the excitatory signal. A diode can be emulated using a capillary tube with the radius larger than the critical value, but with one end partially obstructed. Such a configuration is equivalent to a sequence of two capillary tubes, one with the radius slightly smaller and the other with a radius slightly greater than the critical value. The excitation propagating through the gap is not strong enough to explode in the open space near that end of the capillary tube, but, with properly chosen geometry, can propagate from the gap into the capillary tube. This happens because the spreading of the fast-varying component by diffusion is limited by the capillary geometry–for the same reason the excitation propagates inside a capillary tube, even if its radius is smaller than the critical value. Thus the signal propagates only one way through the gap. Such configurations, in which one end of the capillary tube is partially obstructed, were used by Tóth and Showalter [18] to block undesired back propagation and to ensure unidirectional conductance of the excitatory signal.

Below we describe a new approach, which we believe is biologically relevant to computation in cells. We will present logic gate configurations similar to those described in [18], but the confinement of the signal within specific regions will be realized not by using capillary tubes, but rather by considering excitable discrete stores interacting via diffusion following CICR: Initial external excitation of one or several stores triggers an avalanche process in which the excitation propagates by diffusion between consecutively releasing stores, forming a connected cluster [16]. Eventually, the calcium signal propagates along the cluster to some specific region of the cell, where it affects a particular intracellular process in a manner consistent with the initial stimulus.

## 3. **Biological Computation Using Excitable Calcium Dynamics.**

To describe the exchange of calcium between the store and the cytosol, we use an adiabatic simplification. We will assume that the time scale for calcium release from stores is short compared to the typical time for diffusive propagation between stores: $\tau_{release} << l^2/D$, where $l$ is a typical distance between stores and $D$ is the effective diffusion coefficient of calcium ions. In this case, the store instantaneously releases all the available calcium "puffs") when the free calcium concentration near the store increases above the CICR threshold. Thus, in the regime where this adiabatic separation of time scales is valid, each excitable store $i$ is characterized by only two parameters, the threshold concentration $C_i$ (at which the store puffs), and the number of calcium ions to be released, $N_i$. This adiabatic approximation is a limit case of the Michaelis-Menten dynamics that describes the calcium fluxes between the store and the cytosol. It is obtained in the limit of large Hill coefficients (high cooperativity), and large a CICR rate. Such an approximation may appear overly simplified, but it does have the pedagogic advantage of being easy to analyze, and it does cover a wide range of biologically plausible calcium kinetics. If the timescales are less well separated, similar qualitative results can be obtained, though the complete intracellular calcium dynamics needs to be analysed.

As a result of the external stimulus, one of the stores puffs its stored calcium. The released calcium diffuses away and can trigger other stores to puff, thus starting an avalanche process. The resulting calcium signal is described completely if one determines if and when each store puffs. Assuming that the store $i$, which is

positioned at $\mathbf{r}_i$, releases $N_i$ ions of calcium at time $t_i$, the release adds a Gaussian component

$$\delta c_i(\mathbf{r},t) = \frac{N_i}{(4\pi dD(t-t_i))^{d/2}} \exp\left(-\frac{(\mathbf{r}-\mathbf{r}_i)^2}{4dD(t-t_i)}\right) \tag{1}$$

to the general solution which describes the spatio-temporal dynamics of the free calcium concentration, $c_c$.

In a previous study [16] we derived a propagation criterion by considering the interaction between pairs of stores: A store $j$ will puff only if there exists another store $i$ that has released its calcium, and that release alone is strong enough to raise the free calcium concentration near store $j$ above $C_j$, the CICR threshold of site $j$. This approximation, which neglects the possible cumulative effect of two or more releases occurring simultaneously, leads to an analytical expression for the the maximum distance at which store $i$ can trigger CICR at store $j$:

$$r_{ij}^{max} = \left(\frac{d}{2\pi e}\right)^{1/2} \left(\frac{N_i}{C_j}\right)^{1/d}, \tag{2}$$

where $d$ is the dimensionality of the domain in which diffusion occurs. Here we consider implicitly that the calcium buffers (other than the stores) can be taken into account by the effective diffusion coefficient $D$ (see [20] for a detailed description of the calcium buffering and an analysis as to how its main effect is to renormalize the cytosolic diffusion constant $D$).

Now we note that if the stores are separated by distances less than the respective $r_{ij}^{max}$ and aligned along specific paths which then "conduct" the calcium signals, they are similar to the wires in an electric circuit. These paths can intersect each other at nodes where the calcium signals collide and interact. The relative positions of the stores within a "wire", especially near a node play an important role in the propagation of the signals and therefore in the types of computation they can perform.

**4. Constructing Logic Gates Using Calcium Stores.** How do we turn this idea into a practical method for constructing a variety of logic gates and simple information processing devices such as coincidence detectors? In general, we need take into account the effect of the interaction of more than two stores, and in particular we will allow different stores to have different CICR thresholds $C_i$, or different capacities $N_i$. With this freedom, varying spatial configurations of calcium stores can be used to form small biochemical networks that can perform important biological computations while processing the calcium signals. In this manner, the calcium signals can be precisely regulated [4]: Different extracellular stimuli produce, by means of calcium diffusion interacting with networks of stores, different responses in the cell.

3.1. **Diodes.** The simplest system that can be constructed using such excitable stores in a diffusive medium is the excitable diode. Like a diode in an electrical circuit, the excitable diode will transmit the excitation in one direction but will block it in the opposite one.

Figure 3 presents three basic configurations of stores that can have a diode-like behavior (in figure 3 and in the following examples we will chose the length unit such that $r_{AB}^{max} = 1$). In figure 3(a), all the stores are identical, with the distance between stores $A$ and $B$ being smaller than 1; and the distance between $B$ and

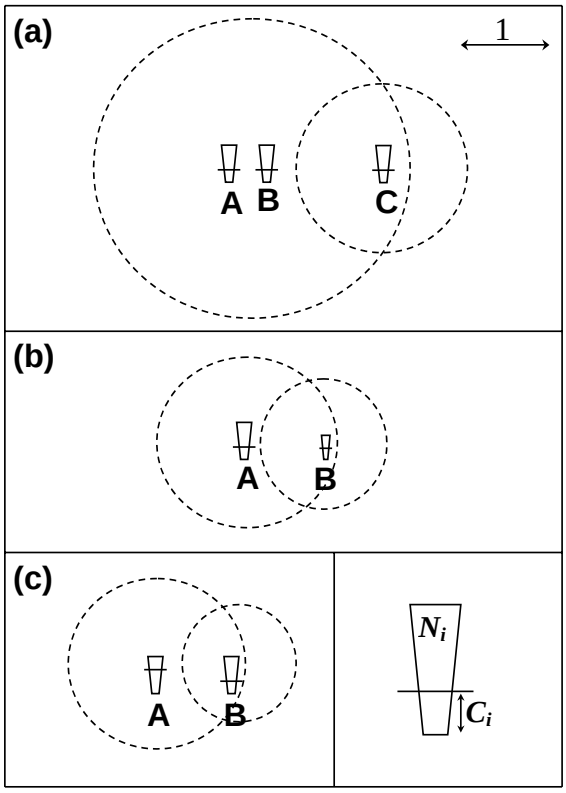


FIGURE 3. Configurations of stores which behave like excitable diodes. Lower-right corner insert shows the convention used to describe the store. The size of the drawn store is proportional to the amount of calcium stored, while the height of the horizontal line is proportional to the CICR threshold. (a) Identical stores. (b) Store $B$ contains a smaller amount of releasable calcium. (c) The excitation threshold of store $A$ has a larger value.

$C$ greater than 1. The puff at store $A$ triggers store $B$ to release, and the two combined releases are strong enough to trigger the release at store $C$. The big circle approximates the boundary of the domain inside which the excitation will propagate from stores $A$ and $B$ (the range of the two combined releases). In the opposite scenario, the release at store $C$ does not result in release at any store other than $C$. The small circle represents the range of store $C$. The unidirectional conductivity of the configuration results from the stronger cumulative effect of two releases. In figure 3(b), the stores have the same excitation threshold ($C_A = C_B$), but store $B$ holds a smaller number of calcium ions ($N_B < N_A = N_C$). The range of store $B$, $r_{BA}^{max}$ (calculated such that the excitation has to propagate to store $A$; see Eq. 2), will be smaller than 1, accordingly. The circles represent the ranges of each store. Store $A$ can excite store $B$, while store $B$ cannot excite store $A$,

and thus the signal propagates only one way. Figure 3(c) presents another possible diode configuration, in which $N_A = N_B$ and $C_A > C_B$.

3.2. *OR* **gates.** If we insert two excitation diodes in two "wires" that merge into a common path, we can obtain a logic *OR* gate. Excitation of either of the two wires will propagate along the common path and will not be transmitted back along the other wire. The behavior of such a system is very similar to that of an *OR* gate obtained with two electrical diodes. A configuration of stores which will behave like an *OR* gate is presented in figure 4(a). The excitation of either store $A$ or $B$ will trigger the weaker store $C$ to release and will eventually propagate to store $D$.

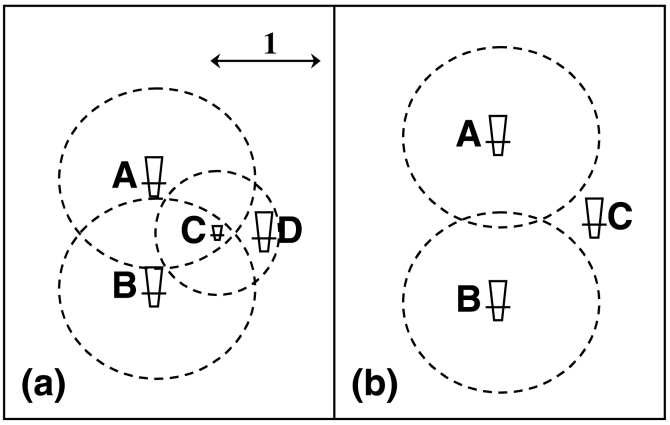


FIGURE 4. *OR* and *AND* gates. (a) *OR* gate. Stimulation at $A$ or $B$ causes successive releases at $C$ and $D$. (b) *AND* gate. Stimulations at both $A$ and $B$ are necessary to trigger response at $C$.

3.3. *AND* **gates.** Another logic gate that can be built with a small number of stores is the *AND* gate. As illustrated in figure 4(b), only excitation of both stores $A$ and $B$ will result in release at store $C$. The configuration has been chosen such that the distances $r_{AC}$ and $r_{BC}$ are both between 1 and $\sqrt{2}$. For simplicity we have also chosen them equal to each other, $r_{AC} = r_{BC} = r$, though in general this is not necessary. To trigger release at store $C$, the excitations at stores $A$ and $B$ should occur almost simultaneously. The maximum delay between them such that store $C$ is still triggered to release decreases as the distance $r$ to store $C$ increases (see figure 5). This synchronicity requirement can be an important factor that contributes to the flexibility of calcium signals: Two interacting input signals can result in propagation towards different regions of the cell, depending solely on the relative delay between the two inputs.

The relative positions of stores $A$, $B$, and $C$ in such a symmetric configuration are completely defined by $r$ and by the angle $\theta = \angle ACB$ (see the insert in figure 5). The behavior of the system of three stores changes with $r$ and also with $\theta$. In polar coordinates $(r, \theta)$ one can identify four domains, which correspond to four qualitatively different computations at store $C$ as a result of combinations in which one or both stores $A$ and $B$ are excited. The four domains are shown in figure 6. Inside the inner circle, whose radius is 1 ($r < 1$), the excitation of only one of the

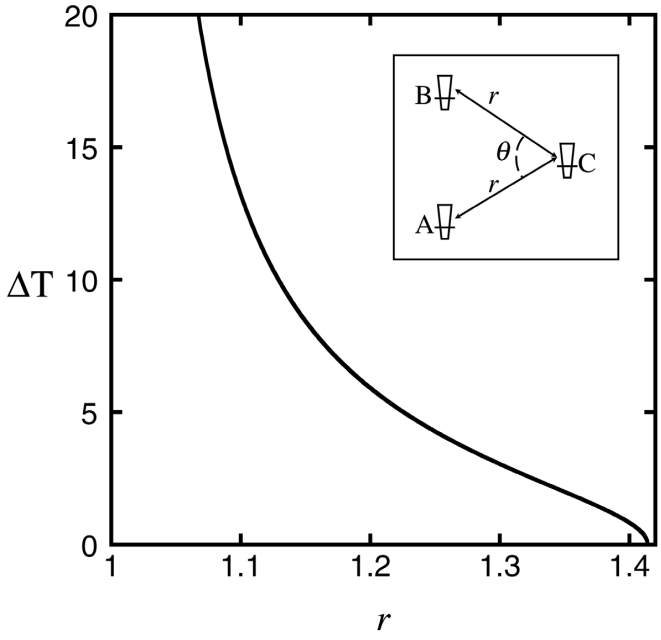


FIGURE 5. Coincidence detection with an $AND$ gate. Insert: a symmetric configuration characterized by the distance $r_{AC} = r_{BC} = r$ and by the angle $\theta$. The plot represents the maximum delay between stimulations at stores $A$ and $B$ that will still trigger response at store $C$. Here always $r_{AB} > 1$. The time unit is chosen such that $D = 1$.

stores $A$ and $B$ will trigger response at store $C$; thus, the system behaves like an $OR$ gate. Outside the circle of radius $r = \sqrt{2}$ even simultaneous stimulations of stores $A$ and $B$ – which produce the strongest concentration increase near store $C$ – are not sufficient to trigger the release at store $C$; thus, such a configuration will not lead to propagation. For $1 < r < \sqrt{2}$, if the distance between $A$ and $B$ is greater than 1 ($r_{AB} > 1$), excitations of both $A$ and $B$ are necessary to obtain response at $C$ – the configuration behaves like an $AND$ gate. If, on the other hand, the distance between $A$ and $B$ is smaller than 1 ($r_{AB} < 1$), it is possible that the stimulation at $A$ (or $B$) first triggers the excitation at $B$ (or $A$); then the two releases at $A$ and $B$, together, are strong enough to trigger the response by store $C$. The system behaves much like the *Diode* configuration as the excitation of $C$ does not propagate to $A$ or $B$. The boundary between the $AND$ and the *Diode* domains shown in figure 6 is given by $r_{AB} = 1$. Between the *Diode* domain and the external circle there exists, however, a very thin subdomain (hardly visible in figure 6), which is still part of the $AND$ domain. This subdomain corresponds to the excitation of $A$ propagating to $B$, but too late to trigger also the excitation of $C$. The curve separating this $AND$ subdomain and the *Diode* domain is given by the condition that the time after which excitation of $A$ propagates to $B$ equals the maximum delay between $A$ and $B$ that triggers response at $C$. This curve is tangent to the external circle at $\theta = 0$ and can be hardly distinguished from it in

figure 6. Figure 6 also shows that the logic gate configurations proposed here are robust with respect to the geometric uncertainty and variability.

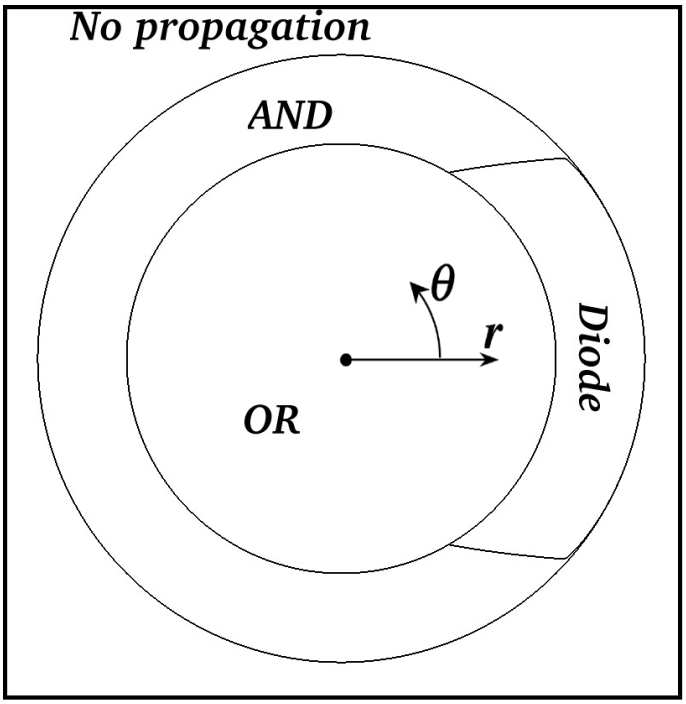


FIGURE 6. Domains of a symmetric configuration in polar coordinates $(r, \theta)$ (defined in the insert of figure 5). For different configurations $(r, \theta)$, different logical operations will be computed.

We expect the behavior of configurations presented here to be generic in the sense that changes in the CICR model used, or cytosolic buffering, if included, will not change the qualitative form of the computation. Thermal noise, however, will cause the logic operation to become fuzzy. The probability of false positive or negative responses will depend on fluctuations in both the excitatory signals and in the biochemistry of the CICR process. The fluctuations in the excitatory signal will depend on the cytosolic volume sensed by the CICR receptors and can be important for micron length scales. Fluctuations in the opening and closing of channels can also occur as a result of the stochastic binding of calcium to the (in)activation sites, and will depend on the details of the kinetics involved.

3.4. $NOT$, $XNOR$ **and** $XOR$**gates.** The construction of a $NOT$ gate is needed to have a complete set of logic gates, which, hooked together in an appropriate manner, are capable of performing any logic task. For this gate, the existence of a clock signal has to be assumed. Here the clock signal arrives simultaneously at stores $A$ and $B$ in figure 7. The two signals that follow the excitations of $A$ and $B$ arrive simultaneously at stores $C$ and $D$, which build an $AND$ gate whose output is measured at store $E$. The geometry of the $AND$ gate is chosen in such a way that only signals with a small relative delay at $C$ and $D$ result in propagation to $E$. If store $C$ is excited by an additional input signal simultaneous with the clock

signal which excites $A$ and $B$, the necessary synchronicity between stores $C$ and $D$ is lost and the excitation does not propagate to store $E$ any more.

A $XNOR$ gate is now easy to make: If a second input signal (not shown) excites store $D$, the configuration behaves like a $XNOR$ gate. The $NOT$ and $XNOR$ gates are obtained based on principles very similar to the corresponding logic gates described in [18].

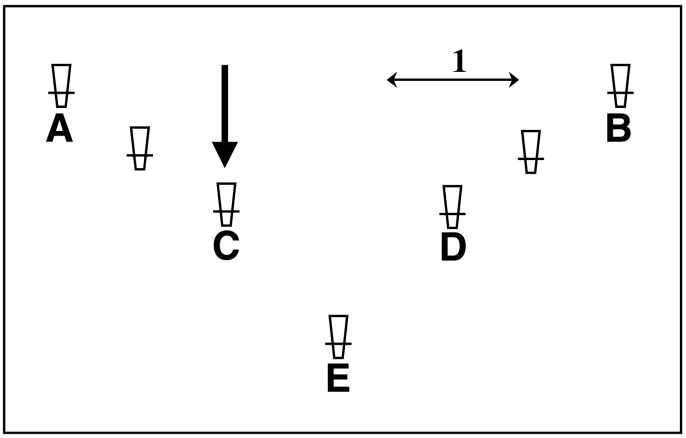


FIGURE 7. A $NOT$ gate. The propagation of a clock signal which excites stores $A$ and $B$ to store $E$ is blocked if an input signal at store $C$ breaks the synchronization of the excitations at stores $C$ and $D$.

What about a $XOR$ gate? The easiest biologically plausible way in which to create a $XOR$ gate is to use the bell-shaped Ca dependency of store release that occurs in many mechanisms of CICR: Below a critical level of the cytosolic calcium concentration, consistent with one node signalling, the store releases its bound calcium. but at high enough cytosolic calcium concentrations, consistent with two calcium waves reaching a store within a short time interval, it does not. Of course, for such a mechanism to work, the properties or spacing of calcium channels in the store membrane must be rather finely in order to determine whether it ends up with $AND$, $OR$ or $XOR$ function.

3.5. **Coincidence Detection.** Our last configuration, described in figure 8, shows the possibility of controlling precisely to which areas of the cell a calcium signal will propagate. If both stores $A$ and $B$ are stimulated, the two resulting signals will propagate in opposite directions along the path of stores that connects $A$ and $B$. The two signals will collide in a point determined by the relative delay between the two stimulations at $A$ and $B$. If the collision occurs near $C$, the higher concentration of calcium that results from the collision can trigger store $C$ to release. Thus by tuning the relative delay between the calcium signals at stores $A$ and $B$ one can control precisely to which region of the cell the calcium signal will propagate. A different delay can result, for example, in excitation of store $D$ instead of $C$.

4. **Concluding Remarks.** In this paper we showed how calcium signals can be controlled by specific configurations of calcium stores. If we replace the instantaneous release by the stores with a more plausible evolution along an excitation

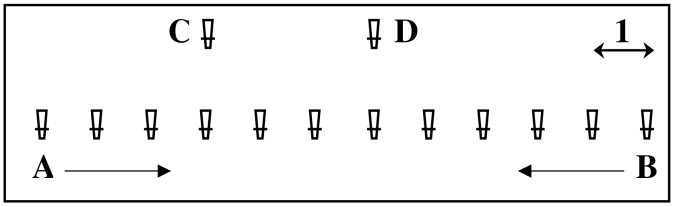


FIGURE 8. Coincidence detection of signals colliding on a path. Different relative delays between the two stimulations at $A$ and $B$ determine the collision point of the two signal and can select precisely where the excitation propagates (to $C$, to $D$, to both $C$ and $D$, or to none of them).

trajectory that corresponds to calcium release, then one obtains the same qualitative behavior described above, only the range of the stores and thus the boundary of the domains in figure 6 will change–their topology will not be affected. We also expect that the incorporation of thermal noise will result in the logical operations becoming fuzzy. Such a network of stores need not necessarily be confined to the cell body, but may be localized in the dendritic arbor or spine of a neuron as in Fig. 1.

Though we have focused on excitable calcium and CICR, the results presented above, describe not only calcium signaling, but also the behavior of any set of geometrically localized excitable systems coupled by diffusion. For example, such excitable biochemical networks in the cell body may be responsible for switching genes on or off during development. The biochemical networks involved can be expected to have evolved during evolution, and be of crucial importance in many intracellular signaling tasks. The experimental identification of such networks appear to be a worthwhile experimental project using confocal microscopic techniques.

5. **Acknowledgements.** We wish to acknowledge support by grants to H.G.E.H. from the US National Science Foundation (IBN-0083653), and to A.F. from the Canadian Institutes for Health Research (MOP-49489) and the Human Frontier Science Program (RG P65/2002).

## REFERENCES

[1] M. Cross and P. Hohenberg, "Pattern formation outside of equilibrium," *Rev. Mod. Phys.*, vol. 65, pp. 851–1112, July 1993.
[2] A. Winfree and S. Strogatz, "Singular filaments organize chemical waves in three dimensions. I. Geometrically simple waves," *Physica D*, vol. 8, pp. 35–49, 1983.
[3] A. Winfree and S. Strogatz, "Singular filaments organize chemical waves in three dimensions. IV. Wave taxonomy," *Physica D*, vol. 13, pp. 221–233, 1984.
[4] M. Berridge, M. Bootman, and P. Lipp, "Calcium - a life and death signal," *Nature*, vol. 395, pp. 645–648, Oct. 1998.
[5] M. Berridge and R. Irvine, "Inositol phosphates and cell signalling," *Nature*, vol. 341, pp. 197–205, Sept. 1989.
[6] M. Berridge, "Neuronal calcium signalling," *Neuron*, vol. 21, pp. 13–26, July 1998.
[7] T. Bliss and T. Lomo, "Long-lasting potentiation of synaptic transmission in the dentate area of the anesthetized rabbit following stimulation of the perforant path," *Journal of Physiology*, vol. 232, pp. 331–356, 1973.

[8] J. Sneyd and J. Sherratt, "On the propagation of calcium waves in an inhomogeneous medium," *SIAM J. Appl. Math*, vol. 57, no. 1, pp. 73–94, 1997.
[9] G. Dupont and A. Goldbeter, "Properties of intracellular $Ca^{2+}$ waves generated by a model based on $Ca^{2+}$-induced $Ca^{2+}$-release," *Biophysical Journal*, vol. 67, pp. 2191–2204, 1994.
[10] G. Dupont and A. Goldbeter, "Oscillations and waves of cytosolic calcium: Insights from theoretical models," *BioEssays*, vol. 14, pp. 485–493, July 1992.
[11] G. Dupont and A. Goldbeter, "One-pool model for $Ca^{2+}$ oscillations involving $Ca^{2+}$ and inositol 1,4,5-trisphosphate as co-agonist for $Ca^{2+}$ release," *Cell Calcium*, vol. 14, pp. 311–322, 1993.
[12] A. Zhabotinsky, "A history of chemical oscillations and waves," *Chaos*, vol. 1, no. 4, pp. 379–386, 1991.
[13] A. Ghosh and M. Greenberg, "Calcium signaling in neurons: molecular mechanisms and cellular consequences," *Science*, vol. 268, pp. 239–247, 1995.
[14] J. Sneyd, A. Charles, and M. Sanderson, "A model for the propagation of intercellular calcium waves," *American Journal of Physiology*, vol. 266, no. 35, pp. C293–C302, 1994.
[15] J. Sneyd, S. Girard, and D. Clapham, "Calcium wave propagation by calcium-induced calcium release: An unusual excitable system," *Bulletin of Mathematical Biology*, vol. 55, no. 2, pp. 315–344, 1993.
[16] C. Pencea and H. Hentschel, "Excitable calcium wave propagation in the presence of localized stores," *Phys. Rev. E*, vol. 62, pp. 8420–8426, Dec. 2000.
[17] G. Shepherd and R. Brayton, "Logic operations are properties of computer-simulated interactions between excitable dendritic spines," *Neuroscience*, vol. 21, no. 1, pp. 151–165, 1987.
[18] A. Tóth and K. Showalter, "Logic gates in excitable media," *Journal of Chemical Physics*, vol. 103, pp. 2058–2065, Aug. 1995.
[19] A. Adamatzky, "Universal dynamical computation in multidimensional excitable lattices," *International Journal of Theoretical Physics*, vol. 37, no. 12, pp. 3069–3108, 1998.
[20] M. Jafri and J. Keizer, "On the roles of $Ca^{2+}$ diffusion, $Ca^{2+}$ buffers, and the endoplasmic reticulum in $IP_3$ induced $Ca^{2+}$ waves," *Biophysical Journal*, vol. 69, pp. 2139–2153, 1995.

Received on Feb. 1, 2004. Revised on March 29, 2004.

*E-mail address*: phshgeh@physics.emory.edu