

# Computing with Calcium Stores and Diffusion

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## Abstract

Intracellular signaling often employs excitable stores of calcium coupled by diffusion. We describe here the ability of such a mechanism to generate a complete set of logic gates required for computation, as well as how they can act as coincidence detectors for biological signals.

*Key words:* Computation, Diffusion, Calcium Induced Calcium Release, Logic Gates, Biological Signalling

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Calcium in well localized stores 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 [1]. Such chemical networks are capable of performing computational tasks [2], and in this paper we show 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.

Computation with coupled excitable systems has been described previously [3,4]. Shepherd and Brayton [3] used a compartmental representation of the dendritic spine system and the Hodgkin-Huxley equations for nerve impulse generation. 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. Tóth and Showalter [4] have shown that the interaction of excitable chemical waves which propagate through capillary tubes can also be the underlying mechanism that emulates logic gate behavior.

Here we present logic gate configurations similar to those described in Ref. [4], but for the case of localized excitable behavior which could, for example, represent local stores of calcium in spines and dendrites. As in Ref. [4], the excitation will also be confined to specific paths, and interactions of signals arriving on different paths will provide the basis for building logic gates and coincidence detectors. The confinement of the signal within specific regions will, however, be realized not by using capillary tubes, but by considering discrete stores of calcium excitable via calcium-induced calcium release (CICR).

To describe the exchange of calcium between the store and the cytosol, we use an adiabatic simplification. The time scale for calcium release from stores is assumed to be short compared to the typical time for diffusive propagation between stores:  $\tau_{release} \ll l^2/D$ , where  $l$  is a typical distance between stores and  $D$  is the effective diffusion coefficient of calcium ions. In this case the store releases effectively instantaneously all the available calcium ("puffs") when the free calcium concentration near the store increases above the CICR threshold. Thus in our simplified model 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 approximation is a limit case of the Michaelis-Menten dynamics that describes the calcium fluxes between the store and the cytosol [5,6]. It is obtained in the limit of large Hill coefficients (high cooperativity), and large CICR rate.

In Ref. [1] we derived a propagation criterion for the calcium signal 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  $j$ :

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

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 an effective diffusion coefficient  $D$ .

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 can collide and interact with each other. The relative positions of the stores within a "wire" and especially near a node play an important role in the propagation of the

signals and therefore in the types of computation they can perform. We will 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 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[2]: different extracellular stimuli produce, by means of calcium diffusion interacting with networks of stores, different responses in the cell.

The simplest system that can be constructed using such excitable stores in a diffusive medium is the excitable diode. In analogy with a diode in an electrical circuit, the excitable diode will transmit the excitation in one direction and will block it in the opposite one. Figure 1 presents three basic configurations of stores that can have a diode-like behavior (in Fig. 1 and in the following examples we will chose the length unit such that  $r_{AB}^{max} = 1$ ). In Fig. 1(a) all the stores are identical, with the distance between stores  $A$  and  $B$  being smaller than 1 and the distance between  $B$  and  $C$  being greater than 1. The puff at store  $A$  triggers the store  $B$  to release, and the two releases combined 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 Fig. 1(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. 1), will be smaller than 1, accordingly. The circles represent the ranges of each store. Store  $A$  can excite store  $B$ , while store  $B$  can not excite store  $A$  and thus the signal propagates only one-way. Figure 1(c) presents another diode configuration, in which  $N_A = N_B$  and  $C_A > C_B$ .

If one inserts two excitation diodes in two “wires” which merge into a common path, one 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 Fig. 2(a). Excitation of either store  $A$  or  $B$  will trigger the weaker store  $C$  to release and will eventually propagate to store  $D$ .

Another logic gate that can be build with a small number of stores is the *AND* gate. As illustrated in Fig. 2(b), only excitation of both stores  $A$  and  $B$  will result in release at store  $C$ . For simplicity we have also chosen them

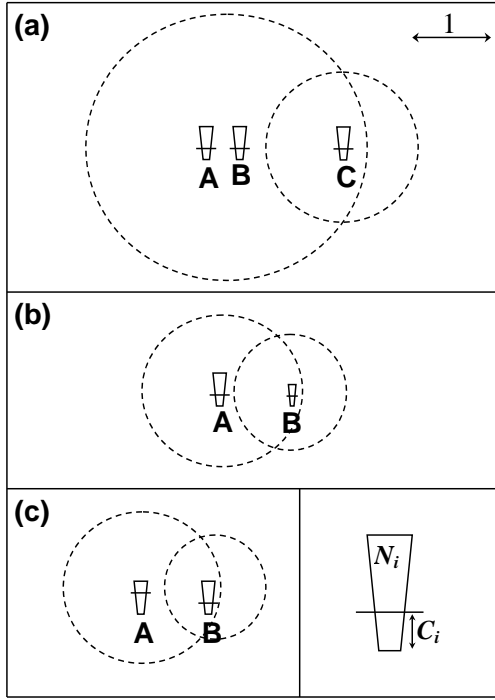


Fig. 1. Configurations of stores which behave like excitable diodes. Lower-right corner insert shows the convention used to describe the store. The size of the drawn store is proportional to the amount of calcium stored, while the height of the horizontal line is proportional to the CICR threshold. (a) Identical stores. (b) Store  $B$  contains a smaller amount of releasable calcium. (c) The excitation threshold of store  $A$  has a larger value.

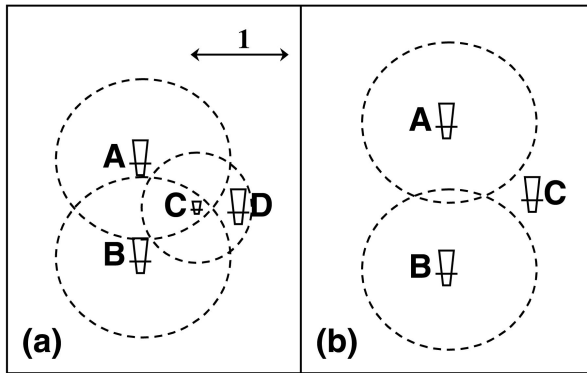


Fig. 2. *OR* and *AND* gates. (a) *OR* gate. Stimulation at  $A$  or  $B$  causes successive releases at  $C$  and  $D$ . (b) *AND* gate. Stimulations at both  $A$  and  $B$  are necessary to trigger response at  $C$ .

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. This synchronicity requirement can be an important factor which contribute 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 construction of a *NOT* gate is needed in order to have a complete set of logic gates which hooked together in an appropriate manner are capable of performing any logical task. The existence of a clock signal has to be assumed, here the clock signal arrives simultaneously at stores  $A$  and  $B$  in Fig. 3. The two signals which 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 input signal simultaneous with the clock signal which excites  $A$  and  $B$ , the necessary synchronicity between stores  $A$  and  $B$  is lost and the excitation does not propagate to store  $E$  any more. If a second input signal excites store  $D$  (not shown), 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 Ref. [4].

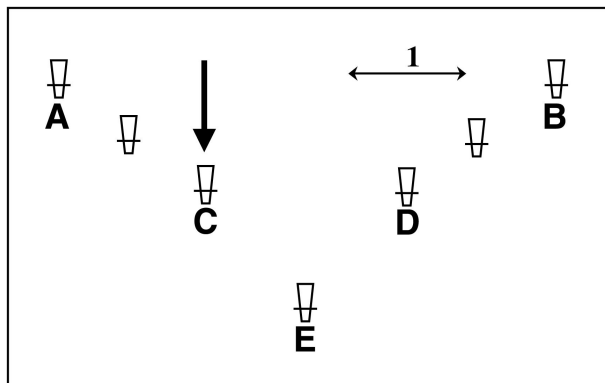


Fig. 3. A *NOT* gate. The propagation of a clock signal which excites stores  $A$  and  $B$  to store  $E$  is blocked if an input signal at store  $C$  breaks the synchronization of the excitations at stores  $C$  and  $D$ .

Our last configuration, described in Fig. 4, shows a possibility of controlling precisely in which areas of the cell the 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 which 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 the store  $C$  to release. Thus by tuning the relative delay between the calcium signals at stores  $A$  and  $B$  one can control precisely in which region of the cell the calcium signal will propagate. A different delay can result, for example, in excitation of store  $D$  instead of  $C$ .

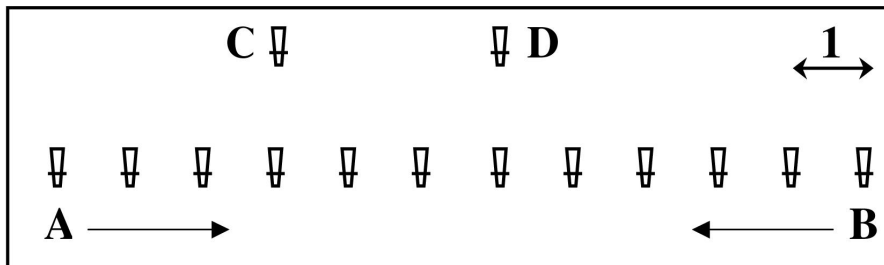


Fig. 4. Coincidence detection of signals colliding on a path. Different relative delays between the two stimulations at  $A$  and  $B$  determine the collision point of the two signal and can select precisely where the excitation propagates (to  $C$ , to  $D$ , to both  $C$  and  $D$ , or to none of them).

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