Wave Block in Cellular Systems: Setting the Range of Calcium Waves in Astrocyte Networks

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ABSTRACT Wave propagation governed by reaction-diffusion equations in homogeneous media has been extensively studied, and initiation and propagation are well-understood in scalar equations such as Fisher’s equation and the bistable equation. However in many biological applications the medium is highly nonhomogeneous, and in one space dimension a typical model is a series of cells, within each of which the dynamics obey a reaction-diffusion equation, and which are coupled by gap junctions. In certain limits such systems can be homogenized and the lowest-order equation is the equation for a homogeneous medium (1), but the applicability of such averaged equations to cellular systems is limited because they cannot predict a finite range of propagation; once a wave is fully-developed it propagates indefinitely. However recent experimental results on calcium waves in numerous systems show that waves propagate through a fixed number of cells and then stop. Here we show how this can be understood within the framework of a simple model for excitable systems.

Until recently, astrocytes were considered passive bystanders in the brain, but it is now known that various stimuli can trigger complex intracellular calcium ([Ca$$^{2+}$$]) responses in these cells. Aggregates of cultured astrocytes can propagate waves that cross cell boundaries without decrement or delay, involving hundreds of cells, and last seconds to minutes (2). [Ca$$^{2+}$$] waves also arise in cardiac tissue, and it has been shown that spatial inhomogeneity in the release sites can block waves that would propagate in a spatially-uniform tissue (3).

Intercellular Ca$$^{2+}$$ waves in astrocytes require some form of cell-to-cell communication, and two major pathways have been identified: direct diffusion of inositol 1,4,5-trisphosphate (IP3) and calcium waves, via gap junctions (4), and indirect communication via a secreted messenger released by stimulated cells (5). It is not known whether these waves are regenerative, but it is often assumed that they are not because the waves only propagate over fixed number of cells and then stop (4). Models based on passive diffusion of IP3, IP3-stimulated release of Ca$$^{2+}$$, and communication via gap junctions have been developed (6), but the problem of predicting the extent of propagation remains unresolved. Our purpose here is to suggest a possible explanation for the finite range of propagation using an analytically tractable model. The results may shed light on wave block in numerous excitatory systems, such as cardiac and neural tissue, and calcium dynamics in a variety of systems. More generally the results suggest how the range of a signal can be controlled in a cellular system like those that arise in developmental problems.

Description of the Model The domain is a one-dimensional array of alternating active regions of length L and passive gaps of length l, as shown in Figure 1. We suppose that the dynamics in the active regions are given by the piecewise linear version of the Fitzhugh-Nagumo equations

$$\frac{\partial u}{\partial t} = D_a \frac{\partial^2 u}{\partial x^2} + \lambda(-v + H(v-a)) - w$$

$$\frac{\partial v}{\partial t} = \epsilon(v - gw)$$

where H(x) is the Heaviside step function. The existence of travelling waves in this system was studied in (7) for the case g = 0. The equation that results when there is no recovery (ε = 0 and w ≡ 0) is called Nagumo’s equation: threshold behavior of this was studied in (8) and we begin with this equation in the active regions. In the passive regions the local dynamics are identical zero and there is only diffusion.

The main tool in establishing conditions under which the presence of gaps can lead to wave block is a comparison principle in a form given in (9). Consider the scalar parabolic equation

$$\mathcal{N}u \equiv \frac{\partial u}{\partial t} - D \frac{\partial^2 u}{\partial x^2} - m(x)(-u + H(u-a)) = 0$$

where m(x) is one in active regions and zero in passive regions. Thus $\mathcal{N}$ is discontinuous on the lines

$$x = j(l + L), x = (j + 1)l + jL$$

for j = 0, 1, ..., N - 1 as well as on any curves $x = c(t)$, where $u(c(t), t) = a$. We will assume, in general, that the operator $\mathcal{N}$ is discontinuous only on a finite collection of curves \{c1(t), c2(t), ..., cM(t)\} which are nowhere horizontal. Generally we will require solutions to be smooth in the complement of C $\equiv \bigcup_{j=1}^{M} c_j(t)$. However, in order to deal with sub- and super-solutions we will allow discontinuous derivatives on C.

COMPARISON THEOREM: Let u and v be continuous functions which satisfy

$$\mathcal{N} \phi \leq 0 \text{ in } (\mathbb{R} \times \mathbb{R}^+) \setminus C,$$

$$\phi(x, 0) \leq 0 \text{ on } \mathbb{R},$$

$$\phi_x(c_j(t)+, t) \geq \phi_x(c_j(t)-, t) \text{ for } t \geq 0.$$ Then

$$u(x, t) \leq v(x, t) \text{ throughout } \mathbb{R} \times \mathbb{R}^+.$$ An important consequence of the comparison theorem concerns the behavior of solutions to the transient problem when the initial datum is a sub- or supersolution. A function U is said to be a sub-solution (supersolution) for $\mathcal{N}$ if

$$\mathcal{N}U \leq \left( \begin{array}{ll} 0 & \text{in } (\mathbb{R} \times \mathbb{R}^+) \setminus C \\
U_x(c_j(t)+, t) & \geq \left( \begin{array}{ll} U_x(c_j(t)-, t) & \text{for } t \geq 0.
\end{array} \right.
\end{array} \right.$$

Figure 1: The one-dimensional domain
**STABILIZATION THEOREM:** Let $U(x)$ be a time independent supersolution (subsolution) for $\mathcal{N}$ and let $u(x, t)$ be the solution of the transient problem

$$
\mathcal{N} u = 0 \quad \text{in} \quad (\mathbb{R} \times \mathbb{R}^+) \setminus C
\quad \quad \quad u(x, 0) = U(x) \quad \text{in} \quad \mathbb{R}.
$$

Then $u(x, t)$ is a nonincreasing (nondecreasing) function of $t$ and approaches the largest (smallest) steady state solution $U^*(x)$ of $\mathcal{N} u = 0$ such that

$$
U^*(x) \leq (\geq) \ U(x).
$$

Here we use time-independent solutions (standing waves) as the comparison solution, and when they exist we say that waves may be blocked, since initial data that lies strictly below the standing wave cannot cross above it. Whether this represents an actual block depends on the nature of the standing waves.

**Construction of standing waves** In order to construct standing waves and understand how their existence depends on the number and size of the inactive regions, we first describe the phase plane for a system that is active for all $x$. The governing equation is

$$
D_a u'' + \lambda (-u + H(u - \alpha)) = 0 \quad (4)
$$

and the first integral of this is

$$
\frac{D_a}{2\lambda} (u')^2 + F(u) = c \quad (5)
$$

where $F(u)$ is a primitive of the reaction term and $c$ is a constant. The heteroclinic connection at $(0, 0)$ and the stable and unstable manifolds at $(1, 0)$ are shown in Figure 2, where here and hereafter we assume that $\alpha \in (0, 1/2)$.

![Figure 2: The invariant manifolds for a homogeneous active system and the four types of standing waves (for a system containing two gaps) discussed later.](image)

Now suppose we introduce a finite number of gaps or passive regions on $(0, +\infty)$, as shown in Figure 1. In passive regions $(x \in (n - 1)(\ell + L), n\ell + (n - 1)L)$ we have

$$
D_p u'' = 0
$$

and in active regions $(x \in (n\ell + (n - 1)L, n(\ell + L))$ we have

$$
D_a u'' + \lambda (-u + H(u - \alpha)) = 0.
$$

At the interfaces between them we must satisfy the matching conditions

$$
u = u
\quad \quad \quad -D_a u' = -D_p u'.
$$

From this one can see how to obtain standing wave solutions. Since the region to the left of $x = 0$ is an active region, there is a solution that begins at $(1,0)$ at $-\infty$ and lies on the branch $\Gamma_3$ of the unstable manifold on $(-\infty, 0)$. This solution must match the solution in the first gap, on which $u' = \text{constant}$, which corresponds to a horizontal line in the phase plane. In active regions between gaps the solution follows one of the level sets of $\mathcal{N}$, and at the end of the last gap the solution must reach either $\Gamma_1$ or $\Gamma_2$, parts of the stable manifold of $(0, 0)$ (cf. Figure 2). Thus the existence question for a fixed number of gaps reduces to whether one can patch together the proper number of horizontal components with portions of the level sets of $\mathcal{N}$. The solutions are always monotone decreasing, and therefore lie strictly in the lower half plane. Other non-monotone standing waves are possible, but we do not consider them here. We can distinguish between four types of standing waves (blocking solutions) depending on where the solution drops below the threshold $\alpha$, as shown in Figure 2 for a system with two gaps.

**Type I:** The solution drops below $\alpha$ within the $N^{th}$ passive region and hits $\Gamma_1$ at the end of the last passive region.

**Type II:** The solution drops below $\alpha$ beyond the last gap. Such solutions must land on $\Gamma_2$ at the end of the $N^{th}$ gap.

**Type III:** The solution drops below $\alpha$ within the $M^{th}$ passive region, $1 \leq M < N$ and hits $\Gamma_1$ at the end of the last gap.

**Type IV:** The solution drops below $\alpha$ within the $M^{th}$ active region and hits $\Gamma_1$ at the end of the last gap.

The simplest case in which all four types of wave exist arises when there are two gaps. In this case there is at most one non-trivial steady state solution of each of the four types, and a typical phase plane is shown in Figure 3 for a dimensionless gap length $\gamma > 1/\alpha - 2$ (scaling defined later). Three dashed curves $\Lambda_1, \Lambda_2,$ and $\Lambda_3$ are shown there: $\Lambda_1$ and $\Lambda_2$ are the loci of the left-hand end points of passive solutions whose right-hand end points lie on $\Gamma_1$ and $\Gamma_2$, respectively, while $\Lambda_3$ is the locus of right-hand end points of solutions whose left-hand end points lie on $\Gamma_3$. $\Gamma_3$ intersects $\Gamma_1$ ($\Gamma_2$) at the point labeled $1$ ($5$), and the steady state solution passing through either of these intersections corresponds to an interior active region of zero length. A solution leaving the point labeled $4$ on $\Gamma_3$ is a solution to a gap problem, i.e. the interior active region has infinite length. The point $2$ ($3$) is the intersection of $\Lambda_3$ and $\Gamma_1$ ($\Gamma_2$). Point $2$ is also the right-hand end point of the horizontal segment which starts at the intersection of $\Lambda_1$ and $\Gamma_3$. A steady state solution with a gap which ends at $2$ ($3$) has an interior active region of infinite length. Let $u_j$ for $j = 1, ..., 5$ be the $u$-coordinate of the intersection of a horizontal line through point $j$ with either $\Gamma_1$ or $\Gamma_2$, as shown in the figure. As long as $\gamma > 1/\alpha - 2$ we have $u_1 < u_2 < \alpha < u_3 < u_4 < u_5$. For any $u_0 \in (u_1, u_2)$ ($u_0 \in (u_4, u_5)$) there is a steady state solution of type $I$ ($II$) with $u = u_0$ at the end of the second gap. For example, the curve $1A1BB'CC0$ in Figure 3 represents a type $II$ solution with $u_0 \in (u_4, u_5)$. For the given gap length, the length of the interior active region is determined by the trajectory $A'B'$ which joins $\Lambda_3$ to $\Lambda_2$. For $u_0 \in (u_2, \alpha)$ ($u_0 \in (\alpha, u_3)$) there

![Figure 3: The phase plane for the two-gap problem](image)
is a steady state solution of type III (IV) with \( u = u_0 \) at the end of the second gap. The path \( LEFGC'0 \) shown in Figure 3 represents a type IV solution with \( u_0 \in (a, u_3) \). The length of the corresponding interior active region is determined by the trajectory \( EFC' \) which joins \( \Lambda_2 \) to \( \Lambda_1 \). The relationships between the gap lengths \( \gamma \) and the corresponding active region lengths \( \beta \) is summarized in Figure 4. \( u_2, u_3, \) and \( u_4 \) coalesce at \( a \) as \( \gamma \to 1/a - 2 \). For \( \gamma < 1/a - 2 \) the curve \( \Lambda_2 \) intersects \( u = a \) below \( C \), and type III and IV solutions no longer exist. For \( 1/2a - 1 < \gamma < 1/a - 2 \) there is a type I solution for \( u_0 \in (u_1, a) \) and a type II solution for \( u_0 \in (a, u_5) \). These solutions coincide when \( u_0 = a \) and determine a finite interior active region length. The relationship between \( \gamma \) and \( \beta \) for \( \gamma \) in this range is shown in Figure 4. Finally, for \( \gamma < 1/2a - 1 \) there are no steady state solutions of any type.

One can now construct a bifurcation diagram for the various types of standing waves as a function of the gap length, as shown in Figure 5. For fixed \( N \) there is a sequence of \( N \) bifurcation points, corresponding to successively earlier block of a wave arriving from the left, as will be seen later in transient simulations.

![Figure 4: The 3D bifurcation diagram for a two-gap system.](image)

The vertical axis represents the \( u \) coordinate of the first intersection of a path with \( \Gamma_1 \) or \( \Gamma_2 \).

![Figure 5: The bifurcation diagram for the standing wave solutions for fixed \( \beta > 0 \).](image)

Analytical construction for general \( N \) Next we determine analytical conditions under which a given type of solution exists for general \( N \), and to simplify the notation we define the dimensionless variables

\[
\xi = (x - n\ell - (n - 1)L)\sqrt{\frac{D_u}{\lambda}}, \quad \beta = L\sqrt{\frac{D_u}{\lambda}},
\]

\[
\eta = (x - (n - 1)(\ell + L))\sqrt{\frac{D_u\lambda}{D_p}}, \quad \gamma = \ell\sqrt{\frac{D_u\lambda}{D_p}}.
\]

The solutions can be represented as follows: in an active region in which \( u \) lies strictly above or strictly below \( a \), the solution is

\[
\begin{pmatrix}
    u_n(\xi) - H(u - a) \\
    u_n'(\xi)
\end{pmatrix} = A(\xi) \begin{pmatrix}
    u_n(0) - H(u - a) \\
    u_n'(0)
\end{pmatrix},
\]

and in a passive region

\[
\begin{pmatrix}
    v_n(\eta) - 1 \\
    v_n'(\eta)
\end{pmatrix} = P(\eta) \begin{pmatrix}
    v_n(0) - 1 \\
    v_n'(0)
\end{pmatrix},
\]

where

\[
A(\xi) = \begin{bmatrix}
    \cosh\xi & \sinh\xi \\
    \sinh\xi & \cosh\xi
\end{bmatrix} \quad \text{and} \quad P(\eta) = \begin{bmatrix}
    1 & \eta \\
    0 & 1
\end{bmatrix}.
\]

Type I and Type II standing waves Suppose that \( u > a \) in the intermediate active regions and let

\[
U_n(\xi) = \begin{pmatrix}
    u_n(\xi) - 1 \\
    u_n'(\xi)
\end{pmatrix}, \quad V_n(\eta) = \begin{pmatrix}
    v_n(\eta) - 1 \\
    v_n'(\eta)
\end{pmatrix}.
\]

Then

\[
V_n(\gamma) = PV_n(0) \quad \text{and} \quad U_n(\beta) = AU_n(0),
\]

where here and hereafter \( P \equiv P(\gamma) \) and \( A \equiv A(\beta) \). From the matching conditions we have

\[
U_n(0) = V_n(\gamma) = PV_n(0),
\]

\[
V_{n+1}(0) = U_n(\beta) = AU_n(0),
\]

and it follows that

\[
V_N(0) = (AP)_N^{-1}V_1(0).
\]

To cross the last passive gap apply \( P \) once more to obtain

\[
V_N(\gamma) = P(AP)_N^{-1}V_1(0) = (AP)_N^{-1}P(V_1(0)). \tag{9}
\]

On \( \Gamma_3, v_1(0) - 1 = v_1'(0) \), and therefore, setting \( \mathbf{1}_T = (1, 1)^T \),

\[
V_N(\gamma) = (v_1(0) - 1)P(AP)^{N-1}\mathbf{1}. \tag{10}
\]

This accounts for all standing wave solutions of Type I or II, which begin at \((1, 0)\) at \(-\infty\) and end at \((0, 0)\) at \(\infty\), and for which all \( N - 1 \) intermediate active regions lie in the superthreshold region \( u > a \). For such solutions \( V_N \) lies on either \( \Gamma_1 \) or \( \Gamma_2 \), and therefore they cross threshold either in the last gap or beyond it. By construction these waves are monotone decreasing and they represent bona fide blocking solutions, since they range from 1 to 0 on \( \mathbb{R} \). We call these \((N, N)\) blocking solutions; their significance \textit{vis-à-vis} the initial value problem will be discussed later.

The condition that \( V_N \) lies on either \( \Gamma_1 \) or \( \Gamma_2 \) imposes a relation between \( v_N(\gamma) \) and \( v_N'(\gamma) \), and therefore (10) is a system of two equations in two unknowns, \( v_1(0) \) and \( v_N(\gamma) \). Consequently we expect that for fixed \( \beta \) there are two one-parameter families of solutions parameterized by \( \gamma \). However there is a minimum or critical gap length below which such solutions do not exist.

One can determine analytically how this critical gap length depends on the length \( \beta \) of the active region and on the number of gaps. The results are summarized in the following proposition, the proof of which will be given elsewhere.

**Proposition 1**

1. For any \( N > 0 \) and any \( \beta > 0 \), the minimum gap length \( \gamma_{N, N}^{\text{min}} \) that produces an \((N, N)\) blocking solution corresponds to that solution for which \( V_N(\gamma) = (a - 1, -a) \).

**Proposition 2**

1. For any \( N > 0 \) and any \( \beta > 0 \), the minimum gap length \( \gamma_{N, N}^{\text{min}} \) is a bifurcation point and for any \( \gamma > \gamma_{N, N}^{\text{min}} \) there exist two monotone \((N, N)\) standing waves, one of Type I and one of Type II.
2. For fixed \( N > 0 \), \( \gamma_{N,N} \) is a monotone increasing function of \( \beta \), the length of the active region.

3. The critical gap length is a monotone decreasing function of the number of gaps, viz. if \( N > M \) then \( \gamma_{N,N}^{\text{crit}} < \gamma_{M,M}^{\text{crit}} \).

4. 
\[
\lim_{N \to \infty} \gamma_{N,N}^{\text{crit}}(\beta) = \frac{1 - 2a}{N} = \frac{\gamma_{1,1}^{\text{crit}}}{N}
\]

The first assertion implies that for any \( N \) the dimensionless critical gap length \( \gamma_{N,N}^{\text{crit}} \) is the solution of
\[
\alpha r_1 - e_1 = (v_1(0) - 1)P(AP)^{N-1}1,
\]
where \( r_1^T = (1, -1)^T \) and \( e_1^T = (1, 0)^T \). This yields two relations, the first of which is
\[
(1 - 2a) \begin{pmatrix} 1 & P(AP)^{N-1}1 \end{pmatrix} = \begin{pmatrix} r_1, P(AP)^{N-1}1 \end{pmatrix},
\]
which defines \( \gamma_{N,N}^{\text{crit}} \) through \( P(\gamma) \), and the second of which,
\[
1 - v_1(0) = \begin{pmatrix} 1, P(AP)^{N-1}1 \end{pmatrix}^{-1}
\]
gives the starting point on \( \Gamma_3 \). From these one finds that for \( N = 1 \)
\[
\gamma_{1,1}^{\text{crit}} = \frac{1}{2a} - 1 = \frac{\gamma_{1,1}}{2},
\]
a result also derived in (10). For two gaps \( \gamma_{2,2}^{\text{crit}} \) is the solution of
\[
(\alpha \sinh \beta) \gamma^2 + \gamma [2a(\sinh \beta + \cosh \beta) - \sinh \beta] + (2a - 1)(\sinh \beta + \cosh \beta) = 0
\]
and for \( \beta = 0 \) this yields
\[
\gamma_{2,2}^{\text{crit}}(0) = \frac{1}{2a} - 1 = \frac{\gamma_{1,1}^{\text{crit}}}{2},
\]
as asserted in part 4 of Proposition 1.

One can also determine the limiting relation for large \( N \) as follows. The eigenvalues of \( AP \) are given by
\[
\lambda^\pm = \cosh \beta + \frac{\gamma}{2} \sinh \beta \pm \sqrt{(\cosh \beta + \frac{\gamma}{2} \sinh \beta)^2 - 1}
\]
and therefore \( \lambda^+ \lambda^- = 1 \) and \( \lambda^- < 1 < \lambda^+ \). In general we can write
\[
AP = \lambda^+ P^+ + \lambda^- P^-,
\]
where \( P^\pm \) are the projections associated with \( \lambda^\pm \). Only the first term contributes in (11) as \( N \to \infty \), and one finds that the limiting relation is
\[
\lim_{N \to \infty} \gamma_{N,N}^{\text{crit}} = A^2 - 1 + \frac{1}{4 \cosh \beta + A},
\]
wherein \( A \equiv 1/\alpha - 1 \). The following tables display the convergence of the numerically-computed critical gap \( \gamma_{\text{crit}}^{\text{max}} \) as a function of the number of gaps for two values of the threshold \( \alpha \); 0.1 (left), and 0.25 (right). For these values of \( \alpha \) the asymptotic value is essentially reached within 10 cells. To translate these values into dimensional form we must set the various parameters, and a typical set is as given in the following table.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of active region</td>
<td>20 microns</td>
</tr>
<tr>
<td>Diffusion in passive region</td>
<td>( D_p = 1 \cdot 10^{-9} \text{ cm}^2/\text{sec} )</td>
</tr>
<tr>
<td>Diffusion in active region</td>
<td>( D_a = 3 \cdot 10^{-6} \text{ cm}^2/\text{sec} )</td>
</tr>
<tr>
<td>Time scale</td>
<td>( \lambda = 10/\text{sec} )</td>
</tr>
</tbody>
</table>

For this set and one finds that
\[
\ell = \frac{\gamma D_p}{D_a \lambda} \sim 2.0 \cdot 10^{-7} \gamma
\]
in centimeters. Therefore a critical \( \gamma \sim O(5) \) corresponds to a critical gap length of approximately 100A, which is remarkably close to the thickness of a gap junction.

Type III and IV standing waves One can also construct Type III or IV standing waves, in which the solution drops below threshold either within the \( M^h \) gap of \( N \) or in the \( M^h \) active region for \( 1 \leq M < N \) (cf. Figure 2). We call these \( (M, N) \) blocking solutions and denote by \( \gamma_{M,N} \) the corresponding gap length at fixed \( a \) and \( \beta \). To construct Type III waves, let \( (v_M(\gamma), v_M'(\gamma)) \) be the solution at the end of the \( M^h \) gap. By hypothesis \( v_M(\gamma) \leq a \). As before, the starting point on \( \Gamma_3 \) is \( (v_1(0), v_1'(0)) \), where \( v_1(0) = 1 + v_1(0) \), and the termination point on \( \Gamma_1 \) is \( (v_N(\gamma), v_N'(\gamma)) \), where \( v_N(\gamma) = -v_N(\gamma) \). It follows from (9) that
\[
\begin{pmatrix} v_M(\gamma) \\ v_M'(\gamma) \end{pmatrix} = e_1 + v_1'(0)(P A)^{M-1} 1.
\]

When \( u < a \) we simply drop the \(-1\) from \( V_n(\xi) \) and \( V_n(\xi) \) as given in (8), and then we have
\[
V_n(\gamma) = v_n(\gamma) r_1 = (P A)^{N-1}-1 \gamma M(\gamma) = (P A)^{N-1}-1 e_1 + v_1'(0)(P A)^{N} P 1.
\]
Criticality corresponds to \( (v_M(\gamma), v_M'(\gamma)) = (a, \rho) \) for some \( \rho \in (-a, 0) \), and defines the critical gap length \( \gamma_{\text{crit}}^{\text{max}} \). For any fixed \( \gamma > \gamma_{\text{crit}}^{\text{max}} \) and \( \beta > 0 \), the foregoing construction produces a unique Type III standing wave with
\[
v_M'(0) = v^n(0) (P A)^{N} P 1.
\]
A similar construction holds for Type IV waves. A number of results concerning these waves are summarized in the following proposition, the proof of which will be given elsewhere.

**Proposition 2**

1. \( \gamma_{M,N}^{\text{crit}} \) corresponds to reaching \( a \) at the end of the \( M^h \) gap. For \( \gamma > \gamma_{M,N}^{\text{crit}} \), there is a unique Type III (Type IV) wave that blocks in the \( M^h \) gap (\( M^h \) active region).

2. For all \( M < N \), \( \gamma_{M,N} > \gamma_{M,1} \), i.e., any gap length that produces a standing wave which reaches threshold in the \( M^h \) of \( N \) gaps is greater than the critical gap length for \( N = M \).

3. For fixed \( \beta > 0 \), \( \gamma_{M,N}^{\text{crit}} \) is a monotone increasing function of \( N \) for fixed \( M \), and a monotone decreasing function of \( M \) for fixed \( N \).
4. If $M < a + N(1 - a)$, $\gamma_{M,N}^{\text{m,n}}(\beta) > 1/a - 2$ and is a monotone decreasing function of $\beta$. If $a + N(1 - a) < M < N$, $\gamma_{M,N}^{\text{m,n}}(\beta)$ has exactly one maximum and it is $> 1/a - 2$.

5. $\gamma_{M,N}^{\text{m,n}}$ is a monotone decreasing function of the threshold $a$.

The critical gap lengths for the various types of blocking solutions can be computed analytically for small $N$ and numerically for any $N$. Some representative results are shown in Figure 6 for $a = 0.4$. Figure 6(a) shows all critical lengths as a function of $\beta$ for $N \leq 3$. Note that as a function of $\beta$, $\gamma_{M,N}^{\text{m,n}}$ increases monotonically from $\gamma_{M,N}^{\text{m,n}}(0) = (1 - 2a)/Na$ to $\gamma_{1,1}$ as $\beta \to \infty$, as in part 2 of Proposition 1, and decreases as the number of gaps increases. In particular, $\lim_{N \to \infty} \gamma_{M,N}^{\text{m,n}}(0) = 0$.

Note also that in the case of $(M,N)$ blocking solutions, $\gamma_{1,3}^{\text{m,n}} \leq \gamma_{3,3}^{\text{m,n}}$ and $\gamma_{2,2}^{\text{m,n}} \leq \gamma_{3,3}^{\text{m,n}}$. Furthermore, both the (1, 2) and the (1, 3) blocking solutions are monotone decreasing functions of $\beta$, as per 4. of Proposition 2. The same is true for the (2, 3) blocking solution. For fixed $\beta$ the critical values of $\gamma$ on the curves (2, 2) and (1, 2) in (a) correspond to the successive bifurcation points shown in Figure 5.

Figure 6(b) shows all critical curves for $N = 10$. For $M \geq 7$, $\gamma_{M,N}^{\text{m,n}}$ exhibits a maximum, while for $M < 7$, $\gamma_{M,N}^{\text{m,n}}$ is a monotone decreasing function of $\beta$. If we fix $\beta > 0$ and increase $\gamma$, Figure 6(b) shows that the first standing wave corresponds to reaching threshold at $N^{1/2} + (N - 1)\beta$, and as $\gamma$ increases, threshold is reached successively at the end of the $(N - 1)^{1/2}$ gap, the $(N - 2)^{1/2}$ gap, etc.

The non-monotonicity of the critical curves for some $M$ predicted by part 4 of Proposition 2 arises first for $N = 4$. This behavior is illustrated in Figure 6(b) for $N = 10$. At $\beta = 0$ Type III and Type IV waves that block in the $7^{\text{th}}$ gap and $7^{\text{th}}$ active region, respectively, exist. This pair coalesces at a subcritical bifurcation when $\beta$ reaches the increasing branch of the curve labeled 7, and they reappear via a supercritical bifurcation when it reaches the decreasing branch and exist for all larger $\beta$. Similar behavior is observed for $M = 8$ or 9 at appropriate $\gamma$, whereas for $M < 7$ the corresponding standing waves exist only for sufficiently large $\beta$ and $\gamma$.

**Stability of steady state solutions**

The significance the various types of steady state solutions resides in their stability properties. The essence of the following theorem is that Type I and III solutions are attractors, while Type II and IV solutions are separatrices. The geometric proof given in (11) for a single gap can be extended to the two-gap case. The analytic proof in the general case will be given elsewhere.

**Theorem** Let $U(x)$ be a monotone decreasing solution to (4) which reaches the threshold value $a$ at $x = z$. If there exists an $h > 0$ such that

(i) the interval $(z, z + h)$ is in a passive region. Then for any solution $u(x, t)$ of the initial value problem with initial datum $u(x, 0)$ slightly above (below) $U(x)$

$$\lim_{t \to \infty} u(x, t) = U(x),$$

(ii) the interval $(z - h, z)$ is in an active region. Then for any solution $u(x, t)$ of the initial value problem with initial datum $u(x, 0)$ slightly above (below) $U(x)$

$$\lim_{t \to \infty} u(x, t) = \tilde{U}(x),$$

where $\tilde{U}(x)$ is the minimal (maximal) steady state solution which lies above (below) $U(x)$.

This result justifies the stability assignments in Figure 5, and the numerical results discussed below further illustrate this result.

**Transient dynamics** To understand the dynamics of wave block we did numerical simulations of the transient Nagumo equation for a two-gap system in different regions of the $(\gamma, \beta)$ parameter space, using a finite element scheme with quadratic basis functions for the space discretization and the trapezoidal rule for the time integration. The finite element discretization in space incorporates the matching conditions at the interfaces between active and passive regions directly.

As shown in Figure 6(a), the curves labeled (1, 2) and (2, 2) separate the $(\gamma, \beta)$ space into 3 regions: (A) $\gamma > \gamma_{1,2}^{\text{m,n}}(\beta)$, (B) $\gamma_{2,2}^{\text{m,n}}(\beta) \leq \gamma \leq \gamma_{1,2}^{\text{m,n}}(\beta)$, (C) $\gamma \leq \gamma_{2,2}^{\text{m,n}}(\beta)$. Figure 7 shows the computational results for a fixed $\beta$ and 3 different gap lengths corresponding to the labels (A), (B) or (C). The initial conditions for all simulations are identical and lie strictly below any standing wave solution pointwise. The parameter values are: $a = 0.2$, $D_a = 10^{-6}\text{cm}^2/\text{s}$, $D_p = 0.5 \times 10^{-8}\text{cm}^2/\text{s}$, $\lambda = 1/\text{s}$, $L = 3 \times 10^{-4}\text{cm}$, and $I = 1.75, 1.5, 1.25 \times 10^{-4}\text{cm}$.

For parameters is region (A) (Figure 7(a)), two (1, 2) and two (2, 2) standing wave solutions coexist (cf. Figure 5). The type II and IV solutions are unstable, while the type I and III solutions are stable. Since the initial condition lies strictly below the existing stable (1, 2) blocking solution, the system converges to this standing wave solution. Furthermore, in region (B) (Figure 7(b)), two (2, 2) blocking solutions exist. Again, because the initial condition lies strictly below the stable (2, 2) standing wave solution, the system converges to it after a small delay in the first gap. Finally, in region (C) (Figure 7(c)) no standing wave solution exists and the wave propagates beyond the two gaps after a delay in both gaps.

**Wave block with recovery** Many excitable systems also show recovery, as embodied in the $w$ variable of the Fitzhugh-Nagumo equation (2), and next we consider the effect of its inclusion on the ease and nature of wave block. Conceptually recovery should facilitate block, but earlier studies show that the situation is more complicated, even in a system without gaps (12). It was shown there that for $\epsilon << 1$, different traveling wave solutions exist, depending on the magnitude of $g$ relative to three critical values:

$g_0 = a/(1-a)$, $g_1 = 2a/(1-2a)$, and $g_2 = (1+2a)/(1-2a)$. When $g \in (0, g_0)$ only a pulse exists; for $g \in (g_0, g_1)$ a pulse, a front and a back coexist; for $g \in (g_1, g_2)$ a front and a back coexist, and when $g \in (g_2, \infty)$ only a front exists. Moreover, for $g \in (g_0, g_1)$ the back is faster than the front, whereas for $g \in (g_1, g_2)$ the situation is reversed.
function of a certain model parameter in (10). Here we study wave, or by convergence to a standing wave.

nature makes the system less excitable. Moreover, our computations show that the critical gap width is a monotone decreasing function of $\varepsilon$. We found that the inclusion of recovery decreases the critical gap width, since recovery by nature makes the system less excitable. Moreover, our computations show that the critical gap width is a monotone decreasing function of $\varepsilon$.

It was found that for $\alpha = 0.25$ and $g \in (0, g_1)$, where a pulse exists, initial data that produces a pulse propagates through the gap for $\gamma < \hat{\gamma}(\varepsilon)$, while for $\gamma \geq \hat{\gamma}(\varepsilon)$ the pulse is blocked and both $u$ and $w$ tend to zero. Furthermore, for $g \in (g_0, g_1)$ and initial data for which a front is initiated, the front propagates beyond the gap for $\gamma < \hat{\gamma}(\varepsilon)$ (see Figure 8(a)), while for $\gamma \geq \hat{\gamma}(\varepsilon)$ the slower front reflects to the faster back, which then propagates in the opposite direction (see Figure 8(b)). This result is consistent with earlier work wherein the homogeneous system was artificially perturbed by increasing the recovery variable at a given point in time (12). There it was observed that for $g \in (g_0, g_1)$ the slower front reflects to a back propagating in the opposite direction with higher speed. Finally, when there is no pulse ($g \in (g_1, \infty)$), the front propagates for gap widths smaller than the critical, while for $\gamma \geq \hat{\gamma}(\varepsilon)$, the system blocks in the form of a standing wave solution, similar to the problem without recovery.

Thus the inclusion of recovery significantly complicates the dynamics: when there is no recovery standing waves represent the only form of blocking solutions, but when recovery is included, wave block occurs by either collapse or reflection of the wave, or by convergence to a standing wave.

Discussion

The results described herein provide insight into the effect of inhomogeneities on wave propagation in excitable media, and in particular, suggest a simple explanation for the observed finite range of propagation in several experimental systems. In a homogeneous medium fully-developed monotone transition waves propagate indefinitely, but as we have shown, the inclusion of inexcitable regions can stop waves after a finite, and predictable, number of gaps have been crossed. The results also show how the size of the active region can determine where block occurs in an array of cells. For example, in reference to the discussion of Figure 6, for very small cells the waves block at the $7^{th}$ cell, for somewhat larger cells the wave propagates further, and for very large cells it again blocks at the $7^{th}$ cell.

Our results are experimentally-testable in excitable media such as the Belousov-Zhabotinskii reaction or cultures of astrocytes. One such experiment, in which it was shown that calcium waves could cross cell-free lanes in astrocyte cultures (5), provided part of the rationale for our analysis, but a more detailed study in a more precisely-controlled system could provide further insight into wave block.

Finally, we note that our results apply whatever the relative sizes of the gaps and active regions. In particular, they apply to problems with point active regions coupled by ‘long’ passive regions, such as arise in models of myelinated nerves, models for spatially-localized calcium channels, and in other contexts. As we mentioned earlier, a detailed analysis of calcium dynamics in cardiac tissue predicted that localization of release could inhibit wave propagation (3), and our results provide a more analytical basis for this observation.

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