Axonal geometry as a tool for modulating firing patterns

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\section{1. Introduction}

Understanding the interplay between neuronal morphology and activity is a fundamental challenge in neuroscience. Modeling the activity response to different neuronal geometries may shed light on form-function interaction as a possible mechanism for information coding. The classic Hodgkin–Huxley model (HH), as presented by Hodgkin and Huxley in 1952\cite{1}, has been extensively studied\cite{2–4}. The model continues to attract interest in numerous fields and is considered a realistic way of studying the response of neurons to a variety of physiological and pathological conditions. Hodgkin and Huxley demonstrated the model, based on data from the squid giant axon, for the space clamp membrane, and expanded the model to that of propagating action potentials, which enables examination of response to current stimuli along the axon and study of the influence of neuronal geometry on activity. The cable model is described by four nonlinear differential equations based on the nonlinear conductance of ion channels\cite{1} (in Section 2).

Due to the complexity of the HH model, many studies use reduced models, such as the FitzHugh–Nagumo model\cite{5,6}, the Morris–Lecar model\cite{7} and the Simplified HH model\cite{8}. In these reduced models, the four original equations are translated into two combined equations with only two variables. A survey and comparison of the different reduced and complete models and their computational complexity is presented in\cite{9–11}. The reduction contributes to an intuitive understanding of the system by enabling a representation of the variables in the phase plane. However, some of the more complex firing patterns of activity are missing.

With the advancement of research in higher organisms, more biological mechanisms were revealed leading to detailed models. Some models expanded the basic HH model with additional types of ionic channels\cite{12–14}. Furthermore, dynamic models

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have been used to describe the sodium and potassium accumulation in the extracellular milieu as a mechanism to affect the neuronal activity [15–17]. Other models took into consideration the effect of the myelin sheath that wraps and insulates axons, mainly in vertebrates [18–20]. Using these extended models can lead to a more realistic prediction of axonal activity and to the underpinnings of different pathologies, such as multiple sclerosis and mild traumatic brain injury [18–22]. To reveal core mechanisms of geometry-based modulations the basic HH model can be used.

For different geometries, the pattern of activity is affected by the electrical stimulation as well. Based on the response of the neuronal excitable membrane to various levels of injected currents, three types of membranes were classified [23]. Type 1 illustrates action potentials that can be generated with arbitrarily low frequency, depending on the strength of the applied current. The frequency-current curve of this type is continuous. Type 2 defines membranes that fire repetitively in a certain frequency band that is relatively insensitive to changes in the strength of the applied current. This type has a discontinuous frequency-current curve. Type 3 describes membranes that generate only a single action potential, and return to a constant voltage, despite the continuing current stimulus. The original values and parameters of the HH equations describe membranes of Type 2 [24–26].

Previous studies of the HH space clamp model [27–30] have shown that constant weak current stimuli below the threshold lead to a quiescent neuron, and no action potentials are developed. Increasing the current stimuli slightly above the threshold leads to the generation of a single action potential. For higher current stimuli, an infinite train of action potentials is generated. As the current stimuli increase, the amplitudes of the action potentials within the train decrease. Hence, the duration of each action potential decreases, leading to higher frequencies and demonstrating a logarithmic relationship. Further increases in the current stimuli produce a single action potential resembling the weak stimuli. The typical responses for various current stimulus regimes and the types of bifurcation points have been analyzed in [31–35].

When cell geometry is taken into account by using the HH cable model, more patterns of activity and propagation behavior along the axon may be demonstrated. Stockbridge et al. have shown, both experimentally and theoretically, that short axons lead to different activity dynamics [36–38]. They showed that at branching points, when one of the daughter branches is short, different conduction may occur along the two branches, leading to more spikes along the short branch. Debanne and colleagues summarized possible effects of the axon itself on modulating the carried information that has been studied, including frequency-dependent propagation failures by geometrical factors [39–41].

In this paper, we investigated the influence of axonal morphology on firing patterns. For this purpose we simulated simple demyelinated axons with the original HH parameters (in Section 2). We presented the response to current stimuli injected into the axon and focus on two current stimulus regimes that lead to distinct phenomena. The first is that of stimuli that lead to a small finite number of spikes, in which we demonstrated that the number of action potentials is controllable and may be adjusted to any finite number, expanding previous observations of limited short trains (two or three spikes) [42–45]. The second phenomenon for which we reported occurs only in the cable model; the periodic appearance of a few action potentials in series followed by a single failure. To date, only a single action potential followed by one failure has been presented [46]. We demonstrated more complex patterns with a tunable number of action potentials combined with failures, thus enabling control of the number of action potentials before failures by stimulus modulation. Moreover, we examined the influence of axonal morphology, length and radius, on the pattern of activity. Our results demonstrate the interplay between form and function, illustrating ways in which axonal activity can be modulated, and proposing that this behavior is instrumental in information coding.

Studying the effect of morphology on neuronal electrical response is essential for a better understanding of brain activity. Moreover, neuronal structure can undergo significant alteration in pathological conditions and following injury. For instance, critical swelling caused by brain trauma or neurological disorders leads to change in effective axonal radius [47]. Such morphological deformation may modify neuronal firing, causing defective function. Therefore, revealing the relation between structure and activity may open new avenues to the research of pathological conditions, disease dynamics and potential therapeutics.

2. Methods

The Hodgkin Huxley cable model is described by the following equations [1]:

\[
\frac{\partial^2 V}{\partial x^2} = \frac{C_m}{2R} \frac{\partial V}{\partial t} + g_K n^4 (V - V_K) + g_{Na} m^3 h (V - V_{Na}) + g_l (V - V_l) - I_{ext}(x, t)
\]

\[
\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \\
\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \\
\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h.
\]

(1)

The membrane potential is represented by \(V\). The sodium activation, sodium inactivation and potassium activation are represented by the gating variables \(m, h\) and \(n\), respectively. The radius of the axon is represented by \(a\), and the specific resistance of the axoplasm is represented by \(R\). The \(\alpha\) and \(\beta\) parameters are the opening and closing gate rate constants which vary with voltage:

\[
\alpha_n = 0.01 (V + 10) / (\exp((V + 10) / 10) - 1)
\]
Fig. 1. Schematic diagram of a cable-like axon. We injected current into the left end and observed the voltage response along the axon.

\[ \beta_n = 0.125 \exp \left( \frac{V}{80} \right) \]
\[ \alpha_m = 0.1 \frac{V + 25}{\exp \left( \frac{V + 25}{10} \right) - 1} \]
\[ \beta_m = 4 \exp \left( \frac{V}{18} \right) \]
\[ \alpha_h = 0.07 \exp \left( \frac{V}{20} \right) \]
\[ \beta_h = \frac{1}{\exp \left( \frac{V + 30}{10} \right) + 1}. \]

The maximal ionic conductances are given as:
\[ \bar{g}_K = 36 \text{ mS/cm}^2, \quad \bar{g}_{Na} = 120 \text{ mS/cm}^2, \quad \bar{g}_l = 0.3 \text{ mS/cm}^2. \]

The reversal potentials of potassium and sodium are:
\[ V_K = -77 \text{ mV}, \quad V_{Na} = 50 \text{ mV}. \]

The exact value of leakage reversal potential rendering the total ionic current zero at the resting potential is:
\[ V_L = -54.401 \text{ mV}. \]

The membrane capacitance is:
\[ C = 1 \mu F/cm^2. \]

We used the equations stated by Hodgkin and Huxley, including their original values, using the convention of the negative voltage and defining the rest potential as \(-65 \text{ mV}\). The original temperature of the HH experiment was 6.3 °C. Changes in temperature influence the time constants of the gating variables which multiply the \( \alpha \) and \( \beta \) parameters by the \( \Phi \) parameter as \( \Phi = 3^{(T - 6.3)/10} \) \[1\]. Note that the temperature also slightly impacts the rest potential of the axon. The \( I_{ext} \) parameter represents the current injected into the membrane.

The original radius in the HH model was 238 \( \mu m \), and the specific resistance was \( R = 35.4 \Omega \cdot cm \). We simulated a simple cylinder with a length of 2 cm with sealed terminations. The initial conditions were defined to set the voltage along the axon as the rest potential (\(-65 \text{ mV}\)). We set the derivative of voltage with respect to distance to zero at the boundaries. In order to avoid boundary condition effects, we first used axons which were sufficiently long (2 cm length for the studied radius). Then we examined the response for shorter axons reflecting the influence of boundaries. We used the Crank–Nicolson method \[34\] for the numerical simulation, and based our algorithm on \[48,49\].

To examine the response of current stimuli along the axon, we injected current into one end of a cylindrical cable-like axon and observed the response at the injection point and at the end of the axon (see Fig. 1).

The numerical simulation was performed using Matlab software. We chose the step sizes to be: \( \Delta x = 0.01 \text{ cm} \) and \( \Delta t = 0.01 \text{ ms} \). The units were: distance \([\text{cm}]\), voltage \([\text{mV}]\), current density \([\mu A/cm^2]\), capacitance \([\mu F/cm^2]\), conductance \([\text{mS/cm}^2]\), time \([\text{ms}]\) and frequency \([\text{AP/s}]\).

3. Results

3.1. Finite train of action potentials

In the cable model, as in the space clamp model, a constant low current stimulus leads to the generation of a single action potential. Higher current stimuli may generate infinite trains of action potentials. In a narrow range of currents between these two regimes, there is a stimulus regime that leads to a controllable finite number of spikes, where only a finite number of spikes develop, after which the response returns to constant voltage. This response is transient and therefore depends on the initial conditions. The occurrence of this phenomenon is independent of axon length or radius, and exhibits similar behavior to that of the space clamp model. Fig. 2(a) and (b) presents an example of the generation of six action potentials, at the stimulus point (Fig. 2(a)) and along the axon (Fig. 2(b)) for an injected current stimulus of 0.7072 mA/cm², in a 2 cm length axon with a 238 \( \mu m \) radius (as the original HH radius). It can be seen that at the point of stimulus, the action potential amplitudes within the finite train decrease with time, though farther along the axon the spikes converge to equal amplitudes. The intervals between the spikes increase from 18 ms between the first two spikes, to 20 ms between the last pair of spikes. These interval differences remain along the axon. Fig. 2(c) presents in a stair-like diagram the number of action potentials as a function of the current stimulus in the ‘finite train of action potentials’ regime for long axons. It can be seen that the diagram structure converges at a certain current, beyond which infinite train of action potentials are generated.
3.2. Spike series separated by failures

Further increase in the current stimuli above the currents that produce infinite trains leads to the generation of single action potentials resembling the weak stimuli. Between these current regimes, there is the ‘spike series separated by failures’ region. In this current region, a controllable number of spikes are followed by a failure. This borderline phenomenon behavior strongly depends on axon length. Interplay between currents along the axon and through the membrane is the reason for partial development of spikes and failures, beginning at the site of stimulation.

In Fig. 3 we present simulation results for an axon of 2 cm length with a radius of 238 μm. The resulting membrane voltages for two different current stimuli are plotted and represent examples of typical behaviors. For a current stimulus of 3.7 mA/cm²,
we observe alternating action potentials and failures (Fig. 3(a)). The voltage generated at the stimulus point (indicated as location 0) creates a pattern of a ‘single spike followed by a single failure’ with low amplitudes. As the electrical response propagates along the axon, the higher amplitude oscillations become full action potentials with almost identical amplitudes, whereas the failures remain unchanged (the blue curve). Farther along the axon, the ‘failed’ spikes are almost obscured and the response is very nearly ‘all or none’ (the red curve). For smaller radii, this disappearance occurs at a shorter distance along the axon, demonstrating an axonal length-radius ratio effect. For a lower current stimulus of 3.6 mA/cm², every third action potential fails (Fig. 3(b)). Note that the ‘failures’ are represented by a double period in the phase plane. This phenomenon only exists in the full HH model and not the reduced models that contain only two variables, because of the trajectories’ inability to intersect in a loop. The spike series lengthens as the current stimulus decreases, while the current required for spike initiation decreases. The larger the number of spikes before failure, the narrower the range in which this pattern exists. This behavior creates a convergence structure, resembling the behavior at the ‘finite train of action potentials’ region.

Fig. 3(c) represents the bifurcation diagram of the membrane voltage at the injection point of the axon. The maximum and minimum voltage values are plotted for the entire stimulus range. Spikes produced within 100 ms after the onset of the stimulus were discarded to exclude the transition state. The region in which the spike series are separated by failures occurs between currents around 3.5 mA/cm² and 4 mA/cm². Excluding this regime, the plot structure is qualitatively similar to that of the space clamp model bifurcation diagram. Fig. 3(d) represents the staircase-like systematic diagram of the response to current stimuli presented in Fig. 3(c). It demonstrates the different response types at the different current stimuli regions. Fig. 3(e) is an enlargement of the ‘spike series separated by failures’ area in Fig. 3(c), demonstrating the convergence behavior. In this graph, we can distinguish between current ranges that lead to diverse numbers of spikes before failures. Between these ranges there are narrow regions with varied spike amplitudes, indicating irregular behaviors.

3.3. The influence of axonal length

The behavior in the ‘spike series separated by failures’ regime is highly influenced by axonal length. For long axons, we see the typical behavior of any number of spikes before failure occurs. However, for shorter axons, the activity pattern is different and more firing patterns are observed.

We examined the activity patterns for axon lengths shorter than 2 cm (axon radius of 238 μm). Fig. 4(a) presents the bifurcation diagram of 1 cm axon length. Fig. 4(b) is an enlargement of the ‘spike series separated by failures’ regime, representing development of only one or two action potentials before failure (the figure includes both maxima and minima values per spike). In a narrow range between the current stimuli levels which leads to double action potentials and that which results in a single action potential-failure pattern, an irregular behavior occurs. Fig. 4(c) illustrates the case of a current stimulus of 4.064 mA/cm² in which the number of spikes between failures is not constant. A slight change in the current stimulus leads to a significantly different response.

The bifurcation diagram of 0.75 cm axon length is presented in Fig. 4(d) with an enlarged image displayed in Fig. 4(e). A distinction can be made between the two types of behaviors at the edges of this region: the left edge is a spike series followed by failure, and the right is a series of failures followed by a spike. For example, a current stimulus of 5.67 mA/cm² leads to the development of only one spike for every three failures (Fig. 4(f)). Fig. 4(g)–(i) represent bifurcation diagrams for 0.5 cm, 0.3 cm and 0.1 cm axon lengths, respectively. It can be seen that for these short axonal lengths, the ‘spike series separated by failures’ region shrinks and disappears. The bifurcation diagram attained for shorter lengths becomes similar to that of the space clamp model.

Fig. 5 exhibits a systematic analysis of the firing patterns as a function of axonal length and current stimulus. The response is plotted for lengths between 0.1 cm and 2 cm. It can be seen that for a radius of 238 μm, 2 cm length of the axon is considered sufficiently long. For that radius, all axons above 2 cm in length demonstrate similar behavior. The largest middle area in the graph indicates the ‘trains’ regime, where consecutive action potential trains are generated. The adjusted regime for higher currents, marked as ‘1:1’, indicates a single spike followed by a single failure response. Between these two regimes, several spikes followed by a failure occur. These narrow regimes are separated by ranges of irregular responses, labeled in gray. The ‘blockage’ regime indicates the activity response for high current stimulus, where there is no development of spike trains and only a single spike can develop. This phenomenon occurs when high voltage applied, causing the ion channels to fail relieving sodium activation blocking spike trains.

For long axons (longer than 1.2 cm), any number of spikes may develop before a failure. As the axon length decreases, this pattern begins to collapse with a minimum occurrence of action potentials per failure at an approximate value of 1 cm. At axon lengths below 0.8 cm, the generation of more than two action potentials before a failure re-emerges. In lengths shorter than 0.9 cm, an additional phenomenon occurs for higher current stimuli in the ‘spike series separated by failures’ region; namely, frequency of failures becomes greater than that of action potentials. When axon length further decreases, the two sides of this regime converge and collapse, disappearing at an approximate axon length of 0.5 cm. Shorter axons may generate only action potential trains with no failures.

3.4. The axonal length-radius ratio

For any axonal radius, the pattern of response diagram is similar to that presented in Fig. 5 (comparison not shown). For each radius, a range of lengths and current stimuli can be defined leading to the same pattern of response. For long axons (above
Fig. 4. Bifurcation diagrams for different axonal lengths with axonal radius of 238 μm. (a) Bifurcation diagram for 1 cm length. (b) Zoom into the ‘spike series separated by failures’ regime in 4(a). (c) An irregular response to current stimulus of 4.064 mA/cm² at the end of the 1 cm length axon. (d) Bifurcation diagram for 0.75 cm length. (e) Zoom into the ‘spike series separated by failures’ regime in (d). (f) Single spike followed by multiple failures for a stimulus of 5.67 mA/cm² at the end of the 0.75 cm length axon. (g) Bifurcation diagram for 0.5 cm length. (h) Bifurcation diagram for 0.3 cm length. (i) Bifurcation diagram for 0.1 cm length.

Fig. 5. Response diagram as a function of axonal length and current stimulus. The gray areas indicate irregular responses. For each regime, the number of spikes (left) and number of failures (right) are indicated.
1.5 cm in Fig. 5) the response diagram is stable. As the axonal radius increases, the membrane area increases. Greater current is required for stimulation and the velocity of action potential propagation along the axon accelerates. Therefore, the definition of ‘long axons’ depends on the axonal radius. The ratio between axonal radius and effective length required for similar behavior for short axons is the predictable square root relation, meaning the length proportional to the square root of the axon radius. For a sufficiently long axon, axonal radius does not affect firing pattern behavior. Thus, increasing axonal radius is equivalent to decreasing axonal length.

3.5. The action potential train frequency

Fig. 6 represents the frequency of the action potential train per current stimulus (frequency–current curve) for the three different axonal lengths of 2 cm (Fig. 6(a)), 1 cm (Fig. 6(b)), and 0.5 cm (Fig. 6(c)). To determine the frequency of the action potential trains, we measured the number of local maxima of the voltage response per second for each current stimulus. The first 100 ms after onset of stimulus were discarded to exclude the transition state.

For a long axon of 2 cm (Fig. 6(a)), the lowest current stimulus that generates an infinite train of action potentials is 0.71 mA/cm², resulting in a frequency of 52 AP/s. As the current stimulus grows, the frequency increases as well, reaching a maximum frequency of 97 AP/s at 2.96 mA/cm², followed by a brief decrease in frequency (down to 88 AP/s). For higher currents (between 3.6 mA/cm² and 4 mA/cm²), a small arch of frequencies is observed representing a regime where every other oscillation fails. Therefore, the frequency is approximately half of the maximum frequency. In the current range between the two arches, there are transitory curves. As the axon length decreases, the maximum frequency increases. For example, for 0.5 cm axonal length, the maximum frequency reaches 126 AP/s (Fig. 6(c)) and the small arch almost vanishes.

4. Discussion

In this study, we explored the influence of axon geometry on electrical activity by numerical simulation of the Hodgkin–Huxley cable model, charting a spatio-temporal analysis. We examined electrical response along the axon as a result of constant current stimuli applied at one edge of the axon. There are three known typical activity responses: the ‘single spike’ response for low current stimuli, ‘infinite trains of action potentials’ for mid current stimuli and again ‘single spike’ response for high current stimuli [27,28,30]. Here, we observed two borderline phenomena between the known ‘single spike’ and the ‘infinite trains of action potentials’ regimes: the ‘finite train of action potentials’ and the ‘spike series separated by failures’. For the first phenomenon, we demonstrated the ability to set the length of the spike series accurately in a controlled manner. We found that as the current stimulus increases within this regime, the number of spikes per train increases, reaching an infinite train response asymptotically at a finite critical stimulus. Higher current stimuli revealed the second unique phenomenon, the ‘spike series separated by failures’. Within this regime, the number of spikes before a failure can be adjusted from single spikes to a series of any number of spikes. This phenomenon also includes specific cases of single spikes followed by several failures and regimes exhibiting irregular behavior. To examine the effect of morphology on these patterns of activity, we tested the response to current stimuli along varying axonal lengths and a constant diameter. We found that axonal morphology plays a critical role in electrical response. Changing axon length modified electrical response dynamics; the ranges of current stimuli that lead to the described various responses, have changed with axonal length. In addition, several patterns were found to be unique to specific lengths. For instance, a train of one spike followed by multiple failures occurs only in mid-range axonal lengths (in our example it is around ten times the diameter). Our results have demonstrated a morphology-dependent firing pattern scheme (Fig. 5). Interestingly, the phenomenon of action potential failures along the axon creating intermittent trains was also observed experimentally. Swelling sites along the axon and branching points have been shown to trigger the inability of action potentials to develop [50–52]. More complex stimuli lead to failures also along smooth axons [53–56].

Spike failure phenomenon, which may be an important tool in modulating information, is directly derived from the axonal axial space. The activity in the axon is combined of two currents, an outward radial flow through the membrane and an internal continuous current along the axon. In general, the balance between these two currents as dictated by membrane ion channels,
depends on time and voltage and may lead to inactivation and spike failures [36]. We have shown that between the two regimes, ‘trains’ and ‘blockage’ (Fig. 5), there is a mid-regime that is highly sensitive to the membrane current leading to an instability response. Within this mid-regime the response alternates between these two states, creating the ‘spike series separated by failures’ pattern. We have demonstrated that the failures are already created close to the stimulus point, where high frequency small amplitude oscillations are generated. Only some of these oscillations lead to the opening of ion channels, reflected by a sharp-tip of voltage above the smooth oscillation (the black line in Fig. 3(a) and (b)). Farther along the axon, these oscillations develop to full spikes, while the smooth oscillations disappear (red lines).

We have demonstrated that for short axons (proportional to the square root of the radius) the morphology is a dominant factor in the pattern of activity. The sealed end of the axon affects the balance between the two axonal currents, radial and axial. The high impedance at the end of the axon prevents leakage of current along and outside the axon. For very short axons the influence of the axial current along the axon is almost diminished, until the spatial coupling has no longer effect and no spike failures occur, as in the space clamp model. In the space clamp model, non-constant current stimuli are needed to generate such activity patterns. Quasi-periodic and chaos firing patterns have been reported for the space clamp model as a result of different types of stimulations including sinusoidal current stimuli [57–61], neurons exposed to electric field [62–66], and periodic sequence pulse stimulation [67–69]. The controlled HH model, that includes a dynamic feedback filter, allows modification of the Hopf bifurcation characteristics. Controlling the bifurcation range may enable establishment of novel therapeutic approaches for dynamical diseases [70,71].

Our results demonstrate a tight relationship between the geometry and the axonal activity. The sensitivity of electrical response to morphology may be interpreted as a tool for modulating neuronal activity. The presented firing patterns demonstrate a potential role of morphology as innate mediator of neuronal activity, in addition to other factors, such as external ion concentrations. It may also raise the question whether different patterns of activity reflect a purposely mechanism for information coding, or, maybe an outcome of physical constraints. Specifically, our results demonstrate different activity patterns along demyelinated axons in a simple model system, the squid, but may be of high relevance for axons in mammalian models, as the gray matter in the brain, which are demyelinated as well. Morphological deformations of the axon may change the model control parameters, leading to abnormal axonal dynamics. Such disruptions may shed light on the trigger of dynamical diseases such as Parkinson’s and epilepsy [72,73], leading to potential treatments that can be offered in order to compensate neuronal deformations. For example, affecting the ‘neuronal structure’ virtually can be performed by modification of the axoplasm resistance. For very short axons the high impedance at the end of the axon prevents leakage of current along and outside the axon. For very short axons the influence of the axial current along the axon is almost diminished, until the spatial coupling has no longer effect and no spike failures occur, as in the space clamp model. In the space clamp model, non-constant current stimuli are needed to generate such activity patterns. Quasi-periodic and chaos firing patterns have been reported for the space clamp model as a result of different types of stimulations including sinusoidal current stimuli [57–61], neurons exposed to electric field [62–66], and periodic sequence pulse stimulation [67–69].

Moreover, it has been shown that in other biological systems, including neural networks, activity at the edge of chaos close to critical dynamics is optimal for information processing purposes and robustness [74,75]. Our results demonstrate complex irregular response already at the single cell level. Analytical study of the space clamp model has been previously performed in [32] and others. For the more complex cable model, such analysis is hard to perform and has been previously studied only under assumptions such as ‘traveling wave’ and ‘reduced models’ [1,76,77]. In this work we have conducted a detailed mapping of the full cable model, which necessitates a numerical approach in order to study the influence of morphology on neuronal activity. We have revealed high sensitivity to stimulation signals and geometry, demonstrating a potential ability to control patterns of activity. These novel results may shed light on physiological information coding mechanisms at the cellular level and may contribute to the understanding of neural dynamical diseases and pathological conditions.

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