

New Mechanism for Neural Pattern Formation

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(Received 8 September 1995)

We show how the diffusive effects of a neuron's dendritic tree can induce a Turing-like instability in a purely excitatory or inhibitory recurrent neural network. A crucial feature of the model is the existence of a correlation between the location of a synaptic connection on the tree and the relative separation of the associated neurons within the network. [S0031-9007(96)00385-7]

PACS numbers: 87.10.+e, 07.05.Mh, 82.40.Bj

The standard mechanism for pattern formation in spatially organized neural network models is based on the competition between local excitatory and more long-range inhibitory interactions between cells [1, 2]. Examples include a model of ocular dominance stripe formation in the visual cortex [3, 4] and a model for the generation of visual hallucination patterns [5]. In these models one specifies the distribution of neural connections solely as a function of the separation between presynaptic and postsynaptic neurons. However, this neglects an important aspect of the synaptic organization of cortex, namely, the spatial location of a synapse on the dendritic tree of a neuron [6]. There is growing evidence that dendritic structure could play an important role in information processing [7, 8]. Of particular interest here is the observation that the dendritic location of a synapse is often correlated with the relative positions of cells in the cortex. For example, recurrent collaterals of pyramidal cells in the olfactory cortex feed back onto the basal dendrites of nearby cells and onto the apical dendrites of distant pyramidal cells [6, 7]. A similar feature is thought to occur in other areas of cortex (see the canonical microcircuit of Douglas, Martin, and Whitteridge [9]). Thus a synapse tends to be located further away from the soma or cell body as the separation between neurons increases. This results in a reduction in the effectiveness of the synaptic connection due to diffusion along the dendritic tree. On the other hand, there is growing evidence that such a reduction may be compensated by a number of mechanisms including an increase in the density of synapses at distal locations and voltage-dependent gates on dendritic spines [8].

In this Letter, we show that the passive membrane properties of a neuron's dendritic tree can induce spatial pattern formation in a purely excitatory or inhibitory recurrent network. This provides an alternative mechanism for neural pattern formation that relies on the combined effect of (i) diffusion along the dendritic tree and (ii) recurrent interactions via axodendritic synaptic connections. To expound the basic idea, we shall follow Ermentrout and Cowan [5] and consider a one-dimensional network of analog neurons distributed along the x axis. Let $U(x, t)$ denote the somatic membrane potential of the neuron located at $x \in \mathfrak{R}$ at time t . The output firing rate

of the neuron is written as $f(U(x, t))$ where f is a nonlinear sigmoid function that is strictly monotonically increasing and bounded. We take $f(U) = 1 + \tanh(\kappa U)$ where κ is a gain parameter. For simplicity, the dendritic tree of a neuron is represented by a uniform one-dimensional cable. The dendritic membrane potential at the point $\xi \in \mathfrak{R}$ on the cable is denoted by $V(\xi, x, t)$. Let $W(\xi, x, x')$ be the connection from a neuron at x' impinging on a synapse located at ξ on the dendritic cable of a neuron at x .

Using standard cable theory [10], one can write down the following equations for U and V :

$$\begin{aligned} \frac{\partial U}{\partial t} &= -\frac{U(x, t)}{\hat{\tau}} - I(x, t), \\ \frac{\partial V}{\partial t} &= D \frac{\partial^2 V}{\partial \xi^2} - \frac{V(\xi, x, t)}{\tau} + I(\xi, x, t) \\ &\quad + \int_{-\infty}^{\infty} W(\xi, x, x') f(U(x', t)) dx' + I_{\text{ext}}(\xi, x), \end{aligned} \quad (1)$$

where $I(x, t) = \int_{-\infty}^{\infty} I(\xi, x, t) d\xi$ and $I(\xi, x, t) = \rho(\xi) [U(x, t) - V(\xi, x, t)]$. Here $I(\xi, x, t)$ is the current density flowing from the soma to the cable at ξ and $\rho(\xi)$ is a conductance (in appropriate units). We assume that the function $\rho(\xi)$ has compact support, i.e., it is localized to the contact region between the soma and the dendritic cable. We have also included an external bias I_{ext} . In order to simplify our analysis, we shall assume that $\tau^{-1} + \rho = \epsilon$ such that ϵ is independent of ξ and set $\hat{\tau}^{-1} + \int \rho(\xi) d\xi = \hat{\epsilon}$. Furthermore, we impose the homogeneity condition $W(\xi, x, x') = W(\xi, x - x')$ with $W(\xi, x)$ a symmetric function of x .

In the limit of zero diffusion ($D \rightarrow 0$) with $\epsilon \gg \hat{\epsilon}$, V can be treated as a fast variable and Eqs. (1) and (2) reduce to the standard form

$$\begin{aligned} \frac{\partial U}{\partial t} &= -\hat{\epsilon} U(x, t) + \int_{-\infty}^{\infty} W(x - x') f(U(x', t)) dx' \\ &\quad + I_{\text{ext}}(x), \end{aligned} \quad (3)$$

with $W(x) = \epsilon^{-1} \int W(\xi, x) \rho(\xi) d\xi$. Equation (3) is the basic model of nerve tissue studied by various authors [1, 2, 5, 11]. It is known from these works that in the case of local excitation and long-range inhibition one

can obtain large-scale spatially organized neural activity. Suppose, for simplicity, that the external bias $I_{\text{ext}}(x) = -\int_{-\infty}^{\infty} W(x-x') dx'$ so that the resting state $U(x) = 0$ for all x is a fixed point of the dynamics. In an analogous fashion to Turing or diffusion-driven instabilities in reaction-diffusion systems [1, 12], one finds that the homogeneous steady state is stable to small uniform perturbations but is (linearly) unstable to small spatially varying perturbations of the form $U(x, t) = e^{\nu t + ipx}$ where p is the wave number of the pattern and ν is the so-called growth factor.

We wish to derive conditions for a Turing-like instability in the full model described by Eqs. (1) and (2). We assume that the homogeneous zero solution $U(x) = 0$, $V(\xi, x) = 0$ is a fixed point of the system by taking a negative external bias $I_{\text{ext}}(\xi, x) = -\int_{-\infty}^{\infty} W(\xi, x, x') dx'$. Substitution of the solution $U(x, t) = Ae^{\nu t + ipx}$ and $V(\xi, x, t) = B(\xi)e^{\nu t + ipx}$ into Eqs. (1) and (2) linearized about the homogeneous zero solution $U(x, t) = 0$, $V(\xi, x, t) = 0$ yields

$$(\epsilon + \nu)B(\xi) = D \frac{d^2 B}{d\xi^2} + [\kappa \tilde{W}(\xi, p) + \rho(\xi)]A, \quad (4)$$

$$(\hat{\epsilon} + \nu)A = \int_{-\infty}^{\infty} \rho(\xi)B(\xi) d\xi, \quad (5)$$

where $\tilde{W}(\xi, p)$ is the Fourier transform of $W(\xi, x)$ with respect to x . On Fourier transforming Eq. (4) with respect to ξ and using Eq. (5), we obtain the dispersion relation $\Delta(\nu, p) = 0$ where

$$\Delta(\nu, p) = \nu + \hat{\epsilon} - \int_{-\infty}^{\infty} \frac{\tilde{\rho}(-k)[\kappa \tilde{W}(k, p) + \tilde{\rho}(k)] dk}{\epsilon + \nu + k^2 D} \frac{dk}{2\pi} \quad (6)$$

with $\tilde{W}(k, p) = \int_{-\infty}^{\infty} d\xi e^{ik\xi} \int_{-\infty}^{\infty} dx e^{ipx} W(\xi, x)$ and $\tilde{\rho}(k) = \int_{-\infty}^{\infty} d\xi e^{ik\xi} \rho(\xi)$.

The condition for a Turing-like instability can be expressed as follows: (i) $\Delta(\nu, 0) \neq 0$ for all $\text{Re} \nu \geq 0$ and (ii) there exists a pair $(\nu(p), p)$ such that $\Delta(\nu(p), p) = 0$ with $\text{Re} \nu(p) \geq 0$ and $p \neq 0$. It follows from Eq. (6) that these conditions depend crucially on the distribution of axodendritic connections within the network. Motivated by our previous observations concerning the synaptic organization of cortical tissue, we make the following assumptions concerning the distribution $W(\xi, x)$: (a) The average distance of a synapse from the soma $|\xi|$ increases with the separation $|x - x'|$ between neurons. This property can be realized by a distribution of the form

$$W(\xi, x) = \frac{W(\xi)}{\sqrt{2\pi}\sigma} [e^{-(x-\xi)^2/2\sigma^2} + e^{-(x+\xi)^2/2\sigma^2}], \quad (7)$$

where σ determines the degree of spread of axon collaterals about the points $\bar{\xi} = \pm x$. (b) The density of synapses is larger at distal locations. We model this by taking

$$W(\xi) = W_0 + W_1|\xi| \quad (8)$$

for constant W_0, W_1 . The weights are assumed to be either purely inhibitory ($W_{0,1} < 0$) or purely excitatory ($W_{0,1} > 0$). For simplicity, we impose the additional condition that the soma is connected to the dendritic cable at a single point $\xi = 0$ so that $\rho(\xi) = \rho_0 \delta(\xi)$. [More generally, it is reasonable for $W(\xi)$ to be approximately constant over the domain where $\rho(\xi) \neq 0$.] Substituting Eqs. (7) and (8) into Eq. (6) gives

$$\Delta(\nu, p) = \hat{\epsilon} + \nu - \frac{\rho_0^2}{2} \sqrt{\frac{1}{\hat{\nu}D}} - 2\kappa\rho_0 F(\nu, p), \quad (9)$$

$$F(\nu, p) = \left[W_0 + W_1 \sqrt{\frac{D}{\hat{\nu}}} \frac{\hat{\nu} - Dp^2}{(\hat{\nu} + Dp^2)} \right] \frac{e^{-p^2\sigma^2/2}}{\hat{\nu} + p^2D}, \quad (10)$$

where $\hat{\nu} = \nu + \epsilon$.

We shall use Eq. (9) to prove that a purely inhibitory or a purely excitatory network with a distribution of axodendritic connections satisfying Eqs. (7) and (8) can undergo a Turing-like instability. To reduce the number of free parameters, we make some further simplifications without altering the essential behavior. First, we set $\sigma = 0$, which corresponds to the case of monosynaptic connections $W_0 = 0$ and $2\kappa\rho_0 W_1 = W \neq 0$. (Note that it is straightforward to show that a Turing instability cannot occur if $W_1 = 0$.) Second, we neglect the ν dependence of the third term on the right-hand side of Eq. (9) and set $\epsilon_0 = \hat{\epsilon} - \rho_0^2/2\sqrt{\epsilon D}$. Finally, the units of length and time are fixed by setting $\epsilon = D = 1$. Equation (9) then reduces to the simpler form $\Delta(\nu, p) = \epsilon_0 + \nu - WH(\nu, p)$ where

$$H(\nu, p) = \frac{1}{\sqrt{1+\nu}} \frac{1-p^2+\nu}{(1+p^2+\nu)^2}. \quad (11)$$

A number of properties of $H(\nu, p)$ should be noted: (i) $H(\nu, 0) \geq H(\nu, p)$ for all ν , and $H(\nu, 0)$ is a monotonically decreasing function of ν with $H(0, 0) = 1$. (ii) $H(0, p) < 0$, for all $p > 1$ and $H(0, \sqrt{3}) \leq H(\nu, p)$ for all p, ν . A solution to the dispersion relation for a fixed p may be obtained graphically by considering the intercept of $H(\nu, p)$ with the curve $y(\nu) = W^{-1}[\epsilon_0 + \nu]$. (By symmetry we need only consider positive values of p .)

First, consider the case of a purely excitatory network. Property (i) of $H(\nu, p)$ shows that the zero solution is stable provided that $0 < W < \epsilon_0/H(0, 0)$ and is unstable otherwise. However, this does not lead to a Turing-like instability since the range of wave numbers over which the system is unstable invariably contains the origin. Now consider the case of a purely inhibitory network ($W < 0$). It follows from property (ii) that for $|W|$ sufficiently small there does not exist a solution to the equation $\Delta(\nu, p) = 0$ when $\nu \geq 0$, which implies that the zero solution is linearly stable. However, as $|W|$ increases, a critical value $W_c \equiv \epsilon_0/H(0, \sqrt{3}) = -8\epsilon_0$ is reached for

which $\Delta(0, \sqrt{3}) = 0$ so that $\Delta(\nu(p), p) = 0$, $\nu(p) \geq 0$ over an interval $[\sqrt{3}, p(W)]$ when $W < W_c$. Thus the conditions for a Turing-like instability hold. One expects the resulting pattern to have a spatial variation closely related to the wave number of the fastest growing linear mode within the range $[\sqrt{3}, p(W)]$. The existence of a stable spatial pattern can be confirmed numerically for the full nonlinear model as shown in Fig. 1.

So far we have assumed that the growth factor is real. If we consider ν to be complex then it is possible for a Turing-like instability to occur due to a pair of complex roots crossing the imaginary axis. Such a scenario is a precursor for dynamic pattern formation in which there exists an oscillating, spatially varying pattern of network activity. [In order to obtain such behavior in the reduced system (3), one would require at least two distinct populations of neurons coupled together [2, 5].] A necessary condition for dynamic pattern formation is that there exists a pair $\omega, p \neq 0$ such that $\Delta(i\omega, p) = \epsilon_0 + i\omega - H(i\omega, p) = 0$ with H defined in Eq. (11). (Without loss of generality, we take $\omega, p \geq 0$.) Equating real and imaginary parts leads to the pair of equations

$$\frac{\epsilon_0}{W} = H_1(\omega, p) \equiv A_+(\omega)a(\omega, p) + \omega A_-(\omega)b(\omega, p), \tag{12}$$

$$\frac{1}{W} = H_2(\omega, p) \equiv A_+(\omega)b(\omega, p) - A_-(\omega)a(\omega, p)/\omega,$$

with $A_{\pm}(\omega) = ([\sqrt{1 + \omega^2} \pm 1]/2)^{1/2}$ and

$$a(\omega, p) = \frac{(1 - p^2)(1 + p^2)^2 + \omega^2 + 3\omega^2 p^2}{[(1 + p^2)^2 + \omega^2]^2}, \tag{13}$$

$$b(\omega, p) = \frac{(1 + p^2)^2 - \omega^2 - 2(1 - p^4)}{[(1 + p^2)^2 + \omega^2]^2}.$$

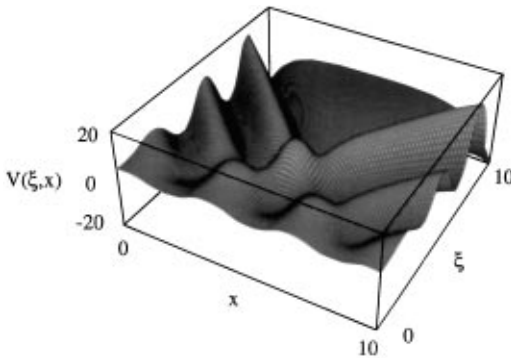


FIG. 1. Spatial pattern formation in a one-dimensional inhibitory network of neurons distributed over the finite interval $[0, L]$ and evolving according to Eqs. (1) and (2). The steady-state dendritic potential $V(\xi, x)$ is plotted as a function of dendritic coordinate ξ and network coordinate x . The dendritic tree of each neuron is modeled as a finite cable of length L attached to the soma at one end such that $U(x) = V(0, x)$ and $\partial V(\xi, x)/\partial \xi|_{\xi=L} = 0$ at the other end. The dimensions of various physical quantities are fixed by setting $D = \epsilon = \kappa = 1$. Also $L = 10$, $\epsilon_0 = 1.0$, $\rho(\xi) = \delta(\xi)$. The weight distribution is $W(\xi, x) = \xi W_1[\delta(\xi - x) + \delta(\xi + x)]$ with $W_1 = -10$.

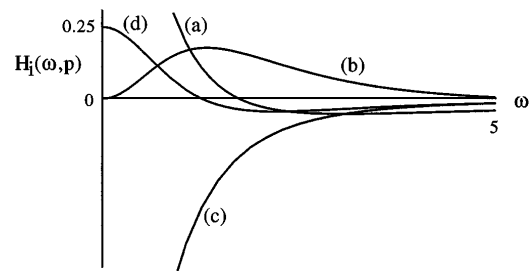


FIG. 2 Plot of function $H_i(\omega, p)$, $i = 1, 2$, against ω for wave numbers $p = 0, 1$. (a) $i = 1, p = 0$; (b) $i = 1, p = 1$; (c) $i = 2, p = 0$; (d) $i = 2, p = 1$.

The functions H_1 and H_2 are plotted in Fig. 2. It can be seen that for $p = 1$ there exists a unique solution $\omega(p)$ to $H_1(\omega(p), p) = \epsilon_0 H_2(\omega(p), p)$ with $H_{1,2}(\omega(p), p) \geq 0$; there is no such solution when $p = 0$. Hence a dynamic Turing instability can arise in the case of an excitatory network. The bifurcation point is obtained by determining the minimum positive value of W for which $W^{-1} = H_2(\omega(p), p)$ has a solution. The result when $\epsilon_0 = 1$ is $p \approx 0.8$, $\omega \approx 0.1$, $W \approx 7.3$. [A dynamic Turing instability does not arise for an inhibitory network since there exists a solution to $H_1(\omega(p), p) = \epsilon_0 H_2(\omega(p), p)$ with $H_{1,2}(\omega(p), p) \leq 0$ at $p = 0$.]

Although we have restricted ourselves to linear stability analysis, it is possible to establish the existence of spatial patterns at the nonlinear level using bifurcation theory along similar lines to Ref. [5]. We briefly indicate how to proceed in the case of a static pattern. To simplify the analysis we impose periodic boundary conditions such that $U(x + \Lambda) = U(x)$ for all x , etc. The solution space is thus restricted to continuous, bounded, periodic functions. Let λ be a bifurcation parameter associated with the weight distribution; that is, set $W(\xi, x) = \lambda w(\xi, x)$ where w is independent of λ . Suppose that as λ is increased a critical value λ_c is reached signaling the onset of a Turing-like instability. At the critical point $\lambda = \lambda_c$, we have $\Delta(0, p_c) = 0$, $p_c = 2\pi n_c/\Lambda \neq 0$ for some integer n_c with $\Delta(\nu, p)$ defined in Eq. (6). The basic idea is to investigate the nature of stationary solutions ($\nu = 0$) of Eqs. (1) and (2) around the bifurcation point. Since the dendritic membrane potentials appear linearly in these equations, we can eliminate them to obtain a nonlinear Volterra integral equation of the form

$$U(x) = \lambda \int_{-\infty}^{\infty} K(x - x') \tanh[\kappa U(x')] dx', \tag{14}$$

where $K(x) = \int_{-\infty}^{\infty} e^{-\sqrt{\epsilon/D}|\xi|} w(\xi, x) \rho(\xi) d\xi$. (A factor of $[2\hat{\epsilon}\sqrt{\epsilon D}]^{-1}$ has been absorbed into λ and a convolution term linear in $U(x)$ has been neglected for simplicity.) Set $\lambda - \lambda_c = \eta \lambda_1 + \eta^2 \lambda_2 + O(\eta^3)$, $U(x) = \eta U_1(x) + \eta^2 U_2(x) + O(\eta^3)$ and expand Eq. (14) as a perturbation series in η . This leads to an

ordered sequence of equations of the form $\hat{L}U_1(x) = 0$, $\hat{L}U_i(x) = [K * G_i](x)$, $i \geq 2$, where \hat{L} is the linear integral operator obtained by linearizing Eq. (14); that is, $\hat{L}U(x) = U(x) - \kappa\lambda_c[K * U](x)$, and $*$ denotes the convolution operator. Here G_i is a function of $U_k(x)$ and λ_k for all $k < i$. The first equation has the solution $U_1(x) = A \cos(p_c x)$ for some constant A with $1 = \lambda_c \kappa \tilde{K}(p_c)$. The remaining equations can be solved systematically provided that an associated set of solvability conditions is satisfied (the so-called Fredholm alternative [13]). Define the inner product of two periodic functions U, V by $(U, V) = \int_0^{2\pi/\Lambda} U(x)V(x) dx$. The solvability conditions are then generated by taking the inner product of each equation with respect to the lowest order solution U_1 and exploiting the fact that the operator \hat{L} is self-adjoint, that is, $(U, \hat{L}V) = (\hat{L}U, V)$. [Recall that $W(\xi, x)$ is a symmetric function of x .] The result is $(U_1, \hat{L}(K * G_i)) = 0$ for all $i \geq 2$. Using the solvability conditions for $i = 2, 3$, it can be shown that $\lambda_1 = 0$ and $\lambda_2 = \kappa^2 \lambda_c A^2 / 4$. The fact that λ_2 is positive indicates that one has a supercritical bifurcation, which is generally associated with the formation of a stable pattern.

In conclusion, the above results establish analytically a mechanism for pattern formation in which the diffusive effects of the dendritic tree play a crucial role. In the limit of zero diffusion, Eq. (3), the effective weight distribution defined by Eqs. (7) and (8) becomes $W(x) = (\sigma \epsilon \sqrt{\pi/2})^{-1} W_0 \rho_0 \exp(-x^2/2\sigma^2)$; such a weight distribution cannot lead to a Turing instability. As noted previously, we also require $W(\xi)$ to be an increasing function of $|\xi|$. This provides a competitive mechanism that counteracts the effective weight reduction due to diffusion. Our results are robust with respect to the particular choice of $W(\xi)$. For example, one could replace the linear function in Eq. (8) by a quadratic or cubic function. More generally, since a Turing instability is structurally stable, our conclusions do not depend on the various simplifying assumptions introduced for mathematical clarity. Of course, having established the existence of a new mechanism for pattern formation, it is important to explore how the full nonlinearities of the system effect the shape and stability of the resulting patterns, as well as the precise dependence on the various biological and physical parameters of the system. Therefore, we are currently carrying out detailed numerical simulations of Eqs. (1) and (2), the results of which will be presented elsewhere.

There are a number of possible extensions of this work. First, a study of more general choices of dendritic tree topology. Here one would need to solve Eq. (4) with appropriate boundary conditions at the terminal nodes and branching nodes of the tree. One could, for example, use the Green's function approach developed by the author elsewhere [14]. Second, to consider the role of dendritic structure in networks of "integrate-and-fire" neu-

rons. This would involve replacing $f(U)$ in Eqs. (2) or (3) by a series of delta-function spikes and resetting U after each spike. Recent work has shown the emergence of collective excitations in integrate-and-fire networks with local excitation and long-range inhibition [15, 16], as well as for purely excitatory connections [17, 18]. Although a form of dendritic interaction has been included in these works using time delays and synaptic transfer functions, as far as the author is aware, no explicit connection has been made between dendritic structure and pattern formation. An integrate-and-fire neuron is more biologically realistic than a firing-rate model, although it is still not clear that details concerning individual spikes are important for neural information processing. An advantage of firing-rate models from a mathematical viewpoint is the differentiability of the output function; integrate-and-fire networks tend to be analytically intractable without recourse to further approximations such as mean field theory [17].

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