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NEURAL ACTIVITY WAVES AND THE RELATIVE REFRACTORY STATES OF NEURONS

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1 Introduction

Waves of neural activity with velocities of $10 - 90$ cm/sec have been recorded with microelectrodes and electrode grids from hippocampal slices [Miles et al. 1988, Novak and Wheeler 1989] and with velocities of $20 - 30$ cm/sec from the cortical surface [Rosenbluth and Cannon 1942]. These waves take many forms, for example, travelling waves [Haglund et al. 1992, Petsche and Šterc 1968], standing waves [Nunez 1988] and rotating waves [Shevelev et al. 1993]. The organization of large masses of neurons into synchronized waves of activity lies at the basis of phenomena such as the EEG and evoked potentials.

One mechanism for the spread of neural activity involves the diffusion of K^+ []. This produces waves of spreading depression which travle at much slower velocities that the above phenomena, i.e. $1 - 3$ mm/min. For a discussion of spreading depression the reader is referred to the article by Winfree (this HANDBOOK).

Here we focus on activity waves which spread through neural networks by nerve conduction. In §2 we define the possible states of neurons in a network. Section 3 briefly reviews wave phenomena in neural networks. In particular we draw attention to the important role played by the relative refractory state of a neuron in shaping the spatio–temporal dynamics. In §4 we demonstrate how a relative refractory state can be incorporated into a continuum model for a neural network and in §5 we extend this analysis to a network equation model. An example of an interesting wave phenomena which can arise in such networks, i.e. a "meandering" standing wave pattern, is discussed in §6.

2 Relative refractory states

Consider a slab or slice of tissue with neural packing density $\rho(\underline{x})$, where ρ is the number of neurons per unit volume of tissue. At any time t, neurons are in one of three states: quiescent (sensitive), activated, or relative refractory. The duration Δ_a of the active state is commonly referred to as the "absolute refractory period" and lasts about 1 to 3 msec. The absolute refractory period is followed by a period of *relative refractoriness* of $\sim$ 5–200 msec,denoted by Δ_r, during which the neuron can be made to fire; however, a higher input is required than when the neuron was at rest. This relative refractory period arises because of the interplay of two processes: 1) the rapid decay of the threshold to its resting value (complete within 3–5 msec); and 2) the slower decay of the membrane hyper–polarization to its resting potential (complete within 60–200 msec).

All neurons in the central nervous system possess a relative refractory state. Itcan be anticipated that this state will have a non–trivial influence on network dynamics since the threshold depends on the time elapsed since the neuron last fired and hence on the past history of the neuron.

3 Wave phenomena

Our focus is on the wave phenomena which arise in networks composed on neurons in which the interneuronal connectivity is based on anatomical studies. Here we briefly discuss the wave properties which arise in neural networks in which the probability of connectivity, $P(r)$, is an exponentially decreasing function of inter-neuronal distance, r, i.e.

$$P(r) \sim \beta \exp(-r/\sigma)$$

where β and σ are positive constants [Sholl, 1956]. The relationship between neural connectivity and propagation velocity has recently become a topic of active interest [Chu, et al, 1994; Ermentrout and McLeod, 1993; Idiart and Abbott, 1993].

3.1 1–D lines

Most models of wave phenomena in neural networks neglect the relative refractory state. An early example is the Wilson–Cowan model describing wave propagation in a 1–D network composed and excitatory and inhibitory neurons.

When the inhibition is weak, a propagating wave can be initiated by a brief narrow pulse that gives rise to a pair of waves travelling in opposite directions from the region of stimulation. Fig.1 shows such an effect. Wave pairs are generated once per cycle as long as the stimulus pulse $P(x,t)$ persists, and each wave travels away from the locus of stimulation without attenuation. It follows that a very brief stimulus will generate a single wave pair, whereas a stimulus of longer duration will generate a succession of such pairs. The propagation velocity is a function of the connectivity parameters β and σ, whereas the wavelength depends upon P. For $\sigma_{ie} = 50\mu$m the propagation velocity is 4 cm/sec.

3.2 2–D excitatory slabs

The first authors to stress the importance of a relative refractory neural state for shaping the spatio–temporal dynamics of neural networks were Farley and Clark (for review see Farley, 1965]. Their numerical simulations of networks composed of excitatory integrate and fire neurons subjected to periodic point stimulation highlighted the intimate relationship between the tightness of the connectivity and the time course of the relative refractory state in shaping the wave properties.

If the network is more "loosely connected" and the recovery dynamics are adjusted so that re–firing in the refractory trough becomes possible, then it is possible for the whole network to undergo synchronous bulk oscillations [Farley, 1965]. In some cases these bulk oscillations can continue, in others they cease spontaneously. In addition to these large amplitude bulk oscillations, migrating localized oscillatory bursts of activity can occur.

As the network becomes tighter and the relative refractory state more prolonged, the network produces both travelling circular and spiral waves [Beurle 1962, Chu et al. 1994, Farley 1965, Milton et al. 1993]. Figure 2 shows, for example, a travelling spiral wave generated in response to prolonged point stimulation. Under these conditions a spiral wave does not arise if the relative refractory state is neglected.

For physiologically plausible choices of the parameters (i.e. a space constant of $\sim 250\mu$m these travelling waves have velocities of $20 - 25$ cm/sec with wavelength of $1 - 4$ mm. The probability that a spiral occurs in such networks increases with the tightness of the connectivity [Chu, et al, 1994; Farley, 1965]. Such networks have been shown to possess three stable states [Milton et al. 1993]: a state in which all neurons are at rest, and two self–maintaining states: one associated with spirals and another with disorganized spatial patterns. It has been suggested that the spiral waves arise via an exchange of stability in a manner similar to a sub–critical Hopf bifurcation. Moreover in such networks spirals may arise from certain initial conditions and not others. Finally, spirals do not appear to arise from central point stimulation if $P(r)$ is not a monotone decreasing function [Chu et al. 1994].

4 Neural continua model

Our goal is to derive a network equation which incorporates a relative refractory state as a first step towards understanding the spatio–temporal dynamics of the type shown in Figure 2. We are able to derive this model by discretizing the appropriate continua model of a neural network (/S 5). In this section we simply state the continua model (more details can be found in Wilson and Cowan, 1972; Mundel, Milton and Cowan, in preparation).

Let the proportions of neurons in the active, quiescent and relative refractory state be denoted, respectively, $q(\underline{x},t)$, $a(\underline{x},t)$ and $r(\underline{x},t)$, so that q + a + r = 1. It can be shown that the proportion of neurons, $e(\underline{x},t)dt$, activated at the point $\underline{x}$, in the interval dt in such a network is given by

$$\begin{aligned} e(\underline{x},t+\Delta)dt &= \left[1-\int_{t-\Delta_a}^{t} e(\underline{x},t')\,dt' - \int_{t-\Delta_r}^{t} r(\underline{x},t,t')\,dt'\right]\varphi[v-\theta_q]dt \\ &\quad + \int_{t-\Delta_r}^{t} \varphi[v-\theta(t-t')]\; r(\underline{x},t,t')\,dt'dt \end{aligned} \tag{1}$$

where Δ is the synaptic delay. The proportion of neurons which were activated during the interval $(t', t'+dt')$ and which are still refractory, is given by (Wilson and Cowan, 1972)

$$\frac{dr(\underline{x},t,t')}{dt} = -\varphi[v-\theta(t-t')]r(\underline{x},t,t') \tag{2}$$

subject to the initial condition $r(\underline{x},t,t) = e(\underline{x},t)$, the solution of which is:

$$r(\underline{x},t,t') = e(\underline{x},t')\; exp\left[-\int_{t'}^{t}\varphi[v(s)-\theta(s-t')]ds\right].$$

Given that the membrane time constant $\tau \sim 3-5$ msec, it is clear that any fluctuations faster than ~ 100 Hz will be filtered out by neural membrane impedances. Thus it is appropriate to define new variables, $\hat{y}$, as

$$\hat{y}(t) \;=\; \frac{1}{\tau}\int_{-\infty}^{t} e^{-(t-s)/\tau}\; y(\underline{x},s)ds \;\sim\; \frac{1}{\tau}\int_{t-\tau}^{t} y(\underline{x},s)ds$$

Thus the "time–coarse grained" evolution equation is

$$\begin{aligned} \tau\frac{dE(\underline{x},t)}{dt} &= -E(\underline{x},t) \\ &\quad + \left[1-\Delta_a E - \int_{t-\Delta_r}^{t} r(\underline{x},t,t')\,dt'\right]\varphi[v-\theta_q] \\ &\quad + \int_{t-\Delta_r}^{t}\varphi[v-\theta(t-t')]\; r(\underline{x},t,t')\,dt' \end{aligned} \tag{3}$$

where $E(\underline{x},t) = \frac{1}{\tau}\int_{-\infty}^{t} e^{-(t-t')/\tau} e(\underline{x},t')dt'$ is a time coarse grained version of $e(\underline{x},t)$. Equations (3)–(4) are the fundamental ones which govern the origin and propagation of fronts and waves in a slab of tissue.

5 Network Equations

The network formulation can be obtained from the continuum model in Section 2 by using the relation

$$\rho(\underline{x}) = \sum_{i=j}^{N} \delta(\underline{x} - \underline{x}_j). \tag{4}$$

where $\delta(\underline{x})$ is the multi–dimensional Dirac delta function. If we can rewrite (4) in integral form, neglecting the relative refractory period, and make use of (5) we obtain

$$\tau \frac{dE_i(t)}{dt} = -E_i(t) + [1 - \Delta_a E_i(t)] \ \varphi[v_i - \theta_q]. \tag{5}$$

where $E_i(t)$ is the fraction of time in a long time interval, during which the ith neuron is active, i.e. the mean *firing rate*, and where $v_i(t)$, its membrane potential, is given as:

$$v_i(t) = \sum_{j=1}^{N} w_{ij} E_j(t - \frac{|i-j|}{\nu}), \tag{6}$$

plus any external stimulus that may exist.

In going from (4) to a network equation incorporating relative refractoriness it is not reasonable to time coarse–grain over the relative refractory period, since many of the important dynamical effects occur on comparable time scales (i.e. most EEG rhythms of clinical relevance are in the frequency range of $1-40$ Hz). Thus in contrast to the absolute refractory period, a relative refractory period has a major influence on network dynamics. However, reducing (4) directly to a discrete network form is not straightforward. The difficulty arises because of the form of $\Theta(t-t')$ which depends on the time elapsed since the neuron last fired, and hence on the past history of the neuron.

A mathematically simpler way to do this is to assume that the neural membrane potential depends on one (or more) recovery or state variables, $w^k, k = 1, \cdots, n$; then we can incorporate a relative refractory state into the dynamics of a neuron by modifying (7) [Stein et al. 1974]:

$$\begin{aligned} v_i(t) &= \sum_{j=1}^{N} w_{ij} E_j(t - \frac{|i-j|}{\nu}) - w_i(t), \\ \frac{dw_i(t)}{dt} &= -\lambda w_i + \mu v_i. \end{aligned} \tag{7}$$

where λ and μ are constants. Numerical simulation suggests that the inclusion of such a state variable is sufficient to capture the dynamics of the relative refractory networks described above.

6 Neural activity waves

Numerical simulations of networks described by (10) show that this model is sufficient to captur the dynamics of the integrate and fire models described in /S 3.2 when $k = 1$. More complex dynamics, such as bursting patterns, become possible when $k > 1$.

As is clear from inspection of (10), networks which incorporate a relative refractory state necessarily evolve dynamically in a higher dimensional space. Thus complex wave phenomena can be seen. One example which we have observed is a migrating standing wave pattern that resembles a meandering checkerboard.

7 Conclusions

Since neurons are excitable cells it can be anticipated that some of the wave phenomena described for excitable media with reaction-diffusion type kinetics [see, for example, Winfree in this Handbook] will have their counterparts in the dynamics of neural networks. However, neural networks possess a number of features which distinguish them from the simpler excitable media of chemical and cardiac systems. Most importantly, a) neural networks contain both inhibitory and excitatory connections; b) inter-neuronal connectivity extends beyond nearest neighbour; c) there can be significant delays in the conduction of activity between two neurons; and d) neurons have both absolute and relative refractory periods. However, the major limiting factor to progress in the study of neural waves is the scarcity of experimental methods with sufficient spatio–temporal resolution (from elementary considerations the minimum spatial and temporal resolution would be, respectively, $\sim 0.5-1$ mm and $\sim 0.08-2.5$ msec. Continued study of the properties of these networks as well as improved monitoring techniques will be required before the functional significance of standing, standing and rotating neural activity waves, if any, becomes resolved.

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References

Amari, S., 1971 Characteristics of randomly connected threshold element networks and network systems. Proc. IEEE 59, 1, 35–47.

Beurle, R. L. 1956, Properties of a mass of cells capable of regenerating pulses, Phil. Trans. Roy. Soc. Lond. B 669, 240, 55–94.

Beurle, R. L. 1962, Functional organization in random networks, in *Principles of Self–Organization*, (H. v. Foerster and G. W. Zopf, Eds.), New York: Pergamon Press, pp. 291–314.

Chu, P.H., Milton, J. G. and Cowan, J. D. 1994, Connectivity and the dynamics of integrate–and–fire networks, Int. J. Bifurc. Chaos, in press, Feb.1994.

Farley, B. G. 1965, A neuronal network model and the "slow potentials" of electro–physiology, Comp. in Biomed. Res., 2: 265–294.

Haglund, M.M., Ojemann, G.A. and Hochman, D.W. 1992, Optical imaging of epileptiform and functional activity in human cerebral cortex, Nature, 358: 668–671.

an der Heiden, U. 1979, *Analysis of Neural Networks*, New York: Springer-Verlag.

Hopfield, J.J. 1982, Neural Networks and Physical Systems with Emergent Collective Computational Abilities, PNAS 79, 2554–2558.

Miles, R., Traub, R. D. and Wong, R.K.S. 1988, Spread of synchronous firing in longitudinal slices from the CA3 region of the hippocampus, J. Neurophysiol., 60: 1481–1496.

Milton, J. G., Chu, P.H. and Cowan, J.D. 1993, Spiral waves in integrate–and–fire neural networks, in *Advances in Neural Information Processing Systems*, (S. J. Hanson, J. D. Cowan and C. L. Giles, Eds.), 5: 1001–1007.

Novak, J. L. and Wheeler, B.C. 1989, Two–dimensional source density analysis of propagation delays for components of epileptiform bursts in rat hippocampal slices, Brain Res., 497: 223–230.

Nunez, P. L. 1988, Global contributions to cortical dynamics: Theoretical and experimental evidence for standing wave phenomena, in *Dynamics of Sensory and Cognitive Processing by the Brain,* (E. Basar, Ed.), New York: Springer–Verlag, pp. 173–182.

Petsche, H. and Šterc, J. 1968, The significance of the cortex for the travelling phenomena of brain waves, Electroenceph. Clin. Neurophysiol., 25: 11–22.

Rosenbluth, A. and Cannon, W.B. 1942, Cortical responses to electrical stimulation, *Amer. J. Physiol,* 135: 690–741.

Sholl, D. A. 1956,*The Organization of the Cerebral Cortex,* London: Methuen.

Shevelev, I.A., Tsicalov, E.N., Gorbach, A. M., Budko, K.P., and Sharaev, G. A. *J. Neurosci. Meth.*, 46: 49–57.

Stein, R. B., Leung, K. V., Mangeron, D. and Oguztoreli, M.N. 1974, Improved neuronal models for studying neural networks, Kybernetik, 15: 1–9.

Wilson, H. R. and Cowan, J. D. 1972, Excitatory and inhibitory interactions in localized populations of model neurons, Biophysical J., 12: 1–24.

Wilson, H. R. and Cowan, J. D. 1973, A theory of the functional dynamics of cortical and thalamic nervous tissue, Kybernetik 13, 55–79.

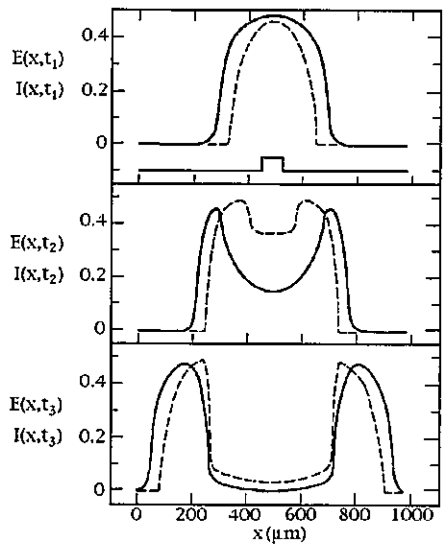

Figure 1: Generation of traveling wave pairs. $E(x,t)$ (solid lines), $I(x,t)$ (dashed lines). The region initially stimulated is indicated in the top graph. $t_1 = 20$ msec, $t_2 = 30$ msec, $t_3 = 50$ msec. Redrawn from Wilson & Cowan (1973).

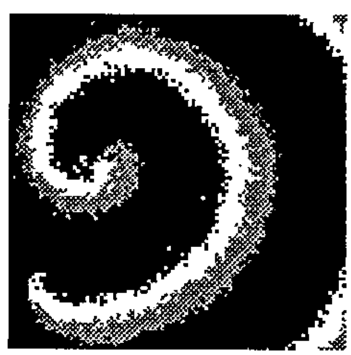

Figure 2: Generation of a travelling spiral in response to prolonged point stimulation. Gray depicts quiescent, Black relative refractory, and White active.

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