Model of the propagation of synchronous firing in a reduced neuron network

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Abstract

We studied the spread of synchronous repetitive firing in an array of purely excitatory neurons. The network consisted of an array of up to 250 by 250 neurons connected locally. We used a modified Rinzel's model for single neurons. Each neuron was connected with two neurons randomly chosen from eight neighbors. We determined the parameters of a network model needed to reproduce synchronized activity in locally connected neurons. The results of simulations in the full array of neurons suggest that the spread of activity and the velocity of spread is dependent on the strength of the connections. We found a range of synaptic weights for which the velocity of propagation is in agreement with measurements of the propagation of epileptiform activity in neocortex.

Key words: Neural network modeling; biophysical neuron model; local excitatory connectivity; traveling wave of excitation

Introduction

Investigation of the generation and propagation of patterns of activity in neural networks is important in understanding the dynamics of the central nervous system. Experimental models of synchronous neural activity including hippocampal slice [5], neocortical slice [7], cultures of dissociated spinal cord neurons [2] and cortical neurons [3] allow measurements of basic physiologic parameters of neurons

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capable of generation and spread of synchronous activity. The hippocampal slice has been used extensively as the basis for neural network models [5] of highly organized neural circuits. These simulations reveal generation and rapid spread of epileptiform activity in hippocampal circuits. In cultures of dissociated spinal cord neurons synchronous activity spreads in less organized networks of neurons. These cultures may serve as models of spread of synchronous activity in networks of neurons lacking specific circuitry. Although neocortical seizures in humans may appear to spread rapidly, measurements of the velocities of propagation of epileptiform activity in neocortical tissue [7] indicate that propagation is actually significantly slower than the axon propagation speed and slower than in hippocampal slices. This suggests the possibility that this process is a cooperative phenomenon involving a large number of sparsely, locally connected cells.

Methods

The network model we considered is a model of synaptically connected reduced neurons generating action potentials. Cells are modeled as single compartment units using modified Av-Ron-Rinzel's reduced model equations [1](see Appendix). The neuron model incorporates two inward currents - I_{Na} and I_{Ca}, three outward potassium currents - the delayed rectifier I_K, the Ca-dependent $I_{K(Ca)}$ and the transient I_A current, and a leak current I_L. The synaptic connection between cells is modeled by a synaptic current I_{syn}. The synaptic conductance is represented by a sum of two exponential functions (see Appendix). The overall strength of a connection is represented by a single synaptic weight parameter and a delay parameter represents all delays between cells. We use a two dimensional array of up to 250 by 250 cells to simulate a two dimensional neural network (e.g. a thin slice or layer of neocortical tissue). We assume that there is no significant inhibition in the network. This can be interpreted either as being similar to a dissociated cell culture after applying a blocker of inhibition (e.g. penicillin, picrotoxin) or cortical tissue where local inhibition is dominated by excitation. Each cell receives excitatory input from two of the nearest eight neighboring cells (Figure 1A); no inhibitory inputs were included. A pseudo-random generator was used to choose connections for each cell. This produced a network with no predefined structure of circuits. All connections have equal strength. Individual cells and synapses have properties based on physiologic data. Simulations were initialized by an input current of $15\ \mu A/cm^2$ applied to one cell for 100 ms, e.g. the selected cell in the center of the array received a input current strong enough to evoke a burst of action potentials at the beginning of the simulation. The membrane potentials for selected cells and histograms of generated action potentials for all cells were recorded. The histograms were later used to generate animations of the spread of activity in arrays of neurons. Recorded membrane potentials for selected cells were used to measure the velocity of the propagation of bursts of action potentials. Results from the measurements

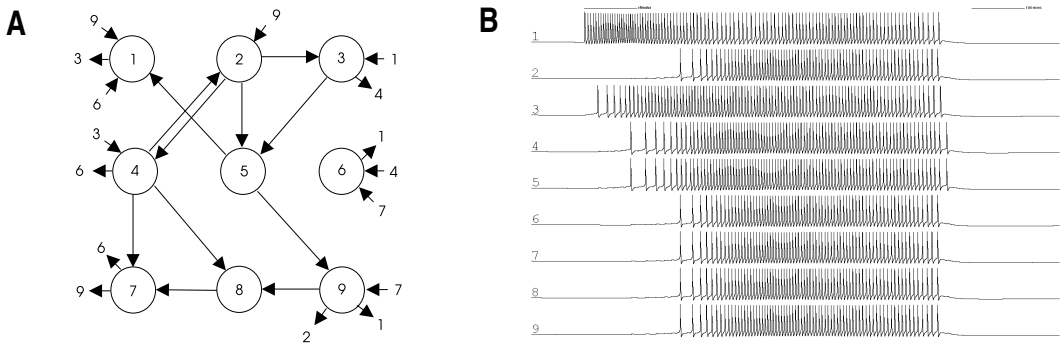

Fig. 1. A. Schematic diagram of randomly connected local network of nine neurons. Each neuron has two excitatory inputs and no inhibitory inputs. B. Traces of simulated membrane potential for all neurons shown in diagram A. The depolarizing current was applied on the input of neuron no. 1 for 100 ms at the beginning of the simulation.Time bar = 100 ms.

for border neurons for several simulations of different randomly connected neural networks were used for calculations of velocity. The ordinary differential equations were solved numerically using the forward Euler method with a time step of 0.01 ms.

Results

Simulations of small networks consisting of 9-25 cells with local random excitatory connections show that at least two excitatory inputs for each neuron are necessary to produce synchronized bursting. Output from a typical simulation is shown in Fig. 1. In this simulation 300 ms synchronized bursting activity was triggered by applying a 100 ms step current to one cell (shown in Fig. 1B). The length of bursting activity in such a small aggregate is dependent upon synaptic weight and the length of the applied input current. Bursts were generated for synaptic weights in the range of 6 to 9. In instances of small values of the synaptic weight only individual bursts in single cells were observed. High values for the synaptic weight cause continuous activity in all neurons. In a square network array (150x150 neurons) with the same local cell connection properties (as described above) we observed the spread of burst firing throughout the neuronal array (Fig. 2A). After increasing the relative strength of current $I_{K(Ca)}$ (increasing conductance $\overline{g}_{K(Ca)}$ from 0.5 to 3.5 mS/cm^2) the continuous firing was replaced by a traveling wave of activity (Fig. 2B). The velocity of propagation increased with the increase of synaptic strength (Fig. 3).The time wave of activity needed to travel from the cell in the center of an array of neurons and the onset of bursting in one of the border cells varied from 1.5 s to 0.25 s when synaptic strength varied from 9 to 120.

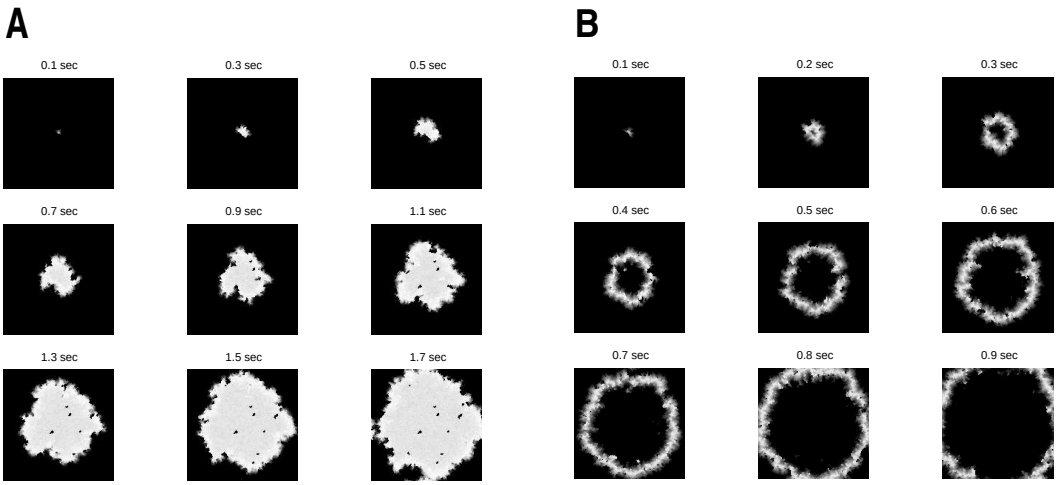

Fig. 2. Pattern of activity in network. Each dark square represents the entire array of neurons. The brightness of each pixel is proportional to number of action potentials fired by respective neurons in the 100 ms interval ending at the given time (black is minimum, white is maximum). The depolarizing current was applied on the input of the neuron in the center of the array for 100 ms at the beginning of the simulation. A. Array of 150 by 150 neurons, for this simulation synaptic weight w is 20, delay is $1.60 \pm 0.4\ ms$, $\overline{g}_{K(Ca)} = 0.5\ mS/cm^2$, and other parameters are as described in Appendix. B. Examples of a traveling wave of activity in an array of 250 by 250 neurons, synaptic weight w is 40, $\overline{g}_{K(Ca)} = 3.5\ mS/cm^2$, all other parameters are same as in panel A.

Discussion

The mechanism of synchronization in these neural networks is based on the assumption that a single burst of action potentials in a presynaptic cell, evokes a burst in the postsynaptic cell. By putting together the intrinsic bursting capability of single cells with excitatory synaptic connections, we show that synchronized bursting can occur in two or more locally connected neurons. This mechanism is fundamental to propagation of burst activity in our network model. Local activity of a group of neurons causes sequential activation of adjacent aggregates of neurons and synchronous activity propagates from one region to another. Our simulation suggests that a relatively small number of random local excitatory connections (two per neuron) in the absence of inhibition can produce the spread of activity in the network. These results are in accordance with physiological observations in various experimental conditions. Intracellular recordings from cultured spinal cord neurons show that sparsely connected cells are capable of generating synchronous bursting activity in absence of inhibition[2]. We considered this model for connectivity for our simulation of a spatially distributed network. We were able to reproduce in this network velocities of spread characteristic for neocortical tissue. We can assume that each cell in our model represents one representative cell from a neocortical column, which has excessive excitatory connections to adjacent columns. Thus, the distance between cells in our network represents the distance between columns in neocortex, ($\approx 1\ mm$)[6]. In this case, the velocity is in the range of 0.02 m/s - 0.1 m/s. These velocities are slower than the velocity of propagating waves of activity measured

in hippocampal slices (0.14 m/s)[5] but are in the range of velocities measured in thalamic (0.01 m/s)[4] and neocortex slices calculated from paroxysmal field potentials (0.07 m/s)[3; 7].

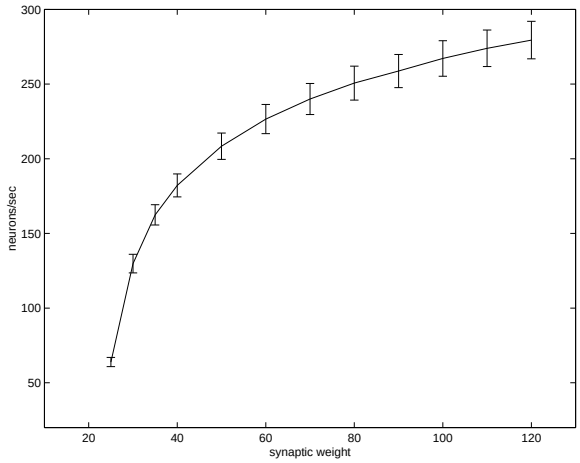

Fig. 3. Illustration of the dependence of velocity of spread of activity on synaptic weight in an array of 250 by 250 neurons. On the vertical axis velocity is represented as the number of neurons per second, computed from the average time needed to spread from the center to a border neuron in the array. Error bars are computed from measurements for 2 or 4 symmetrically located border neurons for simulations of 7 randomly connected networks ($N = 17$). The horizontal axis represents relative synaptic weight.

Appendix

Neuron model equations:

$$C_m \frac{dV}{dt} = I_{syn} - I_{Na} - I_{Ca} - I_K - I_{K(Ca)} - I_A - I_L \tag{1}$$

$$I_{Na} = \overline{g}_{Na} m_\infty^3(V)(1 - W)(V - V_{Na}) \tag{2}$$

$$I_{Ca} = \overline{g}_{Ca} X^2 \frac{K_c}{K_c + C}(V - V_{Ca}) \tag{3}$$

$$I_K = \overline{g}_K W^4 (V - V_K) \tag{4}$$

$$I_{K(Ca)} = \overline{g}_{K(Ca)} \frac{C}{K_d + C}(V - V_K) \tag{5}$$

$$I_A = \overline{g}_A A_\infty(V) B (V - V_K) \tag{6}$$

$$I_L = \overline{g}_L (V - V_L) \tag{7}$$

$$\frac{dW}{dt} = \frac{W_\infty(V) - W}{\tau_W(V)} \tag{8}$$

$$\frac{dX}{dt} = \frac{X_\infty(V) - X}{\tau_X} \tag{9}$$

$$\frac{dB}{dt} = \frac{B_\infty(V) - B}{\tau_{_B}} \tag{10}$$

$$\frac{dC}{dt} = K_p(-I_{Ca}) - RC \tag{11}$$

$$\tau_{_W}(V) = \frac{1}{\lambda}\left(e^{a^{(W)}(V-V_{1/2}^{(W)})} + e^{-a^{(W)}(V-V_{1/2}^{(W)})}\right)^{-1} \tag{12}$$

$$P_\infty(V) = \left(1 + e^{-2a^{(P)}(V-V_{1/2}^{(P)})}\right)^{-1},\ for\ P = W, m, X, A, B \tag{13}$$

Description and values of parameters used in model computations:

V is the membrane potential, W is the recovery variable, C is the intracellular calcium concentration, X and B are respectively the calcium channel activation variable and the transient potassium channel inactivation variable. The steady-state functions m_∞, A_∞, W_∞, X_∞, and B_∞ are modeled as sigmoidal curves (13), determined by two parameters: the half maximum voltage $V_{1/2}$(values are -31, -20, -35, -45 and -70 mV respectively) and a slope a of the curve at this point (values are 0.065, 0.02, 0.055, 2.0, and -0.095 respectively). $K_p = 0.0002$ is the conversion factor from calcium current to concentration and $R = 0.006$ is the removal rate constant of the intracellular calcium concentration. $C_m = 1\ \mu F/cm^2$ is the membrane capacitance. $\tau_{_W}$ is the relaxation time function (12), and $\tau_{_X} = 25\ ms$ and $\tau_{_B} = 10\ ms$ are relaxation time constants for recovery W, calcium activation X, and potassium transients inactivation B variables. Ion currents I_i are described by the product of three terms: the maximal conductance $\overline{g}_i$, the activation and inactivation variable or function, and the driving force $(V - V_i)$. where: $\bar{g}_{Na} = 120\ mS/cm^2$, $\bar{g}_{Ca} = 1.0\ mS/cm^2$, $\bar{g}_K = 15\ mS/cm^2$, $\bar{g}_A = 12.5\ mS/cm^2$, $\bar{g}_L = 0.3\ mS/cm^2$, $\bar{g}_{K(Ca)}$ in the range 0.5-3.5 mS/cm^2 are maximum conductances for the respective channels and $V_{Na} = -50\ mV$, $V_{Ca} = 124\ mV$, $V_K = -72\ mV$, and $V_L = -50\ mV$ are values of the reversal potentials for the respective ions and leak current. $K_d = 0.5$ and $K_C = 2$ are the calcium concentration functions constants.

Synaptic model equations:

$$I_{syn} = \sum_{j=1}^{N_{syn}} w_j g_j(t)(V - E_{syn}) \tag{14}$$

$$g(t) = \overline{g}_{syn} \sum_{i=1}^{N} \left(e^{\frac{-\Delta t_i}{\tau_d}} - e^{\frac{-\Delta t_i}{\tau_o}}\right) \tag{15}$$

where i denotes summation over past action potentials and j over the number of input synapses. $\overline{g}_{syn} = 0.0112\ mS/cm^2$, $E_{syn} = -10\ mV$,$\tau_d = 3\ ms$, $\tau_o = 0.5\ ms$, w_j in range 7-120, Δt_i denotes time elapsed since i-th action potential arrival at the synapse, N is the number of past action potentials with significant contribution to the sum and N_{syn} is the number of synaptic inputs. In these simulations $N_{syn} = 2$.

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