Neurocomputing 4 (1992) 75–87
Elsevier

Long-lasting transients of activation in neural networks

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Abstract

van Ooyen, A., J. van Pelt, M.A. Corner and F.H. Lopes da Silva, Long-lasting transients of activation in neural networks, Neurocomputing 4 (1992) 75–87.

The question has been investigated whether long-lasting transients of activation (i.e. slow waves), observed to occur in the intact cerebral cortex (EEG 'delta' waves and 'K' complexes) as well as in isolated tissue cultured in vitro, can also emerge in a simplified neural network model of interconnected excitatory and inhibitory cells. It is shown that slow waves can indeed occur even if the cells in the network do not have explicitly built-in slow processes. The mechanism underlying the termination of transient activity depends crucially upon the presence of a refractory period and random activity, rather than upon inhibitory suppression. A wide range of characteristic unit firing patterns is associated with transient population activities, even though all the cells in the network model have identical response properties.

Keywords. Slow waves; delta waves; transients; neural networks; noise; cycles; tissue culture; spike trains.

1. Introduction

Bioelectric activity in neural networks depends on both single neuron properties and network organization (e.g. connectivity). Dissociated cerebral cortex cells in vitro, which gradually organize themselves into a highly, synaptically connected network when brought into culture [1–3], are eminently suitable for studying these dependencies experimentally. In such networks, bioelectric activity was found to change with development in a characteristical manner, parallel with changes in neuron properties and network organization. During the early phase of development the synaptic density is low, and bioelectric activity is characterized by "isolated" action potentials and irregular, low intensity bursts. As the synaptic density increases, these firing patterns evolve into highly stereotyped bursts with strong interspike interval dependencies. Because GABA-positive cells cannot be found in this phase, the tendency for bursting could be attributed to strong excitatory synaptic drive. Subsequently, and in parallel with an increasing incidence of GABA-positive neurons, this stereotype gradually becomes replaced by a wide variety of irregular firing patterns characterized by lower interval dependencies.

The action potentials are accompanied by field potentials, which are built up by more or less synchronous synaptic activation in a large number of neurons in the vicinity of the recording electrode. A striking form of field potentials are so-called slow waves, lasting several hundred milliseconds [4–7]. They show a considerable variety of waveforms with respect to polarities,

exact durations and sequences of accompanying action potentials, among various cultures as well as within a given culture at a given time [5]. Slow-wave phenomena occur in a wide range of biological neural networks, from dissociated reaggregated spinal cord cells to the intact cerebral cortex (where they take the form of EEG 'delta' waves [7–9] and 'K' complexes [10]), suggesting that a particular structure of the network may not be required. Since slow waves can last as long as several hundred milliseconds, their duration cannot be derived directly from the classical ipsp duration of ca. 100 ms and epsp duration of ca. 25 ms, as can be done for EEG fluctuations in the alpha frequency range [11]. The occurrence of activity fluctuations of lower frequencies may therefore be an emergent property of a collection of interacting neurons. However, recent investigations have revealed the existence of ion channels with slow kinetics (e.g. calcium dependent potassium channels [12]), so it is still not known whether slow waves are essentially brought about by collective network behaviour, or are a consequence of intrinsic membrane properties which are triggered by input to the cell but which outlast the initial synaptic responses.

The fact that slow waves occur in a wide variety of biological networks, and are generated by synchronous activity, makes them suitable phenomena for studying the relationship between network organization and single neuron properties on the one hand, and bioelectric activity on the other hand. To study such relationships, one needs to record the activity of all the neurons in the network simultaneously. At present, such a goal is not attainable even if sophisticated techniques are used. Using distributed neural network models, on the other hand, one has full access to any state variable of the network, which allows the investigation of how single neuron properties and network organization are causally related to particular (global) activity patterns within the network. Using a neural network model, we have investigated under what conditions, in terms of network structure and single cell properties, slow waves can emerge

1. in a network whose cells have only fast kinetics, and
2. in a network of cells that also have slow kinetics.

2. The model

2.1 Introduction

Because individual neurons are natural information processing units, a distributed network is used in preference to a 'lumped' one. Such a model allows the study of global network behavior in relation to single cell and network properties, and makes possible comparison with observables from experimental studies. Moreover, the capacity for generating complex behavior is much better retained in distributed models than in lumped ones. Because even an assembly of very simple neurons is capable of generating quite complex behavior, we have formulated a relatively simple interaction structure that is paradigmatic for, but does not necessarily simulate in the sense of closely imitate, a biological neural network, and searches whether it is capable of generating the phenomena in which we are interested (see [13]). Interactions that play an essential role in the emergence of particular model phenomena can be pinpointed by adding or removing them from the model. Thus, part of the complexity put into the model may turn out not to be essential for the phenomena under study, while in other respects it may initially have been oversimplified.

2.2 The network model

The network is composed of interconnected inhibitory (i) and excitatory (e) cells placed at the grid points of a two-dimensional grid, the boundaries of which are connected to each other

(i.e. a torus). The network structure parameters are:

1. the size of the network, i.e. the total number of cells;
2. the fraction of *e*- and *i*-cells;
3. the number, strength, and length of outgoing connection per *e*-cell;
4. the number, strength, and length of outgoing connections per *i*-cell.

ad. (2) Neurons are either *e* or *i*, and are randomly placed at the grid points. ad. (3, 4) The parameters of the connections impinging on *e*-cells can be defined separately from those impinging on *i*-cells. Thus, the number of outgoing connections per cell, length and strength of the connections are defined according to the type of connection (i.e., $e \rightarrow e$, $e \rightarrow i$, $i \rightarrow e$ or $i \rightarrow i$). The strength of a connection is expressed in terms of a conductance change at the postsynaptic membrane (see neuron model). Using the spatial distribution *e*- and *i*-cells established under (2), the target cells for the outgoing connections are randomly chosen with equal probability within a circular field, of which the minimum and maximum radius length (i.e. the range) can be given in terms of grid units. Note that a given cell pair can be connected by more than one connection.

2.3 *The neuron model*

The neuron model properties have been chosen such that the observables registered in experimental studies (i.e. single neuron spike trains, intracellularly measured potentials, and extracellularly measured field potentials) can also be used, among others, to observe the behavior of the neural network model.

The neuron model is based on an equivalent electric circuit model (*Fig. 1*) of the cell membrane (e.g. [14]). Each neuron is capable of spatial and temporal summation of its synaptic inputs, both excitatory and inhibitory. Activity of both types of synapses increases the electrical conductance of the neuronal membrane above the resting conductance. The membrane capacitance is ignored here. The membrane potential (V) is then given by

$$V = (E_r + S_e * E_e + S_i * E_i)/(1 + S_e + S_i) \quad (1)$$

where $S_e = G_e/G_r$ and $S_i = G_i/G_r$ indicate the strengths of synaptic inputs expressed as ratios of the synaptic conductance to the resting conductance. The conductance G_r together with the driving potential E_r represent the set of ion channels that generates the resting potential; S_e represents the summed (both spatially and temporally) activity of the excitatory synapses, with E_e as their driving potential; and, in analogy, S_i represents the summed activity of the inhibitory synapses, with E_i as driving potential. From Eq. (1) it can be seen that the membrane potential approaches E_e as asymptotically as S_e increases.

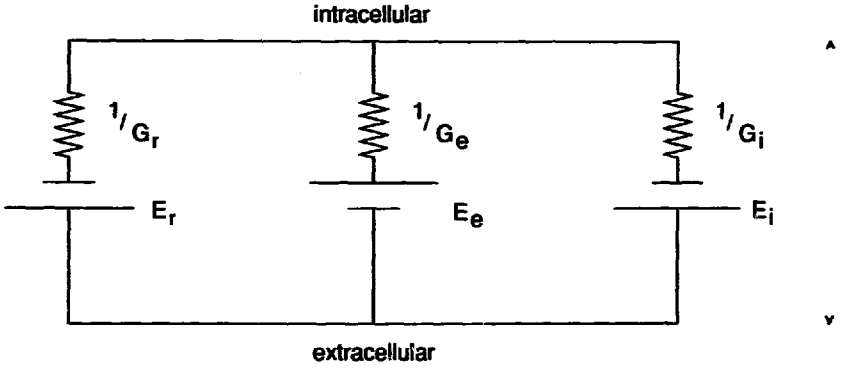

Fig. 1. Electric circuit model of the neuron membrane. E_r is the resting potential membrane, E_e is the driving potential of the excitatory synapses, E_i is the driving potential of the inhibitory synapses, G_r is the resting membrane conductance, G_e is the conductance change for excitatory input, G_i is the conductance change for inhibitory input, and V is the membrane potential.

The limit $V = E_e$ corresponds to the physiological situation in which all Na-channels are open. As the membrane potential then reaches the equilibrium potential for Na, E_e is taken to be 0 mV. In analogy, the membrane potential approaches E_i – the equilibrium potential for K, −83 mV – asymptotically as S_i increases. Equation (1) is used to calculate the instantaneous membrane potential, whereby S_e and S_i are taken to decay according to the time course of epsp and ipsp, respectively. We take

$$S_e(t+1) = D_e * S_e(t) + I_e(t) \quad (0 < D_e < 1) \tag{2a}$$

$$S_i(t+1) = D_i * S_i(t) + I_i(t) \quad (0 < D_i < 1) \tag{2b}$$

where D_e and D_i are decay constants of the excitatory and inhibitory input, respectively, $I_e(t)$ is the summed e-input, and $I_i(t)$ is the summed i-input. The action potential generation per se is not modelled. It is reduced to a threshold rule. If the neuron's membrane potential exceeds the threshold, the neuron will fire. The threshold is set at −60 mV. The default resting potential is set at −73 mV. After firing, the threshold is put up to the value of E_e and then decreases to the default value in order to simulate the absolute and relative refractory period. Each excitatory neuron also has a small probability of generating an action potential independent of whether or not its membrane potential is above the threshold (this firing will henceforth be referred to as random firing). This noise activity might physiologically be conceived of as arising from noisy membranes.

To simulate the long-lasting hyperpolarizing effect of the calcium-mediated post-spike potassium conductance, the resting potential can be lowered by a small amount each time a neuron fires (so that the distance between resting potential and threshold becomes larger); the resting potential then recovers slowly to its default value. This process is governed by the following equation:

$$R_i(t+1) = R_i(t) + D_r * (E_r - R_i(t)) - f * \text{decr} \tag{3}$$

where $R_i(t+1)$ is the resting potential of cell i at time $t+1$, E_r is the default resting potential, D_r is the time constant with which the resting potential recovers to its default value, $f = 0$ if cell i does not fire at time t, and $f = 1$ if it does, and decr is the value with which the resting potential is lowered.

The parameters, once established, are fixed for the duration of a given simulation. Time is partitioned into discrete intervals, and in each time interval, each neuron is updated by calculating its membrane potential based upon all the incoming excitatory and inhibitory inputs. All neurons are updated synchronously, and there are no synaptic delay or conduction times.

2.4 *The parameters*

The neuron and network parameters are given in *Table 1*. The neuron parameter settings for e- and i-cells are kept identical. For simplicity, there are no $i \rightarrow i$ connections ($\text{noc}_{ii} = \text{len}_{ii} = \text{coch}_{ii} = 0$). The $i \rightarrow e$ and $e \rightarrow i$ connections range over the whole network ($\text{len}_{ie} = \text{len}_{ei} = 1,29$). The $e \rightarrow e$ connections are shorter ($\text{len}_{ee} = 1,10$): 'short range excitation'. After firing, the threshold for action potential generation is put up to E_e for two time steps (absolute refractory period)(rp1 = rp2 = E_e = 0 mV). It is reset to the original value in two time steps (relative refractory period) (rp3 = −20 mV; rp4 = −40 mV). Of all the cells, 20% are made inhibitory. The values for the decay time of the excitatory and inhibitory input (D_e and D_i, respectively) are such that an unitary excitatory input ('epsp') last about 10 time intervals and an unitary inhibitory input ('ipsp') about 40 time intervals. In the case of a network of cells that have only fast kinetics, the neuron's resting potential does not change after firing (decr = 0).

Table 1. Neuron and network parameters used in most of the simulations. (Potentials are in mV, random firing probabilities are per time interval, connection ranges are in grid units, and connection strengths are expressed in terms of conductance changes (G)).

E_r	−73	(default) resting potential
E_e	0	saturation potential depolarized state
E_i	−83	saturation potential hyperpolarized state
G_r	1000	resting conductance (relative)
thres	−60	threshold potential for spike generation
rp1	0	threshold one time interval after firing
rp2	0	threshold two time intervals after firing
rp3	−20	threshold three time intervals after firing
rp4	−40	threshold four time intervals after firing
decr	0	decrement resting potential
D_r	1.0	decay constant resting potential
D_e	0.7	decay constant excitatory input
D_i	0.9	decay constant inhibitory input
ranfir_e	0.005	random firing probability of e-cell
ranfir_i	0	random firing probability of i-cell
inhpop	0.2	fraction of inhibitory cells
size	20*20	network size in number of cells
noc_{ee}	5	number of outgoing $e \rightarrow e$ connections per e-cell
len_{ee}	1, 10	$e \rightarrow e$ connection range (min, max)
coch_{ee}	150	$e \rightarrow e$ connection strength
noc_{ii}	0	number of outgoing $i \rightarrow i$ connections per i-cell
len_{ii}	0	$i \rightarrow i$ connection range
coch_{ii}	0	$i \rightarrow i$ connection strength
noc_{ei}	5	number of outgoing $e \rightarrow i$ connections per e-cell
len_{ei}	1, 29	$e \rightarrow i$ connection range (min, max)
coch_{ei}	50	$e \rightarrow i$ connection strength
noc_{ie}	50	number of outgoing $i \rightarrow e$ connections per i-cell
len_{ie}	1, 29	$i \rightarrow e$ connection range (min, max)
coch_{ie}	14	$i \rightarrow e$ connection strength

In the case of a network of cells that also have slow kinetics, the resting potential does change.

3. Results

The network has been studied by means of simulation, searching for areas in the parameter space that give rise to long-lasting transients of activation. The results given here are of a qualitative nature.

3.1 Long-lasting transients in networks of fast cells

Long-lasting transients of activation can emerge in networks whose cells have only fast kinetics. In the randomly generated networks specified by the parameter settings given in *Table 1* (with decr = 0), transients of activation in the order of seconds were found to occur. A typical example of such a transient is shown in *Fig. 2.* The e-population is triggered as the result of random activity. Activity then spreads rapidly throughout the network, as there are powerful $e \rightarrow e$ and $e \rightarrow i$ connections. Because of the strong $e \rightarrow i$ connections, the i-neurons are per-

Table 2. Duration of 10 consecutive transients (T) and inter-transient intervals (IT) for four different random realizations of the network using the parameter settings given in *Table 1* (var. is the variance of the observations).

	network1		network2		network3		network4	
	T	IT	T	IT	T	IT	T	IT
		41		18		170		20
	336		109		1439		1372	
		46		34		50		75
	127		90		432		452	
		37		55		46		45
	585		455		625		955	
		39		120		64		66
	155		70		648		1131	
		24		39		43		56
	125		131		884		649	
		107		50		36		28
	81		80		289		2575	
		22		118		82		114
	123		103		1295		2871	
		60		62		46		26
	1194		108		1562		905	
		43		37		35		38
	1731		87		820		3209	
		54		32		27		43
	160		87		1756		1068	
mean	462	47	132	57	975	60	1519	51
var.	534	23	109	23	480	40	936	27

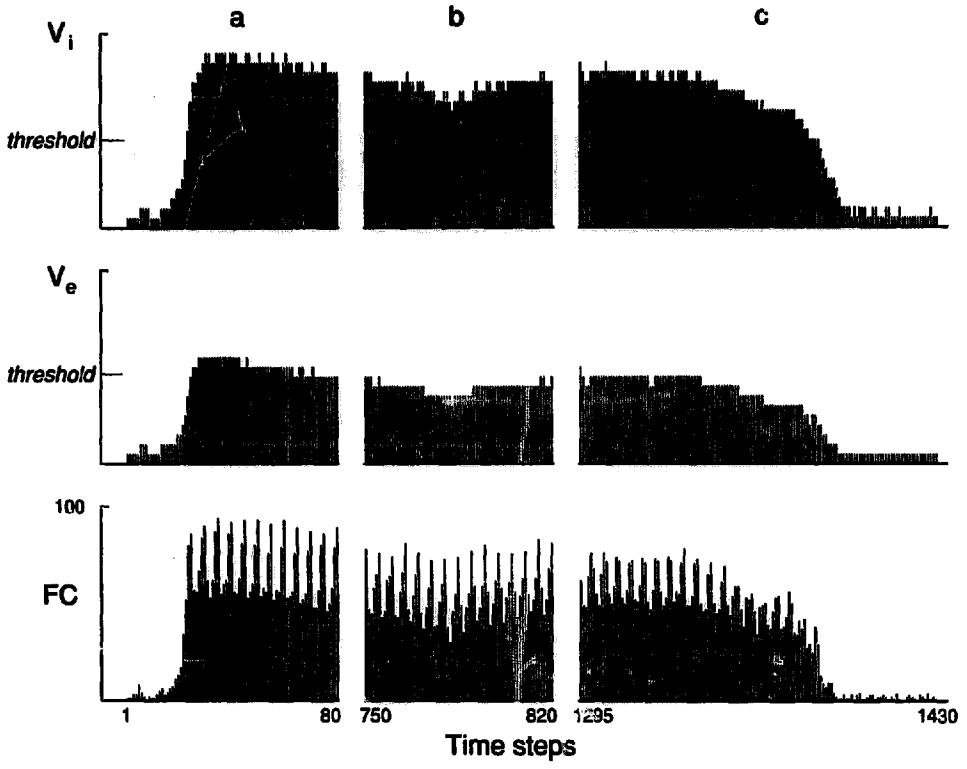

Fig. 2. Example of a long-lasting transient in a network of fast cells, showing from top to bottom the average membrane potential of the inhibitory cells (V_i), the average membrane potential of the excitatory cells (V_e), and the total number of firing cells (FC). The initial phase of the transient (*a*), a part of the middle phase (*b*) and the end phase (*c*) are shown. The firing threshold is indicated on the axis.

manently depolarized and fire constantly at a high rate, thereby providing negative feedback to the *e*-population. A considerable sub-population of *e*-cells maintains a high level of activity, albeit fluctuating, for a considerable period of time, while other *e*-cells are constantly kept inhibited. At a certain time, the *e*-population is no longer capable of sustaining its activity (for reasons that will be explained later on) and dies out, as a result of which the average activity of the *i*-population also drops quickly. Both the *e*-population and the *i*-population now become largely silent except for random activity, which eventually triggers the next transient. The transients show a great variety with respect to their duration, among different randomly generated network realizations as well as within a particular network (*Table 2*). The duration of transients can clearly be much longer than the duration of a unitary inhibitory input (about 40 time intervals) or a unitary excitatory input (about 10 time intervals).

3.1.1 Parameter sensitivity

In this section, the effect of parameter variations on the occurrence of long-lasting transients will be described.

Network size

Long-lasting transients can occur in networks of various sizes, even as small as 2*2, provided that the connection ranges are kept proportional to the network size.

Inhibitory population

The actual fraction of inhibitory cells is not critical as long as noc_{ei} and noc_{ie} are adjusted so as to keep the number of incoming $e \rightarrow i$ con-

nections per i-cell and the number of incoming $i \rightarrow e$ connections per e-cell unaltered. Long-lasting transients can arise even in purely excitatory networks, although they have so far been observed only in small networks (up to about 15 cells).

Connection range
Long-lasting transients can occur also if the $e \rightarrow i$ and the $i \rightarrow e$ connection are not network wide, as in *Table 1*. It is also not essential that the $e \rightarrow e$ connection range be shorter than the other ranges. It is not yet clear what the possible minimum connection ranges are; preliminary experiments suggest that transients can occur in certain short-range networks, in which local activity does not die out but moves, as it were, from one patch of the network to another.

Number of outgoing connections
Decreasing noc_{ie} while keeping $\text{noc}_{ie} * \text{coch}_{ie}$ as before yields, on the average, longer lasting transients within which large fluctuations of activity occur. It appears as though different transients blend into one another, probably as a result of sites in the network that remain active and from where global activity can propagate again. Increasing noc_{ei} while keeping $\text{noc}_{ei} * \text{coch}_{ei}$ as before has no clear-cut effect on transient duration.

Connection strength
Activity, once triggered, will stabilize at a steady-state level if the $i \rightarrow e$ or $e \rightarrow i$ connections are weakened, or if the $e \rightarrow e$ connections are strengthened. Transients become shorter by making the $i \rightarrow e$ connections stronger. Long-lasting transients can still be generated if the $e \rightarrow i$ connections are weakened or strengthened, provided that the $i \rightarrow e$ connections are concomitantly strengthened or weakened, respectively. However, if the $e \rightarrow i$ connections are either too strong or too weak, there are no matching $i \rightarrow e$ connections such that long-lasting transients can still be generated.

Decay times of excitatory and inhibitory input
If the decay time of the excitatory input is made longer ($D_e = 0.8$), while keeping the other parameters unchanged, activity will stabilize at a high level. If the $i \rightarrow e$ connections are strengthened so that transients reappear, long-lasting transients are then found to have become rare, the durations mostly in the range from 150 to 250 time intervals. If the decay time of inhibitory input is shortened ($D_i = 0.8$, $\text{coch}_{ie} = 29$) we find long-lasting transients within which high fluctuations in activity take place.

Random activity
The duration of the intervals between transients is increased by decreasing the probability of random activity. Random activity also influences the durations of the transients itself. If it is too low, a transient is not likely to die out after being triggered: the activity pattern often becomes trapped in a limit-cycle. If random activity is too high, a transient is also not likely to die out, in this case because new activity is being triggered at a high frequency.

Refractoriness
If refractoriness of the e- and i-cells is removed from the model, while keeping the other parameters unaltered, activity will stabilize at a high level. If the $i \rightarrow e$ connections are strengthened so that transients reappear, only short-lasting transients can be generated, all of which last about 80 time intervals, among different network realizations as well as within a given network. The duration of these transients is determined mainly by the decay time of the inhibitory input: the shorter the decay time, the shorter the transients. Whether or not long-lasting transients are possible depends also upon the length of the refractory period. They cannot be generated if the refractory period is relatively too short.

3.1.2 Alternative neuron model

To investigate whether the above-mentioned results are specific for a particular neuron model,

the study was replicated using an alternative formulation for the model. The alternative model neuron is a simplified version of the one used in [11]. It directly describes the effect of excitatory and inhibitory activity on the membrane potential instead of via conductance changes. The behavior of this 'neuron' is governed by the following set of equations. Within a time interval, the membrane potential decays:

$$V(t) \leftarrow E_r + D_d * (V(t) - E_r) \quad \text{if } V(t) > E_r \tag{4a}$$

$$V(t) \leftarrow E_r + D_h * (V(t) - E_r) \quad \text{if } V(t) < E_r \tag{4b}$$

where $V(t)$ is the membrane potential at time t, E_r is the resting potential, D_d and D_h are the decay constants of the membrane potential in the depolarized and hyperpolarized state, respectively. After summing the excitatory and inhibitory input, the membrane potential is updated:

$$V(t+1) = V(t) + (E_e - V(t)) * (1 - \exp(-I/E_e)) \quad \text{if } I > 0 \tag{5a}$$

$$V(t+1) = V(t) + (E_i - V(t)) * (1 - \exp(-|I/E_i|)) \quad \text{if } I < 0 \tag{5b}$$

where $V(t)$ is the membrane potential at time t, E_e is the depolarization saturation level, E_i is the hyperpolarization saturation level, and I is the summed input, both excitatory and inhibitory. In (5a) and (5b), all potentials are expressed relative to the resting potential.

The results obtained with this model are basically the same, though activity, once triggered, is less prone to get trapped in a limit-cycle if random activity is low.

3.1.3 *Firing patterns associated with transients*

A wide range of characteristic firing patterns is associated with transient population activities, although all the cells are identical with respect to their intrinsic properties. In the course of a transient, *e*-cells stop firing at different times as a result of being connected with different coupling strengths. Cells targeted by a relatively low number of (active) *e*-cells (and/or a high number of *i*-neurons) tend to stop firing earlier than cells targeted by a high number of (active) *e*-cells (and/or a low number of *i*-cells). This explains the wide range of firing patterns accompanying transients (*Fig. 3*): cells firing only at the beginning of each transient, cells that fail to fire with every transient, and cells that fire during the entirety of every transient (e.g. all the *i*-

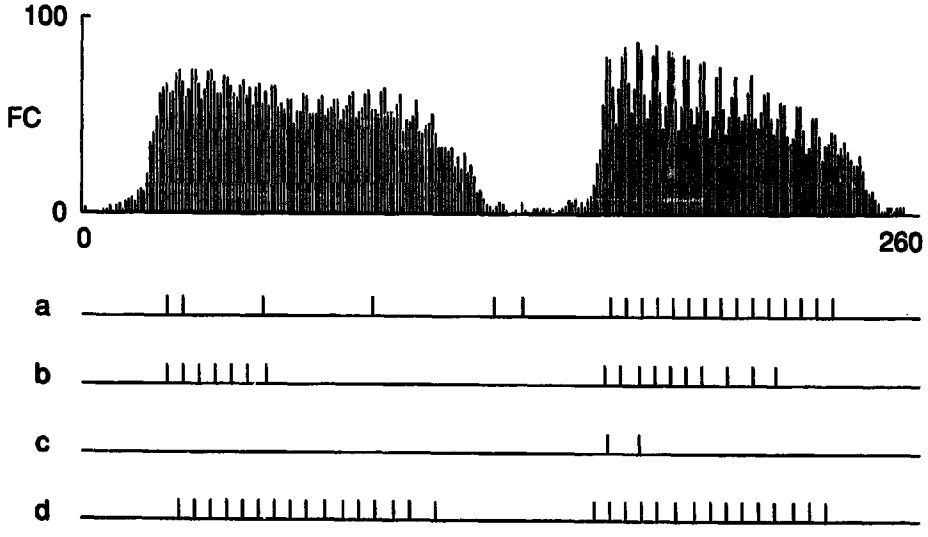

Fig. 3. Examples of firing patterns associated with transients. Two consecutive transients are shown (FC: total number of firing cells). The accompanying firing patterns of four different excitatory cells are shown. *a*: irregular firing; *b*: only during the first phase of a transient; *c*: rarely, not with every transeint; *d*: during the entirety of a transient.

neurons). Since total activity can fluctuate during a transient, there are periods of increased firing of individual neurons as well. Even in the case where the *e*- and *i*-populations are globally in equilibrium, interesting firing patterns of individual cells, such as stereotyped bursting behavior, have been noted.

3.1.4 Termination of transient activity

The mechanism underlying the termination of long-lasting transients of activation has been studied in a small network consisting of only three excitatory cells and one inhibitory cell (see *Fig. 4*), in order to understand how activity may terminate also in larger networks. As in larger networks, global activity in small networks is triggered by random firing. The network then establishes in a limit cycle, repeating a particular pattern of firing over and over again until random firing of one of the excitatory cells interferes with this firing pattern: the cell fires despite its state (the membrane potential may be subthreshold or the cell may be relatively refractory). The limit cycle is subsequently disturbed, and the network may settle into another stable firing pattern. However, random firing can bring the network also into a state that is incapable of sustaining its activity because of the specific configuration of refractory cells (after random firing, a cell is again refractory) and the distribution of membrane potentials over the cells. In this small network, the effect of the inhibitory cell does not play a crucial role, as similar results were obtained in purely excitatory networks. It is likely that this mechanism for terminating transients of activity is also operative in large networks (see Conclusions and discussion).

3.2 Long-lasting transients in networks of slow cells

Long-lasting transients of activation can also emerge in networks whose cells have explicitly built-in slow processes. These processes are thought to reflect the activity of the calcium-dependent potassium channels, which are responsible for hyperpolarizing the cell after repeated firing. The effect of these channels can be simulated by lowering the resting potential each time a neuron fires, provided that the resting potential recovers slowly to its default value. By this mechanism, long-lasting transients can readily be produced even in purely excitatory networks if the amount by which the membrane potential is lowered and the rate of recovery (parameters decr and D_r, respectively) are ap-

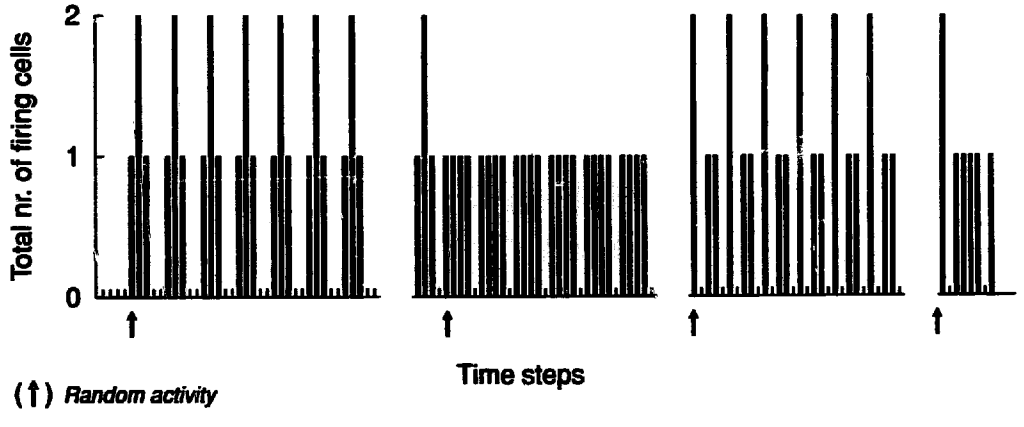

Fig. 4. Transient in a network consisting of three excitatory cells and one inhibitory cell. Denoted is when a cell fires as a result of random activity. Random activity causes the state of the network to change into a new limit cycle, and, finally, into a state that dies out. In reality, each pattern is repeated more times than shown here (indicated by broken axis). Parameters are as follows: size = 2*2, $\text{len}_{ee} = 1, 2$, $\text{len}_{ei} = \text{len}_{ie} = 1, 3$; and $\text{coch}_{ie} = 10$. The rest of the parameter settings are as given in *Table 1*.

propriately set (see *Fig. 5*). As a result of random activity, the *e*-population will become active but will stop firing after a certain period of time because of 'adaptation', i.e. the cells' threshold for action potential generation becomes too high. When the cells are thus silenced, their actual resting potentials recover slowly to the default value, after which time a new transient can be triggered. These transients have durations determined by decr and D_r, although the refractory period may play a role as well in lengthening the period if the network is in a meta-stable state.

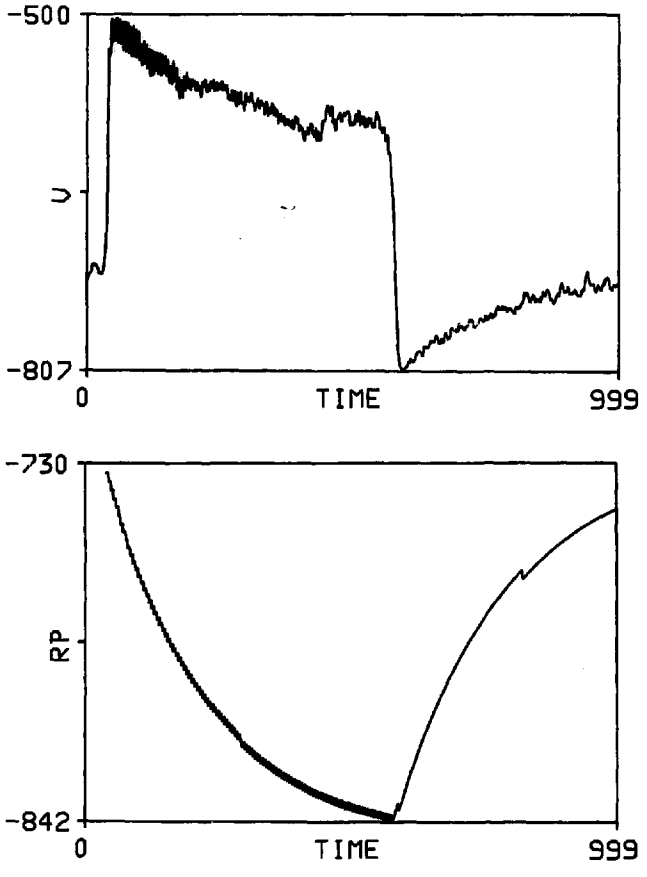

Fig. 5. Transient in a purely excitatory network brought about by lowering the resting potential each time a neuron fires. The top figure shows the average potential (V, in $mV*10^{-1}$) of all the cells, the bottom figure shows the resting potential (RP, in $mV*10^{-1}$) of one cell. The parameters are as follows: decr = 0.3, $D_r = 0.005$, inhpop = noc_{ei} = len_{ei} = $coch_{ei}$ = noc_{ie} = len_{ie} = $coch_{ie}$ = 0. The rest of the parameters are as given in *Table 1*.

The intervals between transients generated by this mechanism are longer than those between transients brought about by the former mechanism. After a transient, the network is left in a less triggerable state (because of the lowered resting potentials). Random activity during this phase will only delay recovery.

4. Conclusions and discussion

4.1 Emergence of long-lasting transients

We have demonstrated here that long-lasting transients of synchronized activity can emerge in a distributed network consisting of neurons with only fast intrinsic kinetics. Thus, although the model is devoid of explicit slow mechanisms, transients emerge that have time characteristics orders of magnitude longer than those of the individual cells. The termination of such transients depends crucially upon the presence of a refractory period and random firing, more than upon inhibitory suppression.

At least in small networks, random firing interferes with the stable activity pattern that has been established among the cells of the network. As a result of random activity, the network may settle into a new stable pattern. However, the network can also be pushed into a state that is unable to sustain its activity (because of the particular distribution of refractory cells). Thus, random firing (noise) in small networks cause state transitions, eventually leading to the termination of activity. It needs to be investigated whether this mechanism for terminating activity transients is also operative in larger networks. It is plausible to suppose that it does, because in large networks

1. long-lasting transients cannot emerge if refractoriness is removed from the model;
2. under conditions which allow the emergence of long-lasting transients, activity does not die out if random activity is stopped shortly after a 'transient' has been triggered;

3. long-lasting transients largely disappear if the excitatory input decays too slowly (D_e too large) relative to the duration of the refractory period, or if the duration of the refractory period is too short relative to the duration of the excitatory input.

It is not yet clear what exactly is the role of inhibition in terminating long-lasting transients in relatively large networks. It seems necessary that the $e \rightarrow i$ and $i \rightarrow e$ connection strengths be chosen such that no steady-state can arise, and a more or less constant inhibitory drive is present.

Long-lasting transients can arise in small, purely excitatory networks. It is not yet clear whether they can also arise in larger networks without inhibitory cells. The connectivity conditions for long-lasting transients to arise in large excitatory networks might be more specific than those in small networks. Noest [15–17] showed that slowly decaying transients of activity can arise in networks composed of extremely simplified, binary excitatory cells, the dynamics of which are defined by transition probabilities. Related phenomena can be found in [18].

In our model, synchronous dynamics has been assumed. However, synchronization can greatly influence the qualitative behavior of a system [19–22]. It remains to be investigated whether long-lasting transients can emerge if strict synchronization is relaxed.

4.2 Spike-train patterns

Although all the cells in the network model are identical with respect to intrinsic properties, different firing patterns of individual cells nevertheless occur in association with transients. Connectivity differences and the global activation state of the network are responsible for this. Even when transients are absent, firing patterns such as 'bursting' and isolated spiking can be observed. On encountering such 'bursting' cells in biological networks, one might normally be inclined to classify them into bursters, and would then search for intrinsic mechanisms that may not exist. This is not to say, of course, that there are no intrinsically bursting cells in biological networks, but rather that one should bear the richness of purely network-generated behavior in mind when considering possible explanations for the observed firing patterns.

4.3 Comparison with experimental data

In the model, the duration of each interval in real time depends on how long the refractory period is taken to last. Since its value can vary among different neurons, no precise time scale can be given. The duration of long-lasting transients emerging in the model is, however, of the same order of magnitude as that of empirically recorded slow waves [5]. Some of their variability, especially with respect to duration among different networks, can also be observed to occur in slow waves. The spike-train patterns associated with transients resemble those observed to accompany slow waves.

Besides being generated spontaneously, slow waves can be evoked by electrical stimuli provided that the stimulus strength exceeds a certain threshold [5]. This threshold shows a developmental trend: high in young tissues and low in older ones. The decrease in threshold is presumably attributable to an increase in synaptic density with development [1, 3]. In the network model, too, there is a threshold for triggering network activity, the level of which depends upon the number and strength of the connections (see also e.g. [23]).

In tissue cultures without 'background' unit-spike activity, spontaneous slow waves were absent, even when the threshold for electrically evoking them was low [5]. This background activity may trigger spontaneous slow waves in tissue culture just as random activity triggers transients in the network model.

Detailed comparisons between long-lasting transients generated by the model and neurobiological slow waves are hampered by the fact

that the waveform of extra-cellularly measured field potentials are influenced not only by membrane potentials but also by many other factors such as the neuron's dendritic morphology and the spatially inhomogeneous conductivity of the extra-cellular medium. However, long-lasting transients generated by the model resemble slow waves in the most conspicuous, qualitative aspects, to wit their duration and synchronous activity in a large number of neurons.

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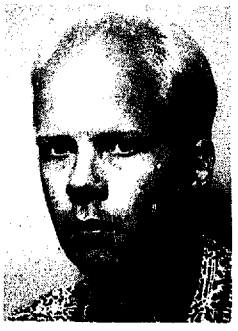

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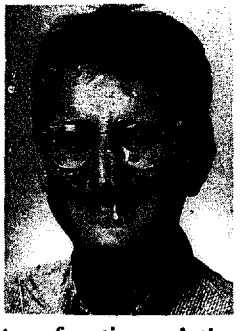

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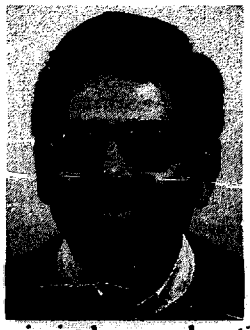

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