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# A neural network model for kindling of focal epilepsy: basic mechanism

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**Abstract.** A simple neural network model is proposed for kindling – the phenomenon of generating epilepsy by means of repeated electrical stimulation. The model satisfies Dale's hypothesis, incorporates a Hebb-like learning rule and has low periodic activity in absence of shocks. Many of the experimental observations are reproduced and some new experiments are suggested. It is proposed that the main reason for kindling is the formation of a large number of excitatory synaptic connections due to learning.

## 1 Introduction

The phenomenon of generating epilepsy in laboratory animals by means of repeated electrical stimulations of the brain – referred to as Kindling – has been studied by biologists since 1961 (Delgado and Sevillano 1961; Goddard et al. 1969), and is still extensively investigated (Lothman et al. 1991; McNamara 1989). Kindling is considered to be a very good laboratory model for studying focal epilepsy. The experiment involves repeated electrical stimulations, via implanted bipolar electrodes, of some region of the forebrain, say the hippocampus. Each stimulation typically consists of a train of short (~few milliseconds) biphasic electrical pulses applied for a short period of time (~few seconds). If the amplitude of the stimulating signal is sufficiently large, the very first or second stimulation elicits a characterestic post-stimulation electroencephalographic (EEG) discharge called the afterdischarge (AD). Electric shocks of such large amplitude are called suprathreshold. The AD typically consists of bunches of high amplitude spikes separated by flat regions with very low activity. Low amplitude – or subthreshold – shocks do not yield an AD initially; but when administered a large number of times, these too produce an AD. Further application of both supra- and subthreshold shocks lead to rapid increase in the amplitude, duration and complexity of the AD. This rapid increase eventually saturates and further stimulations after this stage lead to similar ADs on the average, which are accompanied by convulsions, motor seizures and increased oxygen consumption in the brain (Lothman et al. 1991; McNamara 1989), indicating simultaneous firing of a large number of neurons. This is the so called kindled state. The number of stimulations needed to produce the first seizure, from the occurrence of the first AD, is found to be approximately the same for both suprathreshold and subthreshold shocks (Lothman et al. 1991; McNamara 1989; Racine 1972), and to depend on various other parameters such as the region of the brain being stimulated, and frequency and duration of the stimulating signal (Goddard et al. 1969; Lothman et al. 1991; McNamara 1989; Cain 1981).

In recent years, much attention has been focussed on the development of mathematical models of neural networks (Amit 1989; Rumelhart and McClelland 1986). One of the primary objectives of research in this area is to develop models which mimic some of the complex system behavior observed in the brain. In this paper, we present a neural network based explanation of the process of kindling. Extensive neurophysiological investigations carried out during the last two decades (Bernardo and Pedley 1985; Dichter and Ayala 1987) indicate that epileptogenesis is a complex phenomenon involving factors related to both intrinsic properties of individual neurons (e.g. the intrinsic bursting ability of $CA_3$ Pyramidal cells in the hippocampus (Wong and Prince 1981)) and properties of the synaptic connections (e.g. blockade of synaptic transmission from inhibitory neurons and/or enhancement of transmission from excitatory neurons (Bernardo and Pedley 1985; Dichter and Ayala 1987)) which join the neurons to form a network. In this work, we have concentrated on the network aspect and developed a model which attempts to explain the kindling process as one of "learning" in which increased and correlated neuronal activity induced by the application of repeated electrical stimulations increases the efficacy of excitatory synaptic connections

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through a Hebbian mechanism (Hebb 1949) of synaptic plasticity. The Hebbian mechanism of synaptic plasticity considered by us is similar to the learning mechanisms assumed in neural network models of associative memory (Amit 1989).

There exist a number of experimental observations which lend support to the proposed mechanism of kindling. The process of kindling has many similarities (Cain 1989) with long term potentiation (a long lasting increase of the synaptic efficacy following afferent tetanic stimulations) which is considered (Thompson 1986) to be one of the best available models of the kind of synaptic plasticity that may underlie Hebbian learning. Selective blocking of the *N*-methyl-*D*-aspartate (NMDA) receptor channels, which are known (Bear et al. 1987) to play a crucial role in synaptic plasticity and learning, is found (Sato et al. 1988) to retard and in some cases, block the process of kindling. Observed neurophysiological changes induced by kindling have been interpreted (Sutula et al. 1988) as evidence for "sprouting, axonal growth and synaptic reorganization". Transient epileptic discharges have been found (Ben-Ari and Represa 1990) to set in motion a cascade of events which include mossy fiber sprouting and establishment of new synaptic contacts. Possible relevance of mechanisms of learning and long term memory to kindling was, in fact, suggested several years ago (Goddard and Douglas 1975).

In this work we have constructed and studied by numerical simulations a neural network model based on the premise that kindling is a Hebbian learning process. As discussed below, we find that this model reproduces qualitatively and provides an understanding of a number of observations made in kindling experiments. These include the existence of an AD threshold, initial rapid growth and eventual saturation of the amplitude and duration of the AD, insensitivity to the stimulation amplitude of the number of stimulations needed after the first AD to reach saturation and rare occurrences of spontaneous seizures and status epilepticus in the kindled state. On the basis of the observed behaviour of the model, we also make a few predictions which can be tested by experiments.

## 2 The model

Since we are primarily interested in the collective properties of the neural network, we adopt here a description in which details of the internal structure of individual neurons are left out. The neurons in our model are represented by McCulloch–Pitts (McCulloch and Pitts 1943) binary variables $\{S_i\}$ each of which may take the values 0 and 1. In the usual way (Amit 1989; Rumelhart and McClelland 1986), time is described in units of the order of the absolute refractory period ($\sim$few milliseconds). The variables $S_i(t)$ representing the state of the $i$th neuron at discrete time $t$ is set equal to 1 if it emits a spike during the corresponding time slice, and equal to 0 if it remains quiescent. Since the exact pattern of synaptic connectivity in a particular region of the brain is now known, we have constructed a model which is consistent with a number of neurobiological observations. The first among these is the so called Dale hypothesis of neuronal specificity (Eccles 1964) according to which all the synaptic connections formed by the axon of an excitatory (inhibitory) neuron are excitatory (inhibitory). The synaptic matrix that describes interconnections among the excitatory neurons is constructed in such a way that a large number of low activity patterns ("memories") are stored as attractors of the underlying dynamics. This is similar to the Willshaw model (Willshaw et al. 1969). The assumed low activity of the stored patterns ensures consistency with the observation (Abeles 1982) that under normal circumstances, only a small fraction ($<20\%$) of the neurons emit spikes at any particular instant of time. Similar (but random) sparse excitatory synaptic connections among $CA_3$ Pyramidal cells were assumed in existing neural network models (Knowles et al. 1985; Traub et al. 1989) of the hippocampal slice. Regarding the inhibitory neurons, it is known (Schwartzkroin and Weyler 1980; Traub and Wong 1983) that there are far fewer inhibitory neurons than the excitatory ones and the degree of interconnections among inhibitory neurons is less than that among the excitatory neurons. It is generally believed (Amit and Treves 1989) that the functional properties of a network are governed by synaptic connections among the excitatory neurons, with the inhibitory neurons playing a subservient role of keeping the average activity of the network low. The local nature of the action of inhibitory neurons suggests that they can react to the distribution of activity among the excitatory neurons on a shorter time scale than the excitatory neurons themselves. Due to these reasons, we do not consider explicitly the dynamics of the inhibitory neurons and represent their effect on the excitatory neurons by an inhibitory postsynaptic potential which is a function (Amit and Treves 1989) of the mean activity of the excitatory neurons. We also introduce a set of "slow" synaptic connections among the excitatory neurons and a corresponding slow inhibition. The slow synapses are constructed in such a way that they tend to induce transitions between the stored memory state (Sompolinsky and Kanter 1986; Kleinfeld 1986; Kleinfeld and Sompolinsky 1988). The time delay associated with their action ensures that the network stays in a memory state for some time before making a transition to the next one. Such time delays associated with synaptic transmission are known (Kleinfeld and Sompolinsky 1988) to exist in biological networks. In our model the dynamics of the $N$ excitatory neurons, represented by the binary variables $\{S_i, i = 1, \ldots, N\}$, is governed by the net postsynaptic potential $\{h_i, i = 1, \ldots, N\}$, given by

$$h_i = \sum_{j=1}^{N} [\{J_{ij}S_j - wS_j\} + \lambda\{K_{ij}S'_j - wS'_j\}] . \qquad (1)$$

The synaptic matrix $J_{ij}$ stores $q$ random low activity patterns represented by $q$ $N$-bit "words" $\{\xi_i^\mu, \mu = 1, \ldots, q, i = 1, \ldots, N\}$ of ones and zeros. The total number of ones in each "word" is assumed to

be a small fraction of $N$. The matrix $J_{ij}$ is constructed in a manner analogous to the Willshaw model:

$$J_{ij} = 1 \text{ if } \sum_{\mu=1}^{q} \xi_i^\mu \xi_j^\mu > 0 \quad (i \neq j).$$
$$J_{ij} = 0 \quad \text{otherwise}. \qquad (2)$$
$$J_{ii} = 0.$$

Equation (2) implies that each element of $J_{ij}$ is either zero or one. This is clearly an idealization. However, the results presented here would not be affected strongly if the strengths of the non-zero excitatory synaptic connections were allowed to have some variation. The second term in the first set of curly brackets in (1) represents the contribution of the inhibitory neurons which, as discussed above, is assumed to be proportional to the mean instantaneous activity of the excitatory neurons. The strength of inhibition is given by the parameter $w$, with $0 < w < 1$. The terms in the second set of curly brackets in (1), which depend on the state $\{S_i'\}$ of the network at an earlier time $(t - \tau)$, represent the time delayed inputs. The relative strength of the delayed signal is given by $\lambda$. The synaptic strengths for the delayed signal are modeled (Sompolinsky and Kanter 1986; Kleinfeld 1986) by $K_{ij}$ given by

$$K_{ij} = 1 \text{ if } \sum_{\mu=1}^{q} \xi_i^{\mu+1} \xi_j^\mu > 0 \quad (i \neq j).$$
$$K_{ij} = 0 \quad \text{otherwise}. \qquad (3)$$
$$K_{ii} = 0$$

with $\xi_i^{q+1} = \xi_i^1$. The update rule for the network is the usual one, viz.

**Rule 1.** *If the local field* $h_i \geqslant 0$, *make* $S_i = 1$, *and if* $h_i < 0$ *make* $S_i = 0$.

If the network is in a state corresponding to some pattern $\xi_i^\nu$, $J_{ij}$ try to keep the network in that state but $K_{ij}$ try to shift it to another state $\xi_i^{\nu+1}$. For a sufficiently large value of $\lambda$ and suitably chosen values of the parameters $q$ and $w$, the network produces limit cycles in which it repeatedly goes through the memory states in a fixed sequence. The resulting small-amplitude periodic variation of the network activity is assumed to model the resting EEG (see Fig. 1).

Repeated activation of a synapse may make it refractory due to exhaustion of presynaptic neurotransmitters (Guyton 1986). Earlier computer modeling (Knowles et al. 1985; Traub et al. 1989) of the epileptic hippocampal slice has shown that a certain amount of refractoriness of synaptic transmission between excitatory neurons is necessary for obtaining the experimentally observed "bunching" of spikes in the AD. This refractoriness of synapses $A_{ij}(=J_{ij}$ or $K_{ij})$ is modeled by imposing the following constraint.

**Rule 2.** *If a synapse* $A_{ij}$ *has been active for more than a time period* $t_{max}$, *then for the following period of time* $t_{ref}$, $A_{ij}$ *does not contribute anything to the local field* $h_i$.

The electric shocks are modeled as follows. There are more positive ions and less negative ions near the (implanted) negative electrode due to Coulomb interaction. When an excitatory (inhibitory) input arrives at a synapse near this electrode, larger number of positive ions (smaller number of negative ions) are pumped in compared to the normal situation, leading to excess excitation (reduced inhibition). The reverse of this happens at the positive electrode. Thus a shock can be modeled by changing the strength of inhibition $w$ at the synapses near the positive and negative electrodes in the following way. The local field $h_i$ in presence of an external shock $s$ is given by an equation similar to (1) with the strength of inhibition $w$ replaced by $w - s$ near the negative electrode and $w + s$ near the positive electrode $(0 < s < w)$.

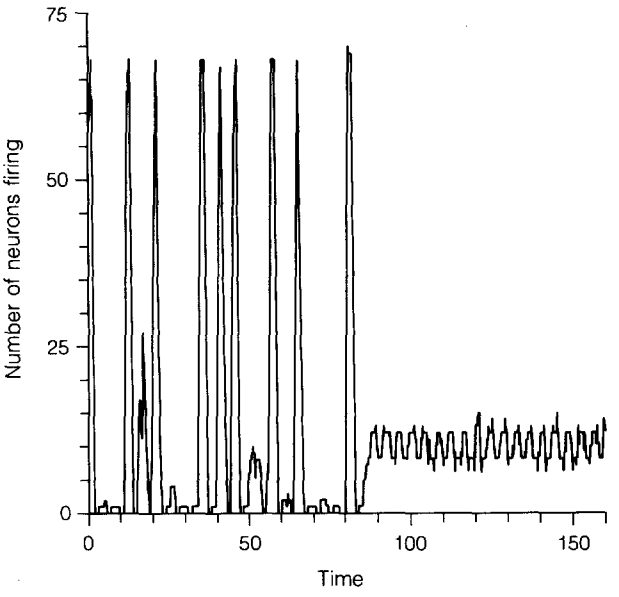


**Fig. 1.** This is the kindled EEG. The number of neurons firing are plotted as a function of time, measured in units of passes. The network relaxes after 80 passes and the last part of the plot is the resting EEG

The most important ingredient of our model is the incorporation of the following Hebb-like learning rule in the network dynamics. According to the classical Hebb rule, correlated excess activity of two neurons causes an enhancement of the strength of the synapse connecting them. In our model, this rule takes the form:

**Rule 3.** *If, over a certain period,* $S_i = 1$ *and* $S_j = 1$ *more often than some average value, make the synaptic strength* $J_{ij} = 1$.

In other words, if the two neurons have above average firing rate over some period, then a synapse is formed between the two. Biologically this may correspond to the activation of an existing but inactive synapse or to the formation of a new synaptic connection. The learning takes place only at the excitatory synapses, as is also suggested by experiments (Kelso et al. 1986; diPrisco 1984). It is generally believed (Bear et al. 1987; Brown et al. 1988) that synaptic plasticity is more likely to take place around the spines of the

excitatory neurons. The classical Hebbian enhancement of synaptic efficacies is approximated in the above form since the synaptic strengths in our model take only two values 0 or 1. When the shock is absent, the above learning rule does not lead to formation of any new synapse because the neurons which simultaneously fire more often than the average value correspond to some stored pattern and hence the corresponding $J_{ij}$s are already equal to 1. However, due to the shock, a different set of neurons fire which do not correspond to a stored pattern and hence some more $J_{ij}$s become 1, thereby increasing the connectivity of the network. As will be shown later, this learning rule is the crucial ingredient that leads to kindling.

The "withering" of synaptic strength is assumed to be of negligible amount, over the period of time the shocks are given, and hence ignored. Also, no learning is incorporated for $K_{ij}$.

## 3 Computer simulations and results

The network described above was simulated using a system of 200 neurons. The neurons were updated sequentially in a random fashion. The time needed for one pass (i.e. random sequential update of all the neurons) was chosen to be the unit of time. In the absence of shocks, it was found that forty patterns, each with only about ten neurons firing, could be stored in a stable fashion. The optimum value of the weight $w$, for the above choice of parameters, was found to be around 0.6–0.7. We chose the number of patterns $q = 20$, $\lambda = 2$ and $w = 0.6$. The delay period $\tau$ was chosen to be equal to that needed for two passes. A synapse could continuously fire for a period $t_{max} = 10$ updates after which it was refractory for a period $t_{ref}$, which was chosen randomly between 6 and 12 passes. We used a learning rule in which two neurons have to fire at least three times in the last ten updates to form a new synapse between the two. External shocks were assumed to change the local fields of two distinct groups of 20 neurons near the two electrodes.

Different subjects (modeled by using networks with different realization of initial patterns $\xi^{\mu}$) were given shocks with different amplitude, varying from 0.1 to $w$. As was done in most of the experiments (Goddard et al. 1969; Lothman et al. 1991; McNamara 1989; Racine 1972) the schedule of shocks consisted of giving a train of biphasic pulses for 320 passes. Each pulse lasted for 2 passes and was repeated after every 7 passes. The network was then allowed to relax in absence of any shock for 160 passes. It was then reset to some resting state and this "schedule" was repeated. This was repeated sixty times (each application of the shock will be referred to as one day in the actual experiment). The following parameters were monitored as a function time: the EEG, which is assumed to be proportional to the activity of the network given by $S_{up} = \sum_{i=1}^{N} S_i$; the total number of excitatory synaptic connections $J_{ij}$ in the block of neurons which feel the shock ($J_{shock}$), in the block of neurons which do not feel the shock ($J_{noshock}$), and in the block connecting the above two blocks of neurons ($J_{cross}$). The total number of synapses is denoted by $J_{sum} = J_{shock} + J_{noshock} + J_{cross}$.

The plot of the number of neurons firing as a function of time, which will be referred to as the EEG, for the resting state is shown in the last part of Fig. 1. Very small shocks, $s < 0.3$ produced at the most 10% change in $S_{up}$ and $J_{sum}$, and failed to produce an AD or kindling. Repeated application of shocks with $0.5 > s > 0.3$ led to an AD after a large number of stimulations. The first AD occurred when $J_{sum}$ was above 4000 (the value of $J_{sum}$ before the application of shocks was $\sim 2000$), with typical values of $S_{up}$ oscillating rapidly between 30 and 0, lasting for about 20 passes, after which the network relaxed back to normal oscillations. As shown in Fig. 2, the number of stimulations required to elicit the first AD decreases as the amplitude is increased and should be measurable experimentally. Shocks with $s > 0.5$ elicit ADs within the first few applications, indicating that these values are suprathreshold.

As shown in Fig. 3, initially, the amplitude of the AD increases rapidly as a function of the number of stimulations. This rapid increase stops eventually and reaches a saturation value. Similar behavior has been observed in the laboratories (Racine 1972) and it is found that when the AD reaches the saturation value, it is also accompanied by seizures and convulsions, signaling the onset of the kindled state. The average number of shocks needed, from the day of the first AD to the day when saturation values of various parameters is reached, is nearly the same for both suprathreshold and subthreshold shocks as shown in Fig. 3.

The ADs for both suprathreshold and subthreshold shocks look similar at the saturation value and a typical EEG is shown in Fig. 1.

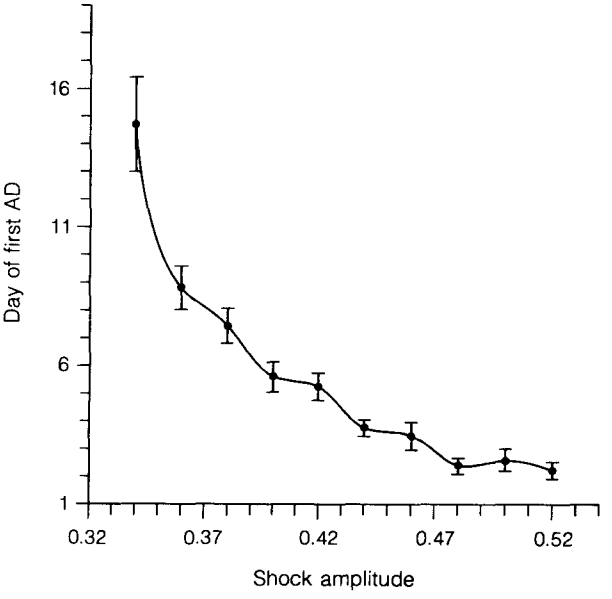


**Fig. 2.** The number of stimulations required to elicit the first AD, averaged over fourteen subjects (for each data point), as a function of the amplitude of the shock

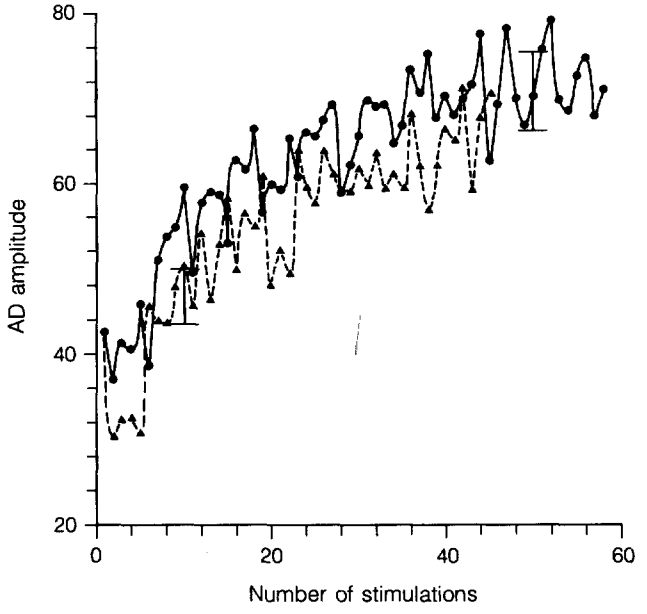


**Fig. 3.** The AD amplitude, averaged over 23 (43) subjects for suprathreshold (subthreshold) shocks, as a function of the number of stimulations after the first AD. The graph for suprathreshold shock ($=0.56$) is given by a solid line and for subthreshold shocks ($=0.4$) by a dashed line. Typical error bars are shown

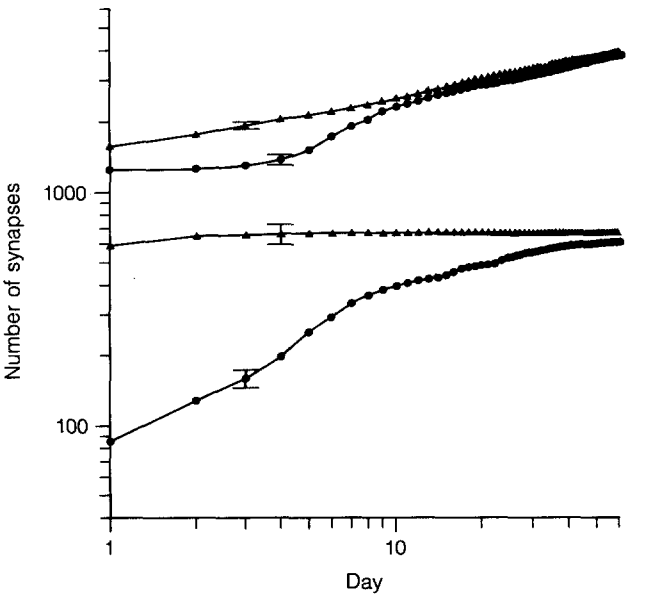


**Fig. 4.** The rate of synapse formation averaged over 23 (43) subjects each for suprathreshold and subthreshold shocks, in different regions of the brain. The plots from top to bottom are; $J_{\text{noshock}}$ for suprathreshold and subthreshold shocks, $J_{\text{shock}}$ for suprathreshold and subthreshold shocks. Typical error bars are shown

These results remained qualitatively the same under the following range of parameters: when $\lambda$ was varied between 2 and 9, the weight $w$ between 0.5 and 0.7, the number of memories $q$ between 10 and 40, the number of neurons given shock between 40 and 80, the refractory period of the synapse between from 2 to 10 passes, and the persistence period for learning between 3 out of 5 updates to 3 out of 10 updates.

## 4 Discussion and conclusions

The results presented above can be understood as follows.

The local field produced by a suprathreshold shock near the negative electrode is highly excitatory, leading to simultaneous firing of nearly all the nearby neurons. During the next pass, the sign of the shock is reversed and a large number of neurons near the other electrode fire. In the next pass, the shock is absent and the excess excitation of the previous two passes leads to excess inhibition and only a few neurons fire. The network then relaxes to the resting state. Since the position of the electrodes is fixed, the set of neurons which feel the shock have larger than average firing rates and hence a large number of synapses are formed in this region within a few stimulations, i.e. $J_{\text{shock}}$ increases rapidly as shown in Fig. 4. Succeeding electrical pulses turn on even more neurons some of which do not see the shock directly but feel the excess excitatory input from too many excitatory neurons firing in the shocked region. This, in turn, leads to increase in $J_{\text{noshock}}$ and $J_{\text{cross}}$. These new synapse tend to pull the network away from the resting state, thereby producing an AD and subsequent increase of AD duration and amplitude as shown in Fig. 3.

A subthreshold stimulus does not alter the strength of excitation or inhibition drastically. Hence, during the first few days, only a few extra neurons fire in the shocked region, leading to small changes in the number of synapses and no AD. As the subthreshold stimuli are repeated, the extra excitatory synapses formed by prior stimulation lead to larger deviations from the resting state and hence a larger rate of synapse formation as shown in Fig. 4. This "snowballing" process eventually leads to the appearance of the AD and subsequent rapid kindling.

The $K_{ij}$ and the prestimulation $J_{ij}$ try to pull the network towards the resting state, and the network relaxes to it after a while even without synaptic refractoriness. Inclusion of synaptic refractoriness puts the network in low activity states for longer periods, thereby increasing the probability of it getting trapped in the resting state. The refractoriness is also responsible for the "bunching" of spikes seen in the AD (see Fig. 1). Thus the epileptic state is transient. The excitatory synaptic connections formed due to shocks correspond to some high activity patterns. Even in the absence of shocks, when the instantaneous state of the kindled network has a large overlap with one of the high activity patterns, the activity of the network shoots up and the EEG looks similar to that of Fig. 1. Similar spontaneous seizures have also been observed in the laboratory experiments (Lothman et al. 1991: McNamara 1989).

In our model, we did not include any "forgetting" i.e. the possibility of reduction of synaptic efficacies either by disuse or by some "unlearning" mechanism

such as Hebbian asynchronous activity. This is not quite realistic because if no forgetting is present, every neural network of the type considered here will, in the course of its natural time evolution, eventually become epileptic as a result of increases in excitatory synaptic connections caused by learning. Since this does not happen in real systems, some forgetting must be present. The time scale of forgetting will be comparable to the time scale of learning under normal circumstances. However, this time scale is much slower than the rate of learning or synapse formation during kindling. For example, in our modeling, the number of synapses increase, by more than 200% within 10 stimulations, but in absence of shocks, less than 10% extra synapses are formed during the same period. This is also borne out by the observation that it takes about 10 days to kindle a laboratory animal, but the kindled state persists for more than 100 days (Goddard et al. 1969). Thus "forgetting" has a negligible effect on the time scale of kindling and can be ignored while studying such phenomena.

The above results and discussion show that kindling occurs due to the formation of a large number of excitatory synapses due to learning. This, we believe, is the first theoretical modelling and explanation of kindling. This work also lends support to the Hebbian scheme of "learning" of time persistent patterns.

We have used this model to study other aspects of kindling such as frequency dependence of kindling time, change in AD threshold due to daily subthreshold stimulation and generation of secondary focus. These results and detailed explanation of work reported here will be presented elsewhere (manuscript in preparation).

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