Chapter 5
Limited spreading: How hierarchical networks prevent the transition to the epileptic state

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5.1 Introduction

An essential requirement for the representation of functional patterns in complex neural networks, such as the mammalian cerebral cortex, is the existence of stable network activations within a limited critical range. In this range, the activity of neural populations in the network persists between the extremes of quickly dying out, or activating the whole network. The latter case of large-scale activation is visible in the transition to the epileptic state. It is known in neuroanatomy that the neuronal network of the mammalian cerebral cortex possesses a modular organization across several levels of organization—from cortical clusters such as the visual cortex at the highest level, to individual columns at the lowest level. Using a basic spreading model of a network without inhibitory units, we investigate how functional activations of nodes propagate through such a hierarchically clustered network. Simulations demonstrate that persistent and scalable activation can be produced in clustered networks, but not in random networks of the same size. Moreover, the parameter range yielding critical activations is substantially larger in hierarchical cluster networks than in same-sized small-world networks. These findings indicate that a hierarchical cluster architecture may provide the structural backbone for the stable and diverse functional patterns observed in cortical networks additional to the known role of inhibitory neurons. Such *topological inhibition* might help to maintain healthy levels of neural activity. For readers who are unfamiliar with the emerging area of network science, we provide a glossary of key terms at the end of the chapter.

Natural systems operate within a critical functional range, sustaining diverse dynamical states [5, 41]. For instance, in neural systems, such as the cerebral cortical

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networks of the mammalian brain, this critical range is indicated by the fact that initial activations result in various neuronal activity patterns that are neither dying out too quickly, nor spreading across the entire network too often as large-scale activation is infrequent [7]. What are the essential structural and functional parameters that allow complex neural networks to maintain such a dynamic balance? In particular, which factors limit the spreading of neural activity through the whole brain, thus preventing a pathological state resembling epilepsy? Preventing the spreading is important as there are few processing steps in the brain as indicated by the the analysis of cortical connectivity [19, 28] and of cortical latencies [54].

Most current models of neural network dynamics focus on maintaining the right balance of activation through functional interactions among populations of inhibitory and excitatory nodes [7, 18]. However, the topology of the networks may also make a significant contribution toward critical network dynamics, even in the absence of inhibitory nodes. Earlier studies at a single level of neural organization had shown that a small-world organization of a network of excitatory neurons was related to patterns of synchrony [37] and epilepsy spreading [11, 40]. In our model, we will observe how hierarchies, in addition to properties of small-world networks, influence network dynamics.

5.1.1 Self-organized criticality and avalanches

Nonlinear dynamics and criticality arise in natural systems through the interplay of many variables and degrees of freedom. In theoretical and computational models, these systems can be represented by differential or difference equations, and typically have at least three variables, or degrees of freedom (the logistic map being a notable exception). The nonlinear aspect of these interactions causes systems to have varying responses to stimuli and input, based on the "state" of the system as a whole. For example, some input at one point in time may have a certain output, but an identical input at some later time can result in a very different output of the system, due to different initial conditions. Taken's theory of embedding [51] and Sauer's extension to time-delay embedding [47] allow one to recreate these state spaces, allowing one to visualize attractors. Thus, one may understand both temporally local and temporally global dynamics: locally, a linear approximation to translate output to input is possible; globally, if one watches the dynamics long enough, one may reconstruct the entire attractor. However, prediction of intermediate-term behavior is not currently possible.

Examination of how these attractors change when variables are changed allows one to identify critical points within a system; these critical points are phase states in which very different types of behavior result from mildly different initial conditions. In some systems, critical points are the attractors of a system; in this case, the variables themselves are less important and it is from the inputs that one sees critical-point transitions in behavior. Such systems are referred to as self-organized critical systems [4, 5]; earthquakes, sandpile avalanches, and large ensembles of neurons are examples. Self-organized critical systems are typically slow-driven

nonequilibrium systems, with a large degree of freedom and high nonlinearity, but there is no set of characteristics that guarantees that a given system will display self-organized criticality [52].

Another characteristic of self-organized critical systems is scale invariance, in which fluctuations have no characteristic time or spatial scale. Spatially extended critical systems which exhibit scale invariance [14] are of increasing interest in many natural systems, including the brain. Variability also exists in the underlying network topology of systems. For scale-free networks, connections between nodes of a network are not uniformly randomly distributed, but follow a power-law of distribution, with certain nodes acting as highly-connected hubs [6]. This type of connectedness gives robustness of operation even with loss of random connections ("damage") between nodes, so long as the hubs are not completely disconnected from the network [2]. A similar response to structural damage as for scale-free networks was observed for cortical networks [30].

5.1.2 Epilepsy as large-scale critical synchronized event

Epilepsy affects 3–5% of the population worldwide. Seizures are the clinical manifestation of an abnormal and excessive excitation and synchronization of a population of cortical neurons. These seizures can spread along network connections to other parts of the brain (depending on the type and severity of the seizure), and can be quite debilitating in terms of quality of life, cognitive function, and development. In the vast majority of cases, seizures arise from medial temporal structures that have been damaged (due to injury or illness) months to years before the onset of seizures [12]. Over this "latent period", cellular and network changes are thought to occur which precipitate the onset of seizures.

It is not understood exactly how these seizures come about, but is thought to be due to structural changes in the brain, as in the loss of inhibitory neurons, the strengthening of excitatory networks, or the suppression of GABA receptors [12, 31]. Cranstoun et al. (2002) reported self-organized criticality in EEG (electroencephalogram) recordings from human epileptic hippocampus; thus applying network analysis to this system may reveal useful information about the development (and possible prevention) of seizures. As the networks that support the spread of seizure activity are the very same networks that also support normal cognitive activity, it is important to understand how this type of activity arises in networks in general [16]. The question of how seizures are initiated (ictogenesis) is also of great interest, as further elucidation of either epileptogenesis or ictogenesis may have considerable impact on the treatment (and possible cure) of epilepsy [24].

5.1.3 Hierarchical cluster organization of neural systems

It is known from the anatomy of the brain that cortical architecture and connections are organized in a hierarchical and modular way, from cellular microcircuits in

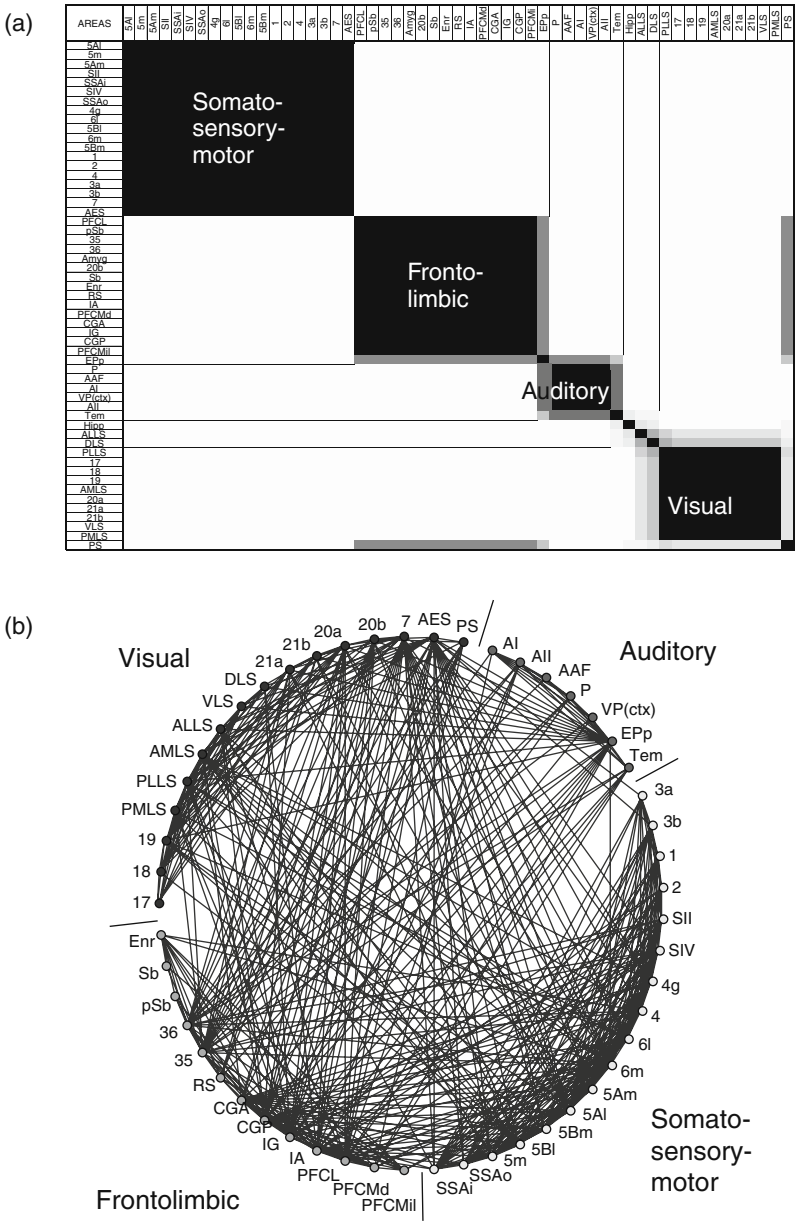

Fig. 5.1 Clustered organization of cat cortical connectivity. (a) Cluster count plot, indicating the relative frequency with which any two areas appeared in the same cluster, computed by stochastic optimization of a network clustering cost function [19]. Functional labels were assigned to the clusters based on the predominant functional specialization of areas within them, as indicated by the physiologic literature. (b) Cat cortical areas are arranged on a circle in such a way that areas with similar incoming and outgoing connections are spatially close. The ordering by structural similarity is related to the functional classification of the nodes, which was assigned as in (a).

cortical columns [8] at the lowest level, via cortical areas at the intermediate level, to clusters of highly connected brain areas at the global systems level [19, 20, 50]. At each level, clusters arise, with denser connectivity within than between modules. This means that neurons within a column, area, or area cluster are more frequently linked with each other than with neurons in the rest of the network.

Cluster organization at the global level is, for example, visible in the pattern of corticocortical connectivity between brain areas in the cat [48, 49]. Based on the structural connectivity of anatomical fiber tracts it is possible to distinguish four clusters which closely resemble different functional tasks (Fig. 5.1). Cluster organization is also visible at the level of cortical areas, for example, about 30–40% of synapses within visual areas come from distant cortical areas or thalamic nuclei [54], thus the majority of connections runs within an area. Within cortical columns of area 17 of the cat, two-thirds of synapses within layers come from external neurons in different layers [8]. Nonetheless, a neuron is more likely to connect to a neuron in the same layer than to a neuron in a different layer. After discussing the transition to the epileptic state in the next section, we will show how the cluster organisation of neural systems can prevent this transition in the normal brain, and we will identify which changes could lead to seizures in epileptic patients.

5.2 Phase transition to the epileptic state

The phase transition to the epileptic ("itctal") state is abrupt from a behavioral point of view (seizures start suddenly), but from an electrical/network point of view, there are subtle connectivity and synchronization-related changes in network activity that can indicate that a seizure will occur soon (with a prediction window ranging from minutes to hours). The existence of this so-called "pre-ictal" period—in which one is neither "inter-ictal" (between seizure states), nor currently having a seizure—has been the subject of intense debate in the literature, but more and more evidence points to its existence [24]. Epileptogenesis typically has a longer timescale of development (months to years) than ictogenesis (weeks to days), but understanding the changes of epileptogenesis and how seizures become more easily generated is also of considerable interest, as characterization of network changes may allow one to treat epilepsy in a more precise manner (i.e., with no systemic drug application or removal of whole brain areas in order to eliminate malfunctioning pathways).

5.2.1 Information flow model for brain/hippocampus

The hippocampus is a well-studied part of the brain, and is an especially important part of the limbic system, as it has to do with memory formation and information processing. Limbic epilepsy, in particular temporal lobe epilepsy, is a particularly debilitating form as it can be difficult to treat surgically without adverse quality-of-life effects [12]. Avoli et al. (2002) examined information flow within

the hippocampus and reported changes of this structure in animal models of limbic epilepsy. They reported a change within the information flow of the hippocampus, involving the loss of connectivity from the CA3 area to the rest of the hippocampus, as well as increased connectivity from the entorhinal cortex, an area normally made quiescent by a 0.5–1-Hz signal from CA3. The time-course of these changes, and the nature of the structure–function alterations as the animal behavior alters (from normal to epileptogenic) are difficult to characterize. This is because these changes occur over an extended period of time, so require large-scale storage and computing facilities in order to contain and analyze data of sufficiently high spatial and temporal resolution, captured over the entire critical period.

5.2.2 Change during epileptogenesis

The Chronic Limbic Epilepsy [35, 36] model is a rodent model of limbic epilepsy in which the animal is kindled into status epilepticus for one hour. Following a recovery period of 12–24 hours, spontaneous seizures occur within 2–8 weeks, which are recurrent and chronic.[1] A total of 32 tungsten microwire electrodes were implanted in the CA1 and dentate gyrus subfields of the hippocampus bilaterally, with $\sim$8 microwires implanted into each field. The electrodes were implanted in two rows spaced 420 μm apart, with each electrode in the row spaced at 210-μm intervals. Electrode voltages were digitized at 16 bits, and recorded continuously at 12 kHz using custom-written acquisition software and a Tucker-Davis Pentusa DSP, which employed a hardware bandpass filter set from 0.5 Hz to 6 kHz.

Two weeks of baseline data were recorded after the animal had had sufficient time to recover from electrode implantation. The animal was then kindled in the manner prescribed for the Chronic Limbic Epilepsy Animal model [35]. Continuous recording began within a day of kindling, and continued until after the spontaneous electrographic and behavioral seizures had ended. A control animal was recorded using the same protocol. All animals were continuously video-recorded to monitor for seizures.

Coherence, defined as

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)},$$

is a measure used to determine the degree of linear similarity between two signals [23, 43]. Coherence has been applied to the human EEG in order to determine the relationship between signals for determining seizure propagation delay [15, 17]. A significant increase (or decrease) in coherence would indicate whether two time-series have quantifiably similar frequency properties (or have more dissimilar frequency properties) over that time period. During the latent period before the onset of a seizure, one might predict that an increase in coherence might occur across

[1] The work described here was undertaken at the University of Florida as part of the "Evolution into Epilepsy" NIH/NHS joint research project (grant no. 1R01EB004752).

the epileptic brain compared to normal animals, or that changes might occur preferentially in different frequency bands.

Averaged coherence of inter-hemispherical activity in high gamma to ripple frequencies (40 to 200 Hz, called "low band" in analysis and subsequent figures) showed a significant suppression of coherence between hemispheres ($p < 0.0015$) in stimulated animals compared to nonstimulated animals (see Fig. 5.2). Medvedev reported findings that coherence decreased in the hippocampus at frequencies from 20–100 Hz, suggesting an "anti-binding" mechanism; our findings indicate that this decrease in coherence is evident for spontaneous epilepsy [38].

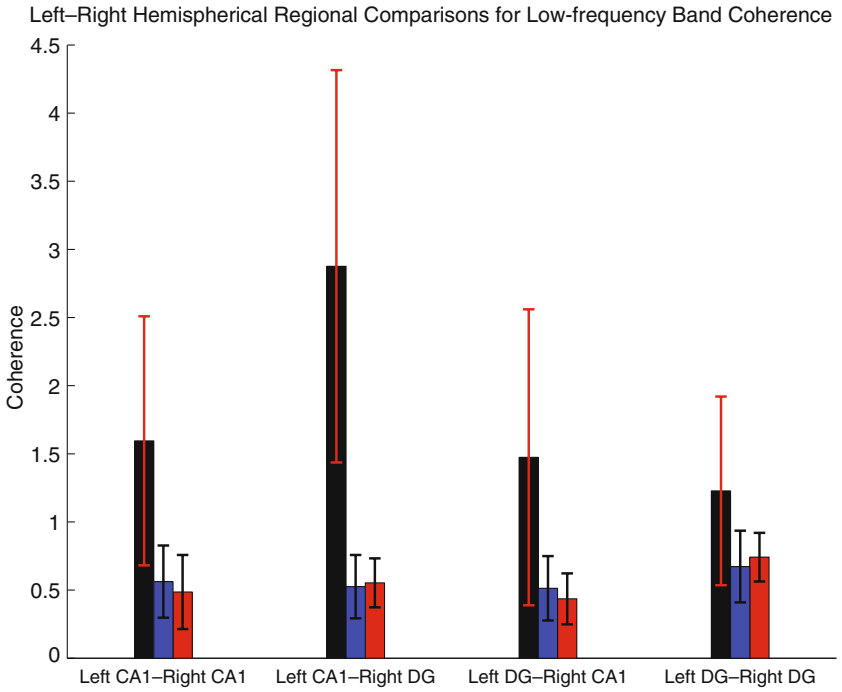

Fig. 5.2 [Color plate] Coherence comparisons of stimulated vs. nonstimulated animals. Mean and standard deviation of coherence in the 40–200-Hz band for two stimulated animals (blue and red bars), and one nonstimulated animal (black bar) are shown. Note that the inter-hemispherical coherence is suppressed in the stimulated animals.

5.3 Spreading in hierarchical cluster networks

5.3.1 Model of hierarchical cluster networks

How can the topology of neuronal networks reduce or enhance the probability of a transition to the epileptic state? We used a basic spreading model to explore the

role played by different network topologies in producing persistent, yet contained, activations. Spreading analysis has also been applied to cortical networks at the global level [33], and to other complex networks with a nonrandom organization [10, 21, 44].

The present model operates without inhibitory units such as cortical inhibitory interneurons, as we were specifically interested in the contribution of network topology. This lack of inhibition is also reflective of structural attributes of cortical networks [34], and other complex networks such as social networks [44].

In our model, individual network vertices represent cortical columns whose connectivity follows the levels of hierarchical organization (Fig. 5.3(a)). Networks were undirected graphs with $N = 1\,000$ vertices and $E = 12\,000$ edges. To create the hierarchical cluster network, 1 000 vertices were divided up into 10 disjoint sets ("clusters"), each consisting of 100 vertices. Each cluster was further split into 10 "subclusters" containing 10 vertices each. The network was wired randomly, such that 4 000 edges (one third of the total 12 000 connections) connected vertices within the same subclusters, 4 000 edges connected vertices within the same clusters, and 4 000 were randomly distributed over all nodes of the network (Fig. 5.3(b)). The edge density in these networks was 0.025 whereas the clustering coefficient was 0.15. The characteristic path length (2.6), however, was similar to that of random networks (2.5), indicating properties of small-world networks [53].

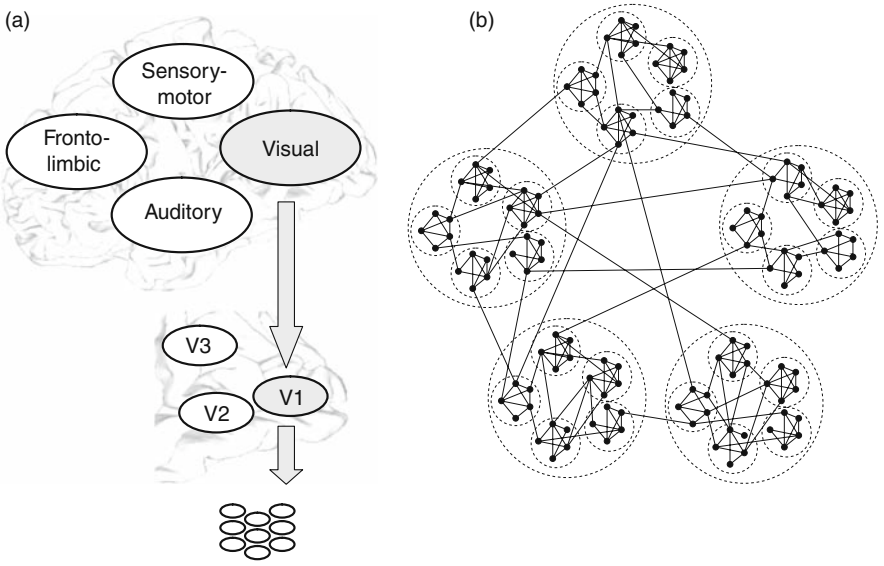

Fig. 5.3 (a) The hierarchical network organization ranges from cluster (e.g., visual cortex), to subcluster (e.g., V1), to individual nodes (cortical columns). (b) Schematic view of a hierarchical cluster network with five clusters, each containing five subclusters.

We compared spreading (i.e., propagation of activation) in hierarchical networks with spreading in random and small-world benchmark networks with the same number of vertices and edges [25]. The small-world networks with a rewiring

probability of $p = 0.5$ had similar clustering coefficient values (0.11) and characteristic path lengths (2.6) to that of the hierarchical networks, but lacked the characteristic cluster architecture. We also generated Erdös-Rényi random networks [13].

5.3.2 Model of activity spreading

We used a simple threshold model for activity-spreading in which a number i of randomly selected nodes were activated in the first step. An additional component was the extent of localization of the initial activation i_0. For initialization, i ($i \leq i_0$) nodes among the nodes 1 to i_0 were randomly selected and activated in the first time-step. The network nodes were numbered consecutively. For example, by setting i_0 to 10, 20 or 100, only nodes in the first subcluster, the first two subclusters, or the first cluster, respectively, were activated during initialization. Thus, i determined the number of initially activated nodes while i_0 controlled the localization of initial activations, with smaller values resulting in more localized initial activity. At each time-step, inactive nodes become activated if at least k neighbors were activated (neighbors of a node are nodes to which direct connections exist). Activated nodes could become inactive with probability ν. As default we used $k = 6$ and $\nu = 0.3$. The state of the network was determined after 200 steps of the simulation as activity was either dying out (zero activation), spreading through the whole network (more than 50% of the nodes were active), or balanced for an intermediate activation level.

5.3.3 Spreading simulation outcomes

Across different simulation conditions, hierarchical cluster networks show a larger variety of behaviors than do random or small-world networks, and produce persistent yet balanced network activity for a wider range of initial conditions.

Examples exhibiting the behaviors of the different networks are shown in Fig. 5.4. The figure shows the result of 20 simulations in the three network types when 10%

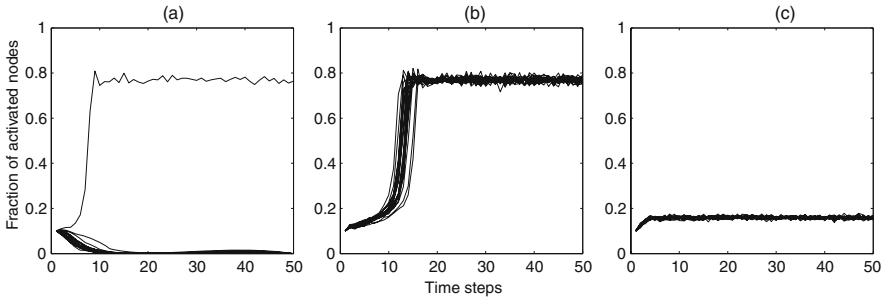

Fig. 5.4 Examples for spread of activity in (a) random, (b) small-world and (c) hierarchical cluster networks ($i = 100, i_0 = 150$), based on 20 simulations for each network.

of the nodes were randomly selected for initial activation. In the random network, activity dies out in most cases. In the small-world network, spread of activity results in almost complete activation (NB: 100% activation cannot be achieved due to the deactivation probability for active nodes at each step). In contrast, the hierarchical cluster network produces cases in which spreading is limited. Such persistent activation can be sustained with different patterns and varying extent of involved nodes (see Fig. 5.5).

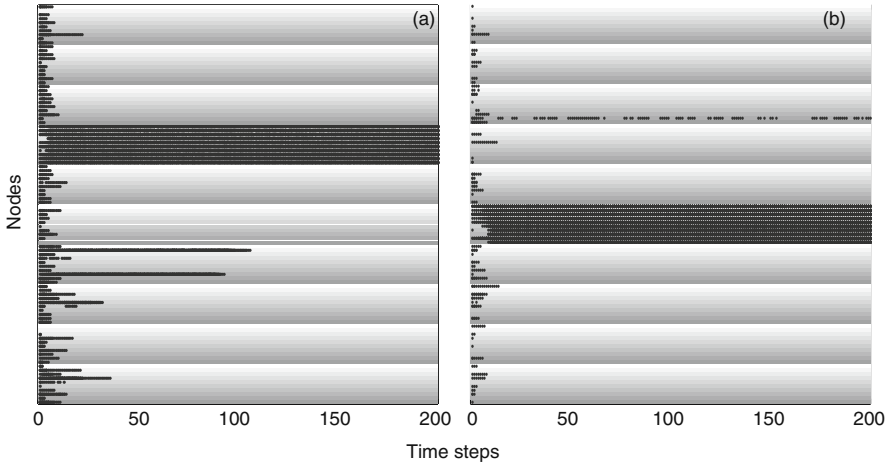

Fig. 5.5 Examples for different sustained activity patterns in hierarchical cluster networks ($i = 90, i_0 = 1000$). Graded gray background shading indicates the 10 subclusters within each of the 10 clusters. Black dots represent nodes active at the respective time-step. (a) One cluster showing sustained activity. (b) One cluster remaining active with frequent co-activation of one external subcluster.

5.3.3.1 Delay until large-scale activation

Does the "speed" with which the whole network can become activated depend on the network topology? For those cases where large-scale activation was observed, we looked at the number of time-steps required to reach this state. For the random network, if activity spread at all, it did so rapidly, typically in less than 10 time-steps. Even if the initial activity was in the borderline range for all-or-none network activation, not more than 15 time-steps were required in any of the cases. This was in contrast to the small-world and hierarchically clustered networks, for which a wide range of delay times was observed. For the small-world network, delayed spreading depended on whether initial activity was strictly localized ($i_0 = i$). Setting $i_0 = i = 90$ typically resulted in about 40 time-steps for spreading, whereas for $i_0 = 190, i = 90$, spreading in the small-world network appeared similar to that in the random network. By contrast, for the hierarchically clustered network, spreading to the global

level did not arise when the initial activation was too strictly localized. A maximum delay for spreading was achieved by localizing the initial activity within two or three clusters (e.g., delay around 40 steps for $i_0 = 200, i = 90$). Thus neighborhood clustering in the small-world and hierarchical networks slows down the spreading of activation. Note that the increase in delay compared to the random network is larger than would be expected from the increase of the characteristic path length. These results indicate that limiting the number of short-cuts or connections between clusters acts as a bottleneck for the spreading of activation. We will come back to this point later.

5.3.3.2 Robustness of sustained-activity cases

The higher likelihood of sustained activation in hierarchical networks is largely independent of our choice of model parameters. We systematically explored the network activation behaviors resulting from different settings of the initial node activation and localization parameters. Both the number of initially activated nodes and their localization had a critical influence on the resulting spreading patterns [25]. Since at any given time only a fraction of neurons in a neural system will be in the activated state, we limited the maximum number of initially active nodes to 250, that is, one-quarter of all network nodes. Persistent contained activity in hierarchical networks was robust for a wide range of initial localization and activation parameters (indicated by the gray parameter domain in Fig. 5.6). For small-world networks, however, parameters needed to be finely tuned in order to yield sustained activity. Thus, hierarchical networks showed sustained activity for a wider range of initial activation conditions.

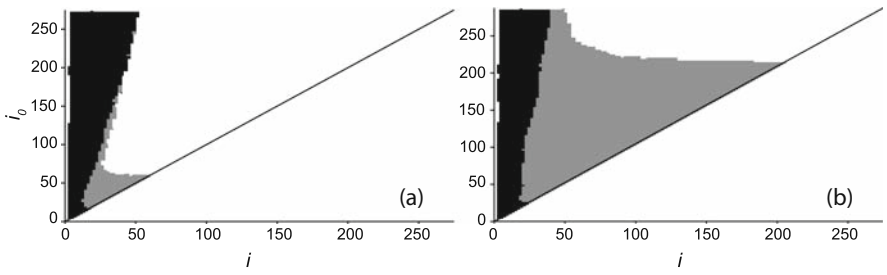

Fig. 5.6 Parameter space exploration of the critical range for all combinations of initial activation parameter i and localization parameter i_0, based on 1000 test cases. Simulation outcomes are indicated by gray level (black: activity died out; gray: limited spreading; white: complete spreading). (a) Small-world network; (b) hierarchical cluster network.

The results were also robust in terms of the spreading parameters k and ν. Using a Monte Carlo approach, for each pair of k and ν, we generated 20 small-world and 20 hierarchical networks. For each network, the dynamics for 1000 randomly chosen parameters i and i_0 were tested (see Fig. 5.7). A trial was considered to show

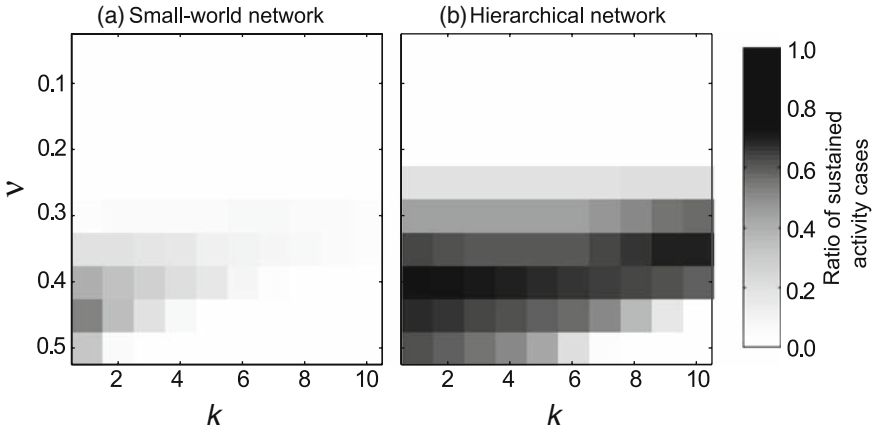

Fig. 5.7 Ratio of sustained activity cases depending on the spreading parameters k (activation threshold) and v (deactivation probability) for (a) small-world, and (b) hierarchical cluster networks.

sustained activity if at least one, but no more than 50%, of all nodes were activated at the end of the simulation. For each pair of spreading parameters k and v, the average ratio of cases for which sustained activity occurred, related to the ratio of the gray space in Fig. 5.6, was larger for hierarchical cluster networks than for small-world networks. The maximum ratio was 67% of the cases for hierarchical cluster networks compared to 30% for small-world networks.

Sustained spreading in hierarchical cluster networks still occurred for different ratios of connectivity within and between clusters and subclusters. However, results differed for large changes in the proportion of connections between modules (clusters or subclusters; see [25] for details): *Reducing the proportion of connections between modules* led to a higher proportion of cases with sustained activity. While the total number of edges was kept constant, the number of connections between cluster and subclusters was reduced. Now, three or more clusters could be persistently activated without a subsequent spread through the whole network (Fig. 5.8a). In these cases, the limited number of inter-cluster connections formed a bottleneck for activation of the remaining clusters. *Increasing the proportion of connections between modules* blurred the boundaries of local network modules and reduced the proportion of cases with sustained activity, but the proportion was still larger than that for small-world networks. However, for these networks, initially contained activation was able to spread through the network at later stages of the simulation (Fig. 5.8b). These results for spreading dynamics are in line with earlier studies on the important role of inter-cluster connections for structural network integrity [26].

For the above model, activated nodes might stay active for a long time, potentially until the end of the simulation. However, energy resources for sustaining neural network activations are limited in real neural systems. For instance, exhaustion occurs during epileptic seizures, reducing the duration of large-scale cortical activation. Therefore, we also tested the effect of restricting the number of

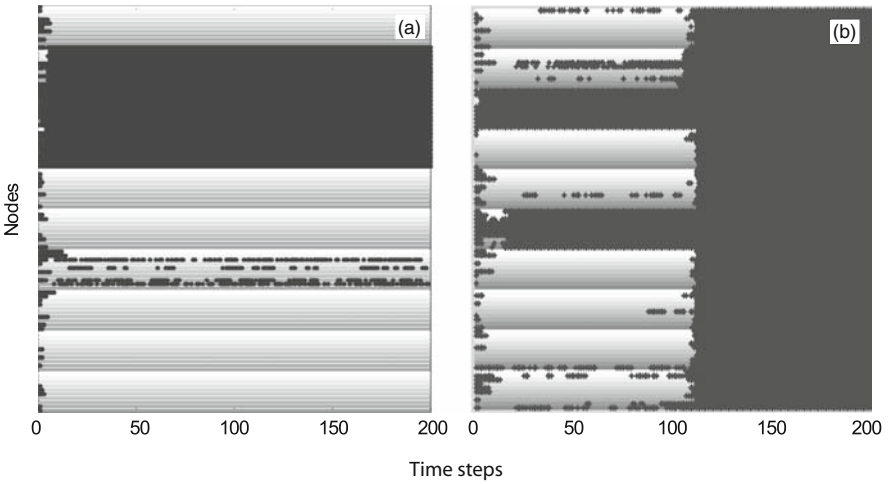

Fig. 5.8 (a) Sustained activity in three clusters, without subsequent spreading through the rest of the network, was possible when the number of connections between clusters was reduced. These few inter-cluster connections created a bottleneck for further activity spreading. (b) When the number of inter-cluster connections was increased, activity was more likely to spread through the entire network. The figure shows an activation that is initially limited to two clusters and subsequently spreads through the whole network.

time-steps that nodes could be consecutively active from seven steps to a single step. Sustained network activation could still occur in the hierarchical cluster network, despite different degrees of limiting node exhaustion: sustained activity was largely independent of the exhaustion threshold parameter. The range of parameters for which sustained activity occurred remained similar to that in the previous analyses, with no clear correlation to the number of steps (average ratio of sustained-activity cases over all pairs of the spreading parameters was 0.272 ± 0.068).

We also tested whether these findings were specific to the threshold activation model described here. Simulations with integrate-and-fire (IF) neurons [32] as network nodes led to similar results. In comparison to random networks, hierarchical cluster network simulations showed easier activation, and exhibited intermediate states of activation [T. Jucikas, private communication]. Thus, our results do not appear to depend on the specific activation model, but are general properties of the topology of the network.

5.4 Discussion

Our simulations demonstrate the strong influence of network topology on spreading behavior. Clustered networks are more easily activated than random networks of the same size. This is due to the higher density of connections within the clusters,

facilitating local activation. At the same time, the sparser connectivity between clusters prevents the spreading of activity across the whole network. The prevalence of persistent yet contained activity in hierarchical cluster networks is robust over a large range of model parameters and initial conditions. In contrast, small-world networks *without* hierarchical modules frequently show a transition to the putative epileptic state of large-scale activation.

The present hierarchical cluster model, which reflects the distributed multilevel modularity found in biological neural networks, is different from previously studied "centralistic" hierarchical modular networks in which most nodes are linked to network hubs [45]. While developmental algorithms have been suggested for the latter type of network, there are currently no algorithms for producing the hierarchical cluster networks presented here. However, single-level clustered network architectures can be produced by models for developmental spatial growth [27, 29, 42] or dynamic self-organization of neural networks [22]; such models may serve as a starting point for exploring the biological mechanisms for developing multilevel clustered neural architectures.

Present results provide a proof of concept for three points. First, persistent but contained network activation can occur in the absence of inhibitory nodes. This might explain why cortical activity does not normally spread to the whole brain, even though top-level links between cortical areas are exclusively formed by excitatory fibers [34]. While the involvement of inhibitory neurons and other dynamic control mechanisms may further extend the critical range, the present results indicate that the hierarchical cluster architecture of complex neural networks, such as the mammalian cortex, may provide the principal structural basis for their stable and scalable functional patterns. Second, in hierarchical clustered networks, activity can be sustained without the need for random input or noise as an external driving force. Third, multiple clusters in a network influence activity spreading in two ways: bottleneck connections between clusters limit global spreading, whereas a higher connection density within clusters sustains recurrent local activity.

5.5 Outlook

It will be important to see how the *topological inhibition* based on the cluster architecture relates to *neuronal inhibition* from inhibitory interneurons. For topological inhibition, an increase in the number of axons between clusters will enhance the likelihood for activity spreading. At the cortical level, this could be visualized as changes in white matter volume that could be detected by tract tracing or diffusion tensor imaging. An alternative way to increase the probability of activity spreading to other clusters would be a larger connection strength of existing inter-cluster connections. For neuronal inhibition, the most effective way for inhibitory neurons to limit large-scale activity spreading from its own cluster to another cluster would be to reduce the activity in excitatory neurons that project to the other cluster. This would be the network analogue to the frequent positioning of inhibitory synapses

close to the axon hillock to prevent the spreading of activation at the individual neuron level. If activity of another cluster—independent of the activity level of an inhibitory neuron's own cluster—is to be reduced, a direct long-range inhibitory projection to that cluster is needed.

The model of topological inhibition may have practical implications and may guide future research. For instance, it might be worthwhile to test whether epileptic patients show a higher degree of connectivity between cortical network clusters or other changes in structural connectivity which would facilitate spreading. Such changes might be reflected in certain aspects of functional connectivity [1, 46], or might be demonstrated more directly by observing structural changes in brain connectivity (using, for example, diffusion tensor imaging).

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Glossary: Graph theory and network science

Adjacency (connection) matrix The adjacency matrix of a *graph* is an $n \times n$ matrix with entries $a_{ij} = 1$ if node j connects to node i, and $a_{ij} = 0$ if there is no connection from node j to node i.

Characteristic path length The characteristic path length L (also called "path length" or "average shortest path") is the global mean of the finite entries of the *distance matrix*. In some cases, the median or the harmonic mean may provide a better estimate.

Clustering coefficient The clustering coefficient C_i of node i is the number of existing connections between the node's neighbors divided by all their possible connections. The clustering coefficient ranges between 0 and 1 and is typically averaged over all nodes of a *graph* to yield the graph's clustering coefficient C.

Cycle A *path* which links a node to itself.

Degree The degree of a node is the sum of its incoming (afferent) and outgoing (efferent) connections. The number of afferent and efferent connections is also called the in-degree and out-degree, respectively.

Distance The distance between a source node i and a target node j is equal to the length of the shortest path.

Distance matrix The entries d_{ij} of the distance matrix correspond to the *distance* between node j and i. If no path exists, $d_{ij} = \infty$.

Graph Graphs are a set of n nodes (vertices, points, units) and k edges (connections, arcs). Graphs may be undirected (all connections are symmetrical)

or directed. Because of the polarized nature of most neural connections, we focus on directed graphs, also called digraphs.

Path A path is an ordered sequence of distinct connections and nodes, linking a source node i to a target node j. No connection or node is visited twice in a given path. The length of a path is equal to the number of distinct connections.

Random graph A graph with uniform connection probabilities and a binomial degree distribution. All node degrees are close to the average degree ("single-scale").

Scale-free graph Graph with a power-law degree distribution. "Scale-free" means that degrees are not grouped around one characteristic average degree (scale), but can spread over a very wide range of values, often spanning several orders of magnitude.

Small-world graph A graph in which the *clustering coefficient* is much higher than in a comparable random network, but the *characteristic path length* remains about the same. The term "small-world" arose from the observation that any two persons can be linked over few intermediate acquaintances [39].

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