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RESEARCH ARTICLE

Robust emergence of small-world structure in networks of spiking neurons

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Abstract Spontaneous activity in biological neural networks shows patterns of dynamic synchronization. We propose that these patterns support the formation of a small-world structure—network connectivity optimal for distributed information processing. We present numerical simulations with connected Hindmarsh–Rose neurons in which, starting from random connection distributions, small-world networks evolve as a result of applying an adaptive rewiring rule. The rule connects pairs of neurons that tend fire in synchrony, and disconnects ones that fail to synchronize. Repeated application of the rule leads to small-world structures. This mechanism is robustly observed for bursting and irregular firing regimes.

Keywords Self-organization · Spiking neuron · Modularity · Neural network

Introduction

Fodor (1983) introduced the notions of modularity and isotropy to describe what an optimal information processing architecture looks like. Modules are distinct entities of several elementary components that perform specific processing tasks, separable from those of other modules (Ravasz et al. 2002); Isotropy implies that information is broadcasted equally to all possible other functional brain regions. To Fodor, isotropy and modularity were mutually exclusive properties, because modularity requires information encapsulation; processing within a module should be isolated from global contextual information. Fodor, therefore, proposed that modularity and isotropy belong, respectively, to different subsystems of our human information processing architecture. Whereas modularity is a property of input systems plus language, isotropy belongs to the central cognitive system.

More recently, Carruthers (2003, 2005a, b) and Barrett (2005; Barrett and Kurzban 2006, in press) provided arguments that encapsulation is not a necessary or even relevant requirement for a multi-modular (or massively modular) cognitive architecture. This means we need to reconsider Fodor's argument about the subsystems. We may raise the question: would it be possible to combine modularity and isotropy in one and the same system?

We propose that the combination of modularity and isotropy is realized in systems with small-world network connectivity. Small-world networks are characterized by a *high clustering coefficient* in combination with a *low characteristic path length* (Watts and Strogatz 1998), whereas both path length and clustering coefficient are high in regular network structures and low in random ones. The notion of clustering involves the presence of ''triangles'' in the connectivity structure of the network. If a site A is connected to sites B and C, then, if the clustering coefficient is high it is likely that a connection between B and C exists.

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Characteristic path length, on the other hand, is a measure of how many intermediate nodes need to be visited, on average, to reach an arbitrary site B starting from an arbitrary node A. Because of their high clustering coefficient, small-world networks are optimized for local communication and because of their short path lengths they are optimized for global communication (Latora and Marchiori 2001). Small world networks offer the best of both worlds.

As the brain consists on all levels of many specialized and interacting regions, the efficiency of their interactions, both globally and locally is of crucial importance for almost any brain function. Small world networks, therefore, offer an optimal infrastructure for interactions within and between brain regions. Clustering provides the functional architecture to support modularity in brain functional architecture: sites within a module process interrelated information, so their communication is optimal if they are locally interconnected. The path length is of importance for how easy it is to connect arbitrary sites. This property, therefore, provides support for isotropy in brain functional architecture.

From an evolutionary perspective, it is therefore plausible that small-world connectivity is found throughout the brain. Its prominence is increasingly being recognized in the neurosciences; small-world structure has been detected on the large scale using magneto-encephalography in the functional connectivity of brain areas (Stam 2004), as well as on the small scale, in the anatomy of the visual cortex (Mountcastle 1997)[1] and the connectivity arising in cultured neuronal networks (Shefi et al. 2002). On the other hand, it is unlikely that details of brain connectivity structure are dictated by the human genome. We propose that evolution has predisposed the development of this connectivity structure through adaptive self-organization.

Our present article addresses the question: are there any known, basic mechanisms, by which small-world structure could develop? Watts and Strogatz (1998) introduced a simple rewiring scenario for generating small-world networks. By replacing a small number of short-range connections with long-range ones in an initially regular network, the characteristic path length could be reduced substantially with only minimal changes to the clustering coefficient. The proposed scenario, although simple and elegant, is not always plausible for the evolution of small-world networks in the brain. Even though the development of brain tissue is genetically pre-programmed, it is extremely unlikely that the extensive rewiring of synapses that follows their initial attachment (Zhang and Poo 2001) starts off from a regular network structure. A basic mechanism will have to start off from unstructured random network conditions in order to explain the emergence of small-world structure in general.

Perhaps the most widely accepted basic mechanism for self-organization in neural networks is adaptive plasticity. Usually, this is taken to mean that synapses change in strength depending on experience. On the other hand, a good deal of functional differentiation has already occurred in the brain prior to experience. Functional differentiation can still be considered as a product of adaptive plasticity if we take spontaneous activity into account. Unlike most artificial neural networks, brain dynamics is characterized by spontaneous ongoing activity, in which dynamic patterns of synchronization can be observed. Adaptation to patterns of synchrony in spontaneous activity can occur independently of and prior to experience. We propose to apply the Hebbian principle of ''what fires together wires together'' to spontaneous neural activity.

Spontaneous activity takes a characteristic form in early development of the brain. In mammals prior to or briefly after birth, activity in the developing neural circuits often has the form of recurrent bursts, leading to massive synchronization (Feller 1999; Van Pelt et al. 2004). In the retina, for instance, such activity is essential for the development of the lateral geniculate nuclei prior to birth (Penn et al. 1998). The number of neurons in the nuclei projecting to the visual cortex is reduced if this spontaneous activity is blocked by tetrodotoxin (Catalano and Shatz 1998). Bursting activity in the brain is traditionally associated with pathological conditions and indicative of epilepsy. In epileptic activity depolarizing potentials involve global activity. There is evidence of a low-dimensional chaotic signal at the level of EEG (Babloyantz and Destexhe 1986; Breakspear et al. 2005). Developing circuits show a different form of spontaneous bursting. Bursts of synchronized activity in immature rat hippocampal slice preparations are locally generated from different initiation sites (Menendez de la Prida and Sanchez-Andres 2000) and are weakly chaotic (Nakatani et al. 2003).

This type of deterministic activity appears to play a constructive role in the perinatal development of the neuronal network architectures. Maeda et al. (1998) found that bursts of synchronized spikes led to long-term potentiation (LTP) of synapses in neurons cultured in vitro. Postsynaptic bursting was found to be

[1] Although this author did not make explicit claims that the structures they observed were small worlds, the combination of modules (micro columns) and a limited number of long-range connections was observed that, according to Watts and Strogatz (1998) is characteristic of small world networks.

associated with Hebbian induction of long term potentiation (Otsu et al. 1995; Pike et al. 1999). These observations give us sufficient grounds to propose that small-world networks emerge through Hebbian plasticity in adaptation to spontaneous activity in developing neuronal networks.

In a first attempt to demonstrate this effect, an adaptive rewiring scenario was proposed in a number of previous studies (Gong and van Leeuwen 2004; Van den Berg and van Leeuwen 2004). These studies, instead of model neurons, involved spontaneous synchronization in coupled maps. Coupled maps are networks of real-valued nonlinear oscillators that are updated in discrete time. The various regimes that occur under different parameter values have been studied extensively in globally coupled maps (Kaneko 1990) and in regular (Kaneko 1989), randomly connected (Manrubia and Mikhailov 1999), and small-world networks (Gade and Hu 2000). Like all coupled oscillator systems, coupled maps show spontaneous synchronization of their activity. Patterns of synchronized activity and their stability vary with the choice of parameter values for the network. For instance, globally coupled maps have coherent, ordered, or partially ordered phases and disordered phases in different regions of their control parameter space. ''Order'' refers to a state of exact synchrony; partially ordered phases consist of sharply demarcated clusters of synchronized units. In randomly coupled networks, especially the sparsely coupled ones, there are only fuzzy synchronization and fuzzy clusters. Fuzzy synchronization is separated in the parameter space from the fuzzy clustering phases by a region of intermittent activity.

For intermittent and fuzzy clustering regimes, an adaptive rewiring scenario (Gong and van Leeuwen 2004) produced a small-world network structure. The small-world structure emerges as a result of iteratively rewiring an initially randomly connected network. A pair of units receives a connection if their activity patterns are maximally synchronized. The new connection replaces one between two units that are not synchronized. Iterative rewiring in adaptation to dynamic synchrony is a simple but effective mechanism for the development of small-world structures in brain networks. Interestingly, the activity in the final network was intermittent, independent of whether rewiring started out from intermittent activity. It was concluded that small-world structure and intermittent activity establish a symbiotic relationship.

In our present study we apply the proposed adaptive rewiring scenario to a network of spiking model neurons. We consider a network in which the units represent single neurons a step towards greater biological realism, compared to basic oscillator maps. A first question, therefore, is: are there any regimes of spiking neurons in which the system evolves towards a small world. Various dynamic regimes that occur in coupled maps are analogous to those in spiking neurons (Alexander and Cai 1991). In particular, therefore, how does regular bursting activity (the model neuron analogue of intermittency in coupled maps) compare in this respect with irregular firing (the analogue of fuzzy clustering in coupled maps)? A second question, relating to the predominance of intermittency after rewiring in coupled maps, is: how do the activity regimes of model neurons change as a function of the evolution of the network.

Method

To investigate whether adaptive rewiring enables a network to evolve into a small-world structure, we used the Hindmarsh–Rose model neuron (Rose and Hindmarsh 1989). This model is a simplified Hodgkin–Huxley neuron. Hodgkin and Huxley (1952) originally used four linked first-order differential equations to model the membrane potential of a giant squid axon. Their model has served as a basis of most work in recent decades but its complexity imposes considerable computational costs in modeling large-scale networks (Izhikevich 2004). Unlike even simpler models such as the leaky integrate-and-fire model, in Hindmarsh–Rose model-neurons action potentials are explicitly modeled. The model exhibits realistic neuronal response properties, including a range of periodic, chaotic, and irregular bursting behavior depending on a single input parameter (Hindmarsh and Rose 1984; Kaas-Petersen 1987; Hansel and Sompolinsky 1992).

Dynamically coupled Hindmarsh–Rose model neurons may be characterized by different qualitative response properties depending on coupling strength. Hansel and Sompolinsky (1992) found that in a globally coupled assembly of these model neurons with uniform excitatory coupling between them, low frequency periodic firing, chaotic bursting or high-frequency periodic firing emerged depending on the connection strength. In these simulations, uncoupled neurons exhibited a wide range of dynamical behaviors (quiescence, low or high frequency spiking, regular bursting, chaotic bursting), thus suggesting that the observed population response was an emergent property. Given that the qualitative firing properties of

Hindmarsh–Rose model neurons are sensitive to network coupling conditions; these can be used effectively to explore the interaction between neuronal response properties and evolution of connectivity in plastic neural networks.

In Hindmarsh–Rose model neurons the membrane potential (x) of is governed by an exogenous input (I), the activity of other neurons that are linked to it, a recovery variable (y) and a slow adaptation current (z). There are three first order differential equations linking x, y and z:

$$\dot{x}_i = y_i - ax_i^3 + bx_i^2 - z_i + I_i + \sum_{j\in A} S_j - V \tag{1}$$

$$\dot{y}_i = c - dx_i^2 - y_i \tag{2}$$

$$\dot{z}_i = r[s(x_i - x_{i_0}) - z_i] \tag{3}$$

where a, b, c, d, r, s are constant parameters, the subscript i denotes the neuron number and x_{i_0} is the initial value of x_i. S_j is the binary neuronal output from the jth neuron and A is the set of the neurons that are neighbors of the ith neuron in the network. The coupling equations used are same as in Raffone and van Leeuwen (2003) except that in their study the binary neuronal output from each neuron in set A was multiplied by a weight. We consider only the case when the inputs are not weighted. As we were concerned with the modeling of neuronal development in the absence of exogenous stimuli, I was set to zero. V is an inhibition term. S and V are defined as follows:

$$S_j = \Theta(x_j - x^*) \tag{4}$$

$$V = \beta \sum_{j\in\{A,i\}} S_j/N_{A_j} \tag{5}$$

where Θ is the Heaviside step function, x^* is a threshold potential which was set to zero. Note that the inhibitory term is normed (i.e. divided by N), whereas the excitatory term is not. In this manner, the number of excitatory connections determines the contribution of each neuron to the overall state of activity of the network, but the inhibitory connections do not. This is appropriate as, in the present network, connections from inhibitory interneurons are not explicitly modeled. Whereas interactions between neurons are usually modeled as event-driven, the zero threshold assures that system dynamics involve a high frequency of firing. This may be considered adequate for developing neural networks, as excitation prevails over inhibition in networks of immature neurons due to the high concentration of Cl^- ions in these neurons.

In Eq. 5, β is the coupling strength,N_{A_j} is the number of neighboring units A in the jth neuron. Whereas a realistic network would include a population of inhibitory inter-neurons, these are here represented by effective inhibitory coupling among the principal neurons. Both excitatory and inhibitory coupling were instantaneous, as in previous studies in networks with these model neurons (e.g. Hansel and Sompolinsky 1992; Raffone and van Leeuwen 2003). These studies have shown that zero time lag excitatory coupling generates synchronization effects, and zero time lag inhibitory coupling generates spike desynchronization. We fixed excitatory strength and varied inhibitory strengths to adjust qualitative firing patterns of neurons (regular bursting versus irregular spiking). In both regimes, strengths were chosen that secure stable neuronal firing rates and allow excitation-mediated spike synchronization while preventing complete synchronization.

In the simulations, a = 1.0, b = 3.0, c = 1.0, d = 5.0, r = 0.006, s = 4.0, andx_{i_0} were homogeneously distributed random numbers between – 0.6 and 1.6, as in Raffone and van Leeuwen (2003).

In our simulations, a network of Hindmarsh–Rose spiking neurons was given an initial connection pattern based on a randomly chosen subset of connections from a full connectivity matrix. In all simulations, networks of 300 nodes with an excitatory connection density of 10% were used. These values assure that the network remains fully connected during the rewiring process (Van den Berg and van Leeuwen 2004). The connections were unidirectional.

The network was allowed to evolve using a rewiring algorithm that was similar to that used by Van den Berg and van Leeuwen (2004) and Gong and van Leeuwen (2004). The rewiring was stopped when the characteristic path length and its clustering coefficient remained the same from the previous time or until they had been updated for a maximum of 15,000 times (both actually occurred—in the figures reporting the results early terminations can be identified). The model was implemented in MATLAB7.0/SIMULINK. A variable step solver (ode23) was used.

The rewiring procedure is as follows:

1. The model is run for 500 ms.
2. One neuron is selected randomly and the synchrony between the chosen neuron and all other neurons is calculated.
3. If the neuron with the highest synchrony is one of the postsynaptic neurons of the chosen neuron, the connection between the two is left unchanged. If there is no connection between the two, establish a connection by setting the neuron as a postsynaptic

neuron of the chosen neuron and disconnect the chosen neuron with the neuron that gives the lowest synchrony.
4. Steps 2–3 are repeated until a given number of connections have been rewired.
5. The clustering coefficient and characteristic path length are updated.

The algorithm is the same as in Gong and van Leeuwen (2004), except that in Step 4, for reasons of computational efficiency, instead of one several connections were rewired. In our algorithm, this number is set equal to 10% of the available nodes, resulting in 30 rewirings per epoch. The rewiring rule is Hebbian in the sense that ''what fires together wires together'', but not in the specific sense of Hebb's rule, where a synaptic weight is changed by a certain amount depending on the level of correlated activity. The rewiring algorithm simulates the effect that synchronous firing promotes the creation of synapses and asynchronous firing results in their deletion (Nishiyama et al. 2000).

The synchrony between the two neurons as used in the rewiring procedure was defined as:

$$\mathrm{Sync}_{ij} = \sum_{k=1}^{K} \left\| S_i(k) - S_j(k) \right\| \tag{6}$$

where S_i and S_j are the binary spiking states of the two neurons concerned as defined in the previous subsection. Sync_{ij} is zero if two neurons are totally synchronized and it increases with decreasing synchrony between the two neurons. The number $K = 500$ ms, meaning that the synchrony is calculated over the entire interval since the last rewiring. This definition of synchrony was adopted in Gong and van Leeuwen (2004) for reasons of simplicity, but could be replaced, if preferred, by a measure based on the number of co-occurring spikes in a given time window or cross-correlation. The clustering coefficient (C) and the characteristic path length (L) are defined as follows:

$$C = \frac{1}{N} \sum_{i=1}^{N} \frac{m_i}{n_i(n_i - 1)} \tag{7}$$

$$L = \frac{1}{N(N-1)} \sum_{i=1}^{N} \sum_{j=1, j \neq i}^{N} \mathrm{spl}_{ij} \tag{8}$$

N is the size of the network and n_i is the number of neurons in the neighborhood of the neuron i. The neighborhood of a neuron is the collection of all its postsynaptic neurons. m_i is the number of connection within the neighborhood of the neuron i. spl_{ij} is the shortest path length between neuron i and neuron j. By definition, C lies between zero and unity whereas L will be greater than unity (as the shortest path length possible between two neurons will be greater or equal to one).

Results

We performed our investigation with two types of neuronal firing behavior in the initial random network configuration: regular bursting and irregular spiking. Given that we are dealing with spontaneous activity, we refrained from using external input strength (I) to obtain these firing pattern of neurons. In previous studies (e.g. Hansel and Sompolinsky 1992), these activity patterns of model neurons were obtained, depending on the strength of excitatory coupling. In our study, we kept the strength of excitatory connections fixed and uniform. We obtained the activity patterns instead by varying the strength of global inhibitory coupling (β parameter). With $\beta = 1.2$, bursting spike patterns occur (Fig. 1a), whereas a coupling strength of $\beta = 1.5$ results in irregular spiking patterns (Fig. 1b).

Thirty-two runs of the algorithm, half for each coupling condition, were performed, the results of which are shown in Fig. 2. To evaluate the clustering coefficients and characteristic path lengths in the networks generated by our algorithm, we introduced a *regular* and several *random* networks with the same number of nodes and connection density. The regular network consists of a one-dimensional ring, in which the number of outward connections to its immediate neighbors was the same for each node. This network yields a clustering coefficient $C(0) = 0.371$ and a characteristic path length $L(0)$ of 5.06. In the random networks, the number of postsynaptic connections per neuron ranged from 14 to 50. A typical random network has a clustering coefficient $C(1) = 0.096$ and path length $L(1) = 1.97$. We calculated normalized clustering coefficients CN and characteristic path lengths LN by dividing against those of the regular network. Thus, for the typical random network $\mathrm{CN} = C/C(0) = C(1)/C(0) = 0.258$ and $\mathrm{LN} = L/L(0) = L(1)/L(0) = 0.389$.

As shown in Fig. 2, in all our simulations, LNs increase somewhat, but reach a platform quickly. This phenomenon is known from Watts and Strogatz (1998): small-world networks have characteristic path lengths that are almost as good as random networks. CNs

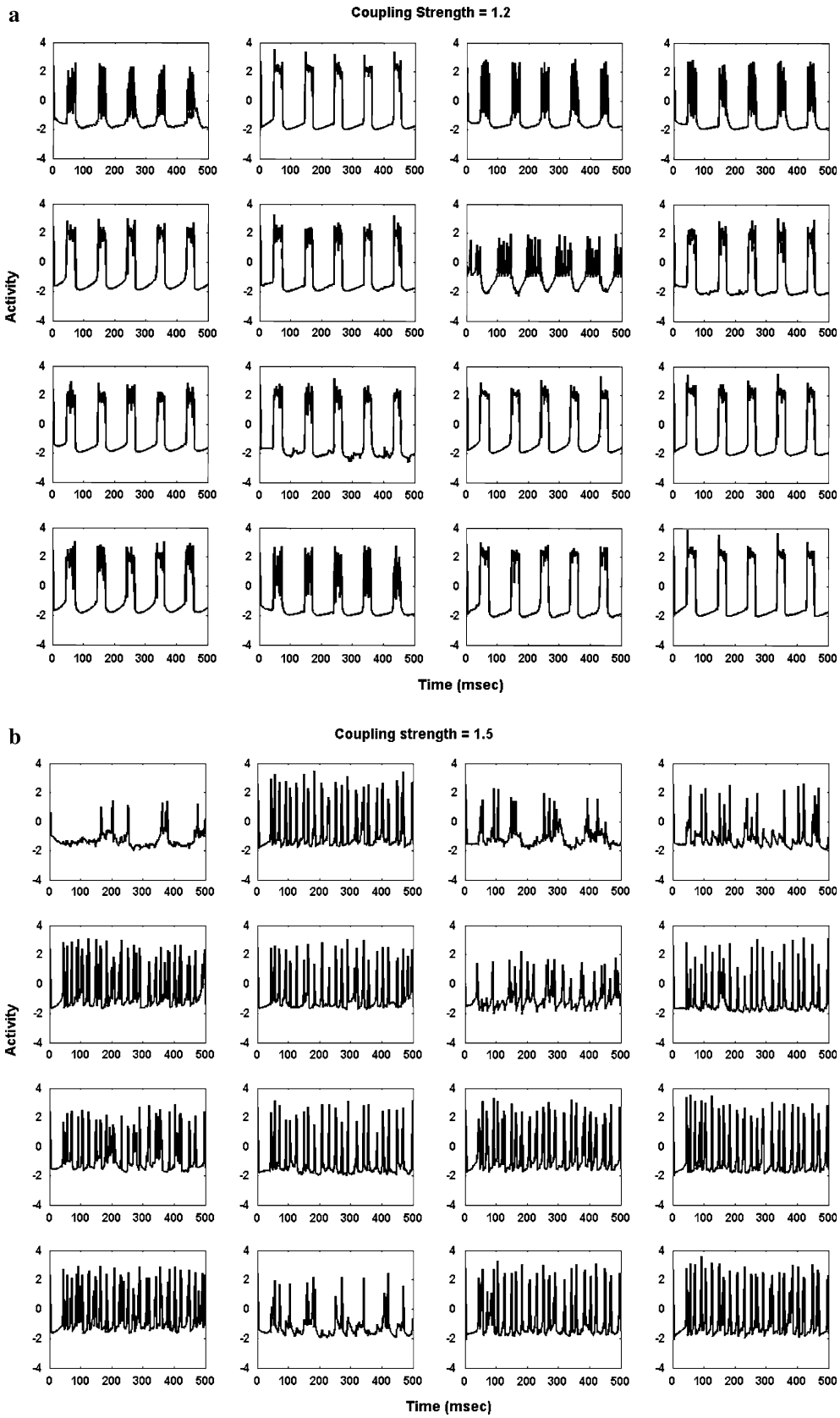

Fig. 1 Activity in 16 of the 300 neurons from the model with random connections and coupling strength $\beta = 1.2$ (**a**) or 1.5 (**b**)

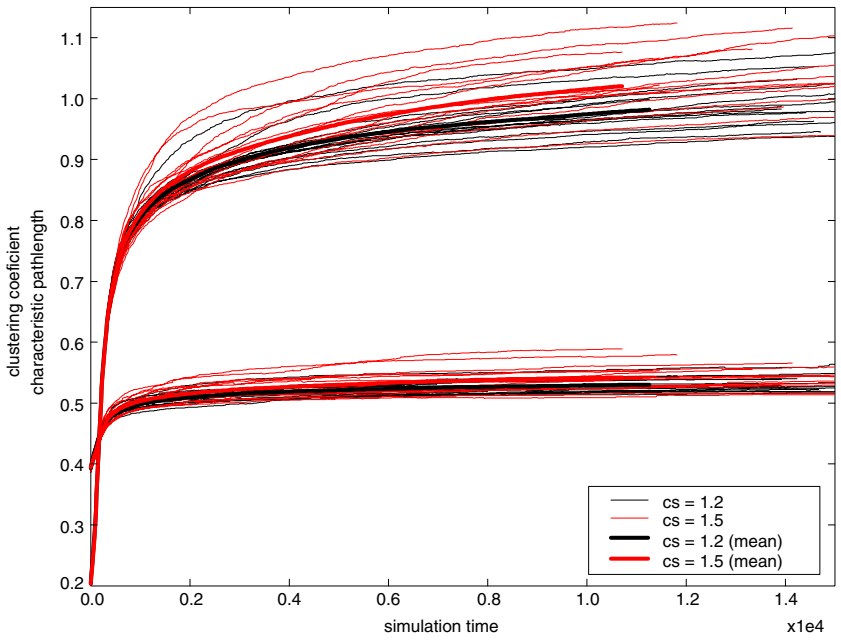

Fig. 2 Trajectories of normalized clustering coefficients and characteristic path lengths during adaptive rewiring, starting from initially random connectivity conditions, 16 runs for networks with coupling strength 1.2 (black) and 16 with coupling strength 1.5 (red). Path lengths and clustering coefficients were normalized against those of the regular network arranged as a ring (note that these are not the theoretical maxima, which means that these parameters may occasionally reach values greater than 1). Mean values of the clustering coefficients and characteristic path lengths of the coupling strength conditions are drawn in thick lines

gradually rise during the simulations as a result of the adaptive rewiring. The networks, therefore, gradually evolve towards small-world connectivity. This occurs both for bursting (inhibitory coupling strength of 1.2) and irregular firing neurons (inhibitory coupling strength of 1.5). For both coupling conditions, there is considerable variability in the rate with which CN and LN evolve. On average, however, both are higher for irregular than for regular bursting neurons, respectively: $t(30) = 2.64$, $p = 0.01$ and $t(30) = 2.02$; $p = 0.05$ two-tailed, for independent samples measured at the time point where the first run terminates.

The pre-synaptic connection distribution changed during the rewiring from a normal distribution to the ones shown in Fig. 3. We observe a tendency towards multi-modality that is stronger for irregular spiking than for regular bursting neurons. We have no clear explanation for this result.

We compared spike patterns before (Fig. 1) and after the completion of the rewiring scenario (Fig. 4). Whereas the initial regimes are clearly distinct, regular bursting and irregular firing, the activity after rewiring appears to be a mixture of the two, with irregular and bursting activities alternating. The result, therefore, may be compared to Gong and van Leeuwen (2004); small world structure promotes semi-regular activity, even if under the initial connectivity structure, the motions of the activity patterns were quite different. This result suggests that the combination of irregular bursting and small-world structure is likely to be a robust phenomenon in neural network development. The result, therefore, can help explain the ubiquity of small world structure in cortical networks. Besides, it predicts that whenever this occurs, it should be found in combination with semi-ordered activity.

Discussion and conclusions

Dynamic synchronization and coherence have previously been observed in networks of spiking neurons. Patterns of coherence were studied in Hodgkin–Huxley neurons (Lago-Fernandez et al. 2000; Kwon and Moon 2002) and in networks of Hindmarsh–Rose neurons (Bucolo et al. 2002). Synchrony (Masuda and Aihara 2004) and self-sustained dynamic activity (Roxin et al. 2004) have been described in small-world network of leaky integrate-and-fire neurons. While these studies showed how small-world structures could facilitate signal propagation and coherence in neuronal networks, they did not offer an insight into how an initially random, sparsely coupled network evolves into a small-world structure.

In an adaptive rewiring scenario, initially random networks of Hindmarsh–Rose neurons show small increases in characteristic path lengths, combined with substantial increases in clustering coefficients. In other words, these networks evolve into small-world structures. This occurs, regardless of whether these networks initially show periodic bursting or irregular spiking activity. When the evolution is completed, the activity in the resulting network is a dynamical mixture of bursting (temporal clustering of spikes) and irregular spiking activity. Phenomenologically

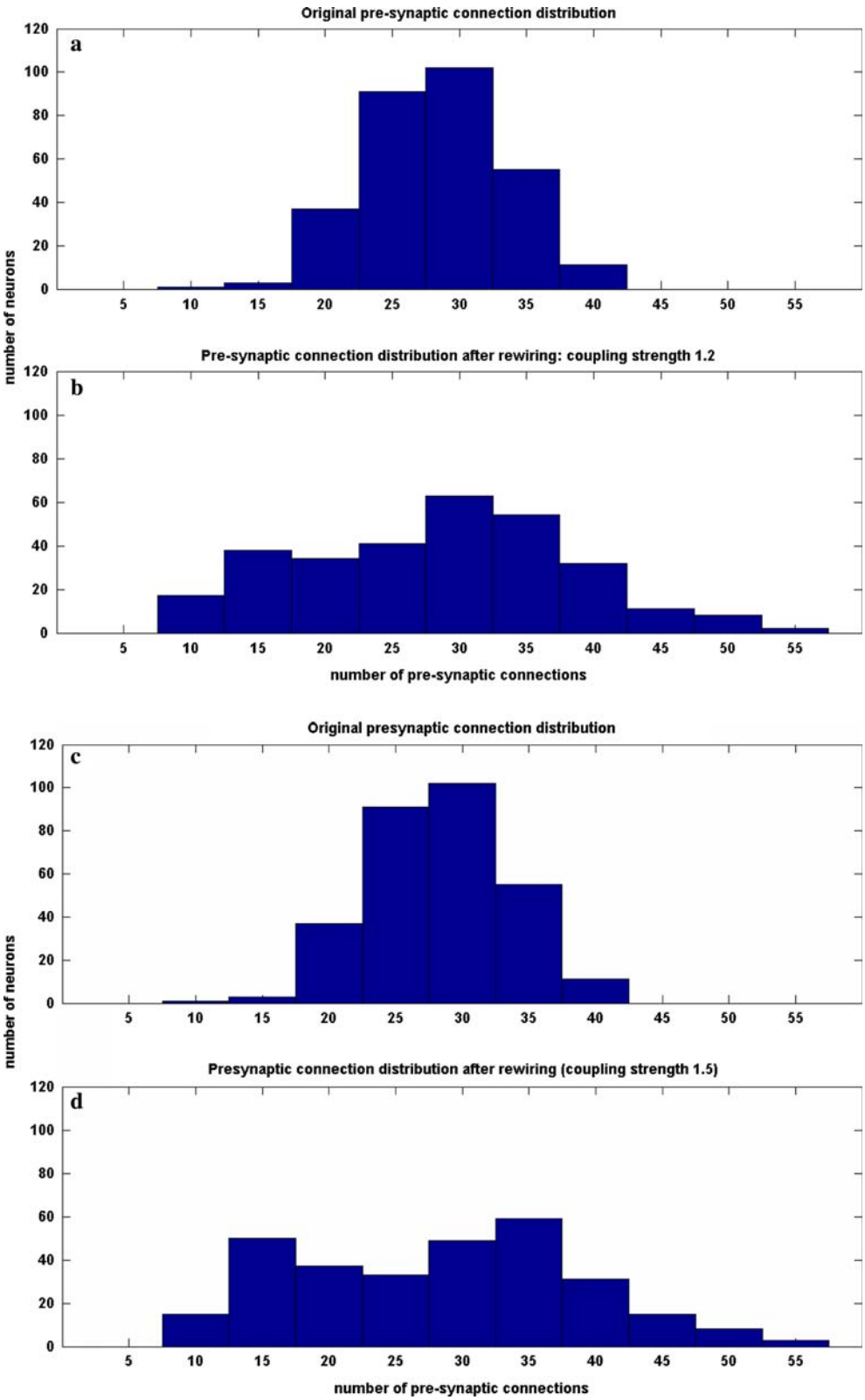

Fig. 3 Pre-synaptic connection distribution after rewiring of the networks with coupling strengths $\beta = 1.2$ and $\beta = 1.5$

speaking, during bursting episodes, repeated spiking after short time intervals enables the entrainment in firing of multiple neurons within formed clusters, and irregularly dispersed spikes express interactions and overlap between inter-neuron clusters. The results seem to indicate that the rewiring mechanism

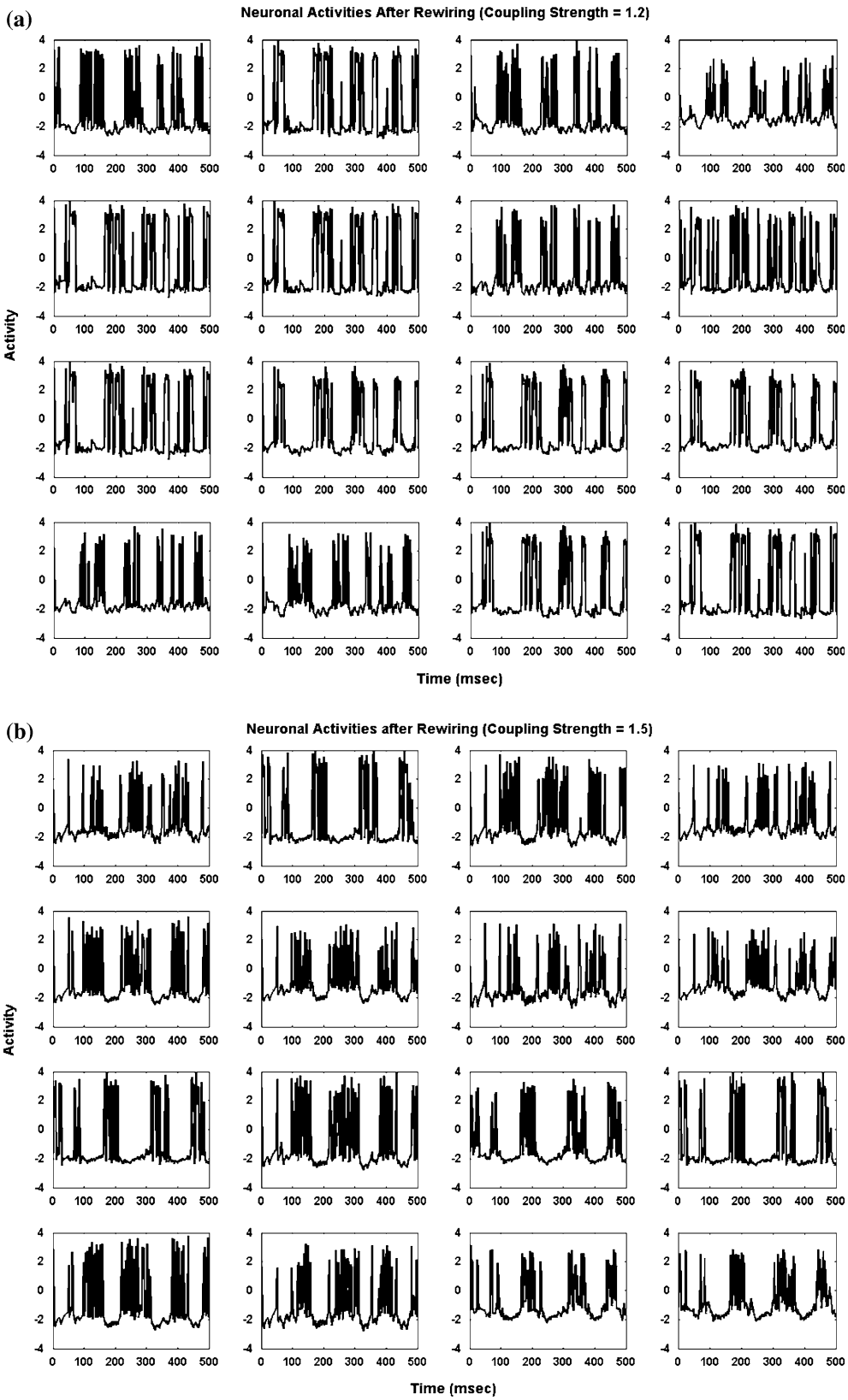

Fig. 4 The neuronal activities after the rewiring with coupling strength $\beta = 1.2$ (**a**) and $\beta = 1.5$ (**b**). The activities shown belong to the same 16 neurons shown in Fig. 1

employed enhances the tendency of the network to show bursting activity, even if the original random network does not burst.

When spontaneous firing generates small world networks starting from random initial connectivity and different activity regimes, we may conclude that it is a

robust phenomenon. As a small-world structure, the system is optimally pre-configured for the functional coordination of different regions within the network. An issue still to be studied is how robust is this configuration under perturbation. In particular, when the system starts to learn from experience, will it still maintain this optimal structure? If learning distorts the structure, biological neural networks may sometimes need time-out for maintenance of their large-scale structure. During such ''off'' periods, the brain will revert to large-scale oscillations of the type shown in immature tissue, to restore its small-world connectivity. Given what we know, this might be a plausible role for slow-wave sleep.

Mechanisms such as bursting could make adjustments over time to network connectivity. Subtle differences could be observed between the networks that result from regular bursting and irregular spiking. When rewiring starts out from bursting activity, networks result that are more clustered and have longer characteristic path lengths. In other words, they are closer to regular networks than the ones that arise from irregular firing, which are comparatively closer to random networks.

The same observation is reflected in the pre-synaptic connection distribution resulting from these two different regimes. As shown in Fig. 4, networks resulting from regular bursting activity tend to have a more uniform connectivity distribution, whereas those resulting from irregular firing have a somewhat more pronounced multi-modal distribution. Even though this difference is only small, it may be meaningful. For coupled maps Van den Berg and van Leeuwen (2004) observed multi-modality as the outcome of the rewiring scenario. Multi-modality, which becomes much more pronounced with larger network sizes, is associated with the formation of hubs. Whereas clusters are important for efficiency of local communication, hubs play an important role in the global efficiency. Networks that are optimal for information processing in distributed networks represent an optimum in the trade-off between these two. Where exactly the optimum is located depends on what is given a greater weight: interactions within or between clusters. In the first case, the clustering coefficient is more important than the path length, and in the second case, vice versa. Our study shows that when clustering is more important, the optimal structure could be obtained starting with regular bursting behavior. When path length is more important, irregular spiking is a better starting point.

Why would such small-world structures emerge? We can only try to give an intuitive answer, here. The spontaneous synchronization that occurs in our network is structured (unlike stochastic noise or turbulence) and sufficiently complex (unlike ordered behavior such as periodic or static attractors) to mimic realistic attributes of information processing. Small worlds are optimal for processing distributed information. Thus we may consider the rewiring algorithm as an optimization process for organizing the type of activity that shares these attributes with processing activities in neural systems.

The simulated adaptive rewiring is a Hebbian process; it reinforces existing regularities in firing patterns by embodying them into connection patterns. Without regularities in the firing signals, rewiring would just merely transform a random network into another random network. Without sufficient complexity and intrinsic variability in neuronal firing, however, the network configuration would ultimately become regular. Hence, semi-regular activity will lead to the preferred, semi-regular (i.e. small-world) network structures. Consistent with this interpretation, the activity that is intuitively more regular initially (bursting) leads to small-world networks of a slightly more regular kind, as compared to initial conditions of irregular firing.

This work represents a step towards understanding the role of neuronal activity in brain development. The simple adaptive rewiring scenario appears sufficient to describe a basic principle for development. It was applied successfully to model neurons that were closer to biological reality than the coupled logistic equations for which the rewiring scheme was tested earlier (Van den Berg and van Leeuwen 2004; Gong and van Leeuwen 2004). However, there are many oversimplifications in our model. These regard model neurons and their coupling, as well as the rewiring algorithm itself.

With respect to the selection of model neuron equations and choice of parameters for the network, further steps should be taken to make the model more realistic with respect to the physiology of developing neurons. With respect to the choice of connections, the current model unrealistically includes excitatory and inhibitory connections between the same neurons. Future extensions should include a population of interneurons, which provide inhibitory coupling among principal neurons. Another issue we must consider is the role of differential external input to the developing networks. During development of the visual system, the retina, dorsal lateral geniculate nucleus and visual cortex all generate spontaneous rhythms of different kind; waves, spindles, and slow oscillations, respectively (McCormick 1999). At present, our model does not distinguish activity patterns generated by sensory

neurons from those intrinsically arising within the network.

With respect to the adaptive rewiring scenario, perhaps the clearest over-simplification is that synapse creation and deletion based on synchrony (Nishiyama et al. 2000). Future developments will have to consider more ubiquitous forms of synaptic plasticity, such as spike-timing dependent plasticity with asymmetric learning windows. The most pressing issue is that the degree of synchrony between units, on which the rewiring scenario is based, is determined regardless of whether units are connected. Moreover, the degree of synchrony is compared globally across all pairs. The problem is, therefore, first: how can unconnected neurons sense their degree of synchronization and second: how can global comparison effectively be localized. In brains, unconnected neurons cannot sense their degree of synchronization. In biological synapses, neurotransmitters flow out of the synaptic cleft and spill over from existing connections to neighbouring synapses (Barbour and Hausser 1997). This ''crosstalk'' may allow unconnected neurons to detect their synchronization. To model the spatial diffusion process, a weight term could be incorporated in Eq. 1. Spatial diffusion can then be used to solve the second problem: how to localize the comparison of synchrony. A model that takes spatial diffusion into account, should consider that the coefficient of diffusion is larger for GABA than for glutamate (Sem'yanov 2005). Thus, inhibition effects are sensed over a wider area than excitation, which is more specific. In our current model, this distinction is already made to some extent: excitatory connections have a more specific effect than inhibitory ones, whose contribution depends on the number of neighbors.

Besides weights to enable spatial diffusion of the rewiring process, temporal diffusion should be considered also. Spike-time dependency could be introduced to provide a graded measure of synchrony. This would accommodate the temporal characteristics of the diffusion process. The disconnection and connection of neurons during the rewiring could then be replaced by a gradual change in the synaptic strength. This would allow us to explore different models for initial attachment based on synchrony, for instance as a random process, without any specific assumptions about the growth or elimination of neurons and connectivity.

The introduction of spatiotemporal diffusion to the rewiring process based on mechanisms such as diffusion may increase the biological realism of the algorithm. Nevertheless, it ultimately still provides too static a picture of neural development. In further developments we may consider taking into account axonal and neural growth and migration. With respect to growth the most obvious simplification in our current model is that the total amount of neurons and connections remains the same during the application of the algorithm. One possibility would be to start off with a network many connections and then prune those that are uncorrelated (Changeux and Danchin 1976; Edelman 1987). However, there is growing evidence for a theory of development based on construction, rather than elimination (Quartz 1999). In biological networks, selective growth and elimination of connections result in a net increase in connectivity (Antonini and Stryker 1993) and structural complexity (Katz and Shatz 1996). When neurons and connections were added to a network op coupled maps, in Gong and van Leeuwen 2003, a scale-free network resulted from the current rewiring scenario. In the present study, we did not observe the emergence of such a structure, which is compatible with the experimental results from an in vitro study (Shefi et al. 2002) that showed neurons organized into a small-world (but not scale-free) structure. This finding is not surprising at all as network growth was found to be crucial for the emergence of scale-free networks (Barabasi and Albert 1999). It remains an open issue, whether growth results in scale-free networks for spiking neurons.

With respect to neural and axonal migration and path finding, how these processes are regulated is currently a fast developing area of research in developmental neuroscience. For our algorithm, we simply assumed is that genetic regulation produces a random structure. In addition, we assumed that this structure is completed prior to the onset of activity-based rewiring. Both are clear oversimplifications (see, for instance, Mason and Erskine 2000), that will eventually be removed as we incorporate a larger proportion of the rapidly accumulating knowledge into our model.

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