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Interneuron Diversity series: Circuit complexity and axon wiring economy of cortical interneurons

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The performance of the brain is constrained by wiring length and maintenance costs. The apparently inverse relationship between number of neurons in the various interneuron classes and the spatial extent of their axon trees suggests a mathematically definable organization, reminiscent of 'small-world' or scale-free networks observed in other complex systems. The wiring-economy-based classification of cortical inhibitory interneurons is supported by the distinct physiological patterns of class members in the intact brain. The complex wiring of diverse interneuron classes could represent an economic solution for supporting global synchrony and oscillations at multiple timescales with minimum axon length.

One of the main challenges of neuroscience is to understand how complex behaviors of the brain emerge from its cellular constituents. The mammalian cortex consists of two basic neuron types: excitatory principal cells and inhibitory interneurons. In contrast to the more homogeneous principal cell population, interneurons are exceptionally diverse in their morphological appearance and functional properties [1–7]. To date, there is no universally accepted taxonomy of cortical interneurons. Classification schemes vary from a dozen or so defined classes [1–7] to views that regard interneurons as a single group with virtually unlimited heterogeneity of its members [1]. Interneurons differ from each other in intrinsic biophysical properties and in morphological and molecular biological features, as well as in connectivity [2]. This article considers how wiring of interneurons affects their contribution to network performance and suggests that connectivity is a useful approach for examining how complex functions (e.g. oscillations) emerge from elementary features (e.g. inhibition) [8].

Building networks for multiple functions

The repertoire and complexity of network performance can be augmented in two fundamentally different ways. The first approach is to use relatively few constituents in large numbers. However, physical realization of this approach in growing networks is problematic. If the network is sparsely connected (e.g. feedforward 'synfire' chains of pyramidal cells across many layers [9]), signals become too long to propagate across the network owing to synaptic and conduction delays. However, if the network is densely recurrent, the number of connections should scale with the network size by some rule. Whereas all-to-all wiring is possible in a tissue culture involving dozens of neurons, it becomes less and less feasible when millions of neurons are involved, owing to space and energy supply limitations [10,11]. The second approach for increasing network performance is adding novel types of constituents (e.g. functionally different types of interneurons), whose activity can exert qualitatively different effects on network functions [12]. Combining distinct computational elements endows networks with the ability to carry out novel computations (e.g. oscillations of different frequencies). Mathematical modeling indicates a power-law relationship between the number of computation types (complexity) and the number of distinct constituents in physical networks (e.g. electronic devices and the Internet) [12,13]. The economy of wiring in physical systems has received special attention recently (Box 1) and excellent reviews are available on this topic [13–16].

Brains have evolutionary goals but implementation of brain structures has physical constraints [11,17]. Brain systems with 'simple' computational demands evolved only a few neuron types. The basal ganglia, thalamus and the cerebellum possess a low degree of variability in their neuron types. By contrast, cortical structures have evolved in a manner that most closely resembles a relatively sparsely connected network of few principal cell types and many classes of GABAergic interneurons. An important, but hitherto unaddressed, issue is whether diversity of interneurons increases with the evolution of the mammalian cortex. Even if the same interneuron types are present in small and large brains, some unique wiring rules must be implemented so that functions have a preserved continuity in brains of various complexities. One hypothesis is that the diversity of interneurons in the mammalian cortex [1–7] reflects a compromise between computational needs and wiring economy [10,18]. The diversity of interneurons in the hippocampus and neocortex might have evolved to meet the need for multiple functions, as will be discussed in this review. To date, the many facets of

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Box 1. Small-world and scale-free network architecture

How fast can a message propagate from one neuron ('node') to distant neurons in large networks? If one defines a 'characteristic path length' l_{path} as the average number of monosynaptic connections in the shortest path between two neurons, how does it scale with the network size N? In a completely random network with a sufficiently large number of links per node, l_{path} can be very short (and the network is a 'small world'). But what if, more realistically, most connections are local? This question was studied in a landmark paper by Watts and Strogatz [14]. They first prescribed a local architecture with neighboring connections, for which l_{path} increases linearly with N. Then they reconnected a fraction ρ of existing links to nodes that were chosen uniformly at random over the entire network (Figure Ia). Surprisingly, they found that even with a small number of shortcuts ($\rho \approx 0.05$), the dependence of l_{path} on N becomes $\sim \log(N)$. The small number of shortcuts dramatically reduces the average path length l_{path} of the network. For example, if $N = 10^6$, with local connections l_{path} is also $\sim 10^6$, whereas with a small world architecture $l_{path} \approx \log 10^6 = 6$. Hence, a 'small-world' architecture can be realized with only a few shortcuts (long-range connections).

In the Watts–Strogatz model, the reconnection was assumed to be uniform across the network. What if the reconnection probability $p(i,j)$ from node i to node j decreases with the distance $d(i,j)$? Intuitively, if $p(i,j)$ is local, (e.g. a narrow Gaussian or exponential distribution), there would be no chance for long-range connections. However, if $p(i,j)$ decreases with $d(i,j)$ as a power law, $p(i,j) \sim d(i,j)^{-\alpha}$, then there is a significant (although small) probability for connections across long distances, especially if the exponent α is small so that $p(i,j)$ falls off slowly with $d(i,j)$, and a small world becomes realizable. Power distributions lack a characteristic scale and, hence, are 'scale-free'. Many recent studies have been devoted to 'scale-free networks' where the number k of links per node obeys a power law, $P(k) \sim k^{-\gamma}$. The skewed distribution with a heavy tail means that there are a few nodes ('hubs') with an exceptionally large number of links [13,58,59]. Although it is unlikely that the concepts of small-world and scale-free networks directly apply to neural networks in the brain, the demonstration of the effectiveness of a few but costly long-range connections in growing networks has important relevance for brain wiring. Most importantly, they demonstrate that complex networks can be described mathematically.

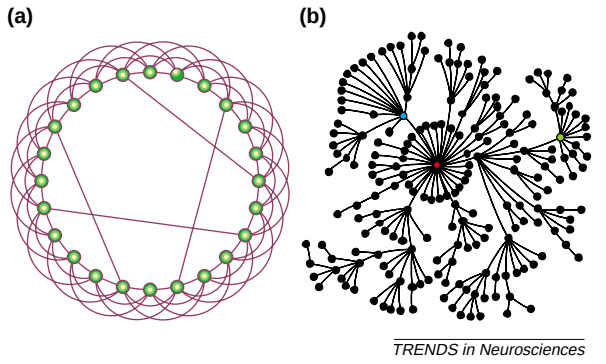

Figure I. Abstract architectural plans of connectivity. **(a)** A network of nodes (e.g. neurons) arranged on a ring. A small-world network has most connections between neighboring nodes, but with a few (four in this illustration) randomly reconnected long-distance 'shortcuts'. **(b)** A scale-free network exhibits a power-law distribution of numbers of connections per node; the skewed distribution with a heavy tail yields the formation of a few 'hubs' with exceptionally large numbers of links [58]. Reproduced, with permission, from Ref. [60] © (2001) Nature Publishing Group (http://www.nature.com/).

hippocampal interneurons have been documented more extensively than those of neocortical interneurons [2]. Nevertheless, the available database from early Golgi studies, immunocytochemistry and neocortical slices already indicates a rich multiplicity of neocortical interneurons [4,5,7,19] and their basic similarity to hippocampal interneurons [5]. Examples of how interneurons implement novel functions in the brain include sculpting stimulus selectivity of cortical neurons in sensory and memory systems [20,21] or generating coherent oscillations at different frequencies [22]. Given the hypothesis that diversity reflects a compromise between computational needs and wiring economy, we need to discover the rules that can describe how interneuron diversity and connectivity result in economical computational complexity.

Scalable interneuronal clocks: connectivity is of the essence

Complex brains have developed specialized mechanisms for keeping time: inhibitory interneuron networks [23]. Oscillatory timing can transform unconnected principal cell groups into temporal coalitions, providing maximal flexibility and economic use of their spikes [24]. Various architectures of inhibitory and excitatory neurons can give rise to oscillations [25–28]. The simplest one consists of interneurons of the same type [26,28–34]. Let us illustrate the importance of connectivity using this simplest network.

Suppose that the goal of a interneuron network is to provide oscillatory timing for the principal cells and that this function should be preserved in different animals – that is, independent of the brain size. How should the network be wired? Because synchronization requires a minimum connectedness, one possibility is to keep a given fractional connectivity among other neurons, regardless of the network size. However, physical implementation of this strategy is often not feasible or economic, because for a network of size N, the total number of synaptic connections increases very quickly ($\sim N^2$). For example, according to the fractional rule, if a minimum of 10% connectivity is needed for the generation of a rhythm, the required total number of connections is 1000 for a small network of 100 neurons, whereas it is $\sim 10^9$ for a population of 10^5 neurons. Thus, it is easy to understand why the brain has not opted for this solution. An alternative strategy is to have a fixed number of random synaptic links per neuron, independent of the network size, in which case the total number of synaptic connections grows only linearly with the network size. However, because neurons are distributed in physical space, members physically distant from each other will require excessively long axons and have excessively long conduction delays. The most economic wiring solution is to establish connections locally [35] (Figure 1), including functionally crucial gap junctions among dendritically overlapping interneurons [36–39]. However, this economy of wiring results in a different problem: physically distant neurons are not connected to each other and this 'disconnectedness' increases monotonically with network size. In other words, synaptic path length (i.e. average number of synapses between randomly chosen pairs; Box 1), and consequently synaptic delays, become excessively long for synchronization in larger size networks. A solution must compensate for the constraints of axon conduction and synaptic delays.

Computational modeling has revealed that in a randomly connected network (Box 1) of basket neurons, there

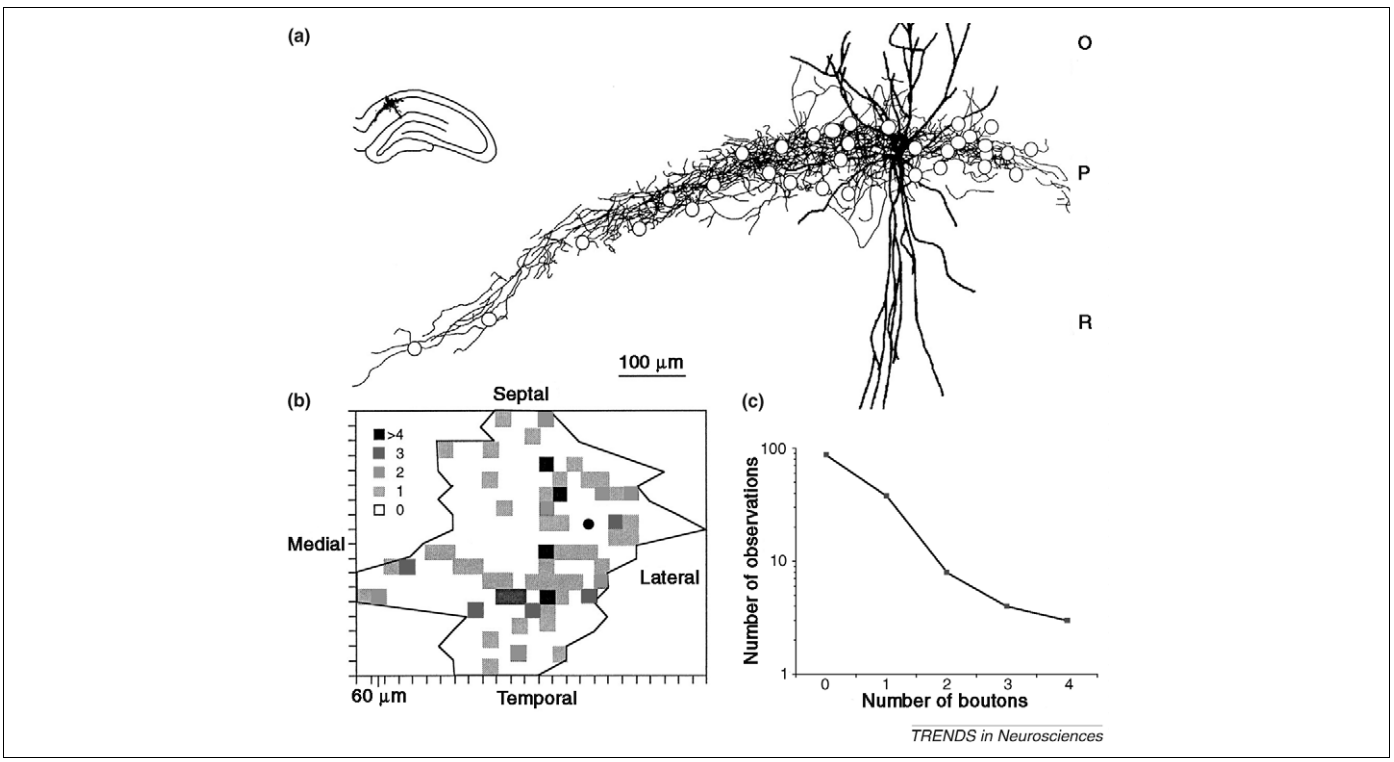

Figure 1. Connections among basket cells are local. **(a)** *In vivo* labeled and fully reconstructed basket neuron (dendrites and axon) contacting other basket cells (circles). Inset: position of the neuron in the CA1 region. **(b)** Two-dimensional reconstruction of interneuron–interneuron contacts, viewed from above. Shading reflects increasing bouton density per square. Black circle indicates position of the soma. **(c)** Density of synaptic contacts (ordinate) in 60 μm squares shown in (b). Total axon length of a CA1 basket cell in the rat is ~50 mm, with ~10 000 boutons, ~60 of which contact other putative basket cells. Abbreviations: O, stratum oriens; P, stratum pyramidale; R, stratum radiatum. Adapted, with permission, from Ref. [33] © (1996) by the Society for Neuroscience and Ref. [35] © (1995) by the Society for Neuroscience.

is a critical threshold for synchrony, defined as a minimum fixed number of synaptic connections per cell, independent of the network size [33] (Figure 2). This finding illustrates that it is not necessary for each cell to be connected to a fixed fraction of other cells as the network size scales up. Virtually all previous oscillation models used densely connected or random networks similar to that shown in Figure 2 (although see Refs [26,40]). These models function because random connectivity ensures that neighboring and distant basket cells in small and large networks have the same opportunity to synchronize. However, random connectivity is not economic because in larger brains distant connections require longer axon lengths and/or more effective myelination, and transmitting action potentials over large distances is energetically costly [10,15]. More importantly, real-world networks are hardly ever random, and this is especially true for interneuron connections. Most interneuronal connectivity is local [35] (Figure 1), hence the synonym for interneurons of 'local circuit neurons'.

Figure 3 illustrates how specific architecture affects network synchrony, using two populations: a locally connecting majority (basket cells) and a smaller fraction of long-range cells that connect with other cells according to a probability that falls off as an inverse power law with distance (Box 1). As expected from the aforementioned considerations, high-density local connectivity of model basket cells alone does not give rise to global coherence because with increasing network size, the 'synaptic path length' of the network (Box 1) becomes excessively long (Figure 3a). However, mathematical theory suggests that the synaptic path length can be dramatically decreased by a few randomly placed 'short-cuts' that connect distant parts of the network (Figure 3b,d; Box 1). In theory, this could be achieved by a few long axons of a subset of basket cells. However, such connections are not known. Instead, it could be that the small number of specialized 'long-range' interneurons, with their axons distributed over large areas within and across anatomical regions (Figure 4) [41], serves this exact role. In support of this conjecture, inclusion of a small percentage of model neurons with long-range connections in the model results in a clear oscillatory rhythm (Figure 3). Synchrony increases dramatically with the relative number of long-range neurons but only to a limit. Increasing long-range connections above a certain share (proportion of total connections, $p > 0.2$) enhances network synchrony only modestly. Therefore, long-range network synchrony can be achieved with a small fraction of the local connectivity being replaced by long-range connections yet keeping the total wire length at a minimum (Figure 3d). These simulations support the hypothesis that an effective design for network synchronization with a minimal wire-cost can be achieved by the division of labor between a larger population of local and a small subpopulation of long-range interneurons. This architecture is of a class called 'small-world' networks (Box 1). An added advantage of this architecture is that local and global synchrony can be selectively biased by discretely targeting locally connecting and long-range interneurons, respectively (e.g. phase-resetting of global oscillations) [42]. These simulations illustrate that a desired functional outcome can be

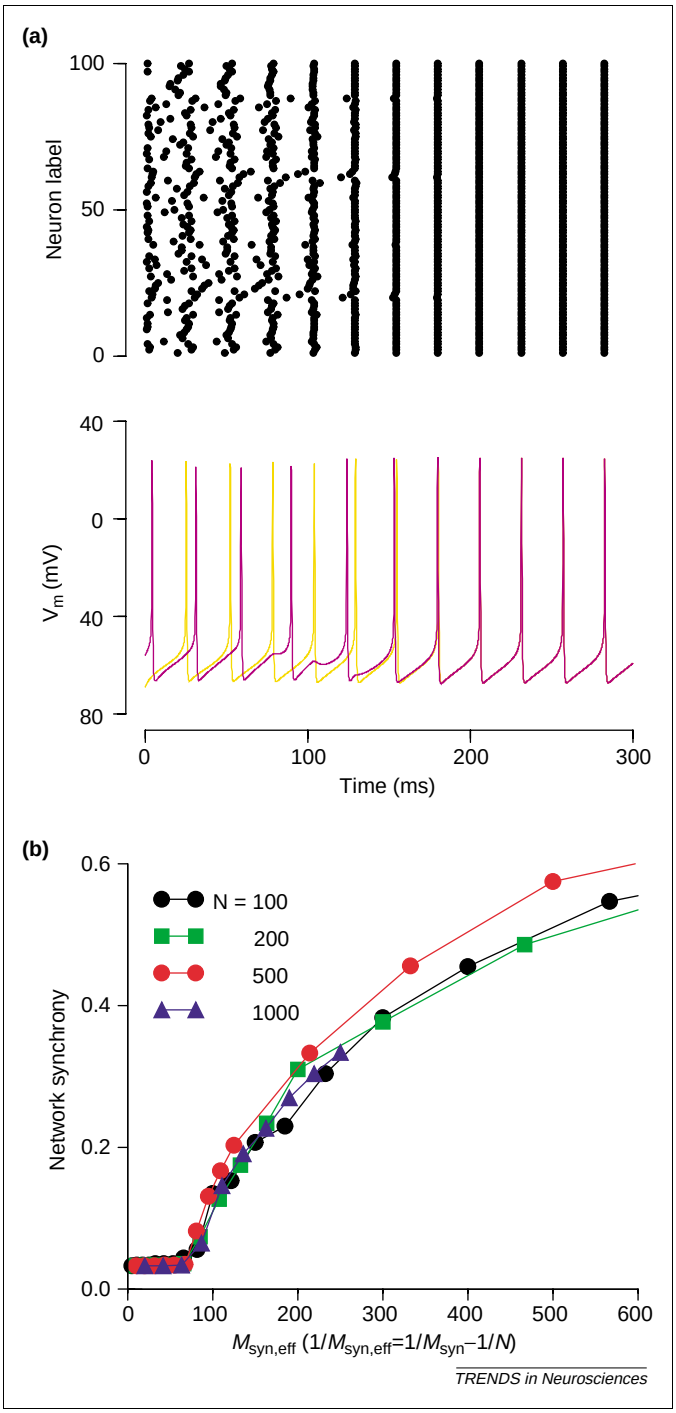

Figure 2. Minimal connectivity (connection 'threshold') is required for large-scale synchronization in a randomly connected network of GABAergic cells; this is independent of the network size. **(a)** An example of network synchronization in a fully connected regular network. Upper panel: the rastergram of spikes (dots) of 100 neurons (ordinate) as a function of time. Lower panel: membrane potentials of two neurons chosen for illustration. Neurons discharge independently initially, but quickly become synchronized by mutual inhibition. **(b)** Network synchrony as a function of the mean number of synaptic inputs per cell, M_{syn} in randomly connected networks of different sizes ($N = 100$, 200, 500 and 1000; the correction $1/N$ takes into account the finite size effect). Note the critical threshold of connectedness (each interneuron connected to ~60–80 peers) for synchrony, which is independent of the network size. Adapted, with permission, from Ref. [33] © (1996) by the Society for Neuroscience.

achieved by numerous ways in computational models. To consider any model relevant, its architecture should reflect real-brain function and constraints. Here, a network for a single-band oscillation has been considered. However, cortical networks support multiple, coupled oscillations at various temporal scales [22] and numerous other functions [2], which require more interneuron types and economic wiring. It should be stated, though, that the static small-world and scale-free models discussed here might not faithfully capture the true nature of interneuron organization. Nevertheless, these models illustrate that complex hierarchies can be described quantitatively and that costly distant wiring can be minimized by appropriately designed architectural rules [13,18].

Functional diversity of interneurons increases computational power at a low wiring cost

As already discussed, integrating functionally novel types of neurons into networks increases their computational diversity [12,13]. Functionality can be defined by the intrinsic, biophysical properties of interneurons [1,3,4,6] and/or by their placement in the network [43]. In terms of their connectivity to the principal cells [2,5,13,44], three major groups of cortical interneurons are recognized: (i) interneurons controlling principal cell output (by perisomatic inhibition), (ii) interneurons controlling the principal cell input (by dendritic inhibition) and (iii) long-range interneurons coordinating interneuron assemblies. These major groups are divided into further functional classes. Output control is achieved by chandelier cells and at least two types of basket neurons [43]. Input control is brought about by interneurons that specifically target the dendritic domains of every excitatory afferent projection to the cortex [5,35,44,45]. Several additional subclasses target two or more dendritic regions [1,3], whereas others can target somata and nearby dendrites with similar probability [35,46]. The distinguishing characteristic of the third major group is that they are inter-regional, and thus can be considered 'long-range' [47]. Their distant clouds of terminal boutons are separated by myelinated axon collaterals that provide fast conduction for temporal synchrony of all terminals. This group includes back-projection cells [41] (Figure 4), septally projecting interneurons [48] and other types with inter-regional connections [49].

As predicted from theoretical considerations [12–14] and preliminary computer modeling (Figure 3), the specific wiring of interneurons can support numerous and flexible functions. For example, collaboration of different interneuron types might support global oscillations at different frequencies [26,39,50,51] and various modes of synaptic plasticity [52–54]. Progress in this direction will benefit from precise knowledge about interneuron connectedness and the relative incidence of neurons in the postulated classes. From the available evidence, a hierarchical organization appears to emerge (Figure 5). Chandelier cells do not, or only scarcely, innervate each other or other interneurons. Basket cells are connected to nearby basket cells and perhaps to other nearby cell types [35,37,38]. The connectivity among the various dendrite-targeting neuron types is not understood well but several classes are known to be interconnected within the same class [36] and also to connect to basket and/or chandelier cells [45]. Finally, the long-range group is likely to innervate all interneuron classes [47]. In addition to synaptic connectivity, nearby

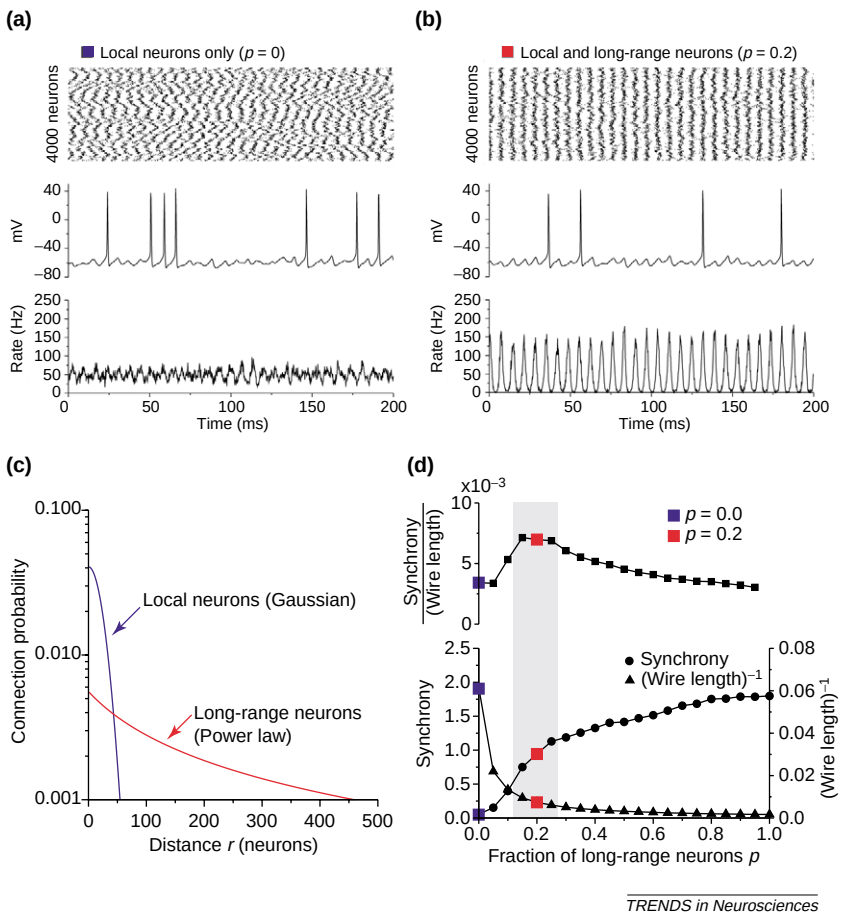

Figure 3. Trade-off between synchronization and wire length economy. **(a)** Oscillations in a local network with Gaussian connectivity (characteristic length = 20 neurons). The network is essentially asynchronous. Upper panel, spike raster of 4000 neurons; middle panel, the voltage trace of a representative neuron; lower panel: the population firing rate. **(b)** Oscillations in a network with local [Gaussian connectivity as in (a)] and long-range connections (power-law connectivity). A fraction (20%) of cells contact neurons with a power-law distribution $P(r) \sim (r + \kappa)^{-\alpha}$, where r is the distance between cells, $\kappa = 100$ and $\alpha = 1$. Note clear oscillatory rhythm. **(c)** Connectivity probability functions: the Gaussian distributed connections are local (blue). With a power distribution, long-range connections become possible (red). **(d)** With increasing fraction of long-range neurons p, the network synchrony increases, while the inverse of the wire-length of connections decreases (lower panel). Upper panel: an efficiency function is defined as synchrony/length of wire. There is an optimal range of the value p (gray shade) corresponding to high synchrony at a low wire-cost (a small ratio of long-range and short-range connections).

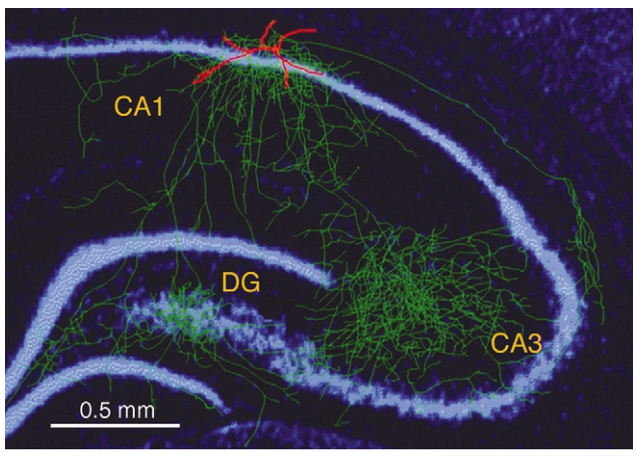

Figure 4. Axon arbors of long-range interneurons span large anatomical areas, as shown here for an *in vivo* filled 'backprojection' interneuron. The 3D reconstructed axon collaterals (green) are projected onto CA1, CA3 and dentate gyrus (DG) regions of a coronal section. The cell body and dendrites are in red. Total axon length is >100 mm, and total bouton number is >25 000. Adapted, with permission, from Ref. [41] © (1994) American Association for the Advancement of Science (http://www.sciencemag.org).

interneurons of the same class are also connected by dendritic gap junctions [36–39].

The hierarchy of interneuron organization shares some important features with systems characterized by small-world architecture [14] and/or the power law [13] (Box 1). Theory [13,14] and modeling (Figure 3) suggests that neurons with only local connections and those with most widespread connections should be most and least numerous, respectively. Other classes are expected to have some intermediate incidence, with some mathematically definable relationship among the classes [13]. According to this hypothesis, the most numerous interneurons belong to the perisomatic control group, followed by the specific (single) and less-specific (multiple) dendritic control groups, and the least numerous cells are the long-range interneurons [1] (Figure 5). Thus, most wiring is local and neurons with long-range connectivity and large global impact are rare. Mathematical considerations also predict the scaling relationship among the interneuron classes in brain structures of varying sizes. Accordingly, the ratio of interneurons with local and distant connections (i.e. the slope of the power law function in Figure 5) should be much larger

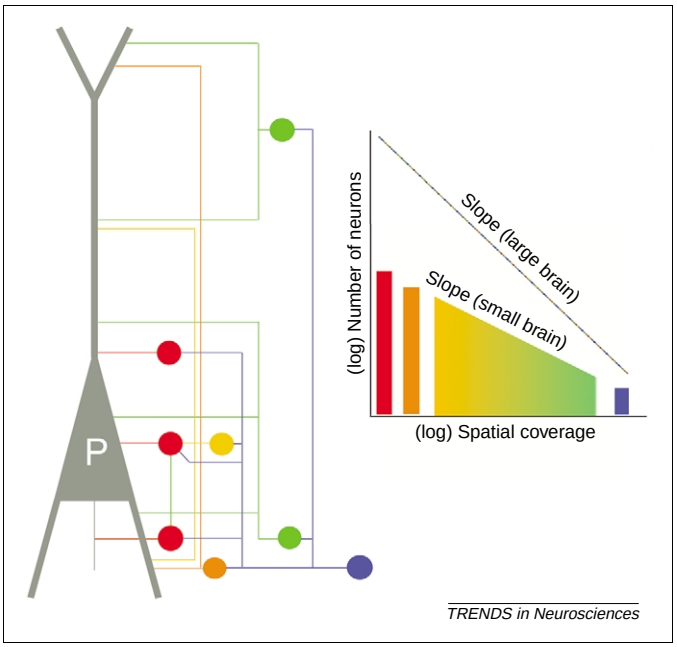

Figure 5. A hypothetical connection scheme of cortical interneurons. Connections and cell body locations are based on information gathered in the hippocampus [2] (P, principal neuron). The graph shows a hypothesized relationship between spatial coverage and the number of neurons in a given class. Perisomatic (red) interneurons with small spatial coverage are most numerous, whereas long-range interneurons (blue) that interconnect different regions are few. Many other classes [1] (green and yellow) might occupy an intermediate coverage. The slope of this hypothesized relationship should vary with network size. With increasing brain size, the number of interneurons with local connections increases more rapidly than neurons with more extensive spatial coverage. The power law shown here is for illustration purposes only, to indicate that a mathematically defined relationship might exist between spatial coverage and number of neurons in particular interneuron classes.

in the rodent neocortex than in the rodent hippocampus, and orders of magnitude larger in the human brain than in the rodent cortex, for achieving the same magnitude of global synchrony (Box 1).

Support for the postulated hierarchical organization of interneurons comes from functional observations in the intact hippocampus. On the basis of discharge frequency and the relationship to the phase of hippocampal theta oscillations in the behaving rat, only one or two overlapping interneuron groups could be recognized [2,55]. However, when their relationship to sharp-wave-associated population synchrony was examined, several putative classes with distinct firing patterns were observed [50], with further subgroups distinguished by their preferred theta phase [56] (Figure 6). Several members of these putative classes have been identified by juxtacellular labeling and, importantly, the functional classes characteristically differ from each other in their connectivity patterns [56,57]. These findings support the hypothesis that differential wiring of interneurons contributes crucially to shaping network output.

Concluding remarks

This review has considered whether, and how, the diversity of cortical interneurons reflects optimization between computational performance of the cortex and its axonal wiring costs. In their relationship to principal cells, three major classes of interneurons are recognized:

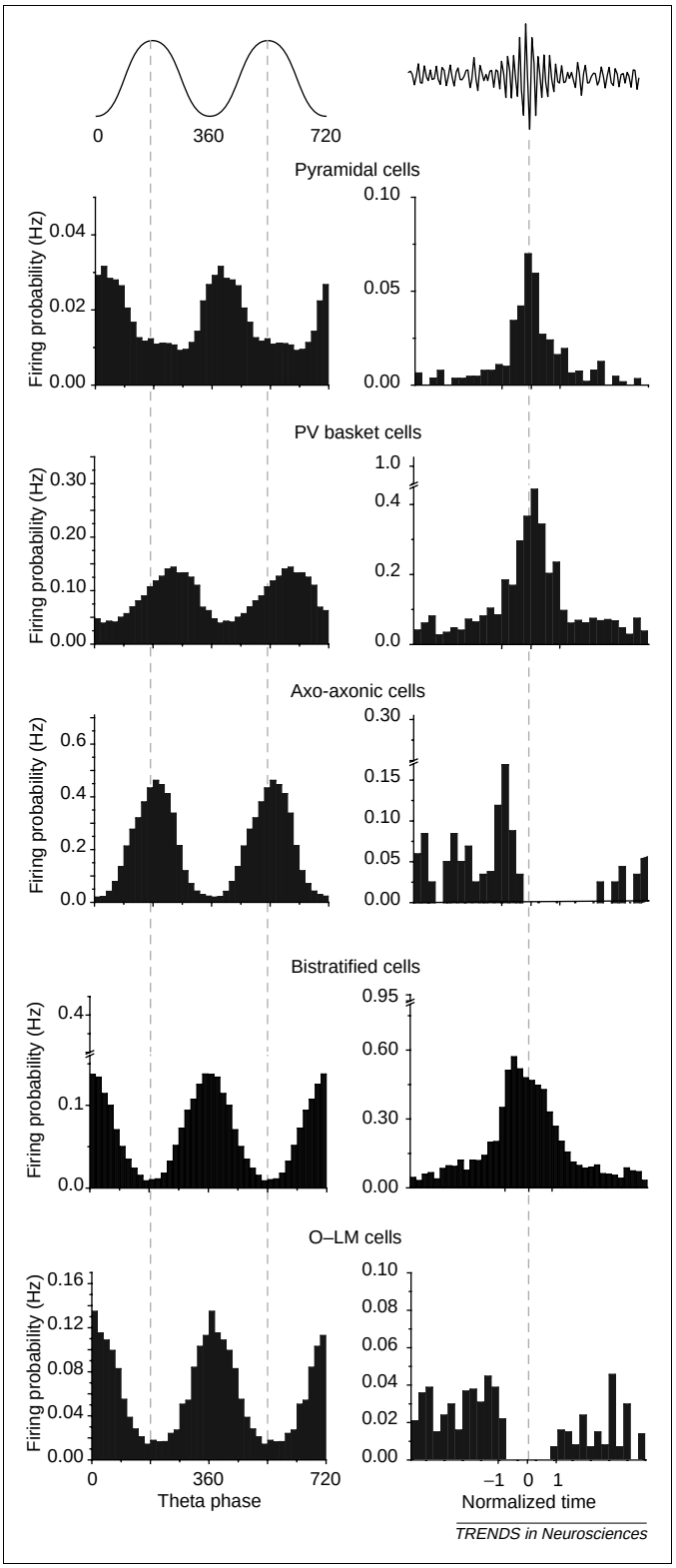

Figure 6. Relationship between circuit (axonal targets) and function properties of interneuron classes in the hippocampus. Mean firing probabilities of different cell types during theta (left) and sharp-wave-related fast 'ripple' oscillations (right). Distinct classes of anatomically defined interneurons contribute differentially to either theta phase or ripple patterns. Adapted, with permission, from Refs [56,57]. Abbreviation: O–LM, stratum oriens interneurons projecting to stratum lacunosum-moleculare.

(i) interneurons controlling principal cell output, (ii) interneurons controlling dendritic inputs and (iii) long-range interneurons coordinating interneuron assemblies. Each class has several further divisions. The number of neurons in the divisions shows an inverse relationship with spatial coverage, a relationship that suggests some mathematically definable organization. The connectivity-based classification is supported by the distinct physiological patterns of class members in the intact brain.

A prerequisite for finding a quantitative relationship among cortical interneuron classes will require large samples. Power-law and small-world network rules suggest that the relative incidence of long-range neurons with large spatial extent decreases dramatically with network size; therefore, finding these neurons in the neocortices of animals with large brains might be very difficult with currently used random sampling methods. Molecular biological markers could replace the laborious *in vivo* labeling methods and address the important issue of whether diversity of cortical interneurons increases with brain complexity. *In vitro* biophysical and pharmacological tools can identify how intrinsic properties of the interneuron classes and divisions support the various *in vivo* observed network patterns. In turn, realistically scaled computer models are needed to understand the complex interactions among the classes and with the principal cell population. It is unlikely that static models, such as small-world or scale-free graphs, can faithfully describe the neuronal networks with evolutionary goals. Nevertheless, they illustrate the important point that costly distant connections can be minimized by appropriate clustering architecture. Connectivity-based classification is only one approach for understanding the problem of interneuron diversity. Nevertheless, because wire-economy is an important constraint of brain evolution, it is likely that it captures some important details of a more comprehensive taxonomy of interneurons.

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