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Developing structural constraints on connectivity for biologically embedded neural networks

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Abstract In this article, we analyse under which conditions an abstract model of connectivity could actually be embedded geometrically in a mammalian brain. To this end, we adopt and extend a method from circuit design called Rent's Rule to the highly branching structure of cortical connections. Adding on recent approaches, we introduce the concept of a limiting Rent characteristic that captures the geometrical constraints of a cortical substrate on connectivity. We derive this limit for the mammalian neocortex, finding that it is independent of the species qualitatively as well as quantitatively. In consequence, this method can be used as a universal descriptor for the geometrical restrictions of cortical connectivity. We investigate two widely used generic network models: uniform random and localized connectivity, and show how they are constrained by the limiting Rent characteristic. Finally, we discuss consequences of these restrictions on the development of cortex-size models.

Keywords Neural networks · Rent's Rule · Network connectivity · Multi-point nets · Network analysis

1 Introduction

The development of realistic models for the brain's connectivity is hindered by the difficulty of acquiring reliable, widespread connection data. Whole-brain imaging techniques, such as fMRI, have shed light into the global structure, revealing projections between cortical areas (Young et al. 1995), and these so-called brain networks have been studied extensively (Sporns and Kötter 2004; Bassett and Bullmore 2006). However, on the detailed level of single neurons, connectivity data are sparse, as only few connections or cells can be reconstructed simultaneously (Young et al. 1995), or only general statistics are accessible (Braitenberg and Schüz 1998). Still, various studies have used the available data in an attempt to construct biologically realistic models of connectivity (Mehring et al. 2003; Häusler et al. 2009; Kremkow et al. 2007). However, given the sparse measurement data, alternative methods have to be found for further constraining these models.

In this article, we derive constraints on connectivity in neural networks arising from the geometry of the neocortex. To this end, we make use of an estimation method for circuit design known as Rent's Rule (Landman and Russo 1971; Christie and Stroobandt 2000). This approach describes the relationship between the size of a network part and its connections to the remainder of the network, two measures that are strongly connected to geometrical properties (Bassett et al. 2010; Hagen et al. 1994). This relationship has been mainly used for pre-placement area prediction in integrated circuits (Stroobandt and Kurdahi 1998; Christie and Stroobandt 2000; Lanzerotti et al. 2004).

In contrast, there exist only some initial attempts to apply Rent's Rule to neural networks (Beiu et al. 2009; Partzsch and Schüffny 2009) and to the connectivity of brain networks (Bassett et al. 2010). In all these cases, mainly a comparison of exponents of the extracted scaling laws is done to check whether candidate models are compatible with the biological substrate.

In this article, we extend the above studies in two directions. First, instead of considering Rent exponents, which are a measure of dimensionality only (Bassett et al. 2010), we

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make use of the whole scaling curve, which respects changes in scaling on different connectivity levels. We introduce an upper limit on this so-called Rent characteristic, calculated from a simple geometrical model of the grey matter. This limit is directly related to biological parameters, and it turns out to be invariant in terms of scaling between different brain sizes (Changizi 2007). Thus, it can be used to constrain connectivity models not only qualitatively, but also quantitatively. Second, we use hyper-graphs in the description of networks (Karypis and Kumar 2000) in contrast to conventional graphs used in previous studies. While the latter is appropriate for digital circuits, fan-in of which is small and can be accounted for by additional approximations (Stroobandt and Kurdahi 1998), it does not capture the highly branching connectivity of axons and dendrites. We derive Rent characteristics for two generic connectivity models, uniform random (Brunel 2000; Newman 2003) and localized (Mehring et al. 2003), and calculate limits on network size and connection density for these by comparing with the limiting Rent characteristic.

The remainder of this article is organized as follows: Sect. 2 introduces Rent's Rule and the Rent characteristic. In Sect. 3, the limiting Rent characteristic of the grey matter is calculated. Section 4 derives Rent characteristics for uniform random and locally connected networks and relates them to the limiting Rent characteristic. Finally, Sect. 5 discusses consequences of these results.

2 Rent's Rule

Rent's Rule describes an empirical relationship between the size of a (sub-)network and its number of connections with the surround (Landman and Russo 1971; Christie and Stroobandt 2000). These two quantities are often connected approximately by a power law:

$$T(G) = \overline{T} \cdot G^r \ . \tag{1}$$

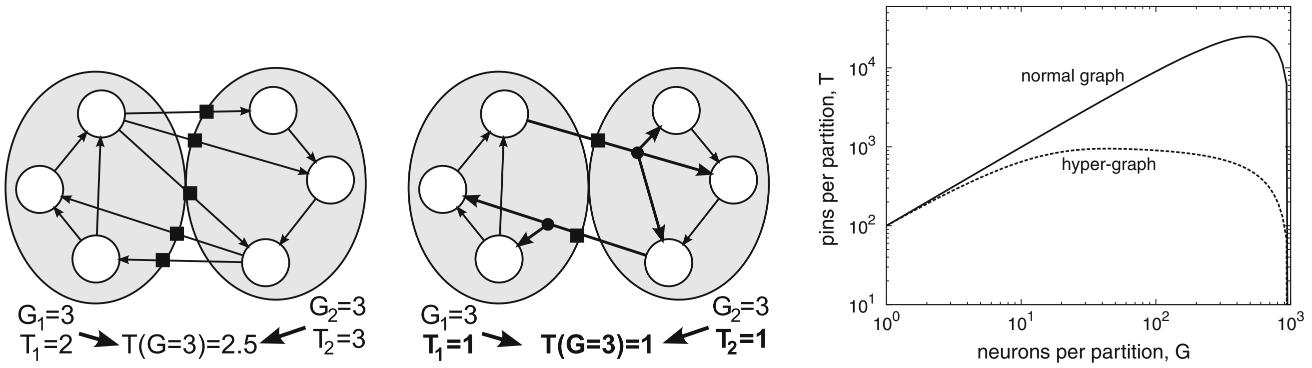
where G represents the number of basic elements in the (sub-)network, and T is the number of connections over the sub-network boundary. When applied to neural networks, G corresponds to the number of neurons, and T reflects the number of external neuron-to-neuron connections. The parameters $\overline{T}$ and r are called *Rent parameters*, with $\overline{T}$ corresponding to the number of connections per basic element and r determining the scaling of T with the sub-network size. Consequently, the so-called *Rent exponent* r can be regarded as a measure of connection complexity (Christie and Stroobandt 2000; Partzsch and Schüffny 2009).

Rent's Rule can also be related to geometrical properties: Assuming constant element density, the size of the network, G, is proportional to the volume occupied by the network. Similarly, if the cross section of a connection is constant, the (maximum) number of connections over the network boundary, T, is proportional to the surface area of the network's volume. For a 2D space, e.g. taking a square with side length d, it follows that G grows quadratically ($G \sim d^2$), but T only linearly ($T \sim d$) with d, resulting in $T \sim G^{1/2}$. Thus, the inherent Rent exponent is $r = 1/2$. A similar argument leads to $r = 2/3$ for a three-dimensional (3D) space (Hagen et al. 1994), or $r = 1 - 1/D$ for a D-dimensional space (Bassett et al. 2010).

Initial formulations of Rent's Rule counted the connections of a network to the outside world; most commonly, however, the relationship is used to characterize the connectivity inside a network, with r then being called the *inner* Rent exponent (Christie and Stroobandt 2000). Therefore, the network is divided into partitions by a partitioning algorithm that minimizes the number of connections between partitions. Recursively applying this algorithm, a sequence of complete partitionings, i.e. sets of partitions that cover each basic element exactly once, is generated (Hagen et al. 1994). Naturally, the number of partitions K increases thereby. For each partitioning of the sequence, the mean partition size (N/K) and the mean number of connections (per partition) over partition boundaries can be extracted, as illustrated in Fig. 1a, resulting in a discrete, empirical function $T_{\text{char}}(G)$. This relationship is called *Rent characteristic* henceforth. As an example, Fig. 1c shows the expected Rent characteristic for a uniform random graph in logarithmic scale. Because Rent's Rule results in a straight line in a log–log plot, the Rent parameters may be extracted by a linear fit to the Rent characteristic. In doing so, the data points for the largest partitions are commonly excluded, because they often show an adaptation to the outside connections of the complete network, differing from the inner connectivity (Hagen et al. 1994; Christie and Stroobandt 2000; Partzsch and Schüffny 2009).

Differing from the above definition of the number of pins T, the original study by E. F. Rent summed all pins of basic elements in a partition instead of counting only those that connect to outside the partition (Lanzerotti et al. 2004). This definition of T was used in Beiu et al. (2009) to extract Rent parameters for the mammalian neocortex from the power-law scaling of white-to-grey matter volume. However, by definition, these results characterize the total number of connections in the brain, not their distribution inside the brain network, which we are interested here. In relation to the definition of T introduced above, the power law extracted by the original interpretation describes the scaling of the parameter $\overline{T}$ with network size N (i.e. brain size).

In a previous article, we have already used Rent's Rule as defined in conjunction with Eq. 1 for characterizing neural networks (Partzsch and Schüffny 2009). However, counting each neuron-to-neuron connection separately as applied there does not reflect an efficient implementation: Instead of dividing connections at the sender and wiring them to



(a) **(b)** **(c)**

Fig. 1 Illustration of the different definitions of the Rent characteristic: **a** normal graph definition, counting each (incoming) neuron-to-neuron connection separately; **b** hyper-graph definition, counting only one connection per sending neuron; **c** corresponding Rent characteristics for a uniform random graph (Newman 2003) with $N = 1000$ neurons and connection probability $p = 0.1$

each receiving neuron separately, connections from the same sender neuron can be transmitted via one wire to a partition and then distributed locally inside the partition. For integrated circuits, the fan-out of an element's output is small, so that it can be approximately accounted for in calculations using a fan-out distribution (Stroobandt and Kurdahi 1998). In contrast, neural networks exhibit connections with a huge fan-out. This has to be accounted for during partitioning the network and when calculating the Rent characteristic. The above mentioned efficient implementation can be modelled by a hyper-graph, which is a graph (hyper-)edges of which can connect more than two nodes. In our case, one sender neuron with all neurons receiving connections from it form one hyper-edge. This edge is counting only once per partition in the Rent characteristic, as illustrated in Fig. 1b. Special partitioning algorithms, such as HMetis (Karypis and Kumar 2000), have been developed for this kind of graphs.

The Rent characteristic derived for hyper-graphs has very different properties compared to the formulation for normal graphs. In a network with N neurons, each partition can have a maximum of N hyper-edges. Thus, the Rent characteristic saturates at N, as demonstrated by the dashed line in Fig. 1c. As a consequence, the power law of Rent's Rule is restricted to a relatively small region. Therefore, the whole Rent characteristic has to be taken into account instead of the Rent parameters only. Still, the starting point ($\overline{T}$) and the slope of the Rent characteristic (r) determine at which partition size saturation is reached.

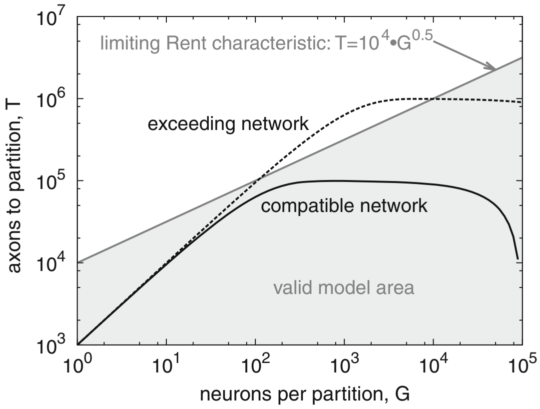


Fig. 2 Illustration of the limiting Rent characteristic of a substrate: a network can be embedded in a certain substrate only if its Rent characteristic stays below the limit of the substrate (compatible network); otherwise, this is not feasible (exceeding network)

With the hyper-graph definition, the relation to geometry can be further developed. If a network is to be embedded into a certain geometrical substrate, then it must not exceed the connection density of the substrate. This is a constraint for the network that can be expressed with the Rent characteristic: From the dimensionality of the substrate, a Rent exponent r_{sub} can be derived as described above, and the neuron and connection densities determine the number of connections $\overline{T}_{\text{sub}}$ that can be routed to a single element. The power law resulting from these two Rent parameters can be regarded as the *limiting Rent characteristic* of the substrate: It determines the maximum number of connections that can enter a partition of a certain size without exceeding the substrate's maximum connection density. Thus, the Rent characteristic derived from an optimally partitioned network must not exceed the limiting Rent characteristic at any partition size to allow the network to be embedded in the substrate, as illustrated in Fig. 2. Please note that this is a necessary condition, but does not guarantee the feasibility of embedding. If a network cannot be embedded in a certain substrate, then its elements may be moved apart to have more space for routing. This was already found to be unavoidable when scaling up a network with too high Rent exponent for a substrate (Donath 1979; Hagen et al. 1994). Effectively, this decreases the element density, which corresponds to an increase of $\overline{T}_{\text{sub}}$, thus shifting the limiting Rent characteristic upwards.

In the next section, we adopt this approach to cortical networks, calculating a limiting Rent characteristic for the neocortex from a simple geometrical model.

3 Rent's Rule and biological scaling laws

The mammalian neocortex consists of a folded sheet at the outside, called grey matter, that hosts neuron bodies, dendrites and axons, and an inner volume, called white matter, that almost exclusively contains myelinated axons, i.e. long-range connections (Abeles 1991). Because the geometrical shape of the white matter is difficult to capture and crucially depends on the species, we restrict ourselves to the grey matter henceforth. Consequences of this simplification are discussed in Sect. 5.

For our analysis, we assume that the grey matter is a planar sheet with height h_c. For an arbitrarily shaped cut-out of this sheet, we can determine the number of neurons G in it and the maximum number of connections (pins) T from the surrounding matter. The volume of the cut-out, V, is proportional to the number of neurons in it:

$$G = \rho_N \cdot V \ , \tag{2}$$

with ρ_N denoting the mean density of neurons. The maximum pin count of the cut-out can be determined by relating its surface area A to the minimum cross-sectional area of a pin, A_T:

$$T = \eta_A \cdot \frac{A}{A_T} \ . \tag{3}$$

In this equation, η_A denotes the utilization of the surface area by the pins, accounting for possible empty space in between. We assume a pin to be an axon with diameter d_a entering the partition, so that we use $A_T = 1/4 \cdot \pi d_a^2$. As mentioned, Eqs. (2) and (3) hold for an arbitrarily shaped volume. We want to determine the minimum number of pins T for a cut-out with G neurons to arrive at the maximally constraining Rent characteristic achievable by our approach. Consequently, we use shapes that have minimal surface area for a given volume.

For large volumes, the shape is restricted by the height of the cortical sheet. Considering that connections may not enter from outside the sheet, we choose a circular cylinder with cortex height and varying radius r in this case, such that pins only exist on the lateral area of the cylinder. Thus, its volume V_c and pin area A_c are given as:

$$V_c = \pi h_c \cdot r^2 \ , \quad A_c = 2\pi h_c \cdot r \ . \tag{4}$$

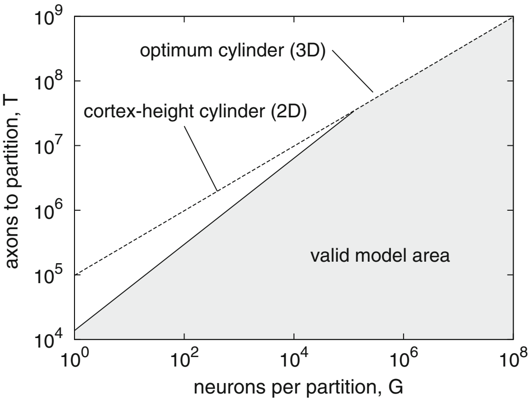


Fig. 3 Limiting Rent characteristic for the human neocortex as calculated in Eqs. (5) and (7). Parameters are taken from measurements: $\rho_N = 44.0 \times 10^6\,\text{cm}^{-3}$, $h_c = 2.69\,\text{mm}$ (Pakkenberg and Gundersen 1997) and $d = 0.6\,\mu\text{m}$ (estimated minimum from Fig.1 in Harrison et al. 2002)

Combining these expressions with Eqs. (2) and (3) results in the Rent characteristic for this case:

$$T_c(G_c) = \frac{8\eta_A}{d_a^2} \cdot \left(\frac{h_c}{\pi \cdot \rho_N}\right)^{1/2} \cdot G_c^{1/2} = \overline{T}_c \cdot G_c^{1/2} \ . \tag{5}$$

As a consequence of the restricted sheet height and pins entering only at the lateral area, the Rent exponent is the same as for a 2D substrate, confirming the intuitional notion of the cortical sheet being essentially 2D.

For small volumes, the cortical sheet does not impose restrictions on the shape and on the pin direction. In this case, a sphere is the shape with minimum surface area A_o for a given volume V_o, defined by its diameter d:

$$V_o = \frac{1}{6}\pi \cdot d^3 \ , \quad A_o = \pi \cdot d^2 \ . \tag{6}$$

Inserting these expressions in Eqs. (2) and (3) results in the Rent characteristic:

$$T_o(G_o) = \frac{4\eta_A}{d_a^2} \cdot \left(\frac{6}{\pi \cdot \rho_N}\right)^{2/3} \cdot G_o^{2/3} = \overline{T}_o \cdot G_o^{2/3} \ . \tag{7}$$

This expression is valid until the sphere reaches cortex height, corresponding to $G_o < 1/6 \cdot \pi \rho_N h_c^3$. As expected, the Rent exponent is the same as for a 3D substrate.

Figure 3 shows the limiting Rent characteristic for parameters of the human neocortex. For the calculations, we have assumed a complete utilization of the surface area by incoming axons, setting $\eta_A = 1$. As expected from the above derivation, the increase of axon count with partition size corresponds to a 3D substrate locally, but switches to a 2D substrate at approx. 10^5 neurons in the partition. The intersection point of the two regions can be calculated from Eqs. (5) and (7):

$$G_{\text{is}} = \frac{4}{81}\pi \cdot h_c^3 \cdot \rho_N \ . \tag{8}$$

Because the number of axons T is derived from maximally utilizing the boundary area of the partitions volume, realistic models must not exceed the limiting Rent characteristic at any partition size, as introduced in Sect. 2. An exception to this general constraint has to be considered at the local scale because of the extension of a neuron's dendrites: The employed hyper-graph definition of Rent's Rule models the extension of the axons, but assumes neurons to be points. In the derivation of the limiting Rent characteristic, these points were placed in a sphere or cylinder. However, owing to the extension of the dendrites, single neurons and small groups of neurons may occupy a much wider space than modelled by the corresponding sphere or cylinder. Effectively, the surrounding shape of the partition is changed, increasing the surface area of that partition while keeping its volume constant. In consequence, more axons could enter that partition than the maximum predicted by the limiting Rent characteristic. For estimating an upper limit, it could be assumed that the total volume of a single neuron is occupied by a conjunction of cylinders (i.e. dendritic branches) with minimum diameter ($d = 0.6\,\mu$m). The resulting total cylinder length would be ~80 mm in this case, allowing for $T = 5.4 \cdot 10^5$ axons to connect to the neuron, which by a factor 64 exceeds the one calculated by the limiting Rent characteristic. However, this is an overestimate, because dendrites vary in diameter, the soma was not taken into account, and the neuron's volume was calculated directly from the density of neurons, which does not take the spacing between neurons into account. Furthermore, because dendrites only spread over a rather restricted area (Young et al. 1995), their effect is bounded to small partitions and can be expected to gradually diminish when increasing the partition size. Overall, the extension of the 2D part of the limiting Rent characteristic may be taken as a rough estimate.

Nevertheless, even a model that exploits this exception, exceeding the limiting axon count at small partitions, has to conform to the limiting Rent characteristic at a more global scale. Thus, it would have to compensate its high local connection count with a low Rent exponent. In contrast, a model with a high Rent exponent could fit into the limiting Rent characteristic if it had a low number of synapses per neuron, shifting its Rent characteristic sufficiently down. However, this would correspond to few local and many long-range synaptic connections, which would be costly from a metabolic point of view (Chklovskii 2004). Thus, it may be argued that the brain grows connections as locally as possible to maintain its function, which corresponds to exploiting the limiting Rent characteristic at small to medium partition sizes.

The limiting Rent characteristic imposes constraints on the scaling of connectivity. Thus, it is interesting to compare it to well-known scaling relationships found in the brain (Braitenberg 2001; Changizi 2007). As a fundamental difference, these relationships concern the scaling between species, i.e. for different number of neurons N in the whole brain network, whereas the limiting Rent characteristic constrains the scaling with the number of neurons G in a partition of a single network with fixed size N. Consequently, the parameters of the limiting Rent characteristic are dependent on the brain scaling relationships. The scaling of the relevant parameters d_a, h_c and ρ_N is given by Changizi (2007) as $d_a \sim N^{1/6}$, $h_c \sim N^{1/6}$ and $V_{\text{grey}} \sim N^{3/2}$, which corresponds to $\rho_N \sim N^{-1/2}$. This results in the parameters $\overline{T}_c$ and $\overline{T}_o$ scaling as:

$$\begin{aligned} \overline{T}_c &\sim \frac{h_c^{1/2}}{d_a^2 \cdot \rho_N^{1/2}} \sim \frac{N^{1/12}}{N^{1/3} \cdot N^{-1/4}} \rightarrow \overline{T}_c \sim \text{const}(N) \\ \overline{T}_o &\sim \frac{1}{d_a^2 \cdot \rho_N^{2/3}} \sim \frac{1}{N^{1/3} \cdot N^{-1/3}} \rightarrow \overline{T}_o \sim \text{const}(N)\,. \end{aligned} \tag{9}$$

Together with the constant Rent exponents (cf. Eqs. (5) and (7)) it follows that the limiting Rent characteristic is approximately constant over brain size, i.e. the scaling dependencies of neuron density, grey matter height and axon diameter with respect to the number of neurons cancel out in the limiting Rent characteristic. Notably, it thus constitutes a constraint on connectivity that is mainly invariant of the species, expressed in the number of neurons N. This somewhat confirms the statement by Changizi that the brain scaling relationships are mainly following from physical constraints (Changizi 2007, Fig. 1). While Changizi motivated this via similar behavioural complexity over brain size, our analysis shows that already on the connectivity level a remarkable invariance is present between species.

With the species-invariant limiting Rent characteristic, candidate models for connectivity in biological neural networks can be assessed quantitatively, as described in the following.

4 Rent characteristic of neural network models

In this section, we analytically derive the Rent characteristic for two generic network models: uniform random networks and locally coupled networks.

Uniform random networks are a common model for studying properties of a connection structure (Newman 2003) and neural network behaviour (Brunel 2000). In such a network, each possible connection between neurons exists with constant probability p. A similar uniformity assumption, called Peter's rule, is used for reconstructing cortical connectivity from single connection measurements, stating that synaptic connections are evenly distributed over the neurons in a cortical layer (Binzegger et al. 2004). Based on such measurements, extended uniform models consist of several neuron types or layers with connection probabilities varying between layers and neuron types, but being constant otherwise (Häusler et al. 2009; Kremkow et al. 2007). In the

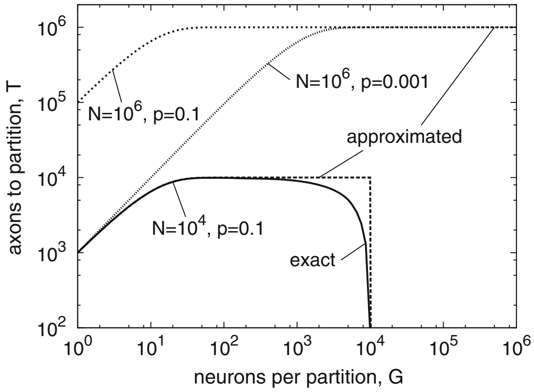


Fig. 4 Rent characteristic of uniform random graphs

following, we restrict ourselves to the case were p is constant throughout the network. The expected number of connections (hyper-edges) T entering a partition with G neurons can be calculated from the number of neurons outside the partition, $(N - G)$, and the probability that an outside neuron does not have a connection to one of the neurons in the partition, $(1 - p)^G$, resulting in

$$T=(N-G)\cdot\left(1-(1-p)^G\right) \approx N\cdot\left(1-(1-p)^G\right) \tag{10}$$

The approximation on the right-hand side is valid as long as the partition size G does not approach the network size N. We use this approximation for the following calculations, because its condition is met for the investigated cases.

Figure 4 shows the Rent characteristic of different uniform random graphs. As can be expected from Eq. (10), it increases with $r = 1$ from the starting point $\overline{T} = N \cdot p$ and saturates at $T \rightarrow N$. Thus, the starting point of the Rent characteristic is equal to the expected number of synapses per neuron. As evident from Fig. 4, the approximation of Eq. (10) is only deviating from the exact solution in the saturation region of the Rent characteristic; the critical area where the curve enters saturation is not affected.

Because the Rent characteristic of uniform random graphs has a Rent exponent greater than those of the limiting Rent characteristic of the neocortex derived in Sect. 3, it will exceed the derived limit for sufficiently large network sizes and connection probabilities. This limit can be quantified, as is shown in the following.

The maximum size of a uniform random graph is reached if its Rent characteristic equals the limiting Rent characteristic at some partition size, but does not intersect it. Then, at the critical point, the limiting Rent characteristic is the tangent of the random graph's Rent characteristic. In consequence, the slope of the Rent characteristic in Eq. (10), i.e. the local Rent exponent, is equal to the slope of the limiting Rent characteristic, which is either $r = 1/2$ or $r = 2/3$. This slope can be calculated in the double-logarithmic domain from Eq.(10):

$$r = \frac{\mathrm{d}(\log(T))}{\mathrm{d}(\log(G))} = -\frac{\log(1-p)\cdot(1-p)^G\cdot G}{1-(1-p)^G}\,. \tag{11}$$

With the substitution $z = (1 - p)^G$, this results in

$$r = -\frac{z\log(z)}{1-z}\,. \tag{12}$$

This equation can be solved numerically for z, resulting in $z(r = 1/2) = 0.285$ and $z(r = 2/3) = 0.466$. With back-substitution, the location of the critical point (i.e. the potential tangent) for a random graph with size N can be derived:

$$G_{\mathrm{tang}} = \frac{\log(z(r))}{\log(1-p)}\,,\quad T_{\mathrm{tang}} = N\cdot(1-z(r))\,. \tag{13}$$

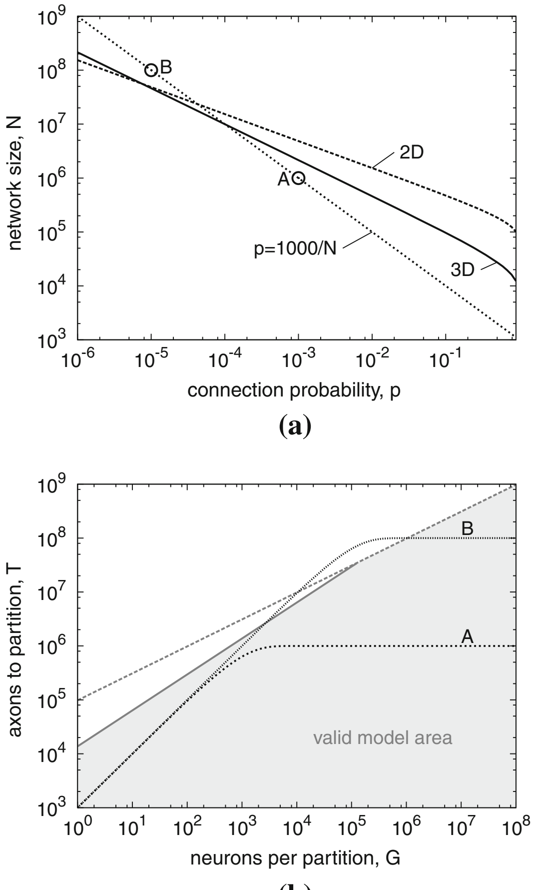
Finally, the maximum network size N_{lim} of a random graph fitting in the limiting Rent characteristic is calculated by equalling T_{tang} with Eqs. (5) and (7) (i.e. T_c or T_o, in the following named as T_x):

$$\begin{aligned} T_{\mathrm{tang}} &= T_x = \overline{T}_x\cdot G_{\mathrm{tang}}^{r_x} \\ \rightarrow\ N_{\mathrm{lim}} &= \frac{\overline{T}_x}{1-z(r_x)}\cdot\left(\frac{\log(z(r))}{\log(1-p)}\right)^{r_x}\,. \end{aligned} \tag{14}$$

Figure 5a shows the limit network size with respect to the connection probability. As can be seen, the 3D part of the limiting Rent characteristic is more restrictive for small, dense random graphs, whereas the 2D part constrains sparse, large-size networks. Fully connected networks ($p = 1$) are restricted to $N \leq 1.5 \cdot 10^4$ neurons. While increasing the network size at constant connection probability leads to a relatively early arrival at the maximum network size (vertical shift in Fig. 5a), holding the expected number of synapses per neuron constant by an adapted connection probability increases the valid range of uniform random graphs (compare dotted line in Fig. 5a). For a realistic 1000 synapses per neuron, the network size is restricted to approx. $N \leq 10^7$ neurons. This is also validated by comparing the random graph's and the limiting Rent characteristic, as shown in Fig. 5b: While for a network size of $N = 10^6$ the Rent characteristic stays completely inside the valid model area (case A), it violates the geometrical constraints for $N = 10^8$ (case B).

As an alternative to uniform random networks, locally coupled networks have been proposed as a generic model for the connectivity in biological neural networks (Mehring et al. 2003). These networks are based on findings that the relative frequency of connections between certain cortical neurons decreases with the distance of their soma (Hellwig 2000). To derive a Rent characteristic for this type of connectivity, we adopt the approach in Mehring et al. (2003), placing (point) neurons uniformly at random on a 2D sheet with density ρ. The connection probability p is varied with the distance d between neurons as a Gaussian function:

$$p(d) = \mathrm{e}^{-\frac{d^2}{2\sigma^2}}\,, \tag{15}$$



(a)

(b)

Fig. 5 Scaling limit of uniform random graphs: **a** limit network size $N_{\lim}$ with respect to the connection probability p for the two parts (2D/3D) of the limiting Rent characteristic; the *dotted line* represents scaling of a random graph with 1000 synapses per neuron (expected value); **b** limiting Rent characteristic compared with a fitting and a non-fitting Rent characteristic of a random graph, denoted as A and B in plot (**a**)

where σ determines the extension of the local connectivity. To derive a Rent characteristic for this type of network, the neurons in a Rent partition have to be located in the 2D sheet. Therefore, we choose a quadratical region with side length a for simplicity. With the diminishing probability of long-distance connections, practically no connections are made to this region from outside an area with width $k \cdot \sigma$, with a sufficiently large k, e.g. $k = 4$. Thus, as a worst-case estimate, we assume that all neurons inside this surrounding region form a connection to at least one of the neurons in the partition region. From this assumption, the number of axons to the partition, T, can be calculated from the area of the surrounding region:

$$A = 4 \cdot a \cdot k\sigma + \pi (k\sigma)^2 \ \rightarrow \ T = \rho \cdot A \, . \tag{16}$$

In this equation, any boundary effects have been neglected, i.e. infinite network size is assumed. The extension of the Gaussian, σ, and the neuron density, ρ, together determine the expected number of synapses per neuron, S: $S = 2\pi\sigma^2 \cdot \rho$. Combining this relation with Eq. (16) results in:

$$T = k(2S)^{1/2} \cdot G^{1/2} + \frac{1}{2} k^2 \cdot S \, . \tag{17}$$

This Rent characteristic is split into two terms: a term with $r = 1/2$ and a term independent of the partition size. Furthermore, the solution is only dependent on the number of synapses per neuron S, but not on the number of neurons N. This is due to the derivation approach, assuming infinite network size. Consequences of finite network size on the Rent characteristic are discussed at the end of this section.

Owing to the small Rent exponent and the additional constant term, the limiting Rent characteristic is constraining the locally connected network's Rent characteristic at small partition sizes G, but not at large partitions as for uniform random graphs. However, for small partitions, the limiting Rent characteristic may be too restrictive, because the extension of the dendritic trees, increasing the surface area of individual neurons and small neuron groups, is not taken into account (also cf. Sect. 3). Thus, the actual number of connections to small partitions may be bigger than the Rent limit, as long as this limit is not violated at larger partitions. At which point these two regions cross over depends on the extension of the dendritic tree and is left open to debate here. A further approximation that has to be taken into account for small partitions is the worst-case estimate that all neurons in the boundary region send to at least one of the neurons in the partition. The smaller the number of neurons in the partition, the higher is the probability of a neuron in the surround to be not sending to the partition: $P_{\mathrm{noconn}} = (1-p)^G$. Thus, the calculated Rent characteristic is a clear overestimate especially for small partitions.

From the two reasons outlined above, one may allow the local network's Rent characteristic to exceed the limiting Rent characteristic up to a maximum partition size $G_{\lim}$. As the Rent characteristic in Eq. (17) is only dependent on the number of synapses per neuron, equalling this relation with the limits defined by Eqs. (5) and (7) results in a maximum allowed synapse count per neuron, $S_{\max}$:

$$\begin{aligned} S_{\max} &= \frac{2}{k^2} \cdot G \cdot \left(\sqrt{1 + \overline{T}_x \cdot G^{(r_x - 1)}} - 1 \right)^2 \\ &\approx \frac{2}{k^2} \cdot \overline{T}_x \cdot G^{r_x} \, . \end{aligned} \tag{18}$$

Figure 6a shows this relation. As can be seen from the solid/dashed lines, the right-hand-side approximation is valid over the whole plotted range. Comparing the value $S_{\max}(G_{\lim} = 1) = 2 \cdot 10^3$ with the allowed number of synapses per neuron in the limiting Rent characteristic ($\overline{T} = 1.5 \cdot 10^4$), one finds a discrepancy of almost an order

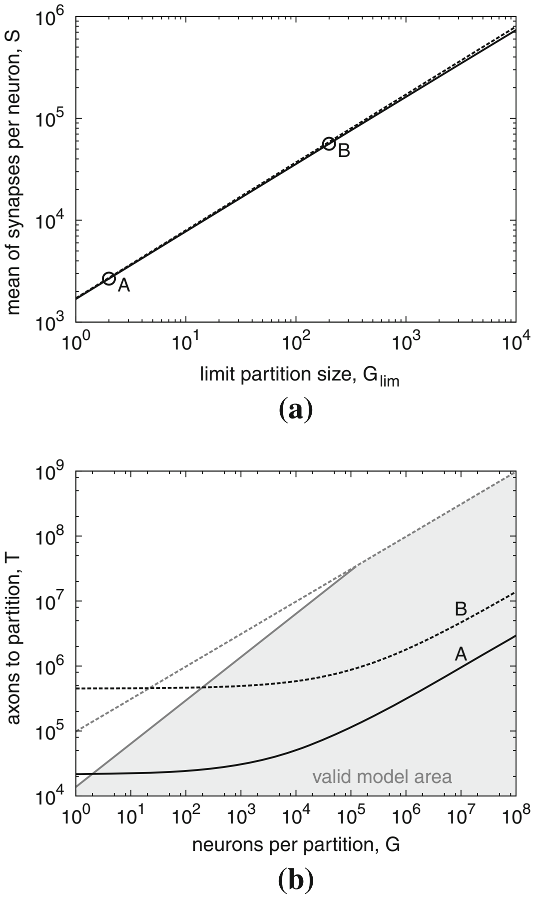


Fig. 6 Constraining of locally connected networks by the limiting Rent characteristic: **a** maximum expected number of synapses per neuron with respect to the maximum partition size for which the limiting characteristic is exceeded (*dashed line*: approximation at the right side of Eq. (18)); **b** limiting Rent characteristic with the two cases (A and B) marked in **a**

of magnitude. This is due to the worst-case estimate used in the derivation of the Rent characteristic for the locally connected networks, showing the strong impact of this simplifying assumption. However, as discussed above, this deviation is expected to rapidly diminish for bigger partitions.

The Rent characteristics plotted in Fig. 6b are for infinite network size. If the network size is finite, then two regions may be separated: for small networks, almost full connectivity is reached, because all neurons are nearby. Then, the Rent characteristic is saturated ($T \approx N$) over almost the entire range of partition sizes. In contrast, for larger networks, the Rent characteristic does not reach saturation at all. This T staying significantly below the maximum possible value, N—even for big partition sizes—can be regarded as an indicator of specific or localized connectivity, because even large, global partitions do only receive connections from a (small) fraction of the remaining neurons in the network.

5 Discussion

Based on the Rent's Rule analysis method from circuit design, we have derived an abstract representation of the geometrical constraints in the mammalian neocortex that connectivity models can be tested against. This limiting Rent characteristic was used to constrain two generic connectivity models, uniform random (Newman 2003) and localized (Mehring et al. 2003) networks. It is clear that both are only abstract models of the cortical connectivity. For example, they neglect the patchy structure of axons (Braitenberg and Schüz 1998), and they do not distinguish between short-range connections staying in the grey matter and long-range connections passing through the white matter (Schüz et al. 2006). Furthermore, they represent two poles of possible connectivity models: while localized connectivity completely ignores long-range connections, uniform random connectivity disregards any locality of connections. It is thus not surprising that the limiting Rent characteristic constrains the localized connectivity on a local scale (i.e. for partitions of a few neurons), while it restricts uniform random connectivity on the global network scale.

From these results, it could be argued that a combination of uniform random and localized connectivity is a reasonably realistic generic connectivity model for the neocortex. In this context, the small-world topology by Watts and Strogatz (1998), replacing a low percentage of localized connections with uniform random connections may be a candidate model. Indeed, it is argued that the brain exhibits the thereby generated small-world property (Changizi 2007). The Rent characteristic of such a network would be a combination of that for localized connectivity (Fig. 6b) at small partitions and that for uniform random connectivity (Fig. 5b) at big partitions. Consequently, it would exploit the limiting Rent characteristic both at small and at global-scale partitions, but not in an intermediate region. However, this would partly conflict with the wiring cost discussion in Sect. 3 (cf. Chklovskii 2004), arguing for exploitation at partition sizes from small to medium. As an alternative model, populations of neurons could be uniformly connected internally, but projections between populations would be distance dependent, exhibiting some form of locality. With such a configuration, almost the whole limiting Rent characteristic could be exploited, especially at intermediate partition sizes. Such a hierarchical organization also has to be consistent with total connection counts in the neocortex (Beiu et al. 2009).

When investigating candidate connectivity models, it has to be taken into account that the derived limiting Rent characteristic is based on a model of the grey matter, i.e. the cortical sheet, only. Therefore, it does not take into account the long-range connections passing through the white matter. Although the white matter is also geometrically constrained, it is difficult to calculate a limiting Rent characteristic including it, because its highly irregular structure due to the folding of the cortex would have to be accounted for. Still, these long-range connections are bound to specific neuron types (Abeles 1991) and could be excluded in a Rent's Rule analysis, so that the remainder of a connectivity model could be tested more confidently against the limiting Rent characteristic.

Despite its restriction to the grey matter, the limiting Rent characteristic seems to capture a fundamental constraint on connectivity in the cortex. This is illustrated by the fact that it is approximately invariant to the mammalian species. In other words, properties of mammalian cortices (neuron density, axon diameter, grey matter thickness) are scaled between species such that a constant connection complexity is achieved, as expressed in the limiting Rent characteristic. This explains and supports the conjecture in Changizi (2007) that scaling laws are caused by anatomical constraints, not by differences in operation or intelligence.

The constancy of the limiting Rent characteristic, stating that also the maximum number of connections to a single neuron is constant over species, seems to conflict with the scaling of the number of synapses per neuron, S, that was found to be dependent on the number of neurons, N, as $S \sim N^{1/2}$ (Changizi 2007). However, as discussed in Sect. 3, the limiting Rent characteristic is too restrictive on the level of single neurons, because it neglects the extension of the dendrites. Furthermore, on a more global scale, it ignores the connections through the white matter, as discussed above. Interestingly, Beiu et al. (2009) estimated from the relative growth of white matter to grey matter volume that the number of connections in the cortex scales as $\sim N^{1.23}$, corresponding to $S \sim N^{0.23}$. Because they essentially counted the connections in the white matter, their result corresponds to long-range connections. The difference in the scalings between Changizi (2007) and Beiu et al. (2009) thus suggests that short-range connectivity increases more rapidly than long-range connectivity in larger brains, which confirms the conclusions of Beiu et al.

A more in-depth analysis of a connectivity model with the limiting Rent characteristic would also have to take into account the conclusion by Stepanyants and Chklovskii (2005) that the number of actual synaptic connections is a factor 3–10 lower than the number of possible contact points (potential synaptic connections in the terminology of Stepanyants and Chklovskii (2005)). Owing to its geometric origin, the limiting Rent characteristic constrains the potential connectivity, while a model represents the actual synaptic connectivity. Furthermore, the analysis would have to regard routing congestion effects, e.g. taking into account route-through wires, which asks for additional connection reserves. Thus, in practice, the Rent characteristic of a realistic network model has to stay well below the limiting Rent characteristic.

The results of this article are also promising for large-scale hardware realizations of biologically realistic neural networks (see, e.g. Schemmel et al. (2010)): Because the silicon substrate is 2D, its connectivity is scaling with a Rent exponent of $r = 1/2$. This matches the Rent exponent of the limiting Rent characteristic for large partitions. Extrapolating this curve to small partitions, a relative connection density of $\approx 10^5$ per neuron can be found (cf. Fig. 3). Thus, a hardware system supporting such a connection density could in principle implement biologically realistic network models irrespective of the network size.

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