Towards comparative theoretical neuroanatomy of the cerebral cortex

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Abstract

Despite differences in brain sizes and cognitive niches among mammals, their cerebral cortices posses many common features and regularities. These regularities have been a subject of experimental investigation in neuroanatomy for the last 100 years. It is believed that such studies may provide clues about cortical design principles and perhaps function. However, on a theoretical side there has been little interest, until recently, in studying quantitatively these regularities. This article reviews some attempts in this direction with an emphasis on neuronal connectivity. It is suggested that the brain development is influenced by different, conflicting in outcome, functional/biochemical constraints. Because of these conflicting constraints, it is hypothesized that the architecture of the cerebral cortex is shaped by some global optimization plan.

Keywords: Theoretical Neuroanatomy, Cerebral Cortex, Optimal Wiring, Brain De-

sign, Metabolism, Scaling.

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1 Introduction

It is generally believed that brains are evolutionary designed in such a way as to perform some functional computation which is vital for animals survival and reproduction, and possibly for higher cognitive functions [2]. In general, bigger mammals have bigger brains - the brain volume V_b scales with body volume V_{body} with the exponent around 3/4 [2,26]. The origin of this scaling law with this particular exponent is unknown, although there were some suggestions that it may be a result of an increased number of sensory receptors on a surface body in bigger animals that require more space for representation in the brain (e.g. [31]). Also, motor output and homeostasis of the whole body, both of each are controlled by the brain, may require more brain representation in larger animals. Despite big span in size (e.g. the volume of the mouse brain is 10^4 times smaller than that of the elephant), inter- and intraspecies variability, brains of different species share common structures and many parameters associated with them exhibit striking regularities [7,9,16,19,23,28,36]. This similarity in structure and form may be an indication of the same basic genetic design principles [31] governing developmental processes. This article focuses on the regularities present in the cerebral cortex, the part of the brain responsible for processing of a sensory information and for higher cognitive function. In particular, I shall review some recent theoretical approaches aiming at providing quantitative framework for understanding neuroanatomical connectivity of the cortex. It is believed that such approaches may ultimately turn out to be helpful in deciphering cortical design principles and additionally may be useful in providing link between "structure and function" [29].

The central theme of this review is the notion that architecture and size of the cerebral cortex are shaped by different constraints with conflicting outcomes. Some of these constraints are related to maintaining functionality and some are connected to biochemical/metabolic costs associated with cortical computations. The hypothesis presented in this review is that, despite those competing constraints, evolution has found ways to develop functional brains, which represent a balanced design that is in some sense optimal. I shall discuss both experimental data and recent theoretical approaches that seem to point in this direction. In particular, I shall present the current state of the art of the neuroanatomical data, and discuss what still remains a challenge both experimental and theoretical.

2 Invariants in the cerebral cortex

Many scaling relations between cortical parameters are a direct consequence of cortical invariants. There are several parameters which are roughly invariant with respect to brain size, across different cortical regions and different species. These invariant parameters are: (i) synaptic density ρ_s [17,43], (ii) surface density of neurons σ_n [41], (iii) the ratio of the number of excitatory to inhibitory synapses [19] (iv) cortical module size [34], (v) density of short-range (intra-cortical) axons and dendrites [9].

From the above invariants one can derive interdependence relations between different cortical parameters [32,33]. To achieve this, first let us introduce some definitions. Synaptic density is defined as $\rho_s = NM/V_g$, where N is the number of neurons in gray matter, M is the average number of synapses per neuron, and V_g is the gray matter volume. Surface density of neurons is defined as $\sigma_n = N/W$, where W is the total surface area of the cerebral cortex. Density of short-range axons is defined as NL_s/V_g , where L_s is the average length of short-range (intra-cortical) axons per neuron.

If we use a scaling relationship between the total cortical surface area W and the gray matter volume V_g , $W \sim V_g^{0.9}$ [27], which is valid for large convoluted brains, then we obtain from the above invariants and definitions that $M \sim V_g^{0.1}$ and roughly $M \sim N^{0.1}$. This means that the number of synapses per neuron increases very weakly with brain size, and additionally, that this number increases similarly weakly with the total number of neurons. The latter implies that cortical networks become more and more sparse in terms of interconnectedness as they get bigger, since the average connectivity $M/N \sim N^{-0.9}$, i.e. it decays quickly with the number of neurons (or the brain size). Why the number of synapses per neuron should increase with brain size? This may be a by-product of an expectation that the average axon (dendrite) length per neuron should increase with brain size. The rationale for this is that axons should catch up, at least partially, with increased brain size in order to maintain some level of crosscommunication with other neurons in the network. Indeed, if we combine invariants (i) and (v), we obtain that the ratio M/L_s is brain size independent. Two conclusions follow from this relation. First, an average inter-synapse distance is roughly constant across species. Second, the axon length L_s scales with brain size in the same manner as the number of synapses does, i.e. the axon length increases with the brain volume very slowly with the exponent 0.1. The uniformity of the inter-synapse interval distribution maybe in some sense optimal for information processing and this may cause the number of synapses per neuron to increase weakly with brain size.

Another consequence of the above invariants is that the number of neurons contained in a module is brain size independent and this follows from combining invariants (ii) and (iv). Since a cortical module is considered to be an elementary unit processing information, this result may suggest that, in a first approximation, brains of different sizes use essentially the same local computational mechanisms. The differences between brains functioning may arise from a larger-scale organization, i.e. connectivity patterns between modules and cortical areas.

The fact that the number of excitatory to inhibitory synapses is constant across different species with different brain volumes may suggest that there exist mechanisms in the brain that try to maintain a global balance between excitation and inhibition [44,52]. Such a balance can be achieved by homeostatic processes that can dynamically adjust the number of synapses and their strength [50]. From a functional point of view, the balance between excitation and inhibition is necessary for a permanent regulation of neuronal activity. In fact, it is an efficient way of preventing both disastrous hyperactivation (when excitation dominates) and equally disastrous, for the brain function, inactivation (when inhibition dominates).

Why are there invariants in the cerebral cortex at all? The precise answer to this question is unknown, however the very fact of their existence can hint us about possible mechanisms that shape architecture of the cortex. Recently, an interesting theoretical idea was proposed [15] that can be used to address that question. These authors considered "thought experiments" with perturbing some cortical processes and looked

how these perturbations influenced local axonal conduction delays in the cortex. They found that conduction delays are minimal when both the volume of axons and the volume of synapses constitute 3/5 of the total cortical volume of gray matter. That prediction is consistent with experimental data for axonal and dendritic volumes [15]. Since the derivation of this fraction is quite general and brain size independent, it is possible that minimization of conduction delays is the main factor behind some of the cortical invariants (i.e. invariants (i) and (v)).

3 Local vs. large-scale connectivity

The cerebral cortex is organized differently at different levels. On a microscopic scale, neurons are connected in sparse local circuits [8,21] with a probability of a direct connection decreasing rapidly with a distance [24]. The average probability of a contact between two neurons, defined as the ratio of the average number of synapses per neuron to the total number of neurons, can be computed from the above invariants [32,33]. It is given by [34]

$$p \sim V_g/N^2,\tag{1}$$

and it decays with brain size as $V_g^{-0.8}$ [34,49].

Early studies [9,25] suggested that local wiring pattern is stochastic, that is, neurons tend to connect with other neurons in a random fashion. Such conclusion was motivated by a discovery that synaptic interbouton intervals along an axon in the rodent cortex are distributed according to a Poisson process and there was no correlation between them [25]. However recent body of evidence suggests that neurons are highly selective in choosing their targets (e.g. [11,54]). Only certain classes of neurons are connected by a given class, and a such defined connectivity pattern seems to be almost deterministic. Thus, there seems to be little correlation between apparent stochasticity in the bouton distribution and selectivity in neuronal connections.

More recently Anderson et al [4] studied the distribution of interbouton intervals in more detail and across different neuronal classes. These authors found in the cat visual cortex that interbouton intervals in initial axonal segments are distributed according to a Poisson process, but in most other segments and cases they can be fitted well to a gamma distribution except for very long intervals. At those long intervals distributions exhibit heavy tails, however they could not be fitted to a single power law. Additionally, they found that parameters characterizing each distribution are very similar for cells within the same class but differ among classes. These results indicate that the synapses are distributed in somewhat more ordered way than was thought previously, and these findings are consistent with the idea of specificity. It remains a challenge for the future, both experimental and theoretical, to develop models of such connectional specificity (see also Conclusions section).

One can draw also another conclusion from the interbouton interval distribution. This distribution should correlate to a certain degree with the distribution of the number of synapses per neuron, since for a given axonal length the number of synapses is inversely proportional to the average interbouton interval. The presence of heavy tails in the distribution of interbouton intervals might translate to the distribution of synapses per neuron having such heavy tails as well. However, one should be cautious with this, since there is no simple mathematical one-to-one relationship between these two quantities. This feature of long tails in the number of synapse distribution, if proved experimentally correct, can have interesting implications for cortical computation (see e.g. [48]).

On a macroscopic scale cortical networks are organized into areas with distinct cytoarchitectonic and neuroanatomical properties. Large-scale connectivity between areas has been investigated by Young and colleagues [42,55,56] in cat and monkey. In a series of papers they classified the area connectivity using multidimensional scaling method [56]. The main conclusion from their work is that areas tend to connect mostly with their neighbours and only rarely with remote areas. This architecture resembles the so-called "small world" networks [53], which seem to possess a suitable structure for efficient communication between network components [47]. There are two main classes of small world networks that have become an object of intense current research. One class is known as Erdos-Renyi networks [22], in which the distribution of the number of connections has a pronounced peak at some finite value that can be approximated by a gamma distribution. Second class of small world networks that has received an extraordinary attention recently, is known as scale-free networks [6]. In this type of networks the distribution of connections has a long tail and follows a power law. It is interesting to investigate which of these two types is actually realized in the cortical large-scale organization. In Figs. 1 and 2 we plot the cumulative distribution

of connections between cortical areas for cat (Fig. 1) and for monkey (Fig. 2) using data of connectivity matrices from Young et al [54]. The cumulative distribution C(k)is defined as a proportion of the number of areas having at least k connections with other areas. It would give a power law if a regular distribution, defined as a proportion of the number of areas having precisely k connections, had a power law decay. The log-log plots do not yield straight lines in either of these cases, which indicates that cortico-cortical connectivity is not organized as a scale-free network. This result taken together with the possibility of long-range tails in the distribution of the number of synapses suggest that microscopic and macroscopic cortical organization can differ not only quantitatively but also qualitatively.

What are the factors that influence the connectivity between cortical areas? This question was a subject of a theoretical approach which aimed at relating connectivity to other cortical parameters [34]. The average connectivity Q between two arbitrary chosen areas A and B, (this is a different quantity than the average probability of connection p between two neurons) is defined as a probability that at least one of the cortical modules (columns or barrels) in A is connected to B. It was found that Q depends on other parameters in the following from [34]:

$$Q \approx 1 - \exp\left(-\frac{aL_0^2}{\xi^2 K^2}\right),\tag{2}$$

where L_0 is the average axon length in white matter, ξ is the average linear size of a cortical module, K is the total number of cortical areas, and the dimensionless param-

eter a characterizes a particular cortical geometry and a pattern of axonal organization in white matter. From this formula, it follows that the connectivity depends mainly on two factors: the average axon length in white matter and the number of cortical areas.

Equation (2) is important for two reasons. First, it can have a practical application in determining axonal length in white matter, since it is difficult to do it directly experimentally. Second, it was found, based on scaling laws for the above parameters, that the average connectivity Q is either only weakly dependent or independent of brain size [34]. This is in contrast to the connectivity p between neurons (see Eq. (1)), which decays quickly with brain size. The finding that Q only weakly decays with the brain volume, also provides some hint about the large-scale cortical connectivity. It may suggest that brain evolutionary design tries to prevent isolation of cortical areas as the brain gets bigger.

4 Optimal wiring

Considerations of the previous section suggest that the wiring pattern in the cortex is not random but there is some plan associated with it. This is not a new idea - it has a long history in neuroscience dating back to early neuroanatomists like Cajal [10]. But what is precisely that wiring plan in the cortex? Is it the same in gray matter as in white matter? These are not easy questions to answer in full detail because of the complexity of different neuronal types and thousands of connections between them in gray matter on the one hand, and technical problems with investigating axonal organization in white matter, on the other hand. Despite these difficulties, there are some reasons to believe that the connectivity pattern in the cortex is somehow optimized. One strongly advocated optimization principle related to gray matter is called the principle of minimal axon length [14,15,39,51], and states that the total axonal length or equivalently the axon length per neuron (if we divide the total axonal length by the total number of neurons) should be as small as possible in order for the cortex to be functional. A support for this hypothesis was provided by Cherniak [13] by analyzing data from the nervous system of a nematode worm *Caenorhabditis elegans*, the only organism fully characterized in terms of connectivity. He has found that the total length of neural connections is indeed minimized. From a theoretical point of view, the demand of minimal axon length is related primarily to the demand of small conduction delays between neurons [15]. Large delays would interfere with efficient information exchange between neurons and this could lead to loss of some functions, which is clearly undesirable. Thus, one can associate optimal wiring in the cortical gray matter with the requirement of minimal conduction delays, which is equivalent to the principle of minimal axon length (although the axonal length per neuron is not exactly the same as the maximal axonal pathlength, which is more directly related to conduction delays, these two quantities should be strongly correlated).

All the above considerations were related to the wiring pattern on a level of local circuits in the gray matter. It is interesting to ask if the same principle applies to long-range (cortico-cortical) connections via white matter? Recently, this question was addressed [35] in the macaque brain. It was found that 11 cortical areas in the prefrontal cortex are indeed connected through the axons that minimize their total length. The

calculation was based on all possible arrangements of the cortical areas and it was found that their actual positioning in the brain is the one that minimizes the wire length. Although, this computation was performed only in a limited part of the cortex, there is a belief that it can be generalized to the whole cortex, thus providing yet another support for the principle of minimal axon length/conduction delays.

Is wiring length the only quantity that is evolutionary optimized in the brain? Other candidates for optimization on a large scale can include: metabolic energy consumed by the whole cortex, the number of cortical areas, and some abstract complexity. That processes operating in the brain try to minimize their metabolic expenditure should not be surprising if one recalls that the brain is energetically an expensive tissue, a hypothesis put forward by Aiello and Wheeler [1]. The metabolic energy rate of the whole cortex at rest scales with the gray matter volume as $V_g^{0.8}$ [26,34], which implies that energy consumption per 1 g of the gray matter decreases with brain size. Using this experimental result and another fact that glutamatergic excitatory synapses are the main users of metabolic energy [5,45,46], one can derive that the number of active synapses at any given instant should decay with brain size as $V_g^{-0.2}$ [34]. This result is consistent with the notion that brains may minimize their metabolism as well [3,38].

The increase in the number of cortical areas with brain size has been advocated by Kaas [30,31]. By having more areas, brains can perform more functional tasks in local specialized circuits, thus restricting activity to specific regions. This can be more optimal in terms of saving biochemical resources than could be more distributed largescale processing. Recently it has been suggested by Sporns et al [47] that the large-scale cortical organization of "small world" type can support highly complex dynamics of neuronal activity. Similar type of dynamics has been observed *in vivo* [52] and this led these authors to propose that the cortical architecture optimizes some abstractly defined complexity.

In the next section, I shall introduce 3 hypothetical functional principles of the brain operation that constitute brain's "computational power". I shall argue that the brain architecture cannot optimize all quantities associated with these principles simultaneously. Rather, the optimal design is a compromise between optimizing each of those quantities separately.

5 Trade-offs in the brain design

The first observation that the minimization of axonal length itself cannot be "the best solution" to the brain design was provided in [32,33]. The argument is that, on average, if axonal length is small then more synaptic steps are needed to connect two arbitrary neurons in the network, i.e. communication in the network is less efficient. Since synapses consume a large portion of metabolic energy [45,46], it implies that decreasing axonal length causes larger metabolic use if no function is supposed to be lost. However, the brain has a limited amount of energy available that is controlled by body biochemistry and this leads to a trade-off. Thus the brain design must choose a compromise between the two extremal solutions, and it is impossible to have both short axons and low metabolic energy rate at the same time. This reasoning can be

put in a more quantitative language that takes into account the cortical invariants and architecture [32].

Another argument indicating that brains are under pressure of different sorts of constraints was presented recently [34]. It was shown that bigger brains could face size and architectonic problems, if some functional requirements were satisfied simultaneously. Three simple hypothetical functional principles were proposed (for extended discussion, see [34]): (i) the number of areas should increase with brain size as quickly as possible, (ii) the area-area connectedness should not decay with brain size, (iii) the temporal delays between areas should not increase with brain size. Obviously, one can imagine more similar "reasonable" principles operating both on a large and local scales. However, for the sake of argument, let us focus on the above three, characterizing large-scale cortico-cortical organization of the cortex. I assume that these 3 functional principles constitute the brain's computational power.

If we assume that white matter is composed primarily of cortico-cortical axons, then one can derive [34] that the ratio of white matter to gray matter volumes V_w/V_g obeys

$$V_w/V_g \sim V_g^{-0.1} \frac{K^3 Q^{3/2}}{\tau^2},$$
(3)

where τ is the average conduction delay between cortical areas. From this, it follows that if evolution wants to keep this delay relatively brain size independent and simultaneously to increase the number of areas with brain size at high rate, then this would lead to an excessive scaling of the white matter volume with gray matter (longer long-range axons). This, in turn, would imply bigger brains as a whole, and that would cause mechanical problems for a body. To prevent this type of design catastrophe, evolution has to compromise part of the brain's theoretical computational power. It is done, as experimental data shows, by simultaneously: (i) increasing slightly temporal delays as brains get bigger [40], (ii) decreasing the rate of growth of the number of areas with brain size [12], and (iii) decreasing slightly connectivity Q with brain size [34].

It is very likely that brains have to face more functional/architectonic compromises that wait to be discovered. These may involve constraints on cellular and molecular levels (e.g. [37]). For instance, different dendritic shapes can be a result of such compromises. Also, axons may be under mechanical stress which may lead effectively to cortical convolutions [51], which in turn can reduce significantly the total axonal length [51].

6 Conclusions

In this review, there have been presented different types of constraints which may affect the developmental design of the cerebral cortex. Because many of these constraints lead to conflicting outcomes, it is suggested that there exists some global optimal design plan that guides the brain throughout the development. Such an optimal design is probably a product of an evolutionary pressure on genes, which control development. Thus, in order to construct theories of optimal cortical design, one has first to gain a much better understanding of the influence of genes and gene products (proteins) on the developmental process. This is challenging, however, both experimentally and theoretically. From a theoretical perspective, it is not a trivial question to relate a local nature of molecular/chemical interactions of gene products to the globality of the organizational plan. It seems that diffusion may play some role in this connection, since it enables transport of chemicals over large distances, and thus leads effectively (although with some delay that can vary between a fraction of a second to days) to global communication [18].

The examples shown in this review may suggest that the evolutionary brain design had to optimize not one parameter but probably many parameters simultaneously in order to make brains functional. Such optimization is not a trivial problem and it leads to multiple trade-offs in some abstract multidimensional parameter space. It is possible that brain design solves this multidimensional optimization problem by adjusting different parameters in order to operate in a "global minimum". The challenge for the future is to try to identify the relevant optimization parameters, and to verify this hypothesis. However, to achieve this, more reliable neuroanatomical data across many species are needed. For instance, only for two mammals: monkey and cat, we know the detailed large-scale connectivity matrix [56]. Quantitative local connectivity has been investigated to some rather modest extent only in mouse and rat [24,25]. This is clearly too little for theoretical developments. More effort should be put in such studies for other animals, as well.

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Figure Captions

Fig. 1a

Cumulative distribution of the large-scale connectivity between cortical areas for the cat cortex.

Fig. 1b

Log-Log plot of the cumulative distribution of the large-scale connectivity between cortical areas for the cat cortex.

Fig. 2a

Cumulative distribution of the large-scale connectivity between cortical areas for the monkey cortex.

Fig. 2b

Log-Log plot of the cumulative distribution of the large-scale connectivity between cortical areas for the monkey cortex.

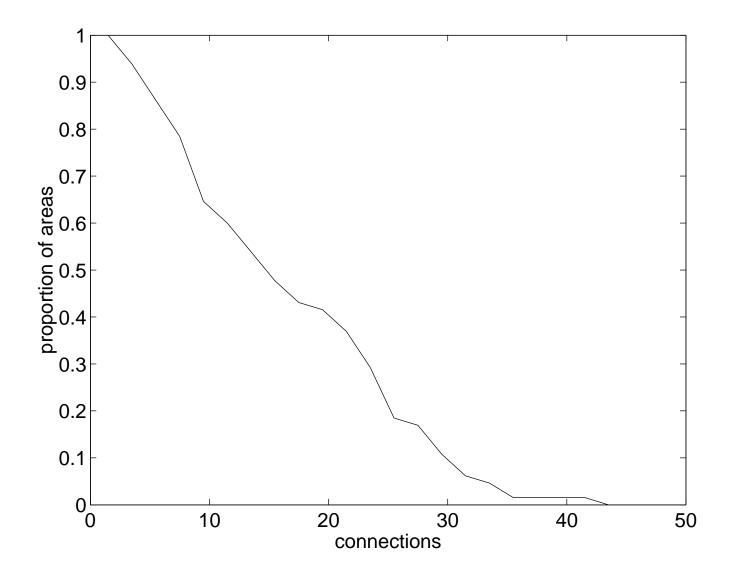


Figure 1a

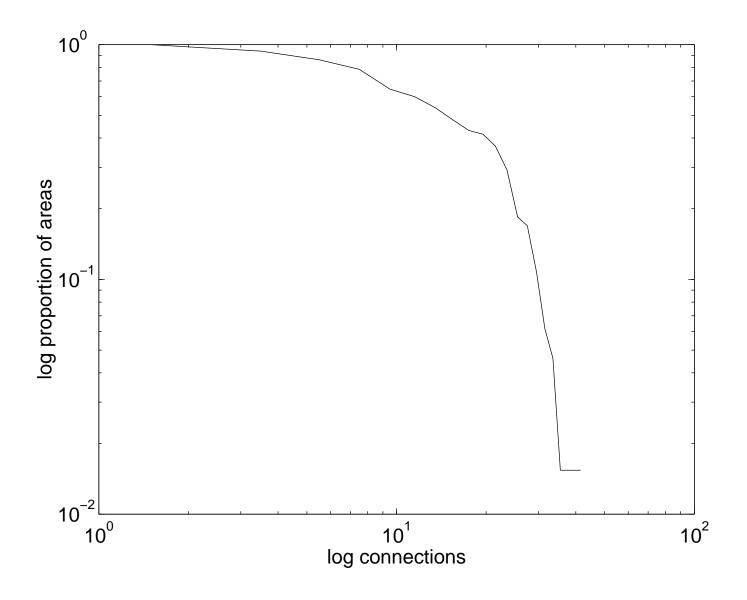


Figure 1b

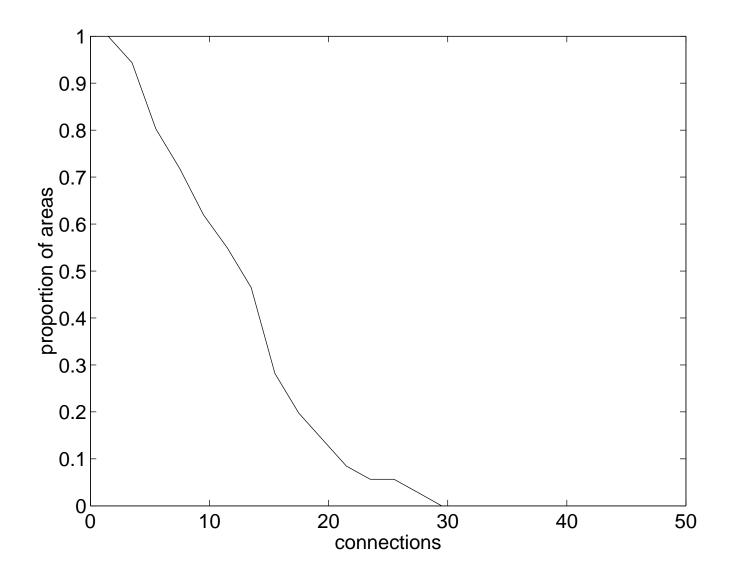


Figure 2a

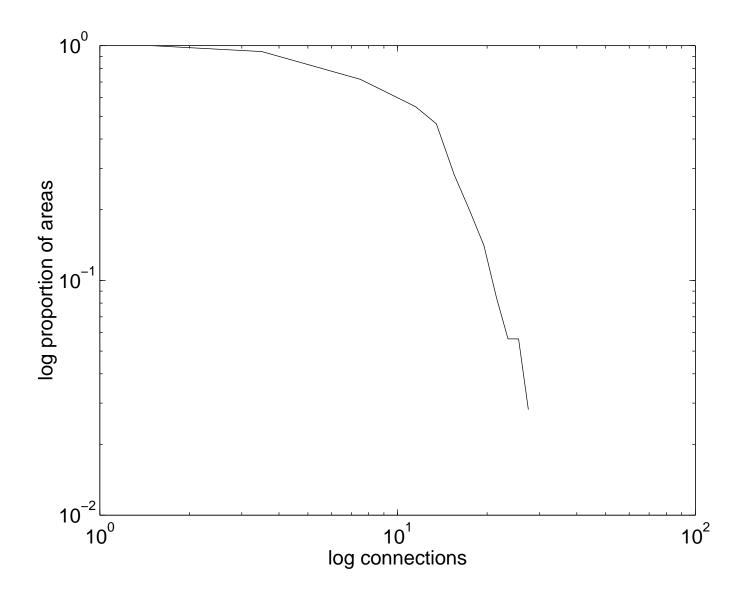


Figure 2b