Investigating brain wiring by simple statistical models

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Abstract

Axonal connections in the mouse brain show exponential scaling in the number of connections with their length, recently referred to as the **exponential distance rule (EDR)** [1, 2]. This work investigates the theoretical and experimental background for extending this rule to the brain connectomes of other species, including **drosophila, mouse, macaque and human** [3]. Our mathematical formulation of brain region level **coarse-graining** observed in the experimental data indicates the existence of the EDR rule for all species. We find that the simplest **distance minimization** scheme reproduces the EDR rule. Our results may suggest that some general properties of the brain's structural connectivity can be interpreted by simple statistical and/or geometrical considerations with no relation to the complex network organization of the brain.

1 Motivation & objectives

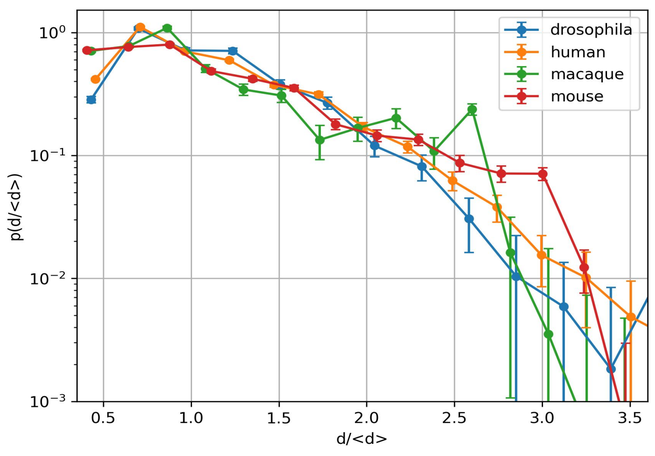
Recently structural brain connectomes are more and more exhaustively reconstructed by non-invasive (diffusion tensor imaging) and invasive experimental methods, like retrograde or anterograde tract tracing (fluorescent materials are injected into well defined brain areas). One retrograde tract tracing experiment showed for example that the number of axons crossing the white matter decreases exponentially with their length, referred to as the **exponential distance rule (EDR)** [1, 2].

We propose to understand better this rule by looking more closely at the available data of other connectomes beyond the one belonging to the mouse.

Exponential functions crop up all over in physics, usually resulting from trivial processes, which makes unrevealing it's originating principle in the case of brain wiring very intriguing. Here we propose that the simplest **distance minimization** scheme may reproduce the distributions observed in experiments.

2 Data

The relevant information in this study are the **axonal lengths (distances)**, and the **weight (num. of axons) of neuron bundles** connecting brain regions of different **areas** (See Fig. 1, 2).



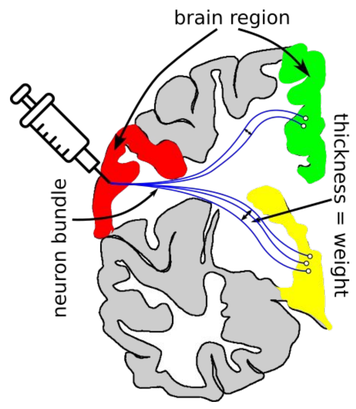


Fig. 1: Illustration of the tract tracing technique over the left-half of the brain. Brain regions are defined with different colors, neuron bundles connect them. The number of neurons within a bundle defines the connection's weight.

Fig. 2: Weighted distance distribution of inter region connections from anterograde tract tracing and diffusion tensor imaging data [3]. They show **nearly exponential(!)** distribution.

On the other hand the length distribution of individual neurons exhibits a **very clear exponential** trend (see the lhs of Fig. 3) known as the exponential distance rule (EDR) in contrast to the weighted distance distribution of inter region connections shown in Fig. 2 or the rhs of Fig. 3.

It appears that **gamma distributions** are more suitable for describing their connection distance distribution (See Fig. 4).

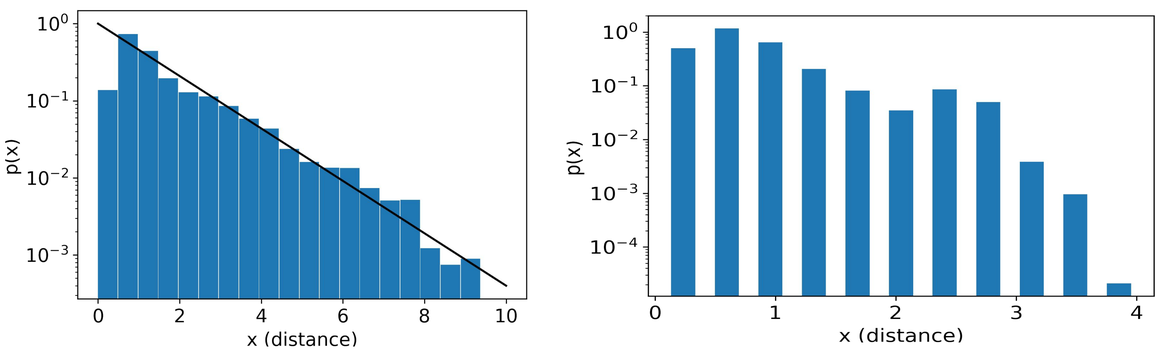


Fig. 3: Distance distribution of 1 984 074 individual neurons (left panel) in the mouse brain versus the weighted inter region distance distribution in the macaque brain obtained from a 29 area parcellation with neuronal projection thicknesses (right panel). Both data are obtained from retrograde tract tracing experiments [2].

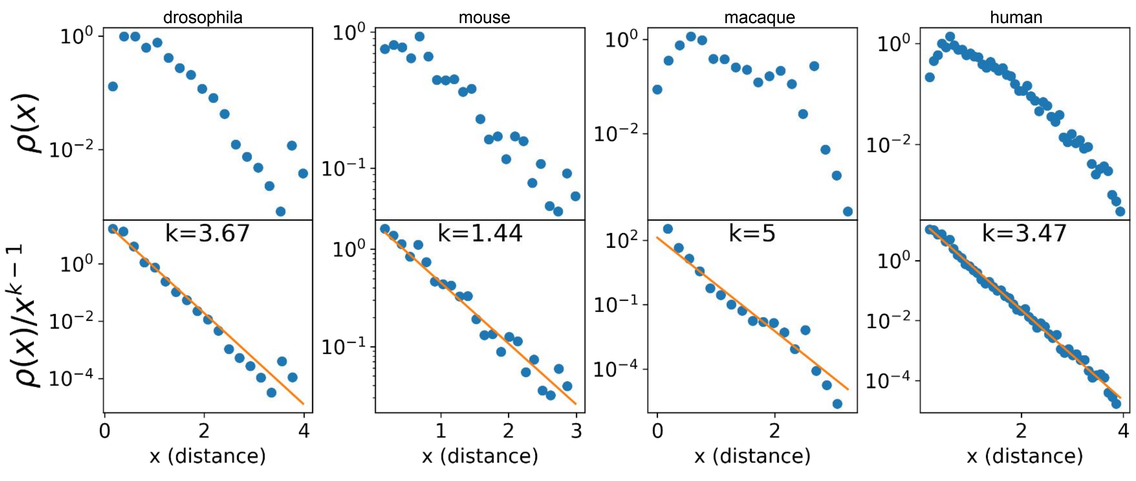


Fig. 4: Gamma distribution fitted to the data from [3]. In the upper panels data is represented on a semilogarithmic graph, while the lower panels show the same data fitted with gamma distribution. The y-axes of lower panels are divided by a corresponding power function.

The origin of **gamma distributions** can be explained from the parcellation of the brain and substitution of individual neuron lengths with mean distances between regions and neural bundle thicknesses, i.e. weights (See Section 3).

3 Coarse-graining model

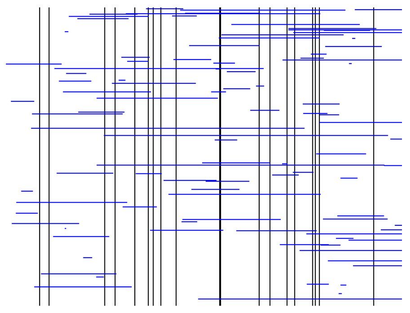


Fig. 5: Illustration of the 1D segments (connections) and cells. Segments are represented with blue horizontal lines, while cell boundaries with black vertical bars.

Let us imagine the infinite real axis. If points are dropped randomly with density α onto this, the size distribution of the created cells will be:

$$f_\alpha(x) = \alpha e^{-\alpha x}$$

Nearly exponential distribution of brain areas justify this choice (See Fig. 6). Segments (connections) of length s distributed according to $f_\beta(s)$ (following the EDR) are placed randomly over the cells (See Fig. 5). A connection of length s will overlap with a number of cells with the distance between the left boundary of the leftmost cell to the right boundary of the rightmost cell denoted by D.

For a given segment of length s the corresponding total cell distance D will be obtained as $D = s + x + y$ where x is the left margin and y will be the right margin (See Fig. 7).

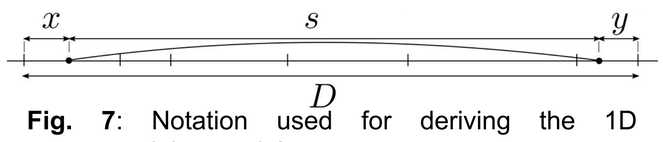


Fig. 7: Notation used for deriving the 1D coarse-graining model.

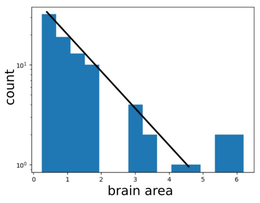


Fig. 6: Distribution of brain region volumes. Data from [4].

For mathematical convenience let us calculate instead of the distance between the centers of marginal cells the distance between their left and right margin, i.e. D. The probability of having distance D given a line segment with length s is:

$$P(D|s) = \int_{\mathbb{R}^2} dxdy f_\alpha(x) f_\alpha(y) \delta(x + y + s - D) = \int dx f_\alpha(x) f_\alpha(D - s - x) = \\ = \alpha^2 (D - s) e^{-\alpha(D-s)}$$

The distribution of distances D comes from this immediately by integrating over all possible s lengths:

$$P(D) = \int_0^D \mathrm{d}s P(D|s) f_\beta(s) = \alpha^2 \beta e^{-\alpha D} \int_0^D \mathrm{d}s (D-s) e^{\Delta s} = \alpha^2 \beta e^{-\beta D} \int_0^D \mathrm{d}q\, q e^{-\Delta q}$$

$$= \alpha^2 \beta D^2 e^{-\beta D} f(\Delta D)\ , \qquad f(x) \equiv \frac{1 - e^{-x}(1 + x)}{x^2}$$

Simulations show exact match with the above (See Fig. 8). All asymptotic/limiting cases lead to gamma distributions with different parameters. This may explain the behaviour of the data that we have seen on Fig. 4.

- Small regions, long connections ($\alpha \gg \beta$, i.e. $\Delta \gg 1$):
  $f(x) = \mathcal{O}(1/x^2)$ as $x \to +\infty$ $\qquad \lim_{\alpha\to\infty} P(D) = \beta e^{-\beta D}$
- Large regions, short connections ($\beta \gg \alpha$, i.e. $\Delta \ll -1$):
  $f(x) = \mathcal{O}(-e^{-x}/x)$ as $x \to -\infty$ $\qquad \lim_{\beta\to\infty} P(D) = \alpha^2 D e^{-\alpha D}$
- Regions and connections of the same length scale ($\beta \approx \alpha$, i.e. $\Delta \approx 0$):
  $f(x) = \frac{1}{2} - \frac{x}{3} + \mathcal{O}(x^2)$ as $|x| \to 0$ $\qquad \lim_{\beta\to\alpha} P(D) = \frac{1}{2}\alpha^3 D^2 e^{-\alpha D}$

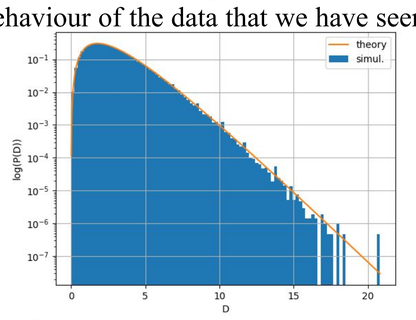


Fig. 8: Simulated vs. analytical distance distributions. Parameters: 10^5 cells, 10^7 segments, $\alpha = 1.2, \beta = 1$

The one-dimensional coarse-graining model fits the data very well (See Fig. 9).

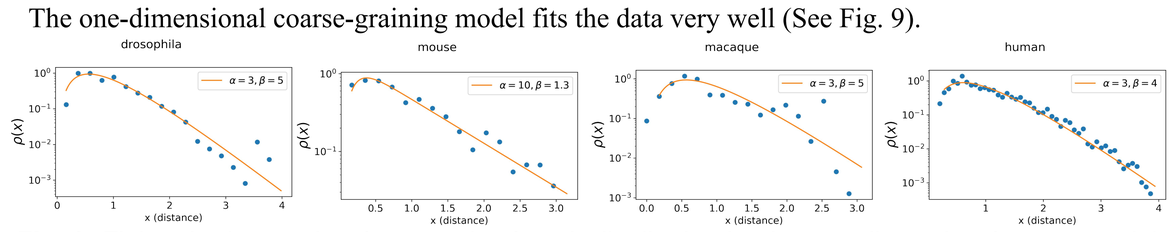
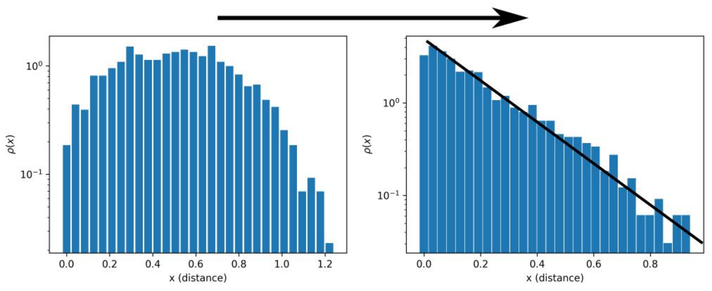


Fig. 9: Fitting the interregional connection length distribution by the one-dimensional coarse-graining model (Data from [3]).

4 Distance minimization in 2D



A simple distance minimization scheme can reproduce the EDR. Nodes of an Erdős-Rényi (ER) graph with a fixed topology are mapped to uniformly distributed but fixed positions in the 2D space such that the total edge length is minimal (See Fig. 10).

Fig. 10: Illustration of distance minimization scheme. Left: Edge length distr. of an ER graph with nodes mapped to uniformly distributed positions in a square shaped 2D area. Right: the same distributions after nodes are reordered such that the total edge length is minimal. Result of simulation.

5 Summary

- The neuron level exponential distance rule is supported by a simple wiring cost (total connection length) minimization model.
- Brain area level coarse-graining of axonal connectivity leads to gamma-like distance distribution interpretable through a one dimensional model.

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Acknowledgements

This work was supported by the *Collegium Talentum Programme of Hungary*, ERANET-FLAG-ERA-ModelDXConsciousness, ERA-Net NEURON programme *ERANET-NEURON-2-UnscrAMBLY* grant by the European Union's Horizon 2020 Research and Innovation Program – grant agreement no.952096 (NEUROTWIN) . PN-III-P4-ID-PCE-2020-0647/Unitatea Executiva Pentru Finantarea Invatamantului Superior a Cercetarii Dezvoltarii si Inovarii

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