Scaling in Nervous Systems

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1. INTRODUCTION

Neuroscience research has origins that date back to Medieval times and even Ancient Greece. However, it was not until relatively recently–after the 19th Century–that studies on the morpho-physiology of the nervous system became more common. This is partly because studies of the brain became more sophisticated after the invention of the microscope and new staining techniques[1]. Using these, pioneering work by Santiago Ramón y Cajal helped lead to the current focus on the neuron as the fundamental unit in the nervous system. The 20th Century was marked by more further progress in neuroscience aided by mathematical and physical studies. Notably, Erlanger and Gasser discovered that the velocity of action potentials was directly proportional to the diameter of the nerve fiber and received a Nobel Prize for their work[2]. Further theoretical and experimental results showed the effects of myelination on conduction velocity, where the conduction velocity was shown to be proportional to the square root of the diameter for unmyelinated fibers [3] and directly proportional to the diameter for myelinated fibers [4]. Perhaps the crowning achievement of this in the 1950s was the general Hodgkin–Huxley (1952) model for the transmission of electrical signals in neurons based on measurements from the giant axon of a squid.

In this chapter, we will review recent work that uses biological scaling relationships and theory to cast new light on the branching patterns of neurons as well as the overall structure of the nervous system. Remarkably, the branching processes of neurons were also first cataloged by Ramon y Cajal, and some of the scaling theory relates to these branching structures. Around the same time, Ramon y Cajal was working, scaling theory was being developed in parallel by Brandt, Snell, and others. Towards the end of the last century and so far in this one, there has been an intensive study of how scaling relationships inform the structure, function, and evolution of animals and plants. Many scaling relationships have been reported in different taxa–both invertebrates and vertebrates. Relevant to neuroscience relate (see Figure 1 and Table 1 for references) brain and body size, white and gray matter, and number of neurons and brain size, which we will now cover. We also highlight the remaining challenges where scaling theory might be useful for advancing neuroscientific understanding.

1.1. Structure, function, and evolution of nervous systems in animals

Structure. The fundamental unit of the nervous system is the neuron, which is a network of branching processes that interacts with other neurons through synaptic connections, forming a network that

performs the function of obtaining information from the environment, transporting this information in the form of electrical and chemical signals, and generating a response. A neuron is characterized by a centralized cell body or soma and two different types of tree-like branching processes–axons and dendrites. Axons generally have branches that decrease in size as they go from the body to near the tips. Moreover, neurons typically have one axon and multiple dendrites. Dendrites form connections with the axons of other neurons at the synapses and are generally characterized by shorter parent branches, compared with the axon, and more extensive branching trees [5].

To talk about the structure and function of nervous systems we simultaneously have to talk about their evolution. We begin by considering simpler systems such as the *Hydra*, whose nervous system is a network of neurons, which is any specialized organ. In contrast, in most vertebrates, the nervous system evolved into highly specialized organs. In humans, for example, the nervous system is organized in central and peripheral regions. The central nervous system includes the cerebrum, cerebellum, and spinal cord, while the peripheral nervous system includes all the nerves and ganglia (groups of soma) that ramify across the whole organism. The cerebrum contains the neuron cell bodies that extend through the cerebellum and the spinal cord and then ramify into terminal nerves.

Function. The nervous system works through nerve impulses and synapses. Nerve impulses are electrical currents that are transmitted unidirectionally from the cell body to the axon. They are produced by a change of electric potential inside and outside the membrane. Nerve impulses are passed from one neuron to another through synapses. Synapses are the location for the exchange of neurotransmitters or ions.

Evolution. The only animals that do not have nervous systems are sponges, which suggests that the nervous system could have evolved independently or have had a single origin and have been lost in this group. To visualize how diverse nervous systems are in animals, as a result of the evolutionary process, let's see a few examples of key taxa. The simplest architecture is found in *Hydra*, where the nervous system is just a network of neurons without any specialized structure. Taking a comparative morphological approach, we will briefly mention the features of the nervous system from cnidarians, passing by platyhelminths, annelids, mollusks, arthropods, echinoderms, to chordates. Cnidarians which include medusas and polyps such as the Hydra, have the simplest form of nervous system. It is a network of neurons with no central processor organ. In platyhelminths or flatworms such as C. elegans, the system includes two nerve cords and a brain. Annelids such as the earthworm also evolved encephalization, having a brain formed by the union of two ganglia. Arthropods have a ganglion system in which some ganglia located in the cephalic region fusions to give origin to the brain. Some mollusks such as cephalopods have a brain while bivalves do not, they have paired ganglia. Echinoderms also do not have a brain but a circular nerve cord. Vertebrates, which include mammals, have an encephalum and spinal cord, that ramifies to peripheral nerves.

2. SCALING RELATIONSHIPS IN THE NERVOUS SYSTEM

2.1. Some examples

A scaling relationship [6, 7, 8, 9, 10, 11, 12, 13, 14] describes a quantitative pattern of the form

$$y = y_0 x^b \tag{1}$$

Here, y is typically a property of biological interest, y_0 is a constant coefficient, x is often a dependent variable such as mass or length, and a is a constant scaling exponent. Two relevant aspects of these relationships are their simplicity, scale invariance [6, 7, 8, 9, 10, 11, 12, 13, 14]. Simplicity is paradoxical as cells are complex, and despite the complexity behind the processes described by this

relationship, a scaling law is a simple mathematical equation that can be used to make predictions. Eq. 1 can be written in log-scale; $log(y) = log(y_0) + alog(x)$, and the parameters can be fitted using simple linear regression. Scale invariance or self-similarity refers to the property of a function $f(x)$ that does not change when the variable x is rescaled by a factor λ; $f(\lambda x) = \lambda^a f(x)$. Scaling relationships in biology are argued to often emerge from complex systems constrained by principles related to optimization [6]. Notably, an exponent a=1 means if we double the size of the system as measured by x, then the y-variable alos doubles. If $a < 1$ the y-variable increases less than double, and if $a > 1$ the y-variable increases more than the double.

Often in the literature, studies focus on scaling relationships among some nervous system component or trait (a rate or time of a process or any feature of the nervous system, such as an attribute of an organ, tissue, or cell) with brain size or body size, or among components, e.g. between white and gray matter. Then, for simplicity, we can distinguish or classify scaling relationships in three categories: trait-body, trait-brain, and trait-trait. We begin with scaling to body size, and at the end of this section, we will mention some challenges we believe exist regarding understanding better, scaling phenomena in the nervous system.

The first studies exploring scaling relationships in the nervous system attempted to analyze the relationships between brain size and body size in mammals. Today there is vast evidence that this relationship holds across among many taxa, and that the exponent of that relationship varies across taxa. For example, in mammals the exponent is often 0.7, in non-human primates 0.75, and in Hominids 1.5 ([15]). For a more complete cataloging of values see [16, 17, 18, 19] (and see [18] for an analysis from invertebrates to vertebrates). Despite different values for the exponent, the form of the relationship is the same in different taxa, so an open question is what determines the variation in the exponent values? Another type of commonly studied scaling in the nervous system is the relationship between different traits of the nervous system and brain mass ([20]; Table 1). There are dozens of quantities (including traits, rates, and times) that scale with brain size (e.g. and also see [20]) or are invariant, i.e. they do not change. Finally, there are also many relationships reported among traits of the nervous system, e.g. gray and white matter volume, or scaling relationships among properties of the network of neurons (see Table 1).

Beyond all these numerous reported empirical relationships that are common across broad taxonomic groups, the question is which mechanisms explain these patterns and is there a corresponding mathematical framework? Below we review some of the models that have been developed to explain some of the empirical scaling relationships.

2.2. Models that predict scaling patterns in the nervous system

Different models have been developed to predict different scaling laws in the nervous system. The simplest model is a generic model of exponential dynamics of both traits (e.g. brain size and body size), which combined gives a power-law ([21, 22], and see also [23]).

Briefly, let's assume that the growth or evolution of a trait y, e.g. synapses per neuron (x), and some other trait, e.g. brain size (y), have the following dynamics,

$$\frac{dx}{dt} = r_x x \tag{2}$$

$$\frac{dy}{dt} = r_y y \tag{3}$$

The solution for this system is

$$x = x_0 e^{r_x t} \tag{4}$$

$$y = y_0 e^{r_y t} \tag{5}$$

If we combine the two previous expressions and after rearranging them,

$$y = C x^{r_y / r_x} \tag{6}$$

where $C = y_0 x_0^{r_y/r_x}$. There is also an alternative way to solve the system of Eqs. 2-3 by equation across dt, and then integrating.

Among the models attempting to explain scaling relationships in the nervous system, just to mention a recent example, there is found the model by Cuntz et al., who generated neuronal branching patterns using optimized graphs [24]. One of these is the predicted scaling laws is, for example, a relationship between the total length of dendritic wiring to the number of branch points and synapses, which scales with an exponent of 2/3 ([25] but see also the recent study by Desai-Chowdhry et al. 2022 [26]; see also below).

Table 1. Examples of scaling relationships of different nervous system components (y) with brain mass (x, g) in mammals. All data comes from [20].

Relationship	Obs. Exponent
Number of synapses	1
Number of neurons	2/3
Synapse density (mm^{-3})	0
Neuron density (mm^{-3})	$-1/3$
Synapses per neuron	1/3
Gray matter volume (g)	1
Network diameter	0
Number of neurons per column	0
Number of neurons per minicolumn	0
Surface area (cm^2)	8/9
Thickness (cm)	1/9
White matter volume (g)	4/3
Soma radius (microns)	1/9
Axon radius (microns)	1/9
Number of neurons per area	1/3
Number of synapses per neurons	1/3
Number of areas	1/3
Number of area-connections per area	1/3
Number of area-connections/number of area	0
Synapses per neuron/number of neurons per area	0

2.2.1. *A branching model for neurons*

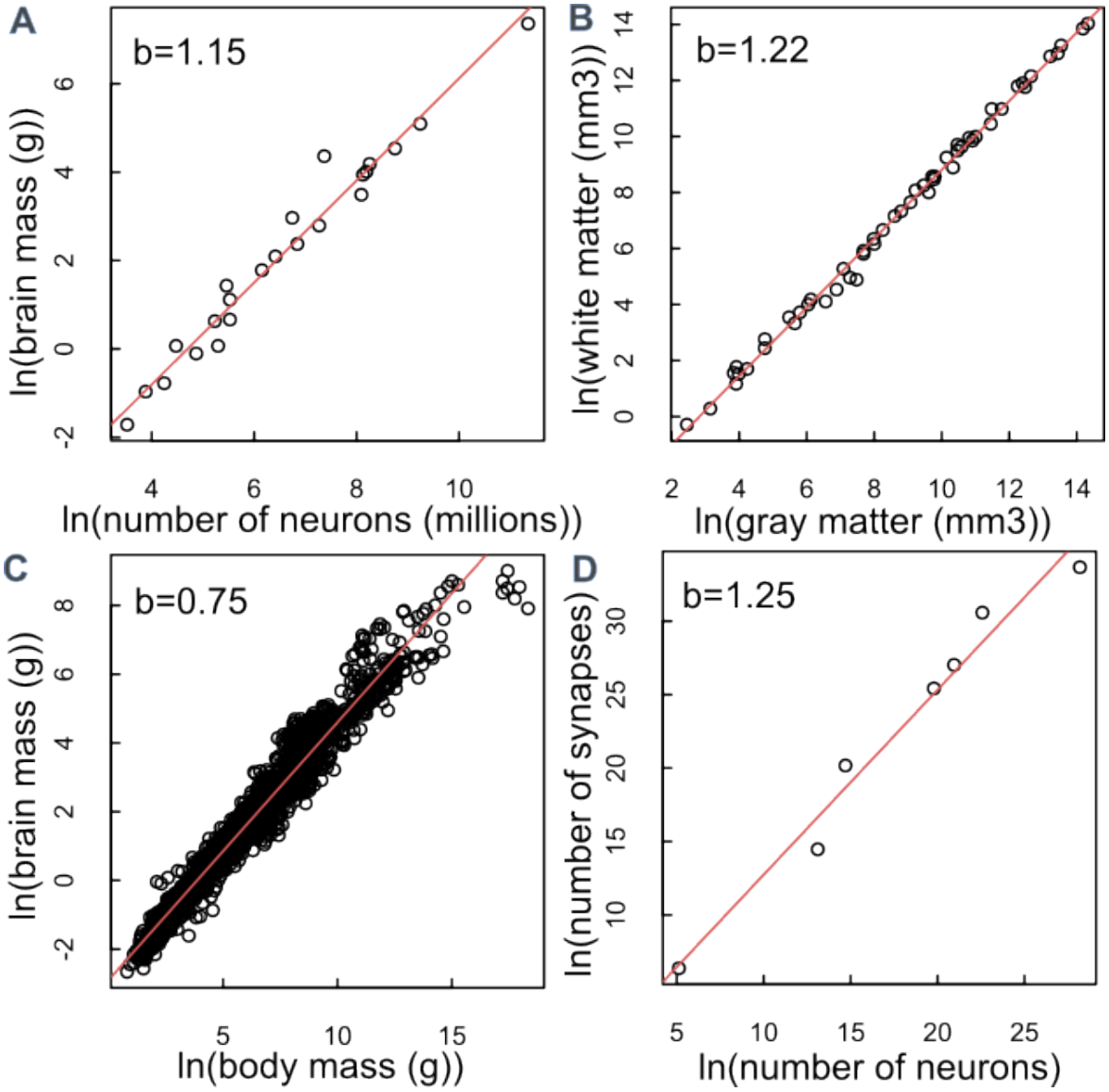

Figure 1: **Examples of scaling laws in the nervous systems of animals.** (A) brain mass (g) versus number of neurons (millions) [27], (B) white matter (mm3) and gray matter (mm3) [28], (C) brain mass (g) and body mass (g) [29], (D) number of synapses and number of neurons [30]

A recent model by Desai-Chowdhry et al. 2022 [26] devised optimization calculations using Lagrange multiplier calculations to derive predictions for how neural branching properties change depending on whether electrical conduction energy, electrical conduction time, charge conservation, material costs, or some combination of these is the fundamental driver of neural structures.

The general form of the model is

$$C = \alpha P + (1-\alpha)T + \sum_i \lambda_i f_i(r_k, l_k, k, N, n, \epsilon) \tag{7}$$

Here, T represents conduction time delay and P is power loss due to dissipation based on the assumption that these neuron processes are like wires through which a current is flowing, subject to electrical Ohmic resistance. The parameter α can be varied between 0 and 1 to consider the trade-off between conduction time delay and power. The remaining terms in this function are constraint functions, representing biological quantities such as material costs that are held constant during the optimization. Each term in the cost function depends on the radius and length of the branch at each branching generation k, where 0 is the branching generation at the parent branch connected directly with the soma, and N is the last branching generation at the tips. The constraint functions f_i depend on the radius and length, r_k and l_k, the branching ratio n (where n = 2 for a bifurcating function), and a parameter describing myelination, ϵ, where $\epsilon = 0$ for unmyelinated fibers and $\epsilon = \frac{1}{2}$ for myelinated fibers to capture the relationship between conduction velocity and myelination [3, 4].

Solving this optimization by minimizing power and time subject to a set of constraints, which we hold to be fixed, we consider a host of specific cases of the general equation to arrive at relationships of the form:

$$1 = \beta_1^P + \beta_2^P \tag{8}$$

Here, β_1 and β_2 are the scaling ratios associated with each of the two daughter branches at a branching junction. They can be expressed as $\beta_1 = \frac{r_{k+1,1}}{r_k}$ and $\beta_2 = \frac{r_{k+1,2}}{r_k}$ where k refers to the branching level of the parent and $k+1$ is the branching level of the daughters. Figure 2 is a visual depiction of the branching levels of a neuron process, taken and modified from Desai-Chowdhry et al, 2022 and Desai-Chowdhry et al, 2023 [26, 31].

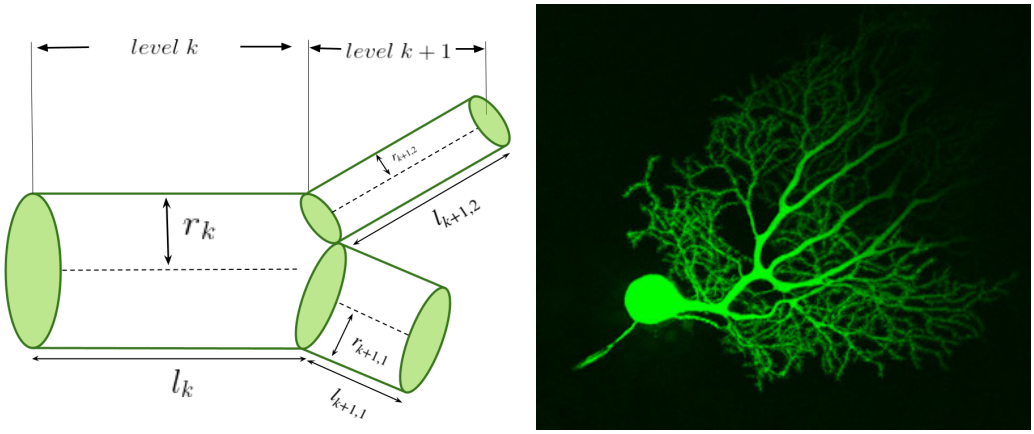

Figure 2: **A hierarchical branching network** A visual depiction of the successive branching levels of a network and the quantities of interest, with asymmetric branching alongside an image of a mouse cerebellar Purkinje neuron and its dendritic branching structure. This image was obtained using confocal microscopy and Lucifer yellow fluorescent dye. We have cropped this image available on CellImageLibrary.Org, distributed by Maryann Martone, Diana Price, and Andrea Thor [32].

Specific cases of this function prioritize either power or time minimizing with a material cost or time delay constraint. The function for power is formulated based on the assumption that the neuron processes are like wires through which there is a current flowing. The power lost due to dissipation depends on the resistance of the current flowing through a wire, which depends on the radius, myelination, and length of each branch. The conduction time delay is formulated based on previous results that have shown a relationship between conduction velocity radius and myelination. When considering asymmetric branching processes, there are multiple possible paths from the soma to the synapse that differ in length and time delay, and this work considers multiple possible interpretations of this conduction time delay term; the total sum of all paths, the path averaged across each branching generation, or one maximum or minimum path [26, 31].

The theoretical predictions for the scaling exponent expressed as P in Equation 8 are compared to empirical values from image reconstruction data from NeuroMorpho.Org from a range of cell types and species ranging in size from insects and rodents to elephants and whales. Figure 3 shows representative images of two types of processes/cells looked at in this study: Purkinje Cells and motoneurons, taken from NeuroMorpho.Org [33]. Table 1 summarizes the results of different specific cases of the function in Equation 7.

Table 1. Theoretical Predictions for Scaling Exponents for Different Cases of the General Cost Function

Function Label	Minimize	Constraint	Power	Corresponding cell/process type
P	P	V	2	Purkinje cell dendrites
$T, \epsilon = 0$	$T_{avg,ummyel}$	V	5/2	PNS dendrites
$T, \epsilon = 0$	$T_{max,unmyel}$	V	5/2	PNS dendrites
$T, \epsilon = 0$	$T_{min,unmyel}$	V	5/2	PNS dendrites
$T, \epsilon = \frac{1}{2}$	$T_{avg,myel}$	V	3	Axons
$T, \epsilon = \frac{1}{2}$	$T_{max,myel}$	V	3	Axons
$T, \epsilon = \frac{1}{2}$	$T_{min,myel}$	V	3	Axons
P^*_{TOT}	P	$T_{tot,ummyel}$	3/4	Asymmetric motoneuron dendrites
$P^*_{MAX/MIN}$	P	$T_{max,ummyel}$	3/2	Motoneuron dendrites
$P^*_{MAX/MIN}$	P	$T_{min,ummyel}$	3/2	Motoneuron dendrites

Peripheral nervous system: PNS

The study finds that both time and energy play important roles, and their relative roles differ for different types of processes (axons and dendrites), whether the process is myelinated or unmyelinated, and the function of the neuron. For example, for neurons that are part of the sensorimotor system, such as motoneurons which connect directly to muscles and sensory neurons in the peripheral nervous system, the median scaling exponents in the data correspond to theoretical predictions of functions that prioritize conduction time delay. This makes sense intuitively since sensorimotor neurons are associated with evolutionary pressures for more rapid response times for reflexive, time-dependent processes. A comparison of the theoretical predictions for Purkinje Cells and motoneurons is shown in Figure 3.

From this model, an allometric scaling relationship is extracted, finding a 1/4 power law relationship between conduction time delay and body mass [26]. Figure 3 shows the validation of this 1/4 power law relationship with data from experimental studies that have looked at conduction time delay across species ranging from shrews to elephants [36].

It is interesting to note the result that conduction time delays are larger in larger animals, as this

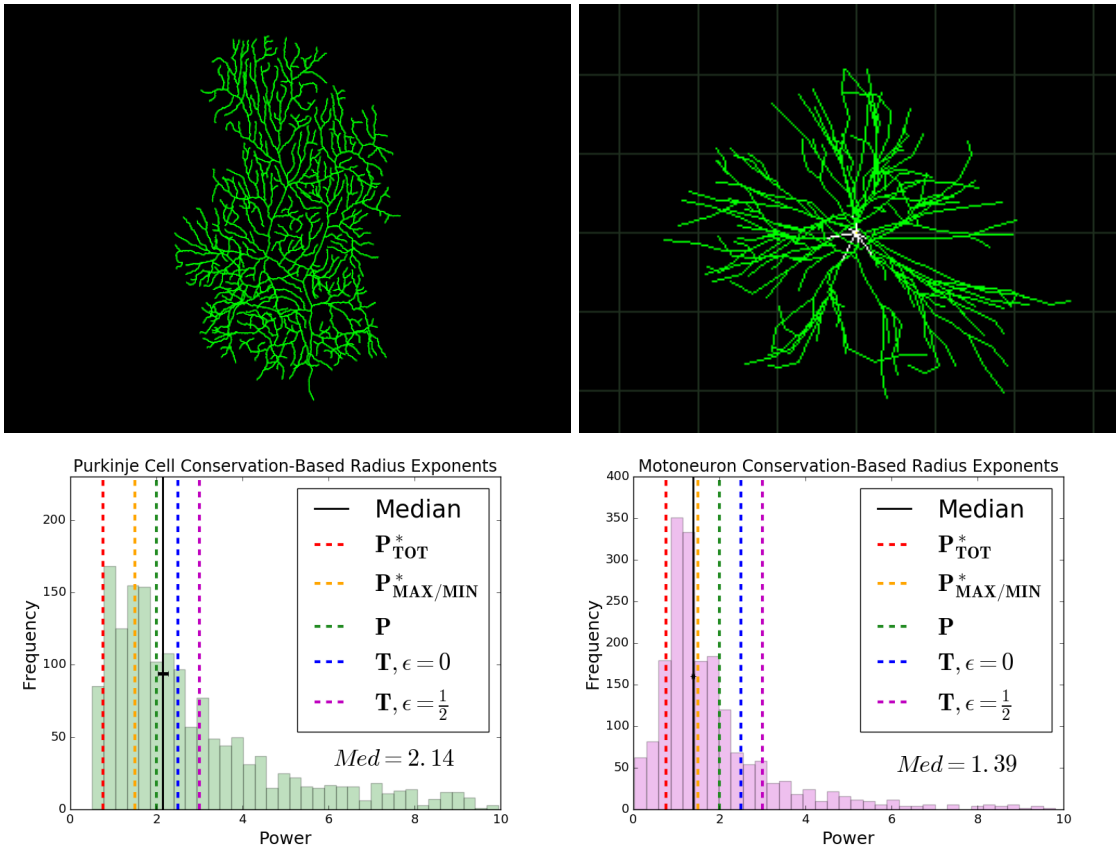

Figure 3: **Comparison of Purkinje cell and motoneuron dendrites median scaling exponents with theoretical predictions, along with representative images of neuron processes from NeuroMorpho.Org** Images of reconstructions from (A) Top left, Purkinje cell from a mouse [34], (B) Top right, Motoneuron from a cat spinal cord [35], (C) Bottom left, comparison of scaling exponents to data for Purkinje cells, (D) Bottom right, comparison of scaling exponents to data for motoneurons. The colored dotted lines correspond to the various theoretical predictions, and the labels of the functions are explicitly defined in Table 1.

might provide a possible explanation for hemispheric specialization in larger animals, as cells that encode similar memories and skills are clustered closer to one another.

Taken together, this work helps provide a more general framework for understanding and deriving the biological and physical principles that determine the structure of neural branching, a problem that dates back to the beginnings of neuroscience and Santiago Ramon y Cajal.

3. CHALLENGES

3.1. Toward a unified theory for scaling laws in the nervous system

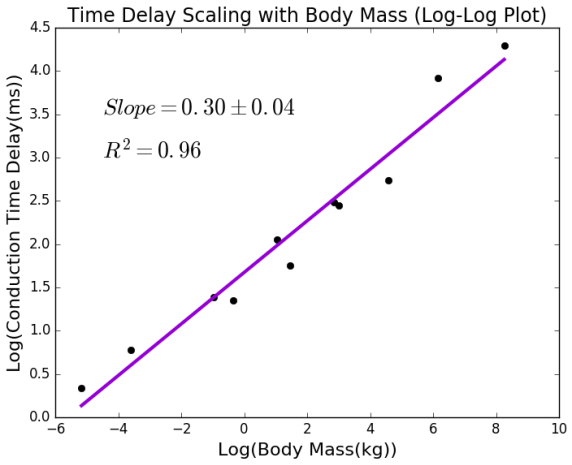

Figure 4: **Scaling of Conduction Time Delay and Species Mass** A scatter plot showing the relationship between the log of the conduction time delay and the log of the body mass of a range of species. Here, the slope, 0.30 ± 0.04, corresponds to the power that relates species mass to conduction time delay. This is close to our theoretical result of $\frac{1}{4}$ (=0.25).

In the spirit of what a unified theory in physics is, the concept of an "efficient theory" has been defined [37, 38]. Above, we defined theory as a mathematical model based on principles and/or assumptions that make testable predictions. More than a theory, an efficient theory is based on a minimal set of assumptions that can make predictions for the largest possible extent of phenomena. An example in biology is metabolic theory, which is based on (at least) three principles (as the same authors say) of the structure of networks, and the optimization of transport across this network can predict many different scaling relationships for plant and animal vascular systems [6]. A more general example is the Barabasi-Albert model for networks [39]. Based on just two assumptions, growth and preferential attachment (or the richer get richer, a previously well-known mechanism), this model can reproduce the structure of networks of proteins and the World Wide Web, among others. Importantly, often in a good or efficient theory, the equations that describe the behavior of the system can be expressed in a dimensionless form, so they are independent of units of measurement. The methodology for non-dimensionalization often can allow collapsing data from different contexts, which shows that regarding particular parameter values that can be influenced by other variables, if the general form of the dependence is the same, then the model is universal. Examples in biology for this include, for example, West's ontogenetic growth [40].

Scaling relationships in the nervous system of animals are pervasive, and include not only relationships among different traits where the brain is the most common predictor but also many neuronal and brain traits with body size. A few models have been proposed to explain the origin of these relationships and some recent approaches based on the network structure are promising in providing a more sophisticated explanation that is closer to metabolic scaling theory. Despite many advances, a unifying theory for scaling relationships in the nervous system across taxa is an open question. Such a theory does not exist yet but it is expected that an efficient one may exist that is based on a minimal set of assumptions and could explain a suite of predictions. Such a theory would be useful for a better

understanding of the nervous system on a first-principles and mechanistic basis. Also, new emergent technologies such as connectomics [41] (the study of networks of neurons) can help by providing data for empirical principles or testing predictions of such a general theory. Neurosciences have entered an exciting era in the last decade and together with new emergent technologies theory integration is fundamental to advancing understanding and prediction.

Acknowledgements

NSF Award "Building and Modeling Synthetic Bacterial Cells" (Award Number 1840301), NSF Award "Towards a unified theory of regulatory functions and networks across biological and social systems" (Award Number 2133863).

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