An optimum principle predicts skewed and heavy-tailed distributions of axon diameters in white matter fascicles

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Goal:
Explore the hypothesis that an "optimum principal" explains the observed skewed and heavy-tailed axon diameter distribution (ADD) in normal nerve fascicles in white matter.

Introduction

Many of the important functional properties of signal conduction along an axon depend on its diameter: (1) the larger the axon inner diameter, the shorter the duration of the pulse and the refractory period, and hence the larger maximal frequency of firing; (2) the conduction speed depends on the axon diameter, so that the larger the axon diameter the faster the action potential propagates along the axon. While according to (1) and (2) it seems beneficial for the fast information transfer to make axons as larger as possible there are opposing reasons to make the axons smaller: (3) the smaller the inner diameter of the axon, the smaller metabolic energy requirements to maintain them; (4) the smaller the axon diameter the more axons can be packed per unit. The last requirement is morphological and in this case it might be argued that the more heterogeneous ADD the more dense and efficient the packing.

We postulate here that the appearance of the skewed and heavy tailed ADD (see Figure 3) are the result of an adaptive process, facilitating the maximal information transfer given the overall constraints of finite packing volume and finite number of fibers.

The axon diameter distribution (ADD) has traditionally been measured by electron microscopy (EM) of excised nerve fascicles [1]. Recently, it was shown that diffusion MRI can also be used to measure the ADD of myelinated axons in porcine optic nerve, sciatic nerve and spinal cord *in vivo* [2]. In all cases and for variety of fascicles it was observed that the ADD are skewed but with highly varying degree of skewness.

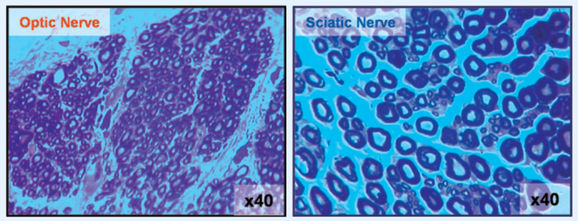

Figure 1: Electron microscope section of a porcine optic nerve (left) and a sciatic nerve (right). Note the large difference in axonal morphometry between the two nerves.

Measuring Axon Diameter: AxCaliber

A newly developed MR technique [2] called AxCaliber enables one to measure ADD *in-vivo* by measuring the MRI signal decays. AxCaliber was used to measure the ADDs in porcine optic and sciatic nerves, and those distributions were fit successfully using γ-variate distribution [2], and the ADD measured were in good agreement with the known morphometry obtained with electron microscopy (Figure 2(b)). Qualitatively similar skewed, heavy-tailed distributions have been observed in anatomical data obtained by others [1].
AxCaliber was able to reconstruct the diameter distribution within the rat's corpus callosum and that ADD is Applications of AxCaliber are expected in longitudinal studies designed to follow nerve growth in normal and abnormal development, as well as in diagnosing disorders and diseases affecting specific populations of axons in the CNS and PNS.

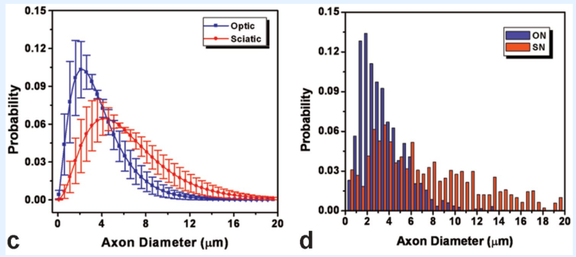

Figure 2: (a) ADDs obtained with AxCaliber from porcine optic and sciatic nerves[2] in figure 1. (b) ADDs obtain with EM

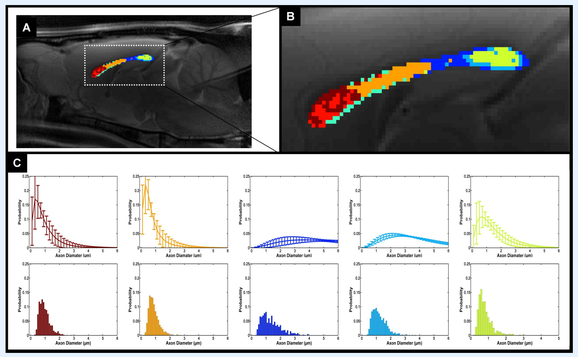

Figure 3: Measurement of the axon diameter distribution in Rat Corpus Callosum. Figure is borrowed from the work of D. Barzany, PJ Basser, Y. Assaf [3, 4]

Optimal Distribution

We use the formulation of the Variational Calculus to find the optimal distribution of the fibers. We express the distribution in terms of the function $n(s)$ which represents the number of fibers whose diameter is in the interval $[s, s+ds)$. We also use the experimentally observed fact that the ratio of outer to "inner" diameter of axon is relatively constant across (≈ 1.4) and thus have only one parameter for describing the size. We optimize $n(s)$ using calculus of variation with constraints of fixed total number of fibers, N, and/or fixed total cross-sectional area, A. Mathematically, we want to find out which $n(s)$ maximizes the functional

$$\int_0^{D_{\max}} F(n(s), n'(s), s)ds \qquad (1)$$

with constraints

$$\int_0^{D_{\max}} n(s)s^2 ds = A$$
$$\int_0^{D_{\max}} n(s)ds = N$$

Other constraints, e.g. metabolic, can also be incorporated within the same framework. We maximize $\int R(n(s), s) \log R(n(s), s)ds$, where $R(n(s), s) = f_r(s)n(s)$, and $f_r(s)$ is the maximal firing rate for a fiber with size s, and $n(s)$ is the number of fibers whose size is in the interval $(s, s+ds)$. The functional $F(n(s), s) = R(n(s), s) \log R(n(s)$ is based on the expression for the upper bound of information that can be encoded in a spike train with maximal rate R. More elaborate models can include also the timing issues between different brain regions in which case a relationship between conduction velocity, v and the diameter can be used. While this relationship is known to be linear, the expression for $f_r(s)$ appears not to be well established. When we model this expression as a simple polynomial $f_r(s) = cs^k$ we are able to obtain a closed form solution for the size distribution, which is

$$p(s) = c(k, \lambda, \gamma)x^{-k}e^{-\lambda x^{2-k} - \gamma x^{-k}}, \qquad (2)$$

where $c(k, \lambda, \gamma)$ is the normalization constant, λ and γ are the parameters which originally were the Lagrange multipliers and can be determined from constraints for N and A. For some cases those can be solved analytically, and e.g., when we relax the condition that the area is fixed $\lambda = 0$ we obtain a special case of γ-like distribution.

$$p(s) = xe^{-x/\sqrt{cN}}$$

We use the model in Eq. 2 to fit the ADD obtained with AxCaliber.

Results

Fitting to the "Optimal Model"

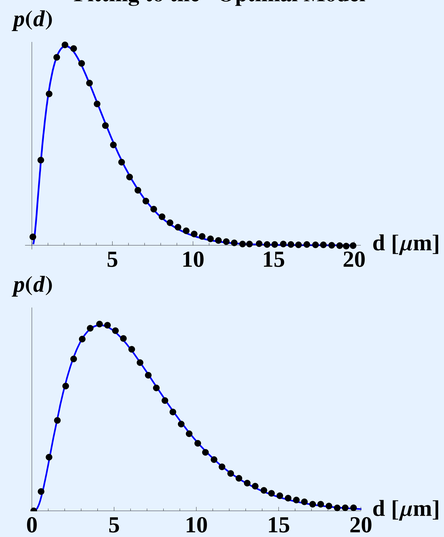

Figure 4: Fitting the data for the optic (top), and sciatic (bottom) nerve ADD to our "optimum" model with only two parameters, λ and γ, with k fixed to 0.45

Summary

- We used variational methods to find optimal $p(d)$ for which the total fascicle's information transfer rate is maximized subject to fixed area and fixed number of fibers.
- This optimum principle predicts a new family of skewed and heavy-tailed distributions that fit the data well.
- Other physical constraints can be incorporated into the current framework, such as metabolic, i.e. minimal power requirements determined by the volume occupied by mitochondria, maximal packing density, etc.
- This optimization can happen either through evolutionary adaptation or as a result of an active process of signal transmission during the neural development of each individual.

References

[1] SSH Wang et al, Functional Trade-Offs in White Matter Axonal Scaling, *Journal of Neuroscience*, 28:4047-4056 (2008)

[2] Y Assaf, T Blumenfeld-Katzir, Y Yovel, and PJ Basser, AxCaliber: A Method for Measuring Axon Diameter Distribution from Diffusion MRI, *Magnetic Resonance in Medicine*, 59:1347-1354 (2008)

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