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**Title**

Tissue Biomechanics: Whales Have Some Nerve.

**Permalink**

<https://escholarship.org/uc/item/9jr20711>

**Journal**

Current biology : CB, 27(5)

**ISSN**

0960-9822

**Author**

Shah, Sameer B

**Publication Date**

2017-03-01

**DOI**

10.1016/j.cub.2017.01.054

Peer reviewed

## Dispatch

### Tissue Biomechanics: Whales Have Some Nerve

Nerves in the mouth of the rorqual whale can double in length during feeding, without incurring damage. Several clever structural features underlie this amazing phenomenon. Such neuroprotective architectural strategies may be conserved, to a lesser extreme, across the organismal spectrum.

Sameer B. Shah



Peripheral nerves — unlike prototypical orthopaedic tissues such as bone, ligaments, cartilage, or muscle — are not often thought of as ‘mechanical’, or load-bearing. However, nerves course over, through, and around a variety of anatomical structures that move when organisms move (Figure 1 A,B here and Figure 1 in [1]). As a consequence, they must stretch, twist, and bend to accommodate movements such as joint articulation, muscle contraction, and skin distension, without damaging the delicate axons within. A failure by nerves to tolerate mechanical loads has severe consequences for motor, sensory, and autonomic function as well as the emergence of pain. Based on nerve conduction measurements in rodents, rabbits, and humans, tensile strains (magnitudes of stretch) of 10–15% are widely cited as thresholds at which nerve conduction is irreversibly impaired [2]. Paradoxically, though, strains far exceeding these thresholds, up to 20-30% in rat and human peripheral nerves, have been

observed, typically in the vicinity of articulating joints [3,4]. These findings suggest that nerves indeed have the capacity to undergo (Au: OK?) large deformations without incurring functional loss. Felice Fontana, in 1781, first suggested a clever protective strategy, describing longitudinal undulations in axons that unraveled during nerve deformation (Figure 1C, [5,6]). In addition, axons are surrounded by a well-organized extracellular matrix (Figure 1D), which bears the brunt of any mechanical loads [7]. Though these aspects of a nerve's response to loading are appreciated conceptually, a deeper understanding of the complex relationships among nerve structure, nerve biomechanical function, and physiological constraints on nerve deformation has remained elusive.


Lillie, Shadwick and colleagues have attacked this knowledge gap in groundbreaking and dramatic fashion by examining nerve structure and biomechanics in a most unusual experimental model — the rorqual whale [1,8]. Nerves running through the ventral groove blubber (VGB) in the floor of the whale mouth experience incredible strains during lunge feeding, in some cases doubling in length during intake. In an earlier correspondence, the authors communicated their initial observations of extreme nerve extension, and hinted at the possibility of a unique structural architecture within the nerve [8]. In a follow-up study published in this issue of *Current Biology*, Lillie *et al.* detail a deeper investigation of the design principles underlying VGB nerve elasticity [1]. They report a remarkable feat of axonal packing, in which two nested levels of waviness provide both slack for extreme nerve extension as well as protection for structures within the nerve (Figure 1E). There are several important insights that emerged from

this study. First, to accommodate large deformations, the level of folding in VGB nerves was observed to be more substantial than anything seen previously. In stark contrast to the gentle waves noted by and since Fontana, undulations in the core of VGB nerves appeared hyper-folded, even buckled. While such folding certainly provides more slack material to unravel during stretch, it also creates tremendous bending strains within each undulation, analogous to the large deformations on the surface of a long rubber eraser that might be bent and buckled between one's fingers. To protect against damage from such bending strains, individual fascicles within the core were also discovered to be wavy, at a smaller length scale, providing strain relief for axons when the nerve core is in a recoiled configuration.

A second key finding was that undulations in the core and fascicle unraveled under different tensions, and were responsible for the nerve's biphasic force-deformation response; the core unraveled first under low tensions (as the feeding pouch begins to fill), and the fascicles followed, unraveling at higher tensions (as the pouch approaches its maximum distension). These observations provide clues as to which regions of the extracellular matrix actually bear mechanical loads at different strains.

 A third finding was that, incredibly, the waviness of both the nerve core and its fascicles  appear to be custom-tuned to their environment. Nerve cores that experienced higher strains, such as those oriented circumferentially, were more wavy, and larger core diameters displayed a longer wavelength. Furthermore, within a given core, surface

regions that strained more during buckling displayed increased fascicular waviness, while deeper regions that strained less exhibited minimal fascicular waviness.

Fourth, the study  provided an elegant theoretical explanation for the physical basis underlying the specific pattern of core bending, which is represented by a sine-generated curve (a geometry distinct from a simple sine wave). Such a curve, though perhaps not intuitively so, in fact describes the geometry of a variety of natural phenomena, including meandering rivers and buckled elastic rods [9]. In its recoiled state, a sine-generated curve minimizes bending strain energy, while concurrently minimizing peak bending strains. Taken in aggregate, data from this study suggest that nature has devised a regionally specific, energetically favorable nerve architecture to accommodate forces and deformations throughout the whale feeding process.

Though this study fills several knowledge gaps, it also raises a number of important questions. Developmentally, how does such remarkable structural organization emerge? Is it pre-patterned or does the mechanical environment during organism growth influence nerve architecture? The development of the gut offers a compelling example of regional mechanical patterning of structure, where differential mechanical loads on the mesentery appear to drive intestinal looping [10]. Could similar differentials play a role in defining the architecture of a nerve? [11] Conversely, from a clinical or veterinary perspective, how does nerve architecture adapt following a persistent change in the mechanical environment of a nerve? For example, nerves may be lengthened in the context of entrapment neuropathy [12], peripheral nerve surgery [13], or limb

lengthening [14,15], and nerve lengthening has also been recently posed as a neuroregenerative strategy [16,17]. Are any resultant mechanically induced changes to nerve architecture reversible? Finally, what are the biological pathways underlying a nerve's response to loading and what other protective mechanisms have been built into nerves of different species? Given the biological, physiological, and translational relevance of answering such questions, to suggest that whale nerves have drawn attention to a fascinating and significant direction of research is not a stretch.

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Departments of Orthopaedic Surgery and Bioengineering, University of California, San Diego, La Jolla, CA (Au: Please indicate zip), USA. Veterans Affairs San Diego Healthcare System, San Diego, CA (Au: Please indicate zip), USA.

E-mail: sbshah@ucsd.edu

  
Figure 1. (Au: Please include title for figure)

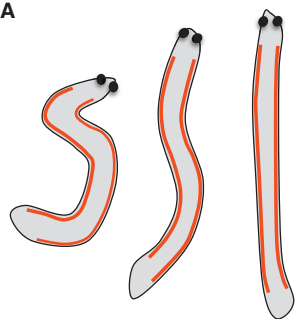
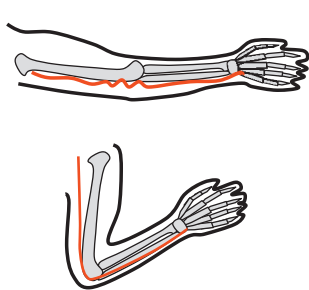
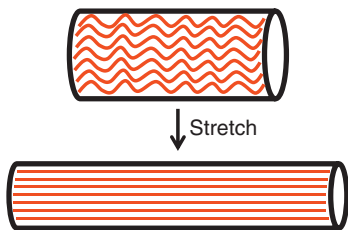
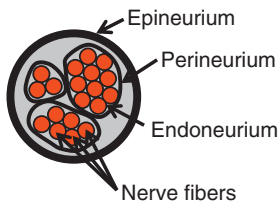
Movement of organisms imposes mechanical loads on peripheral nerves. Schematics of nerves observed to stretch during (A) *Caenorhabditis Elegans* (nematode) crawling (touch receptor nerves) and (B) elbow flexion (ulnar nerve) are shown in red [4,18]. An



extreme version of nerve stretch occurs during rorqual whale feeding, as described in  the this issue [1]. (C) Undulations in axons and fascicles, first described by Fontana in 1781 [5], provide strain relief, thereby protecting neural elements from deformation-induced damage. In mammals, this waviness creates an optical effect known as the 'bands of Fontana' [19]. (D) A well-organized extracellular matrix, consisting of endoneurium (surrounding nerve fibers),  perineurium (surrounding fascicles), and epineurium (ensheathing the entire nerve), bears mechanical loads in peripheral  nerves. (E) Lillie *et al.* observed that superposed waviness of the nerve core and of fascicles enable the dramatic extension of ventral groove blubber (VGB) nerves during rorqual whale lunge feeding [1,8].

### **In Brief**

Nerves in the mouth of the rorqual whale can double in length during feeding, without incurring damage. Several clever structural features underlie this amazing phenomenon. Such neuroprotective architectural strategies may be conserved, to a lesser extreme, across the organismal spectrum.

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