ULTRASONIC BIOEFFECTS ON PERIPHERAL NERVES

Robert Muratore
Quantum Now LLC
Huntington, New York 11743

and

Jeffrey J. Vaitekunas
Cybersonics, Inc.
Erie, Pennsylvania 16510

Introduction

A century of studies has demonstrated that the nervous system is sensitive to incident ultrasound. A comprehensive review of these effects was published in 2011 by Gavrilov.[1] From his detailed listing of acoustic carrier frequencies, pulse repetition frequencies, intensities, and exposure time, one overarching lesson can be learned: the nervous system responds in some way to nearly any acoustic energy to which it is exposed.

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The details of specific responses to specific stimuli vary with what the authors of each study were monitoring. In particular, the responses depend on the portion of the nervous system being insonified. However it is possible to make some additional general statements about the response of peripheral nerves to acoustic energy.

Although nerves are long, they can be influenced by insonifying just a small portion of their length. There is a spectrum of effects that varies with dose, from nothing at all at sub-threshold insonification levels through complete thermal ablation at high doses. These effects act differently on different neuronal fibers within the nerve. Finally, the mechanisms of low-dose effects, e.g., reversible stimulus and inhibition, are not fully understood.

Of the four tissue types parsed by anatomists (epithelial, connective, muscular, and neural), all four make up or are intimate with the peripheral nerves. The implications for acoustics mean that the differential acoustic properties of these tissues can affect the delivered acoustic dose. In addition, for thermal effects, the thermal properties will affect the temperature distribution. In particular, nerves are often co-located with blood vessels.

Anatomists further divide the nervous system into the central nervous system (CNS) and the peripheral nervous system (PNS). Acoustic manipulation of the CNS (brain and spinal cord) is beyond the scope of this paper, but is an important and growing field of study. The PNS has receptor, or sensory, pathways and effector, or motor, pathways. The motor pathways are somatic (under conscious control), typically innervating skeletal muscle, or autonomic, typically innervating smooth and cardiac muscles, glands, and adipose tissue. The autonomic pathways are sympathetic or parasympathetic.

The gastrointestinal tract is innervated by sympathetic and parasympathetic fibers. The order of magnitude of the number of neurons involved with digestion is roughly equal to the order of magnitude of the number of neurons in the spinal cord. Because of this, the autonomic system of the gastrointestinal tract is often considered separately as the enteric system. The enteric neurons are diffusely distributed throughout the abdomen, wrapping around the digestive organs and innervating the smooth muscles and other features.

The nervous system responds to insonification over a wide range of acoustic parameters

As an illustration of the wide range of ultrasound to which the nervous system responds, consider the fingertips. The sensory pathways of the PNS begin with the Pacinian corpuscles, Meissner corpuscles, Ruffini corpuscles, Merkel cells, and free nerve endings monitoring the receptive fields in the skin and other organs. In his review article, Gavrilov[1] presented data for receptive fields in fingertips. Figure 1, adapted from his data, is a graph of the threshold intensities required for human sensations of touch, heat, and pain as a function of ultrasound frequency. The incident acoustic intensities for just this modality range from 8 to 3200 W/cm^2.

It is not necessary to insonify the entire length of a neuron to evoke a response

Nerves and nerve fibers are highly asymmetrical targets, ranging from 0.1 micron (for a fine fiber) to 2 mm (for a large nerve) in cross sectional diameter with some lengths in excess of 1 m. Practical acoustic focal regions tend to be much smaller than the length of a neural fiber, but much larger than the width of the fiber; the extremely high frequencies needed to target an individual fiber would have limited penetration into tissue. In addition, such precise targeting would be difficult. Thus, multiple fibers and other tissues adjacent to the desired target will be insonified by the ultrasound focal region, and only a very short segment of the target will be insonified.

Fortunately, for some applications, it is not a problem to insonify multiple fibers within a nerve; for other applications, the differential response of nerve fibers can be exploited (see below). Furthermore, blocking conduction of a short fiber segment is often effective at blocking conduction along the entire fiber. This is particularly true with ablation.

One promising application of high intensity focused ultrasound ablation is renal sympathetic denervation[2] to

treat resistant hypertension. Among the modalities for denervation is radiofrequency ablation via a catheter inserted into the renal artery. Outward from the lumen, the radiofrequency energy passes through (and damages) three concentric layers of the arterial wall: the tunica intima (consisting of endothelium and the internal elastic membrane), the tunica media (consisting of smooth muscle tissue), and the tunica externa or adventitia, a connective tissue sheath containing nerve fibers.[3] Catheter based ultrasonic ablation can focus the ultrasonic energy, avoiding high intensities within proximal tissues, and instead ablating the renal nerve branches in the adventitia.[4]

Nerves exhibit a spectrum of responses to varying ultrasonic dose

Over the past several decades, numerous experiments of the effects of ultrasound on nerves were performed in many laboratories with *ex vivo* preparations, including non-mammalian nerves. Some experiments were performed *in vivo*, and some clinically. Variations in firing rate, compound action potential, and temporary and permanent inhibition were observed.[1,5]

A conceptual graph of an idealized response of nerve activity to ultrasonic dose is illustrated in Fig. 2. The horizontal dose axis intercepts the vertical activity axis at the normal activity level exhibited by a nerve before insonification. The dashed lower horizontal line represents a cessation of nerve activity. The vertical activity axis intersects the horizontal dose axis at the threshold of responsiveness. Here, nerve activity can mean enhanced firing rate, direct stimulus of firing, amplitude of the compound action potential (related to the number of fibers recruited), or entrainment to the stimulus.

As acoustic dose rises beyond the threshold, the nerve is stimulated. Nerve activity increases with dose. Eventually a peak level of stimulation is reached. Beyond that, increasing dose leads to a lower stimulus. A cross-over level is reached at which there is no apparent effect on the nerve. Beyond that, the nerve is reversibly inhibited.

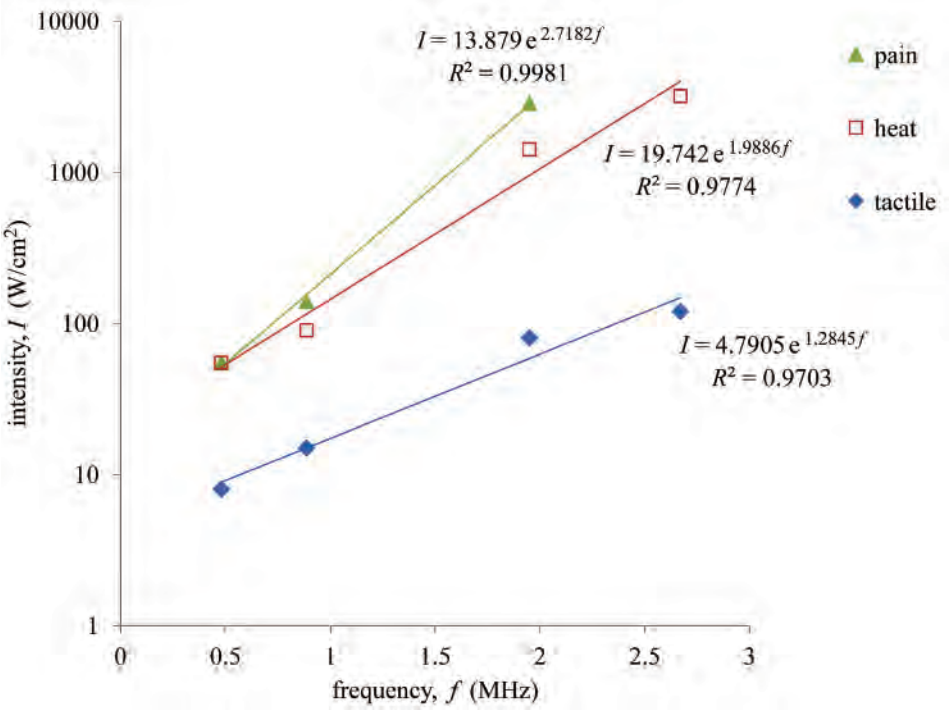
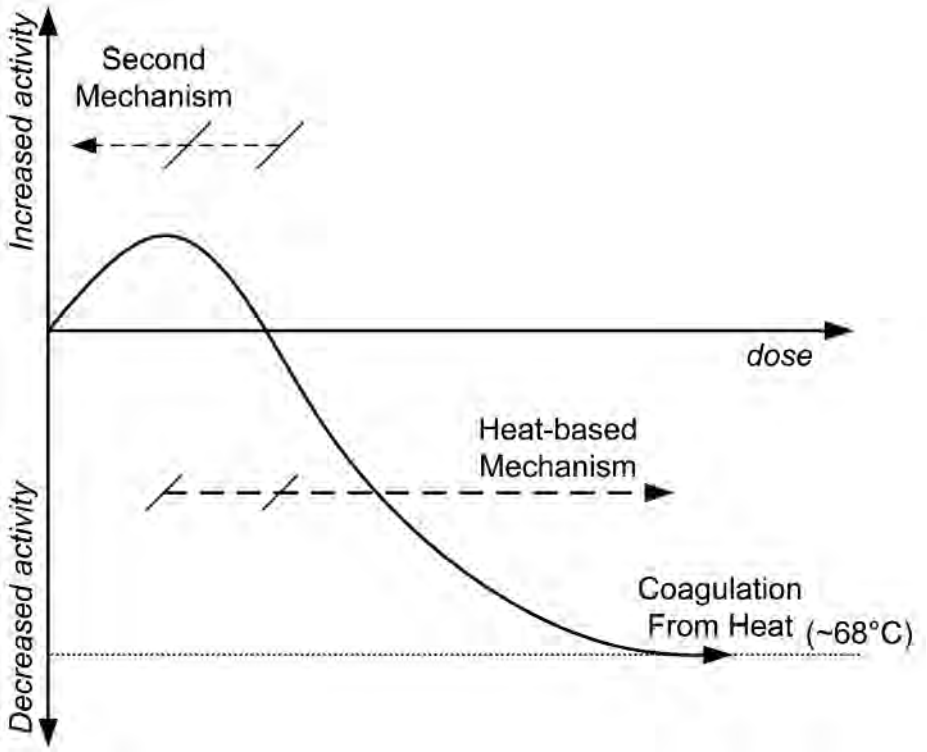


Fig. 1. Sensitivity of the receptive fields in fingertips to incident ultrasound. The threshold intensities required for human sensations of touch, heat, and pain in fingertips increase exponentially as a function of ultrasound frequency. This illustrates the wide range of just a small part of the body (the fingertips) to a wide range of just a single acoustic parameter (intensity). After Gavrilov.[1]



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At very high doses, another threshold is passed and nerve damage becomes irreversible. Eventually, complete ablation occurs.

The neurolytic mechanism at high doses is thermal coagulation, but the low-dose mechanisms are unknown and are labeled here as a unified "second" mechanism. This graph is based on work by Vaitekunas,[6] and is consistent with work by Takagi[7] Young,[8] and Colucci[9] demonstrating reversible blocking of *ex vivo* frog sciatic nerves, Foley[10] demonstrating neurolysis of *in vivo* rabbit sciatic nerves, and Jabbary[5] demonstrating reversible blocking of *ex vivo* lobster ventral nerves.

Different fibers within a nerve respond differently to the same incident ultrasound beam

A peripheral nerve is composed of several layers. The outermost layer is the epineurium, made of tough connective tissue. The perineurium is the middle matrix of connective tissue surrounding fascicles and blood vessels. The fascicles are composed of individual neural fibers (axons) embedded in the endoneurium matrix of connective tissue. The individual axons are typically myelinated, that is, wrapped with Schwann cells rich in glycolipids and glycoproteins. The epineurium and perineurium are composed of regular bands of collagen fibers with periodicities as wide as 170 microns,[11] with a potential for acoustic interference above 10 MHz.

Nerves can contain sensory (afferent) and motor (efferent) fibers together. For example, the vagus (cranial nerve X) contains sensory and motor fibers, whereas the hypoglossal (cranial nerve XII) contains only motor fibers.[3]

The individual fibers are classified by the Erlanger-Gasser system (Aα, Aβ, Aγ, Aδ, B, and C). Originally based on conduction velocities of action potentials (the fastest Aα at 120 m/s through the slowest C at 0.6 m/s), the thickness of the fibers (25 microns down through 0.1 microns) was soon correlated with the velocities.[12] The different fibers have greater or lesser sensitivity to various stimuli. Type A, the coarsest fibers, are the most susceptible to pressure. Type C, the finest fibers, are the most susceptible to local anesthetic. The ultrasonic dose required for conduction blocking in fibers appears to be proportional to the cross-sectional diameter of the fibers;[13] thus, to elicit a similar response, type A fibers require a higher dose than do type C fibers.

The difference in sensitivity allows the possibility of differential conduction blocking. Monteith[14] is exploiting this in trigeminal neuralgia therapies. The finest fibers tend to carry signals from pain receptors. Thus it is possible for a skilled practitioner to differentially damage a nerve, that is, to adjust the therapeutic ultrasound dose to block conduction of the finer pain fibers but retain sensation and motor control carried by the coarser fibers.

The mechanisms of bioeffective insonification of nerves at sub-ablation ultrasonic doses are not fully characterized

The intractability of the problem of identifying the mechanisms responsible for the sub-ablation bioeffects on the nervous system is perhaps best illustrated by repeating a phrase from the opening of this article: work has proceeded for 100 years. The first decade of work led to the identification of the three broad classes of interaction of ultrasound with biological tissue: thermal, mechanical (bubbles or strain-related effects), and radiation force.

Added to this are the various acoustical parameters available for adjustment, e.g., carrier frequency band, incident intensity, waveform shape (pulse width and pulse repetition frequency), and beam shape (unfocused, focal length, spherical, cylindrical, and complex shapes from phased arrays). There are the safety indicators, mechanical index (MI) and thermal index (TI), heating for which the Pennes bioheat transfer equation[15] is well understood, and some advances in defining inertial cavitation dose;[16] otherwise, the concept of dose is itself fuzzy.

Compounding the possibilities are the many types of nerves and their varied locations and functions.

Finally, there are many ways in which the nerves can respond. The site of the interaction of the ultrasonic energy and the tissue can be the integrins, the membranes *per se*, the internal organelles (e.g., phase changes in the cytoskeleton), streaming which changes local ion concentrations, triggering of genetic expressions and apoptosis, demyelination,[10] enhanced blood flow to the nerve from indirect heating (as with physiothermy), sonoporation, and other mechanisms. Expressions of the nerves can include an increase or decrease in action potential threshold, inhibition, increased or decreased spontaneous firing rate, and entrainment to the ultrasound pulses.

Conclusions

The sensitivity of the peripheral nervous system to incident ultrasound is remarkable. That sensitivity, which varies among the fibers within a nerve, and the ability to influence a nerve by insonifying just a small portion of it, and to stimulate, inhibit, or irreversibly damage a nerve by increasing the intensity or time of exposure, provide a complex set of possible clinical applications, and a rich set of intellectual challenges. AT

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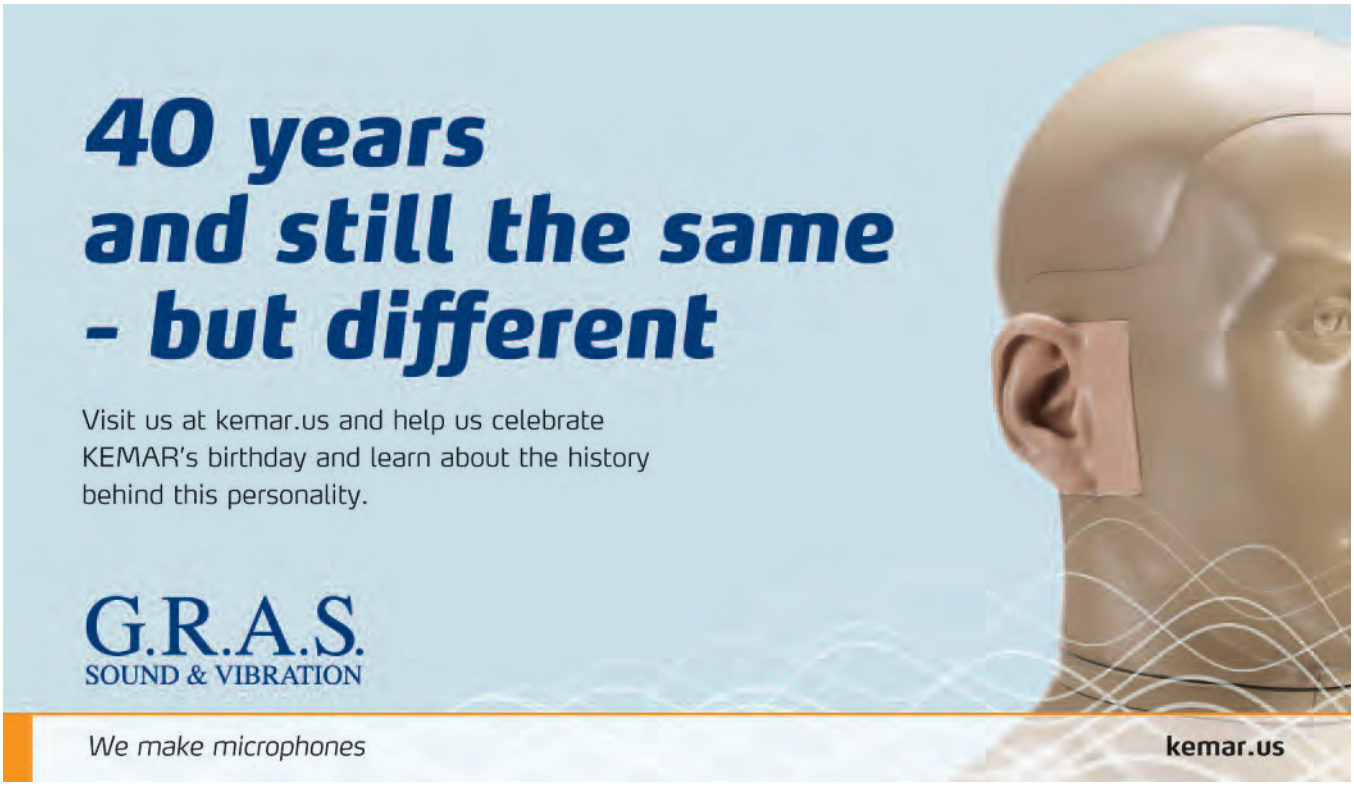

Robert Muratore received his B.E.S. degree from The Johns Hopkins University in bioengineering, his M.S.E. from Princeton University in mechanical engineering, and his Ph.D. from Syracuse University in biophysics. He has worked in ultrasound for fifteen years, beginning with his work in Dr. Frederic Lizzi's group at Riverside Research. He has served as president of the Ultrasonic Industry Association and co-chair of the 11th International Symposium on Therapeutic Ultrasound. He is a founding editor of the *Journal of Therapeutic Ultrasound*. His research focuses on ultrasonic therapies, originally via ablation and more recently via sub-ablation stimuli. He consults and teaches in the New York City area.

Jeffrey Vaitekunas holds a B.S. degree in Electrical Engineering from Purdue University, an M.S. in Theoretical and Applied Mechanics (Applied Mathematics) from Northwestern University and a Ph.D. in Bioengineering/Engineering Mechanics from the University of Cincinnati, culminating with a dissertation titled: Ultrasonic Surgical Instruments: A Multi-Variate Study for Cutting-Rate Effects. Jeff has been involved with ultrasonic technology for over twenty-five years, with over twenty years working in the high-power medical field. Holding 22 US issued patents and many publications, of particular note to this article is US Patent No. 7,553,284 titled Focused Ultrasound for Pain Reduction. Jeff's initial foray into the ultrasound-nerve interaction occurred serendipitously when, while playing with a prototype laparoscopic ultrasonic coagulation device, he accidentally caused loss-of-sensation in his pointer finger, the sensation returning over a week after the insonification event. This event led to his continuing interest in ultrasound / nerve interactions.