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(54) Titre : DISPOSITIF, SYSTEME ET PROCEDE DE STIMULATION DE TERMINAISONS NERVEUSES MECANO-SENSIBLES

(54) Title: DEVICE, SYSTEM, AND METHOD FOR MECHANOSENSORY NERVE ENDING STIMULATION

(57) **Abrégé/Abstract:**

A device for stimulating mechanosensory nerve endings can include: a housing having an internal chamber and first and second openings; a membrane covering the first opening of housing, said membrane being sufficient flexibility to vibrate upon receiving vibratory stimulation from a vibratory mechanism; and a coupling mechanism at the second opening configured for being fluidly coupled to the vibratory mechanism, wherein the entire device consists of magnetically unresponsive materials. The housing can be cylindrical, or any polygon shape. The membrane can be integrated with the housing or coupled thereto, such as with adhesive. Optionally, the membrane can be removably coupled to the housing.



## ABSTRACT

A device for stimulating mechanosensory nerve endings can include: a housing having an internal chamber and first and second openings; a membrane covering the first opening of housing, said membrane being sufficient flexibility to vibrate upon receiving vibratory stimulation from a vibratory mechanism; and a coupling mechanism at the second opening configured for being fluidly coupled to the vibratory mechanism, wherein the entire device consists of magnetically unresponsive materials. The housing can be cylindrical, or any polygon shape. The membrane can be integrated with the housing or coupled thereto, such as with adhesive. Optionally, the membrane can be removably coupled to the housing.

## CROSS-REFERENCE TO RELATED APPLICATIONS

This invention was made with government support under NIH R01 DC003311, NIH P30 HD02528, AND NIH P30 DC005803 awarded by the National Institute of Health. The government has certain rights in the invention.

Adaptation is a dynamic process reflected by a decrease in neuronal sensitivity due to repeated sensory stimulation, which can span a wide range of temporal scales ranging from milliseconds to lifetime of an organism. Attenuation of sensory responses due to adaptation is a common mechanism in sensory systems (visual, auditory, olfactory and somatosensory), which is stimulus specific (since it depends on factors like stimulus strength and frequency), and generally more pronounced at cortical rather than subcortical levels (Chung et al., 2002). Since sensory systems have a distinct number of outputs to represent a wide range of environmental stimuli, adaptation is considered essential to dynamically reassign the limited set of outputs to encode varying ranges of stimuli. As such, devices and systems for implementing studies to monitor adaptation in sensory systems have been researched and developed.

The delivery of electrical currents through the skin to activate sensory nerve terminals was studied, but electrical currents are an unnatural form of stimulation, and may bypass peripheral mechanoreceptors while activating fibers from deep and superficial receptors (Willis & Coggeshall, 1991). This approach to stimulation potentially results in an altered pattern of afferent recruitment due to differences in the electrical impedance of nerve fibers based on spectra, and collateral activation of efferent nerve fibers proximal to the stimulus site. Moreover, if biomagnetic techniques such as magnetoencephalography scanning (MEG) are used to study the cortical response adaptation, electrical stimulation presents a

5 source of interference in the neuromagnetic recordings. Also, piezoelectric transducers to  
provide vibratory stimulation were studied, and have an excellent frequency response.  
However, the piezoelectric transducers have limited displacement amplitudes, and require  
large source currents to operate the piezoelectric crystal. Proximity of these transducers to  
the MEG sensor array produces substantial electrical interference. Disk vibrators (Kawahira  
10 et al., 2004; Shirahashi et al., 2007) can provide vibratory stimulation, but operate at a single  
frequency and are incompatible with MRI and MEG due to multiple noise sources (electric,  
magnetic, acoustic). Recently, pneumatic manifolds were used to generate tactile stimuli  
using air-puffs (Huang et al., 2007) and Von Frey filaments (Dresel et al., 2008) in the MRI  
scanner. However, the time required to instrument the participant can limit protocol  
15 application, and the movement of face or limbs during a stimulation session may alter the site  
of stimulation.

Therefore there is a continued need for improved devices and systems for  
implementing studies to monitor adaptation in sensory systems have been researched and  
developed

## 20 BRIEF SUMMARY OF THE INVENTION

In one embodiment, a device for stimulating mechanosensory nerve endings can  
include: a housing having an internal chamber and first and second openings; a membrane  
covering the first opening of housing, said membrane being sufficient flexibility to vibrate  
upon receiving vibratory stimulation from a vibratory mechanism; and a coupling mechanism  
25 at the second opening configured for being fluidly coupled to the vibratory mechanism,  
wherein the entire device consists of magnetically unresponsive materials. The housing can  
be cylindrical, or any polygon shape. The membrane can be integrated with the housing or  
coupled thereto, such as with adhesive. Optionally, the membrane can be removably coupled  
to the housing.

30 In one embodiment, the device can include a lid having an aperture therethrough.  
The lid can be configured to couple the membrane to the housing. The lid and housing can  
include corresponding fasteners so that the lid can fasten to the housing. The corresponding  
fasteners can include one or more of the following: a snap coupling, a tongue and groove,  
corresponding threads, adhesive, or a clip.

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5           In one embodiment, the coupling mechanism for receiving the vibratory stimulation can include a fluid coupling mechanism that fluidly couples the internal chamber to the vibratory mechanism. For example, the coupling mechanism can include a luer lock. Optionally, the coupling mechanism can be located in a wall of the housing. In another option, the coupling mechanism can be located opposite of the membrane with respect to the  
10 internal chamber.

          In one embodiment, the device can include a tube coupled to the coupling mechanism and capable of being coupled to the vibratory mechanism. The tube can have a length sufficient to extend out of a magnetic field of an MRI or MEG so that an opposite end of the tube is capable of being coupled to a component having magnetically responsive  
15 components, and where the magnetically responsive components do not react to the magnetic field.

          In one embodiment, the membrane has a cross-sectional profile corresponding to a cross-sectional profile of the housing. In one aspect, the membrane is flexibly resilient and/or elastic. In one aspect, the membrane is less than about 0.5 mm thick. In another  
20 aspect, the membrane is less than about 0.127 mm or about 0.0005 inches. The thickness of the membrane can vary greatly. The membrane is configured to vibrate sufficiently to activate cutaneous mechanoreceptors which then convey neural impulses along primary somatosensory pathways and are encoded in the brain. . The membrane can have a positive vibration displacement of at least 1 mm. Preferably, the vibration displacement is at least  
25 about 4 mm.

          In one embodiment, the present invention can include a system for stimulating mechanosensory nerve endings. Such a system can include: a device as described herein; a vibratory mechanism configured for being fluidly coupled with the coupling mechanism of the device; and a magnetically unresponsive tube configured to fluidly couple the device to  
30 the vibratory mechanism.

          In one embodiment, the vibratory mechanism is configured to oscillate fluid into and/or from the chamber so as to vibrate the membrane or to cause pressure changes in the fluid. Optionally, the vibratory mechanism can include a servo motor. In one aspect, the

5 vibratory mechanism is fluidly coupled with the magnetically unresponsive tube which is fluidly coupled to the coupling mechanism.

In one embodiment, the system can include a computing system capable of being operably coupled with the vibratory mechanism. In one aspect, the computing system is operably coupled with the vibratory mechanism.

10 In one embodiment, the system includes an MRI system.

In one embodiment, the system includes a MEG system.

In one embodiment, the present invention can include a method for stimulating mechanosensory nerve endings. Such a method can include: providing a device or system as described herein; placing the membrane on skin of a subject; and oscillating the membrane  
15 on the skin.

In one embodiment, the mechanosensory nerve endings are stimulated in an MRI.

In one embodiment, the mechanosensory nerve endings are stimulated in an MEG.

In one embodiment, the mechanosensory nerve endings are stimulated as part of physical therapy.

20 In one embodiment, the simulation is for motor rehabilitation in patients with developmental sensorimotor disorders or injury.

During any of the testing, the method can include monitoring the brain of the subject during the nerve ending stimulation.

These and other embodiments and features of the present invention will become more  
25 fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

#### BRIEF DESCRIPTION OF THE DRAWINGS

To further clarify the above and other advantages and features of the present invention, a more particular description of the invention will be rendered by reference to  
30 specific embodiments thereof which are illustrated in the appended drawings. It is appreciated that these drawings depict only illustrated embodiments of the invention and are therefore not to be considered limiting of its scope. The invention will be described and explained with additional specificity and detail through the use of the accompanying drawings in which:

5        Figures 1A-1B include brain MRI images (Figure 1A panels A and B) and the tactile stimulation response to frequency (Figure 1B panels A-F). These figures show source reconstruction results for one subject. Dipoles are localized bilaterally in response to lip stimulation (Figure 1A panel A), and contralaterally for right hand stimulation (Figure 1A panel B). Dipoles locations and orientations are shown in orthogonal (axial and coronal) MRI slices. The S1 dipole strength across time is illustrated for each stimulation rate in the panels on the right (Figure 1B panels A-F)

      Figures 2A-2B include graphs that illustrate a comparison of primary somatosensory cortex (S1) peak dipole strengths at 2, 4, and 8 Hz for lip and hand stimulation.

      Figures 3A-3C include graphs that illustrate a comparison of S1 peak dipole strength latency for lip and hand stimulation at 2 (Figure 3A), 4 (Figure 3B), and 8 Hz (Figure 3C).

      Figures 4A-4B illustrate an embodiment of a TAC-Cell device showing a polyethylene cylinder, 0.005" thick silicone membrane, and Luer tube fitting which links the cell to the servo-controlled pneumatic pump.

      Figure 5 includes a schematic diagram of the TAC-Cell stimulus control system.

20        Figure 6 includes a graph that illustrates sample stimulus voltage pulse and the corresponding TAC-Cell displacement response. The mechanical response time (MRT) of the TAC-Cell is 17 ms.

      Figure 7 is an image illustrating a TAC-Cell device secured on the midline of the upper and lower lip vermilion using double-adhesive tape prior to the MEG recording session. The TAC-Cell device can also be secured on other body portions, such as on the glabrous surface of the right hand (index and middle digits), and the oral angle on the face.

      Figure 8 illustrates patterned stimulus trains used as input to the TAC-Cell pneumatic servo controller for MEG sessions. 125 pulse trains at 2, 4, and 8 Hz were applied in separate runs to the glabrous skin of the hand and lower face. Each pulse train consists of six 50 ms pulses regardless of train rate.

      Figures 9A-9C include graphs that show the TAC-Cell displacement in millimeters versus time in seconds for 2 Hz, 4 Hz, and 8 Hz.

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5           Figure 10 includes a graph that shows the facial stimulation at 2 Hz, 4 Hz, and 8 Hz and the corresponding decrease in the mean global field potential cortical MEG response which shows adaptation to the stimulation.

#### DETAILED DESCRIPTION

10           Generally, the present invention relates to the use of the relatively high temporal resolution of the MEG technique with skin stimulating vibration in milliseconds to compare and characterize the short-term adaptation patterns of the nervous system (e.g., using human hand and lip stimulating vibration) primary somatosensory cortex S1 in response to trains of synthesized pneumatic cutaneous stimuli provided by the skin stimulating vibrations. The spatial resolution of MEG has proved sufficient to map the S1 representation of the human  
15   body including the lips, tongue, fingers, and hand, but can be used on other body part as well. Although previous studies have shown that a vibrotactile adaptation mechanism exists in both hand and face, little is known about the short-term adaptation mechanisms of either hand or face S1 to repeated punctate mechanical stimuli in humans. The stimulating vibration can be induced using a MRI/MEG compatible tactile stimulator cell (TAC-Cell). It  
20   is thought that repetitive cutaneous vibration stimuli can result in frequency-dependent patterns of short-term adaptation manifested in the evoked neuromagnetic S1 responses. It is also thought that there may be a significant difference between spatiotemporal characteristics of the adaptation patterns of the face and hand because of fundamental differences in mechanoreceptor innervations and function in motor behavior.

25           The TAC-Cell device can non-invasively deliver patterned cutaneous stimulation to the face and hand in order to study the neuromagnetic response adaptation patterns within the primary somatosensory cortex (S1). Individual TAC-Cells can be positioned on any cutaneous body surface, such as the glabrous surface of the right hand, and midline of the upper and lower lip vermilion as described herein. A 151-channel magnetoencephalography  
30   (MEG) scanner can be used to record the cortical response to tactile stimulus provided by the TAC-Cell, which consisted of a repeating 6-pulse train delivered at three different frequencies through the active membrane surface of the TAC-Cell. The evoked activity in S1 (contralateral for hand stimulation, and bilateral for lip stimulation) can be characterized from the best-fit dipoles of the earliest prominent response component. The S1 responses

5 manifested significant modulation and adaptation as a function of the frequency of the punctate pneumatic stimulus trains and stimulus site (glabrous lip versus glabrous hand).

The TAC-Cell can be useful for activating the human somatosensory brain pathways using punctate, scalable stimuli in the MRI/MEG scanner environment. The TAC-Cell is non-invasive and efficient at nerve stimulation applications.

10 Accordingly, the present invention includes devices, systems, and method of using the TAC-Cell to stimulate mechanosensory nerve endings in the skin of the face and hand. The device is prepared from non-magnetic responsive materials (e.g., materials that do not respond to magnetic fields, such as non-ferromagnetic, non-antiferromagnetic, non-ferrimagnetic, non-diamagnetic, or other similar materials). Such stimulation can be used in  
15 brain imaging instruments, such as magnetic resonance imaging (MRI) and magnetoencephalography (MEG) brain scanners. During use, the device stimulates nerves, which then allows imaging of the brain response during peripheral nerve stimulation.

The device can include a container with one open end that is fitted with a micro membrane over the opening and having a cap with an aperture that fits over the membrane  
20 and fastens to the cylinder. The container also has another opening with a fitting to receive fluid ( e.g., hydraulic liquid or pneumatic gas, such as air) into and out from the chamber within the container, where the change in pressure in response to movement of pressure causes the micro membrane to vibrate similar to a drum. The opening and fitting can be configured to connect to a pressure source that can supply a fluid, such as air or the like, to  
25 cause the vibration by rapidly oscillating the fluid into and out from the chamber. The TAC-Cell can be used as a neurotherapeutic intervention device has considerable potential in adult and pediatric movement disorders. The TAC-Cell can have other configurations to provide the vibratory stimulation as described herein, and operate so as to be compatible with MRI and/or MEG.

30 The TAC-Cell can be used to stimulate mechanosensory nerve endings in the skin of the face and hand or other body parts for brain imaging and potential motor rehabilitation applications in humans. The TAC-Cell can be used in a clinical research setting for motor rehabilitation in patients with (1) developmental sensorimotor disorders, and (2) adults who have sustained cerebral vascular stroke. Other uses of TAC-Cell are also contemplated, such

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5 as in physical therapy, monitoring brain activity during a brain scan, or combined with electroencephalography.

The TAC-Cell can be configured as a small-bore pneumatic actuator that has a membrane configured to vibrate in response to pneumatic changes provided from a pneumatic device. The TAC-Cell can be configured to be MRI/MEG compatible, non-  
10 invasive and suitable for both adults and children, with and without neurologic insult/disease. In one example, the TAC-Cell can be prepared from a cylindrical (e.g., 19.3 mm diameter) chamber prepared from a material that is not magnetically responsive (e.g., a polyethylene vial), and includes a vibratory membrane (e.g., 0.005" silicone membrane sheet) attached to an opening of the cylindrical chamber such that the vibratory membrane can vibrate in  
15 response to fluid pressure changes within the cylindrical chamber. For example, the vibratory membrane can be placed between the lip of the cylindrical chamber and a retaining ring. However, other coupling configurations can be used to couple the vibratory membrane to the cylindrical chamber, such as by adhering the membrane to the chamber. These size parameters can be varied to a diameter (or cross-sectional dimension of the sheet) at about  
20 0.5 mm, 1 mm, 1.5 mm, 2 mm, 3 mm, 5 mm, or even larger up to 2 cm, 5 cm, and possibly even bigger. Also, the materials of the TAC-Cell chamber and/or membrane can vary as long as being magnetically unresponsive. That is, the materials of TAC-Cell are not magnetically responsive. As such, the chamber can be prepared from various polymers and ceramics, where the membrane is prepared from polymers and some rubbers. The variation  
25 of the materials while maintaining the magnetically unresponsive characteristic can be achieved with a myriad of materials.

The TAC-Cell can be included in a TAC-Cell system that includes other components, such as a pneumatic device that provides the vibratory fluid that vibrates the membrane. Also, the TAC-Cell system can include an MRI and/or MEG or other scanner. An example  
30 includes a 151-channel CTF MEG scanner that is configured to record the cortical neuromagnetic response to a pneumatic tactile stimulus produced by the TAC-Cell. The pneumatic device can be configured to provide the TAC-Cell with a vibratory stimulus that includes a repeating 6-pulse train (50-ms pulse width, intertrain interval = 5 s, 125 reps/train

5 rate, train rates [2, 4, & 8 Hz, see Figure 8]); however, other variations and patterns of pneumatic tactile stimulation can be performed.

The TAC-Cell device/system can also include a fastener that secures the TAC-Cell to a subject on the skin. An example of such a fastener includes adhesive, strapping, a clamp, an adhesive collar, a double-adhesive tape collar, or other types of non-ferrous attachment,  
10 such as adhesives, clips, wrappings, bandages, and the like can be used for attachment of the TAC-Cell to a subject. The fastener can be configured to secure the TAC-Cell at various locations across the skin, such as on the face, hands, fingers, finger tips, palms, feet, feet bottoms, arms, legs, torso, or any other location. For example, some skin locations that a fastener can be configured for holding a TAC-Cell thereto can include: a glabrous surface of  
15 the right hand (index/middle finger), and midline of the upper and lower lip vermillion.

A single TAC-Cell can be attached to any portion of the skin of a subject. Alternatively, an array of TAC-Cell devices can be attached to one or more portions of skin of a subject.

Additionally, the present invention can include a multichannel TAC-Cell array (e.g.,  
20 multiple TAC-Cell devices) that can be used to simulate the sensory experiences associated with apparent motion and direction in the face and hand or other parts of the body. The TAC-Cell array may include several TAC-Cells placed in a spatial pattern that can be activated in a sequence (e.g., w/small time delays such as 10 ms from one adjacent TAC-Cell to another). Alternatively, the placement and activation can be random or predesigned. The  
25 TAC-Cell array can be used as a new form of neurotherapeutic stimulation (intervention) to induce and accelerate mechanisms of brain plasticity and recovery in patients suffering from acute cerebrovascular stroke affecting movements of the face (speech, swallowing, gesture) and hand (manipulation).

The TAC-Cell can be in other variations and embodiments. For example, the TAC-  
30 Cell can have: a 'dome' membrane; textured membrane; membrane integrated to the TAC-Cell body (e.g., without retainer collar); miniaturization of the pneumatic servo controllers and high-speed pneumatic switches (valves) is feasible when available; integrated oscillating feature to move membrane, such as micro servo or pumps; other various features can be modified. The TAC-Cell could potentially be driven by the servo electronics.

5           Also, the TAC-Cell can be driven by a magnetically responsive pneumatic device, which is installed distally from the TAC-Cell device and a magnetically unresponsive tube can fluidly couple the TAC-Cell with the pneumatic device.

          The TAC-Cell membrane can be oscillated by pneumatic servo control of a pneumatic device so as to provide vibratory stimulus generation at the skin. A fluid conduit  
10       prepared from a magnetically unresponsive material can pipe the vibratory fluid to the TAC-Cell so as to vibrate the membrane. The active 'pulsating' surface of the TAC-Cell can be used to generate a punctate mechanical input to the skin (e.g., vibration can be 4.25 mm displacement with 25 ms rise/fall time), where the rise and oscillation can vary depending on fluid oscillation and the cross-section profile and size of the membrane. However, all of the  
15       dimensional, oscillatory, material or other parameters can be varied within reason.

          As shown in Figures 4A-4B, one embodiment of the TAC-Cell device 400 has a housing 402 with an internal chamber 402a and a membrane 403 over one opening 404 of the chamber 402a, where the membrane 403 is configured to vibrate in response to a vibratory mechanism. As shown, an optional annular ring 405 is used to couple the membrane 403 to  
20       the housing 402 so as to cover the opening 404. The TAC-Cell device 400 can include a neck 406 coupled to the housing 402, and the neck 406 can have an internal lumen 408 that extends from the chamber 402a to an opening 412. The neck 406 can also have a coupling component 410 at the opening 412 that can be coupled to a pneumatic device, such as through a tube. The coupling component 410, for example, can be configured as a luer  
25       fitting.

          In one embodiment, the housing 402, membrane 403, ring lid 404 (with aperture if membrane is not integrated with housing), neck 406, and coupling component can be plastic, polymeric, rubber, silicone, polyethylene, polypropylene, ceramic, or the like as long as not magnetically responsive.

30       Figure 5 shows an embodiment of a TAC-Cell system. As shown, the TAC-Cell is fluidly coupled to a servo motor through a pneumatic line. The servo motor can include a position sensor that is operably coupled to a servo motor controller. Also, the servo motor controller can receive input from a central processing unit (CPU), such as with a 16 bit ADC/DAC. Additionally, the servo motor controller can be operably coupled to an amplifier

5 that can amplify the signal from the servo motor controller before being provided to the servo motor. As such, the TAC-Cell can be controlled and receive fluid pneumatic vibrations from a remote servo motor through a magnetically unresponsive pneumatic line.

Accordingly, the TAC-Cell 402 can have a fluid coupling between the chamber 402a that can be connected to an external vibratory mechanism (e.g., servo motor) to generate an  
10 oscillatory action. The servo can be a sophisticated servo system that regulates and generates the pressure to drive the membrane 403. The servo or other vibratory mechanism can be located a large distance from the housing 402 and membrane 403 so that there are no metallic or other magnetically responsive components associated with the housing 402 and membrane 403, which allows for use in brain scanners.

15 In one embodiment, the housing can be similar to a standard vile, such as a sample vile one or chemistry vial. The vial lid can be machined so that an opening (aperture) is formed in the lid, and a membrane (e.g., 5,000th of an inch thick silicone membrane) can cover the opening of the vial and vibrate through the opening of the cap. The housing can be configured to include a fluid coupling mechanism, such as a Luer fitting. The fluid coupling  
20 mechanism can be located at the bottom of the housing, or at any other location in the housing. The fluid coupling (e.g., Luer-loc fitting) can accept a silicon tube or other magnetically unresponsive tube that is fluidly coupled to the vibratory mechanism at the other end.

The vibratory mechanism can be computer controlled (e.g., CPU) so that the pressure  
25 inside the TAC-Cell is controlled and very precisely regulated. The vibratory mechanism can drive the TAC-Cells, a membrane is displaced very rapidly so it bulges up or is sucked into the cylinder and the 10-90% rise/fall time can be on the scale of 25 ms. In a 25,000th of a second the membrane can travel over 3.6 mm or other dimension depending on the dimension of the membrane, and that produces a very robust stimulus to the surface of the  
30 skin which in turn drives the somatosensory nerves in the skin.

Previously, providing stimulus in an MRI or MEG has been difficult because of the problems associated with stimulating somatosensory systems in a magnetic environment like the MRI or the MEG. The magnetically unresponsive TAC-Cell can provide cutaneous or tactile stimulus without being compromised by a magnetic field. This allows for feeling the

5 pressure change on the skin, and allowing a medical professional to be able to see what is  
happening inside the brain of the subject having the pressure change on their skin. The TAC-  
Cell can provide a way to objectively test an entire pathway in the human nervous system  
using the two scanner technologies the MRI and MEG. The sensation of the TAC-Cell is  
like tapping on skin because the stimulus comes on and off so fast. The membrane  
10 stimulator has a good frequency response of up to about 30 Hz. Examples herein show 2, 4,  
and 8 Hz. The TAC-Cell can vibrate the skin surface and activate thousands sensory nerve  
terminals in the skin, which sends a nerve volley (signal) through the spinal cord or brain  
stem, and then finally to the thalamus and relayed to the somatosensory cortex.

Accordingly, TAC-Cell provides a pneumatic tactile stimulation cell membrane for  
15 somatosensory stimulator that is MRI compatible and MEG compatible, and can be used in  
human neuromagnetic cutaneous stimulation. It could also be used with any animal, such as  
fish, birds, reptiles, mammals, and the like.

The TAC-Cell could be used for basic neurologic assessment of brain function using  
MRI and MEG scanning technologies, specifically to map the integrity of trigemino-thalamo-  
20 cortical (face) and medial lemniscal-thalamo-cortical (hand-forelimb/foot-hind limb)  
somatosensory pathways in human brain, and properties of neural adaptation.

The TAC-Cell can be used to study animals using a MEG scanner to map the brain  
response to the TAC-Cell vibration stimulation. The TAC-Cell can be used for activation of  
the somatosensory pathways in the human brain.

25 Figure 10 herein shows a servo-controlled stimulus waveform, which serves to drive  
the pneumatic pump, which in turn modulates pressure within the TAC-Cell. They are  
discrete, quick pulses, which are just a few milliseconds in duration. The waveform in the  
lower trace shows the brain neuromagnetic response. As shown for face stimulation, the  
brain is firing within about 50 ms after each stimulus pulse.

30 The TAC-Cell can stimulate the brain so that it is highly visible stimulation in brain  
scans (see Figure 1A). The TAC-Cell device is useful for diagnostics in mapping out a  
lesion, and can be used to determine if a neural signal pathway is interrupted. Also, the  
TAC-Cell device can identify whether a patient sustained damage during a stroke. The TAC-  
Cell can also be used in the rehabilitation of a damaged brain. As such, the TAC-Cell can be

5 used for activating the nervous system, and as therapeutic stimulus to help the brain re-wire after it's been injured.

In physical therapy, the TAC-Cell can be used to replace the electrical stimulators. One shortcoming with electrical stimulators is that it reverses the order in which nerve cells are recruited. Another shortcoming is that electrical stimulation does not distinguish between  
10 sensory and motor fiber activation. When you introduce electrical current to the skin, the neurons with the lowest threshold to current stimulation will fire first and may involve a mixed activation of sensory and/or motor neurons. The TAC-Cell eliminates this problem and selectively activates mechanoreceptive afferent neurons and does not directly stimulate motor neurons. Under natural forms of cutaneous stimulation (i.e., touch, pressure, vibration  
15 as opposed to the use of electrical currents), normal recruitment order and neuron type is preserved. The TAC-Cell is particularly well suited to selectively simulate the A $\beta$  primary afferents associated with the fast adapting type I (FA I) and type II (FA II), and the slow adapting (SA I and SA II) sensory nerve fibers found in skin which encode touch, vibration, texture, and skin stretch. Thus, the TAC-Cell is superior to electrostimulation in these  
20 regards.

The single or TAC-Cell array can be used in all different types of ways for different stimulation studies. This can include right body studies, left body studies, bilateral stimulation, and hemispheric lateralization.

In an example of an array, five TAC-Cells can be placed at predetermined locations,  
25 and each TAC-Cell is individually controlled by an individual fluid line. When the TAC-Cells are arranged in a straight line, and then turning the individual cells on with a time delay, such as a 10 ms time delay between each TAC-Cell, the brain interprets this perception as apparent motion or movement. This can provide a virtual experience of motion for the healing brain, and the perception and the experience of motion that will actually help  
30 damaged neurons and cortex re-wire and form connections. This is part of brain plasticity.

The TAC-Cell device can be used for stimulation of either the lip or hand with the same patterned stimulus, and can be effective to induce short-term adaptation of S1. Difference in short-term adaptation patterns of the hand and lip may be a function of the difference in mechanoreceptor typing in cutaneous and subcutaneous regions and also due to

5 the difference in facial and limbic musculature. There may also be difference with other parts of the body. The magnitude of attenuation of S1 response depends on the stimulus frequency and pulse index with attenuation being most prominent at 8 Hz for both hand and lip stimulation and less prominent at 2 Hz. The significant difference between the latencies of peak dipole strengths of hand and lip S1 is attributable to the difference in axon length and  
10 distance from the mechanosensory nerve terminals in the lip and hand to their central targets in S1.

The TAC-Cell can be used for basic neurologic assessment of brain function using MRI and MEG scanning technologies, specifically to map the integrity of trigemino-thalamo-cortical (face) and dorsal column-medial lemniscal-thalamo-cortical (hand-forelimb/foot-  
15 hindlimb) somatosensory pathways in human brain. Comparison of the spatiotemporal adaptation patterns between normal healthy adults and different clinical populations such as children with autism, adults with a traumatic brain injury or a cerebrovascular stroke may shed new insight on fundamental sensory processes.

For example, repeated tactile stimulation in autistic children resulted in  
20 hypersensitivity, and an enhanced but slower adaptation response. A suppressed GABAergic inhibition mechanism due to the reduction in the proteins utilized for synthesizing GABA is believed to be responsible for these abnormal response characteristics.

Another embodiment can include patterned somatosensory stimulation for motor rehabilitation using TAC-Cell or TAC-Cell arrays. Sustained somatosensory stimulation can  
25 increase motor cortex excitability and has implications in motor learning and recovery of function after a cortical lesion. Thus, in addition to functional mapping of somatosensory pathways, the TAC-Cell may find application as a new neurotherapeutic intervention device for the rehabilitation of adult and pediatric movement disorders.

#### EXPERIMENTAL

30 Ten healthy females (Mean age = 24.8 years [SD = 2.9]) with no history of neurological disease participated in this study. The TAC-Cell used is a custom, small-bore pneumatic actuator based on a 5-ml round vial with a snap-type cap (Cole-Parmer, Part no. R-08936-00). The polyethylene cap was machined to create an internal lumen with a diameter of 19.3 mm. A 0.005" silicone membrane (AAA-ACME Rubber Company) was

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5 held securely between the vial rim and modified snap-type cap. When pneumatically charged, the active silicone membrane surface of the TAC-Cell generated a peak displacement of 4.25 mm with a 27 ms rise/fall time (based on 10% to 90% slope intercepts).

A custom non-commutated servo-motor (H2W Technologies, Inc., NCM 08-25-100-2LB) coupled to a custom Airpel® glass cylinder (Airpot Corporation, 2K4444P series) 10 operating under position feedback (Biocommunication Electronics, LLC, model 511 servo-controller) and computer control was used to drive the TAC-Cell with pneumatic pressure pulses. The computer was equipped with a 16-bit multifunction card (PCI-6052E, National Instruments). The stimulus control signals were custom programmed with LabVIEW® software (version 8.0, National Instruments) in our laboratory. These signals served as input 15 to the servo controller, and were also used to trigger data acquisition by the MEG scanner. This hardware configuration achieved synchronization between stimulus generation and MEG data acquisition. A 15-foot silicone tube (0.125" ID, 0.250" OD, 0.063" wall thickness) was used to conduct the pneumatic stimulus pulse from the servo motor to the TAC-Cell placed on the participant in the MEG scanner. Mechanical response time (MRT), 20 defined as the delay between leading edge of the pulse train voltage waveform and the corresponding TAC-stimulus displacement onset, was constant at 17 ms for all stimulus rates (Figure 6). The reported peak dipole strength latency values reflect correction for the MRT of the TAC-Cell.

As shown in Figure 7, double-adhesive tape collars 450 were used to secure separate 25 TAC-Cells 400 at two skin locations of a subject 460, including the glabrous surface of the right hand (index/middle finger) (not shown), and midline of the upper and lower lip vermilion (shown). Placement at each skin site was completed within 1 minute.

Pneumatic servo control was used to produce pulse trains [intertrain interval of 5 s, 125 reps/train rate]. Each pulse train consisted of 6-monophasic pulses [50-ms pulse width] 30 (Figure 8). Short-term adaptation of the cortical neuromagnetic response to TAC-Cell patterned input was assessed using a randomized block design of three pulse train rates, including 2, 4, and 8 Hz at each skin site. The 2, 4, and 8 Hz stimulus blocks lasted for approximately 16, 14, and 12 minutes respectively. The order of stimulation frequency and stimulation site condition was randomized among subjects.

5           Figure 7 also shows the subject 460 being analyzed with a whole-head MEG system 440 (CTF Omega) equipped with 151 axial-gradiometer sensors was used to record the cortical response to the TAC-Cell inputs. A magnetically unresponsive tube 420 is coupled to the coupling mechanism 410. Localizing coils 430, 436 were placed at 3 positions including the nasion, and left and right preauricular points to determine the head position with respect  
10   to the sensor coil. Two bipolar electrodes 432 were used to record electrooculograms (EOG), which were used to identify trials affected by ocular movement artifacts and eye-blinks. Registration landmarks were placed at the same 3 positions used for positioning the localizing coils. Following the MEG recording session, TAC-Cells were removed from the skin sites, and participants were immediately placed inside a MRI scanner in an adjacent  
15   suite to image their brain anatomy.

          The MEG data was digitally bandpass filtered between 1.5 Hz and 50 Hz using a bidirectional 4th order Butterworth filter. Trials corresponding to 1s before and after the pulse train stimulus were visually inspected for artifacts and those containing movement or eye-blink artifacts were discarded. The remaining trials for each experimental condition  
20   were averaged and the DC was offset using the pre-stimulus period as baseline. Not less than 90 trials per subject in each experimental condition were used in averaging.

          CURRY™ (COMPUMEDICS NeuroScan) is a specialized signal processing software used to analyze the data obtained from MEG recordings. CURRY™ can also be used to co-register anatomical MRI images with MEG data to map the biomagnetic dipole  
25   sources. Thus, source reconstruction was performed in CURRY™ using a spherically symmetric volume conductor model fitted to each individual subject skull segmented from the MRI data. The source space was defined as a regular grid of points throughout the brain volume (averaged distance between points was 4 mm). Current density analysis was performed using Minimum Norm Least Squares (MNLS) applied for the first responses in  
30   the train (i.e. characterized by the best Signal-to-Noise Ratio (SNR)) to identify the spatial peaks of activity that correspond to the S1 activity. Location constrained dipole analysis (with dipole positions set at the spatial maximum retrieved by MNLS) was subsequently used to estimate the dipole direction and peak strength ( $\mu\text{Amm}$  = microampere-millimeter) for the S1 activity following each pulse in the trains.

5       Peak dipole peak strengths and latencies were compared for significant differences between stimulation site (lip and hand), frequency (2, 4, and 8 Hz), and pulse index within the trains using a three-way ANOVA. Differences in the corresponding dipole locations in the left hemisphere for lip and hand stimulation, respectively, were tested for statistical significance using a one-way ANOVA. SPSS software (version 17, SPSS Inc.) was used for  
10   statistical analysis.

For the digits stimulation, the earliest prominent response component that was consistently observed across subjects peaked at  $74.3 \pm 6.7$  ms following each cutaneous pulse. For the lips stimulation the earliest component peaked at  $50.3 \pm 5.8$  ms across subjects. For both stimulation sites, these early components were followed by several late components  
15   with different temporal morphologies and spatial patterns of magnetic field.

For the earliest components of the response, the distribution of the evoked magnetic field across the sensor array was consistent with the presence of a source in the contralateral S1 for the hand stimulation condition, and bilateral S1 for the lips stimulation. This was confirmed by results of the source reconstruction, exemplified in Figure 1A. In Figure 1A,  
20   the marked areas indicate the following: 100 (dipole activation of the face representation in the primary somatosensory cortex); 102 (dipole activation of the face representation in the primary somatosensory cortex); and 104 (dipole activation of the contralateral hand representation in the primary somatosensory cortex). Dipolar sources were consistently localized within the hand representation of the left S1 (hand stimulation), and bilaterally  
25   within the face representation of the S1 (lip stimulation).

The mean dipole locations for the lip and hand S1 responses are reported in Table 1. A comparison between the dipole locations in the left hemisphere for lip versus hand stimulation using a one-way ANOVA on each of the three Cartesian coordinates showed a significantly different S1 source along all three directions: lateral ( $p < 0.001$ ), anterior ( $p =$   
30   0.008), and inferior ( $p < 0.001$ ). The results are in agreement with the somatotopic organization of the primary somatosensory cortex (Penfield and Rasmussen, 1968), with the lip S1 represented more towards the base of the postcentral gyrus, i.e. more laterally, anteriorly, and inferiorly than the hand S1.

5           The peak dipole strength was used to quantify the magnitude of cortical response as a function of stimulation rate and serial position within the trains. Latencies of the S1 responses were determined from the peak dipole strength and corrected for mechanical response time (MRT). A three-way ANOVA of dipole strength peaks, with factors of stimulation site, stimulation frequency, and pulse index within trains of stimuli, showed  
10 statistically significant main effects of frequency ( $p < 0.001$ ) and pulse index ( $p < 0.001$ ). The interactions between the stimulation site and frequency ( $p = 0.016$ ), and frequency and pulse index ( $p = 0.003$ ) were also statistically significant.

          The peak dipole strength of the S1 response (Figure 2A-2B) shows a progressive attenuation with the serial position of the stimuli in the train. The sharp attenuation of the  
15 neuromagnetic response that was apparent for the 8 Hz stimulation condition prevented us from analyzing the latencies beyond the 3rd dipole strength peak for both lip and hand stimulation conditions. The magnitude of the S1 adaptation was slightly greater for the lip when compared to the hand among the 3 different test frequencies and this may be explained in part by differences in mechanoreceptor representation and mechanisms of central  
20 integration along lemniscal and thalamocortical systems.

          A three-way ANOVA of the S1 peak latencies, with factors of stimulation site, stimulation frequency, and pulse index of the stimulus in the trains, showed that the main factor of stimulation site ( $p < 0.001$ ) was statistically significant. None of the interactions were significant in this case. This reveals that TAC-Cell evoked S1 response peak latencies  
25 were significantly different between the hand and lip at all 3 stimulation frequencies (Figure 3A-3C), which is consistent with a shorter conduction time of the trigeminal pathway.

          The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore,  
30 indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

## TABLES

### Table 1

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| Right Hand stimulation |           |          |          | Lip stimulation |          |          |                  |          |          |
|------------------------|-----------|----------|----------|-----------------|----------|----------|------------------|----------|----------|
| Left hemisphere        |           |          |          | Left hemisphere |          |          | Right hemisphere |          |          |
| x (mm)                 | y (mm)    | z (mm)   |          | x (mm)          | y (mm)   | z (mm)   | x (mm)           | y (mm)   | z (mm)   |
| Mean±SD                | -48.2±6.9 | 10.8±8.1 | 93.8±6.8 | -58.2±5.0       | 14.5±7.9 | 76.3±4.8 | 57.2±5.6         | 18.4±9.6 | 76.6±8.4 |

5

- Dipole locations for lip (contralateral and ipsilateral hemispheres), and hand (contralateral hemisphere) S1 associated with 2, 4, and, 8 Hz TAC-Cell stimulation. Mean  $\pm$  standard deviations across subjects are expressed in a Cartesian system of coordinates based on external landmarks on the scalp, with the x-axis going from left to right through pre-auricular points, y-axis from the back of the head to nasion, and z-axis pointing towards the vertex.

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## CLAIMS

1. A device for stimulating mechanosensory nerve endings, the device comprising:
  - a housing having an internal chamber and first and second openings;
  - a membrane covering the first opening of housing, said membrane being sufficient
  - 10 flexibility to vibrate upon receiving vibratory stimulation from a vibratory mechanism; and
  - a coupling mechanism at the second opening configured for being fluidly coupled to the vibratory mechanism, wherein the entire device consists of magnetically unresponsive materials.
2. A device as in claim 1, wherein the housing is cylindrical.
- 15 3. A device as in one of claims 1-2, wherein the membrane is integrated with the housing.
4. A device as in one of claims 1-3, wherein the membrane is removably coupled to the housing.
5. A device as in one of claims 1-4, further comprising a lid having an aperture
- 20 therethrough.
6. A device as in claim 5, wherein the lid is configured to couple the membrane to the housing.
7. A device as in one of claims 5-6, wherein the lid and housing include corresponding fasteners so that the lid can fasten to the housing.
- 25 8. A device as in claim 7, wherein the corresponding fasteners are one or more of the following: a snap coupling, a tongue and groove, corresponding threads, adhesive, or a clip.
9. A device as in one of claims 1-8, wherein the coupling mechanism for receiving the vibratory stimulation includes a fluid coupling mechanism that fluidly couples
- 30 the internal chamber to the vibratory mechanism.
10. A device as in one of claims 1-9, wherein the coupling mechanism includes a luer lock.
11. A device as in one of claims 1-10, wherein the coupling mechanism is located in a wall of the housing.

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5           12.     A device as in one of claims 1-11, wherein the coupling mechanism is located opposite of the membrane with respect to the internal chamber.

          13.     A device as in one of claims 1-12, further comprising a tube coupled to the coupling mechanism and capable of being coupled to the vibratory mechanism.

          14.     A device as in claim 13, wherein the tube has a length sufficient to extend out  
10 of a magnetic field of an MRI or MEG so that an opposite end of the tube is capable of being coupled to a component having magnetically responsive components, and where the magnetically responsive components do not react to the magnetic field.

          15.     A device as in one of claims 1-14, wherein the membrane has a cross-sectional profile corresponding to a cross-sectional profile of the housing.

15           16.     A device as in one of claims 1-15, wherein the membrane is flexibly resilient and/or elastic.

          17.     A device as in one of claims 1-16, wherein the membrane is less than about 0.5 mm thick.

          18.     A device as in claim 17, wherein the membrane is less than about 0.127 mm.

20           19.     A device as in one of claims 1-18, wherein the membrane is configured to vibrate sufficiently so that the stimulation is received in the brain.

          20.     A device as in one of claims 1-19, wherein the membrane has a positive vibration displacement of at least 1 mm.

          21.     A device as in claim 20, wherein the vibration displacement is at least about 4  
25 mm.

          22.     A system for stimulating mechanosensory nerve endings, the system comprising:

          a device in accordance with any one of claims 1-21;

          the vibratory mechanism configured for being fluidly coupled with the coupling  
30 mechanism; and

          a magnetically unresponsive tube configured to fluidly couple the device to the vibratory mechanism.

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5           23.     A system as in claim 22, wherein the vibratory mechanism is configured to oscillate fluid into and/or from the chamber so as to vibrate the membrane or to cause pressure changes in the fluid.

          24.     A system as in one of claims 22-23, wherein the vibratory mechanism includes a servo motor.

10           25.     A system as in one of claims 22-24, further comprising a computing system capable of being operably coupled with the vibratory mechanism.

          26.     A system as in one of claim 22-24, wherein the vibratory mechanism is fluidly coupled with the magnetically unresponsive tube which is fluidly coupled to the coupling mechanism.

15           27.     A system as in one of claims 25-26, wherein a computing system is operably coupled with the vibratory mechanism.

          28.     A system as in one of claims 22-27, further comprising an MRI system.

          29.     A system as in one of claims 22-27, further comprising a MEG system.

          30.     A method for stimulating mechanosensory nerve endings, the method  
20 comprising:

          providing the device or system as in any one of claims 1-29; and

          placing the membrane on skin of a subject; and

          oscillating the membrane on the skin.

          31.     A method as in claim 30, wherein the mechanosensory nerve endings are  
25 stimulated in an MRI.

          32.     A method as in claim 30, wherein the mechanosensory nerve endings are stimulated in an MEG.

          33.     A method as in claim 30, wherein the mechanosensory nerve endings are stimulated as part of physical therapy.

30           34.     A method as in claim 30, wherein the simulation is for motor rehabilitation in patients with developmental sensorimotor disorders or injury.

          35.     A method as in claim 30, further comprising monitoring the brain of the subject during the nerve ending stimulation.

Application number / Numéro de demande: US2010 046 792

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Unscannable items received with this application  
(Request original documents in File Prep. Section on the 10<sup>th</sup> floor)

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Lip

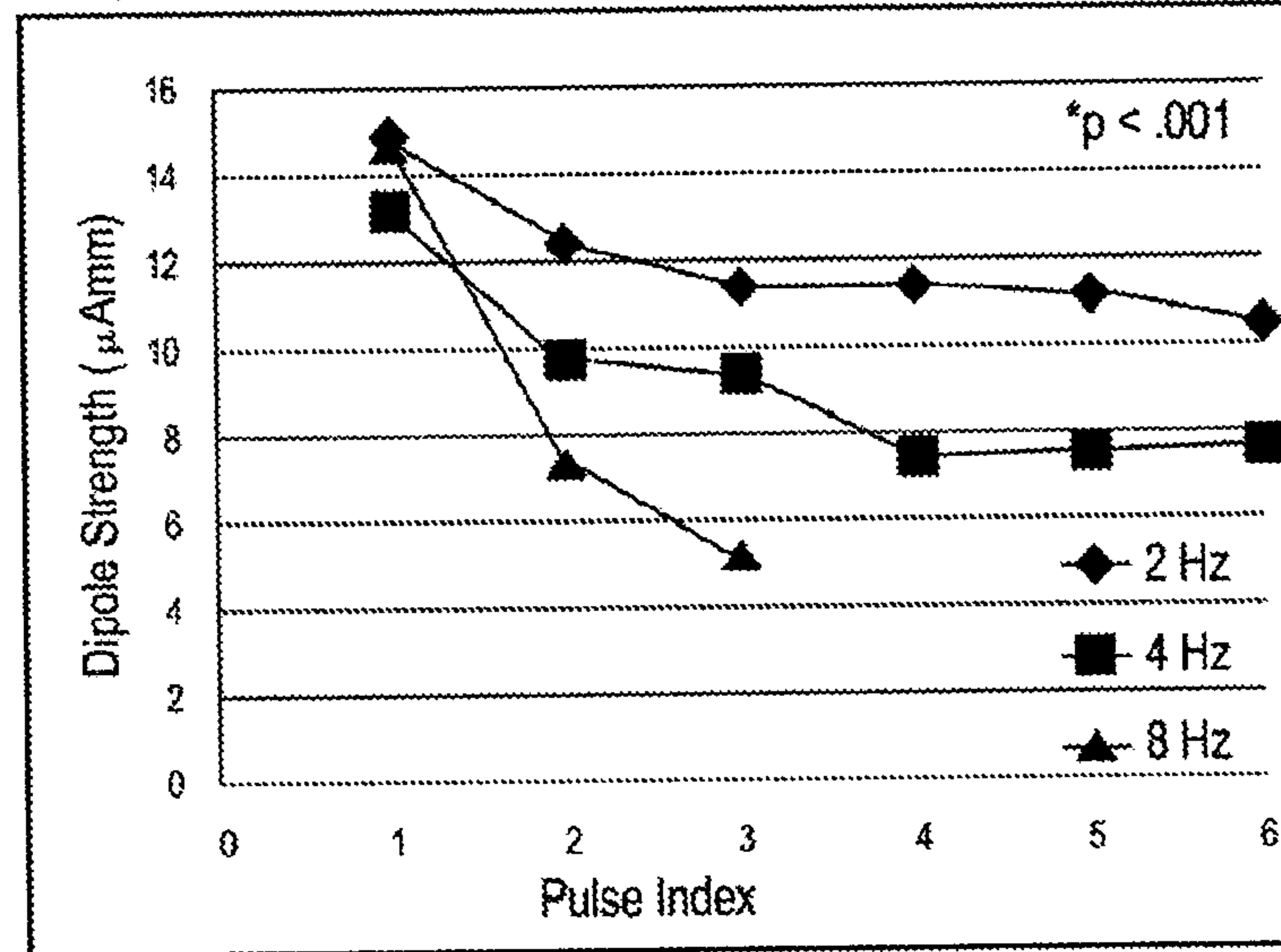


Fig. 2A

Hand

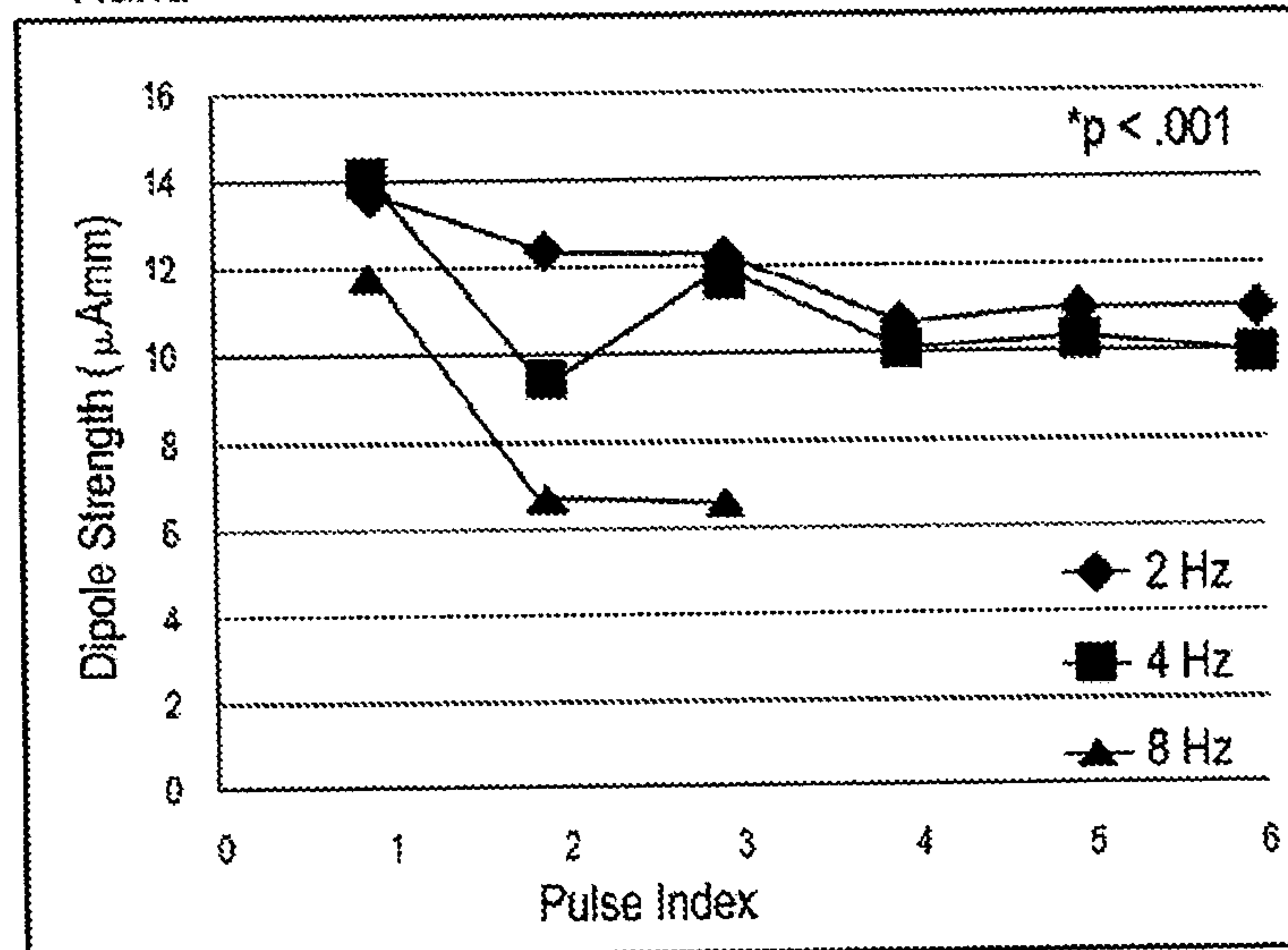
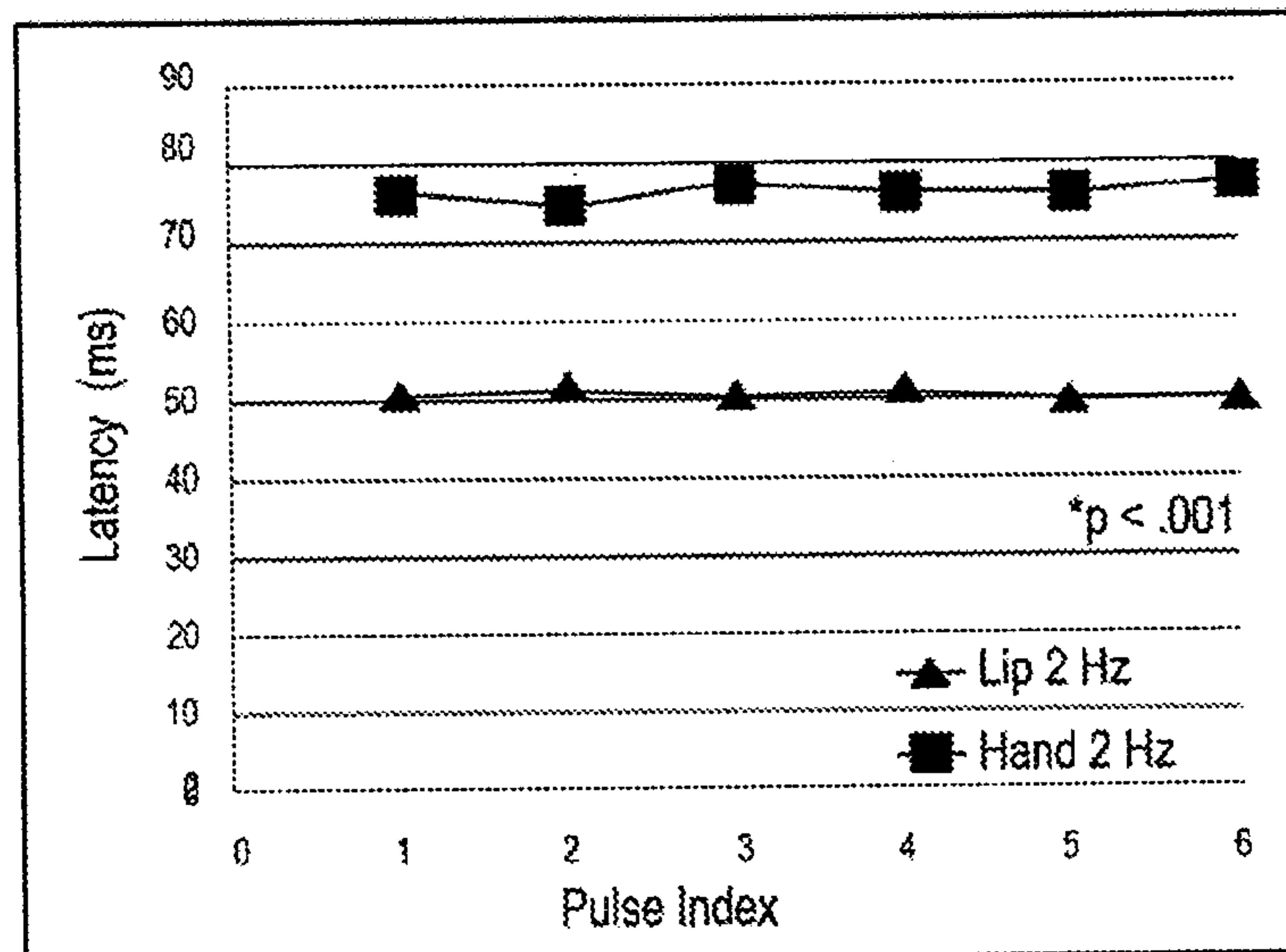
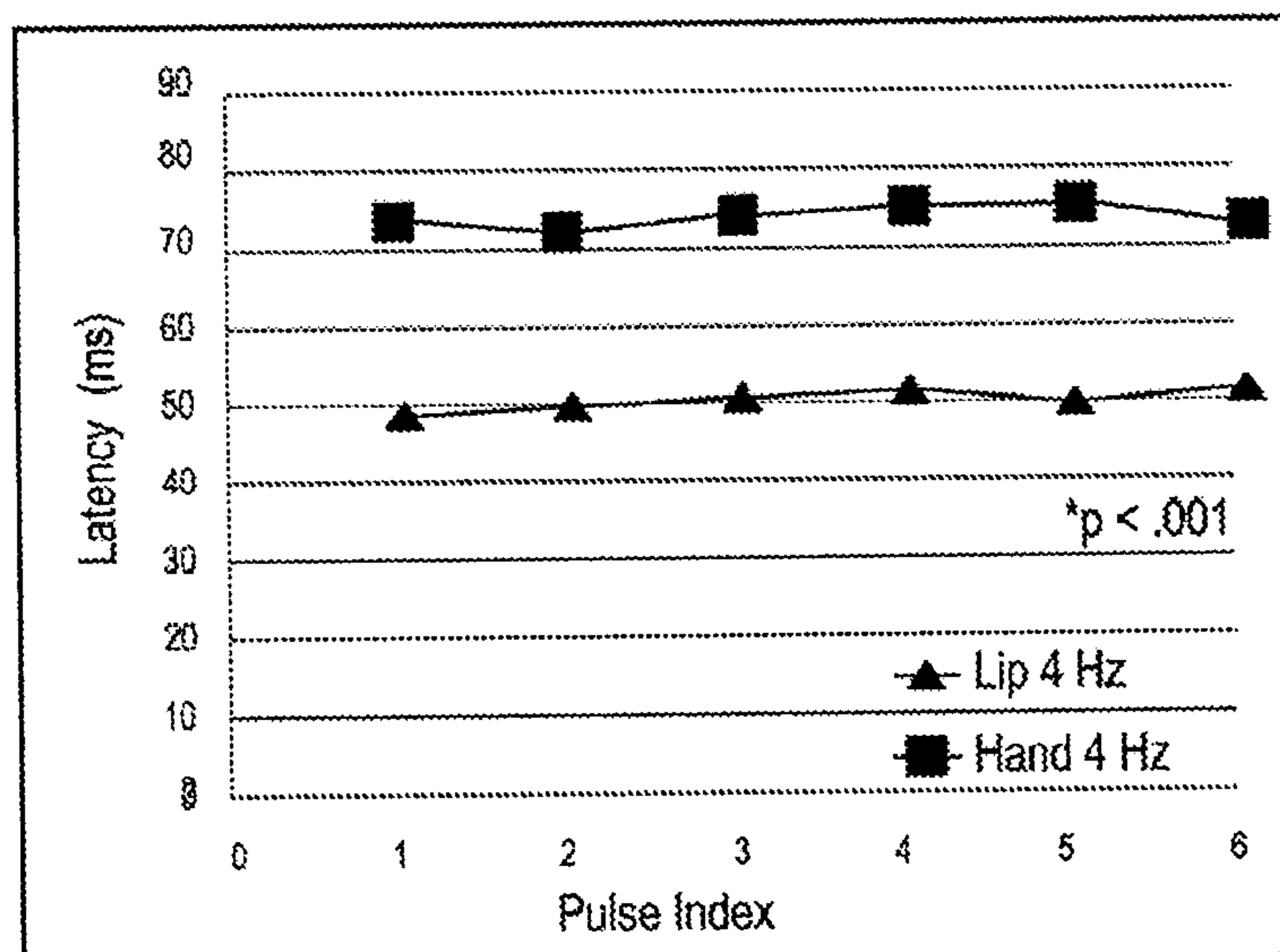
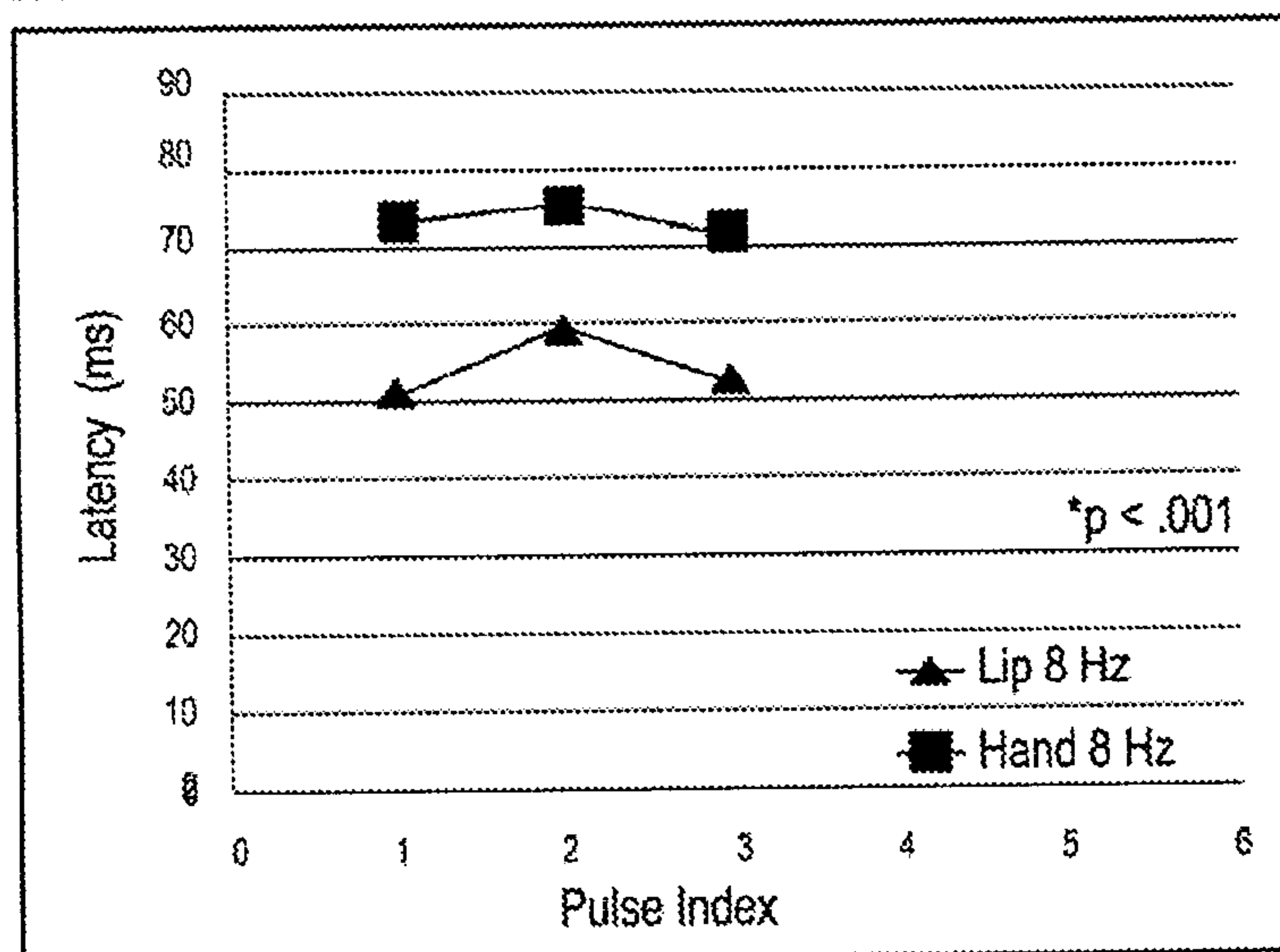
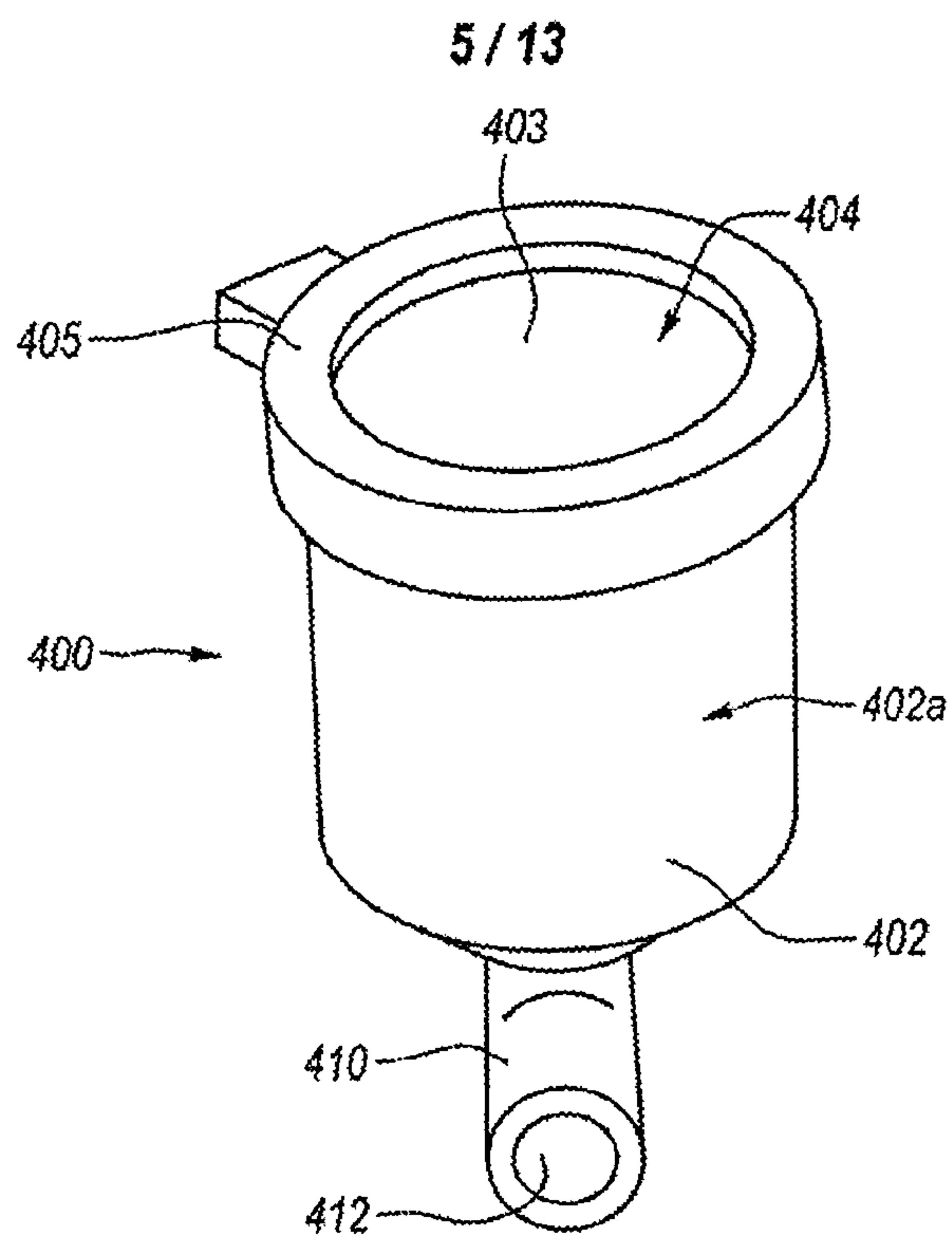


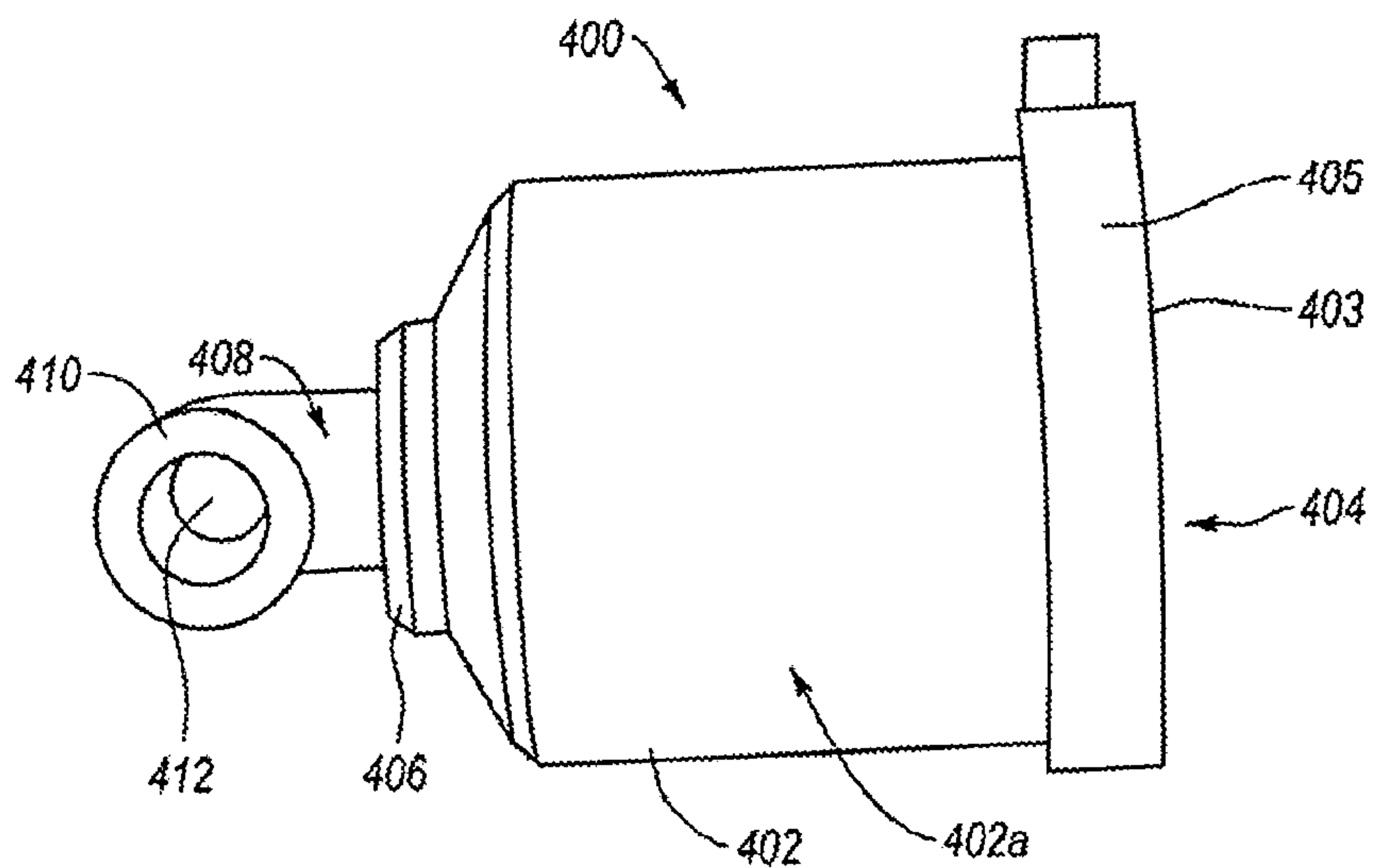
Fig. 2B

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**Fig. 3A****Fig. 3B****Fig. 3C**

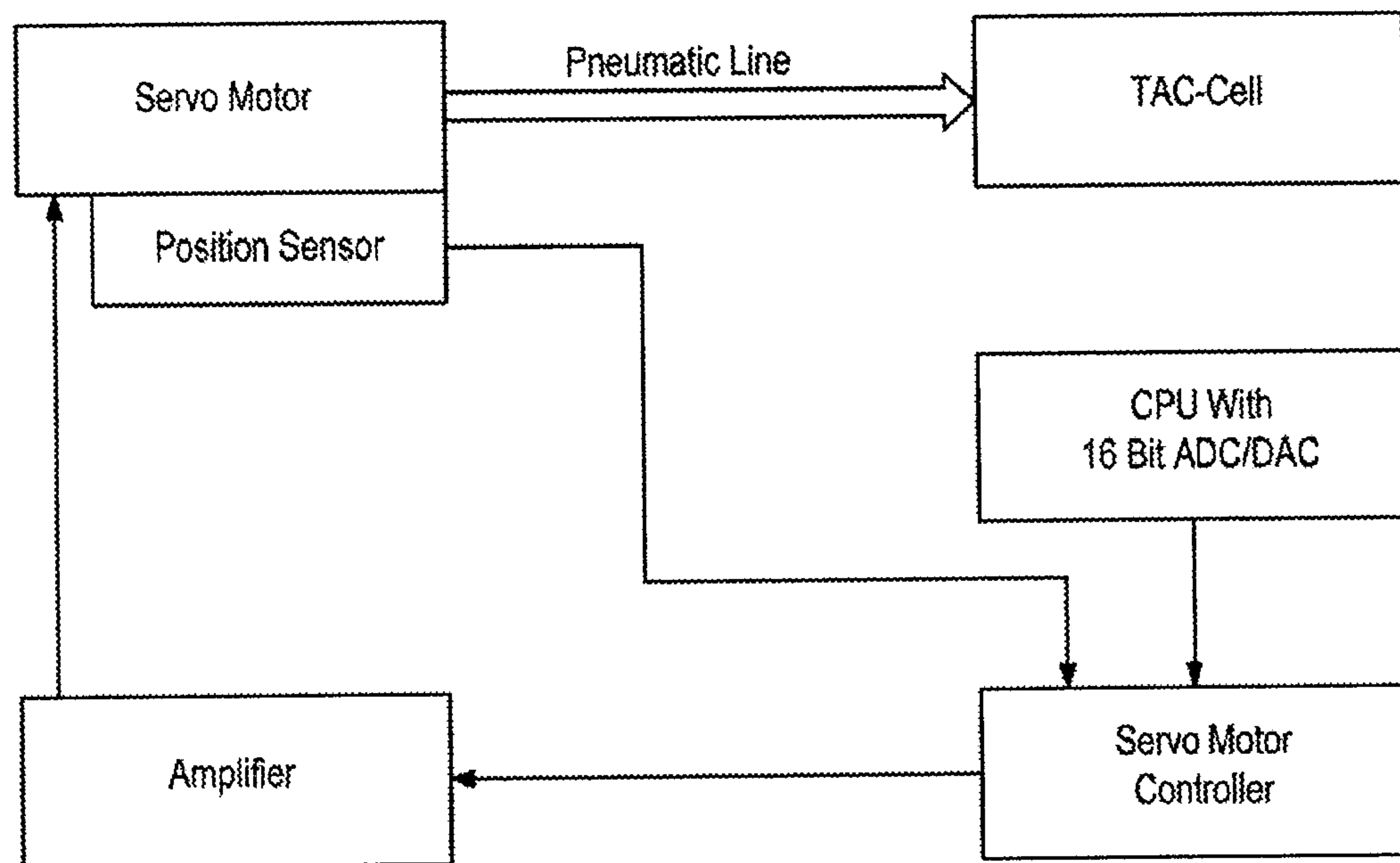


**Fig. 4A**



**Fig. 4B**

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**Fig. 5**

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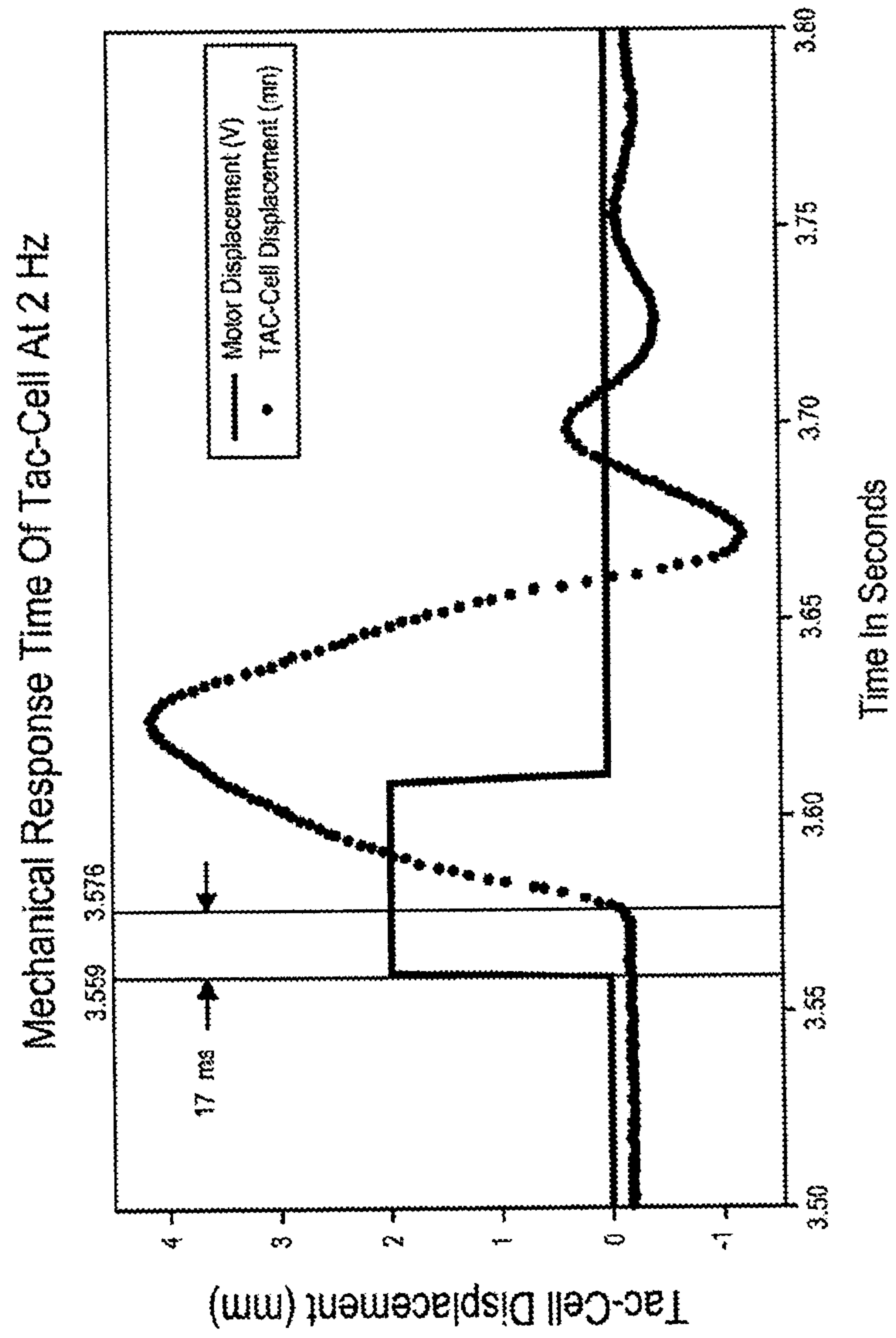
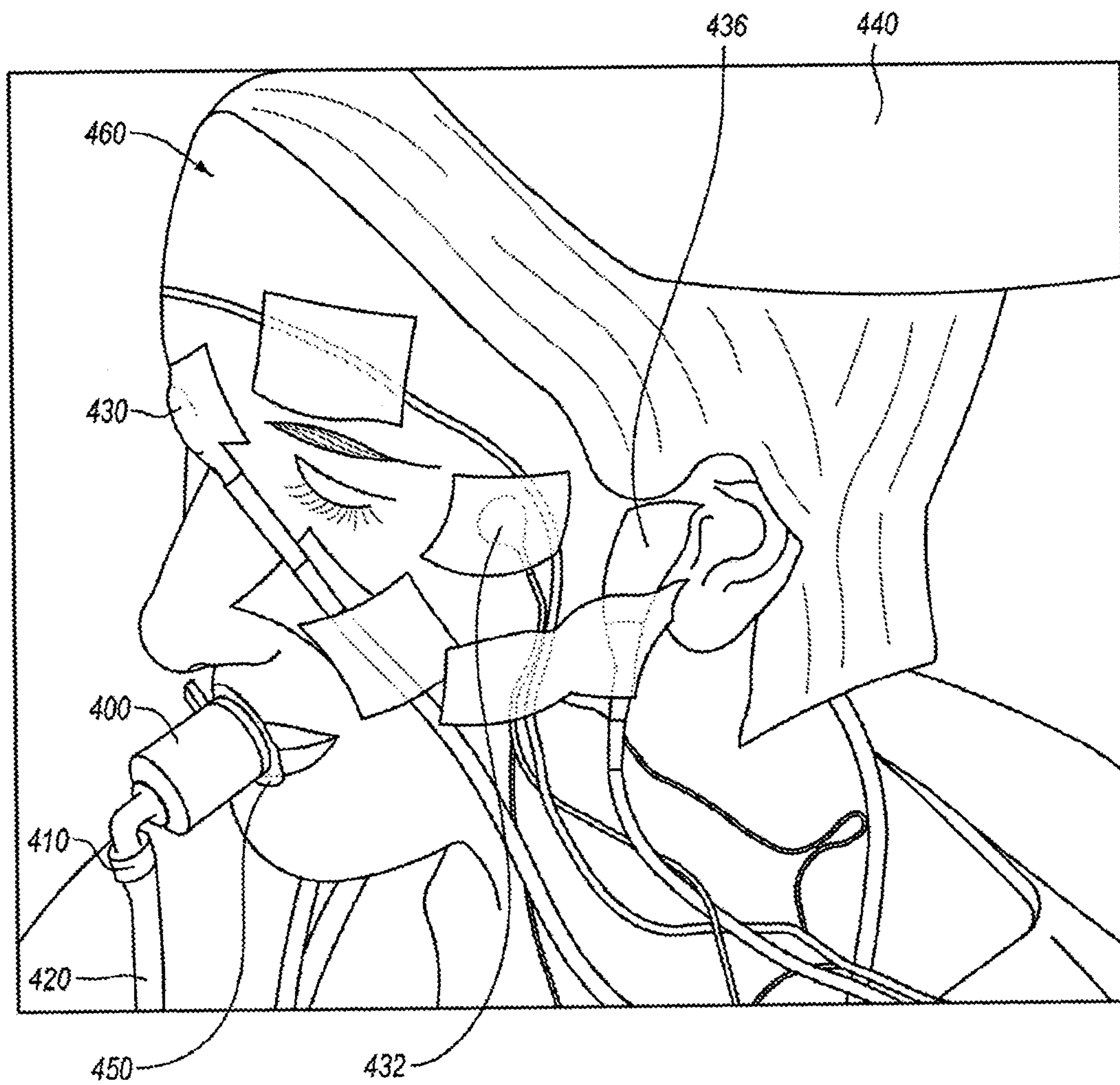


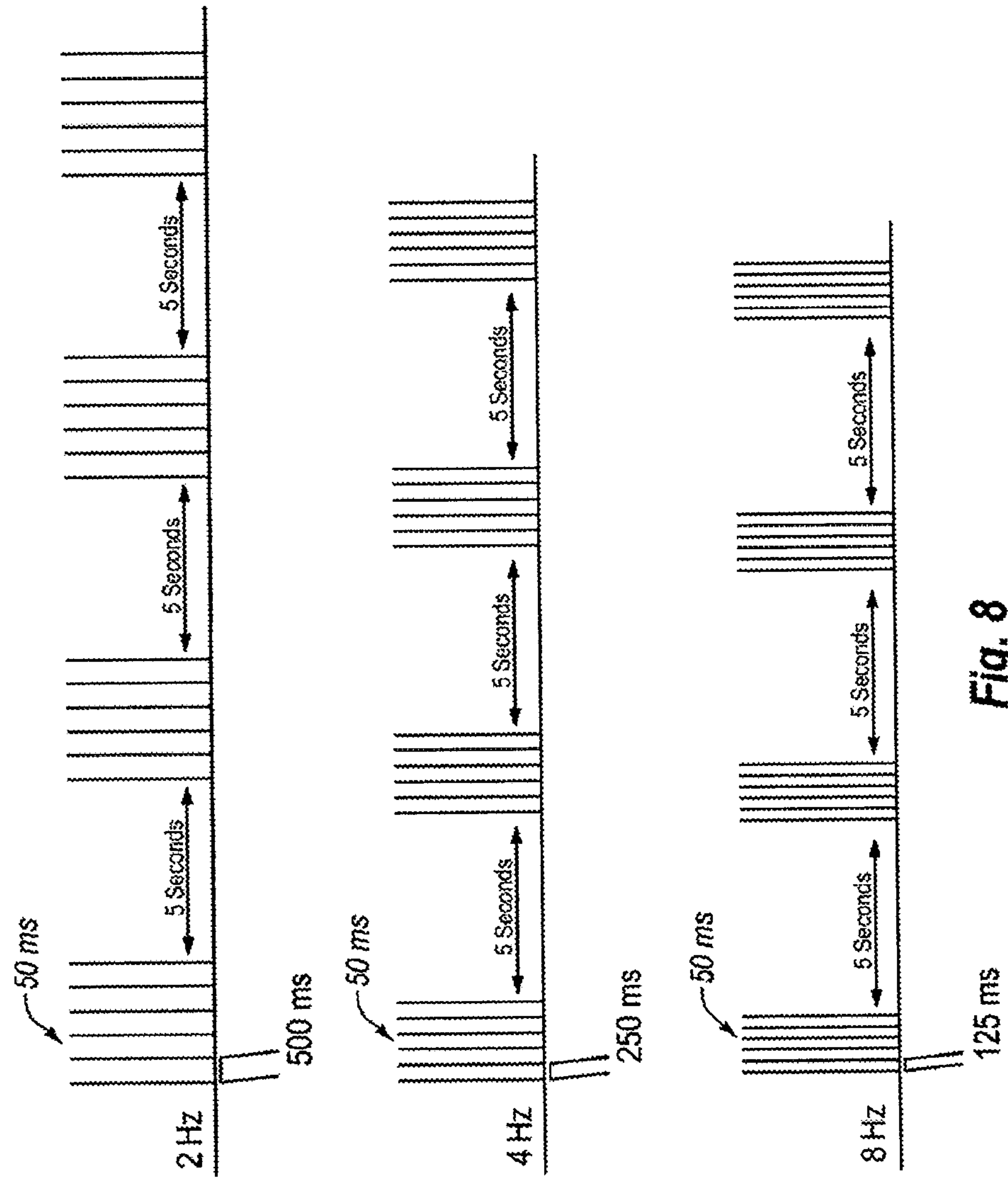
Fig. 6

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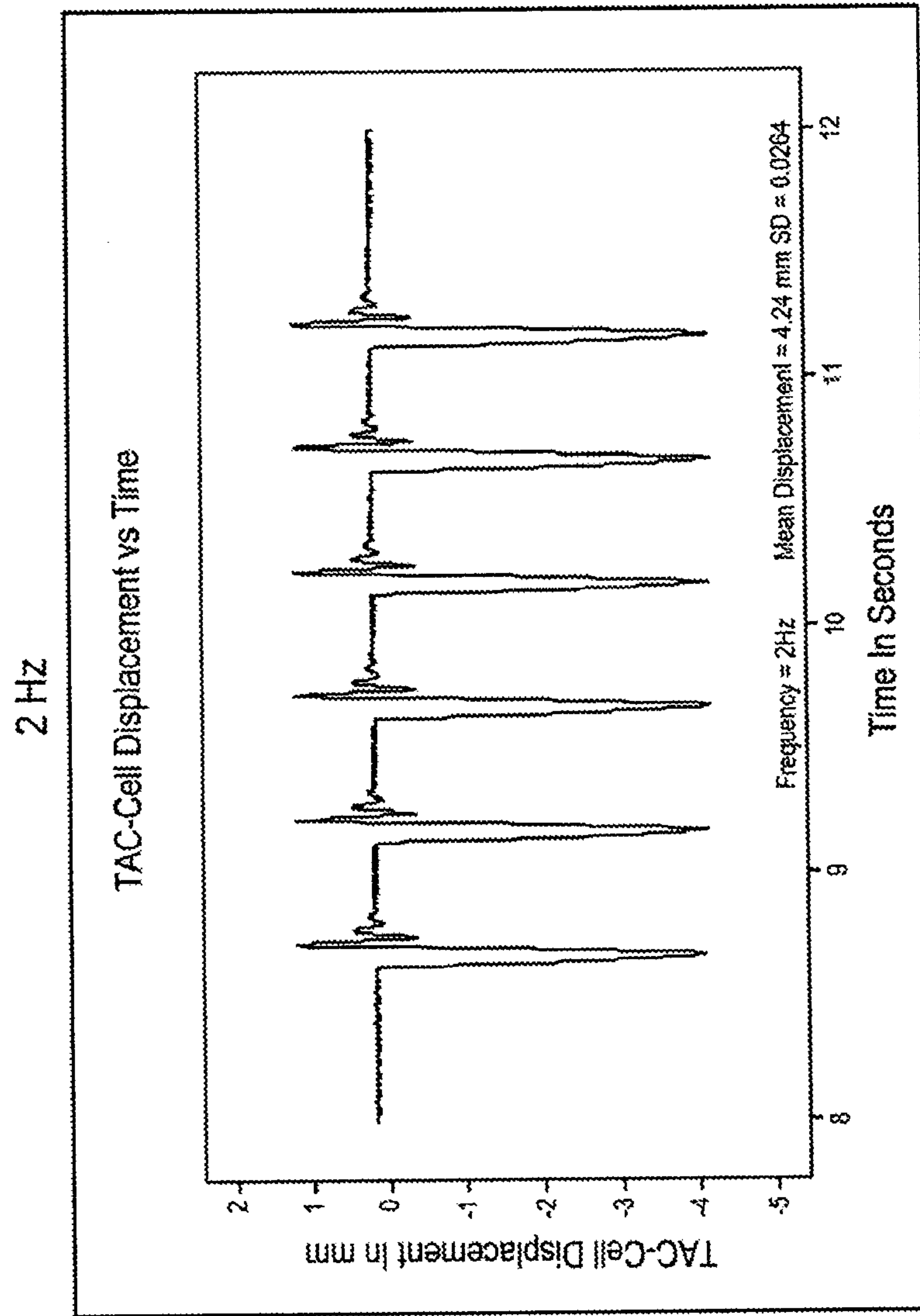


**Fig. 7**

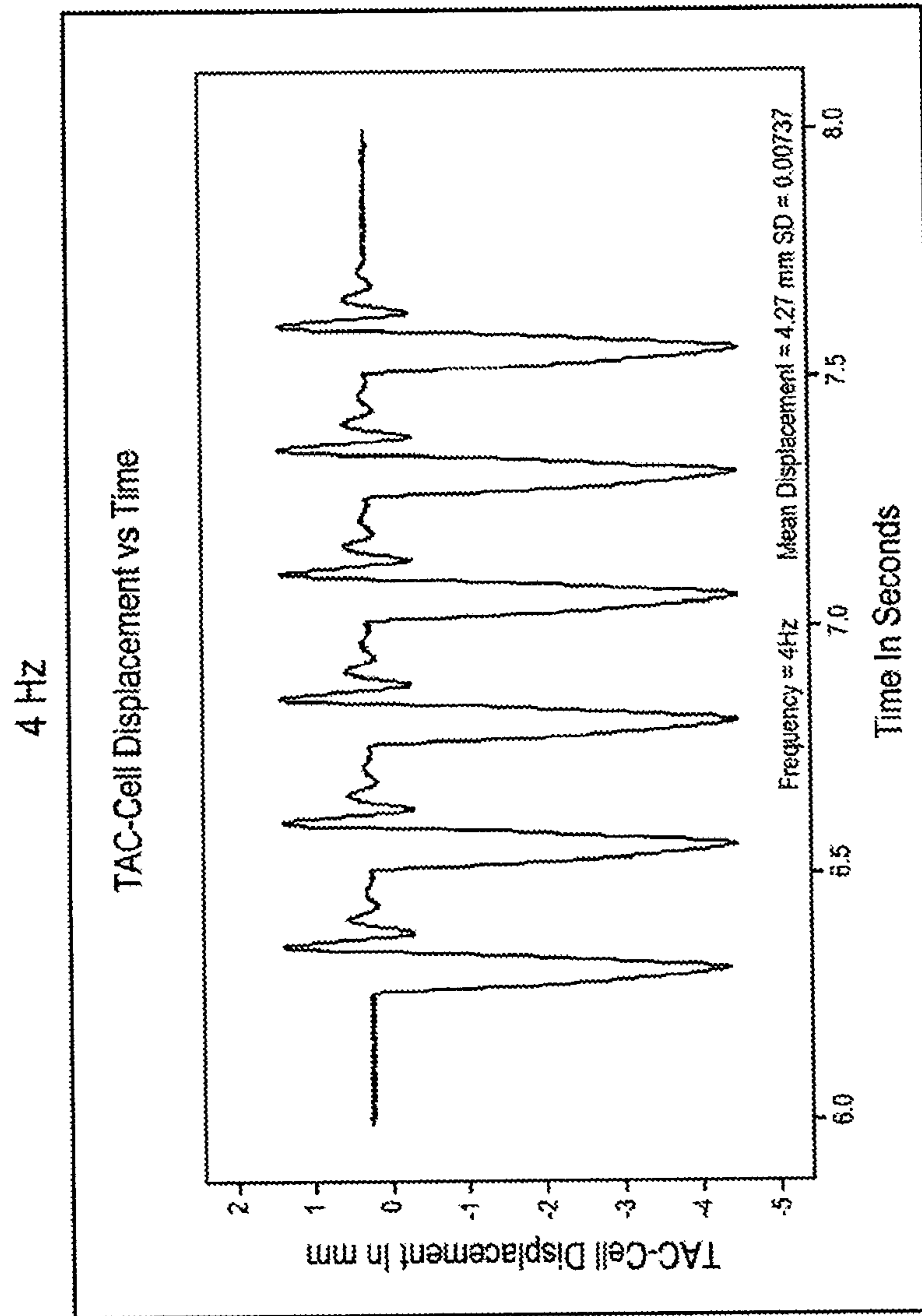
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**Fig. 8**

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**Fig. 9A**

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**Fig. 9B**

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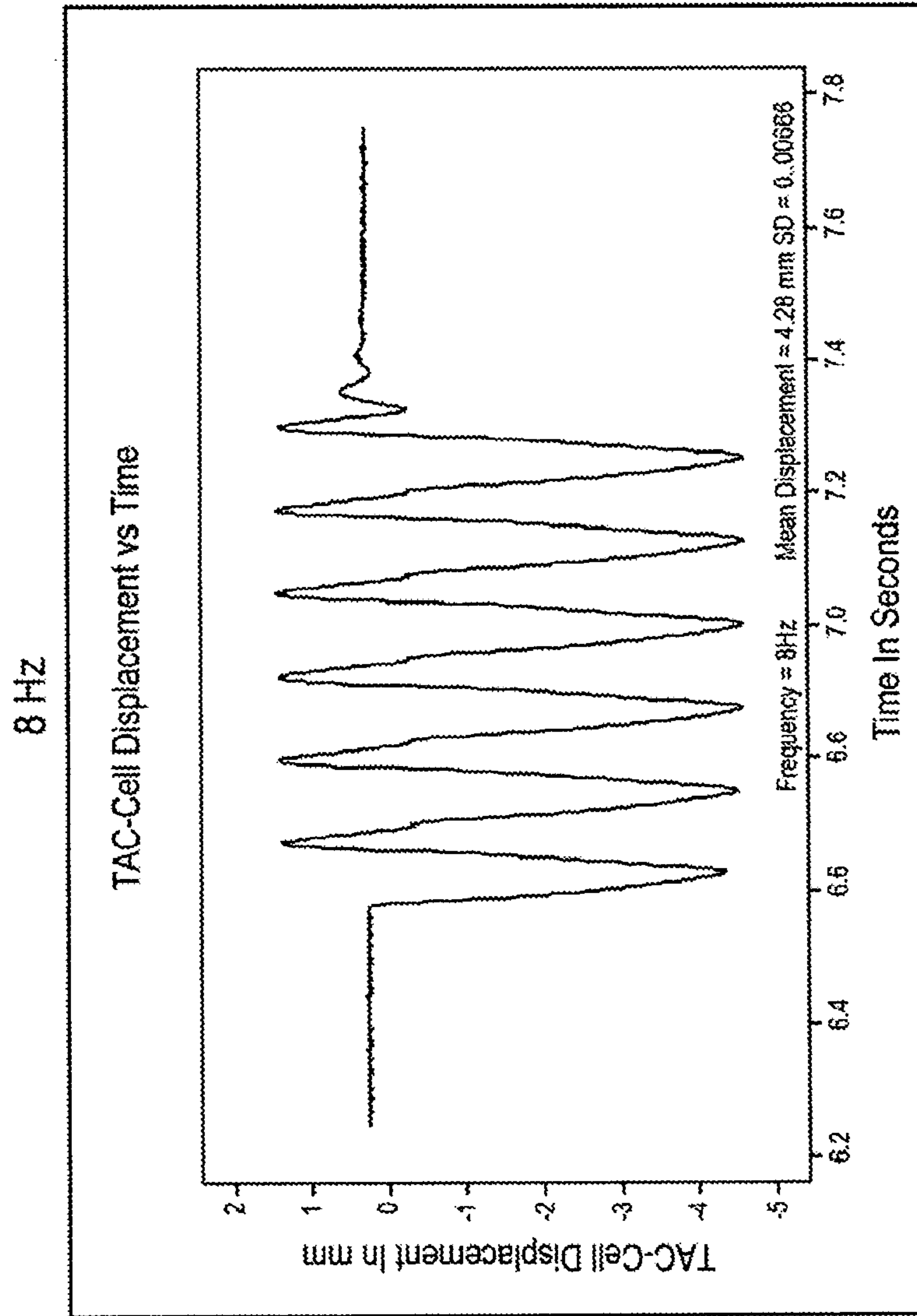
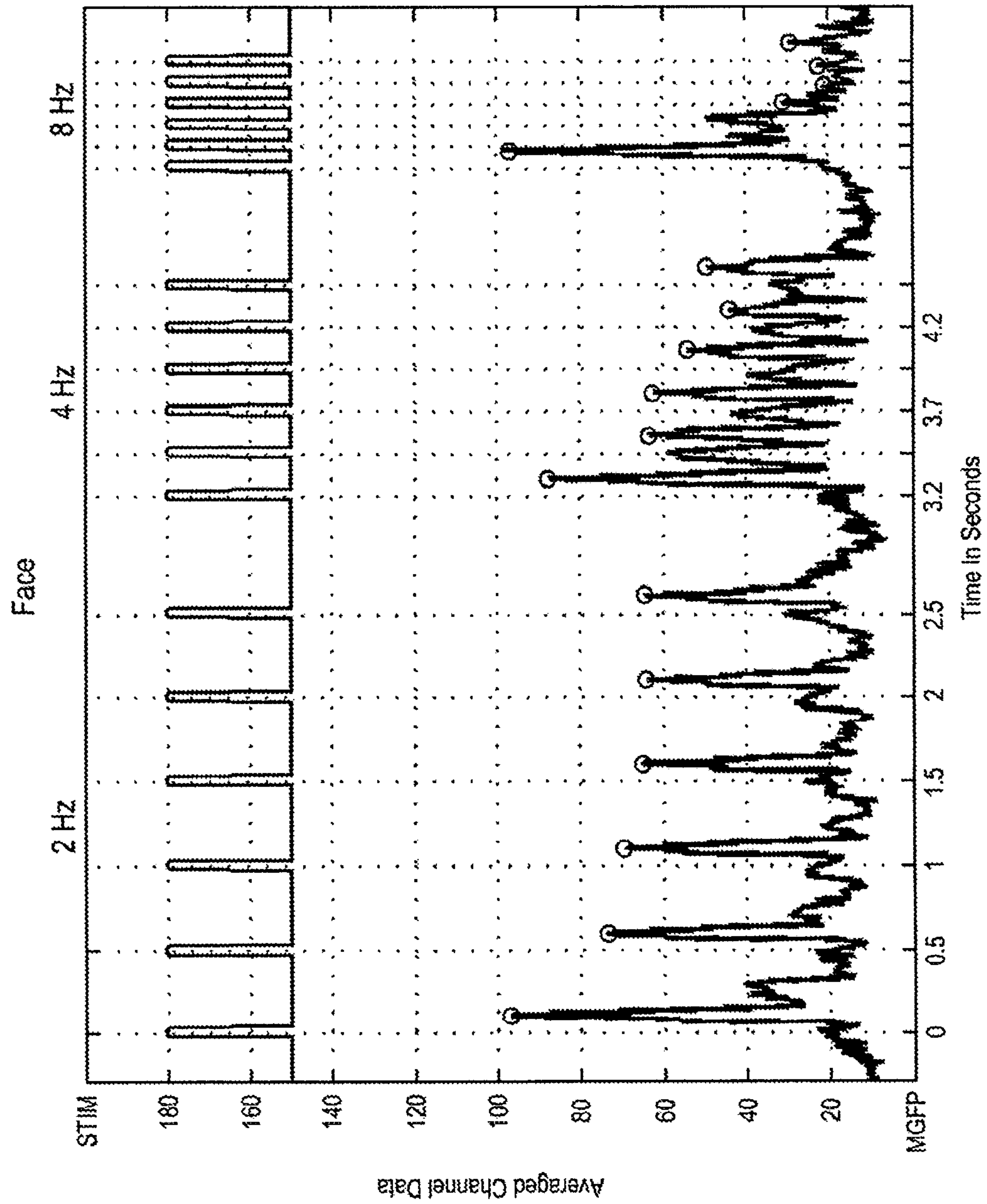


Fig. 9C

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**Fig. 10**