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**Wagner et al.**(10) **Pub. No.: US 2017/0296816 A1**(43) **Pub. Date: Oct. 19, 2017**(54) **APPARATUS AND METHOD FOR  
STIMULATION OF BIOLOGICAL TISSUE***A61N 2/00* (2006.01)*A61N 1/40* (2006.01)*A61N 1/36* (2006.01)(71) Applicants: **Timothy Andrew Wagner**, Somerville,  
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MA (US)*A61N 1/36* (2006.01)*A61N 1/362* (2006.01)*A61B 8/08* (2006.01)*A61N 7/00* (2006.01)(21) Appl. No.: **15/642,784**(52) **U.S. Cl.**(22) Filed: **Jul. 6, 2017**CPC ..... *A61N 1/36014* (2013.01); *A61N 7/02*(2013.01); *A61F 7/00* (2013.01); *A61H 1/005*(2013.01); *A61N 1/20* (2013.01); *A61N 1/32*(2013.01); *A61N 7/00* (2013.01); *A61N**5/0622* (2013.01); *A61N 2/02* (2013.01);*A61N 2/006* (2013.01); *A61N 2/002*(2013.01); *A61N 1/40* (2013.01); *A61N**1/36025* (2013.01); *A61N 1/36017* (2013.01);*A61N 1/36003* (2013.01); *A61F 2007/0002*(2013.01); *A61N 1/36082* (2013.01); *A61N**1/362* (2013.01); *A61B 8/0816* (2013.01);*A61N 2007/0026* (2013.01)**Related U.S. Application Data**(63) Continuation of application No. 14/564,559, filed on  
Dec. 9, 2014, which is a continuation of application  
No. 11/764,468, filed on Jun. 18, 2007, now Pat. No.  
8,929,979.(60) Provisional application No. 60/814,843, filed on Jun.  
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(57)

**ABSTRACT**

An apparatus for generating focused currents in biological tissue is provided. The apparatus comprises an electric source capable of generating an electric field across a region of tissue and means for altering the permittivity of the tissue relative to the electric field, whereby a displacement current is generated. The means for altering the permittivity may be a chemical source, optical source, mechanical source, thermal source, or electromagnetic source.

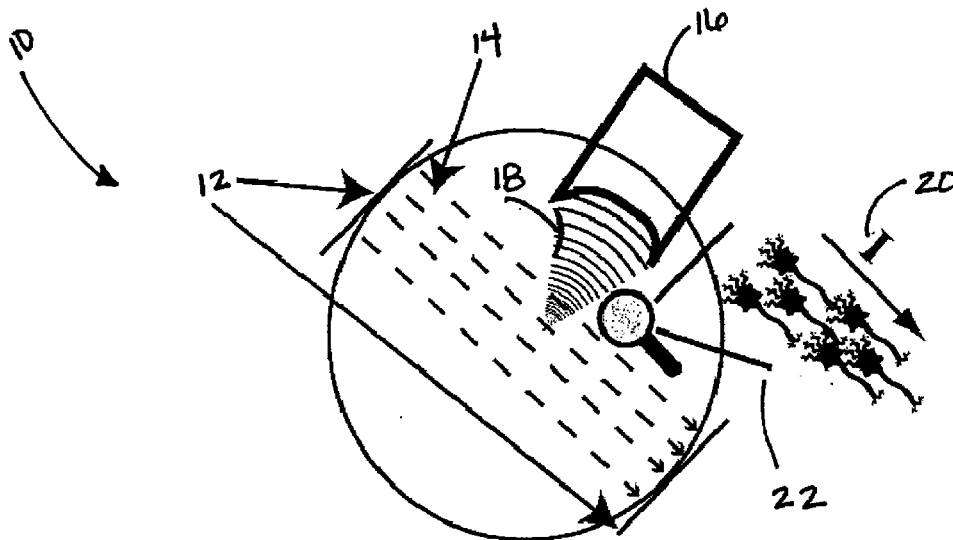


FIGURE 1

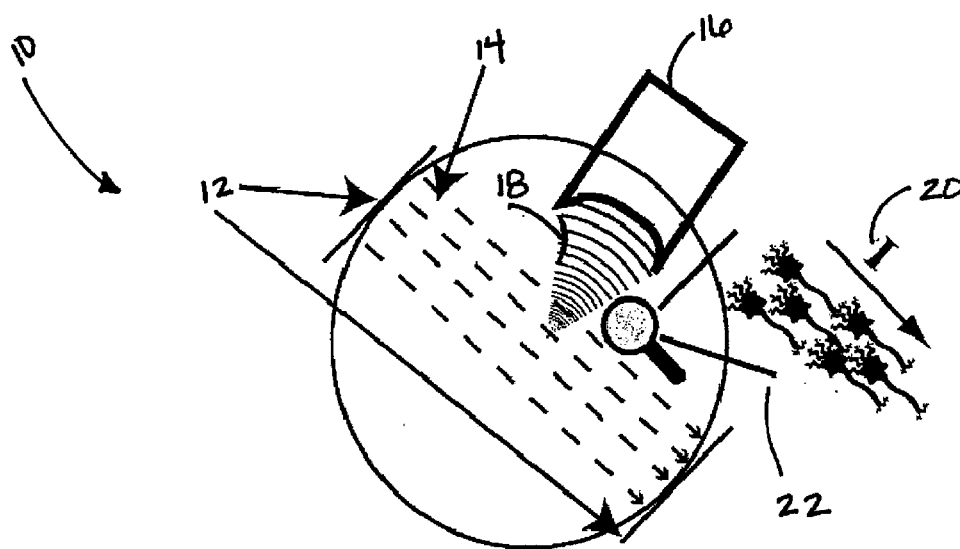


FIGURE 2

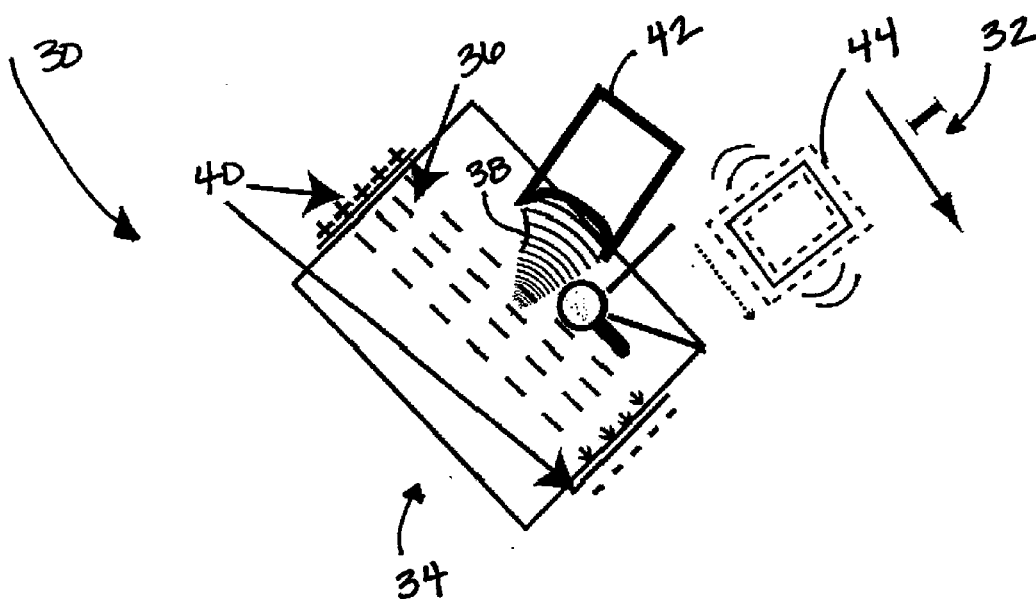


FIGURE 3

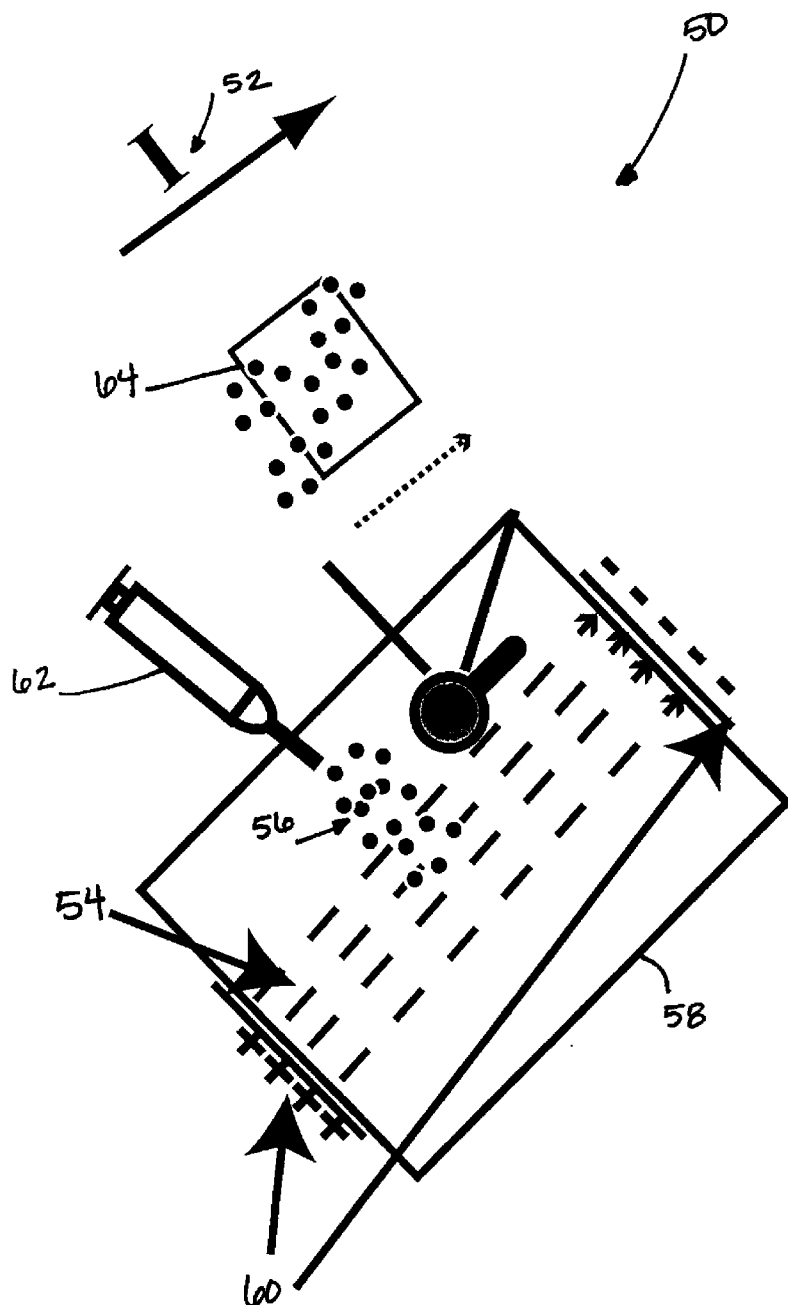


FIGURE 4

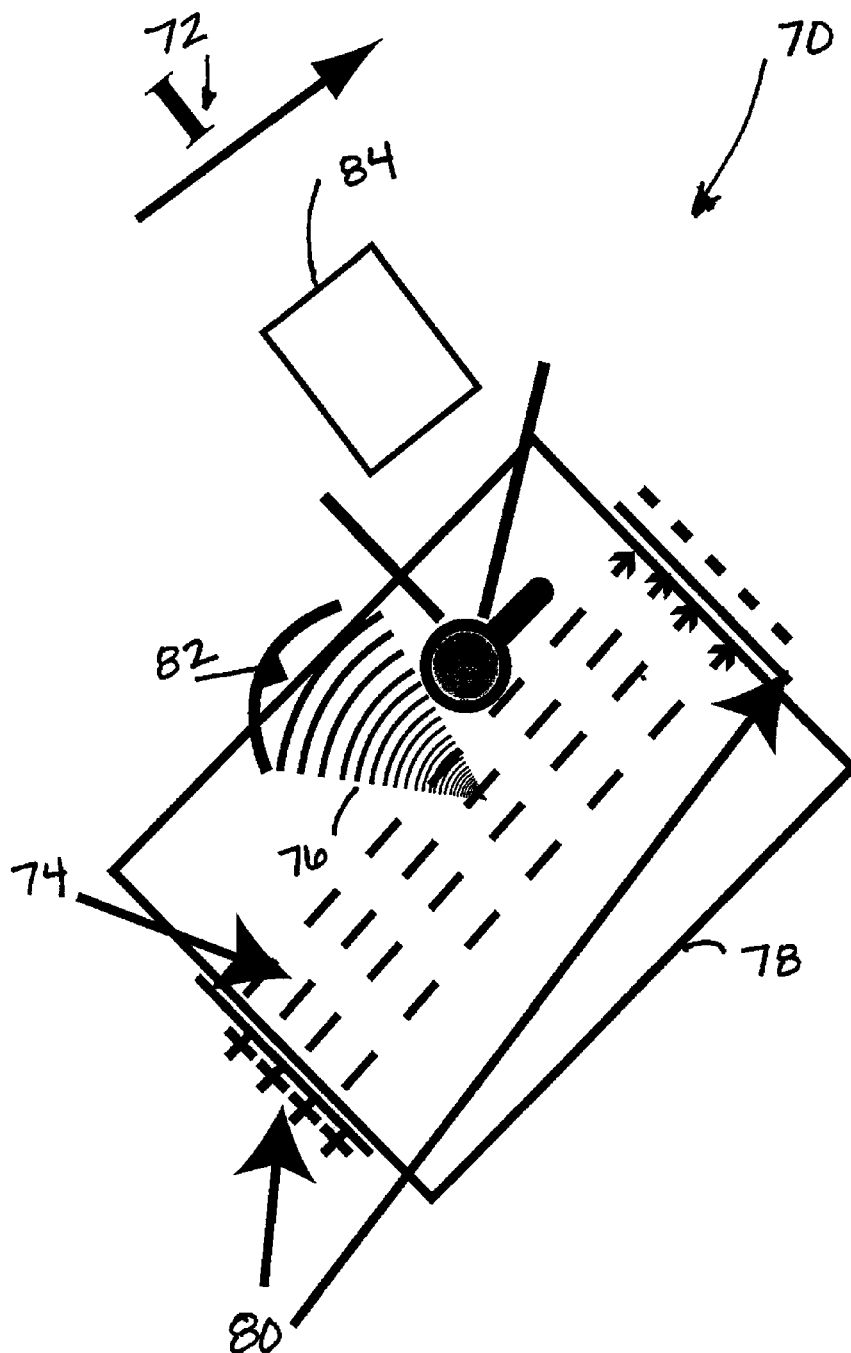
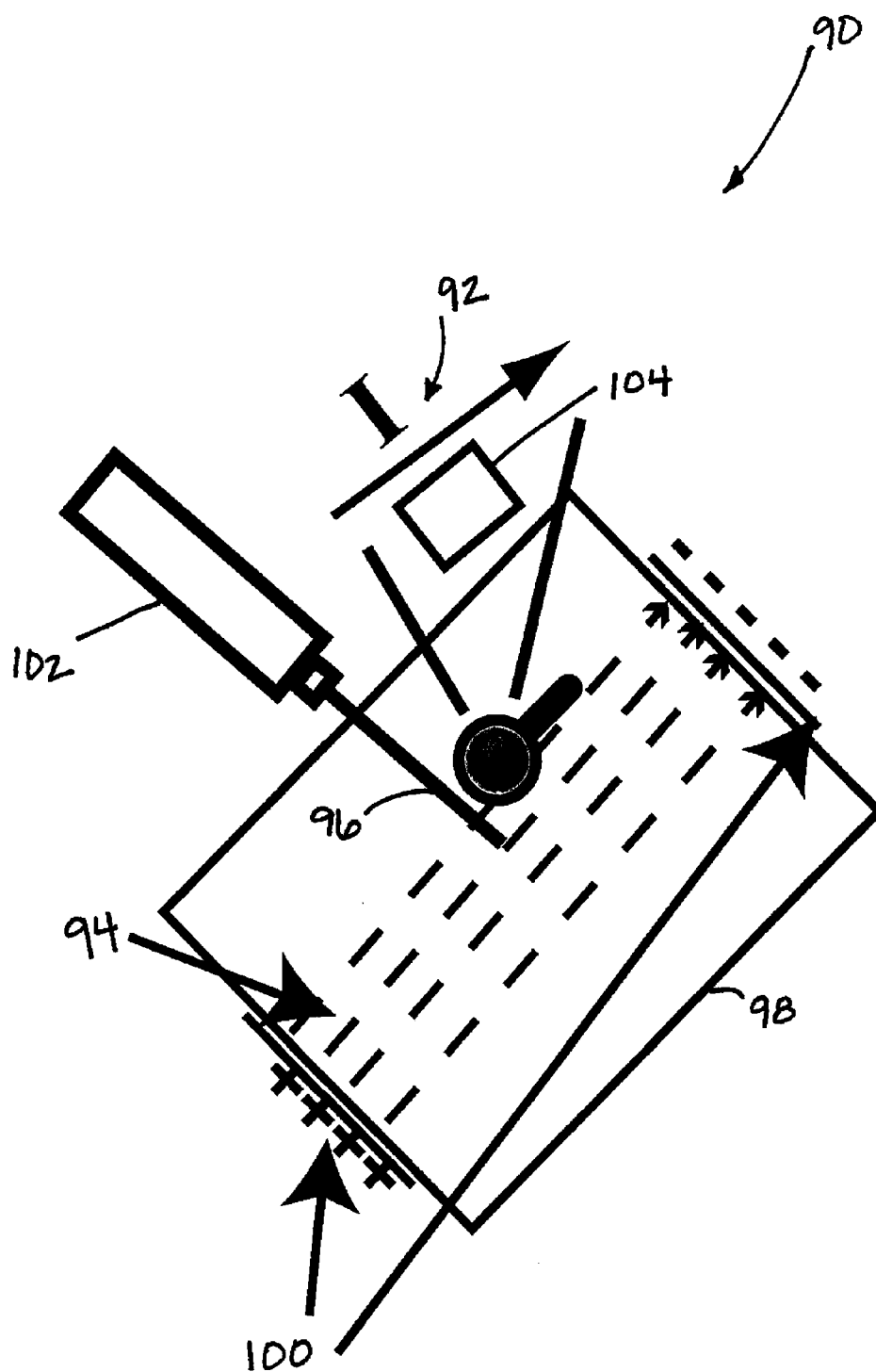


FIGURE 5



## APPARATUS AND METHOD FOR STIMULATION OF BIOLOGICAL TISSUE

### CROSS REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/814,843, filed on Jun. 19, 2006, the contents of which being incorporated herein by reference in its entirety.

### I. BACKGROUND OF THE INVENTION

#### A. Field of the Invention

[0002] The present invention relates generally to the field of altering currents in the presence of an applied electric field or applied current source within biological material and more particularly to a method and apparatus to generate displacement currents in living tissue by altering local tissue permittivity characteristics via mechanical, electrical, optical, chemical, and/or thermal means relative to an applied electric field to stimulate biological tissue.

#### B. Background Information

[0003] Electric stimulation of living tissue in humans and other animals is used in a number of clinical applications as well as in clinical and general biological research. In particular, electric stimulation of neural tissue has been used in the treatment of various diseases including Parkinson's disease, depression, and intractable pain. Focused stimulation of the brain usually involves performing surgery to remove a portion of the skull and implanting electrodes in a specific location within the brain tissue. The invasive nature of these procedures makes them difficult and costly, and is responsible for a great deal of morbidity. Alternately, non-invasive stimulation methodologies such as transcranial direct current stimulation and transcranial magnetic stimulation are easy to implement and are not associated with significant morbidity, however, the areas stimulated are large, typically not well characterized, and can be significantly perturbed by natural or pathological features of the brain tissue. Recently, ultrasound stimulation of brain tissue has been explored with limited success.

[0004] Numerous methods exist for generating currents for biological tissue stimulation. These methods range from implanting electric sources in the tissue to inductively generating currents in tissue via time-varying magnetic fields. A common method for generating currents in tissues is to implant current sources within the tissue. Examples of this method are illustrated, for example in U.S. Pat. No. 5,895,416 to Barreras, Sr. et al., U.S. Pat. No. 6,128,537 to Rise, U.S. Pat. No. 7,146,210 to Palti, and U.S. Pat. No. 6,091,992 to Bourgeois et al. Currents can also be produced in tissues with sources external to the tissues, such as via external magnetic fields which induce currents in tissues. This method is shown, for example, in U.S. Pat. No. 6,066,084 to Edrich et al., U.S. Pat. No. 5,061,234 to Chaney, U.S. Pat. No. 6,234,953 to Thomas et al. Another example is shown in U.S. Pat. No. 7,146,210 to Palti which implements electromagnetic radiation. Methods employing currents produced via electric sources placed in external contact to the tissue such that the currents attenuate through other tissues superficial to the region of tissue to be stimulated are illustrated in U.S. Pat. No. 4,989,605 to Rossen and

U.S. Pat. No. 4,709,700 to Hyrman. None of these techniques generate currents via a permittivity perturbation in the presence of an applied electric field. As such, these techniques suffer from limitations in the level of invasiveness, focality, penetration, and/or cost.

[0005] The concept of combining fields for the generation of altered displacement currents is relatively unexplored in the area of biological tissue stimulation. In the area of brain stimulation, magnetic fields have been explored with ultrasound techniques in the area of "hall effect stimulation," for example, as in U.S. Pat. No. 5,476,438 Edrich et al., whereby "ionized particles within the nerve tissue and, particularly, electrons are mobilized" such that positive and negative ions are separated in the area of the orthogonal magnetic field where the ions are moving under the influence of ultrasound. This method does not attempt to generate a displacement current through the modification of tissue permittivities, but rather just local ionic separation via applying a magnetic field to moving ions. With the strength of magnetic fields used in modern medical procedures, this technique is ineffective for stimulation. See Rutten, et al. (1996). Also in the area of brain stimulation, U.S. Pat. No. 6,520,903 to Yamashiro proposes a method to enhance energy transfer of magnetic fields by photonic fields focused on the tissue, but it does not attempt to generate a displacement current via a tissue permittivity perturbation. Additionally, in the area of brain stimulation, U.S. Pat. No. 5,738,625 to Gluck (hereinafter "Gluck") proposes the use of magnetic fields with a combined ultrasound field and/or microwave fields in order to change the membrane potential of a neuron to a static value significantly different from the cell's resting potential and a separate active depolarized state. Gluck proposes the modification of tissue conductivity via ultrasound such that currents induced by a magnetic field could flow on the paths of altered conductivity. Gluck also proposes the use of ultrasound to push nerves in and out of the fields generated by the magnetic field. Gluck implements a method altering which nerves are exposed to a magnetic field (or currents) and thus the magnetic based method of Gluck suffers from a loss in efficiency due to subsequent current attenuation.

[0006] Furthermore, Gluck proposes a method in which microwave and ultrasound fields are combined in a way that may lead to non reversible changes to nerves. See Donald I. McRee, Howard Wachtel, Pulse Microwave Effects on Nerve Vitality, Radiation Research, Vol. 91, No. 1 (July, 1982). The present disclosure does not suffer from these safety concerns or cause nerve damage by requiring the use of such high frequency electric fields. In addition, the disclosed invention herein is not constrained to apply only to neural tissue exhibiting distinct states of quiescence and activity, and would therefore be appropriate for dynamically changing action potentials that characterize almost all neural activity and for neurons with dynamic firing properties.

[0007] Other methods have been proposed for altering tissue conductivities for adapting current flow, such as U.S. Pat. No. 6,764,498 to Mische and U.S. Pat. No. 6,887,239 to Elstrom et al., but similarly, these methods do not provide a method that generates a new current component through the modification of the tissue electromagnetic properties.

[0008] Other studies have proposed techniques to affect neural stimulation with combined fields but all suffer from inherent limitations in that the techniques do not attempt to generate displacement currents for stimulation but attempt to

affect stimulation through other means. See Rutten, W. L. C., E. Droog et al.; The influence of ultrasound and ultrasonic focusing on magnetic and electric peripheral nerve stimulation, J. Nilsson, M. Panizza and F. Grandori; Pavia Advances in Magnetic Stimulation, Mathematical Modeling and Clinical Applications, Italy, 2: 152. (1996) (hereinafter "Rutten"); Mihran, R. T., F. S. Barnes et al., Temporally-Specific Modification of Myelinated Axon Excitability in Vitro Following a Single Ultrasound Pulse, Ultrasound Med Biol 16(3): 297-309. (1990) (hereinafter "Mihran"); and Fry, W. J., Electrical Stimulation of Brain Localized Without Probes—Theoretical Analysis of a Proposed Method, J Acoust Soc Am 44(4): 919-31. (1968) (hereinafter "Fry").

[0009] Mihran and Rutten focus on altering ionic stretch receptors in neural elements. Thus by not focusing on the generation of displacement currents through the appropriate combination of electric and mechanical fields, these studies are limited in applicability and effectiveness. More specifically, the Mihran study combines ultrasound with electrical stimulation to test the effects of stretch receptors on nerves. Mihran does not attempt to generate new currents for stimulation. Mihran purposely decouples the electric and mechanical fields. The primary focus of Rutten is to combine ultrasound and transcranial magnetic stimulation (TMS), however, the study attempts electrical stimulation and ultrasound in an attempt to analyze the effects of stretch receptors similar to Mihran. Rutten does not attempt to combine the effects for the generation of new current components or alter the applied stimulatory currents in any way.

[0010] Fry presents an idea regarding how to generate a current modification in the brain by modifying the tissue conductivity via ultrasound and thus driving neural stimulation through a conductivity change alone. Fry proposes a theoretical, pseudo invasive, method based on the use of ultrasound and electrodes placed on the brain surface. The method is based on the alteration of tissue conductivity via temperature/pressure changes generated from ultrasound to alter currents generated by the brain surface electrodes. The method has never been shown to work for neural stimulation, possibly because the theory is limited by many constraints. By focusing on modifying just the tissue conductivity to alter currents generated with higher frequency electric fields, the source strengths required for stimulation are not trivial. Therefore, the method necessitates electrodes that must be placed on the exposed brain surface, or much stronger current sources, which if placed on the scalp surface, would suffer from the limitations of Transcranial Electrostimulation (TES) and Electroconvulsive Therapy (ECT), i.e., current strengths which activate pain receptors on the scalp surface or with strengths necessary for stimulation that may potentially lead to scalp burns. And the ultrasound intensities that are necessary for this theoretical stimulation are large enough in magnitude that concerns arise including temperature rise in the tissue, tissue cavitation, and the possibility of tissue ablation. Thus, these safety limitations would preclude one from applying this type of stimulation for any duration of time, either with electrodes on the surface of the scalp or the brain.

[0011] The concept of mechanical and electric fields being interrelated in biological tissues has been explored in the pursuit of imaging as illustrated in U.S. Pat. No. 6,645,144 to Wen, et al. and U.S. Pat. No. 6,520,911 to Wen via electroacoustic, thermoacoustic, and Hall effects. These methods are focused on using one physical field to glean

information about the other and not in a combinatory way for biological tissue stimulation.

[0012] The prior art techniques do not attempt to generate capacitive currents, i.e., displacement currents, via a permittivity perturbation relative to an applied electric field for biological tissue stimulation. It is thus evident from the above that there is a need for an improved apparatus and method to generate displacement currents in living tissue by altering local tissue permittivity characteristics via mechanical means relative to an applied electric field to stimulate biological tissue. It is evident that there is a need for an improved method for stimulating biological tissue by altering local tissue permittivity that is less invasive and has improved focality. It is further evident that there is a need for an apparatus and method whereby actual currents are generated as opposed to methods where the currents are altered in path or methods altering which nerves are exposed to a magnetic field. It is also evident that there is a need to generate currents below tissue boundaries without subsequent current attenuation and loss in efficiency as takes place with magnetic and electrical based methods. It is evident that there is a need for a safe method that does not cause nerve or tissue damage by requiring the use of high frequency electromagnetic fields, high intensity electromagnetic fields, and/or high intensity ultrasound fields. It is also evident that there is a need for a tolerable method that does not require field strengths that activate pain receptors during stimulation. Additionally, it is evident that there is a need for an apparatus and method that is not constrained to apply only to neural tissue exhibiting distinct states of quiescence and activity, and would therefore be appropriate for dynamically changing action potentials that characterize almost all neural activity and for neurons with dynamic firing properties.

## II. SUMMARY OF THE INVENTION

[0013] Accordingly, an apparatus for generating currents in biological tissue is provided. The apparatus according to the disclosure includes an electric source capable of generating an electric field across a region of tissue and a means for altering the permittivity of tissue relative to the electric field, whereby the alteration of the tissue permittivity relative to the electric field generates a displacement current in the tissue. The means for altering the permittivity may include a chemical source, optical source, mechanical source, thermal source, or electromagnetic source. In one embodiment, the apparatus implements an ultrasound source as mechanical means for altering the permittivity of the tissues. In another embodiment the apparatus further includes a means for altering the conductivity of tissue relative to the electric field, whereby the ohmic current is altered.

[0014] In one exemplary embodiment, the apparatus includes an electric source capable of generating an electric field across a broad region of tissue or tissues. The apparatus also includes an ultrasound device that generates a mechanical field focused on the sub-region of tissue whereby the combined effects of the electric field and the mechanical field generate an altered current with a newly generated displacement current within the sub-region of tissue, via the alteration of tissue electromagnetic properties.

[0015] The electric source according to the present disclosure may be applied in a variety of ways to achieve a specified outcome. For example, the electric source may generate a field that is pulsed, time varying, a sequence of



time varying pulses, or time invariant. Additionally, the means for altering permittivity may be a pulsed signal, time varying signal, or a sequence of time varying pulse signals. The electric source and/or means for altering the tissue permittivity may be applied non-invasively. For example, electrodes may be configured to be applied to the specified tissue, tissues, or adjacent tissues. As one alternative, the electric source may be implanted inside the specified tissue, tissues, or adjacent tissues. Generally, the electric source is current that has a frequency from about DC to approximately 100,000 Hz.

**[0016]** In one exemplary embodiment, the electric field is applied broadly and the means is focused on a specific brain structure or multiple structures for therapeutic purposes. The electric field may be applied broadly and the means may be focused on a structure or multiple structures, such as brain or nervous tissues including dorsal lateral prefrontal cortex, any component of the basal ganglia, nucleus accumbens, gastric nuclei, brainstem, thalamus, inferior colliculus, superior colliculus, periaqueductal gray, primary motor cortex, supplementary motor cortex, occipital lobe, Brodmann areas 1-48, primary sensory cortex, primary visual cortex, primary auditory cortex, amygdala, hippocampus, cochlea, cranial nerves, cerebellum, frontal lobe, occipital lobe, temporal lobe, parietal lobe, sub-cortical structures, peripheral nerves, and/or spinal cord.

**[0017]** The apparatus and method may assist in the treatment of a variety of ailments including Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Alzheimer's Disease, Dystonia, Tics, Spinal Cord Injury, Traumatic Brain Injury, Drug Craving, Food Craving, Alcohol Craving, Nicotine Craving, Stuttering, Tinnitus, Spasticity, Parkinson's Disease, Parkinsonism, Depression, Obsessions, Schizophrenia, Bipolar Disorder, Acute Mania, Catonia, Post-Traumatic Stress Disorder, Autism, Chronic Pain Syndrome, Phantom Limb Pain, Epilepsy, Stroke, Hallucinations, Movement Disorders, Neurodegenerative Disorders, Pain Disorders, Metabolic Disorders, Addictive Disorders, Psychiatric Disorders, Traumatic Nerve Injury, and Sensory Disorders. Similarly, the electric field and the means for altering permittivity may be focused on specific brain structures to enact procedures such as sensory augmentation, sensory alteration, anesthesia induction and maintenance, brain mapping, epileptic mapping, pre-surgical planning, neuroprosthetic interaction or control with nervous system, stroke and traumatic injury neurorehabilitation, bladder control, assisting breathing, cardiac pacing, muscle stimulation, and treatment of pain syndromes, such as those caused by migraine, neuropathies, and low-back pain; or internal visceral diseases, such as chronic pancreatitis or cancer.

**[0018]** In another embodiment, the apparatus according to the present disclosure includes an electric source capable of generating an electric field across a region of tissue and a means for altering the permittivity of the tissue relative to the electric field, whereby a displacement current is generated. The apparatus further includes a means for altering the conductivity of the tissue relative to the electric field, whereby the ohmic current is altered.

**[0019]** A method for stimulating biological tissue is also provided. The method includes applying an electric source to biological tissue and altering the permittivity of tissue relative to the electric source by applying a means for altering the permittivity of tissue relative to the electric field. The alteration of the permittivity of the tissue relative to the

electric field generates a displacement current in the tissue. The means for altering the permittivity may be a variety of sources including a chemical source, optical source, mechanical source, thermal source, or electromagnetic source. For example, a mechanical source such as an ultrasound source may be applied to mechanically alter the tissue. The tissue can be neural tissue, endocrine tissue, electrically receptive tissue, muscle tissue, connective tissue, or skeletal tissue. In a further embodiment, the apparatus further includes a means for altering the conductivity of the tissue relative to the electric field, whereby the ohmic current is altered.

### III. BRIEF DESCRIPTION OF THE DRAWINGS

**[0020]** The above-mentioned and other features and objects of this invention, and the manner of attaining them, will become more apparent and the invention itself will be better understood by reference to the following description of embodiments of the invention taken in conjunction with the accompanying drawings, wherein:

**[0021]** FIG. 1 is a plan view of one embodiment of an apparatus for stimulating biological tissue constructed in accordance with the principles of the present disclosure;

**[0022]** FIG. 2 is a top plan view of an exemplary embodiment of an apparatus for stimulating biological tissue constructed in accordance with the principles of the present disclosure;

**[0023]** FIG. 3 is a top plan view of an exemplary embodiment of an apparatus for stimulating biological tissue implementing a chemical source for altering permittivity constructed in accordance with the principles of the present disclosure;

**[0024]** FIG. 4 is a top plan view of an exemplary embodiment of an apparatus for stimulating biological tissue implementing a radiation source for altering permittivity constructed in accordance with the principles of the present disclosure; and

**[0025]** FIG. 5 is a top plan view of another exemplary embodiment of an apparatus for stimulating biological tissue implementing an optical beam for altering permittivity constructed in accordance with the principles of the present disclosure.

### IV. DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

**[0026]** It is envisioned that the present disclosure may be used to stimulate biological tissue in-vivo comprising an electric source that is placed on the body to generate an electric field and a means for altering the permittivity of tissue relative to the electric field, whereby the alteration of the tissue permittivity relative to the electric field generates a displacement current in the tissue. The exemplary embodiments of the apparatuses and methods disclosed can be employed in the area of neural stimulation, where amplified, focused, direction altered, and/or attenuated currents could be used to alter neural activity via directly stimulating neurons, depolarizing neurons, hyperpolarizing neurons, modifying neural membrane potentials, altering the level of neural cell excitability, and/or altering the likelihood of a neural cell firing. Likewise, the method for stimulating biological tissue may also be employed in the area of muscular stimulation, including cardiac stimulation, where amplified, focused, direction altered, and/or attenuated cur-

rents could be used to alter muscular activity via direct stimulation, depolarizing muscle cells, hyperpolarizing muscle cells, modifying membrane potentials, altering the level of muscle cell excitability, and/or altering the likelihood of cell firing. Similarly, it is envisioned that the present disclosure may be employed in the area of cellular metabolism, physical therapy, drug delivery, and gene therapy.

**[0027]** Detailed embodiments of the present disclosure are disclosed herein, however, it is to be understood that the described embodiments are merely exemplary of the disclosure, which may be embodied in various forms. Therefore, specific functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the present disclosure in virtually any appropriately detailed embodiment.

**[0028]** The components of the tissue stimulation method according to the present disclosure are fabricated from materials suitable for a variety of medical applications, such as, for example, polymeric, gels, films, and/or metals, depending on the particular application and/or preference. Semi-rigid and rigid polymers are contemplated for fabrication, as well as resilient materials, such as molded medical grade polyurethane, as well as flexible or malleable materials. The motors, gearing, electronics, power components, electrodes, and transducers of the method may be fabricated from those suitable for a variety of medical applications. The method according to the present disclosure may also include circuit boards, circuitry, processor components, etc. for computerized control. One skilled in the art, however, will realize that other materials and fabrication methods suitable for assembly and manufacture, in accordance with the present disclosure, also would be appropriate.

**[0029]** The following discussion includes a description of the components and exemplary methods for generating currents in biological tissues in accordance with the principles of the present disclosure. Alternate embodiments are also disclosed. Reference will now be made in detail to the exemplary embodiments of the present disclosure illustrated in the accompanying figures wherein like reference numerals indicate the similar parts throughout the figures.

**[0030]** Turning now to FIG. 1, which illustrates an exemplary embodiment of an apparatus 10 to alter currents, e.g., amplify, focus, alter direction, and/or attenuate in the presence of an applied electric field or applied current source by the combined application of a mechanical field within a biological material to stimulate the biological cells and/or tissue in accordance with the present disclosure. For example, the apparatus 10 illustrated in FIG. 1 according to the present disclosure may be applied to the area of neural stimulation. An initial source electric field 14 results in a current in the tissue. The electric field 14 is created by an electric source, current or voltage source. As described in further detail below, the permittivity of the tissue is altered relative to the electric field, for example by a mechanical field, thereby generating an additional displacement current.

**[0031]** Electrodes 12 are applied to the scalp and generate a low magnitude electric field 14 over a large brain region. While electrodes 12 are used and applied to the scalp in this exemplary embodiment, it is envisioned that the electrodes may be applied to a number of different areas on the body including areas around the scalp. It is also envisioned that one electrode may be placed proximal to the tissue being stimulated and the other distant, such as one electrode on the

scalp and one on the thorax. It is further envisioned that electric source could be mono-polar with just a single electrode, or multi-polar with multiple electrodes. Similarly, the electric source may be applied to tissue via any medically acceptable medium. It is also envisioned that means could be used where the electric source does not need to be in direct contact with the tissue, such as for example, inductive magnetic sources where the entire tissue region is placed within a large solenoid generating magnetic fields or near a coil generating magnetic fields, where the magnetic fields induce electric currents in the tissue.

**[0032]** The electric source may be direct current (DC) or alternating current (AC) and may be applied inside or outside the tissue of interest. Additionally, the source may be time varying. Similarly, the source may be pulsed and may be comprised of time varying pulse forms. The source may be an impulse. Also, the source according to the present disclosure may be intermittent.

**[0033]** A mechanical source such as an ultrasound source 16 is applied on the scalp and provides concentrated acoustic energy 18, i.e., mechanical field to a focused region of neural tissue, affecting a smaller number of neurons 22 than affected by the electric field 14, by the mechanical field 18 altering the tissue permittivity relative to the applied electric field 14, and thereby generating the altered current 20. The mechanical source may be any acoustic source such as an ultrasound device. Generally, such device may be a device composed of electromechanical transducers capable of converting an electrical signal to mechanical energy such as those containing piezoelectric materials, a device composed of electromechanical transducers capable of converting an electrical signal to mechanical energy such as those in an acoustic speaker that implement electromagnets, a device in which the mechanical source is coupled to a separate mechanical apparatus that drives the system, or any similar device capable of converting chemical, plasma, electrical, nuclear, or thermal energy to mechanical energy and generating a mechanical field.

**[0034]** Furthermore, the mechanical field could be generated via an ultrasound transducer that could be used for imaging tissue. The mechanical field may be coupled to tissue via a bridging medium, such as a container of saline to assist in the focusing or through gels and/or pastes which alter the acoustic impedance between the mechanical source and the tissue. The mechanical field may be time varying, pulsed, an impulse, or may be comprised of time varying pulse forms. It is envisioned that the mechanical source may be applied inside or outside of the tissue of interest. There are no limitations as to the frequencies that can be applied via the mechanical source, however, exemplary mechanical field frequencies range from the sub kHz to 1000s of MHz. Additionally, multiple transducers providing multiple mechanical fields with similar or differing frequencies, and/or similar or different mechanical field waveforms may be used—such as in an array of sources like those used in focused ultrasound arrays. Similarly, multiple varied electric fields could also be applied. The combined fields, electric and mechanical, may be controlled intermittently to cause specific patterns of spiking activity or alterations in neural excitability. For example, the device may produce a periodic signal at a fixed frequency, or high frequency signals at a pulsed frequency to cause stimulation at pulse frequencies shown to be effective in treating numerous pathologies. Such stimulation waveforms may be those implemented in rapid

or theta burst TMS treatments, deep brain stimulation treatments, epidural brain stimulation treatments, spinal cord stimulation treatments, or for peripheral electrical stimulation nerve treatments. The ultrasound source may be placed at any location relative to the electrode locations, i.e., within, on top of, below, or outside the same location as the electrodes as long as components of the electric field and mechanical field are in the same region. The locations of the sources should be relative to each other such that the fields intersect relative to the tissue and cells to be stimulated, or to direct the current alteration relative to the cellular components being stimulated.

**[0035]** The apparatus and method according to the present disclosure generates capacitive currents via permittivity alterations, which can be significant in magnitude, especially in the presence of low frequency applied electric fields. Tissue permittivities in biological tissues are much higher than most other non biological materials, especially for low frequency applied electric fields where the penetration depths of electric fields are highest. This is because the permittivity is inversely related to the frequency of the applied electric field, such that the tissue permittivity magnitude is higher with lower frequencies. For example, for electric field frequencies below 100,000 Hz, brain tissue has permittivity magnitudes as high as or greater than  $10^8$  (100,000,000) times the permittivity of free space ( $8.854 \times 10^{-12}$  farad per meter), and as such, minimal local perturbations of the relative magnitude can lead to significant displacement current generation. As the frequency of the electric field increases, the relative permittivity decreases by orders of magnitude, dropping to magnitudes of approximately  $10^3$  times the permittivity of free space ( $8.854 \times 10^{-12}$  farad per meter) for electric field frequencies of approximately 100,000 Hz. Additionally, by not being constrained to higher electric field frequencies, the method according to the present disclosure is an advantageous method for stimulating biological tissue due to lowered penetration depth limitations and thus lowered field strength requirements. Additionally, because displacement currents are generated in the area of the permittivity change, focusing can be accomplished via the ultrasound alone. For example, to generate capacitive currents via a permittivity perturbation relative to an applied electric field as described above, broad DC or a low frequency electric source field well below the cellular stimulation threshold is applied to a brain region but stimulation effects are locally focused in a smaller region by altering the tissue permittivity in the focused region of a mechanical field generated by a mechanical source such as an ultrasound source. This could be done noninvasively with the electrodes and the ultrasound device both placed on the scalp surface such that the fields penetrate the tissue surrounding the brain region and intersect in the targeted brain location, or with one or both of the electrodes and/or the ultrasound device implanted below the scalp surface (in the brain or any of the surrounding tissue) such that the fields intersect in the targeted region.

**[0036]** A displacement current is generated by the modification of the permittivity in the presence of the sub threshold electric field and provides a stimulatory signal. In addition to the main permittivity change that occurs in the tissues, which is responsible for stimulation (i.e., the generation of the altered currents for stimulation), a conductivity change could also occur in the tissue, which secondarily alters the ohmic component of the currents. In a further

embodiment, the displacement current generation and altered ohmic current components may combine for stimulation. Generally, tissue conductivities vary slightly as a function of the applied electric field frequency over the DC to 100,000 Hz frequency range, but not to the same degree as the permittivities, and increase with the increasing frequency of the applied electric field. Additionally in biological tissues, unlike other materials, the conductivity and permittivity do not show a simple one-to-one relationship as a function of the applied electric field frequency. The permittivity ranges are as discussed above.

**[0037]** Although the process described may be accomplished at any frequency of the applied electric field, the method in an exemplary embodiment is applied with lower frequency applied electric fields due to the fact the permittivity magnitudes of tissues, as high as or greater than  $10^8$  times the permittivity of free space, and the electric field penetration depths are highest for low frequency applied electric fields. Higher frequency applied electric fields may be less desirable as they will require greater radiation power to penetrate the tissue and/or a more pronounced mechanical source for permittivity alteration to achieve the same relative tissue permittivity change, i.e., at higher applied electric field frequencies the permittivity of the tissue is lower and as such would need a greater overall perturbation to have the same overall change in permittivity of a tissue as at a lower frequency. Applied electric field frequencies in the range of DC to approximately 100,000 Hz frequencies are advantageous due to the high tissue permittivity in this frequency band and the high penetration depth for biological tissues at these frequencies. In this band, tissues are within the so called 'alpha dispersion band' where relative tissue permittivity magnitudes are maximally elevated (i.e., as high as or greater than  $10^8$  times the permittivity of free space). Frequencies above approximately 100,000 to 1,000,000 Hz for the applied electric fields are still applicable for the method described in generating displacement currents for the stimulation of biologic cells and tissue, however, both the tissue permittivity and penetration depth are limited for biological tissues in this band compared to the previous band but displacement currents of sufficient magnitude can still be generated for some applications. In this range, the magnitude of the applied electric field will likely need to be increased, or the method used to alter the permittivity relative to the applied electric field increased to bring about a greater permittivity change, relative to the tissue's permittivity magnitude for the applied electric field frequency. Additionally, due to potential safety concerns for some applications, it may be necessary to limit the time of application of the fields or to pulse the fields, as opposed to the continuous application that is possible in the prior band. For tissues or applications where the safety concerns preclude the technique in deeper tissues, the technique could still be applied in more superficial applications in a noninvasive manner or via an invasive method. Higher frequency applied electric fields, above 1,000,000 to 100,000,000 Hz, could be used in generating displacement currents for the stimulation of biologic cells and tissue. However, this would require a more sufficient permittivity alteration or electromagnetic radiation, and as such is less than ideal in terms of safety than the earlier bands. For frequencies of the applied electric field above 100,000,000 Hz, biologic cell and tissue

stimulation may still be possible, but may be limited for specialized applications that require less significant displacement currents.

**[0038]** The focus of the electric and mechanical fields to generate an altered current according to the present disclosure may be directed to various structures within the brain or nervous system including but not limited to dorsal lateral prefrontal cortex, any component of the basal ganglia, nucleus accumbens, gastric nuclei, brainstem, thalamus, inferior colliculus, superior colliculus, periaqueductal gray, primary motor cortex, supplementary motor cortex, occipital lobe, Brodmann areas 1-48, primary sensory cortex, primary visual cortex, primary auditory cortex, amygdala, hippocampus, cochlea, cranial nerves, cerebellum, frontal lobe, occipital lobe, temporal lobe, parietal lobe, sub-cortical structures, spinal cord, nerve roots, sensory organs, and peripheral nerves.

**[0039]** The focused tissue may be selected such that a wide variety of pathologies may be treated. Such pathologies that may be treated include but are not limited to Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Alzheimer's Disease, Dystonia, Tics, Spinal Cord Injury, Traumatic Brain Injury, Drug Craving, Food Craving, Alcohol Craving, Nicotine Craving, Stuttering, Tinnitus, Spasticity, Parkinson's Disease, Parkinsonianism, Obsessions, Depression, Schizophrenia, Bipolar Disorder, Acute Mania, Catonia, Post-Traumatic Stress Disorder, Autism, Chronic Pain Syndrome, Phantom Limb Pain, Epilepsy, Stroke, Auditory Hallucinations, Movement Disorders, Neurodegenerative Disorders, Pain Disorders, Metabolic Disorders, Addictive Disorders, Psychiatric Disorders, Traumatic Nerve Injury, and Sensory Disorders. Furthermore, electric and mechanical fields to generate an altered current may be focused on specific brain or neural structures to enact procedures including sensory augmentation, sensory alteration, anesthesia induction and maintenance, brain mapping, epileptic mapping, neural atrophy reduction, neuroprosthetic interaction or control with nervous system, stroke and traumatic injury neurorehabilitation, bladder control, assisting breathing, cardiac pacing, muscle stimulation, and treatment of pain syndromes, such as those caused by migraine, neuropathies, and low-back pain; or internal visceral diseases, such as chronic pancreatitis or cancer.

**[0040]** In the focused region of tissue to which the mechanical fields are delivered, the excitability of individual neurons can be heightened to the point that the neurons can be stimulated by the combined fields, or be affected such as to cause or amplify the alteration of the neural excitability caused by the altered currents, either through an increase or decrease in the excitability of the neurons. This alteration of neural excitability can last past the duration of stimulation and thus be used as a basis to provide lasting treatment. Additionally, the combined fields can be provided in multiple, but separate sessions to have a summed, or carry-over effect, on the excitability of the cells and tissue. The combined fields can be provided prior to another form of stimulation, to prime the tissue making it more or less susceptible to alternate, follow-up forms of stimulation. Furthermore, the combined fields can be provided after an alternate form of stimulation, where the alternate form of stimulation is used to prime the tissue to make it more or less susceptible to the form of stimulation disclosed herein. Furthermore, the combined fields could be applied for a chronic period of time.

**[0041]** FIG. 2 illustrates a set up **30** to perform a method for generating an altered current with a newly generated displacement current **32** for stimulation in biologic tissue **34** through the combined effects of an electric field **36** and a mechanical field **38**. A tissue or composite of tissues **34** is placed adjacent to the anode and cathode of an electric source **40** which generates an electric field **36**. The electric field **36** is combined with a mechanical, e.g., ultrasound field **38** which can be focused on the tissue **34** and generated via an ultrasound transducer **42**. In a sub-region of tissue **44** where the mechanical field **38** is focused and intersects with the electric field **36**, a displacement current **32** is generated. By vibrating and/or mechanically perturbing the sub-region of tissue **44**, the permittivity of the tissue **44** can be altered relative to the applied electric field **36** to generate a displacement current **32** in addition to the current that would be present due to the source electric field **36** and altered due to conductivity changes in the tissue caused by the mechanical perturbation.

**[0042]** By providing the mechanical field **38** to the sub region of tissue **44**, the permittivity can be altered within the electric field **36** by either new elements of the sub region of tissue **44** vibrating in and out of the electric field such that the continuum permittivity of the tissue is changed relative to the electric field **36**, or that the bulk properties of the sub region of tissue **44** and the permittivity, or tissue capacitance, change due to the mechanical perturbation. An example of altering the permittivity within the electric field can occur when a cell membrane and extra-cellular fluid, both of different permittivities, are altered in position relative to the electric field by the mechanical field. This movement of tissues of different permittivity relative to the electric field will generate a new displacement current. The tissues could have permittivity values as high as or greater than  $10^8$  times the permittivity of free space, differ by orders of magnitude, and/or have anisotropic properties such that the tissue itself demonstrates a different permittivity magnitude depending on the relative direction of the applied electric field. An example of altering permittivity of the bulk tissue occurs where the relative permittivity constant of the bulk tissue is directly altered by mechanical perturbation in the presence of an electric field. The mechanical source, i.e., ultrasound source may be placed at any location relative to the electrode locations, i.e., within or outside the same location as the electrodes, as long as components of the electric field and mechanical field are in the same region.

**[0043]** Tissue permittivities can be altered relative to the applied electric fields via a number of methods. Mechanical techniques can be used to either alter the bulk tissue permittivity relative to an applied electric field or move tissue components of differing permittivities relative to an applied electric field. There are no specific limitations to the frequency of the mechanical field that is applied as previously discussed, however, exemplary frequencies range from the sub kHz to 1000s of MHz. A second electromagnetic field could be applied to the tissue, at a different frequency than the initial frequency of the applied electromagnetic field, such that it alters the tissue permittivity at the frequency dependent point of the initially applied electric field. An optical signal could also be focused on the tissues to alter the permittivity of the tissue relative to an applied electric field. A chemical agent or thermal field could also be applied to the tissues to alter the permittivity of the tissue relative to an applied electric field. These methods could also be used in

combination to alter the tissue permittivity relative to an applied electric field via invasive or noninvasive methods.

**[0044]** For example, FIG. 3 shows a set up 50 for generating an altered current with a newly generated displacement current 52 through the combined effects of an electric field 54 and a chemical agent 56. A tissue or composite of tissues 58 is placed within an electric source 60 which generates an electric field 54 and combined with chemical source 62 which releases a chemical agent 56 that can be focused on the tissue 58. In the area that the chemical agent 56 is released in the tissue 64, the electric field 54 transects the sub region of tissue 64, and the chemical agent 56 reacts with the sub region of tissue 64 to alter the tissue's relative permittivity relative to the applied electric field 54. This generates a displacement current 52 in addition to the current that would be present due to the source electric field 54. The chemical agent 56 may be any agent which can react with the tissue or cellular components of the tissue 64 to alter its permittivity relative to the electric field 54. This may be by a thermoreactive process to raise or lower the tissue 64 temperature or through a chemical reaction which alters the distribution of ions in the cellular and extra-cellular media, for instance, along ionic double layers at cell walls in the tissue 64. Similarly, the conformation of proteins and other charged components within the tissue 64 could be altered such that the permittivity of the tissue is altered relative to the low frequency electric field 54. The agent could also be any agent that adapts the permanent dipole moments of any molecules or compounds in the tissue 64, temporarily or permanently relative to the low frequency electric field 54. The chemical reaction driven by the chemical agent 56 must work rapidly enough such that the permittivity of the tissue is quickly altered in the presence of the electric field 54 in order to generate the displacement current 52. The reaction may also be such as to fluctuate the permittivity, such that as the permittivity continues to change displacement currents continue to be generated. In addition to the main permittivity change that occurs in the tissues, a conductivity change could also occur in the tissue, which secondarily alters the ohmic component of the currents. A biological agent may be used in place of, or in addition to, the chemical agent 56. This embodiment may have particular application for focused drug delivery where an additional chemical or biological agent is included to assist in therapy of the tissue, or where the altered current could drive an additional electrochemical reaction for therapy. For example, this could be used in areas such as focused gene therapy or focused chemotherapy.

**[0045]** Another example is shown in FIG. 4, which illustrates a set up 70 for applying a method for generating an altered current with a newly generated displacement current 72 through the combined effects of a low frequency electric field 74 and an electromagnetic radiation field 76. A tissue or composite of tissues 78 is placed within a low frequency electric field 74 which is generated by an electric source 80 and combined with radiation source 82 which generates a radiation field 76 that can be focused on the tissue 78. In the area that the radiation field 76 is focused in the tissue 78, the electric field 74 transects the sub component of tissue 84, where the radiation field 76 interacts with the sub component of tissue 84 to alter the tissue's relative permittivity relative to the applied electric field 74, and as such generates a displacement current 72 in addition to the current that would be present due to the source electric field 74 or the

radiation source field 76 alone. The electromagnetic radiation field 76 could, for example, interact with the tissue 84 by altering its temperature through ohmic processes, alter the distribution of ions in the cellular and extra-cellular media for instance along ionic double layers along cell walls through the electric forces acting on the ions, or alter the conformation of proteins and other charged components within the tissue through the electric forces such that the permittivity of the tissue is altered relative to the low frequency electric field 74. Furthermore, the electromagnetic field 76, could interact with the tissue 84 by moving components of the tissue via electrorestrictive forces, as would be seen in anisotropic tissues, to alter the continuum permittivity of the tissue relative to the low frequency electric field 74. In addition to the main permittivity change that occurs in the tissues, a conductivity change could also occur in the tissue, which secondarily alters the ohmic component of the currents.

**[0046]** FIG. 5 shows a set up 90 for applying a method for generating an altered current with a newly generated displacement current 92 through the combined effects of an electric field 94 and an optical beam 96. A tissue or composite of tissues 98 is placed within electric field 94 generated by an electric source 100 and combined with optical source 102 which generates optical beam 96 that can be focused on the tissue 98. In the area that the optical beam 96 is focused on the tissue, the electric field 94 transects the sub component of tissue 104, where the optical beam 96 reacts with the tissue to alter the tissue's relative permittivity relative to the applied electric field 94, and as such generates a displacement current 92 in addition to the current that would be present due to the source electric field 94. The optical beam 96 could, for example, interact with the tissue by altering its temperature through photothermal effects and/or particle excitation, alter the distribution of ions in the cellular and extra-cellular media for instance along ionic double layers along cell walls by exciting the movement of ions optically, ionizing the tissue via laser tissue-interactions, or alter the conformation of proteins and other charged components within the tissue such that the permittivity of the tissue is altered relative to the low frequency electric field 94. In addition to the main permittivity change that occurs in the tissues, a conductivity change could also occur in the tissue, which secondarily alters the ohmic component of the currents.

**[0047]** In another embodiment, a thermal source to alter the permittivity of the tissue may be used. In such embodiments, a thermal source such as a heating probe, a cooling probe, or a hybrid probe may be placed external or internal to the tissue to be stimulated. A thermal source may alter the permittivity of the tissue through the direct permittivity dependence of tissue temperature, mechanical expansion of tissues in response to temperature changes, or by mechanical forces that arise due to altered particle and ionic agitation in response to the temperature alteration such that permittivity of the tissue is altered relative to an applied electric field. In addition to the main permittivity change that occurs in the tissues, a conductivity change could also occur in the tissue, which secondarily alters the ohmic component of the currents. This embodiment may be useful for stimulation in the presence of an acute injury to the tissue where the thermal source could be used to additionally assist in the treatment of the tissue injury, for example with a traumatic brain injury or an infarct in any organ such as the heart. The tissue could

be cooled or heated at the same time stimulation is provided to reduce the impact of an injury.

**[0048]** In a further embodiment, the method according to the present disclosure is applied in the area of muscular stimulation, where amplified, focused, direction altered, and/or attenuated currents could be used to alter muscular activity via direct stimulation, depolarizing muscular cells, hyperpolarizing muscular cells, modifying membrane potentials, and/or increasing or decreasing the excitability of the muscle cells. This alteration of excitability or firing patterns can last past the duration of stimulation and thus be used as a basis to provide lasting treatment. Additionally, the stimulation can be provided in multiple, but separate sessions to have a summed, or carry-over effect, on the excitability of cells and tissue. Additionally, the stimulation could be provided to prime the tissue by adjusting the muscle cell excitability to make it more or less susceptible to alternate follow up forms of stimulation. The stimulation could be used after another form of stimulation was used to prime the tissue. Furthermore, the stimulation could be applied for a chronic period of time. This embodiment may be useful for altering or assisting cardiac pacing or function, assisted breathing, muscle stimulation for rehabilitation, muscle stimulation in the presence of nerve or spinal cord injury to prevent atrophy or assist in movement, or as substitution for physical exercise.

**[0049]** In yet another embodiment, the method according to the present disclosure can be applied the area of physical therapy, where amplified, focused, direction altered, and/or attenuated currents could be used to stimulate blood flow, increase or alter neuromuscular response, limit inflammation, speed the break down of scar tissue, and speed rehabilitation by applying the focus of the current generation to the effected region in need of physical therapy. It is envisioned that the method according to the present disclosure may have a wide variety in the area of physical therapy including the treatment or rehabilitation of traumatic injuries, sports injuries, surgical rehabilitation, occupational therapy, and assisted rehabilitation following neural or muscular injury. For instance, following an injury to a joint or muscle, there is often increased inflammation and scar tissue in the region and decreased neural and muscular response. Typically, ultrasound is provided to the affected region to increase blood flow to the region and increase the metabolic re-absorption of the scar tissue while electrical stimulation is provided separately to the nerves and muscles; however, by providing them together, a person could receive the benefit of each individual effect, but additionally amplified stimulatory and metabolic effects through the altered currents. The other methods for generating altered currents discussed within could also be used to assist in physical therapy via the displacement currents that are generated.

**[0050]** Furthermore, the method according to the present disclosure may be applied to the area of cellular metabolism, where currents could be used to interact with electrically receptive cells or charged membranes to alter the tissue or cellular dynamics. It is envisioned that this embodiment could provide treatment for various diseases where electri-

cally receptive cells respond to the newly generated displacement currents and altered current distribution.

**[0051]** Furthermore, the method according to the present disclosure may be applied to the area of gene therapy. Amplified, focused, direction altered, and/or attenuated currents could be used to interact with electrically receptive cells or receptors within the cell to influence protein transcription processes and alter the genetic content of the cells. The altered current densities in the tissue can interact with the tissue to stimulate this altered gene regulation. Additionally, the displacement currents generated by the method could further be used to assist in drug delivery and/or gene therapy through the altered current influence on the delivery of agents.

**[0052]** While the inventions have been illustrated and described in detail in the drawings and foregoing description, the same is to be considered as illustrative and not restrictive in character, it being understood that embodiments have been shown and described and that all changes and modifications that come within the spirit of these inventions are desired to be protected.

1.-55. (canceled)

**56.** A method for treating an ailment of a subject, the method comprising:

non-invasively providing electrical energy transcranially to a region of tissue of the subject, wherein the electrical energy is provided by one or more electrodes operably applied to a head of the subject; and injecting a chemical agent into a sub-region of tissue of the subject, wherein the combined effect provides a treatment that affects the ailment of the subject.

**57.** The method according to claim 56, wherein the ailment is a movement disorder.

**58.** The method according to claim 56, wherein the electrical energy is direct current (DC) electrical energy.

**59.** The method according to claim 56, wherein the electrical energy is non-invasively and transcranially applied to a motor cortex of the subject.

**60.** The method according to claim 56, wherein the electric energy is an electric field.

**61.** The method according to claim 60, wherein the electric field is pulsed.

**62.** The method according to claim 60, wherein the electric field is time varying.

**63.** The method according to claim 60, wherein the electric field is pulsed a plurality of times, and each pulse may be for a different length of time.

**64.** The method according to claim 60, wherein the electric field is time invariant.

**65.** The method according to claim 56, wherein injecting the chemical agent is via a syringe.

**66.** The method according to claim 56, wherein the electrical energy and the chemical agent are provided simultaneously.

**67.** The method according to claim 56, wherein the electrical energy and the chemical agent are provided sequentially.

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