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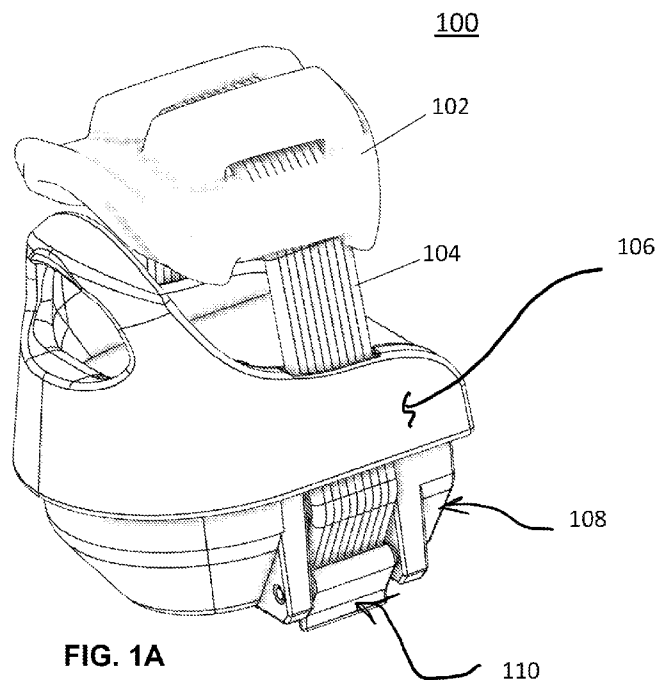


FIG. 1A

(57) Abstract: The present embodiments relate generally to therapeutic techniques and more particularly to effective treatment of neurological disorders using noninvasive methods and apparatuses. Some embodiments relate to more effective vibrotactile stimulation, i.e., stronger physiological effects with less vibration power/amplitude, by means of a vibrotactile mechanical stimulator (tactor).

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METHODS AND APPARATUSES FOR NON-INVASIVE TREATMENT OF NERVOUS SYSTEM DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to United States Provisional Application No. 63/595,598, United States Provisional Application No. 63/595,630, United States Provisional Application No. 63/595,675, United States Provisional Application No. 63/595,643, United States Provisional Application No. 63/595,664, United States Provisional Application No. 63/595,684, United States Provisional Application No. 63/595,696, and United States Provisional Application No. 63/595,701, all filed November 2, 2023, the contents of which are all incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0002] The present embodiments relate generally to therapeutic techniques and more particularly to effective treatment of neurological disorders using noninvasive methods and apparatuses.

BACKGROUND

[0003] Pharmacological and surgical treatments of Parkinsons disease (PD) may be limited because of side effects and reduced therapeutic efficacy. Vibrotactile Coordinated Reset (vCR) stimulation was designed as an alternative or additional treatment for PD and other brain disorders characterized by abnormally synchronized neuronal activity. Specifically, vCR delivered to the patients fingertips was developed to provide a non-invasive alternative to deep brain stimulation (DBS) for PD therapy.

[0004] A goal of vCR stimulation is to make neuronal populations unlearn abnormal synaptic connectivity patterns, in this way inducing long-lasting desynchronization of disease-related neuronal synchrony and, in turn, cause long-lasting and sustained relief. To this end, vibrotactile stimuli are delivered in a spatio-temporally patterned manner, e.g., to the fingertips to disrupt abnormal neuronal synchrony.

[0005] However, while pilot studies revealed encouraging effects of vCR [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinsons Disease. *Frontiers in Physiology* 12:624317 (2021)], there are still significant limitations, as set forth below.

[0006] Slow washin and long stimulation sessions: It takes therapeutic effects a long time, i.e., weeks and months, to build up. Furthermore, during this build-up phase, long stimulation duration, e.g., in total 4 hours daily, are required. Consequently, not all patients are willing and/or able and/or patient enough to be so compliant.

[0007] Limited spatial selectivity: By design, CR stimulation requires sequential stimulation of spatially separate neuronal subpopulations. Larger spatial overlaps of the stimulated subpopulations typically reduce the amount of the stimulation effects. In fact, stimulation effects may even completely vanish for sufficiently large overlaps [B. Lysyansky, O.P. Popovych, P.A. Tass: Desynchronizing antiresonance effect of the m : n ON-OFF coordinated reset stimulation. *Journal of Neural Engineering* 8, 036019 (2011); P.A. Tass, L. Qin, C. Hauptmann, S. Dovero, E. Bezard, T. Boraud, W.G. Meissner: Coordinated reset has sustained after-effects in Parkinsonian monkeys. *Annals of Neurology* 72, 816-820 (2012)]. This is particularly relevant in the context of vibrotactile stimulation because vibratory bursts, i.e., vibratory perpendicular skin displacements, cause mechanical skin waves which propagate like a shear wave [J.M. Pereira, J.M. Mansour, B.R. Davis: Analysis of shear wave propagation in skin; application to an experimental procedure. *J. Biomechanics* 23(8) (1990) 745-751]. For instance, when touching objects, mechanical waves propagate from the fingertips throughout the entire hand, so that vibration signals at remote skin locations can contain information to distinguish between different objects [Y. Shao, V. Hayward, Y. Visell: Spatial patterns of cutaneous vibration during whole-hand haptic interactions. *PNAS* 113(15) (2016) 4188-4193]. As a consequence of the propagating waves, not only mechanoreceptors directly underneath the moving contactor surface of the mechanical stimulator receive stimulation, but also mechanoreceptors in remote skin locations that get activated by the spreading vibratory wave. This may jeopardize spatially selective stimulation as required for CR stimulation.

[0008] Individual variations require personalization: Several patient-related parameters vary between patients as well as within patients in the course of the treatment. For instance, skin thickness, skin elasticity, skin viscosity, characteristics of the subcutaneous tissue are individual characteristics of every single patient that may vary with, e.g., age, gender, skin type, pigmentation, and smoking habits. In addition, PD patients do not only suffer from motor impairments, but also from sensory impairments as well as an impairment of sensorimotor integration (i.e., the matching of motor and sensory commands in the brain). For instance, receptive field sizes are enlarged in PD patients, impairing the proprioceptive input from the skin and rendering it significantly more coarse-grained than in healthy controls [Conte A, Khan N, Defazio G, Rothwell JC, Berardelli A.: Pathophysiology of somatosensory abnormalities in Parkinsons disease. *Nature Reviews Neurology* (2013) pp. 9:687-97.]. These individual characteristics impact the skin vibrations evoked by the contactor of the mechanical stimulator, the propagation of the resulting vibratory waves as well as their neuronal processing. Accordingly, stimulation should account for and be adapted to these characteristics in a personalized manner. However, in the vCR pilot studies performed so far, PD patients were typically stimulated with identical parameter sets, i.e., in a onesize-fits-all approach [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinsons Disease. *Frontiers in Physiology* 12:624317 (2021)].

[0009] Fixation for fingertip stimulation: In the pilot studies performed so far [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinsons Disease. *Frontiers in Physiology* 12:624317 (2021)], the mechanical stimulator was attached to fingertips by means of Velcro. However, this fixation means turned out to be insufficient as different positions of the hand, e.g., palm facing upwards vs. downwards vs. positions in between, led to markedly different contact pressure. Accordingly, while using the same technical stimulation parameters, especially the identical vibration amplitude, the time-varying hand position leads to time-varying effective stimulation, in particular, time-varying stimulation strength. Hence the conditions under which stimulation is

applied are not sufficiently controlled. Consequently, stimulation may be rendered less effective due to reduced contact pressure and, hence, sub-optimally weak stimulation strength during relevant portions of the stimulation sessions.

[0010] Annoying noise: Mechanical devices delivering vibrotactile stimulation to the skin, e.g., linear motors or Piezo actuators, typically produce airborne sound (if not ideally shielded) not only the desired skin stimulation. In addition, when vibrotactile stimulation is delivered to the skin of the head, for instance, for the treatment of migraine, tinnitus or movement disorders, the stimulated subject typically hears the stimulation mediated by air conduction (from nearby stimulators) as well as bone conduction. Stimulation-associated sound may disturb patients, specifically when applied to the head of a subject, in this way compromising their compliance. Hence, vibratory stimulation should be effective at low noise levels.

[0011] It is against this technological backdrop that the present Applicant sought a technological solution to these and other problems rooted in this technology.

SUMMARY

[0012] The present embodiments relate generally to therapeutic techniques and more particularly to effective treatment of neurological and psychiatric disorders using noninvasive methods and apparatuses.

[0013] Some embodiments relate to more effective vibrotactile stimulation, i.e., stronger physiological effects with less vibration power/amplitude, by means of a vibrotactile mechanical stimulator (tactor), comprising a combination of one or more elements among: (i) Shock absorber: The oscillating mass is coupled to the housing by a spring serving as shock absorber to effectively reduce the vibration of the tactor housing. (ii) Nondisc contactor: To increase the physiological/medical effects of vibrotactile stimuli, a physiologically more effective contactor shape. (iii) Wavebreaking hole: As additional feature (in one possible embodiment), a wavebreaker type (non-annular) perimeter around the hole further reduces the spread of surface waves in the free surround of the contactor. By means of a specific fingertip fixation enabling the tactor housing to be mounted to fingertips of different size, the simulator

can be used in cases ranging from small to large fingertips, with hardly changing contact pressure.

[0014] A factor of some embodiments enables physiologically more effective vibratory stimulation at considerably lower vibration amplitudes and, hence, significantly reduced noise levels. When mounted to fingertips through the specific fingertip fixation, vibrations of the housing of the factor are considerably reduced so that, in turn, the propagation of skin vibration waves is significantly reduced. The wave-breaking hole additionally reduces the wave propagation.

[0015] Some embodiments relate to enabling more effective non-invasive stimulation, by realizing a 3-(physiological) channel electrotactile stimulation of just one part of the skin, for example, one fingertip. Stimulation can easily be applied, e.g., at night in a convenient manner. A 3-channel electrotactile stimulation of embodiments achieves physiologically more effective non-invasive stimulation with considerably lower battery requirements and no noise. Stimulation can be delivered through only one stimulation site, e.g., one fingertip. Other embodiments can use more than one stimulation sites, e.g., two or more fingertips. This can be done in early stages of the therapy, whereas later on single-site therapy can be used as maintenance therapy.

[0016] Some embodiments relate to enabling more effective non-invasive stimulation using vibrotactile and electrotactile fingertip stimulation. According to certain general aspects, the present embodiments effectively reduce unwanted mechanical and proprioceptive stimulation while securely mounting controller and battery for a fingertip stimulation array. The present embodiments allow for vibrotactile and/or electrotactile and/or electrical and/or infrared fingertip stimulation with minimal amount of artificial hand stimulation. Furthermore, the present embodiments enable reduction of moisture buildup, discomfort, e.g., caused by friction. In addition, embodiments enable a safe connection between a low weight controller and the fingertip stimulators. Continuous physiological input to the non-covered skin of the hand enables sensory input that enhances favorable plasticity mechanisms and, hence, therapeutic effects.

[0017] Some embodiments relate to enabling more effective non-invasive stimulation, by combining vibrotactile and electrotactile stimulation. On the one hand, the combination

enables to achieve a sufficient electrode-skin contact. On the other hand, the combined stimulation enables using different physiological channels (per stimulation site), utilizing different mechanoreceptor channels, to achieve significantly stronger and more effective stimulation at lower amplitudes of the vibrotactile stimulation. The hybrid stimulation of embodiments achieves physiologically more effective non-invasive stimulation at considerably lower vibration amplitudes and, hence, significantly reduced noise levels. In addition, the combination of vibrotactile and electrotactile stimulation modalities, realizes a considerably larger inventory of effective stimuli. This increases therapeutic efficacy and counteracts habituation effects.

[0018] Some embodiments relate to methods and apparatuses that use compound pulses and/or continuous stimulation with modulated amplitudes. For example, instead of pulses that are circumscribed in time, various embodiments include a device that delivers continuous stimulation with specifically modulated vibration amplitudes. One compound pulse can contain more than only one supra-threshold part. These stimuli enable spatially more focal and/or shorter activation. In addition, shorter stimuli enable greater temporal jitter of stimulus onsets (as explained below). This is one aspect of embodiments, in addition to the remarkably precise Bluetooth connection between both controllers.

[0019] Some embodiments relate to or include personalization/calibration. For example, pedestals are adapted to the patient's vibratory threshold and, hence, reflect a fundamental parameter of the patient's sensory information processing. The vibratory threshold varies between patients. They may also vary within patients in the course of the treatment. This can be a consequence of the design of the compound pulses.

[0020] Some embodiments employ temporal jitter of stimulus onsets and/or temporal jitter of suprathreshold vibration amplitudes and/or temporal jitter of vibratory burst durations and/or subthreshold vibration amplitude and/or vibration frequency. In these and other embodiments, the compound pulses enable shorter vibratory pulse and, in turn, greater temporal jitter of stimulus onsets. In particular, in combination with amplitude randomization and/or vibratory burst randomization this may cause a further increase of the stimulation efficacy. In general, variation/jitter/randomization of more than one quantity may increase the stimulation

effect. In one embodiment, the variations of the different quantities are not correlated. In another embodiment, the variation of two or more quantities may be correlated.

[0021] Another embodiment uses methods to prevent in-channel masking effects. For example, to avoid mutual masking effects and habituation, the interval between any two subsequent vibrotactile stimuli, specifically vibratory bursts, delivered to the same stimulation channel (i.e., “in-channel”) should optimally amount to 3-5 times the vibrotactile stimulus’ duration. Compound stimuli enable to increase the temporal jitter of the stimulus onsets. However, to further increase the extent of temporal jitters not inducing in-channel masking effects, embodiments use specific methods to adapt stimulus parameters and stimulation patterns.

[0022] Some embodiments relate to specific hard- and firmware apparatuses as well as stimulation methods to overcome the limitations mentioned above, among others. Embodiments enable considerably more precise vibrotactile and/or electrotactile stimulation, i.e., stronger physiological effects with less vibration power/amplitude, by avoiding interhemispheric inhibition by delivering wireless multisite stimulation to remote and/or bilateral stimulation sites at highest temporal precision. Some embodiments provide for specific pairing of stimulus activations (i.e., varying and/or nonmirror-pairing) in case of bilateral stimulation. A wireless synchronization mechanism of embodiments can be applied to a large class of applications, including but not limited to, e.g., noninvasive stimulation in a general sense, e.g., vibrotactile and/or electrotactile stimulation of different body parts together with visual and/or auditory and/or olfactory stimulation, with all or at least some of these devices being wirelessly connected. In addition, embodiments enable connection of such devices with invasive devices such as deep brain stimulators and/or spinal cord stimulators and/or epicortical stimulators etc.

[0023] Some embodiments relate to a method and device that delivers non-invasive, in particular, sensory stimulation treatment in a way that counteracts habituation, e.g., by increasing and rewarding patients’ attention, alertness, curiosity level and activating additional brain areas besides primary sensory brain areas. In this way the present embodiments counteract habituation and increases the therapeutic effects, e.g., by boosting the propagation of desynchronizing effects through disease-related brain circuits.

[0024] Some embodiments relate to methods and apparatuses for automatically/autonomously calibrating relevant stimulation parameters for non-invasive and invasive multichannel CR stimulation and related stimulation techniques, random reset stimulation as well as combinations thereof. Several embodiments use vibrotactile and/or electrotactile stimulation.

[0025] The present embodiments can potentially be applied to a wide range of disorders. Abnormal neuronal synchronization and abnormal synaptic connectivity patterns are not only found in Parkinsons disease, but are also characteristic of a larger number of disorders of the central and peripheral nervous system, for instance, movement disorders, essential tremor, tic disorders, Tourette's syndrome, tremor in multiple sclerosis, dystonia, chronic stroke, epilepsy, depression, migraine, tension headache, spasticity, incomplete spinal cord injury, obsessive/compulsive disorder, attention deficit hyperactivity disorder (ADHD), irritable bowel syndrome, chronic pain syndromes, e.g., complex regional pain syndrome, neuropathic pain and trigeminal neuralgia, pelvic health disorders, e.g., pelvic pain or overactive bladder, tinnitus, dissociation in borderline personality disorder and post-traumatic stress disorder.

BRIEF DESCRIPTION OF DRAWINGS

[0026] FIGs. 1A and 1B illustrate an example tapper assembly according to embodiments in unexploded and exploded format, respectively.

[0027] FIG. 2 illustrates one potential version of a vibration motion generating device according to embodiments.

[0028] FIG. 3 is an exploded view of an example motor assembly according to embodiments.

[0029] FIG. 4 illustrates aspects of how a contactor according to embodiments is allowed to touch the finger surface very consistently no matter what skin profile is presented from the tapper housing.

[0030] FIG. 5 provides an overall view of an example tapper assembly view showing the device and the connecting cable.

[0031] FIG. 6 shows an example Large Finger insertion according to embodiments.

- [0032] FIGs. 7A to 7C illustrate an example of how a large finger is inserted, and the strap ends are tightened and latched in place with the star levers according to embodiments.
- [0033] FIGs. 8A and 8B illustrate an example Small Finger insertion according to embodiments.
- [0034] FIGs. 9A to 9C further illustrate an example Small Finger Insertion of embodiments.
- [0035] FIGs. 10A and 10B show an example of star Levers in open position, and latched in closed position, respectively.
- [0036] FIG. 11 illustrates an example Octaberry Contactor according to embodiments.
- [0037] FIG. 12 illustrates many possible shapes of contactors and surround shapes according to embodiments.
- [0038] FIG. 13 illustrates an example of different contactor and surround shapes according to embodiments.
- [0039] FIG. 14 illustrates another example of different contactor and surround shapes according to embodiments.
- [0040] FIG. 15 illustrates an example embodiment with two different pairs of contactors.
- [0041] FIG. 16 illustrates an example of a pressure sensor according to embodiments.
- [0042] FIG. 17 is a contactor ground view of an octaberry according to embodiments.
- [0043] FIG. 18 is a graph which shows $f(\beta)$ vs. β , where $\beta = R_i/R$. R_i denotes the radius of the hole, and $2R$ is the length of each side of the octagon according to embodiments.
- [0044] FIG. 19 is a graph illustrating how the total circumference scales with β according to embodiments.
- [0045] FIGs. 20-22 show examples of the ground view of contactor embodiments.
- [0046] FIG. 23 is a schematic illustration of an example contactor for 3-channel electrotactile stimulation according to embodiments.
- [0047] FIG. 24 is a schematic illustration of an example contactor for double 3-channel electrotactile stimulation according to embodiments.
- [0048] FIG. 25 illustrates an example fingertip pulse oximeter according to embodiments.

[0049] FIG. 26 is a schematic showing the cross section of upper ('1') and lower ('2') part of an example pulse oximeter-type housing of a 3-channel electrotactile single-finger stimulator according to embodiments.

[0050] FIG. 27 is a schematic illustrating an example zero-baseline monophasic pulse form with non-vanishing net dc current with amplitude I_E and duration T_E according to embodiments.

[0051] FIG. 28 is a schematic illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in an embodiment.

[0052] FIG. 29 is a schematic illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in an embodiment.

[0053] FIG. 30 is a schematic illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in an embodiment.

[0054] FIG. 31 is a schematic illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in an embodiment.

[0055] FIG. 32 is a schematic illustrating an example asymmetric balanced biphasic waveform with vanishing baseline and zero average current as used in an embodiment.

[0056] FIG. 33 is a schematic illustration of an example 3:2 ON-OFF CR RVS (rapidly varying sequences) stimulation with electrotactile stimulation according to embodiments.

[0057] FIG. 34 is a top view of an example controller with fixation band according to embodiments.

[0058] FIG. 35 is a top view of another example controller with fixation band according to embodiments.

[0059] FIG. 36 is a top view of another example controller with fixation band according to embodiments.

[0060] FIG. 37 is a bottom view of an example fixation band according to embodiments.

[0061] FIG. 38 is a bottom view of another example fixation band according to embodiments.

[0062] FIG. 39 is a side view of an example fixation band according to embodiments.

[0063] FIG. 40 is a side view of another example fixation band according to embodiments.

- [0064] FIG. 41 illustrates another example embodiment.
- [0065] FIG. 42 is a schematic showing an example base of one embodiment of a circular hybrid contactor.
- [0066] FIG. 43 is a schematic showing an example base of one embodiment of a stretched octaberry.
- [0067] FIG. 44 is a schematic illustrating an example 100 ms vibratory pulse starting at 0.1 s, around constant indentation 0.5 mm, according to embodiments.
- [0068] FIG. 45 is a schematic of an example steplike stimulus starting at t_1 and ending at t_2 , with vanishing indentation baseline according to embodiments.
- [0069] FIG. 46 is a schematic of an example smooth steplike stimulus starting at t_1 and ending at t_2 , with vanishing indentation baseline according to embodiments.
- [0070] FIG. 47 is a schematic of an example steplike stimulus starting at t_1 and ending at t_2 , with non-vanishing indentation baseline according to embodiments.
- [0071] FIG. 48 Schematic illustrating a zero-baseline monophasic pulse form with non-vanishing net dc current with amplitude I_E and duration T_E according to embodiments.
- [0072] FIG. 49 is a schematic illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment.
- [0073] FIG. 50 is a schematic illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment.
- [0074] FIG. 51 is a schematic illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment.
- [0075] FIG. 52 is a schematic illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment.
- [0076] FIG. 53 is a schematic illustrating an example asymmetric balanced biphasic waveform with vanishing baseline and zero average current as used in another embodiment.
- [0077] FIG. 54 is a schematic illustrating an example steplike mechanical stimulus and the corresponding electrotactile stimulus train according to embodiments.
- [0078] FIG. 55 is a schematic illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift according to embodiments.

[0079] FIG. 56 is a schematic illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with non-zero phase shift according to embodiments.

[0080] FIG. 57 is a schematic illustrating an example hybrid (i.e., combined vibratory and electrotactile) stimulation with increasing 1:n cycle ratio between vibratory and electrotactile (e.g., with n increasing from 1 to 3 in the course of the vibratory burst according to embodiments).

[0081] FIG. 58 is a schematic illustrating an example 2:1 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where one electrotactile stimulus is delivered per 2 vibratory cycles according to embodiments.

[0082] FIG. 59 is a schematic illustrating an example 1:2 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where two electrotactile stimuli are delivered per vibratory cycle according to embodiments.

[0083] FIG. 60 is a schematic illustrating an example 1:3 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where three electrotactile stimuli are delivered per vibratory cycle according to embodiments.

[0084] FIG. 61 is a schematic illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift according to embodiments.

[0085] FIG. 62 is a schematic illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with different vibratory and electrotactile stimulus duration according to embodiments.

[0086] FIG. 63 is a schematic illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally patterned electrotactile stimulus and more complex cycle ratio between vibratory and electrotactile stimulation according to embodiments.

[0087] FIG. 64 is a schematic illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally patterned electrotactile stimulus and more complex cycle ratio between vibratory and

electrotactile stimulation, where the $m:1$ cycle ratio changes during a vibratory burst, with m decreasing from 3 to 1 according to embodiments.

[0088] FIG. 65 is a schematic illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally patterned electrotactile stimulus and more complex cycle ratio between vibratory and electrotactile stimulation, where the final 4 electrotactile stimuli are delivered phase locked to the pedestal according to embodiments.

[0089] FIG. 66 is a schematic illustrating an example 2:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with phase locked electrotactile stimuli coinciding with half of the maxima of the vibratory burst according to embodiments.

[0090] FIG. 67 is a schematic illustrating an example 4:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with phase locked electrotactile stimuli coinciding with a fourth of the maxima of the vibratory burst according to embodiments.

[0091] FIG. 68 is a schematic illustrating an example hybrid stimulation with temporal jitter between vibrotactile and electrotactile stimuli according to embodiments.

[0092] FIG. 69 is a diagram illustrating an example of a standard vibration signal with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation.

[0093] FIG. 70 is a diagram illustrating an example of a novel vCR vibration signal with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation and sub-threshold pedestal, circumscribed in time, according to embodiments.

[0094] FIG. 71 is a diagram illustrating an example of a vibratory signal with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation and continuous sub-threshold pedestal.

[0095] FIG. 72 is an example schematic illustration of 3:2 ON-OFF CR RVS (rapidly varying sequences) stimulation without pedestals according to embodiments.

[0096] FIG. 73 illustrates the corresponding vCR stimulation pattern with pedestals according to embodiments.

[0097] FIG. 74 is a diagram illustrating an example of the first period of a jitter-free CR sequence (blue hatched stimuli) with jitter intervals (blue rectangles) and final stimuli (solid blue stimuli) (following an OFF period) according to embodiments.

[0098] FIG. 75 is a schematic illustration of an example vibrotactile 3:2 ON-OFF CR RVS pattern with pedestals and uniform randomization of the vibration amplitude according to embodiments.

[0099] FIG. 76 is a schematic illustration of an example vibrotactile 3:2 ON-OFF CR RVS pattern with pedestals and uniform randomization of the vibratory burst durations according to embodiments.

[0100] FIG. 77 is a schematic illustrating an example slow random variation of the pedestal in channel 1 according to embodiments.

[0101] FIG. 78 is a schematic illustrating an example combination of a slow variation of the carrier-type frequency f , a slow random variation of the pedestal and a variation of the burst amplitude in channel 2 according to embodiments.

[0102] FIG. 79 is an example illustration of an in-channel masking prevention (IMP) pause (illustrated by shaded rectangle) of three times the duration of the vibratory burst according to embodiments.

[0103] FIG. 80 is an example illustration of an in-channel masking prevention (IMP) pause (illustrated by shaded rectangle) of three times the duration of the vibratory burst according to embodiments.

[0104] FIG. 81 is an example illustration of a jitter-free CR sequence with in-channel masking prevention pauses (red bars) according to embodiments.

[0105] FIG. 82 is an example illustration of the period $T_{k,k}$ between vibratory bursts k and $k+1$ in the j -th channel according to embodiments.

[0106] FIG. 83 is an example illustration of stimulus trains with different mean period according to embodiments.

[0107] FIG. 84 is an example illustration of a (jitter-free) CR sequence with different percentage of skipped (i.e., inactivated) stimuli according to embodiments.

[0108] FIG. 85 is a schematic illustrating an example interaction between master session timer and local session timer according to embodiments.

- [00109] FIG. 86 is a functional block diagram illustrating example aspects of embodiments.
- [00110] FIG. 87 illustrates an example of the intermingled administration of main stimulation mode (“main mode”) and rare stimulation mode (“rare mode”) according to embodiments.
- [00111] FIG. 88 illustrates an example of the intermingled administration of the main stimulation mode (“main mode”) and two rare stimulation modes (“rare mode 1” and “rare mode 2”) according to embodiments.
- [00112] FIG. 89 illustrates another example of the intermingled administration of the main stimulation mode (“main mode”) and two rare stimulation modes (“rare mode 1” and “rare mode 2”) according to embodiments.
- [00113] FIG. 90 illustrates an example of the intermingled administration of the main stimulation mode (“main mode”) and three rare stimulation modes (“rare mode 1”, “rare mode 2” and “rare mode 3”) according to embodiments.
- [00114] FIG. 91 illustrates an example regular 3:2 ON-OFF CR RVS (rapidly varying sequences) pattern according to embodiments.
- [00115] FIG. 92 illustrates an example of an embodiment #1 rare mode cycle C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00116] FIG. 93 illustrates an example of two embodiment #1 rare mode cycles C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00117] FIG. 94 illustrates another example of two embodiment #1 rare mode cycles C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00118] FIG. 95 illustrates an example of an embodiment #2 rare mode cycle C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00119] FIG. 96 illustrates an example of an embodiment #4 rare mode cycle C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00120] FIG. 97 illustrates an example of an embodiment #4 rare mode cycle C_r interspersed in the main mode vCR pattern from Figure 5 according to embodiments.
- [00121] FIG. 98 is a diagram illustrating an example stimulation pattern for four target sites and a shuffle period of $T_{\text{shuffle}}=2T$ according to embodiments.

[00122] FIG. 99 is a diagram illustrating an example where random jitter was added to the stimulus onset times according to embodiments.

[00123] FIG. 100 is a diagram illustrating an example of how a controller may adapt the stimulation patterns over time such that different stimulation patterns may be used for different stimulation epochs according to embodiments.

[00124] FIGs. 101A to 101K illustrate example aspects of CRS of inhomogeneous and homogeneous networks according to embodiments.

[00125] FIG. 102 illustrates example aspects of a learning procedure according to embodiments.

[00126] FIG. 103 provides simulation results. The top panel shows the Kuramoto order parameter, ρ , and in the bottom panel the mean synaptic weight, $\langle w \rangle$.

[00127] FIG. 104 illustrates estimated relative frequency of occurrence (gray scale) of actions, a , that maximize $Q(1,a) = Q(\text{synch}, a)$ and $Q(2,a) = Q(\text{desynch}, a)$.

[00128] FIG. 105A shows Mean synaptic weight during CR stimulation with rapidly varying sequence ($T_{\text{shuffle}} = T$) for four different CR sequence pools. FIG. 105B shows how the CR sequence pools are named.

[00129] FIG. 106 illustrates mean synaptic weight after stimulation onset averaged over different network and sequence realizations according to embodiments.

[00130] FIG. 107 illustrates trajectories of the Kuramoto order parameter (top) and the mean synaptic weight (bottom) during a session with $K_{\text{max}} = 20$ stimulation epochs according to embodiments.

[00131] FIG. 108 illustrates total reward after each session for subsequent sessions achieved by the RL algorithm according to embodiments.

[00132] FIG. 109 illustrates traces of the simulated patient's condition, the Kuramoto order parameter, ρ , and the mean synaptic weight, $\langle w \rangle$, during the indicated sessions for the two cases in FIG. 108 according to embodiments.

[00133] FIG. 110 is a schematic of a setup to adjust the probability at which CR sequences are drawn during shuffled CR according to embodiments.

[00134] FIG. 111 provides simulated traces of the simulated patient's condition, the Kuramoto order parameter, and the mean synaptic weight according to embodiments.

[00135] FIGs. 112A-112D illustrates simulations for each network type and different initial mean synaptic weights according to embodiments.

[00136] FIGs. 113A-113D provide statistical analysis of mean synaptic weight before, during, and after stimulation for inhomogeneous networks (A,B) and homogeneous networks (C,D) according to embodiments.

DETAILED DESCRIPTION

[00137] The present embodiments will now be described in detail with reference to the drawings, which are provided as illustrative examples of the embodiments so as to enable those skilled in the art to practice the embodiments and alternatives apparent to those skilled in the art. Notably, the figures and examples below are not meant to limit the scope of the present embodiments to a single embodiment, but other embodiments are possible by way of interchange of some or all of the described or illustrated elements. Moreover, where certain elements of the present embodiments can be partially or fully implemented using known components, only those portions of such known components that are necessary for an understanding of the present embodiments will be described, and detailed descriptions of other portions of such known components will be omitted so as not to obscure the present embodiments. Embodiments described as being implemented in software should not be limited thereto, but can include embodiments implemented in hardware, or combinations of software and hardware, and vice-versa, as will be apparent to those skilled in the art, unless otherwise specified herein. In the present specification, an embodiment showing a singular component should not be considered limiting; rather, the present disclosure is intended to encompass other embodiments including a plurality of the same component, and vice-versa, unless explicitly stated otherwise herein. Moreover, applicants do not intend for any term in the specification or claims to be ascribed an uncommon or special meaning unless explicitly set forth as such. Further, the present embodiments encompass present and future known equivalents to the known components referred to herein by way of illustration.

[00138] Among other things, the present Applicant recognizes that ideally, therapeutic stimulation of the skin of the fingertips should be performed with constant pressure, irrespective of the position of the hand and fingers. In the vCR pilot studies performed so far [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinson's Disease. *Frontiers in Physiology* 12:624317 (2021)], the factors were mounted to the fingertips with simple Velcro. As a consequence, the contact pressure varied strongly with finger and hand position. In this way, relevant portions of stimulation sessions were performed with insufficient contact pressure, rendering stimulation less effective.

[00139] To overcome this issue among others, embodiments use a custom plastic and rubber enclosure that has an elastomeric band. This band can be tightened or loosened by both clinicians and patients to create a suitable pressure interface between contactor and the skin surface. The device is designed to fit all primary finger sizes from a 5% Asian female size to a 95% Caucasian male size.

[00140] The device of some embodiments has two primary modes of fitment. The first is for larger diameter fingers and has a rubber pad pressing against the fingernail with a wraparound elastic strap providing the necessary skin contact pressure. In this format the arrangement is too large for small fingers so it has a second mode of fitment. The second mode includes the shifting of the rubber pad to a more constrained position which creates a smaller opening for finger compression. Both of these modes use the elastomeric strapping and are adjustable to suit the actual needs of the patient.

[00141] It should be noted that the present embodiments describe fingertips, but the new mechanical stimulator and, in particular, the non-disc-contactor can also be mounted to other parts of the body, e.g., the back of the fingers, the back/palm of the hand, the forearm etc.

[00142] An example tapper assembly 100 according to embodiments is shown in unexploded and exploded format in FIGs. 1A and 1B, respectively. As shown in FIG. 1A, the assembly 100 comprises a finger top soft cover 102, a strap 104, a housing top cover 106, a bottom half 108 and a star lever 110. FIG. 1B illustrates how the strap 104 integrates with the finger top cover 102, which together connect with the housing top cover 106. FIG. 1B further

illustrates how the tapper 112 projects into the top cover 106, while housed in the bottom half 108. The star lever 110 is attached to the bottom half 108 via the star lever pivot rods 114.

[00143] FIG. 2 illustrates one potential version of the vibration motion generating device 202. In the example of FIG. 2, the tapper is comprised of a linear motor 202 that vibrates linearly toward and away from the fingerprint skin surface at a vibration frequency. It is intended to operate at various forces / frequencies. As further shown in the exploded view of FIG. 2, this motor 202 has a central post and other mating components that fasten and align with each other to provide a suspension system that directs and constrains the majority of the vertical motion in a single central axis. The two flat spring elements provide a flexure and a spring return feature as the motor vibrates. Each flat spring is bonded to the moving element/mass 206 in the center area and to the housing 204 on the outer surfaces. This layout provides motor compliance to the user's finger surface and can maintain intermittent contact during motor operation (tapper feature). In general, depending on the length of the connection between contactor and motor, different amounts of indentation will be accomplished during motor operation. With the tapper mounted to the fingertip, in the absence of motor action (i.e., without vibration being delivered), the skin indentation is substantially constant, but varies across the contactor surface. In another embodiment, there may be parts of the contactor that are connected to the skin only during specific parts of the vibration cycle of the motor. These parts of the contactor have no skin contact in the absence of vibration. In yet another embodiment, some parts of the contactor may not be connected to the skin at all, i.e., irrespective of the phase of the motor's oscillation.

[00144] In summary, an example contactor according to embodiments enables two advantageous features of stimulation:

[00145] (i) The skin indentation of the contactor is spatially varying in the absence of vibration. This can be particularly effective for the stimulation of the FA I and FA II mechanoreceptors.

[00146] (ii) For adequately tuned length of the connection between contactor and motor, parts of the contactor have no skin contact during specific phases of the motor's oscillation. These parts repetitively push into the skin and get retracted. Stimulation with revolving skin

contact is particularly effective for the stimulation of SA I and SA II mechanoreceptors. The latter do not strongly respond to vibration.

[00147] Hence, with only one contactor and one set of stimulus parameters (vibration frequency and vibration amplitude) the tapper enables stimulation of all four different mechanoreceptors.

[00148] FIG. 3 illustrates example aspects of a double flat spring architecture of embodiments. In accordance with these aspects, embodiments significantly reduce motor-induced vibrations of the tapper's housing. This is significant because ideally only the top contactor 302 should move, whereas the stationary, non-vibrating housing should block vibratory skin waves from propagating beyond the chosen area. There may be other embodiments of the tapper utilizing more than two flat springs and equivalent elements. However, all of these embodiments are characterized by reduced coupling between the motor elements and tapper housing 204. In particular, any stiff coupling between motor and housing is avoided. In this way, motor oscillations are not directly locked to the housing. The driving vibration motor has a small embedded driving coil and a dedicated moving mass within it in a very small format (small diameter specifically).

[00149] As shown in FIG. 3, embodiments mount an entire small motor assembly to the center area of parallel flat spring elements 304, 310 via a post 316 and bottom hub 314. These flat spring elements are specifically designed with embedded flexures (e.g. 306, 308) to allow perpendicular linear motion. They are also spaced apart to allow / promote controlled axial motion and diminish lateral motion. This provides greater lateral isolation from the housing. The outside portion of the springs is somewhat round and provides the required housing connection (perimeter mounting). The flat springs 304, 310 have cut outs that create flexures for the motor attachment in the center area. The arrangement is very much like a trampoline. This allows very focused linear driving forces/motion exactly where needed. The configuration also provides a soft suspension system that complies with the position of the patient's finger surface. It basically allows the contactor (e.g. implemented as an octaberry 402 in FIG. 4) to touch the finger surface very consistently no matter what skin profile is presented from the tapper housing.

[00150] Other linear motors that are mounted to the finger do not offer this level of isolation because the driving coil is mounted to the housing directly and uses a large magnetic field to transmit motive forces to a center mounted weight. Basically the driving force is mounted directly to the housing and consequently to the finger making the housing vibrate excessively. This problem is mitigated in embodiments by moving the entire driver 316 and moving mass to the center of the suspension springs (flat springs 304, 310).

[00151] In addition, these two flat springs provide an electrical path for the current needed to operate the motor without wires 312 spanning the vibrating center region from the outer fixed region. Each flat spring provides a current path for one half of the circuit needed to drive the vibration motor. This way, there is no need for additional cables that might fatigue and, ultimately, break over time. This increases the longevity and reliability of the tapper. It also significantly enhances vibration consistency and isolation by preventing cable strain variables from influencing the vibrating motion.

[00152] In another embodiment, the strap is replaced by a near constant force spring or band. This is to enable or approximate a constant contact pressure of the tapper to the skin. Patient finger sizes vary significantly from human to human. They also vary from day to day on the same patient as finger diameters can swell or contract. The addition of the constant finger contact force feature allows for these variances without diminishing therapeutic performance.

[00153] It is important to note that this type of vibration device can be used in any number of places on the human body to create therapeutic sensations.

[00154] FIG. 4 illustrates aspects of how a contactor 402 according to embodiments is allowed to touch the finger surface very consistently no matter what skin profile is presented from the tapper housing.

[00155] FIG. 5 provides an overall view of tapper assembly view showing the device and the connecting cable. This cable connects to the driver system that provides pulsed therapeutic signals. The connecting cable comes in various lengths to accommodate large to small finger lengths. Lengths are measured in centimeters between the back of the Tapper assembly wall and the midpoint of the connector jack.

[00156] Large Finger Mode - The finger top soft cover is open to the full width of the housing (lower left to upper right in this view). This allows a large finger to be inserted into the

tapper assembly. A snug fit is required to insure contactor engagement with the patient's fingerprint surface. FIG. 6 illustrates an example showing a large finger insertion aspects. The large finger is inserted, and the strap ends are tightened and latched in place with the star levers, as further illustrated in FIGs. 7A-7C.

[00157] Small Finger Mode - The finger top part is narrowed within the side walls of the housing. This allows a small finger to be inserted into the tapper assembly, as further illustrated in FIGs. 8A and 8B. FIGs. 9A to 9C further illustrate aspects of an example small finger insertion of embodiments. As shown, the small finger is inserted, and the strap is tightened for an even and snug fit. The strap ends are latched in place by the star levers.

[00158] FIGs. 10A and 10B show an example of star levers 1002 in open position, and latched in closed position, respectively. They provide low profile latching with the elastic strap ends and can be operated (tightened and latched) with one hand.

[00159] An example octaberry contactor 1102 according to embodiments is shown from top view in FIG. 11. This shape is specifically designed to maximize skin sensitivity to minimal vibration energy. Basically, it moves up and down to tap the fingerprint skin surface and create the desired sensation.

[00160] The shape of contactor 1102 shown in FIG. 11 is just one of many possibilities as illustrated in FIG. 12. Any of these or other shapes can be mounted within the vibration device. The cross hatched portions of these are moving contactors that can protrude through any hole shape.

[00161] One purpose of the free surround area between contactor and tapper housing is to block or reduce the propagation of skin vibration waves. In the vCR pilot studies performed so far [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinson's Disease. *Frontiers in Physiology* 12:624317 (2021)], the contactor was moving within a simple circular hole of the tactor housing. In another embodiment, the hole in the tactor housing may attain more complex, e.g., non-circular and/or wave-breaking shapes. This is to reduce the energy of the skin vibration wave before it actually reaches the tactor housing, in this way strengthening the damping effect of the tactor housing.

[00162] More particularly, FIG. 12 illustrates different breakwater-type of surrounds embracing the contactor. The five illustrated examples all include a small disk-like contactor 1202. The contactor is surrounded by a low-lying area 1204-1 to 1204-5. The depth of this low-lying area can be chosen such that the skin is not able to touch the bottom of this low-laying area. In another embodiment the skin touches (parts of) the low-lying area. The low-lying area is embraced, e.g., by a circular surround (e.g. 1204-1) or flower-shaped surround (e.g. 1204-2, 1204-3, 1204-4). Other embodiments may contain larger disk-like contactors (not shown) as well as more complex contactors, such as the octaberry (described above, not shown in this figure). In addition, the surround may attain more complex, breakwater-type shapes to contain vibratory skin waves by means of destructive interference. In yet another embodiment within the low-lying area there may be lifted areas. In the example shown in FIG. 12, the low-lying area with lifted areas 1206 can be embraced by a circular surround 1204-5 or by a surround of breakwater-type of shape. The lifted areas can have different shapes, e.g., the height of the lifted areas may increase with increasing distance from the contactor. All these different elements and embodiments are used to break or reduce skin vibratory waves.

[00163] FIG. 13 illustrates different contactor and surround shapes. In the left example embodiment, there is an approximately oval contactor 1302-1 and a complex surround 1304-1. In the right example embodiment, there is a slanted, rectangular contactor 1302-2 with an approximately oval hole 1306 in the middle, and a surround 1304-2 of slanted, rectangular shape.

[00164] FIG. 14 illustrates additional different examples of contactor and surround shapes. In the left example embodiment there is an approximately oval contactor 1402-1 and a complex surround 1404-1. In the right example embodiment, there is a slanted, triangular contactor 1402-2 and surround of slanted, triangular shape 1404-2.

[00165] FIG. 15 illustrates example embodiments with two different pairs of contactors. In the left example embodiment there are two approximately oval contactors 1502-1 and 1502-2, each surrounded by a single approximately oval surround 1504-1 and 1504-2. In the right example embodiment, there are a pair of oval contactors 1502-3 and 1502-4 with a single slanted, rectangular surround 1506. The different features of the different examples illustrated

above can also be combined. For instance, one or both contactors of the contactor pair may contain a hole as shown in FIG. 13.

[00166] In another embodiment, sensors can be included to measure blood oxygen level, temperature, vibration, compression pressure, GPS, acceleration in any axis. These can be added to each tapper (i.e. contactor) in various ways such as: (1) skin surface to tapper surface pressure, temperature and / or vibration; (2) housing; and (3) carrier case.

[00167] An example of a pressure sensor 1602 is shown in FIG. 16. It is comprised of piezo based technology and can be added to a number of locations on the assembly (above fingernail, on fingerprint area, under controller, etc). This example sensor is very thin and is calibrated to suit the range of forces of interest. It, or one like it, can also measure vibration in a range of interest for vibrotactile stimulation. Data from this sensor can be transmitted to any number of control / feedback systems.

[00168] Sensors in embodiments can be used for local and remote monitoring. In this use case, sensors can be used for monitoring such things as patient compliance, quality of therapy, device location, proper use, body motion / associated exercise, closed loop feedback for vibration control, product maintenance, end of life, degradation tracking for service, and pulse oximetry for physiological responses to therapeutic inputs.

[00169] Sensors in some embodiments can also be used for cross finger vibration mitigation.

[00170] Principles of a non-disc contactor, such as an octaberry contactor according to embodiments will now be presented. To compensate for vibration strength losses caused by the shock absorbing tactor design, embodiments are directed to a contactor (i.e., the part of the mechanical stimulator that interacts with the patient's skin and deeper layers) which causes stronger physiological/medical effects with the same amount of force/energy/vibration amplitude. The present Applicant recognizes that the following three characteristics of the contactor surface significantly increase the stimulation effect: increased outer circumference, inner circumference (hole) and non-flat contactor surface.

[00171] As for increased outer circumference, the present Applicant recognizes that typical contactors are discs or disc-like. For example, the contactor used in the vCR pilot studies [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty,

S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinson's Disease. *Frontiers in Physiology* 12:624317 (2021)] was basically a disc.

[00172] A circle has the smallest circumference of all 2D objects with identical area. But contactors with larger circumferences, but same otherwise, elicit significantly stronger stimulation effects such as those reflected in smaller vibration thresholds, i.e., smaller vibration amplitudes are required to elicit a vibration sensation.

[00173] Accordingly, a contactor according to embodiments has a larger outer circumference compared to a simple circle/disc. In one embodiment, the contactor uses a so-called octaberry shape: an octagon with semi-circles attached to the octagon's sides, giving rise to a berry-type shape.

[00174] As for inner circumference (hole), the present Applicant recognizes that previous contactors used for vCR were typically solid discs that did not have a hole [K.J. Pfeifer, J.A. Kromer, A.J. Cook, T. Hornbeck, E.A. Lim, B.J.P. Mortimer, A.S. Fogarty, S.S. Han, R. Dhall, C.H. Halpern, P.A. Tass: Coordinated Reset Vibrotactile Stimulation Induces Sustained Cumulative Benefits in Parkinson's Disease. *Frontiers in Physiology* 12:624317 (2021)]. But a hole in the contactor gives rise to significantly stronger stimulation effects. Accordingly, an example contactor of embodiments has a hole. In one embodiment a contactor is an annular stretched octaberry with outer diameter D_o and inner (hole) diameter D_i .

[00175] FIG. 17 is a contactor ground view of an octaberry according to embodiments, which is an octagon with semi-circles attached to all sides, leading to a berry-type shape 1702 with increased outer circumference without sharp edges or angles that might compromise a subject's skin when applied during longer stimulation sessions. An annular octaberry has a hole 1704 which comes with an inner circumference and, hence, increased total circumference.

[00176] The span S of the octagon is given by

$$S = (1 + \sqrt{2}) * 2R.$$

[00177] The outer diameter D_o reads

$$D_o = S + 2R = (2 + \sqrt{2}) * 2R$$

[00178] The inner diameter D_i ($0 < D_i < S$) should be sufficiently large, e.g., $D_i \geq 2R$, but not too close to the span.

[00179] The total area of an annular 'octaberry' with inner diameter D_i :

$$A_{\text{ann}} = A_{\text{area}} - A_{\text{centerdisk}} = 4[2 * (1 + \sqrt{2}) + \pi] * R^2 - \pi \frac{D_i^2}{4}$$

[00180] Radius of the hole R_i :

$$R_i = \frac{D_i}{2},$$

[00181] With this one can obtain

$$A_{\text{ann}} = A_{\text{area}} - A_{\text{centerdisk}} = 4[2 * (1 + \sqrt{2}) + \pi] * R^2 - \pi R_i^2$$

[00182] Compare the circumference of the annular octaberry with a simple disk of the same area.

$$A_{\text{ann}} = A_{\text{disk}} \Rightarrow \gamma R^2 - \pi R_i^2 = \pi r^2,$$

[00183] where

$$\gamma = 4[2 * (1 + \sqrt{2}) + \pi] \approx 31.88$$

[00184] This yields

$$\gamma R^2 - \pi R_i^2 = \pi r^2$$

[00185] With

$$R_i = \beta R,$$

where $D_i \ll S$ implies $\beta \ll 1 + \sqrt{2}$. This gives:

$$R = r * f(\beta)$$

[00186] With

$$f(\beta) = \sqrt{\frac{\pi}{\gamma - \pi\beta^2}}$$

where $f(1) \approx 0.33$ (see above) and $f(2) \approx 0.40$.

[00187] FIG. 18 is a graph which shows $f(\beta)$ vs. β , where $\beta = R_i/R$. R_i denotes the radius of the hole, and $2R$ is the length of each side of the octagon.

[00188] From this one can obtain for the total circumference, i.e., inner circumference C_i plus outer circumference C_o , of the annular octaberry with inner diameter $D_i = 2\beta R$:

$$C_{\text{ann}} = C_o + C_i = (4 + \beta) * 2\pi R = (4 + \beta)f(\beta) * 2\pi r = (4 + \beta)f(\beta) * C_{\text{disk}}$$

$$\frac{C_{\text{ann}}}{C_{\text{disk}}} = (4 + \beta)f(\beta) = (4 + \beta) \sqrt{\frac{\pi}{\pi - \pi\beta^2}}$$

[00189] FIG. 19 is a graph illustrating how the total circumference scales with β .

[00190] By increasing the inner diameter D_i , one can increase the total circumference substantially. Examples:

[00191] For $\beta = 1$ one gets $\frac{C_{\text{ann}}}{C_{\text{disk}}} = 1.65$

[00192] For $\beta = 1.5$ one gets $\frac{C_{\text{ann}}}{C_{\text{disk}}} = 1.96$

[00193] For $\beta = 2$ one gets $\frac{C_{\text{ann}}}{C_{\text{disk}}} = 2.42$

[00194] Example #1 ($\beta = 2$): Simple disk with $r = 1.5$ mm (diameter = 3 mm).

$R = r * f(2) = 0.605$. The annular octaberry (with identical area) with inner diameter $D_i = 2\beta R = 2.42$ mm has an outer diameter $D_o = (2 + \sqrt{2}) * 2R = 4.18$ mm.

[00195] Example #2 ($\beta = 2$): Simple disk with $r = 3$ mm (diameter = 6 mm).

$R = r * f(2) = 1.2099$.

[00196] The annular octaberry (with identical area) with inner diameter

$D_i = 2\beta R = 4.84$ mm has an outer diameter $D_o = (2 + \sqrt{2}) * 2R = 8.26$ mm.

[00197] Another embodiment of the ground view of a contactor of embodiments is a stretched annular octagon. Stretching serves the following purposes: it further increases the total circumference; and when mounted to fingertips, it works for a large range of fingertip sizes, in particular, for thin fingertips, too.

[00198] Stretched annular octaberry: A stretched octagon provides the basis for a stretched octaberry. An annular stretched octaberry has a hole, e.g., an elliptic hole. FIGs. 20-22 show examples of the ground view of contactor embodiments. These ground views constitute annular stretched octaberries with identical semi-circles and, hence, identical height H compared to a non-stretched octaberry. FIG. 20 illustrates an example annular stretched octaberry with $n = 2$ semi-circles 2002 on the stretched sides of the octagon. FIG. 21 illustrates an example annular stretched octaberry with $n = 3$ semi-circles 2102 on the stretched sides of the octagon. FIG. 22 illustrates an example annular stretched octaberry with $n = 4$

semi-circles 2202 on the stretched sides of the octagon. For $n = 4$ the ratio $L(2)/H = 1.88$ and closest to 2.

[00199] The height of the stretched octaberry is given by

[00200] $H = h + 2R,$

[00201] where the height of the octagon reads

$$h = 2R(1 + \sqrt{2}).$$

[00202] Accordingly, one can obtain

$$H = 2R(2 + \sqrt{2}).$$

[00203] The length of the stretched octaberry reads

$$L = l + 2R,$$

[00204] where the length of the octagon is

$$l = 2R(1 + \sqrt{2}) + n2R - 2R.$$

[00205] where n denotes the number of semi-circles on the stretched sides of the octagon.

With this one can get:

$$L(n) = 2R(n + 1 + \sqrt{2}).$$

[00206] To select an appropriate n for a required L/H ratio, calculate

$$\frac{L(n)}{H} = \frac{n + 1 + \sqrt{2}}{2 + \sqrt{2}}$$

$$\frac{L(1)}{H} = 1 \text{ (unstretched octaberry), } \frac{L(2)}{H} = 1.29, \frac{L(3)}{H} = 1.59, \frac{L(4)}{H} = 1.88, \frac{L(5)}{H} = 2.17$$

[00207] Example: $n = 4$, $H = 3$ mm:

[00208] For example, $H = 3$ mm, comparable to a contactor disk with 3 mm diameter.

[00209] One then gets $L(4) = 5.64$ mm.

[00210] The desired area and circumference can be controlled by means of the elliptic hole. The area of the octagon reads

$$A_8 = 2(2R)^2(1 + \sqrt{2}) + h(n2R - 2R)$$

[00211] and hence

$$A_8 = 4R^2(1 + \sqrt{2})(1 + n).$$

[00212] R is determined by the choice of the height of the octaberry:

$$R = \frac{H}{2(2 + \sqrt{2})} = \frac{3}{2(2 + \sqrt{2})} \text{ mm} = 0.4393 \text{ mm}.$$

[00213] The area of the stretched octaberry is

$$A_{OS} = A_o + (6 + 2n)A_{segment-stretch} = A_o + (3 + n)A_{circle}$$

$$A_{OS}(n) = 4R^2(1 + \sqrt{2})(1 + n) + (3 + n)\pi R^2.$$

[00214] With $R = \frac{H}{2(2 + \sqrt{2})}$ one can obtain

$$A_{OS}(n, H) = \frac{4(1 + \sqrt{2})(1 + n) + (3 + n)\pi}{4(2 + \sqrt{2})^2} H^2$$

[00215] The area of an ellipse is defined by:

$$A_E = \pi ab.$$

[00216] Accordingly, the area of the annular stretched octaberry is given by

$$A_{AOE}(n, H) = A_{OS}(n, H) - A_E$$

[00217] Example: Annular stretched octaberry with identical area as a disk with 3mm diameter:

$$A_{disk} = \pi r^2 = \pi 1.5^2 \text{ mm}^2 = 7.07 \text{ mm}^2.$$

$$A_{AOE}(n, H) = A_{disk} \Rightarrow$$

$$\frac{4(1 + \sqrt{2})(1 + n) + (3 + n)\pi}{4(2 + \sqrt{2})^2} H^2 - \pi ab = \pi r^2$$

[00218] The set of possible ellipses is given by

$$ab = \frac{4(1 + \sqrt{2})(1 + n) + (3 + n)\pi}{4(2 + \sqrt{2})^2} \times \frac{H^2}{\pi} - r^2$$

$$ab = 2.8541 \text{ mm}^2$$

[00219] For example:

[00220] $b = 1.5 \text{ mm} \Rightarrow a = 1.9027 \text{ mm}$

[00221] $b = 1.8 \text{ mm} \Rightarrow a = 2.1955 \text{ mm}$

[00222] Height h and length l of octagon:

$$h = 2R(1 + \sqrt{2}) = H \frac{1 + \sqrt{2}}{2 + \sqrt{2}} \approx 0.7071 * H = 2.1213 \text{ mm}.$$

$$L = 2R(n + \sqrt{2}) = H \frac{n + \sqrt{2}}{2 + \sqrt{2}}$$

$$L \approx 1.5858 * H = 4.7574 \text{ mm}$$

[00223] Outer circumference of stretched octaberry C_{out} :

[00224] This is identical to 7 times the circumference of a circle with radius R , i.e.

$$C_{out} = 7 * 2\pi R = 7\pi \frac{H}{2 + \sqrt{2}} \approx 19.32 \text{ mm}$$

[00225] Inner circumference of the annular stretched octaberry C_{in} :

$$C_{in} \approx \pi(a + b) = \pi(2.1955 + 1.3) \text{ mm} = 10.98 \text{ mm}$$

[00226] Total circumference of the annular stretched octaberry C_{tot}

$$C_{tot} = C_{out} + C_{in} \approx 30.30 \text{ mm}$$

[00227] For comparison, the circumference of a simple disk with radius 1.5 mm is

$$C_{disk} = 2\pi r = 9.42 \text{ mm}.$$

[00228] Hence,

$$\frac{C_{tot}}{C_{disk}} \approx 3.22$$

[00229] The circumference of the annular stretched octaberry is greater compared to the non-stretched version when compared to disks of identical area.

[00230] The circumference of an ellipse is defined by:

$$C_E = 4 \int_0^{\frac{\pi}{2}} \sqrt{a^2 \cos^2 \theta + b^2 \sin^2 \theta} d\theta$$

[00231] A simple approximation (as used above) reads:

$$C_E \approx \pi(a + b)$$

[00232] A more accurate approximation reads:

[00233] As for a non-flat surface, the present Applicant recognizes that the contactor should not be flat, but have a convex or concave or any non-flat surface. In one embodiment the contactor surface is convex which is particularly favorable when mounted to fingertips since it makes the stimulation less dependent on the accuracy of the longitudinal fingertip placement. Even in conditions with sub-optimal placement and longitudinal deviations, the fingertip still receives stimulation due to the longitudinal elongation of the contactor.

[00234] An example apparatus for electrotactile 3-channel stimulation according to embodiments will now be described.

[00235] In one embodiment the contactor for the example apparatus contains an inner and an outer electrode, with inner electrode diameter around 1 mm and inner diameter of the outer, surrounding (reference) electrode around 6 mm. These values can vary from 0.4-1.7 mm or 0.2-2.5 mm (inner electrode diameter) and from 5.5 mm-6.5 mm or 4.5-7.5 mm (inner diameter of the outer electrode). Another embodiment contains an inner electrode with 3 mm diameter and an outer electrode with 10 mm inner diameter. The latter values can vary from 2.5-3.5 mm or 1.5-4.5 mm (inner electrode diameter) and from 9 mm-11 mm or 7.5-12 mm (inner diameter of the outer electrode). A contactor of the present embodiments includes both disk-like and annular electrodes.

[00236] FIG. 23 illustrates an example contactor 2301 for 3-channel electrotactile stimulation according to embodiments. As shown in the schematic of FIG. 23, the base of the example contactor 2301 contains both a smaller inner electrode 2307, surrounded by an insulating surface (white circle between 2307 and 2306), and smaller surrounding electrode 2304 for the delivery of Meissner and Merkel mode stimuli (described in more detail below) and a larger inner electrode (2307 and 2306 coactivated) and larger surrounding electrode 2302 for the administration of Pacinian mode stimuli (described in more detail below). Insulating surfaces (2303, 2305 and white circle between 2306 and 2307) separate the different electrodes. In another embodiment, one or more insulating surfaces can be deepened (and, hence, in greater distance to the skin compared to the rest of the contactor surface).

[00237] FIG. 24 illustrates an example contactor for double 3-channel electrotactile stimulation according to embodiments. As shown in the schematic, a pair of the example embodiment of a two electrode contactor 2301 as shown in FIG. 23 is embedded in an octaberry-shaped contactor. Alternatively, the contactor can attain other, e.g., oval or elliptic forms.

[00238] One advantage of certain of the present embodiments is that only one (anatomical) stimulation site is sufficient for treatment delivery. For example, one fingertip is sufficient as a stimulation target. Accordingly, the contactor for 3-channel stimulation can be mounted to the fingertip by means of devices using constant force springs and/or elastic bands

and/or equivalent mechanisms, e.g., those known from fingertip pulse oximeter devices. The device can conveniently be mounted to the fingertip for periods of minutes up to a few hours or at night (while patient is sleeping).

[00239] FIG. 25 illustrates an example fingertip pulse oximeter in which embodiments can be integrated and FIG. 26 is a schematic showing the cross section of upper 2601 and lower 2602 part of the pulse oximeter-type housing of the 3-channel electrotactile single-finger stimulator. In this embodiment, the fingertip 2604 is mounted on the convex contactor 2603 containing circular and annular electrodes. One of these annular electrodes is schematically illustrated by one white half ring. Other embodiments use non-convex, but concave or planar contactors containing the annular and disk-like electrodes.

[00240] One fingertip stimulator embodiment contains a battery. Another embodiment, comprising several fingertip stimulators can, alternatively, house a battery in a controller, e.g., at the back of the hand as will be described in more detail below.

[00241] In comparison to mechanical, vibrotactile stimulation as described in other embodiments, an aspect of some embodiments include electrotactile stimulation, i.e., stimulation of sensory nerves by administration of electrical current over the skin. Applicant recognizes that this type of stimulation can have several advantages such as:

[00242] Low latency -- electrotactile stimuli elicit responses of sensory nerves at short latencies. In contrast, mechanical, vibratory stimuli require several, e.g., 5, periods of the vibration to elicit dynamically stable responses (phase-locked to the mechanical vibration).

[00243] Energy efficiency -- electrotactile stimulation requires less energy than mechanical, vibrotactile stimulation. This enables smaller batteries for electrotactile wearables as well as only moderately increased battery requirements for hybrid (i.e., combined vibrotactile and electrotactile) stimulation.

[00244] However, changes of the impedance of the electrode-skin interface change the perceived sensation intensity. This constitutes a relevant limitation of electrotactile stimulation. Impedance changes are caused by mechanical as well as physiological changes. Mechanical changes are caused by varying contact area and/or pressure, whereas physiological changes are due to physiological alterations, e.g., sweating at the electrode site. Some of these changes can

be at least partially counteracted by current controlled delivery of the stimulation current. However, relevant mechanical changes, e.g., caused by peeling back electrodes or strong changes of contact area and/or pressure, still remain a challenge.

[00245] To overcome this limitation, some embodiments use hybrid stimulation, where the mechanical stimulation enables sufficiently constant contact area and pressure of the stimulation electrodes, as will be described in more detail below.

[00246] Other (simpler) embodiments use solely electrotactile stimulation with an constant force mounting, e.g., realized by means of one or more constant force springs and/or elastic bands and/or elastic fingerstall.

[00247] Different embodiments use different pulse forms (i.e., waveforms). In addition, one embodiment can use more than one pulse forms. Pulse forms without current balancing (FIG. 27) are not used in preferred embodiments since they may cause skin irritations. Different types of current-balanced pulse forms (with zero average current) can be used by different embodiments, for instance: monophasic pulse forms with non-vanishing baseline and zero average current of positive (FIG. 28) or negative polarity (FIG. 29), balanced biphasic pulse forms with vanishing baseline and zero average current (FIG. 30 and FIG. 31) or asymmetric balanced biphasic waveforms with vanishing baseline and zero average current (FIG. 32). Other embodiments may use other current-balanced pulse forms.

[00248] In general, typical parameter ranges are:

pulse amplitude I_E : up to 50 mA

pulse width T_E : 2-1000 μ s

inter-pulse-pause P_E : 0-1000 μ s, typical values are around 40-50 μ s

Pulse rates, i.e., the rate at which the pulse forms mentioned above are delivered:

1 Hz-25 kHz

Pulses can be delivered as bursts, i.e., groups of sequentially delivered pulses.

Burst rate: 1 – 1000 Hz

Time between bursts: 1-1000 ms

[00249] Some embodiments may use values outside the parameter ranges above.

[00250] FIG. 27 is a waveform diagram illustrating a zero-baseline monophasic pulse form with non-vanishing net dc current with amplitude I_E and duration T_E . Some embodiments do not use such pulse forms for electrotactile stimulation since they can cause rapid skin irritations resulting from electrochemical reactions at the skin-electrode interface. The stimulation pulse starts at t_1 and ends at t_2 . Analogously, zero-baseline monophasic pulse form of opposite polarity (with net dc current) are not used by preferred embodiments either.

[00251] Different embodiments use different electrode designs to stimulate different mechanoreceptors, located in different skin depth and having different preferential nerve fiber directions (relative to the skin surface).

[00252] Meissner corpuscles (belonging to FA I mechanoreceptors) are located in superficial parts of the skin, i.e., in less than 1 mm depth. They react most strongly to low frequency vibration (20-70 Hz), with a resonant frequency at around 30 Hz.

[00253] Pacinian corpuscles (belonging to FA II mechanoreceptors) are located in the deeper parts of the skin, in about 2 mm depth, and react to high frequency vibrations 100-400 Hz, with a resonant frequency around 250 Hz.

[00254] Merkel cells (MCs) are found in the stratum basale, in the bottom part of the epidermis (i.e., the superficial layer of the skin). They are associated with slowly adapting (SA1) somatosensory nerve fibers and respond to low vibrations (5–15 Hz) as well as deep static touch corresponding to shapes and edges.

[00255] Compared to other parts of the glabrous hand, the densities of Meissner corpuscles, Merkel cells and Pacinian corpuscles is highest in the fingertips. Accordingly, fingertips are a strategically favorable stimulation target.

[00256] Different embodiments use different electrode configurations and dimensions (introduced above) together with different stimulation parameters to induce specific effects, e.g.:

[00257] FIG. 28 is a schematic illustrating a monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment. The long negative phases (with amplitude I_C) counterbalances the main (positive) stimulation phase with amplitude I_E and duration T_E . The main (positive) stimulation phase starts at t_1 and ends at t_2 .

[00258] Smaller inner electrode and smaller surrounding electrode embodiments:

[00259] Meissner (FA I) mode: One embodiment uses anodic (+) pulses at frequencies ranging from 1 Hz up to 120 Hz and more, e.g., 250 Hz and even more, e.g., 400 Hz or 500 Hz with pulse amplitudes around 2.4 mA, e.g., in a range from 0.5 mA – 10 mA, and pulse width around 0.1 ms, e.g., in a range from 0.005 ms – 1 ms and more, e.g., 2 ms or even up to 5 ms. These stimuli activate FA I nerve fibers, leading to (low-frequency) vibration sensation. Intriguingly, these nerve fibers can also be stimulated at higher frequencies (e.g. > 120 Hz). Electrode dimensions (and their ranges) were introduced above.

[00260] Merkel mode (SA I): Another embodiment uses the same parameters and electrode dimensions as for the Meissner mode, but cathodic (-) pulses. This causes a different current flow which stimulates nerve fibers connected to the Merkel cells, leading to activation of SA I fibers and in turn, pressure-like sensations. Electrode dimensions (and their ranges) were introduced above.

[00261] Larger inner electrode and larger surrounding electrode embodiments:

[00262] Pacinian mode (FA II): Yet another embodiment uses cathodic (-) pulses with the same pulse width and ranges as for the Meissner mode (but larger electrode dimensions).

[00263] Calibration of electrotactile stimuli comprises different methods, used by different embodiments:

[00264] Constant current stimulation: To cope with physiological impedance changes, standard techniques for constant current stimulation are used. Some embodiments additionally use standard model-based methods to enable sufficiently constant perception of electrotactile stimuli.

[00265] Electrotactile threshold: For each single modality, i.e., for the Meissner, Merkel as well as the Pacinian mode, threshold tests can be used to calibrate the therapeutic amplitudes I_E and durations T_E or determine effective ranges of I_E and T_E as well as the pause P_E (Figure 8). In addition, the electrotactile threshold can be used to monitor treatment effects.

[00266] Cross-modal comparison: In one embodiment, the electrotactile stimuli of the different modes, i.e., Meissner, Merkel and Pacinian mode, are calibrated to be perceived equally equal “loud”, i.e., equally strong. This comparison can be done subjectively by means of an “equal loudness” comparison and/or by comparing the amplitudes of relevant peaks of evoked vibrotactile and evoked electrotactile EEG responses.

[00267] In another embodiment, the strength of electrotactile stimuli of the three different modes can each be calibrated by comparing with a reference vibratory stimulus. This comparison can be done subjectively by means of an “equal loudness” comparison and/or by comparing the amplitudes of relevant peaks of evoked vibrotactile and evoked electrotactile EEG responses.

[00268] Cross-modal compensation of conduction velocities: Since FA I, FA II and SA I mechanoreceptor afferents belong to the same class of nerve fibers ($A\alpha$) they have the same or very similar conduction velocities. Accordingly, one embodiment does not use any conduction velocity compensation methods. Other embodiments use evoked responses each caused by ensembles of the three different modes (Meissner, Merkel and Pacinian mode), respectively, to compensate for delays in peak evoked responses due to different conduction velocities. The differences of the latencies of the evoked responses of a relevant, i.e., early, peak of the evoked response of the three modes are taken into account for the calculation of the stimulus onset times to counteract imbalances of the conduction velocities of the three (FA I, FA II and SA I) modes.

[00269] FIG. 29 is a waveform diagram illustrating a monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment. The long positive phases (with amplitude I_C) counterbalances the main (negative) stimulation phase with amplitude I_E and duration T_E . The main (negative) stimulation phase starts at t_1 and ends at t_2 .

[00270] FIG. 30 is a waveform diagram illustrating a balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment. The second, negative phase (with amplitude $-I_E$ and duration T_E) counterbalances the first, positive stimulation phase with amplitude I_E and duration T_E . P_E denotes the inter-pulse-pause. The main (positive) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (negative) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00271] FIG. 31 is a waveform diagram illustrating a balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment. The second, positive phase (with amplitude I_E and duration T_E) counterbalances the first, negative stimulation phase with amplitude I_E and duration T_E . P_E denotes the inter-pulse-pause. The main

(negative) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (positive) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00272] FIG. 32 is a waveform diagram illustrating an asymmetric balanced biphasic waveform with vanishing baseline and zero average current as used in another embodiment. The second, negative phase (with amplitude $-I_E/2$ and duration $2T_E$) counterbalances the first, positive stimulation phase with amplitude I_E and duration T_E . P_E denotes the inter-pulse-pause. Other embodiments may use pulse forms with opposite polarity, i.e., first negative phase, followed by a positive phase. The main (positive) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (negative) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00273] So far, Coordinated Reset (CR) stimulation means to stimulate different subpopulations at different times by delivering sequences of stimuli at different stimulation sites at different times.

[00274] The present embodiments use a radically different approach: By using 3 different physiological channels, FA I, FA II, SA I fibers, one embodiment periodically delivers stimuli of varying mode to the same stimulation site, e.g., to the identical fingertip. One embodiment uses 3-channel electrotactile CR stimulation (FIG. 33) with period T_{CR} which defines the CR frequency $f_{CR} = 1/T_{CR}$ at which the same stimulation site, e.g., the same fingertip receives the stimuli of different mode: Channel 1, channel 2, channel 3 denote Meissner mode, Merkel mode and Pacinian mode stimuli, delivered to the same fingertip through the corresponding electrodes (as illustrated in FIGs. 23 and 24) and with parameters and polarity as explained above. The same fingertip receives stimuli periodically, at multiples of $T_{CR}/3$. During one CR period one fingertip receives exactly one channel 1 (Meissner mode) stimulus, one channel 2 (Merkel mode) stimulus and one channel 3 (Pacinian mode) stimulus, where the sequence of channels may vary from one CR period to another. This type of CR stimulation is referred to as CR with rapidly varying sequences (CR RVS). In one embodiment, an $m:n$ ON-OFF pattern is used by delivering stimuli for an ON-period of, e.g., three CR periods, T_{CR} , and paused the stimulation for an OFF period of, e.g., two CR periods afterwards.

[00275] FIG. 33 is a waveform diagram of 3:2 ON-OFF CR RVS (rapidly varying sequences) stimulation with electrotactile stimulation. Timing parameters described in more

detail below can be used, except as follows here. Each vertical bar represents either a single electrotactile stimulus as in Figures 6-10 or a burst (group) of these stimuli delivered to the same stimulation site. The different channels denote stimuli of different modes, e.g., Meissner mode (channel 1), Merkel mode (channel 2) and Pacinian mode (channel 3). The CR frequency f_{CR} is typically selected around 1.5 Hz or 2 Hz or, in general, in a range from 0.5 Hz – 5 Hz. Other embodiments use values of f_{CR} outside this range, e.g., between 0.1 Hz-0.5Hz or between 5 Hz – 20 Hz.

[00276] Since the electrotactile stimuli are short (see above), some embodiments use temporal jitters as well as (e.g., randomly) varying amplitudes T_E (as explained in more detail below) to further improve the stimulation effect.

[00277] For illustration, consider fingertip stimulation. The same principle can be applied to other parts of the body. Electrotactile 3-channel stimulation can be delivered through one fingertip. Other embodiments may use more than one fingertip, where stimulus sequences are delivered in a synchronized manner to different fingertips. In particular, all fingertips receive channel 1 (Meissner) stimuli at the same time. The same holds for channel 2 (Merkel) and channel 3 (Pacinian) stimuli, respectively. Another embodiment varies the assignment between fingertip number and channels, e.g., in a random, deterministic, stochastic and/or combined deterministic-stochastic manner. Let us denote the right fingertips by R1 (thumb) – R2 (index finger) – R3 (middle finger) – R4 (ring finger) – R5 (pinky), and analogously L1 - ... - L5 for the left hand.

[00278] The following explains the time varying assignment by considering two fingers, R1 and R2: Assign channels 1,2,3 of finger R1 to channels j,k,l of finger R2 during a certain period of time, e.g., a group of 3 ON cycles (3301, 3302 in FIG. 33) or during a period of time ranging from 1-10 min or more.

R1-ch_1 $\rightarrow$ R2-ch_j

R1-ch_2 $\rightarrow$ R2-ch_k

R1-ch_3 $\rightarrow$ R2-ch_l ,

where R1-ch_1 means that finger R1 receives a stimulus through channel 1 (i.e., a Meissner stimulus).

[00279] For instance, during the first group 3301 of 3 ON cycles (FIG. 33)

R1-ch_1 → R2-ch_1

R1-ch_2 → R2-ch_2

R1-ch_3 → R2-ch_3 ,

during the second group 3302 of 3 ON cycles

R1-ch_1 → R2-ch_3

R1-ch_2 → R2-ch_1

R1-ch_3 → R2-ch_2

etc.

[00280] The time-varying assignment further reduces the abnormal connectivity patterns and increases the long-term therapeutic effects.

[00281] Contactors for double (or more) 3-channel electrotactile stimulation can be used to avoid possible skin irritation by switching between different 3-channel electrode arrangements, e.g., between right and left electrode array in FIG. 24, after certain periods of time, e.g., after groups of 3 ON cycles (FIG. 33) and/or after longer time periods, e.g., after 10 minutes or more.

[00282] According to certain general aspects, embodiments to be described as follows effectively reduce unwanted mechanical and proprioceptive stimulation while securely mounting controller and battery for a fingertip stimulation array. These and other embodiments are characterized by the following features.

[00283] Massively reduced skin coverage: The embodiments provide reliable mounting with only little skin coverage. Mounting of the controller is done with a simple watch-like band over the palm area and does not translate or vibrate in any significant way during therapy. It mounts softly on the outside of the hand where external effects are naturally at a minimum. This enables to reduce moisture buildup, friction as well as unwanted mechanical and proprioceptive stimulation.

[00284] Strongly reduced contact pressure: To reduce unwanted stimulation by the controller and fixation band, both are low weight, especially controller and battery. The band is adjustable to accommodate all hand sizes with the perfect fit and has a soft and porous fabric for

skin ventilation and comfort. This design provides a convenient fit for a large range of hand sizes.

[00285] Adaptive break away design of single digit cables: For safety reasons each fingertip stimulator is connected through one cable by means of a standard headphone type jack connector where the female side of each connection resides in the controller and the male side of each connection is securely integrated with designated tapper cable. The cables can easily be unplugged in the case that the wires get snagged. This is mandatory for patient safety and it allows rapid replacement to various cable lengths to the optimal cable routing arrangement. Cables are specifically designed to be highly flexible while being provided with various length options to insure minimal finger contact or flexure resistance.

[00286] Back of the hand design: In principle, the controller can also be placed on the reverse side, in the palm. However, for safety and ergonomic reasons the placement on the back of the hand is superior. In case of a fall, the patient is able to catch themselves.

[00287] High Flexure cables: The cables take an S-form to keep them close to the hand and, hence, reduce the patient's risk of getting snagged. For this purpose, the fingertip stimulator, e.g. tapper, cables engage the fingertip stimulators at their right bottom area. This directs the cable flexure to occur between fingers instead of on top of them while minimizing cable loops that can be snagged in normal usage.

[00288] Wireless design: Apart from the single digit cables, there are no further cables. In particular, the controllers for right and left hand communicate wirelessly. The wireless nature of the fingertip stimulation arrays will help prevent falls, make it more comfortable for patients to wear the device and, hence, increase compliance.

[00289] FIG. 34 is a top view of an example controller (3402-L, 3402-R) with fixation band, the high flexure cables and (in this embodiment, vibrotactile) fingertips stimulators (in the case of large hands). FIG. 35 is a top view of a controller (3402-L, 3402-R) with fixation band, the high flexure cables and (in this embodiment vibrotactile) fingertips stimulators (in the case of small hands).

[00290] FIG. 36 is a top view of a controller (3602-L, 3602-R) with fixation band, the high flexure cables and (in this embodiment vibrotactile) fingertips stimulators (in the case of

small hands). Controller 3602 has a different design compared to controller 3402 of FIGs. 34 and 35.

[00291] FIG. 37 is a bottom view of an example fixation band 3702, the high flexure cables 3704 and (in this embodiment vibrotactile) fingertips stimulators 3706 in case of a large hand. FIG. 38 is a bottom view of example fixation band 3702, the high flexure cables 3704 and (in this embodiment vibrotactile) fingertips stimulators 3706 in case of a small hand.

[00292] FIG. 39 is a side view of example fixation band 3702, the high flexure cables 3704 and (in this embodiment vibrotactile) fingertips stimulators 3706 in case of a large hand. FIG. 41 is a side view of example fixation band 3702, the high flexure cables 3704 and (in this embodiment vibrotactile) fingertips stimulators 3706 in case of a small hand.

[00293] FIG. 41 illustrates another possible embodiment. This example illustrates a placement 4102 of the controller that is particularly comfortable based on patient testing. This placement typically requires a different fixation, not just a band, but, for instance, an open glove ('open' = glove only covering the palm, not the fingers). Glove (and/or fingertip stimulation) according to embodiments can be useful for the therapy of Parkinson's and other applications. In fact, the embodiments can potentially be applied to a wide range of disorders. Abnormal neuronal synchronization and abnormal synaptic connectivity patterns are not only found in Parkinsons disease, but are also characteristic of a larger number of disorders of the central and peripheral nervous system, for instance, movement disorders, essential tremor, tic disorders, Tourette's syndrome, tremor in multiple sclerosis, dystonia, chronic stroke, epilepsy, depression, migraine, tension headache, incomplete spinal cord injury, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), irritable bowel syndrome, chronic pain syndromes, e.g., complex regional pain syndrome, neuropathic pain and trigeminal neuralgia, pelvic health disorders, e.g., pelvic pain or overactive bladder, tinnitus, dissociation in borderline personality disorder and posttraumatic stress disorder.

[00294] According to certain aspects, the main difference between the apparatus for the solely vibrotactile and the apparatus for the hybrid (vibrotactile and electrotactile) stimulation according to some embodiments is the contactor. For illustration, reference is made to the example contactors for solely vibrotactile stimulation as shown in FIG. 12.

[00295] To compensate for vibration strength losses caused by the shock absorbing tapper design, developed was a contactor (i.e., the part of the mechanical stimulator that interacts with the patient's skin and deeper layers) which causes stronger physiological/medical effects with the same amount of force/energy/vibration amplitude. As set forth above in connection with FIG. 12, the example contactor for vibrotactile stimulation is characterized by three features: increased outer perimeter, inner cavity perimeter (hole) and non-planer contactor surface.

[00296] Compared to the contactor for vibrotactile stimulation as described above, the contactor for hybrid stimulation contains dedicated electrodes.

[00297] According to certain aspects, an example contactor for hybrid electro-mechanical (eletrotactile and vibrotactile) stimulation according to embodiments modifies the contactor (e.g. octaberry) for vibrotactile simulation by adding properly shaped electrodes, thereby using the same or similar design principles to provide optimal vibrotactile stimulation. The contactor and corresponding mechanical stimulator can be mounted on a patient's fingertips or, in other embodiments, on any part of the skin.

[00298] Based on the same reasoning described above in connection with vibrotactile stimulation embodiments, the outer perimeter of the hybrid contactor is chosen to be an Octaberry – or any object that has a circumference that is greater than that of a circle. Likewise, the contactor surface of the hybrid contactor is not planar, but, e.g., concave or (preferred) convex, with the inner part being closest to the skin. Instead of a hole, added are one or more “annular holes” located between inner and outer electrode. These surfaces are deepened (i.e., in greater distance to the skin) compared to the rest of the non-planar vibrotactile contactor surface. The “annular holes” further strengthen the vibrotactile stimulation effects.

[00299] FIG. 42 is a schematic showing a base of one example embodiment of a circular hybrid contactor 4200 (with diameter d) with an inner, disk-like active inner electrode 4201 with diameter a , and an outer/surrounding, annular dispersive return electrode 4202 with outer diameter c and inner diameter b . In one embodiment, the contactor surface is not planar, but, e.g., convex (with the inner electrode being closest to the skin) - to strengthen vibrotactile stimulation effects. In another embodiment, the insulating surface 4203 between inner and outer

electrode can be deepened (and, hence, in greater distance to the skin compared to the rest of the contactor surface) to further strengthen vibrotactile stimulation effects.

[00300] Some design principles of hybrid stimulation with a contactor containing at least two electrodes according to some embodiments will now be described.

[00301] Smaller inner electrode and smaller surrounding electrode: In one embodiment, the contactor contains an inner electrode 4201 and an outer electrode 4202, with inner electrode diameter around 1 mm and inner diameter of the outer, surrounding (reference) electrode around 6 mm. These values can vary from 0.4-1.7 mm or 0.2-2.5 mm (inner electrode diameter) and from 5.5 mm-6.5 mm or 4.5-7.5 mm (inner diameter of the outer electrode).

[00302] Larger inner electrode and larger surrounding electrode: Another embodiment contains an inner electrode with 3 mm diameter and an outer electrode with 10 mm inner diameter. The latter values can vary from 2.5-3.5 mm or 1.5-4.5 mm (inner electrode diameter) and from 9 mm-11 mm or 7.5-12 mm (inner diameter of the outer electrode).

[00303] Another embodiment has one or more inner electrodes with other (non-disk) shapes, e.g., oval shapes, elliptic shapes or other shapes with increased circumference. Yet another embodiment has one or more outer electrodes with other (non-annular) shapes, e.g., “oval rings”, “elliptic rings” or other shapes with increased circumference. In yet another embodiment, inner and outer electrodes of different shapes can be combined. In addition, another embodiment contains more than two pairs of inner and outer electrodes.

[00304] FIG. 43 is a schematic showing a base of one embodiment of a stretched octaberry 4300 (with outer circumference formed by a stretched octagon and added semi-circles) hybrid contactor (with diameter d) with a pair of identical inner (active) electrodes (4302-1, 4302-2) with diameter R_1 , and outer (dispersive return) electrodes (4304-1 and 4304-2) with inner diameter R_2 . Another embodiment can contain non-identical inner, disk-like and outer, annular electrodes. Yet another embodiment can contain more than one identical or non-identical inner, disk-like and/or inner, elliptic and outer, annular and/or elliptic electrodes. In one embodiment, the contactor surface is not planar, but, e.g., convex (with the inner electrodes being closest to the skin) - to strengthen vibrotactile stimulation effects. In another embodiment, the insulating surfaces between inner and outer electrodes (hatched) can be deepened (and,

hence, in greater distance to the skin compared to the rest of the contactor surface) to further strengthen vibrotactile stimulation effects.

[00305] While FIG. 42 illustrates the how the pair of electrodes is contained in the contactor, stronger vibrotactile stimulation effects can be elicited with a non-circular, e.g., octaberry perimeter (FIG. 43).

[00306] Other embodiments can be applied to other parts of the body, not only the fingertips, e.g., to other parts of the hand or to the forearm, feet, leg and/or trunk. In general, the inner diameter a (FIG. 42) of the inner, active electrode typically amounts to 1-10 mm, and outer diameter c (FIG. 42) of the outer, dispersive return electrode ranges from 4-100 mm and $b - a = 1-5$ mm, where b is the inner diameter (FIG. 42) of the outer, dispersive return electrode, but may also attain values outside these ranges.

[00307] Different embodiments use different combinations of vibrotactile and electrotactile stimulation, as will now be described.

[00308] One embodiment uses vibratory stimuli with constant indentation of, e.g., 0.5 mm-1.00 mm without and/or with pedestals as explained in more detail below. One example of a vibratory stimulus is shown in FIG. 44. For example, FIG. 44 is a schematic illustrating an example 100 ms vibratory pulse 4402 starting at 0.1 s, around a constant indentation 0.5 mm.

[00309] Steplike indentation stimuli - Another embodiment uses steplike mechanical stimuli. Different embodiments may use steplike stimuli starting with vanishing (FIGs. 45 and 46) or non-vanishing indentation (FIG. 47). Other embodiments use other pulse shapes, e.g., with different rise and fall shapes, typically containing a plateauing shape in between. Rise and fall times may be short (FIG. 45) or long (FIG. 46), e.g., in the order of, e.g., 1-10 ms or more, e.g., 100 ms or more. In addition, rise and fall time may differ from each other. Some embodiments use long rise and fall times when the vibrotactile stimulus mainly serves to ensure sufficient indentation and, hence, electrode-skin contact for electrotactile stimulation.

[00310] Mechanical stimuli of this kind, especially those with short rise and fall time, stimulate all four types of mechanoreceptors (FA I, FA II, SA I, SA II) of the glabrous skin of the hand. Stimulation duration may range from 1 ms – 100 ms and more, e.g., 200 ms or up to 1 s and more. Yet another embodiment may use a series of steplike indentation stimuli.

[00311] FIG. 45 is a waveform diagram of an example steplike stimulus starting at t_1 and ending at t_2 , with vanishing indentation baseline according to embodiments.

[00312] FIG. 46 is a waveform diagram of an example smooth steplike stimulus starting at t_1 and ending at t_2 , with vanishing indentation baseline according to embodiments.

[00313] FIG. 47 is a waveform diagram of an example steplike stimulus starting at t_1 and ending at t_2 , with non-vanishing indentation baseline according to embodiments. Dashed line for comparison to FIG. 45.

[00314] As set forth above, in comparison to mechanical, vibrotactile stimulation, electrotactile stimulation, i.e., stimulation of sensory nerves by administration of electrical current over the skin, has several advantages including low latency and energy efficiency.

[00315] Changes of the impedance of the electrode-skin interface change the perceived sensation intensity. This constitutes a relevant limitation of electrotactile stimulation. Impedance changes are caused by mechanical as well as physiological changes. Mechanical changes are caused by varying contact area and/or pressure, whereas physiological changes are due to physiological alterations, e.g., sweating at the electrode site. Some of these changes can be at least partially counteracted by current controlled delivery of the stimulation current. However, relevant mechanical changes, e.g., caused by peeling back electrodes or strong changes of contact area and/or pressure, still remain a challenge. To overcome this limitation, embodiments use hybrid stimulation, where the mechanical stimulation enables sufficiently constant contact area and pressure of the stimulation electrodes.

[00316] Different embodiments use different pulse forms (i.e., wave forms). In addition, one embodiment can use more than one pulse forms. Pulse forms without current balancing (e.g. FIG. 48) are not used in some embodiments since they may cause skin irritations. Different types of current-balanced pulse forms (with zero average current) can be used by different embodiments, for instance: monophasic pulse forms with non-vanishing baseline and zero average current of positive (e.g. FIG. 49) or negative polarity (e.g. FIG. 50), balanced biphasic pulse forms with vanishing baseline and zero average current (e.g. FIGs. 51 and 52) or asymmetric balanced biphasic waveforms with vanishing baseline and zero average current (e.g. FIG. 53). Other embodiments may use other current-balanced pulse forms.

[00317] In general, example parameter ranges are:

pulse amplitude I_E : up to 50 mA

pulse width T_E : 2-1000 μ s

inter-pulse-pause P_E : 0-1000 μ s, typical values are around 40-50 μ s

Pulse rates, i.e., the rate at which the pulse forms mentioned above are delivered:

1 Hz-25 kHz

Pulses can be delivered as bursts, i.e., groups of sequentially delivered pulses.

Burst rate: 1 – 1000 Hz

Time between bursts: 1-1000 ms

[00318] Some embodiments may use values outside the parameter ranges above.

[00319] FIG. 48 is a waveform diagram illustrating a zero-baseline monophasic pulse form with non-vanishing net dc current with amplitude I_E and duration T_E . Some embodiments do not use such pulse forms for electrotactile stimulation since they can cause rapid skin irritations resulting from electrochemical reactions at the skin-electrode interface. The stimulation pulse starts at t_1 and ends at t_2 . Analogously, zero-baseline monophasic pulse form of opposite polarity (with net dc current) are not used by preferred embodiments either.

[00320] Different embodiments use different electrode designs to stimulate different mechanoreceptors, located in different skin depth and having different preferential nerve fiber directions (relative to the skin surface).

[00321] Meissner corpuscles (belonging to FA I mechanoreceptors) are located in superficial parts of the skin, i.e., in less than 1 mm depth. They react most strongly to low frequency vibration (20-70 Hz), with a resonant frequency at around 30 Hz.

[00322] Pacinian corpuscles (belonging to FA II mechanoreceptors) are located in the deeper parts of the skin, in about 2 mm depth, and react to high frequency vibrations 100-400 Hz, with a resonant frequency around 250 Hz.

[00323] Merkel cells (MCs) are found in the stratum basale, in the bottom part of the epidermis (i.e., the superficial layer of the skin). They are associated with slowly adapting (SA1) somatosensory nerve fibers and respond to low vibrations (5–15 Hz) as well as deep static touch corresponding to shapes and edges.

[00324] Different embodiments use different electrode configurations and dimensions (introduced above) together with different stimulation parameters to induce specific effects, as will be described below.

[00325] FIG. 49 is a schematic illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment. The long negative phases (with amplitude I_C) counterbalances the main (positive) stimulation phase with amplitude I_E and duration T_E . The main (positive) stimulation phase starts at t_1 and ends at t_2 .

[00326] For example designs with smaller inner electrode and smaller surrounding electrode, the following aspects are considered.

[00327] Meissner (FA I) mode: One embodiment uses anodic (+) pulses at frequencies ranging from 1 Hz up to 120 Hz and more, e.g., 250 Hz and even more, e.g., 400 Hz or 500 Hz with pulse amplitudes around 2.4 mA, e.g., in a range from 0.5 mA – 10 mA, and pulse width around 0.1 ms, e.g., in a range from 0.005 ms – 1 ms and more, e.g., 2 ms or even up to 5 ms. These stimuli activate FA I nerve fibers, leading to (low-frequency) vibration sensation. Intriguingly, these nerve fibers can also be stimulated at higher frequencies (e.g. > 120 Hz). Electrode dimensions (and their ranges) were introduced above.

[00328] Merkel mode (SA I): Another embodiment uses the same parameters and electrode dimensions as for the Meissner mode, but cathodic (-) pulses. This causes a different current flow which stimulates nerve fibers connected to the Merkel cells, leading to activation of SA I fibers and in turn, pressure-like sensations. Electrode dimensions (and their ranges) were introduced above.

[00329] For example designs including a larger inner electrode and larger surrounding electrode, the following aspects are considered.

[00330] Pacinian mode (FA II): Yet another embodiment uses cathodic (-) pulses with the same pulse width and ranges as for the Meissner mode (but larger electrode dimensions).

[00331] Calibration of vibrotactile stimuli with or without pedestals is described in more detail below. Calibration of electrotactile stimuli comprises different methods, used by different embodiments, as described as follows:

[00332] Constant current stimulation: To cope with physiological impedance changes, standard techniques for constant current stimulation are used. Some embodiments additionally

use standard model-based methods to enable sufficiently constant perception of electrotactile stimuli.

[00333] Electrotactile threshold: Threshold tests can be used to calibrate the therapeutic amplitudes I_E and durations T_E or determine effective ranges of I_E and T_E as well as the pause P_E (e.g. FIG. 51). In addition, the electrotactile threshold can be used to monitor treatment effects.

[00334] Cross-modal comparison: The strength of electrotactile stimuli can be calibrated in comparison with a reference vibratory stimulus. This comparison can be done subjectively by means of an “equal loudness” comparison and/or by comparing the amplitudes of relevant peaks of evoked vibrotactile and evoked electrotactile EEG responses. In another embodiment, the equal loudness calibration can also be done only between electrotactile stimuli (without vibratory reference stimulus).

[00335] FIG. 50 is a waveform diagram illustrating an example monophasic pulse form with non-vanishing baseline and zero average current as used in another embodiment. The long positive phases (with amplitude I_C) counterbalances the main (negative) stimulation phase with amplitude I_E and duration T_E . The main (negative) stimulation phase starts at t_1 and ends at t_2 .

[00336] FIG. 51 is a waveform diagram illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment. The second, negative phase (with amplitude $-I_E$ and duration T_E) counterbalances the first, positive stimulation phase with amplitude I_E and duration T_E . P_E denotes the inter-pulse-pause. The main (positive) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (negative) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00337] FIG. 52 is a waveform diagram illustrating an example balanced biphasic pulse form with vanishing baseline and zero average current as used in another embodiment. The second, positive phase (with amplitude I_E and duration T_E) counterbalances the first, negative stimulation phase with amplitude $-I_E$ and duration T_E . P_E denotes the inter-pulse-pause. The main (negative) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (positive) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00338] FIG. 53 is a schematic illustrating an example asymmetric balanced biphasic waveform with vanishing baseline and zero average current as used in another embodiment. The second, negative phase (with amplitude $-I_E/2$ and duration $2T_E$) counterbalances the first,

positive stimulation phase with amplitude I_E and duration T_E . P_E denotes the inter-pulse-pause. Other embodiments may use pulse forms with opposite polarity, i.e., first negative phase, followed by a positive phase. The main (positive) stimulation phase starts at t_1 and ends at t_2 . The counterbalancing (negative) stimulation phase starts at t_3 and ends at t_4 . Both phases are separated by a pause $P_E = t_3 - t_2$.

[00339] Different embodiments use different types of synchronization of mechanical and electrical stimulation. Typically, electrical stimuli are delivered when the indentation is sufficiently pronounced and/or maximal (for a given mechanical stimulus shape), as described below. However, other embodiments may use more complex types of synchronization.

[00340] Steplike mechanical stimuli serve two example purposes:

[00341] 1. They stimulate all four types of mechanoreceptors (FA I, FA II, SA I, SA II) of the glabrous skin of the hand, with FA I and FA II typically showing strongest responses when indentation starts and/or stops, while SA I and SA II typically also respond while the indentation plateaus.

[00342] 2. They enable a sufficiently strong and reliable contact pressure for the electrotactile stimulation. Consequently, the quality of the electrotactile stimulation increases, especially for dry skin.

[00343] FIG. 54 is a waveform diagram illustrating an example steplike mechanical stimulus 5402 and the corresponding electrotactile stimulus train 5404. Each vertical bar represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli. Other embodiments can use trains with non-constant rate of stimulus delivery or any other sequence of stimuli or bursts of stimuli from FIGs. 49-53. Electrotactile stimuli are typically delivered when the mechanical stimulus enables sufficient indentation and, hence, electrode-skin contact.

[00344] Embodiments described herein favorably administer electrotactile stimuli during phases of the vibratory stimuli with sufficiently strong indentation, in this way enabling reliable contact pressure for the electrotactile stimulation. Consequently, the quality of the electrotactile stimulation increases, especially for dry skin. Different embodiments use different combinations of vibratory stimuli and electrotactile stimuli for different purposes, as follows.

[00345] 1. Low-frequency (< 100 Hz, e.g., around 30-60 Hz) vibratory stimulus (mainly stimulating FA I mechanoreceptors) and phase-locked electrotactile stimuli in Meissner (FA I) mode (see above): The bimodal, i.e., combined vibratory and electrotactile, FA I stimulation provides strong stimulation, in this way enabling short stimuli. Instead of a larger number of, for example, more than 20 vibration periods only a few (< 10) vibration periods provide strong stimulation. This is a major advantage since it significantly reduces in-channel masking and enables temporal jitter of stimulus delivery (described in more detail below).

[00346] 2. High-frequency (> 100 Hz, e.g., around 250 Hz) vibratory stimulus (mainly stimulating FA II mechanoreceptors) and phase-locked electrotactile stimuli in Meissner (FA I) mode (see above): Due to their different response threshold profiles, it is difficult to strongly stimulate both FA I and FA II mechanoreceptors with a sinusoidal vibratory stimulus (of one frequency). For instance, for vibration frequencies greater than approx. 70 Hz, the vibration threshold of FA II mechanoreceptors is smaller, for frequencies greater than 100 Hz considerably smaller than the vibration threshold for FA I mechanoreceptors. Intriguingly, Meissner corpuscles can be strongly stimulated by means of electrotactile stimuli (in Meissner mode, see above) not only at frequencies smaller, but also greater than 100 Hz. A bimodal, i.e., combined vibratory (FA II) and electrotactile (FA I), phase-locked stimulation (e.g. FIG. 54) enables a strong stimulation through two different, converging pathways (FA I and FA II) with comparable propagation delays.

[00347] Propagation delays of vibratory stimuli and electrotactile stimuli can be detected with evoked responses, i.e., by delivering an ensemble of (identical) vibratory stimuli as well as an ensemble of (identical) electrotactile stimuli. Differences in the peak latencies of their evoked responses can be accounted for by means of using phase-shifted 1:1 phase locked bimodal stimuli (e.g. FIG. 56).

[00348] To compensate for the differences of the slow build-up of vibratory stimulus effects as opposed to the quick build-up of electrotactile stimulus effects, different, in particular, time-varying coordination patterns, e.g., with increasing 1:n cycle ratio between vibratory and electrotactile (e.g., with n increasing from 1 to 3, e.g. FIG. 57), can be used. Another embodiment uses a decreasing m:1 cycle ratio, with m decreasing from 3 to 1 (e.g. FIG. 64), as illustrated with a vibratory burst with pedestals (described in more detail below). More

complex, varying cycle ratio patterns (as e.g. shown in FIGs. 63 and 65) can be used to induce specific evoked responses, e.g., to strengthen late responses of brain areas other than primary sensory cortex, in this way increasing the propagation of stimulus effects in brain circuits. In general, due to the different build-up characteristics of vibratory as opposed to electrotactile stimuli, vibratory and electrotactile stimulus can be of different duration (e.g. FIG. 62). Yet another embodiment uses a phase shift between vibratory and electrotactile stimuli to compensate for propagation delay differences.

[00349] 3. High-frequency (> 100 Hz, e.g., around 250 Hz) vibratory stimulus (mainly stimulating FA II mechanoreceptors) and phase-locked electrotactile stimuli in Meissner (FA I) mode (see above): Vibratory stimuli and electrotactile stimuli can have different frequencies, e.g., to induce different perceptions. To deliver electrotactile stimuli when electrode-skin contact is optimal, different m:n cycle ratios between vibratory and electrotactile stimulation can be used, e.g., electrotactile stimulation at half the vibratory frequency (e.g. FIGs. 58, FIG. 66), bursts of 2 (e.g. FIG. 59) or 3 (e.g. FIG. 60) per vibration cycle (close to maximum indentation). Other embodiments use phase shifts between vibratory and electrotactile stimuli to compensate for propagation delay differences.

[00350] 4. High-frequency (> 100 Hz, e.g., around 250 Hz) vibratory stimulus (mainly stimulating FA II mechanoreceptors) and phase-locked electrotactile stimuli in Merkel (SA I) mode (see above): Some embodiments use this combination of FA II and SA I stimuli to provide effective stimuli, which are converging on its way to the cortex. In addition, since pressure-like sensation is qualitatively different from vibration, this type of stimulus can also be intermingled in stimulation patterns using the other stimulus patterns (mentioned above) at a rate of 5-10 % to effectively reduce habituation effects as described in more detail below. In general, due to the variety of combinations of vibrotactile and electrotactile stimuli, stimuli may cause subjectively very different perceptions. Hence, this increases the inventory of therapeutically effective, but perceptually different stimuli to be used to effectively prevent habituation.

[00351] 5. Multiple spatial electrotactile channels per contactor (e.g. FIG. 43): For contactors housing more than one electrode pair for electrotactile stimulation, identical and/or different electrotactile stimuli can be delivered through the different electrode pairs at the same

time. Other embodiments may use more than one electrode pair to enable skin to recover from potential stimulation side effects such as skin irritation and/or prevent from long term side effects and skin irritation. Accordingly, when using vibrotactile stimulation patterns as described in more detail below, delivery of electrotactile stimuli can be switched from one electrode pair to another, e.g., after every vibratory sequence or after groups of vibratory sequences, e.g., ON groups when applying n cycles ON, m cycles OFF vibrotactile coordinated reset stimulation.

[00352] 6. Sub-threshold vibratory (pedestal, as described below) combined with phase-locked suprathreshold electrotactile stimulation: Some embodiments use this type of hybrid stimulation, e.g., to provide sufficient electrode-skin contact for the electrotactile stimulation.

[00353] 7. In another embodiment of the contactor shown in FIG. 43, two (or more) pairs of electrodes of different dimensions can be used, e.g., to deliver different types of electrotactile stimuli. In this way, the pair of electrodes with smaller dimensions enables to deliver electrotactile stimuli of Meissner and/or Merkel mode, whereas the electrode pair with larger dimensions is used to deliver electrotactile stimuli of Pacinian mode.

[00354] FIG. 55 is a waveform diagram illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00355] FIG. 56 is a waveform diagram illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with non-zero phase shift. The non-zero phase shift may compensate for different propagation delays of FA I and FA II mechanoreceptors. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00356] FIG. 57 is a waveform diagram illustrating an example hybrid (i.e., combined vibratory and electrotactile) stimulation with increasing 1:n cycle ratio between vibratory and electrotactile (e.g., with n increasing from 1 to 3 in the course of the vibratory burst. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00357] FIG. 58 is a waveform diagram illustrating an example 2:1 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where one electrotactile stimulus is delivered per 2 vibratory cycles. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00358] FIG. 59 is a waveform diagram illustrating an example 1:2 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where two electrotactile stimuli are delivered per vibratory cycle. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00359] FIG. 60 is a waveform diagram illustrating an example 1:3 phase locked bimodal (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, where three electrotactile stimuli are delivered per vibratory cycle. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00360] FIG. 61 is a waveform diagram illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered together with electrotactile stimuli phase locked to maxima of the suprathreshold burst. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00361] FIG. 62 is a waveform diagram illustrating an example 1:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with different vibratory and electrotactile stimulus duration. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered together with 10 electrotactile stimuli phase locked to maxima of the suprathreshold burst. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00362] FIG. 63 is a waveform diagram illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally

patterned electrotactile stimulus and more complex cycle ratio between vibratory and electrotactile stimulation. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered together with 3 electrotactile stimuli at vibratory onset and 8 electrotactile stimuli at the end of the vibratory burst, all phase locked to maxima of the suprathreshold burst. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00363] FIG. 64 is a waveform diagram illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally patterned electrotactile stimulus and more complex cycle ratio between vibratory and electrotactile stimulation, where the $m:1$ cycle ratio changes during a vibratory burst, with m decreasing from 3 to 1. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered together with electrotactile stimuli. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00364] FIG. 65 is a waveform diagram illustrating an example phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with temporally patterned electrotactile stimulus and more complex cycle ratio between vibratory and electrotactile stimulation, where the final 4 electrotactile stimuli are delivered phase locked to the pedestal. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered together with electrotactile stimuli. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00365] FIG. 66 is a waveform diagram illustrating an example 2:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with phase locked electrotactile stimuli coinciding with half of the maxima of the vibratory burst. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00366] FIG. 67 is a waveform diagram illustrating an example 4:1 phase locked hybrid (i.e., combined vibratory and electrotactile) stimulation with zero phase shift, with phase locked electrotactile stimuli coinciding with a fourth of the maxima of the vibratory burst. A subthreshold pedestal with a 100 ms suprathreshold vibratory burst (described in more detail below) is delivered. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00367] In general, embodiments may use the same or similar stimulation patterns as described in more detail below, with vibratory stimuli using pedestals and/or only suprathreshold stimuli (i.e., no pedestals).

[00368] An additional advantage of hybrid stimulation is a consequence of the short duration of effective electrotactile stimuli. Accordingly, some embodiments use temporal jitter between the onset times of the vibrotactile and the electrotactile stimuli, as illustrated in FIG. 68. For instance, denoting the onset of the k -th vibratory (suprathreshold) stimulus in channel j by $\tau_{k,j}^v$ and the corresponding k -th vibratory electrotactile stimulus in channel j by $\tau_{k,j}^e$, the time difference of both onsets reads $\Delta\tau_{k,j} = \tau_{k,j}^v - \tau_{k,j}^e$. $\Delta\tau_{k,j}$ can be selected by means of random processes and/or based on deterministic, chaotic, stochastic and combined deterministic-stochastic systems and rules. The variations of $\Delta\tau_{k,j}$ can be uncorrelated between channels j . Another embodiment uses temporal jitters defined by cross-channel variations $\Delta\tau_{k,j,l,m} = \tau_{k,j}^v - \tau_{l,m}^e$ being varied based on deterministic, stochastic, random, combined deterministic-stochastic rules.

[00369] FIG. 68 is a waveform diagram illustrating an example hybrid stimulation with temporal jitter between vibrotactile and electrotactile stimuli. Schematic shows two channels of hybrid stimuli with different onsets of vibratory stimuli, here suprathreshold vibratory stimuli, standing out from ongoing vibratory pedestals (described in more detail below), and onsets of electrotactile stimuli, here groups of three vertical bars. Each vertical bar superimposed on the vibrotactile waveform represents either a single electrotactile stimulus as in FIGs. 49-53 or a burst (group) of these stimuli.

[00370] Among other things, the present embodiments relate to methods and apparatuses that enable more effective vibrotactile stimulation, i.e., stronger physiological effects with less vibration power/amplitude. For example, one or more embodiments enable spatially more focal

and/or shorter activation by means of novel (compound) pulses or continuous stimulation with specifically modulated amplitudes.

[00371] Compound stimuli are one important aspect of some embodiments. The vibrotactile stimuli used for vCR are circumscribed in time, i.e., their amplitude is non-zero only during stimulus delivery [P.A. Tass: Vibrotactile Coordinated Reset Stimulation for the Treatment of Neurological Diseases – Concepts and Device Specifications. *Cureus* 9(8) (2017) e1535] (Figure 1). Apart from sine signals, one can use narrow-band, triangular, sawtooth and other signals. However, oscillatory stimuli should predominately target high-frequency or low-frequency bands (see above). In general, the vibrotactile (mechanical) stimulation signal reads

$$x(t) = A(t) \cdot h(t),$$

[00372] where $A(t)$ is the amplitude of the mechanical stimulation signal, and $h(t)$ represents the oscillatory part of $x(t)$. $h(t)$ can be a sine such as:

$$h(t) = \sin(2\pi f t)$$

[00373] where, e.g., in case of a high-frequency burst (see above), $f = 250$ Hz. Note, so far, for long periods of time a mechanical (vibrotactile) stimulator does not deliver any stimulation, $A(t) = 0$, and stimuli (with $A(t) > 0$) are circumscribed in time (Figure 1). The goal of these circumscribed stimuli is to cause a phase reset of abnormal, disease-related synchronized oscillatory neuronal activity. For this, the phase resetting stimulus should ideally be sharp in time as well as confined to separate neuronal subpopulations (see limitations above).

[00374] FIG. 69 illustrates an example of a standard vibration signal with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation. Parameters of single vibratory burst:

[00375] $d_{j,k}$ = duration of j th vibratory burst ($j=1,2,3,\dots$) of the k th channel (e.g., finger)

[00376] $A_{j,k}$ = amplitude of j th vibratory burst ($j=1,2,3,\dots$) of the k th channel (e.g., finger)

[00377] $t_{j,k}$ = onset of j th vibratory burst of k th channel

[00378] $\tau_{j,k}$ = offset of j th vibratory burst of k th channel

[00379] f = vibration frequency = 250 Hz

[00380] For vCR, a vibration signal typically oscillates around a constant indentation of, e.g., 0.5 mm (FIG. 69), see US Patent Publ. No. 20210401664, the contents of which are incorporated herein by reference. A type of vibrotactile stimulus according to embodiments uses a pedestal (i.e., sub-perception stimulus) to render the nervous system more susceptible. The pedestal can be circumscribed in time (e.g. FIG. 70) or – more preferred, since even more effective – sufficiently long (compared to the suprathreshold part) or even continuous (e.g. FIG. 71). The pedestal prepares the nervous system and renders it more susceptible, so that a weaker and/or shorter suprathreshold stimulus causes the same stimulus effect, i.e., the same perceptual strength or the same amount of phase reset of the abnormal neuronal brain rhythm or the same peak amplitude of the evoked brain response. An advantage of the pedestal-induced boost of efficacy is that the mechanical wave propagation in the skin is substantially reduced since the amplitude of the oscillatory vibration signal and/or its duration is substantially reduced.

[00381] FIG. 70 illustrates an example of a vCR vibration signal 7002 according to embodiments with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation and sub-threshold pedestal, circumscribed in time. The vibratory perception threshold is indicated by the dashed line. Parameters of vibratory burst with pedestal 7002 are as follows:

[00382] $d_{j,k}$ = duration of j th vibratory burst ($j=1,2,3,\dots$) of the k th channel (e.g., finger)

[00383] $A_{j,k}$ = amplitude of j th (suprathreshold) vibratory burst ($j=1,2,3,\dots$) of the k th channel (e.g., finger)

[00384] $p_{j,k}$ = amplitude of the pedestal (subthreshold vibration) belonging to the j th vibratory burst ($j=1,2,3,\dots$) of the k th channel e.g., finger)

[00385] f = vibration frequency = 250 Hz

[00386] V_k = vibratory threshold of k th channel (obtained by threshold calibration test)

[00387] $t_{j,k}$ = onset of j th (suprathreshold) vibratory burst of k th channel

[00388] $\tau_{j,k}$ = offset of j th (suprathreshold) vibratory burst of k th channel

[00389] $u_{j,k}$ = onset of pedestal of j th (suprathreshold) vibratory burst of k th channel

[00390] $v_{j,k}$ = offset of pedestal of j th (suprathreshold) vibratory burst of k th channel

[00391] FIG. 71 illustrates an example of a vibratory signal 7102 with high (250 Hz) intra-burst frequency with constant 0.5 mm indentation and continuous sub-threshold pedestal.

The vibratory perception threshold is indicated by the dashed line. A pedestal of sufficient length, e.g., a pedestal duration exceeding the duration of the suprathreshold burst several, e.g., 2-3 (or more) times is typically more effective, so that a shorter suprathreshold stimulus part is sufficient to induce the same stimulus effect, i.e., the same perceptual strength or the same amount of phase reset of the abnormal neuronal brain rhythm and/or the same peak amplitude of the evoked brain response.

[00392] Pedestal-boosted vibratory bursts enable similar/same stimulus effects at smaller amplitudes, where longer and/or continuous pedestals are typically superior to pedestals of limited duration (compared to the duration of the suprathreshold part of the compound stimulus).

[00393] Vibratory perpendicular sinusoidal skin displacements in the 5-60 Hz, especially 30 to 60 Hz range are optimal stimuli for fast-adapting type I (FA I) mechanoreceptors, whereas vibratory stimuli in the approx. 40-400 Hz, especially 100-300 Hz range are optimal stimuli for fast-adapting type II (FA II) mechanoreceptors. The FA I-related frequency range will be denoted low-frequency range (e.g., 30-60 Hz), and FA II-related frequency range will be denoted as high-frequency range (e.g., 100-300 Hz).

[00394] Pedestals and suprathreshold stimulus parts with same frequency f : The pedestal-mediated boost can be applied to high- and low-frequency bursts alike. However, to this end, pedestal and suprathreshold stimulus parts should either be of the same frequency f (or - less preferred - of similar frequency within either the high- or the low-frequency band). A preferred version is to have the same frequency f for both pedestals and suprathreshold stimulus parts.

[00395] Importantly, pedestal and suprathreshold stimulus parts should never be of different frequency ranges, e.g., high-frequency pedestal combined with low-frequency suprathreshold stimulus part or vice versa, since this typically impairs the effect of the suprathreshold stimulus part.

[00396] Pedestals and suprathreshold stimulus parts with narrow-band noise: As an alternative to a sine signal $h(t)$ with single frequency f and time-varying amplitude $A(t)$ as illustrated in FIGs. 73 and 74, one can also use a narrow-band signal $h(t)$ with time-varying amplitude $A(t)$. Of note, the narrow-band signal should be either in the high-frequency or in the

low-frequency range. For this, the frequency range of the narrow band signals should be adapted to the high-frequency or low-frequency ranges provided above, respectively. For instance, low-frequency narrow-band noise could be centered around 20 Hz (0 dB), with spectral values of, e.g., -25 dB at 10 Hz and -57 dB at 60 Hz. A high-frequency narrow-band noise could, e.g., be centered around 200 Hz (0 dB), with spectral values of -40 dB at 100 Hz and -35 dB at 400 Hz. Furthermore, when using narrow band noise, both pedestal and suprathreshold stimulus parts should be in the same frequency range, either low- or high-frequency.

[00397] Continuous stimulation with amplitude modulation: Importantly, pure sine pedestals and suprathreshold stimulus parts (both with the same single frequency f) are typically more effective than pedestals and suprathreshold parts using narrow-band noise. Accordingly, one embodiment uses continuous stimulation with one frequency f , while varying the amplitude $A(t)$.

[00398] Stimulus pauses of a few seconds or minutes may be used to intersect the stimulation occasionally or regularly. During these pauses, the pedestals may vanish and upon restart of the pedestals a different frequency f' (for both pedestals and suprathreshold stimulus parts) may be chosen. Pedestal-free pauses may occur during OFF periods (e.g. FIG. 73) or during pauses occurring on a longer time scale. Turning off pedestals at the beginning of a pause is typically done in a rapid manner, i.e., immediately, with fall times of, e.g., 25 ms. In contrast, restarting a pedestal within a pause should be done sufficiently in advance of the next suprathreshold stimulus, e.g., with an advance amounting to 3-7 times the (average) duration of the (suprathreshold) vibratory bursts (or longer).

[00399] Rise times and fall times: Note, rise times and fall times of the suprathreshold stimulus parts typically differ from those of the pedestals. While rise times of the suprathreshold stimulus parts can be short, e.g., amounting to only 2 ms, the circumscribed pedestals may have considerably longer rise times and fall times, e.g., 25 ms. For some applications, it may be favorable to use quick rise times and fall times of the suprathreshold parts of the stimulus combined with flat plateaus of the suprathreshold amplitude in between. For other applications, however, the shape of the amplitude should favorably be more complex, including asymmetric

shapes for rise and fall as well as slowly oscillating wave forms as opposed to plateauing amplitudes.

[00400] Circumscribed pedestals can be terminated quickly, even immediately after a suprathreshold vibratory burst, e.g., with fall times of 25 ms. In contrast, to be effective, the part of the pedestal preceding the suprathreshold vibratory burst should be of sufficient length, typically in the range of 3-7 times the (average) duration of the (suprathreshold) vibratory bursts (or longer).

[00401] For simplicity, the differences in rise times and fall times of pedestals vs. suprathreshold stimulus parts were not taken into account in the figures. Also, for circumscribed pedestals, the parts of the pedestal preceding and following the suprathreshold stimulus part do not need to be symmetric, in particular, they do not need to be of the same length. Typically, they are not symmetric (see above).

[00402] Using a pedestal means to deliver a long vibratory stimulus with time-varying amplitude. Contrary to previous patents and applications (e.g., US 2013/0041296 A1), the compound stimuli are smeared out in time. The onset timing relationships of subthreshold and suprathreshold parts of the compound stimuli delivered through different channels can differ. For instance, the onsets of the subthreshold parts of compound stimuli delivered through two or more channels can coincide, while their supra-threshold parts can be delivered at different times (e.g. FIG. 73).

[00403] In different embodiments, the time-course of the subthreshold and the supra-threshold parts of the compound stimuli can attain different shapes.

[00404] It should be noted that “pedestal” is a term used in proprioceptive physiology in the context of negative masking: A pedestal with a strength close to threshold reduces the actual perception threshold. This example definition is provided for context only and is not intended to limit the present embodiments.

[00405] It should be further noted that onset and offset of suprathreshold vibratory burst preferably should be in phase with pedestal (e.g. FIG. 70). This causes a quantization of stimulus onset and offset times.

[00406] In one embodiment, the compound stimuli are applied to CR stimulation. On other embodiments the compound stimuli can be used for various single- and multichannel stimulation patterns aiming at inducing long-lasting neuronal desynchronization.

[00407] vCR stimulation without pedestal: vCR stimulation without pedestals (FIG. 72) is characterized by the vCR period T_{CR} , which sets the CR frequency $f_{CR} = 1/T_{CR}$ at which individual fingertips received burst stimuli. Individual fingertips receive stimuli at multiples of $T_{CR}/4$ such that each fingertip receive exactly one stimulus per CR period. Beside this constraint, stimuli are delivered to randomly selected fingertips. This type of CR stimulation is referred to as CR with rapidly varying sequences (CR RVS). In one embodiment, the method uses an $m:n$ ON-OFF pattern by delivering stimuli for an ON-period of, e.g., three CR periods, T_{CR} , and paused the stimulation for an OFF period of, e.g., two CR periods afterwards.

[00408] FIG. 72 is a waveform illustration of 3:2 ON-OFF CR RVS (rapidly varying sequences) stimulation without pedestals. Channels 1-4 denote, e.g., fingertips of index finger, middle finger, ring finger, and pinky of one hand, respectively. Dashed lines 7202 indicate multiples of the vCR period T_{CR} and dotted lines 7206 multiples of $T_{CR}/4$ during individual CR periods. Stimulation bursts are marked by gray rectangles 7204. Parameters: $f_{CR} = 1.5$ Hz ($T_{CR} = 166.7$ ms), burst duration 100 ms, and $f_{burst} = 210$ Hz. The figure shows an OFF period followed by three ON periods which in turn are followed by two OFF periods.

[00409] FIG. 73 illustrates the corresponding vCR stimulation pattern with pedestals. More particularly, FIG. 73 is a waveform illustration of 3:2 ON-OFF CR RVS (rapidly varying sequences) stimulation with pedestals, optimally calibrated for each channel (e.g., finger) separately, with the same format as in FIG. 72. In one embodiment, pedestals 7302 of all channels are turned on and off at the same time. They are turned on, e.g., more than T_{CR}/N before each group of ON periods (N =number of channels), whereas they are turned off at around T_{CR}/N after each group of ON periods. The figure shows an OFF period followed by three ON periods which in turn are followed by two OFF periods.

[00410] The novel compound pulses enable to personalize stimuli to the individual finger of every individual patient. This requires a calibration.

[00411] In one embodiment, the device automatically determines the threshold amplitude. To this end, test stimuli are delivered to the subject, optimally for each stimulus site,

e.g., each fingertip, - less optimally at one or a few (but not all) stimulation sites. In the latter case, the minimum of the measured thresholds is used as threshold for all other stimulation sites. The duration and all other parameters of the test stimuli (carrier frequency f or parameters of the narrow band oscillation) are identical to those of the pedestals. In case of continuous ('infinite') pedestals, the duration of the test stimuli will be selected as, e.g., 3-10 s.

[00412] Threshold detection: For a single stimulation site, the amplitude of the test stimuli is varied in ascending and/or descending and/or randomized order. Subjects are, e.g., asked whether they perceive a test stimulus within a certain time window. The minimum vibration amplitude of perceived stimuli is considered as threshold. The maximum vibration amplitude belonging to non-perceived stimuli is selected as pedestal amplitude. Another option for robust threshold calibration is the two-interval forced choice (2IFC) method, where a subject would be presented with a series of two-interval trials where a stimulus is presented in either the first or second interval (J. Zwislocki, F. Maire, A. S. Feldman, H. Rubin: On the Effect of Practice and Motivation on the Threshold of Audibility. The Journal of the Acoustical Society of America 30, 254 (1958)). Pedestal amplitude is chosen in the range 60%-95% of the (pedestal-free) threshold, preferably in the range 70%-95%.

[00413] Post-calibration test: To make sure the pedestals are subthreshold, test stimuli with the selected pedestal amplitude are administered a few more times and the subject is instructed by embodiments of the device to report (i.e., press a button or give a verbal feedback) whether the subject perceives a stimulus in the corresponding time windows. In case one or more of the test stimuli are suprathreshold (i.e., perceived by the subject), the vibration amplitude is further reduced by the device and a series of test stimuli and/or a 2IFC series is re-administered. This post-calibration test can also be performed with a mixture of subthreshold and suprathreshold stimuli, e.g., with a 2IFC series design. The goal here is whether the subthreshold stimuli are detected by the subject.

[00414] Since vibratory thresholds can vary with temperature, measuring thresholds and, in general, threshold-based calibration should be performed at representative temperatures at which subjects use the device, e.g., at room temperature.

[00415] In one embodiment, vibration amplitudes of all other stimulation sites, e.g., fingers of both hands are calibrated by means of an equal loudness match, i.e., the vibration

amplitudes of all other fingers are chosen so that they are perceived as equally strong (=loud). Calibration tests are performed with vibratory bursts of identical duration as those used for therapeutic sessions.

[00416] In one embodiment, the device uses a temporal jitter of the stimulus onsets. The onset of the j th vibratory burst of the k th channel is calculated by

$$t_{j,k} \in [t_{j,k} - x \frac{For}{2N}, t_{j,k} + x \frac{For}{2N}],$$

[00417] where x denotes the percentage temporal jitter of the temporal onset of the vibratory stimulus in the k -th channel of the j -th period, where $0 \leq x \leq 50\%$ (e.g. FIG. 74). $t_{1,k}, t_{2,k}, t_{3,k}, \dots$ can be uniformly distributed. In another embodiment, $t_{1,k}, t_{2,k}, t_{3,k}, \dots$ can follow a different distribution, e.g., a Gaussian distribution. In other embodiments, $t_{1,k}, t_{2,k}, t_{3,k}, \dots$ can vary according to deterministic, stochastic, random rules or combinations thereof. In one embodiment, the width of the jitter window x is constant for all stimuli applied in a particular channel. In another embodiment, the width of the jitter window x may vary in time. In another embodiment, the width of the jitter window x may be identical in all channels, see, e.g., FIG. 74, where x is constant and identical for all channels. In yet another embodiment, the width of the jitter window as well as its possible time course may differ between different channels.

[00418] FIG. 74 provides an illustration of the first period of a jitter-free CR sequence (blue hatched stimuli 7402) with jitter intervals (blue rectangles) and final stimuli (solid blue stimuli 7404) (following an OFF period). In this example $x = 100\%$.

[00419] In another embodiment there is a temporal jitter of the vibration amplitudes, as illustrated in FIG. 75 for the vibrotactile 3:2 ON-OFF CR RVS pattern with pedestal. In one embodiment, the vibration amplitudes are randomized. Amplitude randomization means that for each single vibratory burst the vibration amplitude $A_{j,k}$ is randomly drawn from a uniform distribution $A_{j,k} \in [A_{min}, A_{max}]$. Another embodiment uses other distributions, e.g., a Gaussian distribution.

[00420] A_{max} denotes the maximal vibration amplitude, i.e., the vibration amplitude as determined by means of the calibration procedure. Different embodiments use different types of minimal vibration amplitudes A_{min} . In one embodiment, A_{min} is the zero amplitude. In another embodiment, A_{min} is the threshold vibration amplitude for the particular channel (e.g., finger). In yet another embodiment, A_{min} is the pedestal vibration amplitude for the particular channel (e.g., finger).

[00421] In other embodiments, $A_{1,k}, A_{2,k}, A_{3,k}, \dots$ can vary according to deterministic, stochastic, random rules or combinations thereof. In one embodiment, the amplitude range $[A_{min}, A_{max}]$ is constant for all stimuli applied in a particular channel. In another embodiment, $[A_{min}, A_{max}]$ may vary in time. In another embodiment, $[A_{min}, A_{max}]$ may be identical in all channels. In yet another embodiment, $[A_{min}, A_{max}]$ as well as its possible time course may differ between different channels.

[00422] FIG. 75 is a waveform diagram showing a vibrotactile 3:2 ON-OFF CR RVS pattern with pedestals and uniform randomization of the vibration amplitude. The figure shows an OFF period followed by three ON periods which in turn are followed by two OFF periods.

[00423] In another embodiment there is a temporal jitter of the durations of the vibratory bursts, as illustrated in FIG. 76 for the vibrotactile 3:2 ON-OFF CR RVS pattern with pedestal. In one embodiment, the vibratory burst durations are randomized. Burst duration randomization means that for each single vibratory burst the duration $d_{i,k}$ is randomly drawn from a uniform distribution $d_{i,k} \in [d_{min}, d_{max}]$. Another embodiment uses other distributions, e.g., a Gaussian distribution.

[00424] d_{max} denotes the maximal burst duration. Different embodiments use different types of minimal vibration amplitudes d_{min} . In one embodiment, $d_{min} = 0$. In another embodiment, d_{min} is the minimal duration required for eliciting a vibration perception for the particular channel (e.g., finger).

[00425] In other embodiments, $d_{1,k}, d_{2,k}, d_{3,k}, \dots$ can vary according to deterministic, stochastic, random rules or combinations thereof. In one embodiment, the burst duration range $[d_{min}, d_{max}]$ is constant for all stimuli applied in a particular channel. In another embodiment, $[d_{min}, d_{max}]$ may vary in time. In another embodiment, $[d_{min}, d_{max}]$ may be identical in all

channels. In yet another embodiment, $[a_{\min}, a_{\max}]$ as well as its possible time course may differ between different channels.

[00426] FIG. 76 is a waveform diagram showing a vibrotactile 3:2 ON-OFF CR RVS pattern with pedestals and uniform randomization of the vibratory burst durations. The figure shows an OFF period followed by three ON periods which in turn are followed by two OFF periods.

[00427] In addition, the amplitude of the pedestals can be varied in a deterministic, random (stochastic) or combined deterministic-stochastic manner, as schematically illustrated in FIG. 77. Typically, but not necessarily, pedestal variation algorithms are used which make sure the amplitude of a pedestal does only change a little or moderately (e.g., not more than 10% or 25%) within a time window amounting to 3-5 times the burst duration of the subsequent stimulus part. Typically, pedestals change slowly, and variations of the pedestals should not come with rise times and fall times of the pedestals exceeding 25 ms.

[00428] FIG. 77 is a waveform diagram illustrating slow random variation of the pedestal 7702 in channel 1. Perception threshold is highlighted by dashed horizontal line. Both channels use different frequencies: $f = 250$ Hz in channel 1 and $f = 200$ Hz in channel 2. While the amplitude of the pedestal in channel 1 varies in time, the burst amplitudes $A_{1,1}$ and $A_{1,2}$ are identical.

[00429] In one embodiment the vibration frequency f is varied in time. Note, the vibration frequency belongs to both subthreshold and suprathreshold parts of the compound stimulus (e.g. FIG. 78). In contrast, in other embodiments described above, the frequency f is used like a constant carrier. Stimulation effects are induced by modulating its amplitude. To avoid habituation effects, the carrier frequency f can be varied in time.

[00430] Smooth and slow variation of the vibration frequency f : In one embodiment, the vibration frequency f can vary slowly, as schematically illustrated in FIG. 78. To this end, the variation of the frequency f can be governed by a deterministic, random (stochastic) or combined random and deterministic process. In this embodiment, the variation of f is a slow process compared to the duration of 3-5 times the duration for the vibratory bursts to ensure an effective phase entrainment of the neuronal discharges of the activated mechanoreceptors as well as the corresponding thalamic sensory neurons and associated cortical neurons. In one

embodiment, the variation of the frequency f is performed in a way that f remains within either the high-frequency or the low-frequency band connected with different mechanoreceptors (see above), e.g., slowly varying f within an interval $[\bar{f} - \Delta f, \bar{f} + \Delta f]$, where $\bar{f}$ is a pre-set center value, and Δf amounts to 10%, 20%, 30% or up to 50% of $\bar{f}$.

[00431] The vibratory (perception) threshold depends on the vibration frequency f . Hence, it is advantageous to vary f only in a relatively small interval, i.e., by choosing $\Delta f = 0.1 \cdot \bar{f}$, and using, e.g., the mean or minimum (perception) threshold obtained by averaging the thresholds obtained for $\bar{f} - \Delta f$, $\bar{f}$, and $\bar{f} + \Delta f$.

[00432] In addition to the variation of the frequency f , other parameters, in particular the amplitude, can be varied too, as explained above and illustrated in Figure 10.

[00433] FIG. 78 is a waveform diagram illustrating a combination of a slow variation of the carrier-type frequency f , a slow random variation of the pedestal and a variation of the burst amplitude (7802-1, 7802-2) in channel 1. Perception threshold is highlighted by dashed horizontal line and, for illustration and simplicity, assumed to be independent of f . Channel 1 uses a constant $f = 250$ Hz.

[00434] Stepwise variation of the vibration frequency f : In another embodiment, the vibration frequency f is kept constant as long as the pedestal amplitude is greater than zero, e.g., during consecutive ON periods (e.g. FIG. 73) and stepwise varied for the subsequent phase with non-vanishing pedestal amplitude, e.g., the subsequent group of ON periods.

[00435] In another embodiment, instead of the sine vibration frequency f , the center frequency of narrow band signals (see above) is varied in time in an analogous way as described here.

[00436] In some embodiments, when applied to the skin of the head, e.g., with mechanical stimulators mounted to a headband, stimulating the forehead or the occiput, it is favorable to use pentatonic tones since due to the proximity to the ears and due to bone conduction, patients hear the vibratory stimuli. Pentatonic tones are typically perceived as pleasant and, when delivered sequentially, simultaneously or in an overlapping mode, do not produce dissonances.

[00437] Headband: M mechanical stimulators (i.e., vibratory stimuli) are placed on the forehead, e.g., symmetrically aligned, half of the stimulators on the right and left side,

respectively. Different pentatonic tones are assigned to the different stimulators, e.g. f_1 and f_3 to the right side and f_2 and f_4 to the left side. Alternatively, the frequency assignment can also change over time. Typically, different stimulators are assigned different pentatonic frequencies, calculated in the following manner.

[00438] Pentatonic scale: There are different pentatonic scales. For example, one can use fundamental pentatonic tones defined by:

[00439] Fundamental tone 1: f_1

[00440] Fundamental tone 2: f_2 , where $f_2/f_1 = 9/8 = 1.125$

[00441] Fundamental tone 3: f_3 , where $f_3/f_1 = 5/4 = 1.25$

[00442] Fundamental tone 4: f_4 , where $f_4/f_1 = 3/2 = 1.5$

[00443] Fundamental tone 5: f_5 , where $f_5/f_1 = 5/3 = 1.66667$

[00444] Fundamental tones 1,...,5 belong to the fundamental octave.

[00445] If pentatonic tones from more than one octave are required, e.g., because more than five mechanical stimulators are mounted in the headband, pentatonic frequencies are calculated according to the following equations. Pentatonic tones (multiples of fundamental pentatonic tones with octave relationship):

[00446] Tone 1: $f_{1k} = 2^k f_1$

[00447] Tone 2: $f_{2k} = 2^k \cdot \frac{9}{8} \cdot f_1 = 2^k \cdot 1.125 \cdot f_1$

[00448] Tone 3: $f_{3k} = 2^k \cdot \frac{5}{4} \cdot f_1 = 2^k \cdot 1.25 \cdot f_1$

[00449] Tone 4: $f_{4k} = 2^k \cdot \frac{3}{2} \cdot f_1 = 2^k \cdot 1.5 \cdot f_1$

[00450] Tone 5: $f_{5k} = 2^k \cdot \frac{5}{3} \cdot f_1 = 2^k \cdot 1.66667 \cdot f_1$

[00451] where $k = 0, 1, 2, 3, \dots$ is the octave index.

[00452] To avoid mutual masking effects and habituation, the interval between any two subsequent vibrotactile stimuli, specifically vibratory bursts, delivered to the same stimulation channel (i.e., "in-channel") and, hence, the same anatomical area of the body, e.g., a fingertip (or other skin area used for stimulus delivery) should preferably amount to 3-5 times the vibrotactile stimulus' duration. Consequently, no vibrotactile stimuli have to be administered in the time window immediately following a vibrotactile stimulus, amounting to 3-5 times the

vibrotactile stimulus' duration. This time window is called in-channel masking prevention (IMP) pause.

[00453] In one embodiment, the IMP of the j th vibratory burst ($j=1,2,3,\dots$) of the k th channel (= finger) is denoted by

$$IMP_{j,k} = \gamma \cdot d_{j,k}$$

[00454] where $d_{j,k}$ = duration of j th vibratory burst ($j=1,2,3,\dots$) of the k th channel (= finger), and γ is a predefined constant in the interval fulfilling $0 \leq \gamma \leq 1$. In yet another embodiment the IMP can be determined with classical masking experiments known to the expert. In that case, for feasibility reasons, the IMP will be determined for only on burst duration or, if the latter varies, for the maximum or average of the burst durations. In addition, for feasibility reasons, the IMP can be detected experimentally for one finger, e.g., the index finger, and – by way of extrapolation – be used for all other fingers, too.

[00455] Different embodiments can use different methods to prevent in-channel masking, e.g., the different options:

[00456] Option #1: Discard unfavorable sequences and replace by favorable sequences

[00457] Option #2: Discard (only) unfavorable stimuli

[00458] Option #3: Reduce duration of preceding stimuli to reduce IMP pause

[00459] In another embodiment the user, e.g., the clinician and/or clinician assistant, can change options, e.g., depending on the clinical outcome.

[00460] These in-channel masking prevention methods presented here work for stimulation patterns with and without pedestals, as illustrated in FIGs. 79 and 80 (without pedestals) and FIG. 81 (with pedestal), respectively.

[00461] For the programming examples below, CR sequence can be defined as follows. In the case of 4-channel stimulation, e.g., the stimulation of 4 fingers, the CR sequence is defined as order of stimulus activations in channels j,k,l,m within a CR period with

[00462] $R_{j,n}$ = channel number of j -th stimulus in the n -th CR period T_{CR} of the right hand and

[00463] $L_{j,n}$ = channel number of j -th stimulus in the n -th CR period T_{CR} of the left hand.

[00464] For instance, in FIG. 79:

[00465] $R_{1,1} = 2$

[00466] $R_{2,1} = 3$

[00467] $R_{3,1} = 1$

[00468] $R_{4,1} = 4$

[00469] $R_{1,2} = 1$

[00470] $R_{2,2} = 2$

[00471] $R_{3,2} = 4$

[00472] $R_{4,2} = 3$

[00473] FIG. 79 is a waveform illustration of an in-channel masking prevention (IMP) pause (illustrated by shaded rectangle) of three times the duration of the vibratory burst. The encircled vibratory burst in channel 3 violates the IMP pause. Hence, this stimulus has to be discarded or the third sequence has to be modified (so that it does not start with channel 3).

[00474] Option #1 -Discard unfavorable sequences and replace by favorable sequences:

[00475] Only allow for sequences that do not violate IMP pause. For instance, in FIG. 79 for the third cycle, sequences commencing with channel 3 are not allowed and has to be replaced by a sequence starting with 1, 2 or 4.

[00476] For example and for illustration, in the absence of temporal jitter and constant vibratory burst duration, i.e., $d_{j,k} = d$ for all j, k , the sequence selection can easily be achieved by the following algorithm:

If $IMP > 0$

If $IMP * d \leq T_{CR}/N$

All sequences are allowed

Elseif $T_{CR}/N < IMP * d \leq 2 * T_{CR}/N$

All sequences disallowed where $R_{N,n} = R_{1,n+1}$ OR $L_{N,n} = L_{1,n+1}$

Elseif $2 * T_{CR}/N < IMP * d \leq 3 * T_{CR}/N$

All sequences disallowed where $R_{N,n} = R_{1,n+1}$ OR $R_{N-1,n} = R_{1,n+1}$

OR $L_{N,n} = L_{1,n+1}$ OR $L_{N-1,n} = L_{1,n+1}$ etc.

end

[00477] where N = number of channels.

[00478] Option #2 - Discard unfavorable stimuli:

[00479] Discard all stimuli that violate IMP pauses, without replacing them. For instance, in FIG. 79 in the third cycle one can discard (only) the first stimulus administered through channel 3. Hence, there will be a missing stimulus.

[00480] Option #3 - Reduce duration of preceding stimuli to reduce IMP pause:

[00481] One can reduce the duration of the stimulus causing an IMP pause which leads to a conflict with a subsequent stimulus. The stimulus causing a conflicting IMP pause will be shortened such that the correspondingly shortened IMP pause will end when the subsequent stimulus starts. For instance, in FIG. 80 in the second cycle one can shorten the last stimulus administered through channel 3 in order to enable the first stimulus in channel 3 of the subsequent cycle to be delivered.

[00482] FIG. 80 is a waveform illustration of an in-channel masking prevention (IMP) pause (illustrated by shaded rectangle) of three times the duration of the vibratory burst. The duration of the encircled vibratory burst in channel 3 was reduced so that the corresponding IMP pause ends before the subsequent vibratory burst in channel 3 begins. In this way, unlike in Figure 6, the subsequent vibratory burst does not violate the IMP pause.

[00483] FIG. 81 is a waveform illustration of jitter-free CR sequence with in-channel masking prevention pauses (red bars 8102). No stimulus violates and IMP.

[00484] To effectively induce long-lasting desynchronization, an additional embodiment uses multi-frequency multichannel stimulation. Multi-frequency stimulation here means that the mean rate of vibratory burst delivery in the different channels, e.g., fingers, is different.

[00485] One can denote the period between vibratory burst k and $k + 1$ in the j -th channel by $T_{j,k}$ (e.g. FIG. 82). $T_{j,k}$ need not be constant within a channel, as illustrated in FIG. 82 for channel 1. The mean period of channel j is denoted by $\langle T \rangle_j = \frac{1}{N_j} \sum_{k=1}^{N_j} T_{j,k}$, where N_j is the number of periods $T_{j,k}$ in the j -th channel during a certain stimulation ON window, i.e., during a certain time when stimulation is delivered.

[00486] In general, one embodiment is characterized by at least one channel having a different mean period than the other channel(s), for instance $\langle T \rangle_1 \neq \langle T \rangle_2$, as illustrated in

Figure 14. This fundamental feature is important to not only reduce abnormal synaptic plasticity, but also specifically reduce abnormal structural plasticity. For example, FIG. 82 is a waveform illustration of the period $T_{j,k}$ between vibratory bursts k and $k+1$ in the j -th channel, here $j = 1$ and $k = 1, 2, 3$.

[00487] In one embodiment, the pulse train in one or more channels is purely periodic, e.g., in the j -th channel $\langle T \rangle_j = T_{j,k}$ for all k . In one embodiment, the mean periods in all channels are different $\langle T \rangle_j \neq \langle T \rangle_l$ for $j \neq l$ as illustrated in FIG. 83. The stimulus trains need not start at the same time. The onset time difference between the pulse train onsets in channels j and l are denoted by $\Delta_{j,l}$. For example, FIG. 83 is a waveform illustration of stimulus trains with different mean period, here $\langle T \rangle_1 < \langle T \rangle_2$ and onset time difference $\Delta_{1,2}$.

[00488] In one embodiment particularly favorable long-term effects are induced by using ratios of the mean period that are close to incommensurate, i.e.,

$$\langle T \rangle_j / \langle T \rangle_l = j/l$$

with large j and l .

[00489] In another embodiment, variations of the period $T_{j,k}$ take into account the IMP, i.e., $T_{j,k} \geq \text{IMP}$ for all j, k .

[00490] Yet another embodiment, uses CR stimulation patterns, as defined above, and differences in the mean periods are introduced by skipping a different percentage of vibratory stimuli in the different channels. The percentage of vibratory stimuli omitted in channel j is denoted by p_j . Skipped stimuli can be selected by means of random, stochastic, deterministic, chaotic or combined deterministic-stochastic algorithms.

[00491] In other embodiments, multi-frequency stimulation is applied to stimuli with pedestals. In this case, the suprathreshold parts of the vibratory bursts are selected as explained above. For example, FIG. 84 is a waveform illustration of a (jitter-free) CR sequence with different percentage of skipped (i.e., inactivated) stimuli (illustrated by shaded rectangles in channels 1 and 3).

[00492] The Coordinated Reset technology aims at disrupting abnormally synchronized neuronal activity by delivering phase resetting stimuli to different neuronal subpopulations engaged in the abnormal synchrony. Reducing the amount of abnormal neuronal synchrony over longer periods of time enables to reduce symptoms and to make networks unlearn their abnormal synaptic plasticity. However, this desynchronization-based approach has limitations since its effects might depend on the amount of synchrony as well as on the specific stimulation parameters compared to the dominant frequency of the abnormal brain rhythm, in particular, when there are more than just one abnormal rhythm (as seen in many brain disorders). In contrast, the present embodiments do not depend on the indirectly reducing synaptic connectivity through desynchronization. Rather, by enabling more dynamic and random stimulus patterns (with pronounced temporal jitters and/or randomization/variation of burst amplitudes and/or burst durations and/or pedestal amplitudes and/or carrier frequencies) it directly and effectively reduces synaptic weights and is more robust with respect to parameter variations, e.g., compared to the dominant frequencies of abnormal neuronal rhythms.

[00493] In contrast to prior approaches, the present embodiments include different mechanisms of action and focuss primarily on a reduction of synaptic weights – irrespective of whether the stimuli induce an acute desynchronization (i.e., desynchronization during stimulus delivery). To this end, one or more embodiments employ stimulus-evoked responses and, hence, do not rely on the presence of abnormal neuronal synchrony. Note, the methods preventing in-channel masking work with and without pedestals.

[00494] Example advantages:

[00495] The new, pedestal-boosted vibratory stimulation requires considerably smaller vibration amplitudes and, hence, devices realizing the vibration signals can be smaller, more lightweight and of cheaper technology.

[00496] Different hardware realizations can include devices such as thoracic breathing sensors + vCR delivered to gastric dermatomes (in particular, TH (5), 6-9, left) for gastric dysfunction (constipation etc.) in PD. For fingertip stimulator array or “gloves”, vibrotactile stimulators can be mounted to different parts of the hand, e.g., to the fingertips and/or the back of fingers (e.g., the proximal part of the back of fingers). For forearm arrays/cuff embodiments, vibrotactile stimulators are mounted to different parts of the forearm, in parallel or vertically

oriented to the forearm's longitudinal direction or in a more complex arrangement. For headband embodiments, headbands can comprise different variants/alignments, enabling forehead stimulation (Trigeminal nerve 1) and/or occiput stimulation (cervical segments C2 and C3). For forehead/ophthalmic nerve (trigeminal nerve 1st branch) stimulation can be used for the treatment of migraines, headaches, depression, obsessive-compulsive disorders, borderline personality disorder and other psychiatric disorders. Stimulator alignment can be in the form of a linear array (e.g., comprising 4-8 vibrotactile stimulators) or two-dimensional array.

[00497] For occiput/C2 and C3 dermatomes stimulation, embodiments can be used for the treatment of dysphagia (swallowing problems), e.g., due to Parkinson's disease, and sialorrhea (excessive drooling), e.g., due to Parkinson's disease. Stimulator alignment can be in the form of a two-dimensional array 2x4 alignment.

[00498] For torso-band applications, a high carrier frequency, e.g., 250 Hz can be used. For instance, 8 tactors placed in different dermatomes, e.g., T10-L5. Application: Treatment of pelvic pain, low back pain, irritable bowel syndrome, as well as Parkinson's disease-related gastroparesis, Parkinson's disease-related gut dysfunction, e.g., constipation and impairment of gut microbiome, and Parkinson's disease-related urinary incontinence.

[00499] For thigh band applications, vibrotactile stimulators can be arranged in dermatomes in L1-L4 (front of thigh) and/or S1-S2 (back of thigh). Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00500] For shank band applications, vibrotactile stimulators can be arranged in dermatomes in L2-L5 and/or S1-S2. Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00501] For insole applications, between 1, 2 or – more preferred at least 3 – up to 20 and more vibrotactile stimulators in the sole. For the treatment of Parkinson's disease, impairment of balance and gait caused by aging and various diseases.

[00502] Fixation of vibrotactile stimulators, e.g., with elastic strap (e.g., for gloves, headbands, forearm arrays and cuffs, thigh bands and shank bands), clothing (e.g., cap instead of or in combination with headband) and insoles (for shoes).

[00503] A therapy and device according to embodiments can potentially be applied to a wide range of disorders. Abnormal neuronal synchronization and abnormal synaptic

connectivity patterns are not only found in Parkinson's disease, but are also characteristic of a larger number of disorders of the central and peripheral nervous system, for instance, movement disorders, essential tremor, tic disorders, Tourette's syndrome, tremor in multiple sclerosis, dystonia, chronic stroke, epilepsy, depression, migraine, tension headache, incomplete spinal cord injury, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), irritable bowel syndrome, chronic pain syndromes, e.g., complex regional pain syndrome, neuropathic pain and trigeminal neuralgia, pelvic health disorders, e.g., pelvic pain or overactive bladder, tinnitus, dissociation in borderline personality disorder and post-traumatic stress disorder.

[00504] Embodiments described as follows can include apparatuses that communicate with each other for a combined therapy. An apparatus is explained for the example of two wirelessly connected vibration gloves. However, the same apparatus can be applied to a number of other applications listed below.

[00505] The solution involves tight synchronization between each finger stimulated in order to deliver optimum treatment. Synchronizing between fingers on the same hand is usually a more trivial exercise as a single clock source can be used along with precise counters as described in examples above. However, that solution does not scale well across the fingers of separate hands. One possible alternate includes providing a wiring harness between hands to allow for synchronization. But even a single wire between two hands/gloves is quite limiting for everyday uses and increases the risk of a patient getting stuck, giving rise to falls. Given the choice, most patients would opt to not have a wire between hands/gloves. Also, for safety reasons a wireless bimanual connection is mandatory.

[00506] A wireless solution where synchronization can be obtained and maintained between gloves becomes an important technology to allow for an improved and safer patient experience as well as an important attribute in increasing usability.

[00507] There are many possible excitations patterns that can be used to stimulate fingers, but many of the patterns excite two fingers on separate hands simultaneously. Simultaneous excitation across two fingers requires tight synchronization between the two gloves, which is expected to be in the sub-millisecond range to leverage plasticity-mediated mechanisms, to avoid interhemispheric inhibition and to deliver a maximized treatment.

[00508] There are many wireless technologies that could be used as the basis for wireless synchronization including: WiFi, ZigBee, Bluetooth Classic, Bluetooth Low Energy (BLE), Sub-GHz, and Others/Custom. WiFi is traditionally a wireless technology targeted for higher bandwidth uses so would not be a good target for a wearable battery powered device. In addition, WiFi is inherently asynchronous, so it would have to be adapted to create synchronization. Zigbee is a low power wireless technology created for sensors and IoT and could be adapted to provide wireless synchronization. Bluetooth classic is traditionally a wireless technology meant for audio connections. It's typically higher power and bandwidth, so it is not as effective in low power situations. BLE is a low power wireless technology made for passing low bandwidth data with a focus on quality of service over timeliness. However, BLE has an advantage that is the technology predominantly used to connect with smart phones. Sub-GHz solutions typically allow for long range in a very favorable band. In this case however, given the fact that the range is within approximately 6 feet, sub-GHz solutions don't provide any practical benefit.

[00509] Most of the low power wireless solutions don't provide a means to allow for high quality wireless synchronization. However, using a more programmable radio, specialized transmissions can be sent that can allow a receiver to synchronize with a transmitter. Note that synchronization requires both tight frequency and phase control.

[00510] For example, in the case of BLE, being able to accurately send transmissions with a known time interval, along with some timing information sent in the frame can provide elements that allow wireless synchronization. However, BLE traditionally requires fully acknowledged transmissions to guarantee quality of service over timeliness. This runs counter-intuitive to time sensitive applications where data becomes useless after a certain time interval expires.

[00511] The timeliness of data can be partially addressed by limiting the re-transmissions to a minimal amount. Custom transmissions in BLE can accomplish this or even recently added isochronous transmission can as well.

[00512] For this application, a session timer is used to provide the master timing and sequencing between all of the fingers. It is expected that the session timer can be wirelessly

communicated in a very accurate manner so that all fingers can remain in sync throughout a treatment.

[00513] The establishment of a session timer is created on one of the devices and then is accurately conveyed to all of the other elements in the system via wireless synchronization (e.g. FIG. 85). This effectively breaks down into a single master session timer and then potentially several recovered session timers, which are meant to accurately re-construct the master session timer. FIG. 85 is a block diagram illustrating the interaction between master session timer 8502 and local session timer 8504.

[00514] In addition to time synchronization, status parameter synchronization is also critical. Items such as battery status, user interface items like a button or LED, faults, etc are all items that would be beneficial for each glove to see it's link partner's status. These basic items being exchanged can also be an expanded list and include items such as: Battery status/life, Button inputs, LED status, Other UI elements, Faults, Tapper status, Waveform parameters, especially parameters that need to be common or related between the gloves, Firmware/hardware versions, Session counts, and a random/pseudo-random seed that needs to be common.

[00515] Since the gloves are wirelessly connected and time synchronized, a separate data channel can be used to exchange data parameters. These data parameters can generally be exchanged in several different manners: on demand (when needed), when changed usually via a notification or indication, or periodically pushed/pollled. There are cases where certain methods may be more advantageous given the parameters. For example, the firmware version may only need to be checked at the start of a link as that cannot change during the link. However, an item such battery status would be better suited as a notification or even periodically pushed or polled. (e.g. FIG. 86)

[00516] Fortunately, BLE provides some good mechanisms for this exchange of information through the use of custom services and characteristics over the Generic Attribute profile (GATT). GATT on BLE delivers a method to have reasonably guaranteed receptions of wireless through the built-in mechanism of acknowledgements and retries. This allows a very high degree of certainty of the data being able to be exchanged without having to worry much about the limits of a wireless channel. The precision of one embodiment of BLE-based

synchronization has a time precision of typically < 0.5 ms between wirelessly connected devices.

[00517] Embodiments are explained herein for the case of vibrotactile and/or electrotactile stimulation of four fingers on both hands (see, e.g. US Patent App. Publ. No. 2021/0401664, the contents of which are incorporated herein by reference in their entirety).

[00518] The following abbreviations are used herein:

[00519] R1 - index finger of the right hand

[00520] R2 - middle finger of the right hand

[00521] R3 - ring finger of the right hand

[00522] R4 - pinky of the right hand

[00523] L1 - index finger of the left hand

[00524] L2 - middle finger of the left hand

[00525] L3 - ring finger of the left hand

[00526] L4 - pinky of the left hand

[00527] Interhemispheric inhibition may cause interference of stimulus effects on bilaterally corresponding neuronal populations, e.g., belonging to right and left index finger.

[00528] An important principle of the example stimulation patterns provided herein is to avoid and/or reduce coincident stimulation of anatomically identical or closely related neuronal populations of two different hemispheres by introducing appropriate pairing patterns.

[00529] Coincidentally activating the same fingers of right and left hand may interference with therapeutic stimulus effects due to interhemispheric inhibition. Hence, anatomically coinciding pairs, i.e., R1 – L1, R2 – L2, R3 – L3, R4 – L4, have to be (i) completely avoided or (ii) used less frequently.

[00530] In addition, to avoid the formation of unwanted interhemispheric connectivity, the precise wireless pairing should be time-varying. Time-variation can be realized on a (iii) slow time scale or, thanks to the high wireless precision, with (iv) temporal jitter.

[00531] All methods, (i)-(iv), increase the therapeutic efficacy.

[00532] Example (i) - avoid anatomically coinciding pairs:

[00533] The device uses the following pairs:

[00534] Pairs1: R1-L2, R2-L3, R3-L4, R4-L1

- [00535] Pairs2: R1-L3, R2-L4, R3-L1, R4-L2
- [00536] Pairs3: R1-L4, R2-L1, R3-L2, R4-L3
- [00537] Pairs1: R1-L2, R2-L3, R3-L4, R4-L1
- [00538] Pairs2: R1-L3, R2-L4, R3-L1, R4-L2
- [00539] Pairs3: R1-L4, R2-L1, R3-L2, R4-L3
- [00540] Pairs1: R1-L2, R2-L3, R3-L4, R4-L1
- [00541] Pairs2: R1-L3, R2-L4, R3-L1, R4-L2
- [00542] Pairs3: R1-L4, R2-L1, R3-L2, R4-L3 etc.
- [00543] In one embodiment, the sequence of pairs 1, pairs 2, pairs 3 is repeated periodically. Variation can also be based on deterministic, stochastic, random, chaotic and combined deterministic-stochastic rules.
- [00544] Example (i) - reduce stimulation of anatomically coinciding pairs:
- [00545] Pairs1: R1-L1, R2-L2, R3-L3, R4-L4 (anatomical coinciding)
- [00546] Pairs2: R1-L2, R2-L3, R3-L4, R4-L1
- [00547] Pairs3: R1-L3, R2-L4, R3-L1, R4-L2
- [00548] Pairs4: R1-L4, R2-L1, R3-L2, R4-L3
- [00549] Pairs1: R1-L1, R2-L2, R3-L3, R4-L4 (anatomical coinciding)
- [00550] Pairs2: R1-L2, R2-L3, R3-L4, R4-L1
- [00551] Pairs3: R1-L3, R2-L4, R3-L1, R4-L2
- [00552] Pairs4: R1-L4, R2-L1, R3-L2, R4-L3
- [00553] Pairs1: R1-L1, R2-L2, R3-L3, R4-L4 (anatomical coinciding)
- [00554] Pairs2: R1-L2, R2-L3, R3-L4, R4-L1
- [00555] Pairs3: R1-L3, R2-L4, R3-L1, R4-L2
- [00556] Pairs4: R1-L4, R2-L1, R3-L2, R4-L3
- [00557] etc.
- [00558] One embodiment repeats the sequence of pairs 1, pairs 2, pairs 3, pairs 4 periodically. Other embodiments can select the pairs based on deterministic, stochastic, combined deterministic-stochastic, random, chaotic rules, e.g., to simply further reduce the frequency of occurrence of the anatomical coinciding pairs.

[00559] The embodiments can be applied to a larger variety of different non-invasive devices, embodiments including, but not limited to those described in US Patent Publ. No. 2021/0401664, the contents of which are incorporated herein by reference in their entirety.

[00560] Additional or alternative applications include:

[00561] Thoracic stimulation array: vibrotactile and/or electrotactile CR delivered to gastric dermatomes (in particular, TH (5), 6-9, left) for gastric dysfunction (constipation etc.) in Parkinson's disease.

[00562] Fingertip stimulation arrays or "gloves": vibrotactile and/or electrotactile stimulators are mounted on different parts of the hand, e.g., the fingertips.

[00563] Forearm arrays/cuff: vibrotactile and/or electrotactile stimulators are mounted to different parts of the forearm, in parallel or vertically oriented to the forearm's longitudinal direction or in a more complex arrangement.

[00564] Headband: Headbands can comprise different variants/alignments, enabling forehead stimulation (Trigeminal nerve 1) and/or occiput stimulation (cervical segments C2 and C3).

[00565] Forehead/ophthalmic nerve (trigeminal nerve 1st branch) stimulation: For the treatment of migraines, headaches, depression, obsessive-compulsive disorders, borderline personality disorder and other psychiatric disorders.

[00566] Stimulator alignment: Linear array (e.g., comprising 4-8 vibrotactile and/or electrotactile stimulators) or two-dimensional array.

[00567] Occiput/C2 and C3 dermatomes stimulation: For the treatment of dysphagia (swallowing problems), e.g., due to Parkinson's disease, and sialorrhea (excessive drooling), e.g., due to Parkinson's disease.

[00568] Stimulator alignment: two-dimensional array 2x4 alignment

[00569] Torso-band: High vibrotactile carrier frequency, e.g., 250 Hz. For instance, 8 tactors placed in different dermatomes, e.g., T10-L5. Application: Treatment of pelvic pain, low back pain, irritable bowel syndrome, as well as Parkinson's disease-related gastroparesis, Parkinson's disease-related gut dysfunction, e.g., constipation and impairment of gut microbiome, and Parkinson's disease-related urinary incontinence.

[00570] Thigh band: Vibrotactile and/or electrotactile stimulators arranged in dermatomes in L1-L4 (front of thigh) and/or S1-S2 (back of thigh). Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00571] Shank band: Vibrotactile stimulators arranged in dermatomes in L2-L5 and/or S1-S2. Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00572] Insole: Between 1, 2 or – more preferred at least 3 – up to 20 and more vibrotactile and/or electrotactile stimulators in the sole. For the treatment of Parkinson's disease, impairment of balance and gait caused by aging and various diseases.

[00573] Detailed tests of two devices (for bimanual stimulation) revealed a timing deviation between stimulus delivery of both sides of about $\pm 50\mu\text{s}$.

[00574] According to certain general aspects, the example embodiments that will now be described relate to a method and device that delivers non-invasive, in particular sensory stimulation treatment in a way that counteracts habituation, e.g., by increasing and rewarding patients' attention, alertness, curiosity level and activating additional brain areas besides primary sensory brain areas. In this way, these and other embodiments counteract habituation and increases the therapeutic effects, e.g., by boosting the propagation of desynchronizing effects through disease-related brain circuits.

[00575] The present embodiments can be applied to multichannel stimulation, especially coordinated reset (CR) stimulation (= main mode). In addition, the present embodiments deliver multichannel stimulation by intermingling it with rare types of stimuli (= rare mode), e.g. FIG. 87. The rare mode occurs during smaller integral time portions, with an occurrence probability of less than 0.2 or 0.1 in relation to the entire stimulation duration. The times when the rare mode is activated, denoted by t_2, t_4, t_6 in FIG. 87, can be chosen based on a deterministic, stochastic (i.e., random) or combined deterministic-stochastic or chaotic algorithm. The duration of the rare mode sessions, denoted by $t_3-t_2, t_5-t_4, t_7-t_6$ in FIG. 87, can be constant or varying (from one rare mode session to another one). In the latter case, the duration of the rare mode session be chosen based on a deterministic, stochastic (i.e., random) or combined deterministic-stochastic or chaotic algorithm.

[00576] FIG. 87 is a waveform illustration of the intermingled administration of main stimulation mode (“main mode”) and rare stimulation mode (“rare mode”). The durations of the main mode sessions are given by t_2-t_1 , t_4-t_3 , t_6-t_5 , t_8-t_7 . The durations of the rare mode sessions are t_3-t_2 , t_5-t_4 , t_7-t_6 .

[00577] Qualitatively different types of stimulation can be used for the rare mode stimulation in different embodiments of the present disclosure. In one embodiment, the same type of stimulation as in the main mode stimulation, but with perceptually significantly different parameters, e.g., perceptually different vibration amplitude (e.g., significantly stronger) and/or period T_{CR} (e.g., significantly faster) and/or stimulus duration (e.g., significantly longer vibratory stimuli). FIG. 88 illustrates a vCR stimulation pattern without any rare mode stimulation. In contrast, FIG. 89 shows an example with intermingled rare mode stimulation. Perceptually different means that the patient can clearly perceive the difference of the main mode stimuli vs. the rare mode stimuli when compared head to head in a psychophysical comparison task (as known to the expert, e.g., by simple pairwise comparison).

[00578] In another embodiment, qualitatively very different stimuli of the same or different sensory modality. For instance, one long stimulus with complex time course of the vibration amplitude.

[00579] In yet another embodiment, longer sequences (containing more than 4 single stimuli) that are qualitatively different, in particular, more complex with respect to their mutual timing characteristics. These stimulus sequences are called sensory tunes.

[00580] In yet another embodiment, no stimulus is delivered during the rare mode stimulation. This type of rare mode is simply a pause.

[00581] In yet another embodiment, combinations of at least two of the embodiments above. Different rare modes can follow each other with (FIG. 88) or without (FIG. 89) a main mode session in between.

[00582] In yet another embodiment, some or all of the previous embodiments can be applied to different parts of the body, in particular, to both sides, in particular, to both hands – or to only one part, e.g., to only one hand. In the case of more than one stimulated part, e.g., in the case of two hands, the rare mode sessions can be applied symmetrically (i.e., the exact same rare modes are used) and/or coincidentally (at the same onset and offset times). In another

embodiment the rare mode sessions can be applied in an asymmetric manner (e.g., different rare mode sessions are applied to both hands) and/or not coincidentally, e.g., with a constant and/or time-varying time shift. The time-varying time shift can vary based on be calculated by means of a deterministic, chaotic, stochastic, random algorithm or combinations thereof. A pause (as in one previous embodiment described above) is a particularly effective type of rare mode in the case of bilateral stimulation, when the pause is only applied to one of the hands at a time, e.g., in FIG. 90, when rare mode 2 is a pause. Applying different types of rare mode stimulation (listed above) to bilateral hand stimulation is illustrated in FIG. 90.

[00583] FIG. 88 is a waveform illustration of the intermingled administration of the main stimulation mode (“main mode”) and two rare stimulation modes (“rare mode 1” and “rare mode 2”), where the two different rare modes do not immediately follow each other. There is a main mode in between different rare modes.

[00584] FIG. 89 is a waveform illustration of the intermingled administration of the main stimulation mode (“main mode”) and two rare stimulation modes (“rare mode 1” and “rare mode 2”), where the two different rare modes may immediately follow each other (without main mode in between).

[00585] FIG. 90 is a waveform illustration of the intermingled administration of the main stimulation mode (“main mode”) and three rare stimulation modes (“rare mode 1”, “rare mode 2” and “rare mode 3”) for the case of bilateral stimulation where rare mode sessions are not symmetrically (and coincidentally) applied to both sides, e.g., both hands.

[00586] FIG. 91 is a waveform illustration of regular 3:2 ON-OFF CR RVS (rapidly varying sequences) pattern. Dashed lines indicate multiples of the vCR period T_{CR} and dotted lines multiples of $T_{CR}/4$ during individual CR periods. A CR period is also called a cycle. In the absence of any rare mode stimuli, there are only main mode cycles, abbreviated by C_m . Labels of y-axis: Roman numerals indicate fingertips on one hand. Vibrotactile stimulation bursts are marked by gray rectangles 9102. Parameters: $f_{CR}=1.5$ Hz ($T_{CR}/4 \approx 166.7$ ms), burst duration 100 ms, and $f_{burst}=250$ Hz. During a cycle, i.e., a stimulation period of length T_{CR} , a sequence of stimuli is administered.

[00587] FIG. 92 is a waveform illustration of an embodiment #1 rare mode cycle C_r interspersed in the main mode vCR pattern from FIG. 91. In the rare mode cycle, the vibration amplitude is the only parameter that differs compared to the main mode cycles C_m .

[00588] FIG. 93 is a waveform illustration of two rare mode cycles C_r interspersed in the main mode vCR pattern from FIG. 91. In the rare mode cycles, the vibration amplitude is the only parameter that differs compared to the main mode cycles C_m . In general, one or more rare mode cycles can be intermingled with the main mode stimulation. In another embodiment, the rare mode stimulation need not be confined to administration of complete rare mode cycles. Rather rare mode stimulation can also use truncated (i.e., incomplete) rare mode cycles, providing a “stumbling” sensation which counteracts habituation, too.

[00589] FIG. 94 is a waveform illustration of two rare mode cycles C_r interspersed in the main mode vCR pattern from FIG. 91. In the rare mode cycles, the vCR period is the only parameter that differs compared to the main mode cycles C_m : The rare mode vCR period T_{CR2} is shorter compared to the main mode vCR period T_{CR1} .

[00590] FIG. 95 is a waveform illustration of an embodiment of rare mode cycle C_r interspersed in the main mode vCR pattern from FIG. 91.

[00591] FIG. 96 is a waveform illustration of an embodiment of rare mode cycle C_r interspersed in the main mode vCR pattern from FIG. 91. The sensory (here vibratory) tune can be delivered during the same period of length T_{CR} .

[00592] FIG. 97 is a waveform illustration of an embodiment of rare mode cycle C_r interspersed in the main mode vCR pattern from FIG. 91. The sensory (here vibratory) tune can also be delivered during more than one cycle, where the cycles length differs from the period length T_{CR} .

[00593] Stimuli with pedestals: Another embodiment uses pulsatile sensory stimuli and/or non-invasive (non-sensory) stimuli with pedestals instead of stand-alone pulsatile stimuli (without pedestals). A variety of stimulus can be used, such as Sensory stimuli (vibrotactile, vibratory, pressure, auditory, visual, thermal (warm and/or cold), olfactory) and Non-invasive, non-sensory stimuli / transcutaneous (electrical, transcutaneous magnetic, transcutaneous ultrasound, transcutaneous laser (e.g., infrared) light).

[00594] The present therapy and device can potentially be applied to a wide range of disorders. Abnormal neuronal synchronization and abnormal synaptic connectivity patterns are not only found in Parkinson's disease, but are also characteristic of a larger number of disorders of the central and peripheral nervous system, for instance, movement disorders, essential tremor, tic disorders, Tourette's syndrome, tremor in multiple sclerosis, dystonia, chronic stroke, epilepsy, depression, migraine, tension headache, incomplete spinal cord injury, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD), irritable bowel syndrome, chronic pain syndromes, e.g., complex regional pain syndrome, neuropathic pain and trigeminal neuralgia, pelvic health disorders, e.g., pelvic pain or overactive bladder, tinnitus, dissociation in borderline personality disorder and post-traumatic stress disorder.

[00595] Different embodiments:

[00596] Fingertip stimulators or "gloves": vibrotactile stimulators are mounted to different parts of the hand, e.g., to the fingertips and/or the back of fingers (e.g., the distal and/or proximal parts of the back of fingers).

[00597] Thoracic vibrotactile stimulation array: vCR delivered to gastric dermatomes (in particular, TH (5), 6-9, left) for gastric dysfunction (constipation etc.) in PD.

[00598] Forearm arrays/cuff: vibrotactile stimulators are mounted to different parts of the forearm, in parallel or vertically oriented to the forearm's longitudinal direction or in a more complex arrangement.

[00599] Headband: Headbands can comprise different variants/alignments, enabling forehead stimulation (Trigeminal nerve 1) and/or occiput stimulation (cervical segments C2 and C3).

[00600] Forehead/ophthalmic nerve (trigeminal nerve 1st branch) stimulation: For the treatment of migraines, headaches, depression, obsessive-compulsive disorders, borderline personality disorder and other psychiatric disorders. Stimulator alignment: Linear array (e.g., comprising 4-8 vibrotactile stimulators) or two-dimensional array.

[00601] Occiput/C2 and C3 dermatomes stimulation: For the treatment of dysphagia (swallowing problems), e.g., due to Parkinson's disease, and sialorrhea (excessive drooling), e.g., due to Parkinson's disease. Stimulator alignment: two-dimensional array 2x4 alignment

[00602] Torso-band: High carrier frequency, e.g., 250 Hz. For instance, 8 tactors placed in different dermatomes, e.g., T10-L5. Application: Treatment of pelvic pain, low back pain, irritable bowel syndrome, as well as Parkinson's disease-related gastroparesis, Parkinson's disease-related gut dysfunction, e.g., constipation and impairment of gut microbiome, and Parkinson's disease-related urinary incontinence.

[00603] Thigh band: Vibrotactile stimulators arranged in dermatomes in L1-L4 (front of thigh) and/or S1-S2 (back of thigh). Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00604] Shank band: Vibrotactile stimulators arranged in dermatomes in L2-L5 and/or S1-S2. Applications: Parkinson's disease, pelvic health disorders, e.g., pelvic pain or overactive bladder.

[00605] Insole: Between 1, 2 or – more preferred at least 3 – up to 20 and more vibrotactile stimulators in the sole. For the treatment of Parkinson's disease, impairment of balance and gait caused by aging and various diseases.

[00606] Among other things, the embodiments to be described as follows relate to methods and apparatuses that enable more effective vibrotactile stimulation, i.e., stronger physiological effects with less vibration power/amplitude. More particularly, the present embodiments relate to methods and apparatuses for automatically/autonomously calibrating relevant stimulation parameters for non-invasive and invasive multichannel CR stimulation and related stimulation techniques, random reset stimulation as well as combinations thereof. Several embodiments use vibrotactile and/or electrotactile stimulation as described above.

[00607] There are several important parameters of vibrotactile and/or electrotactile CR stimulation are, e.g., stimulus intensities, temporal jitter, amplitude, CR sequences. These parameters should ideally be adjusted to every individual patient. However, due to the slow wash-in, i.e., the long time it may take until therapeutic effects build up, it is not feasible to calibrate these parameters by trial and error, performed by test stimulations carried out by trained health care professionals. The below explains how embodiments calibrate optimal CR sequences and stimulus amplitudes. Other embodiments, using the same methods, are used to calibrate and optimize the other stimulation parameters mentioned above.

[00608] A device of embodiments delivers stimuli according to a stimulation pattern that is characterized by a set of stimulation parameters. Stimuli are delivered in cycles of a cycle period T , which will be referred to as CR cycles in the following. Each target site receives exactly one stimulus per CR cycle. The sequence at which the target sites are activated during a CR cycle is referred to as CR sequence in the following. The CR sequence is shuffled after a shuffle period T_{shuffle} . One example of a stimulation pattern for four target sites and a shuffle period of $T_{\text{shuffle}}=2T$ is shown in FIG. 98. There, stimuli are delivered at times that are multiples of $T/4$. In another embodiment a random jitter was added to the stimulus onset times (e.g. FIG. 99). Shuffling of CR sequences can be done randomly according to a probability distribution which determines the probability to select one of the possible CR sequences. Alternatively, pseudorandom CR sequence selection can be performed, or sequences can be selected according to a deterministic algorithm, that ensures variability of the CR sequences.

[00609] The stimulation pattern is characterized by a set of stimulation parameters including the stimulus waveform, the stimulus amplitude, the shuffle period, the cycle period (or equivalently, the stimulation frequency $1/T$), the number of stimulation sites, the locations of stimulation sites, the range of the random jitter, and the set of possible CR sequences and the corresponding frequencies of occurrence, e.g., characterized by a probability distribution.

[00610] In addition to delivering stimuli, the device measures stimulation outcome by means of appropriate feedback signals recorded with one or more sensors and comprises a controller which adapts the stimulation pattern (as specified by the set of stimulation parameters) if necessary to achieve a sustained symptom relief during and after individual stimulation epochs. This is done by delivering stimulation in a sequence of stimulation epochs. During individual epochs stimuli are delivered according to a stimulation pattern as described above and using the current set of stimulation parameters. However, the controller may adapt the stimulation patterns over time such that different stimulation patterns may be used for different stimulation epochs. The performance of the stimulation patterns is assessed in a sequence of assessment periods. This is done by measuring feedback signals with a set of sensors. Possible signals include, LFP power, signals from so-called wearables, data from patient surveys, and assessments performed by clinical personnel. Finally, parameter

adjustments are performed after N assessments. Two possible implementations are shown in FIG. 100.

[00611] For non-invasive vibrotactile and/or electrotactile stimulation of movement disorders or epilepsies, wearables (such as iPhone, Apple watch) enable feedback of stimulation outcome in terms of patient questionnaires, step-related data (stride characteristics, step count etc.) as well as tremor probability and dyskinesia probability.

[00612] The parameter adjustment 10002 can be done using a reinforcement learning algorithm with the goal to learn the best-performing stimulation pattern for each assessment outcome (policy) based on the history of both assessment outcomes and delivered stimulation patterns. Possible learning algorithms include dynamic programming and model-free methods such as temporal difference learning methods, e.g., SARSA and Q-learning, and Monte Carlo control. Examples of parameter adjustment using reinforcement learning algorithms are attached.

[00613] Example 1: Long-lasting desynchronization after stimulation depends on the selected CR sequence and the shuffle period.

[00614] Standard deep brain stimulation (DBS) is a well-established treatment for medically refractory Parkinson's disease (PD) [A.M. Lozano, N. Lipsman, H. Bergman, P. Brown, S. Chabardes, J.W. Chang, K. Matthews, C.C. McIntyre, T.E. Schlaepfer, M. Schulder, Y. Temel, J. Volkmann, J.K. Krauss. Deep brain stimulation: current challenges and future directions. *Nature Review Neurology* 15, 148 (2019)]. While highly effective in adequately selected PD patients, DBS delivered to the subthalamic nucleus (STN) or globus pallidus internus is not effective for all PD symptoms and may cause relevant side effects [A.M. Lozano, N. Lipsman, H. Bergman, P. Brown, S. Chabardes, J.W. Chang, K. Matthews, C.C. McIntyre, T.E. Schlaepfer, M. Schulder, Y. Temel, J. Volkmann, J.K. Krauss. Deep brain stimulation: current challenges and future directions. *Nature Review Neurology* 15, 148 (2019)]. Also, PD symptoms return shortly after cessation of DBS [P. Temperli, J. Ghika, J.-G. Villemure, P.R. Burkhard, J. Bogousslavsky, F.J.G. Vingerhoets. How do parkinsonian signs return after discontinuation of sub-thalamic DBS? *Neurology* 60, 78 (2003)].

[00615] A theory-based stimulation technique, coordinated reset stimulation (CRS), aims at long-lasting desynchronization that persists after cessation of stimulation [P.A. Tass. A model

of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. *Biological Cybernetics* 89, 81 (2003) ; P.A. Tass, M. Majtanik. Long-term Anti-kindling effects of desynchronizing brainstimulation: a theoretical study. *Biological Cybernetics* 94, 58 (2006)]. As shown computationally, in neural networks with synaptic plasticity, CRS-induced desynchronization of PD-related neuronal synchrony [C. Hammond, H. Bergman, P. Brown. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends in Neurosciences* 30, P357 (2007)] may cause an unlearning of abnormal synaptic connectivity and related neuronal synchrony [P.A. Tass, M. Majtanik. Long-term Anti-kindling effects of desynchronizing brainstimulation: a theoretical study. *Biological Cybernetics* 94, 58 (2006)]. In this way CRS moves networks from strongly connected synchronized states (SCSS) to weakly connected desynchronized states (WCDS), ultimately inducing effects outlasting stimulation. Corresponding long-lasting desynchronization and therapeutic effects of CRS were observed in preclinical studies [P.A. Tass, L. Qin, C. Hauptmann, S. Dovero, E. Bezard, T. Boraud, W.G. Meissner. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Annals of Neurology* 72, 816 (2012); J. Wang, S. Nebeck, A. Muralidharan, M.D. Johnson, J.L. Vitek, K.B. Baker. Coordinated Reset Deep Brain Stimulation of Subthalamic Nucleus Produces Long-Lasting, Dose-Dependent Motor Improvements in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Non-Human Primate Model of Parkinsonism. *Brain Stimulation* 9, 609 (2016); J. Wang, S.P. Fergus, L.A. Johnson, S.D. Nebeck, J. Zhang, S. Kulkarni, H. Bokil, G.F. Molnar, J.L. Vitek. Shuffling Improves the Acute and Carryover Effect of Subthalamic Coordinated Reset Deep Brain Stimulation. *Frontiers in Neurology* 13, 716046 (2022)], and in PD patients [I. Adamchic, C. Hauptmann, U.B. Barnikol, N. Pawelczyk, O. Popovych, T.T. Barnikol, A. Silchenko, J. Volkmann, G. Deuschl, W.G. Meissner, M. Maarouf, V. Sturm, H.-J. Freund, P.A. Tass. Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. *Movement disorders* 29, 1679 (2014)]. CRS is a multisite stimulation technique during which phase-shifted stimuli are delivered to separate neuronal subpopulations. CR stimuli are sequentially delivered to the different stimulation sites, forming a *CR sequence* (e.g. FIGs. 101F, 101H, and 101J). CRS is delivered in cycles and each stimulation site is activated exactly once per cycle. For four stimulation sites, there are 4 possible CR sequences during each cycle. The CR sequence is typically shuffled after a shuffle period, $T_{shuffle}$, (e.g.

FIG. 101J). A recent preclinical study found that shuffled CRS outperforms non-shuffled CRS regarding long-lasting therapeutic aftereffects in PD monkeys (Wang et al., 2022).

[00616] CRS is a multisite stimulation technique during which phase-shifted stimuli are delivered to separate neuronal subpopulations. CR stimuli are sequentially delivered to the different stimulation sites, forming a *CR sequence* (e.g. FIGs. 101F, 101H, and 101J). CRS is delivered in cycles and each stimulation site is activated exactly once per cycle. For four stimulation sites, there are 4 possible CR sequences during each cycle. The CR sequence is typically shuffled after a shuffle period, $T_{shuffle}$, (e.g. FIG. 101J). A recent preclinical study found that shuffled CRS outperforms non-shuffled CRS regarding long-lasting therapeutic aftereffects in PD monkeys [J. Wang, S.P. Fergus, L.A. Johnson, S.D. Nebeck, J. Zhang, S. Kulkarni, H. Bokil, G.F. Molnar, J.L. Vitek. Shuffling Improves the Acute and Carryover Effect of Subthalamic Coordinated Reset Deep Brain Stimulation. *Frontiers in Neurology* 13, 716046 (2022)].

[00617] This example includes a computational analysis of why shuffling may improve long-lasting effects of CRS. It is discovered that the effect of non-shuffled CRS depends on the selected CR sequence: “Favourable” CR sequences may drive the network into a WCDS; conversely, “unfavourable” sequences may induce a SCSS (e.g. FIG. 101B). It is shown that long-lasting aftereffects of CRS with long shuffle periods depend on the timing at which stimulation is turned off, whereas short shuffle periods led to consistent long-lasting effects after sufficient stimulation duration (e.g. FIGs. 101C-101E).

[00618] FIGs. 101A to 101K illustrate example aspects of CRS of inhomogeneous and homogeneous networks according to embodiments. FIG. 101A illustrates synaptic connectivity of an inhomogeneous network. Black dots mark connections between presynaptic neurons at locations X_{pre} and postsynaptic neurons at locations X_{post} , in units of the system’s length scale, L . FIGs. 101B-101E illustrate dynamics of the Kuramoto order parameter measuring the degree of synchrony, ρ , mean and the synaptic weight, $\langle w \rangle$, before, during (light rose), and after CRS with non-shuffled sequences (FIG. 101B) and shuffled sequences for different shuffle periods, $T_{shuffle}$, (FIGs. 101C-101E), respectively. Large, $\rho \approx 1$ indicates in-phase synchronized spiking activity. Colours correspond to different CR sequences (see labels in FIG. 101B’). After cessation of stimulation the network approaches either the stable strongly connected

synchronized state (SCSS) or the stable weakly connected desynchronized state (WCDS). FIG. 101A' and 101B'-101E' are the same as FIGs. 101A and 101B-101E but for a homogeneous network. FIG. 101F is a raster plot of neuronal spiking activity (black dots) for neurons at different locations during delivery of non-shuffled CR with CR sequence I-II-III-IV, X . Red colours show the intensity of the spatial stimulus profile (see also panel FIG. 101K). The horizontal black bar marks a 50 ms time interval. FIG. 101G illustrates corresponding, time lags between stimuli delivered to sites I-IV in units of $1/f_{CR}$. The CR frequency was set to $f_{CR} = 10$ Hz. FIGs. 101H and 101I are the same as FIGs. 101F and 101G but for the CR sequence I-III-II-IV. FIG. 101J is a raster plot for CRS with rapidly shuffled sequence, so-called rapidly varying sequences (RVS) CRS, with $T_{shuffle} = 101$ ms. Figure 101K is an illustration of the spatial stimulus profiles used to model the four stimulation sites located at $X_I = -3/8L$ (blue), $X = -1/8L$ (orange), $X = 1/8L$ (green), $X = 3/8L$ (red).

[00619] Simulated was CRS of coupled excitatory leaky integrate-and-fire neurons with spike-timing dependent plasticity (STDP) for two types of networks of synaptic connections: an inhomogeneous network in which the probability for a synaptic connection depended on the neurons' locations (FIG. 101A) and a homogeneous network where the connection probability was the same for all neuron pairs (FIG. 101A'). For both networks, stable abnormal (SCSS) and stable physiological (WCDS) model states coexisted. All parameters are given in [J.A. Kromer and P.A. Tass. Simulated dataset on coordinated reset stimulation of homogeneous and inhomogeneous networks of excitatory leaky integrate-and-fire neurons with spike-timing-dependent plasticity. Data in Brief 54, 110345 (2024)].

[00620] Delivered was CRS and determined was the evolving mean synaptic weight. In the inhomogeneous network, the long-lasting outcome of non-shuffled CRS varied depending on the employed CR sequence (FIG. 101B). Depending on the specific CR sequences, the mean synaptic weight stabilized at low values (WCDS) or high values (SCSS). In contrast, no such differences were observed in the biologically unrealistic homogeneous network (FIG. 101B').

[00621] Two aspects are important for the effect of a CR sequence on the mean synaptic weight: (i) Based on STDP, the time lags between stimuli administered to different sites and, hence, subpopulations determine to which extent the weights of the corresponding synapses increase or decrease [J.A. Kromer and P.A. Tass. Synaptic reshaping of plastic neuronal

networks by periodic multichannel stimulation with single-pulse and burst stimuli. PLoS Computational Biology 18, e1010568 (2022)]. (ii) The overall strength of this plasticity modulating effect depends on how many synapses interconnect these subpopulations. For instance, a strong reduction of many synapses cannot be achieved if the stimulated subpopulations are only sparsely interconnected. Conversely, to minimize the mean synaptic weight and achieve a WCDS, stimuli have to affect densely interconnected subpopulations at time lags that cause a reduction of the synaptic weights.

[00622] In preclinical and clinical studies, CR sequences were typically shuffled [P.A. Tass, L. Qin, C. Hauptmann, S. Dovero, E. Bezard, T. Boraud, W.G. Meissner. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Annals of Neurology* 72, 816 (2012); J. Wang, S.P. Fergus, L.A. Johnson, S.D. Nebeck, J. Zhang, S. Kulkarni, H. Bokil, G.F. Molnar, J.L. Vitek. Shuffling Improves the Acute and Carryover Effect of Subthalamic Coordinated Reset Deep Brain Stimulation. *Frontiers in Neurology* 13, 716046 (2022); I. Adamchic, C. Hauptmann, U.B. Barnikol, N. Pawelczyk, O. Popovych, T.T. Barnikol, A. Silchenko, J. Volkmann, G. Deuschl, W.G. Meissner, M. Maarouf, V. Sturm, H.-J. Freund, P.A. Tass. Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. *Movement disorders* 29, 1679 (2014)]. In FIGs. 101B-101E and FIGs. 101B'-101E', shown are computational results for different T_{shuffle} . In the inhomogeneous network and for T_{shuffle} long compared to the time scale of STDP, the mean synaptic weight slowly oscillates between the stationary values attained for different CR sequences during non-shuffled CRS (compare $T_{\text{shuffle}} = 30 \text{ min}$ and non-shuffled CRS in FIGs 101E, 101B). Cessation of stimulation while the network is close to stationary states induced by unfavourable CR sequences led to unfavourable long-lasting aftereffects, i.e., strong synchronization (see blue trajectory in FIG. 101E, bottom). In contrast, shuffle periods that are short compared to the STDP time scale, e.g., $T_{\text{shuffle}} = 100 \text{ ms}$ (FIGs. 101C, 101J), led to more robust long-lasting outcome and to even lower mean synaptic weights than non-shuffled CRS with sequences that minimize the mean synaptic weight (FIGs. 101B and 101C) as it avoids stimulation-induced reverberations in the network dynamics and the resulting formation of strongly connected clusters. Note that the degree of acute synchrony was lower for longer shuffle periods.

[00623] It is concluded that sufficiently fast shuffling is advantageous for CRS. The performance of nonshuffled CRS in inhomogeneous networks crucially depends on the selected CR sequence. CRS with unfavourable sequences may perform poorly by supporting the formation of strongly connected clusters. In contrast, non-shuffled CRS with specific CR sequences may strongly reduce the overall synaptic weight. However, so far, it is unclear how to determine these favourable sequences, e.g., based on network properties, such as electrode locations, connectome, plasticity mechanisms etc. Computationally, rapidly shuffled CR avoids reverberation of “unfavourable” sequences, which may be the reason why non-shuffled CRS was inferior to shuffled CRS delivered to the STN in monkeys rendered Parkinsonian by MPTP [P.A. Tass, L. Qin, C. Hauptmann, S. Dovero, E. Bezard, T. Boraud, W.G. Meissner. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Annals of Neurology* 72, 816 (2012); J. Wang, S. Nebeck, A. Muralidharan, M.D. Johnson, J.L. Vitek, K.B. Baker. Coordinated Reset Deep Brain Stimulation of Subthalamic Nucleus Produces Long-Lasting, Dose-Dependent Motor Improvements in the 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Non-Human Primate Model of Parkinsonism. *Brain Stimulation* 9, 609 (2016); J. Wang, S.P. Fergus, L.A. Johnson, S.D. Nebeck, J. Zhang, S. Kulkarni, H. Bokil, G.F. Molnar, J.L. Vitek. Shuffling Improves the Acute and Carryover Effect of Subthalamic Coordinated Reset Deep Brain Stimulation. *Frontiers in Neurology* 13, 716046 (2022)]. Computational results suggest that this effect is most pronounced in heterogeneous networks, e.g., with inhomogeneous synaptic connectivity and plasticity mechanisms, likely reflecting biologically more realistic conditions. In contrast, long shuffle periods induce the risk of turning stimulation off at the “wrong” time when the network undergoes a SCSS. Results, obtained in a comparably simple, yet clearly understandable network model, provide hypotheses for more detailed and computation time-demanding computational modelling studies as well as pre-clinical and clinical studies.

[00624] Example 2: Learning optimal CR sequence: In example 2, it is shown how well-performing stimulation parameters for inducing long-lasting desynchronization can be learned using the method and apparatus described in the present disclosure. Embodiments control the degree of neuronal synchrony (associated with Parkinson’s disease symptoms) in a computational model. The neuronal activity in the target brain area is simulated using a

network of excitatory leaky integrate-and-fire (LIF) neurons with spike-timing dependent plasticity. Parameters are set according to Example 1 for the inhomogeneous network.

[00625] In FIG. 102, illustrated is the learning procedure (according to embodiments). Performed is a sequence of stimulation epochs 10202. After each stimulation epoch an assessment 10204 is performed. The stimulation pattern is adjusted every $N=4$ assessments. In the simulations, stimulation epochs of 10 sec were used that were followed by a stimulation-off period of 10 sec during which an assessment of neuronal synchrony was performed. This corresponds to the setup shown in FIG. 102.

[00626] During assessment neuronal synchrony is measured and the system is classified into a state according to the degree of neuronal synchrony. Considered are two states: synchronous activity, corresponding to state 1 (the patient is assumed to suffer from symptoms) and desynchronous activity corresponding to state 2 (the patient does not experience symptoms). For simplicity, all stimulation parameters are fixed according to the values in the table below and the ones in Example 1 except for the CR sequence. A shuffle period of 10 sec is used, such that the CR sequence does not change during a stimulation epoch.

T	stim. amplitude	wave form	#sites	jitter
100 ms	1	single pulse	4	0

[00627] The controller may choose between any of the following CR sequences:

[00628] i) I-II-III-IV,

[00629] ii) I-II-IV-III,

[00630] iii) I-III-II-IV,

[00631] iv) I-III-IV-II,

[00632] v) I-IV-II-III,

[00633] vi) I-IV-III-II.

[00634] Note that all other CR sequences result from these CR sequence by applying a time shift of multiples of $T/4$ for long T_{shuffle} . Initially, the probability to choose any of these CR sequences for a given stimulation step is uniform. The goal is to find the CR sequence that drives the system into a desynchronized state.

[00635] Used was the framework of a Markov Decision process in which state 1 is associated with synchronous activity (time-averaged Kuramoto order parameter during assessment > 0.5) and state 2 is associated with desynchronous activity (time-averaged Kuramoto order parameter during assessment ≤ 0.5). In each state the agent can choose between one of the six CR sequences i-vi (actions). If the agent is in state 2 it receives a reward of $r=1$. If it is in state 1 it receives no reward, $r=0$.

[00636] Since it is not known which action will lead to what transition between states, the problem of finding an optimal stimulation pattern (CR sequence) can be thought of as a model-free control problem.

[00637] Embodiments implement the following algorithm to find the policy, specifying which action is chosen in which state, that maximizes the total reward. This algorithm is based on first-visit Monte Carlo online control (Sutton and Barto, 2018).

[00638] Algorithm:

Initialize $Q(s,a)=0$, $N(s,a)=0$, $k=0$, $\epsilon=1$, and an ϵ -greedy policy $\pi_k(Q)$ in which each action is equally likely to be selected in each state.

Repeat the following:

Simulate the LIF network for N stimulation epochs and assessment periods. The corresponding state-action-reward sequence is denoted as $(s_{(kN+1)}, a_{(kN+1)}, r_{(kN+1)}, s_{(kN+2)}, a_{(kN+2)}, r_{(kN+2)}, \dots, s_{(kN+N)}, a_{(kN+N)}, r_{(kN+N)})$.

Calculate the discounted sum of rewards: $G_{(kN+t)} = r_{(kN+t)} + \gamma r_{(kN+t+1)} + \gamma^2 r_{(kN+t+2)} + \dots + \gamma^N r_{(kN+N)}$

For t in $1, \dots, N$, do

If first visit to (s,a) for current k , then update $N(s,a)$ and $Q(s,a)$ according to

$N(s,a) \leftarrow N(s,a)+1$

$Q(s_{(kN+t)}, a_{(kN+t)}) \leftarrow Q(s_{(kN+t)}, a_{(kN+t)}) + 1/$

$N(s_{(kN+t)}, a_{(kN+t)}) (G_{(kN+t)} - Q(s_{(kN+t)}, a_{(kN+t)}))$

Do $k \leftarrow k+1$

Set $\varepsilon \leftarrow 1/k$

$\pi_k(Q) = \varepsilon$ -greedy with respect to Q .

[00639] For a given $Q(s,a)$, the ε -greedy policy: $\pi_k(a|s)$, such that with probability $1 - \varepsilon$ the action a (CR sequence) that maximizes $Q(s,a)$ is selected in state s ; and with probability ε an arbitrary action a (CR sequence) is selected in state s according to a uniform distribution (Sutton and Barto, 2018).

[00640] A corresponding simulated time trace is shown in FIG. 103.

[00641] An analysis of embodiments focuses on two quantities. The first quantity is the degree of neuronal synchrony, ρ , as quantified by the Kuramoto order parameter

$$\rho = \left| \frac{1}{N} \sum_{k=1}^N e^{i\phi_k} \right|.$$

[00642] Here, ϕ_i , is a phase variable attaining subsequent integer values at the i th LIF neuron's spike times and increasing linearly in time in between spikes of the i th LIF neuron. The second quantity is the mean synaptic weight, $\langle w \rangle$, corresponding to the average weight of all synapses. As demonstrated in Example 1, a stable strongly connected synchronized state and a stable weakly connected desynchronized state coexist, such that the desynchronized one remains stable in the absence of stimulation if the mean synaptic weight attains low values. On the other hand, only the synchronized state is stable for high mean synaptic weight.

[00643] The state-action reward sequence for the trajectory shown in FIG. 103 is (1,iii,0,1,v,0,1,i,0,2,ii,1,2,ii,1,2,ii,1,2,ii,1,2,ii,1,2,ii,1,...). $Q(1,a)$ was maximized for action i (CR sequence I-II-III-IV) and $Q(2,a)$ was maximized for action ii (CR sequence I-II-IV-III).

[00644] To test the robustness of the learning procedure, performed were 2^7 simulations and recorded were the actions that maximized $Q(1,a)$ and $Q(2,a)$. The relative frequency at which corresponding actions were learned is shown in FIG. 104. Note that stimulation led to long-lasting desynchronization in all 2^7 cases.

[00645] FIG. 104 shows the relative frequency at which actions i -vi maximized $Q(1,a)$, i.e., the expected total future reward when being in the synchronized state, and $Q(2,a)$, i.e., the future reward when being in the desynchronized state, and performing action across 2^7

simulation experiments. Any action was learned about equally often when being in the desynchronized state, suggesting that performing any action let the system to remain in the desynchronized state. In the synchronized state; however, action vi was learned to be optimal less often than other actions. This action corresponds to the CR sequence I-IV-III-II. If one compares this with the trajectory shown in FIG. 101B of Example 1, it is seen that stimulation with this CR sequence was indeed not capable of driving the network into the desynchronized state. On the other hand, actions i-iii were learned to maximize future rewards in the synchronized state most often. In FIG. 101C of Example 1, stimulation with the corresponding CR sequences (I-II-III-IV, I-II-IV-IV, and I-III-II-IV), led to a substantial reduction of the mean synaptic weight and drove the network into the desynchronized state. However, the presented learning algorithm was not able to identify the CR sequence I-II-III-IV (action i), that leads to the lowest mean synaptic weight in FIG. 101C of Example 1, as the “best” sequence. This is likely, because states were defined based on the Kuramoto order parameter and not based on the mean synaptic weight, which would be difficult to measure in a clinical setting.

[00646] Example 3: CR with shuffled sequences and non-uniform sequence selection probability -- Based on the observation that stimulation with certain CR sequences leads to lower mean synaptic weights than stimulation with others, Example 3 tests whether synaptic weight reduction during CR with shuffled sequences could be improved when certain sequences were excluded from the pool of CR sequences from which CR sequences are drawn during shuffling. This corresponds to using a non-uniform probability for CR sequence selection during shuffled CR.

[00647] To test this hypothesis, performed were simulations for the LIF model, with similar parameters as in Example 1 for the inhomogeneous network. Applied was CR stimulation with different CR sequence pools starting at time $t=0$ and recorded was the mean synaptic weight. Results for four different CR sequence pools and a shuffle period of 0.1 seconds and four stimulation sites are shown in the FIGs. 105A and 105B.

[00648] FIG. 105A shows Mean synaptic weight during CR stimulation with rapidly varying sequence ($T_{\text{shuffle}} = T$) for four different CR sequence pools. FIG. 105B shows that the CR sequence pools are named as follows: “all” contains all 4 possible CR sequences; “without worst” contains all but the CR sequences I-IV-III-II, II-I-IV-III, III-II-I-IV, and IV-III-

II-I; “without best” contains all but the CR sequences I-II-III-IV, IV-I-II-III, III-VI-I-II, and II-III-IV-I; and “best” contains only the CR sequences I-II-III-IV, IV-I-II-III, III-VI-I-II, and II-III-IV-I. Parameters: $T=0.1$ sec. All other parameters are set to the values used in Example 2

[00649] Results for one network and sequence realization are shown in FIGs. 105A and 105B. It is found that shuffling only between the best-performing CR sequences (“best”), reduces the mean synaptic weight more rapidly after stimulation onset ($t=0$) than considering all CR sequences. Here, “best-performing” refers to the sequence that led to the lowest mean synaptic weight in FIG. 101C of Example 1 and all CR sequences that are equivalent to this CR sequence up to a time shift of multiple of $T/4$ during non-shuffled CR (see FIG. 105A). Note that while shuffled CR with all considered types of CR sequences performs similar at time t_2 , one can find large differences between the mean synaptic weights during shuffled CR with the “best” sequences and shuffled CR with other CR sequences at time t_1 .

[00650] FIGs. 106A to 106C illustrate mean synaptic weight after stimulation onset averaged over different network and sequence realizations. Results are shown for “best” (blue), “without worst” (red), “all” (black), and “without best” (green) CR sequence pools (see FIG. 105B). Lines show averages and dashed region shows the range between minimum and maximum values during individual simulations. Panels Figures 106A, 106B, 106C show results for different shuffle periods of 0.1 sec, 10 sec and 1800 sec, respectively. Parameters are set to the values used in Example 2. It is found that only drawing sequences from the “best” CR sequence pool during shuffled CR reduces the mean synaptic weight during stimulation substantially across different shuffle periods.

[00651] Example 4 - Reinforcement learning for autonomous stimulation amplitude adjustment --In this example, a computational model is used to illustrate how reinforcement learning (RL) can be employed to improve stimulation aftereffects of coordinated reset (CR) stimulation over the course of multiple stimulation sessions. During each session, stimulation ON (stimulation epochs) and OFF periods (pauses) are performed subsequently. During the pauses an assessment of the patient’s condition is performed and based on the outcome the RL algorithm assigns either positive rewards or a negative rewards. Different stimulation sessions can model either treatments of different patients or multiple treatments of the same patient, e.g., at different visits. Based on the “experience” on effective stimulation parameters during the past

stimulation ON periods the algorithm selects the stimulation parameters for the next ones with the goal to maximize positive rewards.

[00652] Specifically, RL is tested to adjust the stimulation amplitude of CR stimulation. Several studies on CR stimulation suggest that there is a finite amplitude window in which CR deep brain stimulation (DBS) is most effective. In more detail, in clinical studies in MPTP monkeys it was found that long-lasting therapeutic effects of CR DBS with high-frequency DBS-like amplitudes were weaker than those of CR DBS with only one third of DBS-like amplitudes [P.A. Tass, L. Qin, C. Hauptmann, S. Dovero, E. Bezard, T. Boraud, W.G. Meissner. Coordinated reset has sustained aftereffects in Parkinsonian monkeys. *Annals of Neurology* 72, 816 (2012)]. Similarly, too strong vibrotactile CR fingertip stimulation might reduce independent recruitment of neuronal populations processing sensory input from different fingertips by stimuli delivered to different fingertips. On the other hand, too weak stimulation might not recruit neurons in target brain regions.

[00653] To automatize amplitude adjustment, RL is tested in a computational model to effectively learn stimulation amplitudes for CR stimulation. Embodiments deliver CR stimulation with amplitude A_k for a stimulation epoch of time T_{stim} . Then, embodiments pause stimulation for T_{pause} and evaluate the patients' condition (e.g., using a survey or biomarkers such as LFP in the target brain region). Depending on the outcome, the RL algorithm may adjust the stimulation amplitude $A_k \rightarrow A_{k+1}$ and the next stimulation epoch starts, followed by another pause and so on. This procedure is stopped after k_{max} stimulation epochs and subsequent pauses. Following, we refer to k_{max} stimulation epochs and subsequent pauses as one *session*.

[00654] To employ RL, represented are the described sequence of stimulation epochs, pauses, and evaluated patients' condition by a Markov Decision Process (MDP). States in the MDP represent the simulated patient's condition which is evaluated using a Likert scale with possible responses: "very bad", "bad", "neutral", "good", "very good." The latter simulates the patient's answers, e.g., in a survey taken during the pause after each stimulation epoch. In our simulations, the responses are simulated by a Gaussian random variable with a mean value that is correlated to the degree of neuronal synchrony and the mean synaptic weight of intrapopulation synapses of a neuronal subpopulation, and a non-zero standard deviation simulating noise in the

patients' responses. The correlation to neuronal synchrony and synaptic connectivity is motivated by previous experimental studies showing that the degree of neuronal synchrony correlates with some of Parkinson's disease symptoms [C. Hammond, H. Bergman, P. Brown. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends in Neurosciences 30, P357 (2007)] and the presence of abnormal synaptic connectivity in animal models of Parkinson's disease [H.-Y. Chu, J.F. Atherton, D. Wokosin, D.J. Surmeier, M.D. Bevan Heterosynaptic Regulation of External Globus Pallidus Inputs to the Subthalamic Nucleus by the Motor Cortex. Neuron 85, P364 (2015); M. Madadi Asl, A. Valizadeh, P.A Tass. Dendritic and axonal propagation delays determine emergent structures of neuronal networks with plastic synapses. Scientific Report 7,39682 (2017); M. Fillion, L. Tremblay, P.J. Bédard. Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Research 444, 165 (1988); T. Boraud, E. Bezard, B. Bioulac, and C.E. Gross. Ratio of Inhibited-to-Activated Pallidal Neurons Decreases Dramatically During Passive Limb Movement in the MPTP-Treated Monkey. Journal of Neurophysiology 83, 1760 (2000)].

[00655] Employed is a network of leaky integrate-and-fire (LIF) neurons from Example 1 for the inhomogeneous network with the same parameters, except for the stimulation amplitude, the width of the stimulation profile, and the CR frequency. In the simulations, we set $T_{\text{stim}} = 10$ sec and $T_{\text{decay}} = 10$ sec. These values were chosen such that sufficiently long simulations were feasible. In clinical studies, these times will likely have to be longer, e.g., in the range of minutes to hours.

[00656] The patient's condition during assessment is simulated as follows: first, measured is the mean synaptic weight of a neuronal subpopulation including 500 neurons (50% of the population) at time $T_{\text{mean}} = 0.85 T_{\text{decay}}$ after each stimulation epoch. This was done to allow the network activity to recover from the acute impact of stimulation so that it correlates with the underlying synaptic connectivity rather than with the stimulus pattern delivered during the stimulation epoch. Then, calculated is the Kuramoto order parameter of that neuronal subpopulation (see Example 1, under point 00641). Both, the Kuramoto order parameter and the mean synaptic weight are floating numbers between zero and one. From these two numbers, calculated are integers between zero and four using the python function `numpy.digitize()` with

bins [0.2, 0.4, 0.6, 0.8] (for the Kuramoto order parameter) and [0.1, 0.2, 0.3, 0.4] (for the mean synaptic weight). The latter is motivated by the observation that the mean synaptic weight in the pathological synchronized state is of the order 0.4. The mean of these two integer numbers is then used as the mean for the Gaussian distributed random number simulating the patient's response. To account for noise, a standard deviation of one is used for this random number. The result is then mapped to an integer number between zero (very good) and four (very bad) using `numpy.digitize()` with bins [0.5, 1.5, 2.5, 3.5]. In all cases, the "right" option in `numpy.digitize()` was set to "True" during calculation. Thus, in a pathological state (synchronized and strongly connected) the simulated patient's condition will most often be "very bad" whereas it will most often be "very good" in a physiological (desynchronized and weakly connected) state. The random fluctuations of the patient's condition simulate other factors impacting a patient's condition, e.g., poor sleep or other life events.

[00657] The patient's condition represents the state in the MDP, i.e., state 0 corresponds to the patient response that they feel "very good" during assessment, state 1 to "good", state 2 to "neutral", state 3 to "bad", and state 4 to "very bad". After the patient's condition has been assessed one out of nine actions is performed, corresponding to the choice of a stimulation amplitude for CR stimulation during the next stimulation epoch. Specifically, CR stimulation is performed with $T_{\text{stim}} = 10$ ms and one of the following nine amplitudes: $A_{\text{stim}} = 0, 0.125, 0.25, 0.375, 0.5, 0.625, 0.75, 0.875$, or 1. After an amplitude (action) has been selected, rewards are given depending on the simulated patient condition (state): state 0 $\rightarrow$ reward 3, state 1 $\rightarrow$ reward 1.5, state 2 $\rightarrow$ reward 0, state 3 $\rightarrow$ reward -1, state 4 $\rightarrow$ reward -2.

[00658] Each stimulation session starts with the LIF network being in the strongly connected synchronized state (see Example 1) and the patient condition "very bad", then k_{max} stimulation epochs and subsequent pauses are simulated. During each pause an assessment of the patient's condition is performed. The goal of the RL algorithm is to maximize the obtained total reward. In theory, the maximum possible total reward is $-2 + k_{\text{max}}$ (condition "very bad" in the very beginning and then condition "very good" during each assessment) and the minimum possible total reward is $-2(k_{\text{max}} + 1)$ (always "very bad"). However, in the simulations it takes a few stimulation epochs to obtain sufficiently low mean synaptic weight

and trigger “very good” simulated patient conditions (see below for representative simulation results).

[00659] RL is implemented using an online Sarsa(λ) algorithm [Sutton and Barto, 2018].

An example algorithm operates as follows:

- Initialize the state action function $Q(s, a) = 0$ for each state s and action a and an ϵ -greedy policy p with respect to $Q(s, a)$
- Loop over sessions:
 - Initialize eligibility trace $E(s, a) = 0$, for each state s and action a .
 - Initialize state $s_0 = \frac{1}{2}$ (start in “very bad” state).
 - Draw action a_t from policy p for state s_t
 - Get reward r_t for performing action a_t in state s_t .
 - Simulate a stimulation epoch of CR stimulation with amplitude corresponding to action a_t and the subsequent pause for the network of LIF neurons from Example 1. Simulate patient response resulting from Kuramoto order parameter, ρ , and mean synaptic weight, $\langle w \rangle$, which results in the next state s_{t+1} .
 - Loop over $k_{\max}$ stimulation epochs:
 - Draw action a_{t+1} from policy p for state s_{t+1}
 - Do the following updates:
 - $\Delta = r_t + \gamma Q(s_{t+1}, a_{t+1}) - Q(s_t, a_t)$
 - $E(s_t, a_t) \leftarrow E(s_t, a_t) + \Delta$
 - For all states s and actions a , do
 - $Q(s, a) \leftarrow Q(s, a) + \alpha \Delta E(s, a)$
 - $E(s, a) \leftarrow \gamma \lambda E(s, a)$
 - Calculate a new policy that is an ϵ -greedy policy p with respect to Q
 - Calculate reward r_{t+1} for performing action a_{t+1} in state s_{t+1} .
 - Simulate the next stimulation epoch of CR stimulation with amplitude a_{t+1} and the subsequent pause for the network of LIF neurons from Example 1. Simulate the patient’s condition, which results in the next state s_{t+1}
 - Update $a_t \leftarrow a_{t+1}, s_t \leftarrow s_{t+1}, \rho_t \leftarrow \rho_{t+1}, \langle w \rangle_t \leftarrow \langle w \rangle_{t+1}$
 - End loop over $k_{\max}$ stimulation epochs
- End loop over sessions

[00660] Used was a constant learning rate of $\alpha = 0.1$ and $\gamma = 1/k_s$, where k_s counts sessions. Selected was the following ϵ -greedy policy: if in state s , select a random action with probability ϵ , and the action a that maximizes $Q(s, a)$ with probability $1 - \epsilon$.

[00661] Representative trajectories of the Kuramoto order parameter, ρ , and the mean synaptic weight, $\langle w \rangle$, are shown in FIG. 107. Over a few stimulation epochs the mean synaptic weight as well as the degree of neuronal synchrony reduces.

[00662] FIG. 107 illustrates trajectories of the Kuramoto order parameter (ρ) and the mean synaptic weight ($\langle w \rangle$) during a session with $K_{max} = 20$ stimulation epochs. Horizontal, black bars mark stimulation epochs and vertical, gray lines mark assessment times. The learning algorithm adjusts the stimulation amplitude according to an ϵ -greedy policy with respect to the current estimate of the state action function $Q(s,a)$ (see above). Parameters: width of stimulation profile $L/16\pi$ and CR frequency 10 Hz.

[00663] To evaluate the learning progress, calculated is the total reward after each session, as shown in FIG. 108. More specifically, FIG. 108 illustrates total reward after each session for subsequent sessions achieved by the RL algorithm presented above. Two cases are considered: case 1 in which a large range of amplitudes leads to a reduction of the mean synaptic weight (parameters as in FIG. 107) and case 2 where only one of the possible amplitudes would lead to a reduction of the mean synaptic weight during a single long ($T_{stim} \rightarrow \infty$) stimulation epoch (width of stimulation profile was set to $6L/8\pi$ and CR frequency to 21 Hz), representing a more difficult test case. The black curve marks the average over the three trials. Note that a total reward of 5.5 corresponds to a case where each of the five possible patient's conditions occurs equally often during assessment (horizontal dashed line). Parameters: $K_{max} = 25$. Different trials correspond to different realizations of random action selection according to the ϵ -greedy policy with respect to respective $Q(s,a)$ and illustrates bias in learning progress.

[00664] In addition, shown are the trajectories of the simulated patient's assessment, the Kuramoto order parameter ρ , and the mean synaptic weight $\langle w \rangle$ in FIG. 108. More specifically, FIG. 108 illustrates traces of the simulated patient's condition, the Kuramoto order parameter, ρ , and the mean synaptic weight, $\langle w \rangle$, during the indicated sessions for the two cases in FIG. 108 for the trials represented by black crosses in FIG. 108. Grayscale marks results after corresponding number of sessions.

[00665] Tested was the learning of the stimulation amplitude for two cases. In case 1, other stimulation parameters were adjusted such that CR stimulation with a wide range of stimulation amplitudes would result in a reduction of the mean synaptic weight during a single long ($T_{stim} \rightarrow \infty$) stimulation epoch, thereby resulting in sustained desynchronization when stimulation is turned off (see, for instance, [Kromer et al., 2020]). In case 2, only one of the possible choices of stimulation amplitudes would cause a reduction of the mean synaptic weight during a single long stimulation epoch, making it a very challenging test case in which a random selection of the stimulation amplitude after each assessment is unlikely to lead to a positive total reward.

[00666] It was found that RL increases the total reward corresponding, on average, to a better simulated patient condition during assessment. Note that a total reward of 5.5 corresponds to the case where each patient response is equally likely, however each session starts with the neuronal network in the synchronized state ($p \approx 1$ and $\langle w \rangle \approx 0.36$) with a simulated patient response of “very bad”. For case 1, the total reward increases above 5.5 within a few sessions. In case 2, the total reward varies across trials with the majority of sessions leading to a total reward of above 5.5, even during the first sessions.

[00667] In example 5, presented are preliminary results from a computational study in which a reinforcement learning algorithm was applied to adjust the probability distribution at which CR sequences are drawn during shuffling in shuffled CR stimulation.

[00668] Example 5: Reinforcement learning for autonomous adjustment of CR sequence pool -- Finally, applied was a similar setup as in Example 4 to adjust the probability at which CR sequences are drawn during shuffled CR (see Example 3). Specifically, the stimulation amplitude is fixed to $A_{stim} = 1$ and an action, α_x , is associated in the MDP with a combination of CR sequences from which sequences are drawn during shuffled CR with uniform probability. All other CR sequences are assigned a probability of zero. Considered are all possible combinations of the 6 CR sequence groups from Example 3. This results in $2^6=64$ possible actions.

[00669] This setup is illustrated in the schematic provided in FIG. 110.

[00670] All CR sequences that are “ON” for an action α_x can be drawn during shuffling (see schematic). Thus, each action corresponds to a different CR sequence pool from which CR

sequences are drawn during shuffled CR. Note that the case where all CR sequences are OFF is considered as stimulation is turned OFF, i.e. $A_{stim} = 0$.

[00671] Learning of CR sequence pools for the stimulation parameters of case 1 from Example 4 were tested. FIG. 111 illustrates learning of CR sequence pools for shuffled CR. Traces of the simulated patient's condition, the Kuramoto order parameter, ρ , and the mean synaptic weight, $\langle w \rangle$, during the indicated sessions for CR sequence pool learning. Parameters: $A_{stim} = 1$, $f_{CR} = 10$ Hz, width of stimulation profile L/16pi. Grayscale marks results after corresponding number of sessions.

[00672] Simulated traces of the simulated patient's condition, the Kuramoto order parameter, and the mean synaptic weight are shown in FIG. 111.

[00673] It was found that RL reduces the time necessary to downregulate the mean synaptic weight, $\langle w \rangle$ (see FIG. 111) suggesting that the stimulation time required to induce therapeutic aftereffects by shuffled CR stimulation can be reduced after adjustment of CR sequence pools by means of RL.

[00674] Here, well-performing refers to better desynchronization effects/symptom relief than a uniform distribution.

[00675] Example Apparatus: A device according to embodiments delivers stimuli which activate neurons. Different embodiments may employ electrical stimuli or optical stimuli directly delivered to the brain or spinal cord through implanted electrodes, epicortical electrodes, subdural electrodes, epidural electrodes, implanted or epicortical or epidural optical fibers. Alternatively, stimulation may be delivered non-invasively, e.g., by means of vibrotactile and/or electrotactile stimuli, infrared neural stimuli, or transcranial stimulation such as transcranial electrical, magnetic, ultrasound, or light stimulation.

[00676] The device stimulates multiple target sites, i.e., locations in the brain or spinal cord or on the skin. In some embodiments one stimulation site may be sufficient. Accordingly, the device comprises one or more depth electrodes with one or more stimulation contacts each. In a different embodiment the device comprises one or more coils for transcranial magnetic stimulation, two or more electrodes for transcranial electrical stimulation, one or more optical fibers for transcranial light or infrared stimulation, one or more epicortical electrodes, one or

more epidural electrodes, one or more ultrasound sources, one or more vibrotactile stimulators, one or more electrical skin or tongue electrodes, one or more thermal skin stimulators.

[00677] Invasive applications: Embodiments can also be applied to invasive or combined invasive and non-invasive stimulation. Examples of invasive stimulation include, but are not limited to deep brain stimulation, spinal cord stimulation, epicortical/epidural stimulation.

[00678] Supplementary Material

[00679] Neuronal network model - Simulations were performed using the model network of excitatory leaky integrate-and-fire (LIF) neurons with STDP from Justus A. Kromer, Ali Khaledi-Nasab, and Peter A. Tass. Impact of number of stimulation sites on long-lasting desynchronization effects of coordinated reset stimulation. *Chaos*, 30(8):084134, 2020 (Kromer et al.). A total of $N = 1000$ neurons were simulated. Neuron center coordinates were randomly distributed in the interval $[-L/2, L/2]$ according to a uniform distribution. L is the system's length scale and set to 5 mm in simulations. In the main text, we considered different topologies of synaptic connections, which are described in detail below.

[00680] The dynamic equations for the membrane potential and synaptic interaction were taken from the above reference. The dynamics of the i th neuron's subthreshold membrane potential, $V_i(t)$, was given by

$$C_i \frac{dV_i}{dt} = g_{\text{leak}}(V_{\text{rest}} - V_i) + g_{\text{syn},i}(t)(V_{\text{syn}} - V_i) + I_{\text{stim},i}(t) + I_{\text{noise},i}(t). \quad (1)$$

[00681] C_i is the membrane capacitance. Terms on the right-hand side represent: the leak current, with leakage conductance g_{leak} and resting potential V_{rest} ; the excitatory synaptic input current, with synaptic conductance $g_{\text{syn},i}(t)$ and reversal potential V_{syn} ; the stimulation current $I_{\text{stim},i}(t)$; and the noisy input current $I_{\text{noise},i}(t)$, modelling input from other brain regions. Neuron i was defined to fire a spike whenever its membrane potential crossed the dynamic threshold potential $V_{\text{th},i}(t)$,

$$\tau_{\text{th}} \frac{dV_{\text{th},i}}{dt} = -(V_{\text{th},i} - V_{\text{th,reset}}). \quad (2)$$

[00682] Rectangular spikes were implemented by setting $V_i(t)$ to V_{spike} for a duration of τ_{spike} . Afterwards, performed was an instantaneous reset: $V_{\text{th},i}(t) \rightarrow V_{\text{th,spike}}$ and $V_i(t) \rightarrow V_{\text{reset}}$.

[00683] Synaptic input was modelled by considering the following dynamics of the synaptic conductances $g_{\text{syn},i}(t)$:

$$\tau_{\text{syn}} \frac{dg_{\text{syn},i}}{dt} = -g_{\text{syn},i} + \kappa \frac{\tau_{\text{syn}}}{N} \sum_{j \in G_i} w_{j \rightarrow i}(t) \sum_{l_j} \delta(t - t_{l_j}^j - t_d). \quad (3)$$

[00684] Here, τ_{syn} is the synaptic timescale, $t_{l_j}^j$ the timing of the l_j th spike of neuron j , and t_d is the synaptic transmission delay. The outer sum runs over the set of presynaptic neurons G_i of neuron i . The strength of synaptic coupling was given by the maximum coupling strength κ . The strengths of individual synapses were scaled by the time-dependent synaptic weights $w_{j \rightarrow i}(t)$. Here, j is the index of the presynaptic and i the index of the postsynaptic neuron.

[00685] Independent Poisson input was delivered to the neurons modelling noisy input from other brain areas. To this end, Poisson spike trains with mean firing rate f_{noise} were fed into the neurons through excitatory synapses. The resulting input currents, $I_{\text{noise},i}(t)$, were given by

$$I_{\text{noise},i}(t) = g_{\text{noise},i}(t)(V_{\text{syn}} - V_i) \quad (4)$$

[00686] with dynamic noise conductances $g_{\text{noise},i}(t)$ that obeyed

$$\tau_{\text{syn}} \frac{dg_{\text{noise},i}}{dt} = -g_{\text{noise},i} + \kappa_{\text{noise}} \tau_{\text{syn}} \sum_{k_s} \delta(t_{k_s} - t). \quad (5)$$

[00687] The noise intensity was set by κ_{noise} . t_{k_i} is the timing of the k_i th spike in the Poisson spike train fed into neuron i .

[00688] Chosen are parameters as in Kromer et al.: $g_{\text{leak}}=0.02 \text{ mS/cm}^2$, $V^{\text{rest}} = -38 \text{ mV}$, $V_{\text{reset}} = -67 \text{ mV}$, $V_{\text{th,spike}}=0 \text{ mV}$, $V_{\text{th,rest}} = -40 \text{ mV}$, $\tau_{\text{th}}=5 \text{ ms}$, $V_{\text{syn}}=0 \text{ mV}$, $\tau_{\text{syn}}=1 \text{ ms}$, $t_d=3 \text{ ms}$, $\kappa=8 \text{ mS/cm}^2$, $\kappa_{\text{noise}}=0.026 \text{ mS/cm}^2$, and $f_{\text{noise}}=20 \text{ Hz}$. The membrane capacitances C_i were Gaussian distributed ($N(\mu C; \sigma C)$, $\mu C=3 \text{ }\mu\text{F/cm}^2$ and $\sigma C=0.05 \mu\text{C}$). For these parameters, the frequency and the range of resulting membrane potential oscillations matched recordings of periodically spiking neurons in the rat subthalamic nucleus (Mark D. Bevan and Charles J. Wilson. Mechanisms underlying spontaneous oscillation and rhythmic ring in rat subthalamic neurons. J. Neurosci., 19(17):7617-7628, 1999).

[00689] The dynamics of the synaptic weights, $w_{i \rightarrow j}(t)$, was determined by STDP. Considered was a nearest-neighbor STDP scheme in which weight updates were performed whenever either a postsynaptic or a presynaptic spike arrived at a synapse (Abigail Morrison,

Markus Diesmann, and Wulfram Gerstner. Phenomenological models of synaptic plasticity based on spike timing. *Biol. Cybern.*, 98:459-478, 2008). The synaptic weight updates, $w_{i \rightarrow j} \rightarrow w_{i \rightarrow j} + W((t_j + t_d) - (t_i + t_a))$, were given by the STDP function

$$W(\Delta t) = \eta \begin{cases} e^{-|\Delta t|/\tau_+}, & \Delta t > 0 \\ 0, & \Delta t = 0 \\ -\frac{\beta}{\tau_R} e^{-|\Delta t|/\tau_-}, & \Delta t < 0 \end{cases} \quad (6)$$

[00690] Here, $\Delta t = (t_j + t_d) - (t_i + t_a)$ is the time lag between the arrival time of the backpropagating postsynaptic action potential (spike) at the synapse, $t_j + t_d$, and the latest presynaptic spike arrival time, $t_i + t_a$ (if the update was triggered by the arrival of a backpropagating postsynaptic spike at the synapse), or the time lag between the current presynaptic spike arrival time, $t_i + t_a$, and the latest postsynaptic spike arrival time, $t_j + t_d$ (if the update was triggered by the arrival of a presynaptic action potential at the synapse) (Mojtaba Madadi Asl, Alireza Valizadeh, and Peter A. Tass. Dendritic and axonal propagation delays determine emergent structures of neuronal networks with plastic synapses. *Sci. Rep.*, 7:39682, 2017). Here, t_d and t_a are the dendritic and the axonal delays, respectively. Considered was only an axonal delay of $t_a = 3$ ms and the dendritic delay was set to zero.

[00691] STDP parameters were chosen according to J.A. Kromer, A. Khaledi-Nasab, P.A. Tass. Impact of number of stimulation sites on long-lasting desynchronization effects of coordinated reset stimulation. *Chaos* 30, 083134 (2020) such that a stable strongly connected synchronized state (SCSS) and a stable weakly connected desynchronized state (WCDS) coexisted for each network considered in the main text (illustrations of these states can be found in Figure 15). $\eta = 0.02$ scaled the weight update per spike. $\tau_R = 4$ yielded an asymmetry in the STDP decay times $\tau_+ = 10$ ms and $\tau_- = \tau_+ \tau_R$. The parameter $\beta = 1.4$ scales the ratio of overall long-term depression, i.e. the integral of the STDP function (Eq. (6)) over time lags that led to negative weight updates, to overall long-term potentiation, i.e. the integral of the STDP function over time lags that led to positive weight updates.

[00692] FIG. 112 illustrates coexistence of a strongly connected synchronized state (SCSS) and a weakly connected desynchronized state (WCDS). Trajectories of the Kuramoto order parameters (see Example 1), ρ , according to Equation (9) (A,B) and corresponding mean synaptic weights, $\langle w \rangle$, for four initial mean synaptic weights ($\langle w(t=0) \rangle = 0, 0:2, 0:4, 0:6$

(from dark to light gray) (C,D). Results for an inhomogeneous network are shown on the left and result for a homogeneous network on the right. The same realization of synaptic connections was used in all simulations for each network type. The corresponding initial, individual synaptic weights were distributed according to a bimodal distribution, i.e. $w_{i \rightarrow j}(t=0) \in \{0; 1\}$, such that the respective mean synaptic weights were realized. Note the logarithmic time axes.

[00693] Network topologies - Considered were two types of networks of synaptic connections: homogeneous networks (FIG. 101A' in the text above) and inhomogeneous networks (FIG. 101A in the text above). In the homogeneous networks, the probability for implementing a synaptic connection between any two neurons was set to 7%. The realization of the resulting synaptic connections that was used in the simulations in the main text is shown in FIG. 101A'.

[00694] In the inhomogeneous networks, the neurons were first sorted according to their center coordinates, X . Then, the neurons were separated into four subpopulations such that the first 250 neurons were part of subpopulation one, the second 250 neurons were part of subpopulation two, and so on. Afterwards, synaptic connections were implemented with a probability of 14% between pairs of neurons in which the presynaptic neuron was part of subpopulation k and the postsynaptic neuron was part of subpopulation l for $(k, l) \in \{(1, 1), (1, 4), (2, 1), (2, 2), (3, 1), (3, 2), (3, 3), (4, 2), (4, 3), (4, 4)\}$. The realization of the resulting synaptic connections that was used in the main text is shown in FIG. 101A.

[00695] Coordinated Reset stimulation: Delivered was CRS to the networks of LIF neurons using different CR sequences. CRS was delivered to four stimulation sites [P.A. Tass. A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations. Biological Cybernetics, 89, 81 (2003)]. The four stimulation sites were located at $X_I = -3L/8$, $X_{II} = -L/8$, $X_{III} = L/8$, and $X_{IV} = 3L/8$. The mean frequency at which each site received stimuli was set to $f_{CR} = 10$ Hz. Considered were the following stimulation patterns:

[00696] Non-shuffled CRS. During non-shuffled CRS each stimulation site received stimuli periodically with frequency f_{CR} . Characterized was the CR sequence at which individual sites receive stimuli using roman letters, e.g., the sequence at which stimuli were administered

to site one first, site two second, site three third, and site four last was denoted as I-II-III-IV (FIG. 101F in the text above).

[00697] Shuffled CRS. During shuffled CRS a new CR sequence was randomly selected every shuffle period, T_{shuffle} . Used was a uniform distribution among all $4!$ possible CR sequences. An exemplary realization of a corresponding CR pattern for $T_{\text{shuffle}} = 1/f_{\text{CR}}$ is shown in FIG. 101J in the text above. Note that the special case $T_{\text{shuffle}} = 1/f_{\text{CR}}$, i.e., shuffling after each CR cycle, is often referred to as CR with rapidly varying sequence (RVS CR) (Peter A Tass and Milan Majtanik. Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. Biol. Cybern., 94:58-66,2006; Ilya Adamchic, Christian Hauptmann, Utako Brigit Barnikol, Norbert fawelczyk, Oleksandr Popovych, Thomas Theo Barnikol, Alexander Silchenko, Jens Volkmann, Gunter Deuschl, Wassilios G Meissner, et al. Coordinated reset neuromodulation for Parkinson's disease: proof-of-concept study. Mov. Disord., 29(13):1679-1684, 2014).

[00698] Individual stimuli were charge-balanced and consisted of an excitatory rectangular pulse of duration $T_p = 0.4$ ms that was followed by an inhibitory one of duration $2T_p$. The amplitudes of the excitatory and inhibitory rectangular pulse were $A_{\text{stim}\mu}/T_p$ and $A_{\text{stim}\mu}/2T_p$, respectively, with $\mu = (V_{\text{th.spike}} - V_{\text{reset}}) = \langle C_i \rangle$.

[00699] The stimulation current each neuron experienced was given by

$$I_{\text{stim},i} = A(t) \sum_j S_j(X_i). \quad (7)$$

[00700] Here, $A(t)$ is the amplitude of the stimulus as described in the previous paragraph. $S_j(X_i)$ is the spatial stimulus profiles for stimulation site j . Specifically, a neuron with center coordinated X_i was affected by a stimulus delivered to site j at a strength of

$$S_j(X_i) = \left(1 + \left(\frac{X_i - X_j}{\sigma_j} \right)^2 \right)^{-1}. \quad (8)$$

[00701] σ_j scales the width of the stimulus profile.

[00702] Embodiments set $A_{\text{stim}} = 1$ for which stimuli are strong enough to elevate the membrane potential of neurons that are close the stimulation site from its reset value to the

spiking threshold during the excitatory rectangular pulse part of a stimulus. The width of the stimulus profile was set to $\sigma_j = L=8$ (see FIG. 101K in the text above).

[00703] Simulations were performed as follows: First, a random network of synaptic connections for the considered network type was generated according to the procedure described above. Initial membrane potentials were distributed uniformly between V_{reset} and $V_{\text{th,rest}}$, and all synaptic conductances were set to zero. Then, the initial synaptic weights were randomly generated such that individual weights either attained zero or one and a predefined mean synaptic weight was realized. Numerical integration was performed using the Euler method with an integration time step of 0.1 ms.

[00704] Simulations for each network type and different initial mean synaptic weights are shown in FIG. 112. For both inhomogeneous and homogeneous networks a stable SCSS and a stable WCDS coexist (see FIG. 112). Measured was the degree of neuronal synchrony using the Kuramoto order parameter (Yoshiki Kuramoto. Chemical Oscillations, Waves, and Turbulence. Springer, Berlin, 1984)

$$\rho(t) = \left| \frac{1}{N} \sum_{k=1}^{N-1} e^{2\pi i \Psi_k(t)} \right| \quad (9)$$

[00705] N is the number of neurons, i the imaginary unit, and $\Psi_k(t)$ is a phase function associated with the inter-spike intervals of neuron k . $\Psi_k(t)$ attains subsequent integer values at the subsequent spike times of neuron k and increases linearly during inter-spike intervals (M. Rosenblum, A. Pikovsky, J. Kurths, C. Schaffer, and P. A. Tass. Phase synchronization: From theory to data analysis. In S. Gielen and F. Moss, editors, Neuro-Informatics and Neural Modelling, Handbook of Biological Physics, volume 4, pages 279{321. Elsevier, Amsterdam, 2001). $\rho(t) \text{ approx. } = 1$ corresponds to synchronized spiking and $\rho(t) \text{ approx. } = 0$ indicates a lack of synchronized spiking.

[00706] In FIG. 112, trajectories starting with high initial mean synaptic weight (light gray) approach a state with synchronized spiking ($\rho \text{ approx. } = 1$) and a mean synaptic weight between approx 0.3 and approx. 0.4, depending on the type of network, corresponding to a SCSS. In contrast, trajectories with low initial mean synaptic weight approach a state with low degree of neuronal synchrony ($\rho \text{ approx. } = 0$), corresponding to a WCSS. Together, this shows

the coexistence of a stable SCSS, modelling pathological neuronal synchrony, e.g., in Parkinson's disease, and a stable WCSS, modelling physiological neuronal activity.

[00707] To study the effect of CRS on networks in the SCSS, chosen was a large initial mean synaptic weight (all synapses were set to one) and simulated was the network for 3000 s, such that the network approached the SCSS. In the SCSS, the mean synaptic weight was between 0.3 and 0.4 for the inhomogeneous networks (FIGs. 101B-101E in the text above and FIGs. 113A and 113B) and approx. 0.4 for the homogeneous networks (FIGs. 101B'-101E' in the text above and FIGs. 113C and 113D.). After 3000 s CRS was delivered for 2 h. After cessation of stimulation, simulated was the network until the mean synaptic weight approached a stationary value. Resulting trajectories of the mean synaptic weights for various CR patterns and both network types are shown in FIG. 101 in the text above.

[00708] FIG. 113 provides statistical analysis of mean synaptic weight before, during, and after stimulation. Mean synaptic weight shortly before cessation of CRS (acute) and approx 5 hours after cessation of CRS (long-lasting) are compared to its values before stimulation (init.). Results are shown for inhomogeneous networks (FIGs. 113A, 113B) and homogeneous networks (FIGs. 113C, 113D), and prior to stimulation (init.); at the end of a 2h session of CRS for non-shuffled CR (non-shuffled), and for shuffled CR (shuffled) with shuffle periods 0.1s, 10s, and 1800s (FIGs. 113A and 113C), and approx 3 hours after cessation of stimulation for the same setups (FIGs. 113B and 113D). Results are shown for five network realization (all) and for the CR sequences I-II-II-IV, I-II-IV-III, I-III-II-IV, I-III-IV-II, I-IV-II-III, I-IV-III-II for non-shuffled CR and for 30 realizations of the CR sequence for each shuffle period and network realization. Horizontal bars mark averages over individual sequence and network realizations. Symbols show results for individual simulations.

[00709] A more detailed statistical analysis of the mean synaptic weight before, during, and after stimulation is presented as follows.

[00710] Mean synaptic weight before, during, and after CRS: Analyzed was the mean synaptic weight of inhomogeneous and homogeneous networks before, during, and after CRS (FIG. 113). Corresponding exemplary trajectories of the mean synaptic weight are shown in FIG. 101 in the text above. Additionally, for both inhomogeneous and homogeneous networks, performed were simulations for five network realizations and recorded the mean synaptic

weights after 3000s of simulation, when the network approached a stationary state. Results are labeled "init." in FIG. 113. Then, simulated was a 2h session of either non-shuffled CRS or shuffled CRS with different shuffle periods (FIG. 113). At the end of the CRS session, recorded were snapshots of the mean synaptic weight (acute) for different realizations of the CR sequences. In the inhomogeneous networks the recorded mean synaptic weights spread out over a wide range with an average of approximately 0.25 for non-shuffled CR and shuffled CR with a shuffle period of 1800 s (FIG. 113A). In contrast, for short shuffle periods (0.1 s and 10s) the mean synaptic weights were close to zero and similar across network realizations and realizations of the CR sequence (FIG. 113A). In the homogeneous networks, the mean synaptic weights were close to zero after 2h of CRS for short shuffle periods; however, shuffled CRS with long-shuffle periods or non-shuffled CR led to non-zero mean synaptic weights (FIG. 113C). After the stimulation session, simulated was the system for another 3 hours. During this time the mean synaptic weights approached either their value in a SCSS or their value in a WCDS. Values of the mean synaptic weights recorded 3 hours after different types of CRS are shown in FIG. 113B for the inhomogeneous and in FIG. 113D for the homogeneous network. In the inhomogeneous network, after non-shuffled CR and shuffled CR with a shuffle period of 1800 s the mean synaptic weight approached either large values or small values depending on the network realization and the realization of the CR sequence (FIG. 113B). In contrast, after shuffled CR with short shuffle periods the system remained in the WCDS after cessation of stimulation, corresponding to long-lasting desynchronization effects of CRS. However, in the homogeneous network all network and sequence realizations led to similar mean synaptic weights at the end of the CRS session (FIG. 113C) and 3 hours after cessation of stimulation (FIG. 113D). Here, the results neither depended on the network realization nor on the realization of the CR sequence.

[00711] The herein described subject matter sometimes illustrates different components contained within, or connected with, different other components. It is to be understood that such depicted architectures are illustrative, and that in fact many other architectures can be implemented which achieve the same functionality. In a conceptual sense, any arrangement of components to achieve the same functionality is effectively "associated" such that the desired functionality is achieved. Hence, any two components herein combined to achieve a particular

functionality can be seen as "associated with" each other such that the desired functionality is achieved, irrespective of architectures or intermedial components. Likewise, any two components so associated can also be viewed as being "operably connected," or "operably coupled," to each other to achieve the desired functionality, and any two components capable of being so associated can also be viewed as being "operably coupleable," to each other to achieve the desired functionality. Specific examples of operably coupleable include but are not limited to physically mateable and/or physically interacting components and/or wirelessly interactable and/or wirelessly interacting components and/or logically interacting and/or logically interactable components.

[00712] With respect to the use of plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity.

[00713] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.).

[00714] Although the figures and description may illustrate a specific order of method steps, the order of such steps may differ from what is depicted and described, unless specified differently above. Also, two or more steps may be performed concurrently or with partial concurrence, unless specified differently above. Such variation may depend, for example, on the software and hardware systems chosen and on designer choice. All such variations are within the scope of the disclosure. Likewise, software implementations of the described methods could be accomplished with standard programming techniques with rule-based logic and other logic to accomplish the various connection steps, processing steps, comparison steps, and decision steps.

[00715] It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation, no such intent is present. For example, as an aid to

understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to inventions containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, typically means at least two recitations, or two or more recitations).

[00716] Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general, such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[00717] Further, unless otherwise noted, the use of the words "approximate," "about," "around," "substantially," etc., mean plus or minus ten percent.

[00718] Although the present embodiments have been particularly described with reference to preferred examples thereof, it should be readily apparent to those of ordinary skill

in the art that changes and modifications in the form and details may be made without departing from the spirit and scope of the present disclosure. It is intended that the appended claims encompass such changes and modifications.

WHAT IS CLAIMED IS:

1. A device for providing more effective vibrotactile stimulation, comprising:
a vibrotactile mechanical stimulator including a non-disc-contactor; and
a housing configured for securing to a patient's fingertip or other part of the body.
2. The device of claim 1, wherein the stimulator further includes a shock absorber.
3. The device of claim 1, wherein the stimulator further includes a wavebreaking hole.
4. The device of claim 2, wherein the shock absorber comprises an oscillating mass that is coupled to the housing by a spring serving as the shock absorber.
5. The device of claim 1, wherein the nondisc contactor is configured to increase the physiological/medical effects of vibrotactile stimuli by means of a physiologically more effective contactor shape.
6. The device of claim 3, wherein the wavebreaking hole includes a wave breaker-type (non-annular) perimeter around the hole that further reduces the spread of surface waves in the free surround of the contactor.
7. The device of claim 1 further comprising a fingertip fixation enabling the housing to be mounted to fingertips of different size, ranging from small to large fingertips, with substantially no change in contact pressure.
8. The device of claim 1, wherein the stimulator comprises a double flat spring architecture.
9. A method for more effective non-invasive stimulation, comprising:
providing a 3-(physiological) channel electrotactile stimulation of one fingertip of a patient.

10. The method of claim 9, wherein the stimulation is applied at night in a convenient manner.
11. The method of claim 9, wherein the stimulation is delivered through only one stimulation site corresponding to the one fingertip.
12. The method of claim 9, wherein more than one stimulation site corresponding to two or more fingertips is used.
13. An apparatus for more effective non-invasive stimulation, comprising:
a contactor for providing electrotactile stimulation containing an inner and an outer electrode, with inner electrode diameter around 1 mm and an inner diameter of the outer, surrounding electrode around 6 mm.
14. The apparatus of claim 13, wherein the dimension values for the inner electrode diameter can vary from 0.4-1.7 mm or 0.2-2.5 mm and for the inner diameter of the outer electrode from 5.5 mm-6.5 mm or 4.5-7.5 mm.
15. An apparatus for more effective non-invasive stimulation, comprising:
a contactor for providing electrotactile stimulation containing an inner and an outer electrode, with inner electrode diameter around 3 mm and an inner diameter of the outer, surrounding electrode around 10 mm.
16. The apparatus of claim 15, wherein the dimension values for the inner electrode diameter can vary from 2.5-3.5 mm or 1.5-4.5 mm and for the inner diameter of the outer electrode from 9 mm-11 mm or 7.5-12 mm.
17. A method for more effective vibrotactile stimulation, comprising:
providing stimuli that enable spatially more focal and/or shorter activation.

18. The method of claim 17, further comprising providing shorter stimuli that enable greater temporal jitter of stimulus onsets.
19. The method of claim 17, wherein providing stimuli includes using compound pulses and/or continuous stimulation with modulated amplitudes.
20. The method of claim 19, further comprising configuring a device to deliver continuous stimulation with specifically modulated vibration amplitudes.
21. The method of claim 19 or 20, wherein one compound pulse can contain more than only one supra-threshold part.
22. The method of claim 17, further comprising a personalization/calibration process.
23. The method of claim 22, wherein the personalization/calibration process includes adapting pedestals to the patient's vibratory threshold and, hence, reflect a fundamental parameter of the patient's sensory information processing.
24. The method of claim 23, wherein the vibratory threshold varies between and within patients in the course of the treatment.
25. The method of claim 17, wherein providing stimuli includes employing temporal jitter of stimulus onsets and/or temporal jitter of suprathreshold vibration amplitudes and/or temporal jitter of vibratory burst durations and/or subthreshold vibration amplitude and/or vibration frequency.
26. The method of claim 25, wherein the compound pulses enable shorter vibratory pulse and, in turn, greater temporal jitter of stimulus onsets.

27. The method of claim 25 or 26, wherein in combination with amplitude randomization and/or vibratory burst randomization, providing an increase of the stimulation efficacy.
28. The method of claim 17, wherein providing stimuli includes preventing in-channel masking effects.
29. The method of claim 28, wherein to avoid mutual masking effects and habituation, the interval between any two subsequent vibrotactile stimuli, specifically vibratory bursts, delivered to the same stimulation channel amount to about 3-5 times the vibrotactile stimulus' duration.
30. A device to effectively reduce unwanted mechanical and proprioceptive stimulation while securely mounting controller and battery for a fingertip stimulation array.
31. The device of claim 30, wherein mounting of the controller is done with a watch-like band over the palm area and does not translate or vibrate in any substantial way during therapy.
32. The device of claim 31, wherein the controller mounts softly on the outside of the hand where external effects are naturally at a minimum.
33. The device of claim 30, wherein to reduce unwanted stimulation by the controller and fixation band, both are low weight, including the controller and a battery.
34. The device of claim 33, wherein the band is adjustable to accommodate all hand sizes with a secure fit and has a soft and porous fabric for skin ventilation and comfort.
35. The device of claim 30, wherein each fingertip stimulator is connected through one cable by means of a standard headphone type jack connector where the female side of each connection resides in the controller and the male side of each connection is securely integrated with designated tapper cable.

36. The device of claim 30, wherein the controller is placed in the palm.
37. The device of claim 30, wherein the controller is placed on the back of the hand.
38. The device of claim 30, wherein the cables take an S-form to keep them close to the hand and, hence, reduce the patient's risk of getting snagged.
39. The device of claim 30, wherein apart from the single digit cables, there are no further cables, and the controllers for right and left hand communicate wirelessly.
40. A method for more effective non-invasive stimulation, comprising:
combining vibrotactile and electrotactile stimulation.
41. The method of claim 40, wherein the combination is configured to achieve a sufficient electrode-skin contact.
42. The method of claim 40, wherein the combined stimulation is configured to use different physiological channels per stimulation site, utilizing different mechanoreceptor channels, to achieve significantly stronger and more effective stimulation at lower amplitudes of the vibrotactile stimulation.
43. A method and device that delivers non-invasive, sensory stimulation treatment in a way that counteracts habituation, including by increasing and rewarding patients' attention, alertness, curiosity level and activating additional brain areas besides primary sensory brain areas.
44. The method and device of claim 43, wherein apparatuses are configured to counteract habituation and increases the therapeutic effects, including by boosting the propagation of desynchronizing effects through disease-related brain circuits.

45. A method for more effective non-invasive stimulation, comprising:
using hard- and firmware apparatuses to provide more precise vibrotactile and/or electrotactile stimulation by avoiding interhemispheric inhibition by delivering wireless multisite stimulation to remote and/or bilateral stimulation sites at highest temporal precision.
46. The method of claim 45, including specific pairing of stimulus activations, including varying and/or nonmirror-pairing, in case of bilateral stimulation.
47. The method of claim 45, combined with visual and/or auditory and/or olfactory stimulation, with all or at least some of these devices being wirelessly connected.
48. The method of claim 45, combined with invasive devices such as deep brain stimulators and/or spinal cord stimulators and/or epicortical stimulators etc.
49. A method for more effective vibrotactile stimulation, comprising:
automatically/autonomously calibrating relevant stimulation parameters for non-invasive and invasive multichannel CR stimulation and related stimulation techniques, random reset stimulation as well as combinations thereof.
50. The method of claim 49, further or alternatively using electrotactile stimulation.
51. The method of claim 49, further comprising a learning procedure including performing assessment after each stimulation epoch.
52. The method of claim 51, wherein during assessment, neuronal synchrony is measured and the system is classified into a state according to the degree of neuronal synchrony.
54. The method of claim 53, wherein two states are considered: synchronous activity, corresponding to state 1 (the patient is assumed to suffer from symptoms) and desynchronous activity corresponding to state 2 (the patient does not experience symptoms).

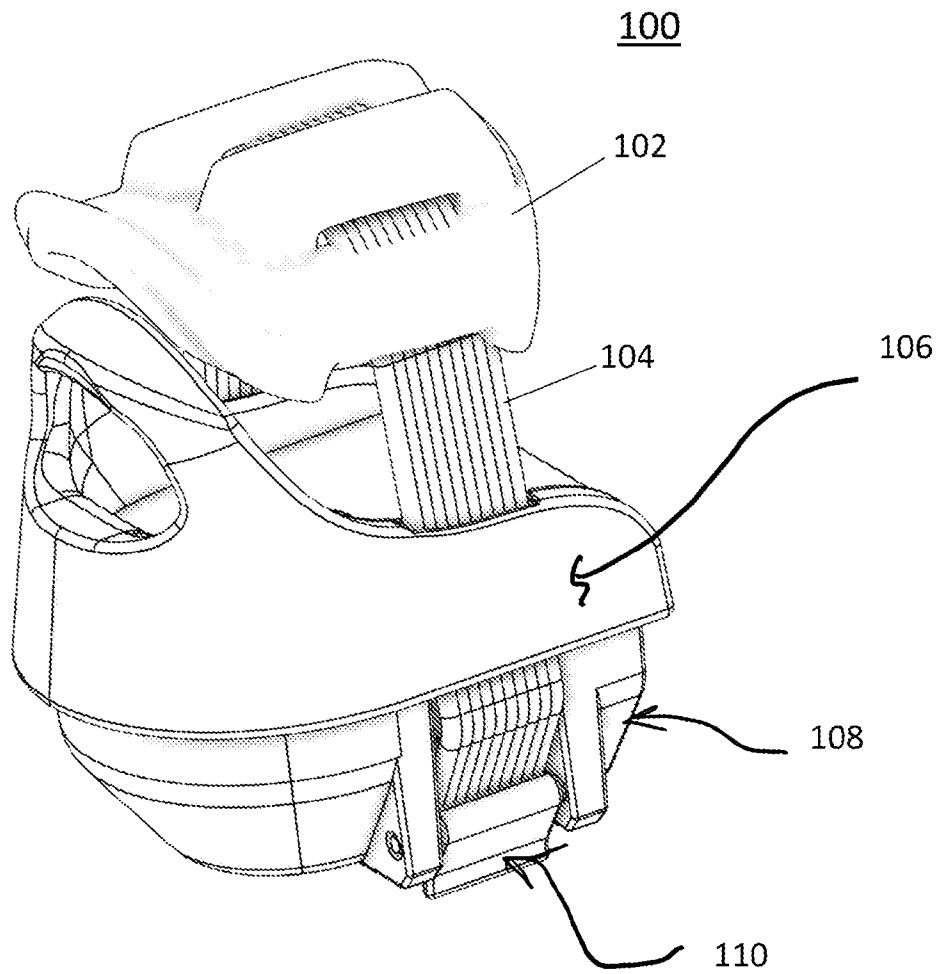


FIG. 1A

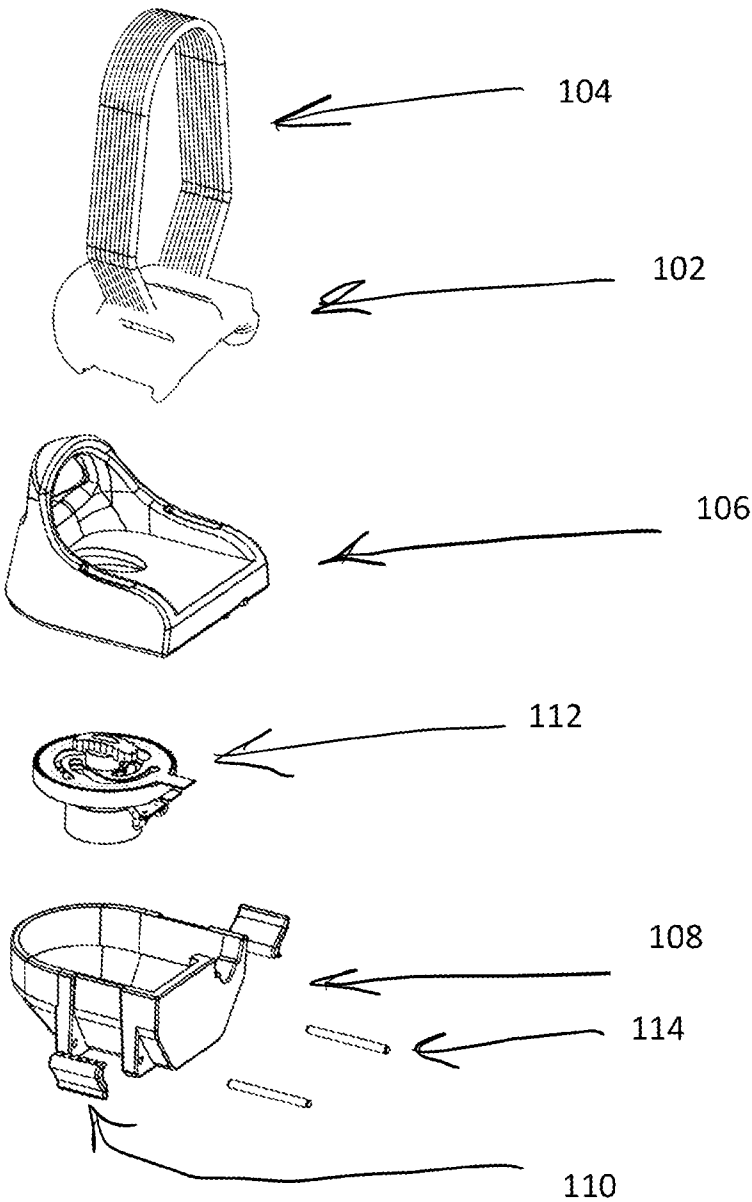


FIG. 1B

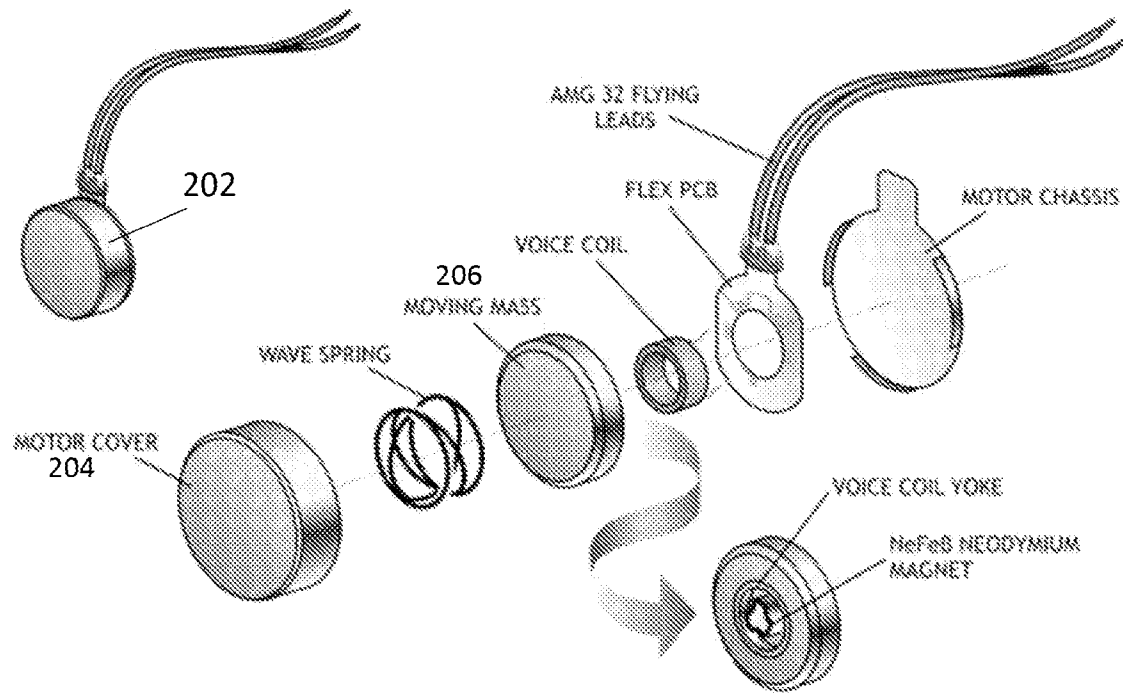


FIG. 2

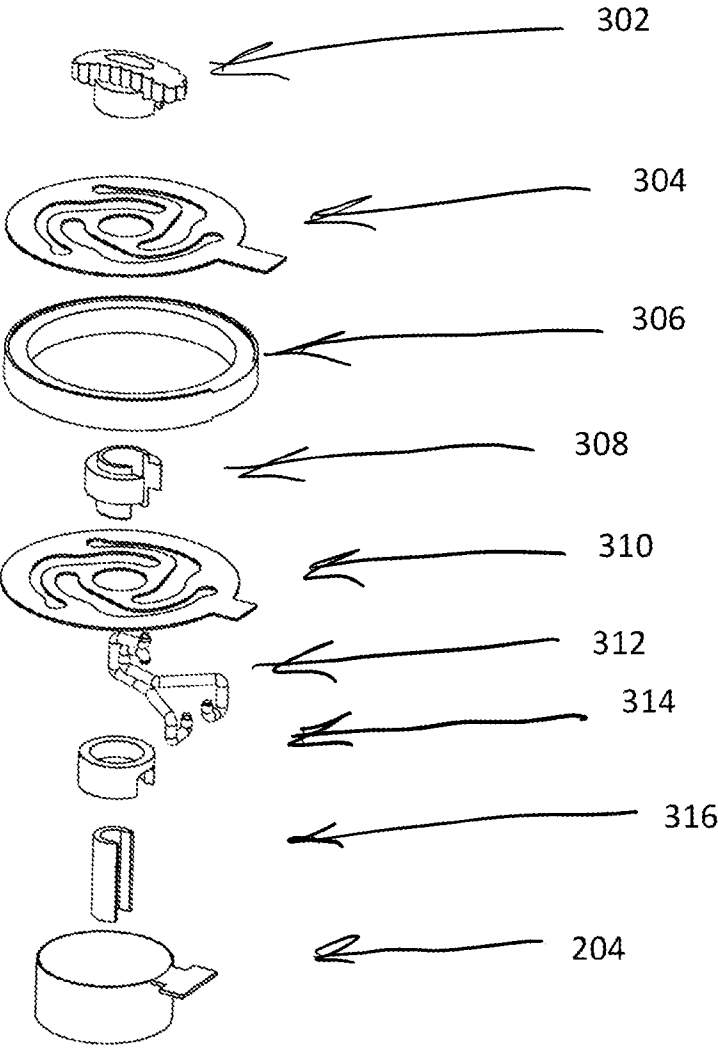


FIG. 3

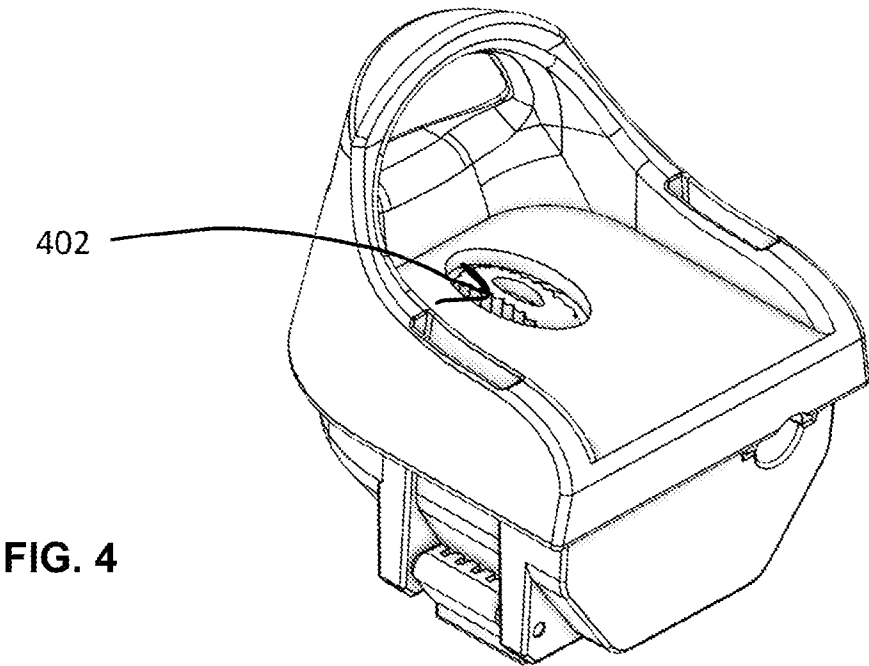


FIG. 4

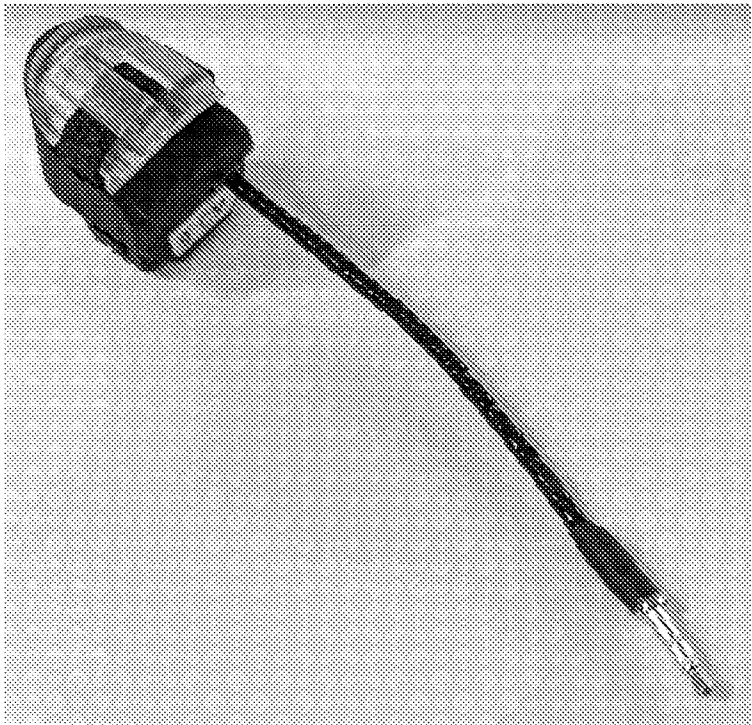


FIG. 5

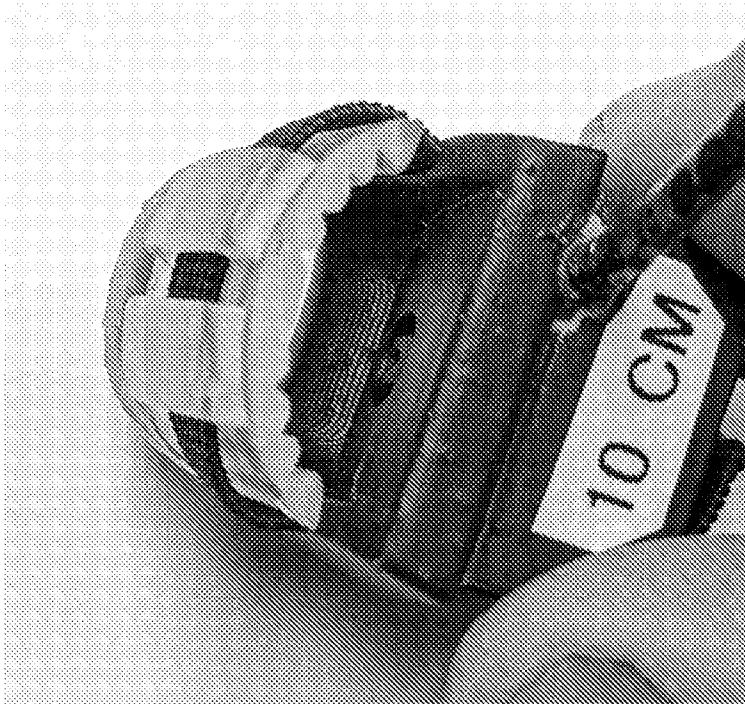


FIG. 6

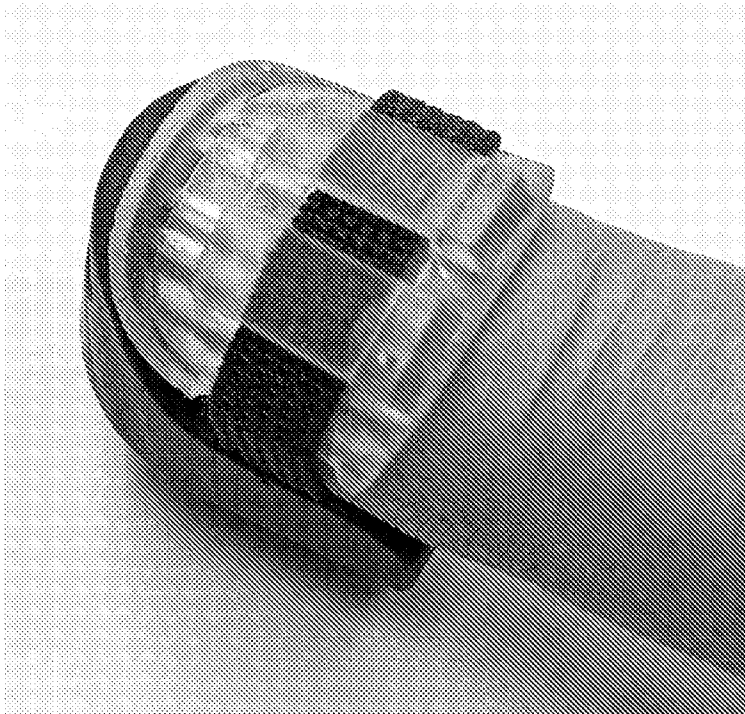


FIG. 7A

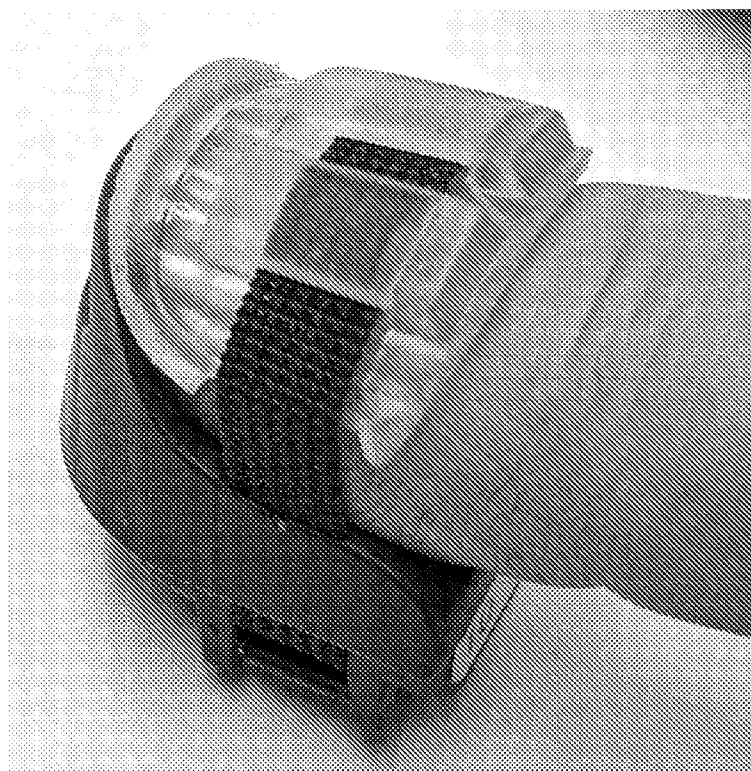


FIG. 7B

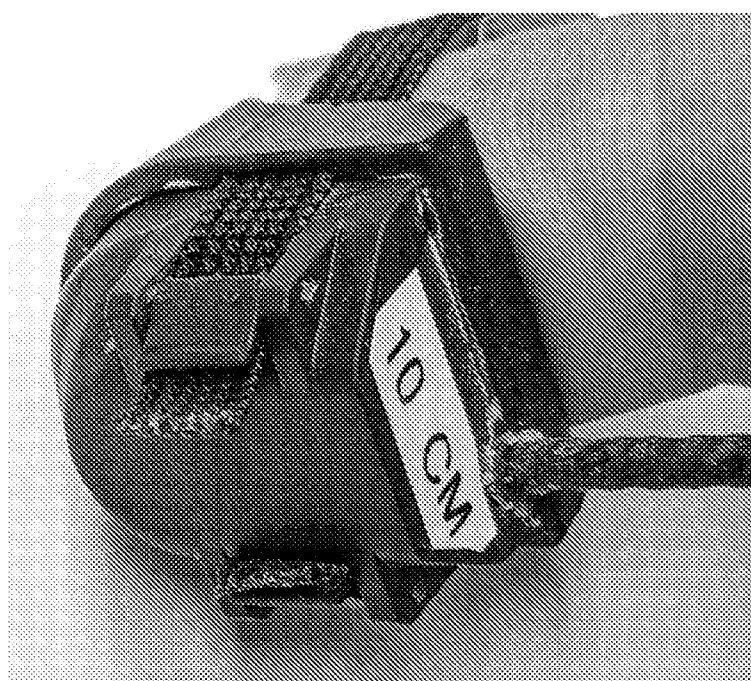


FIG. 7C

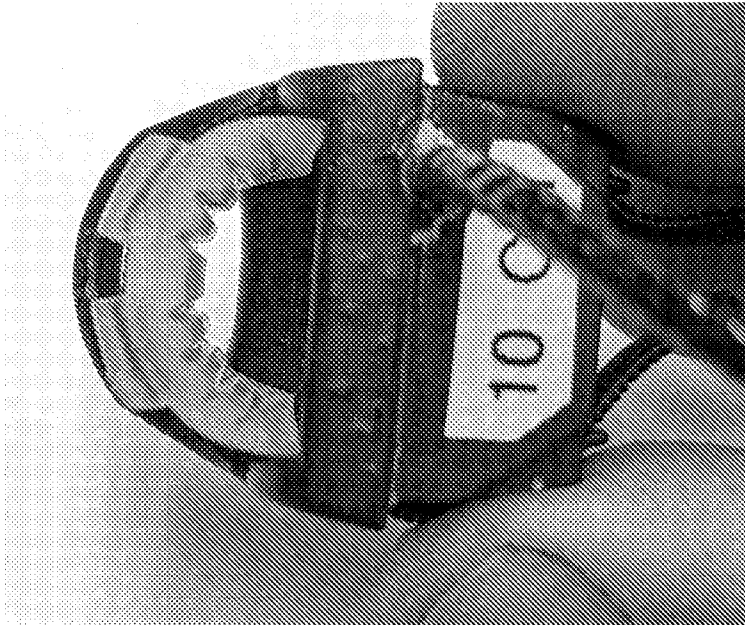


FIG. 8A

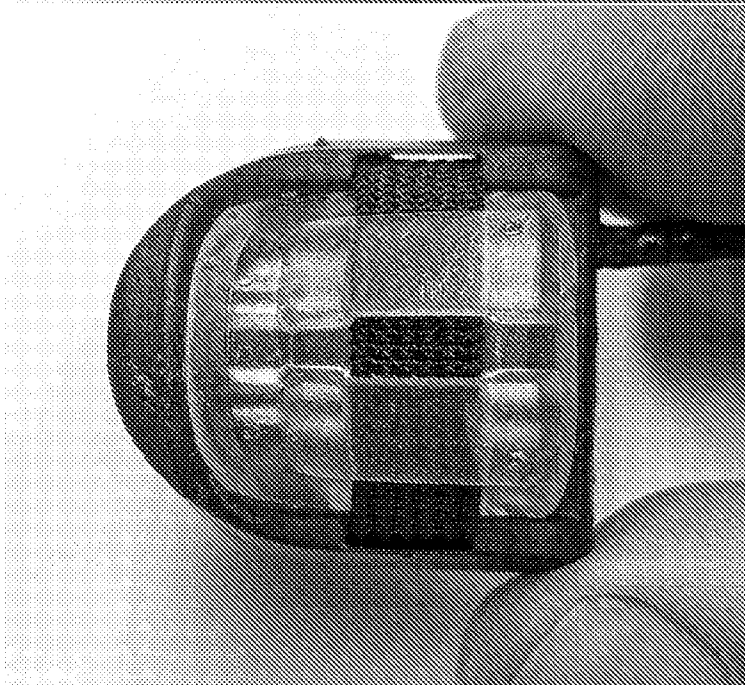


FIG. 8B

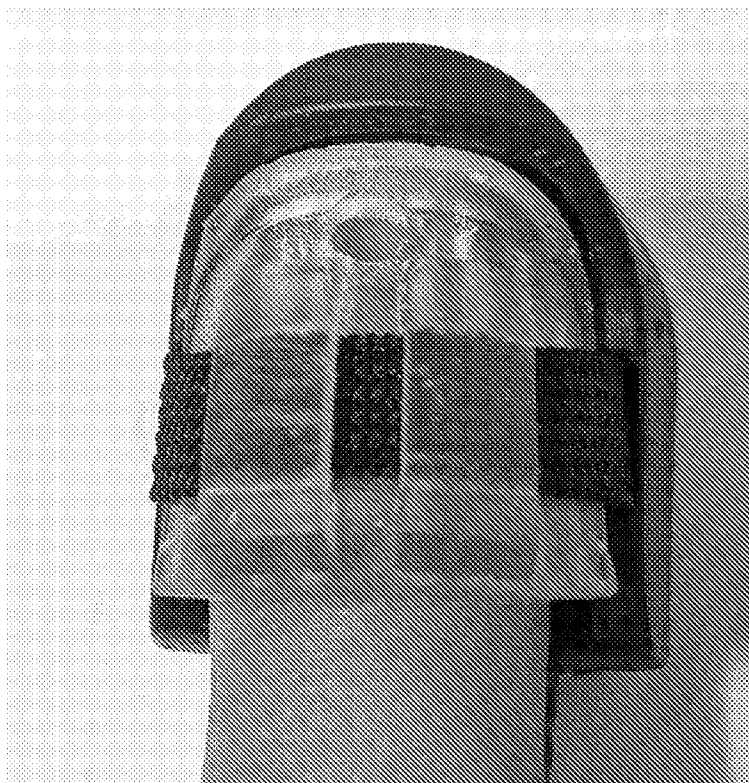


FIG. 9A

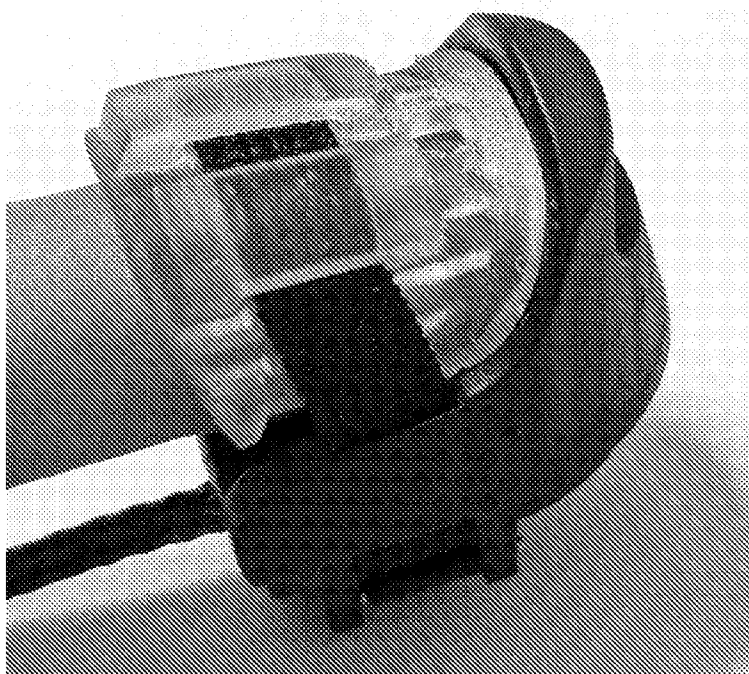


FIG. 9B

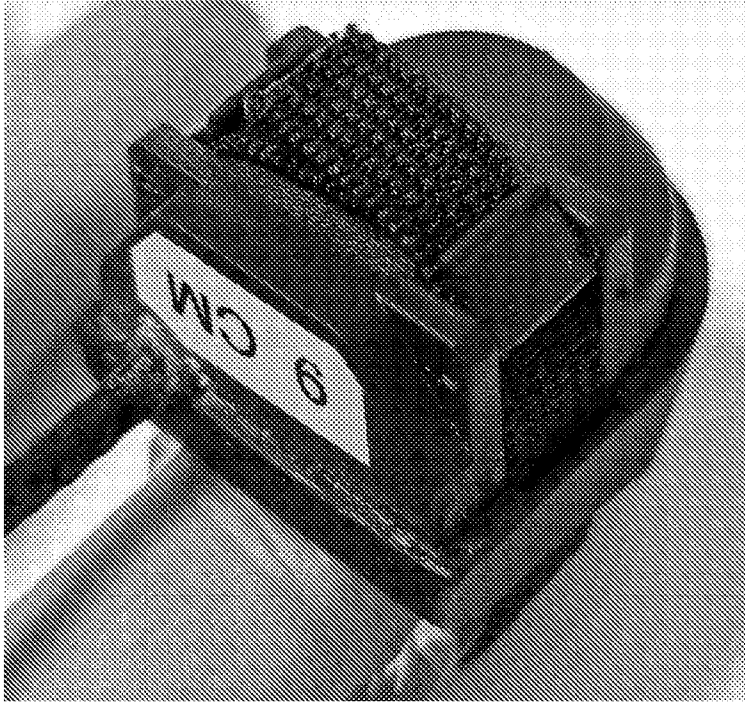


FIG. 9C

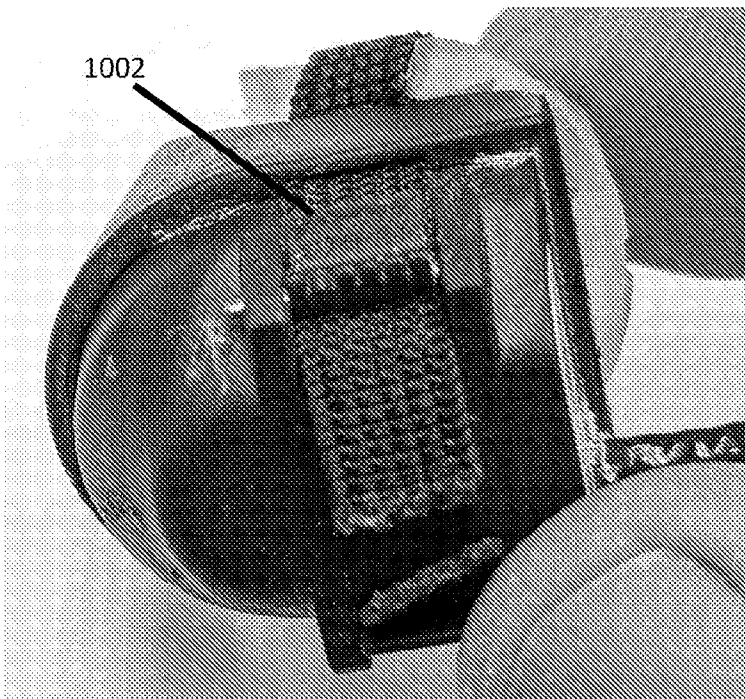


FIG. 10A

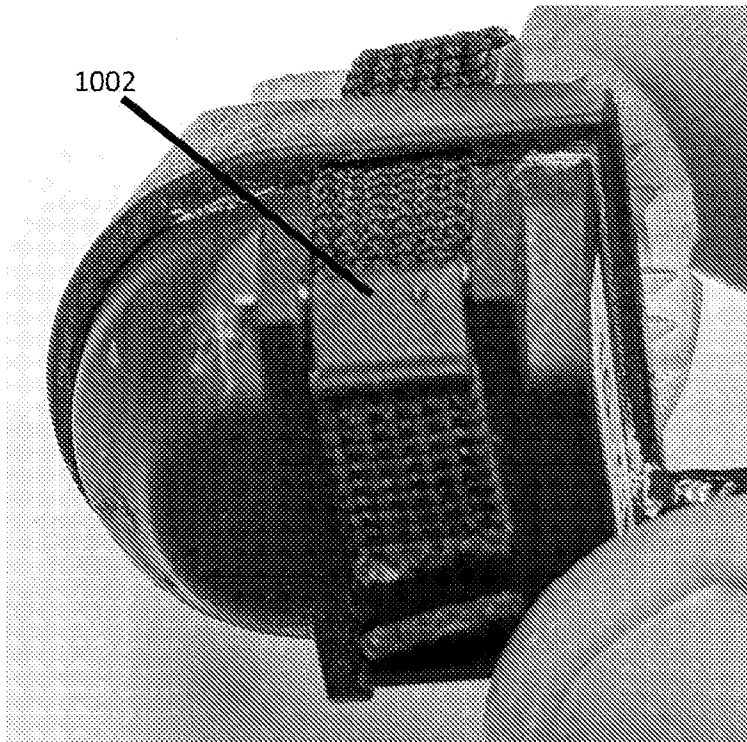


FIG. 10B

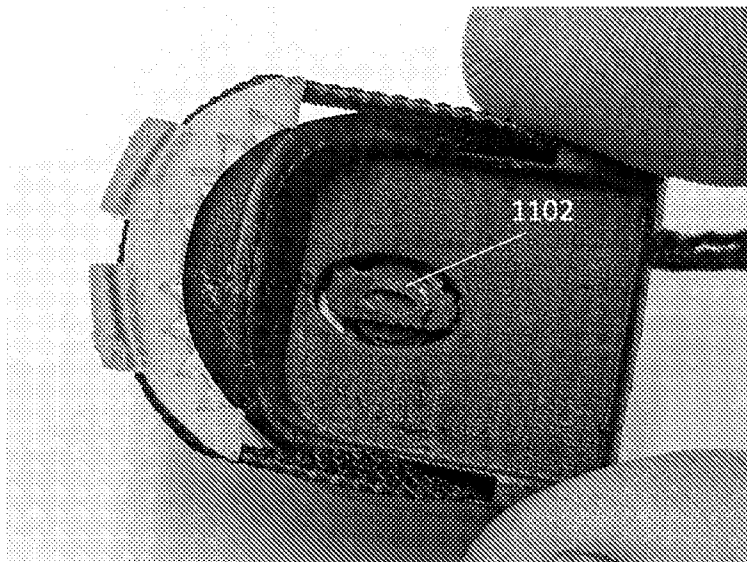


FIG. 11

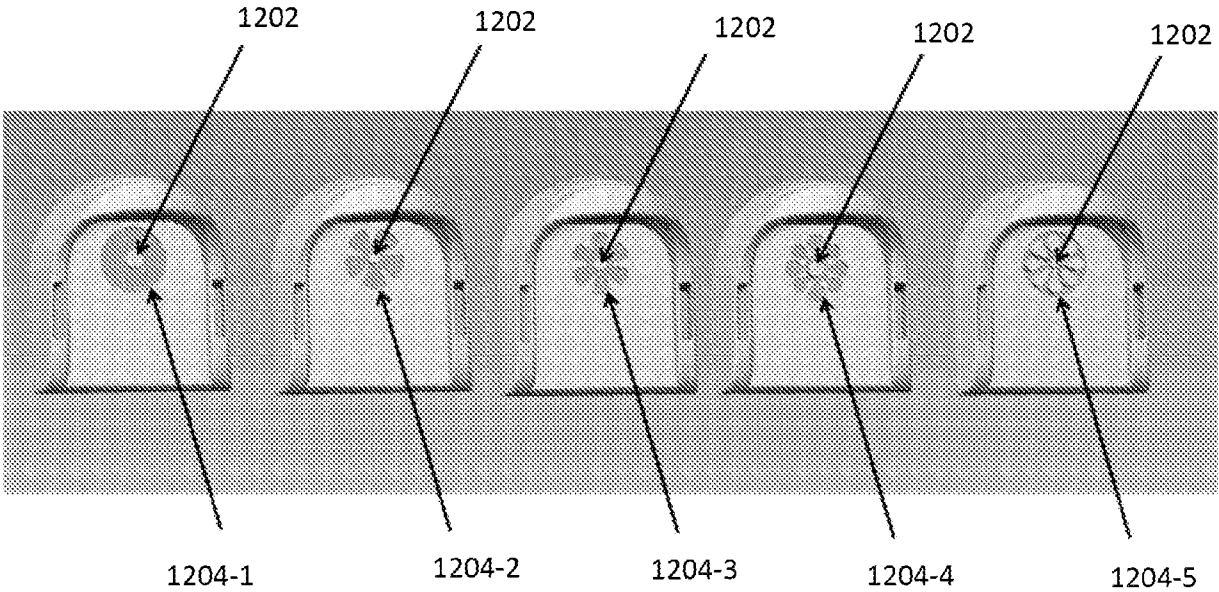


FIG. 12

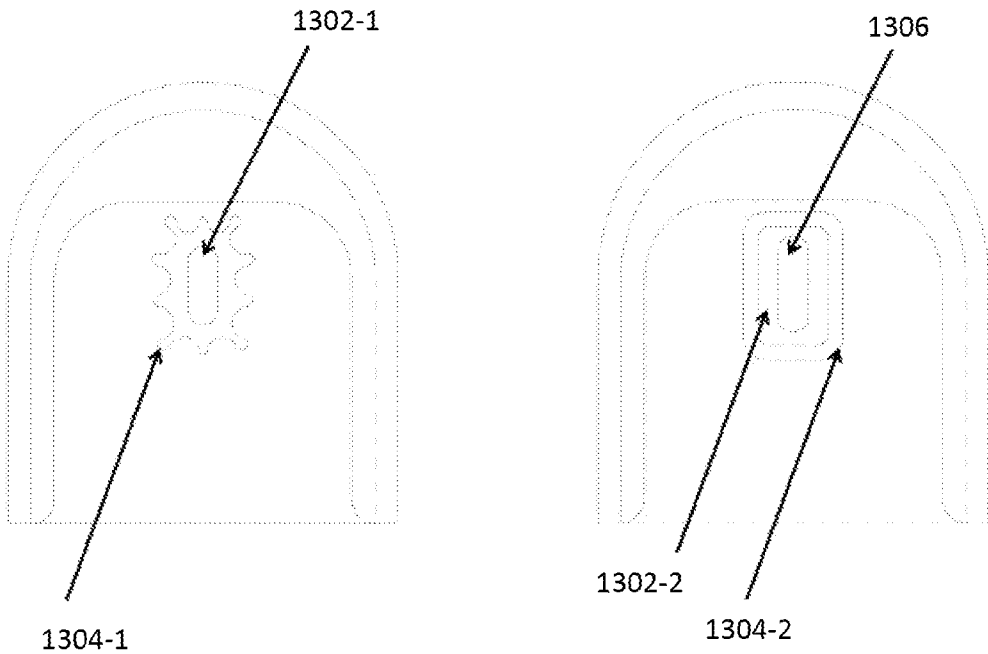


FIG. 13

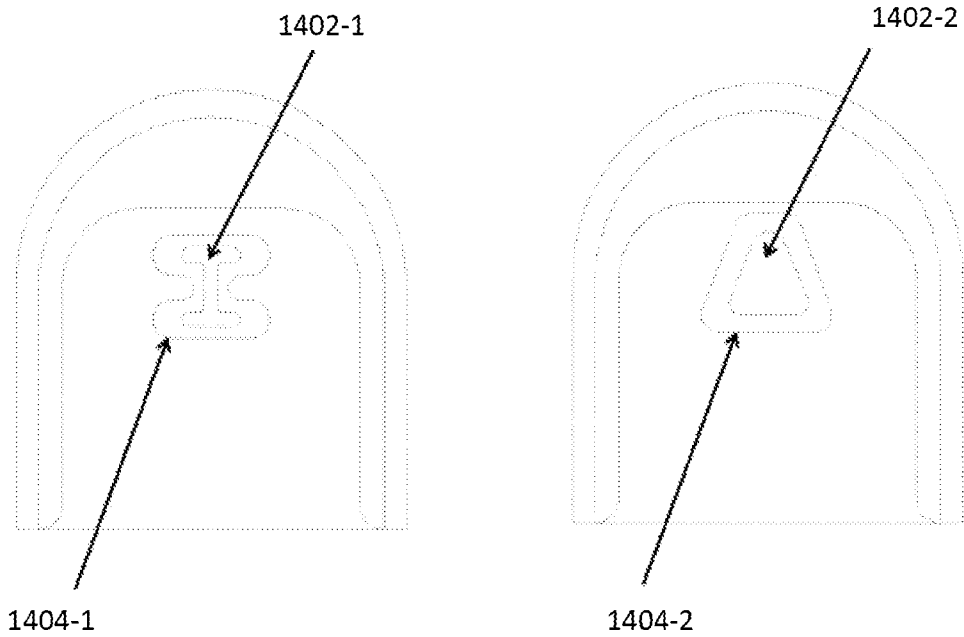


FIG. 14

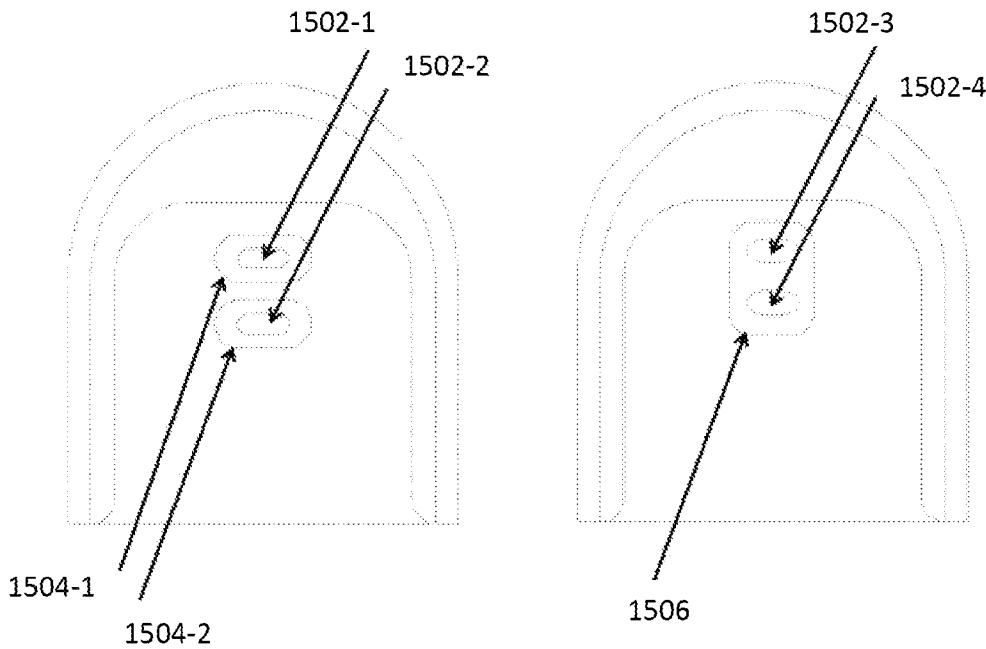


FIG. 15

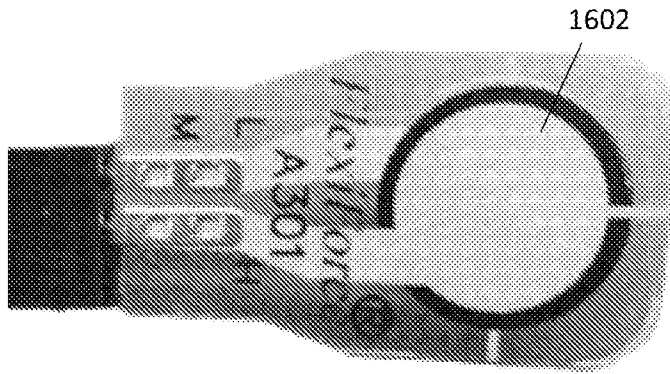


FIG. 16

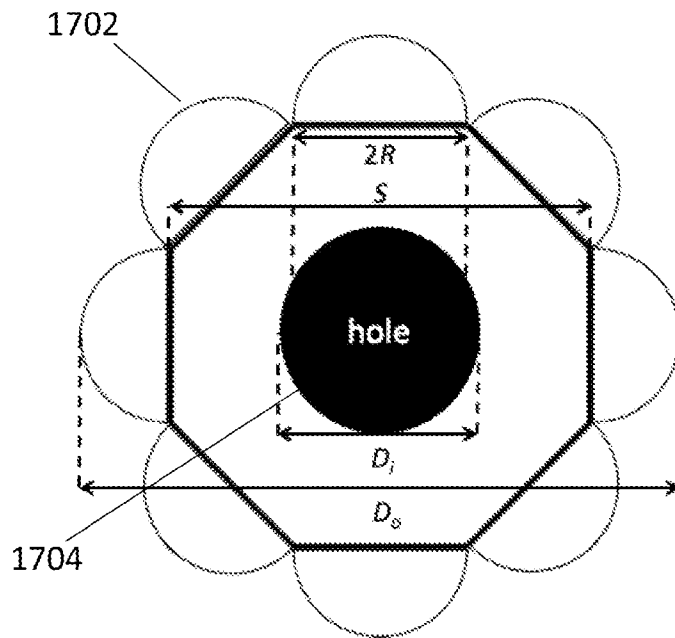


FIG. 17

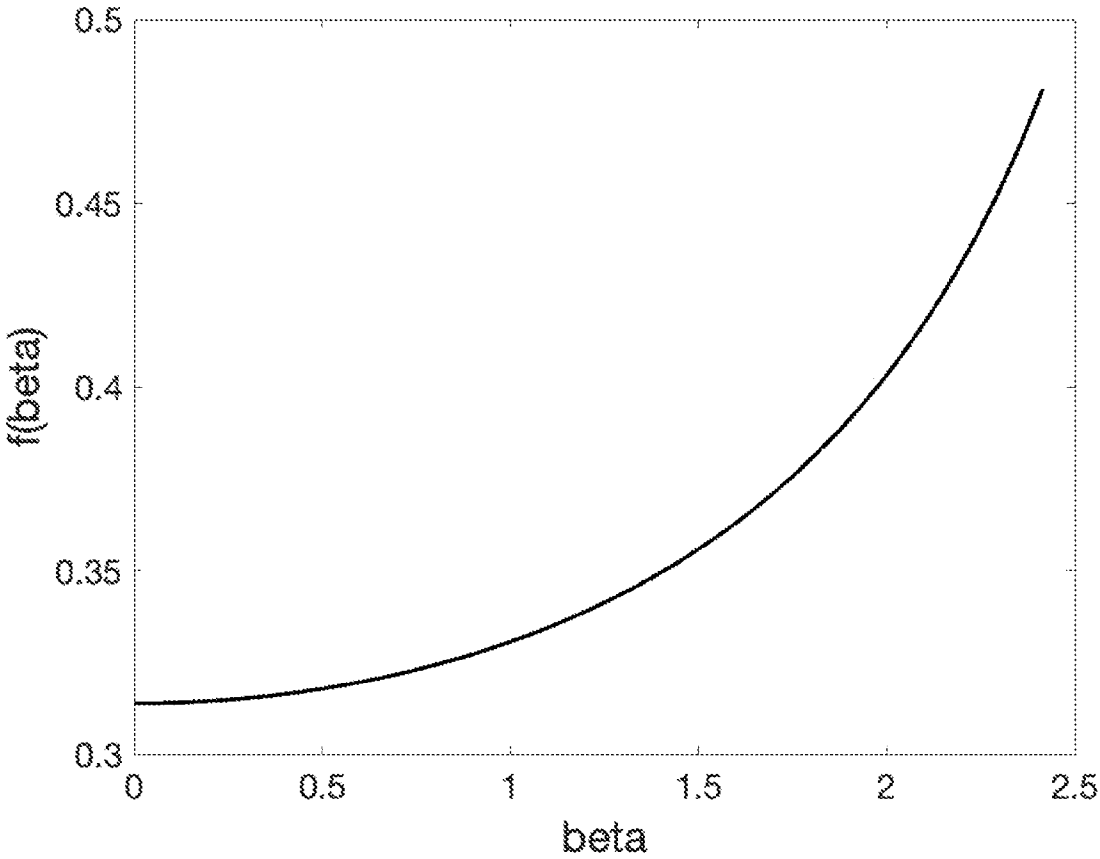


FIG. 18

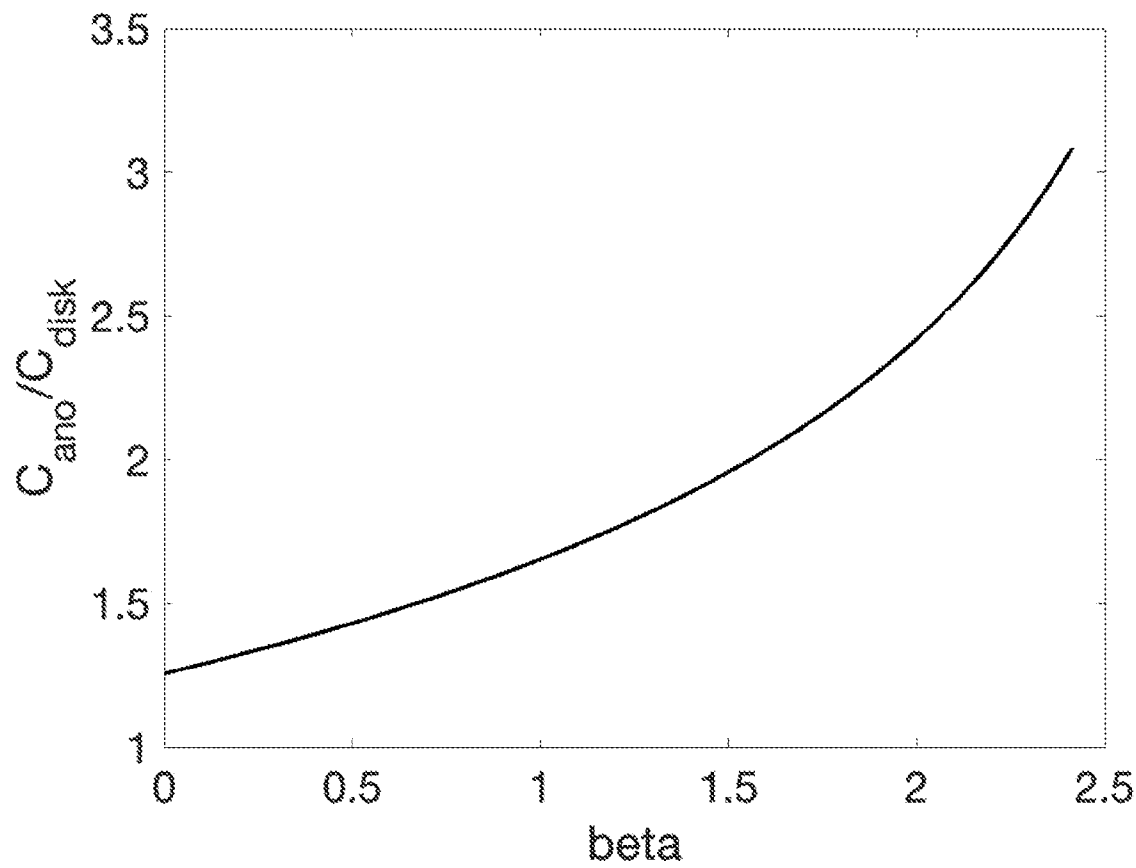


FIG. 19

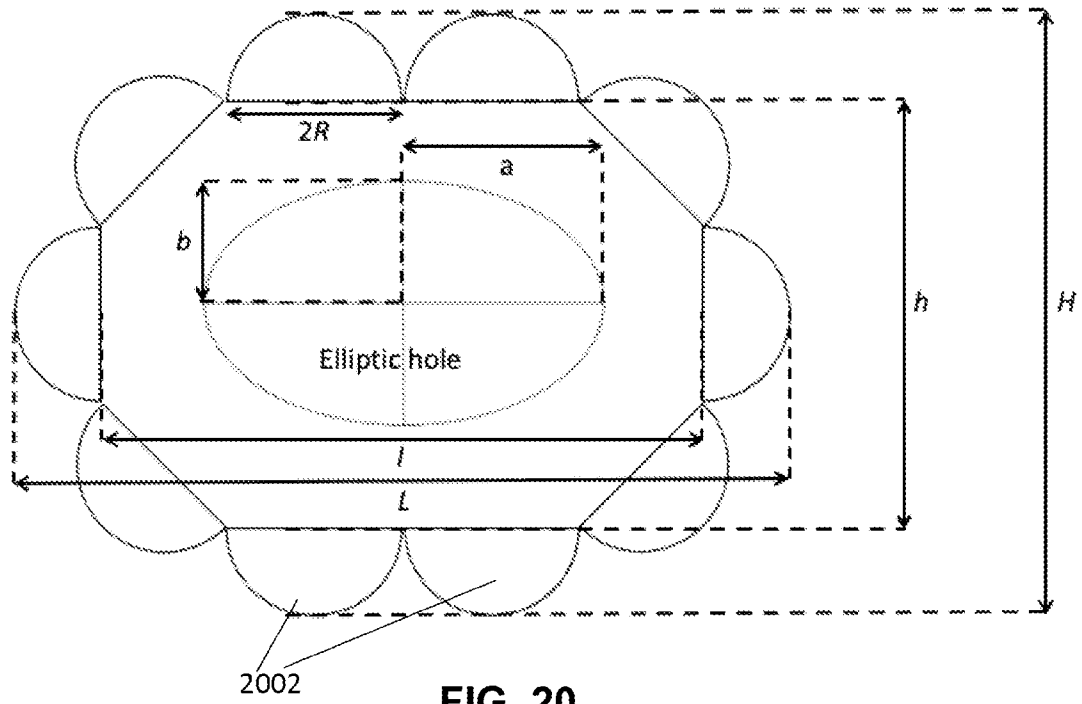


FIG. 20

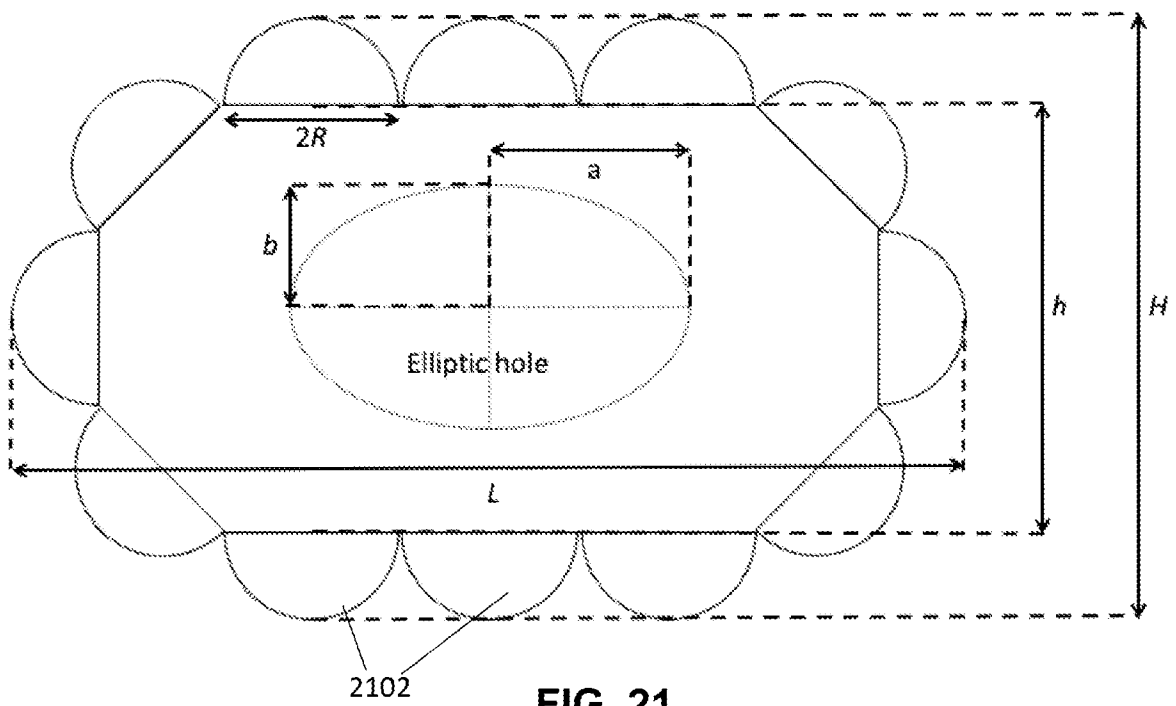


FIG. 21

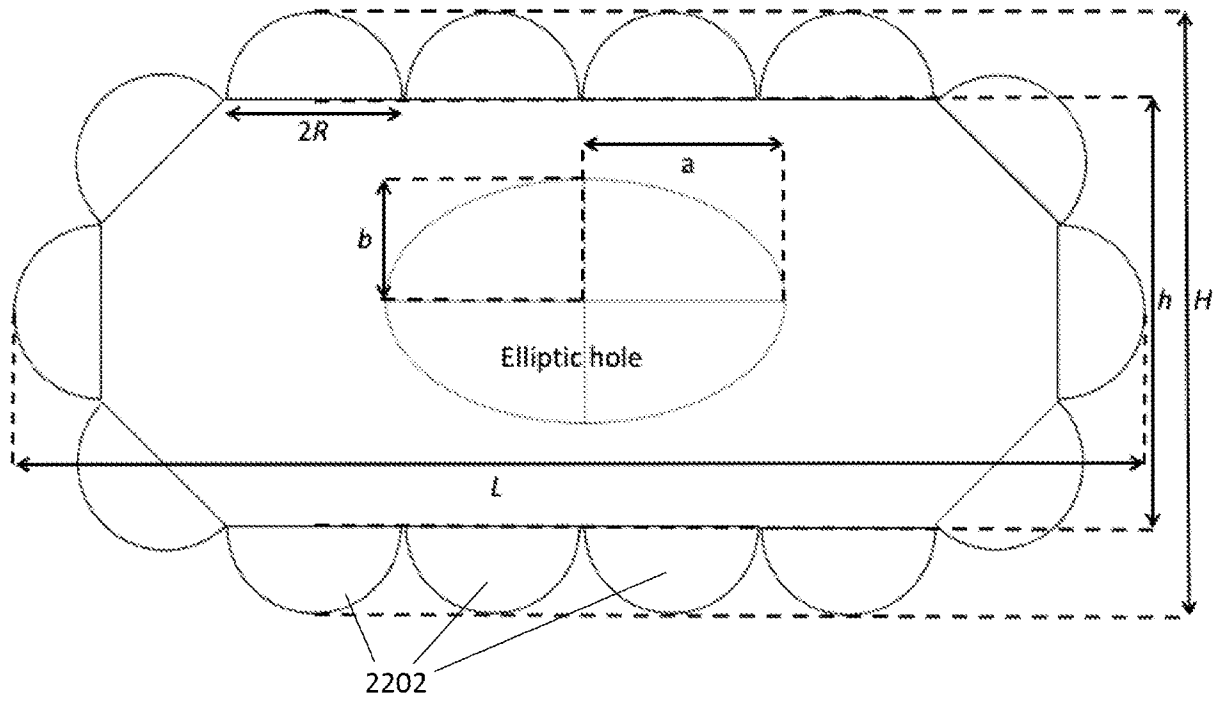


FIG. 22

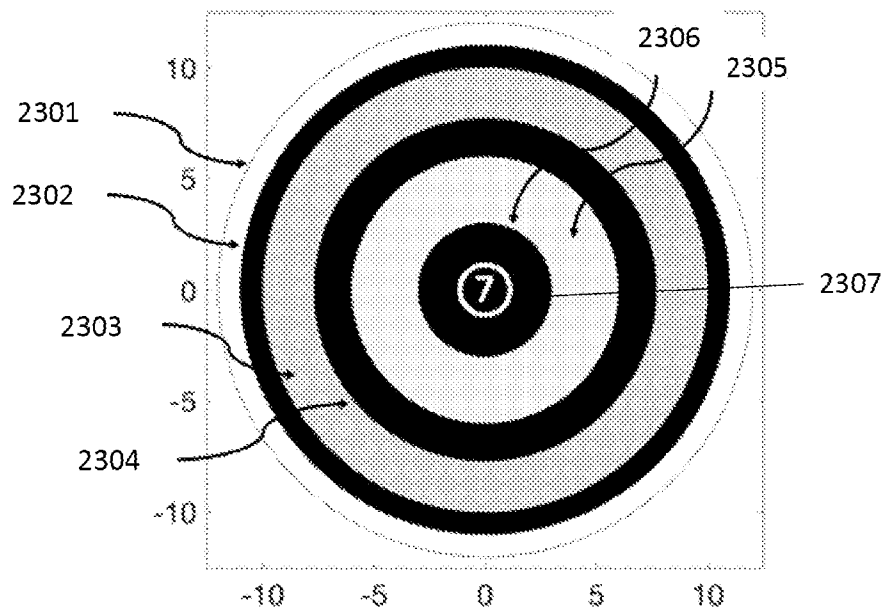


FIG. 23

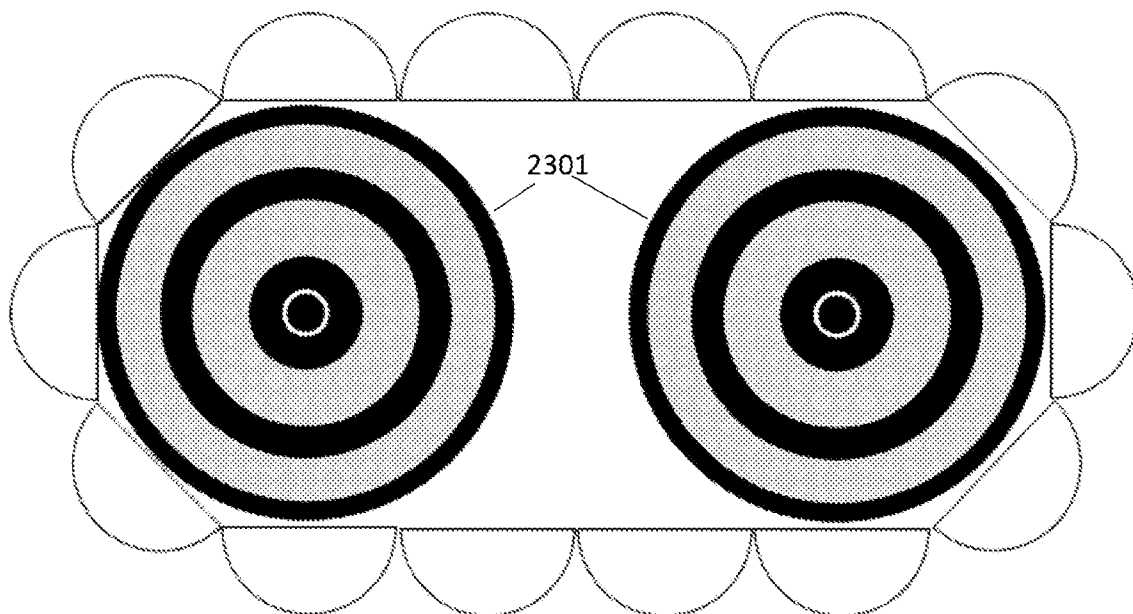


FIG. 24



FIG. 25

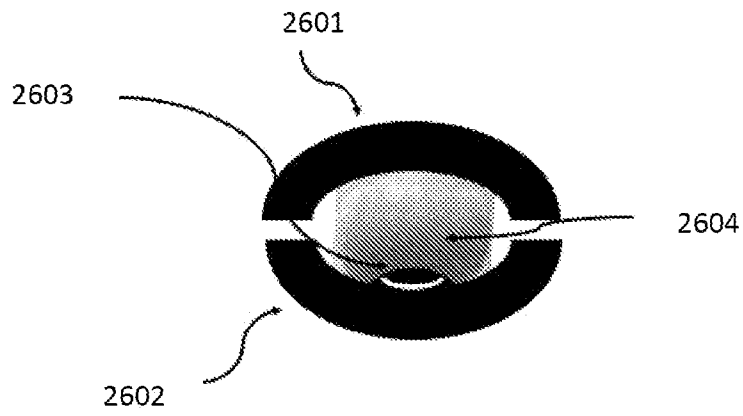


FIG. 26

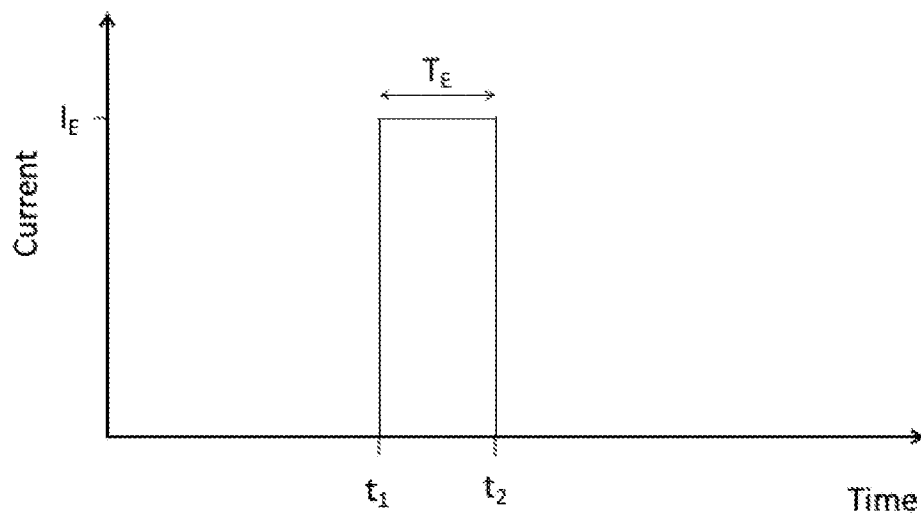


FIG. 27

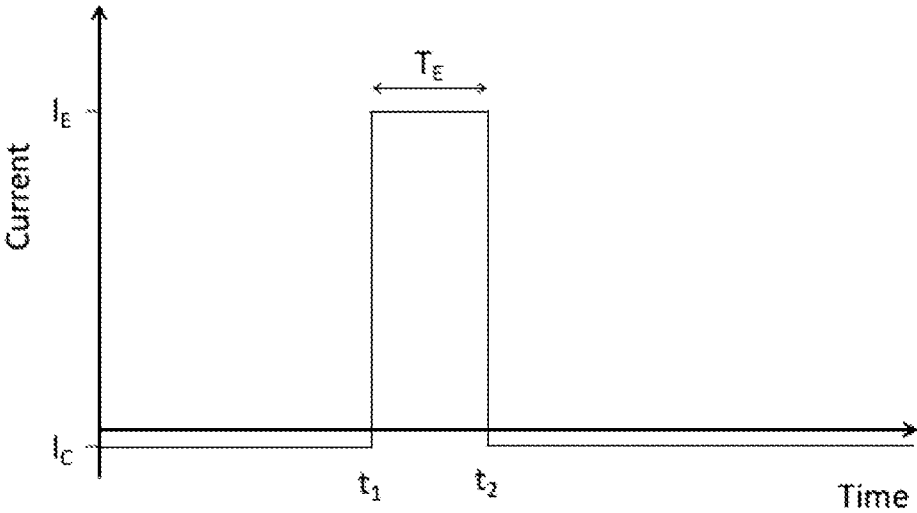


FIG. 28

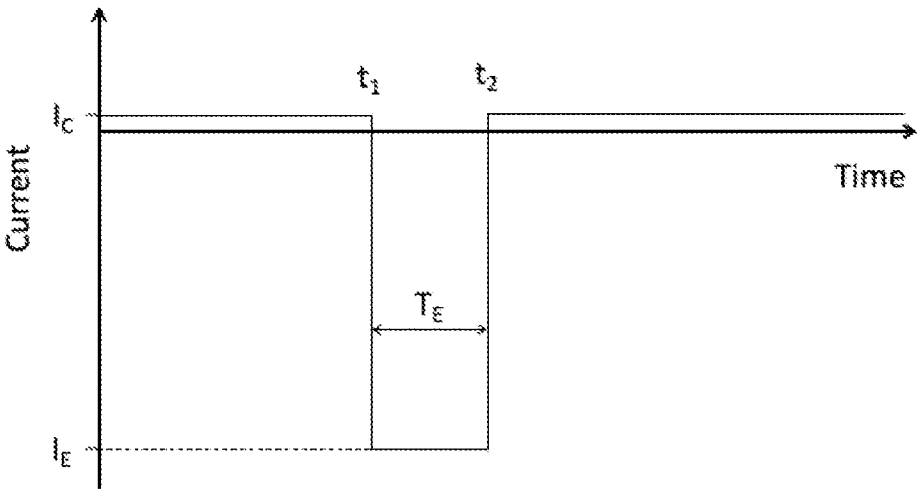


FIG. 29

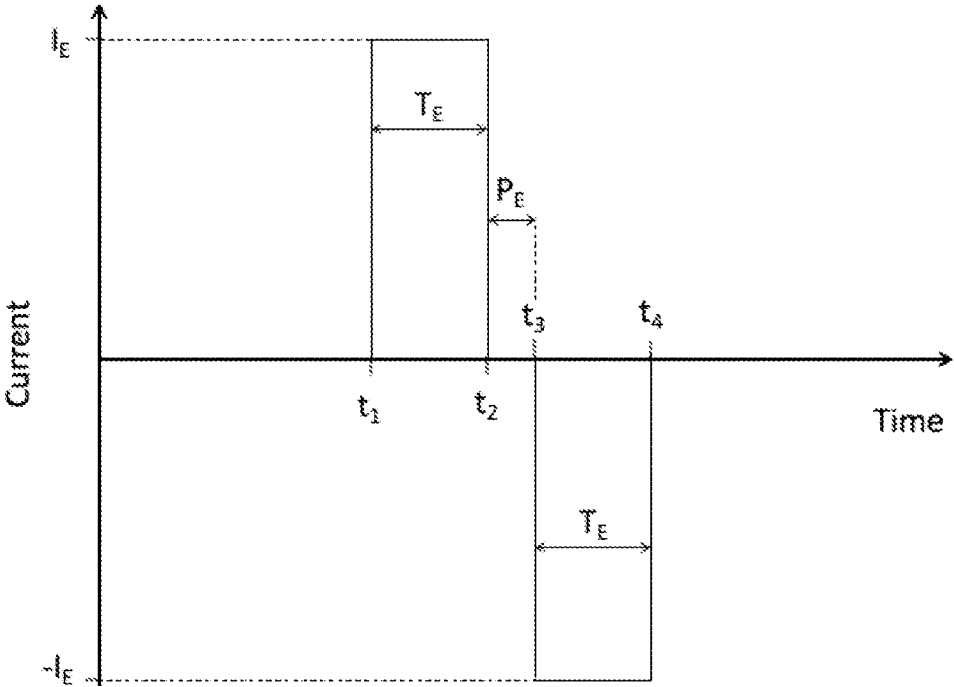


FIG. 30

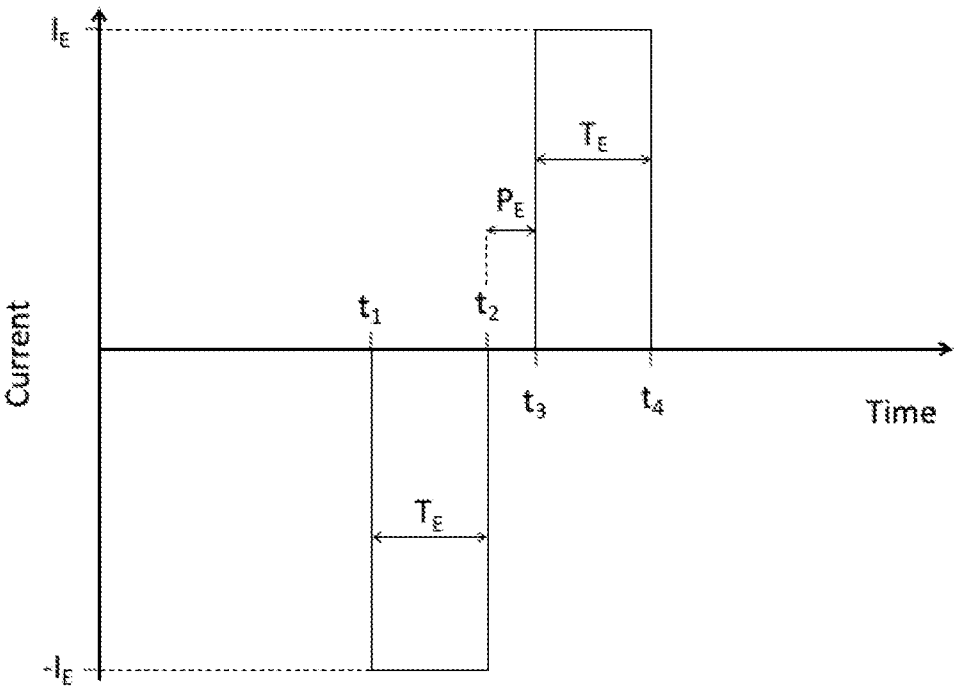


FIG. 31

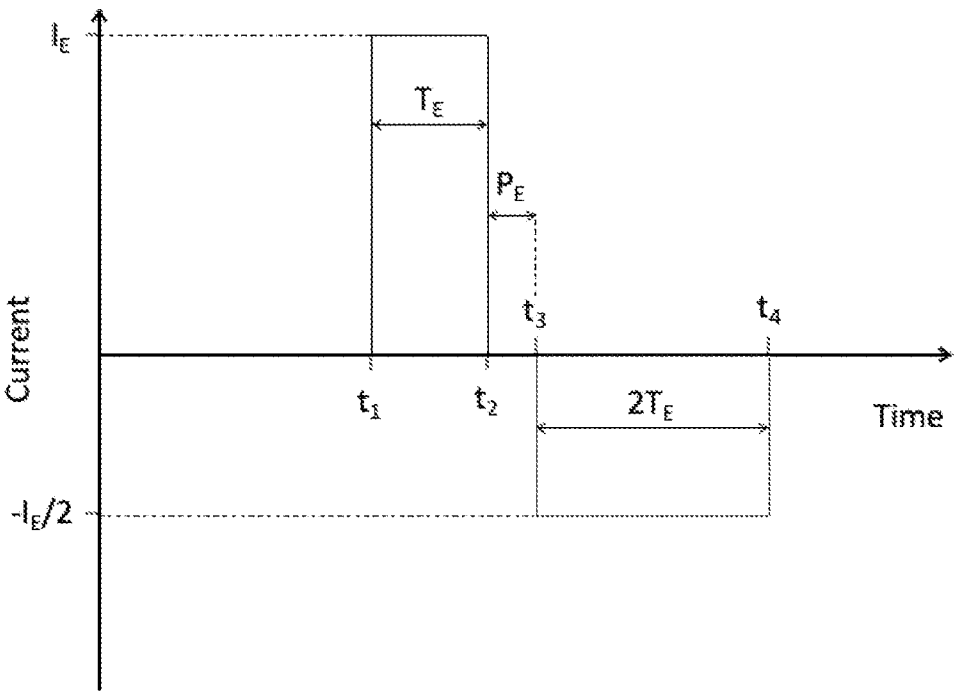


FIG. 32

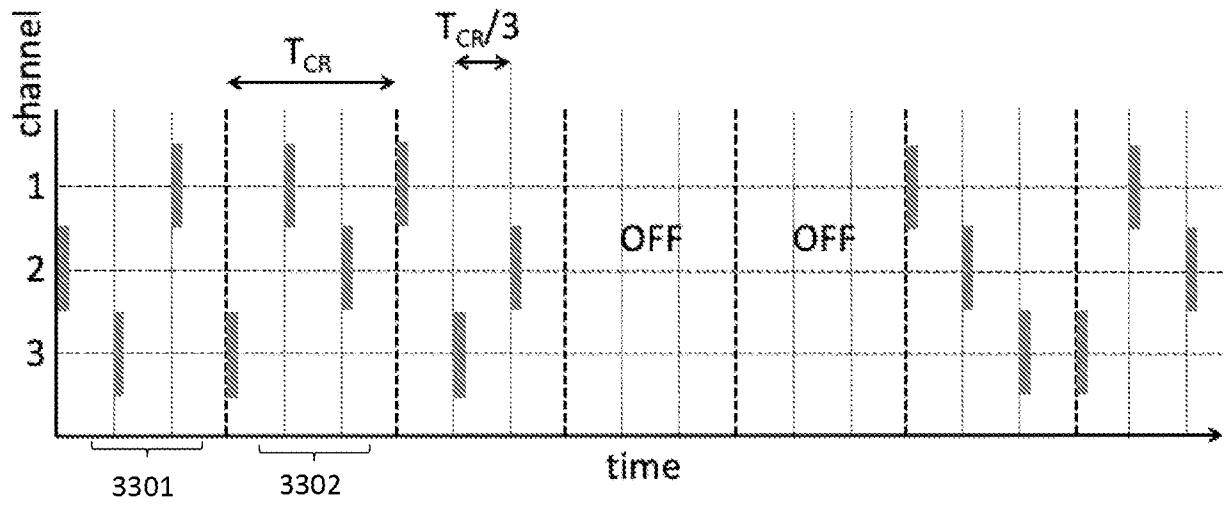


FIG. 33

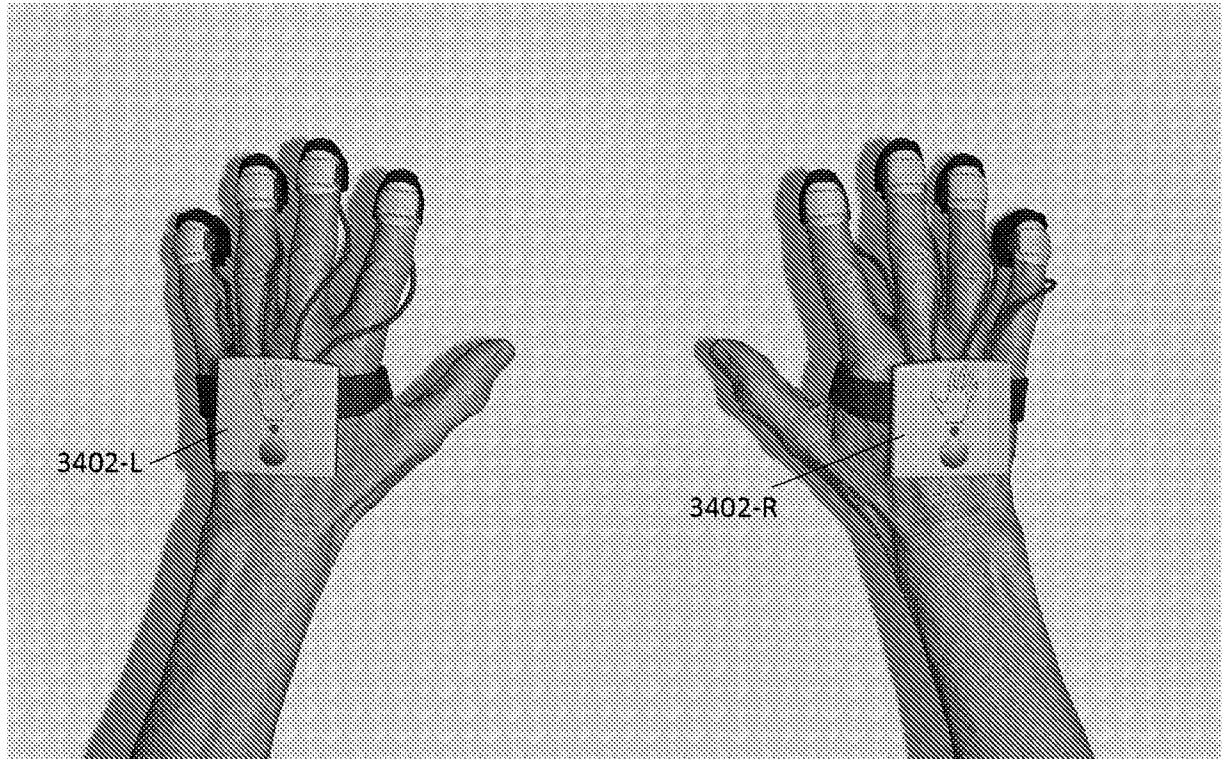


FIG. 34

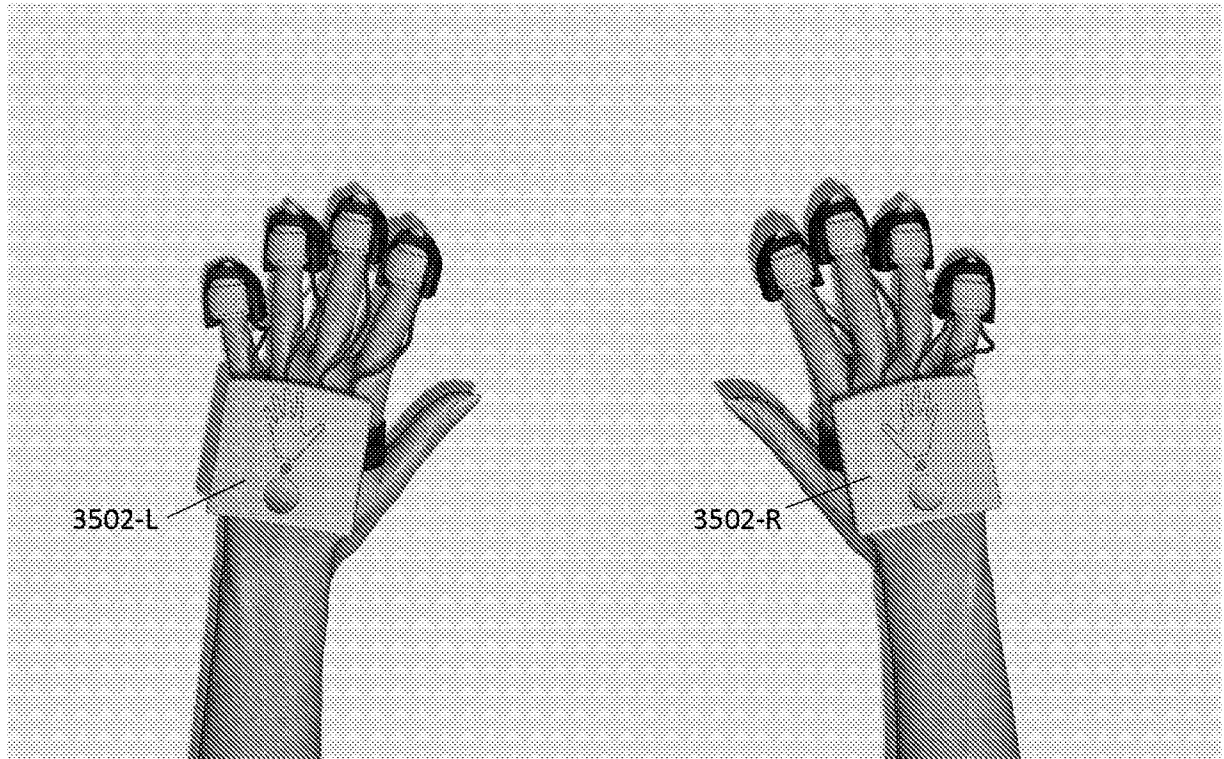


FIG. 35

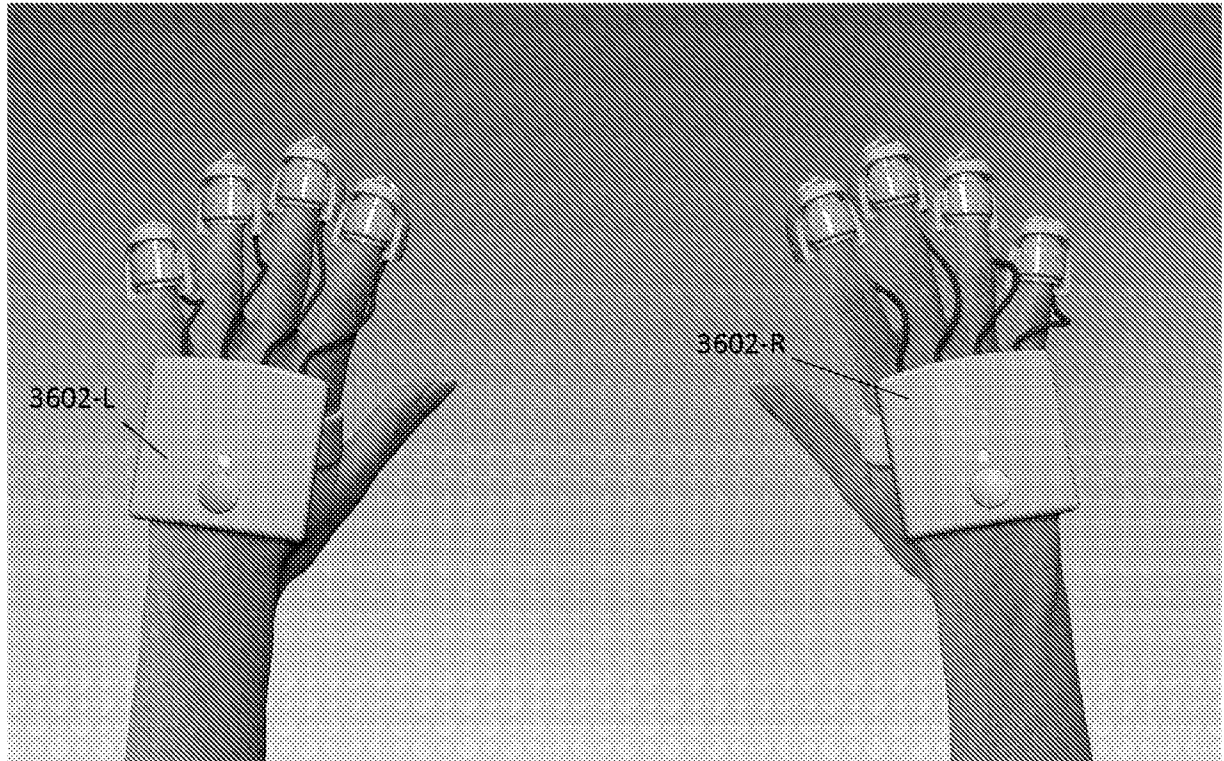


FIG. 36

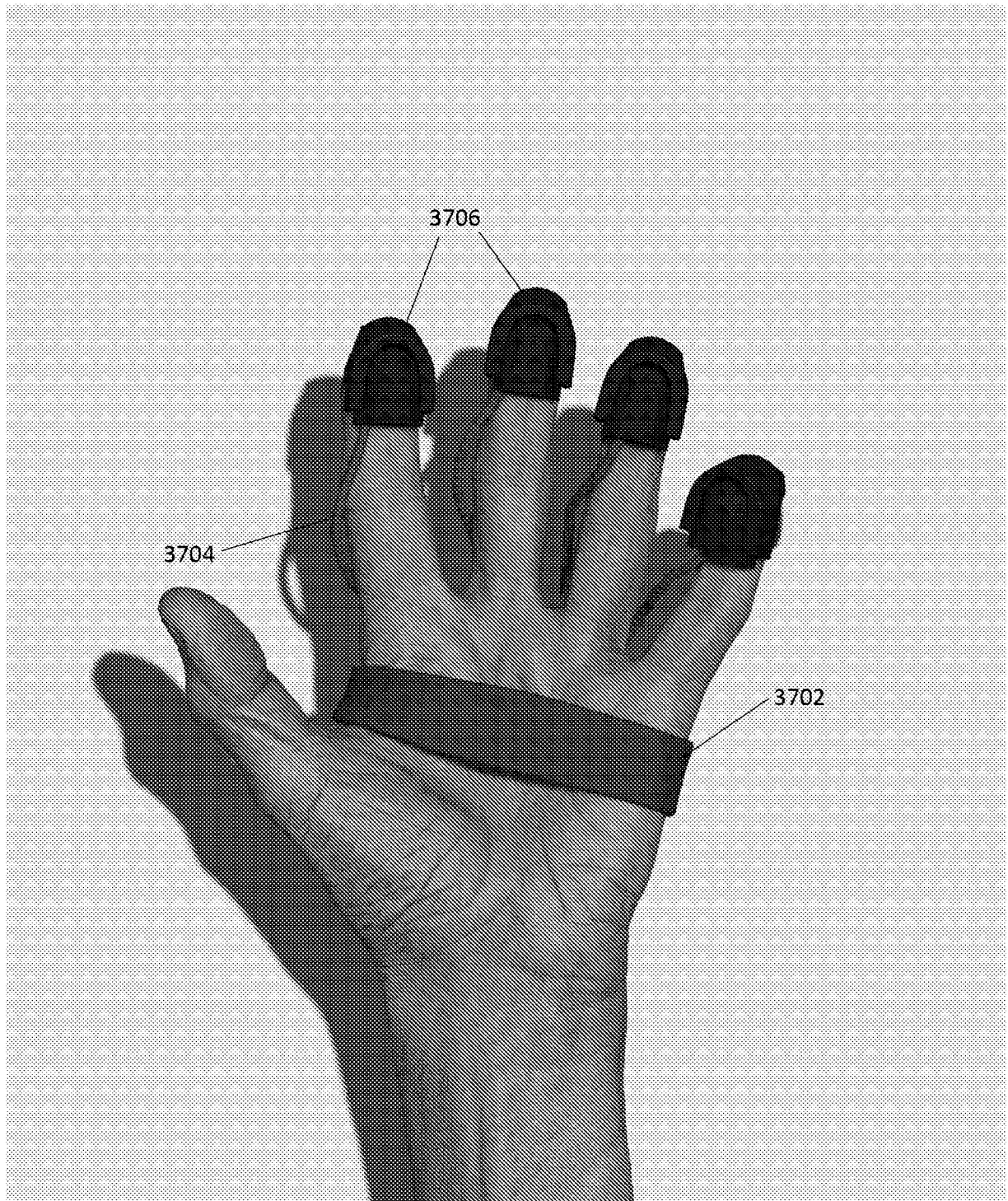


FIG. 37

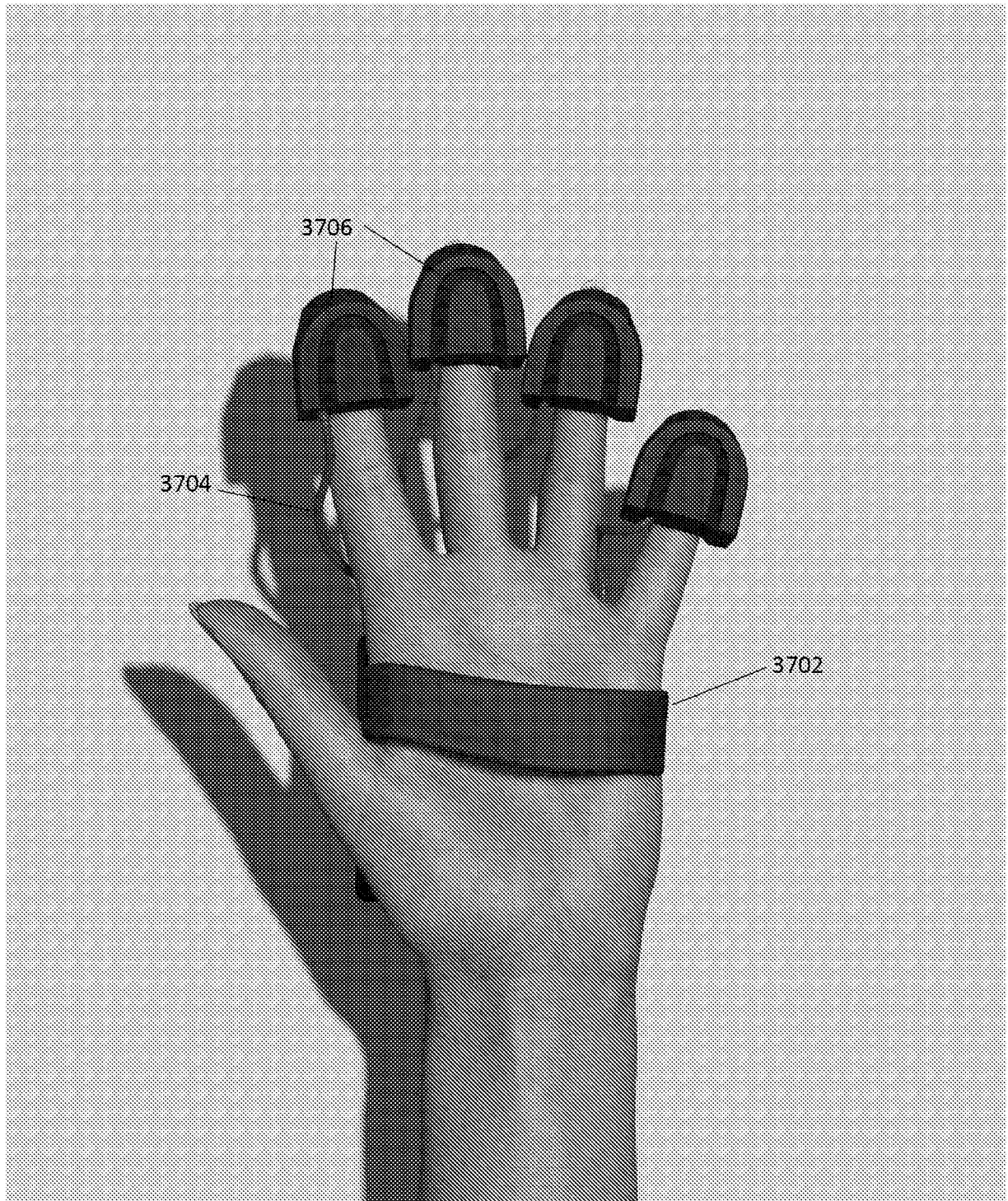


FIG. 38

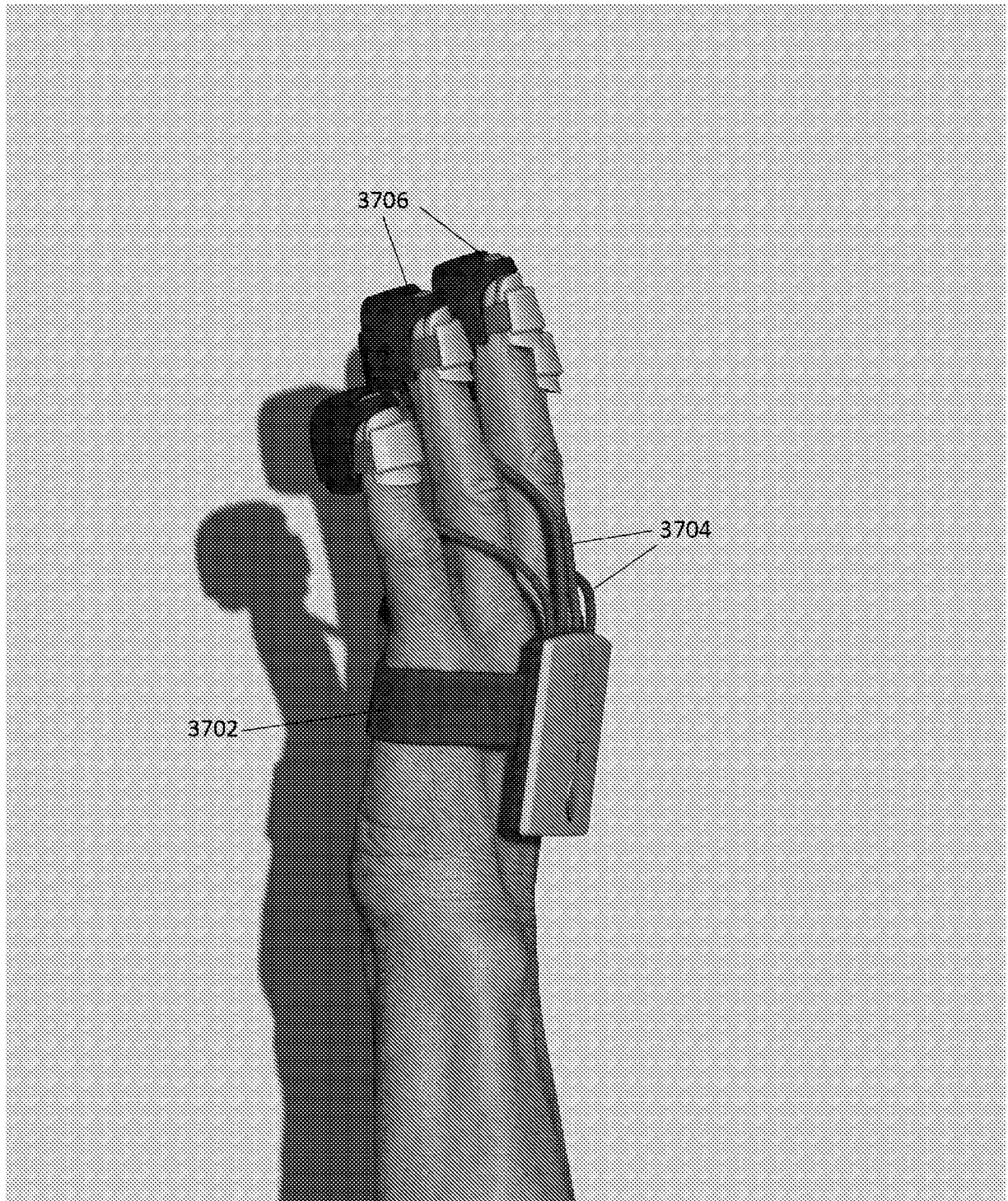


FIG. 39

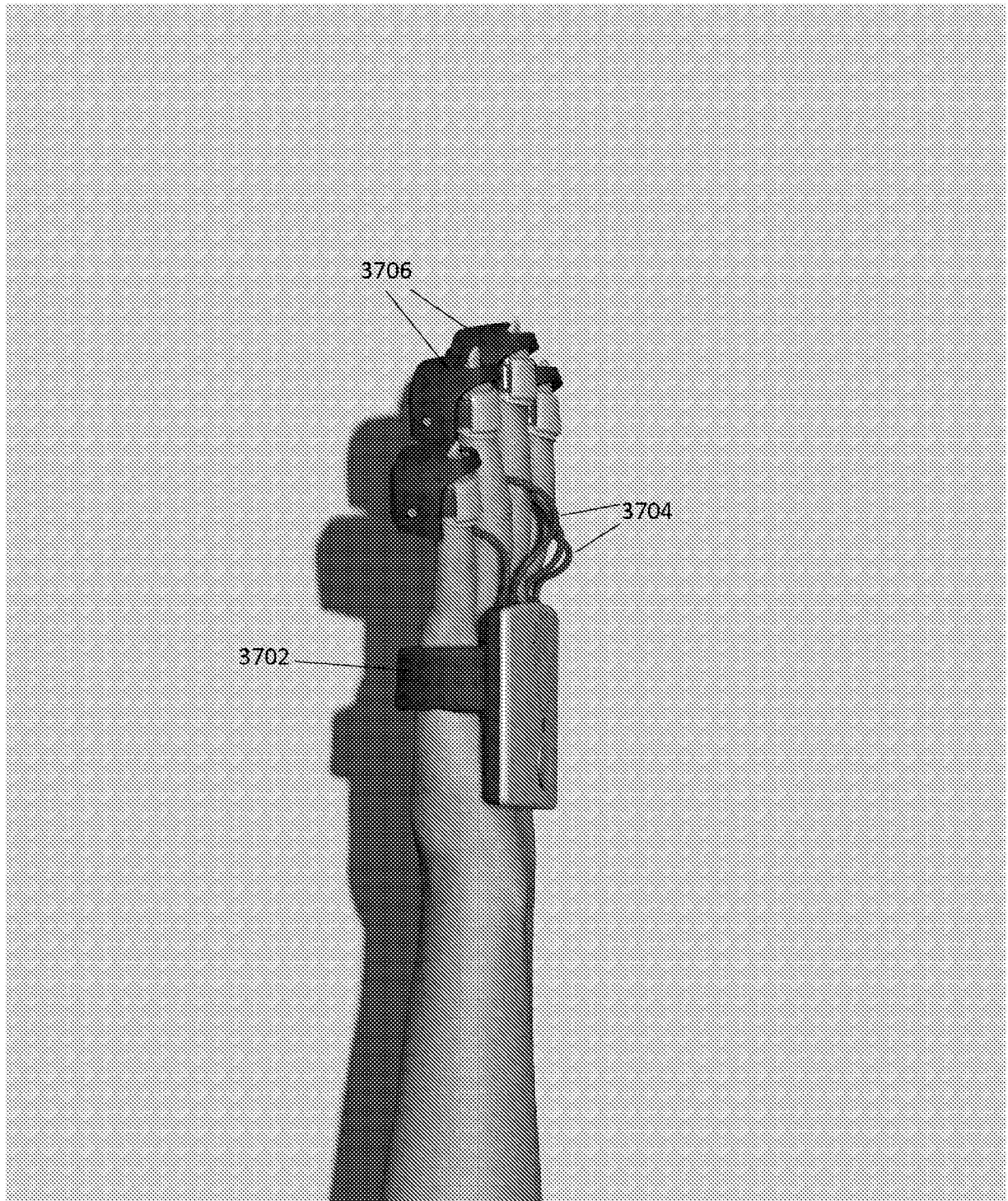


FIG. 40

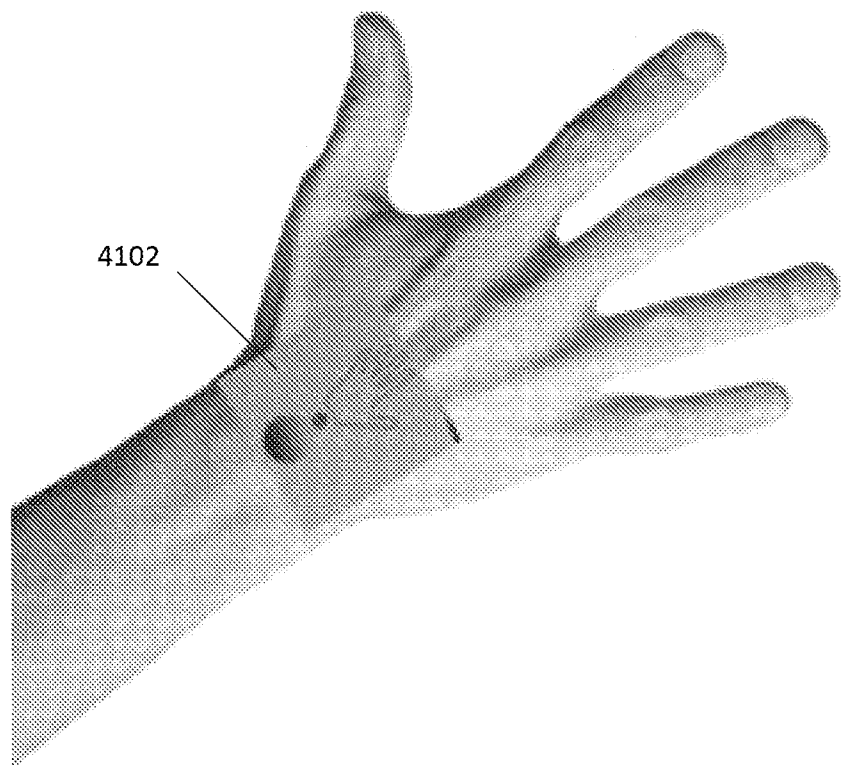


FIG. 41

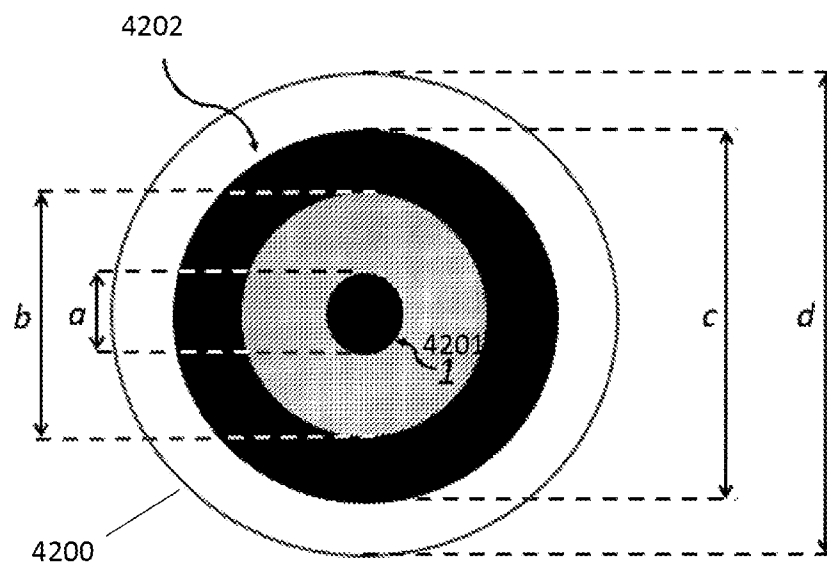


FIG. 42

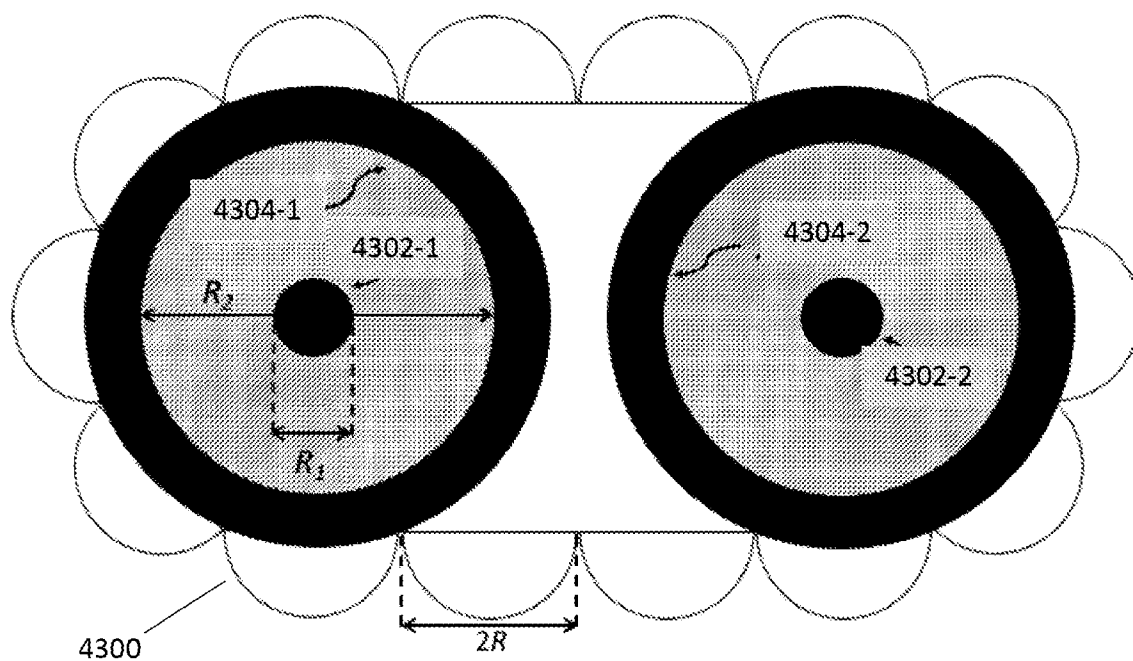


FIG. 43

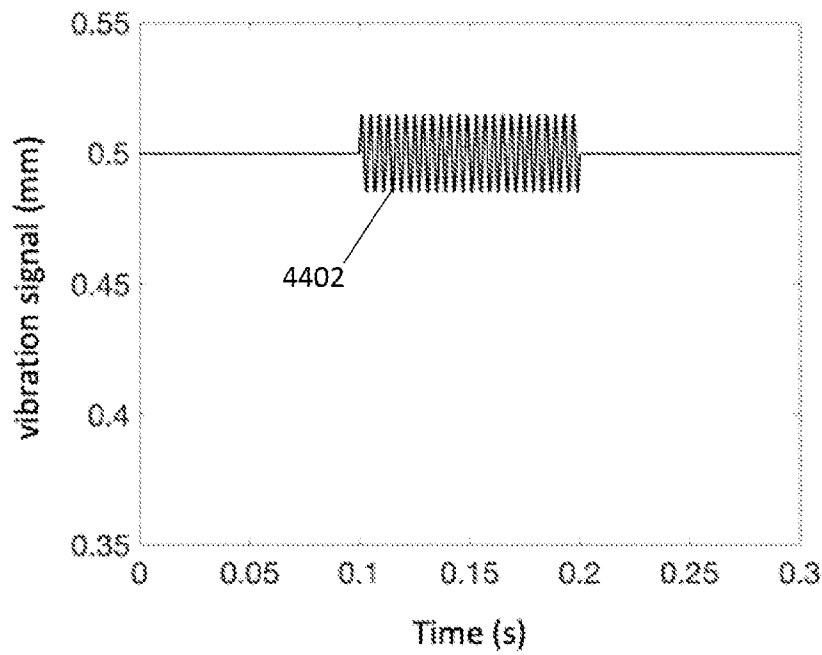


FIG. 44

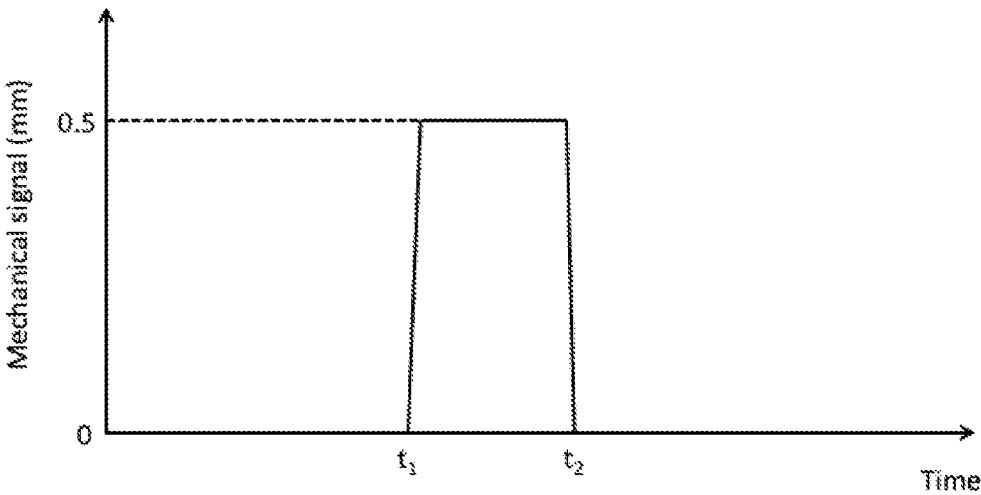


FIG. 45

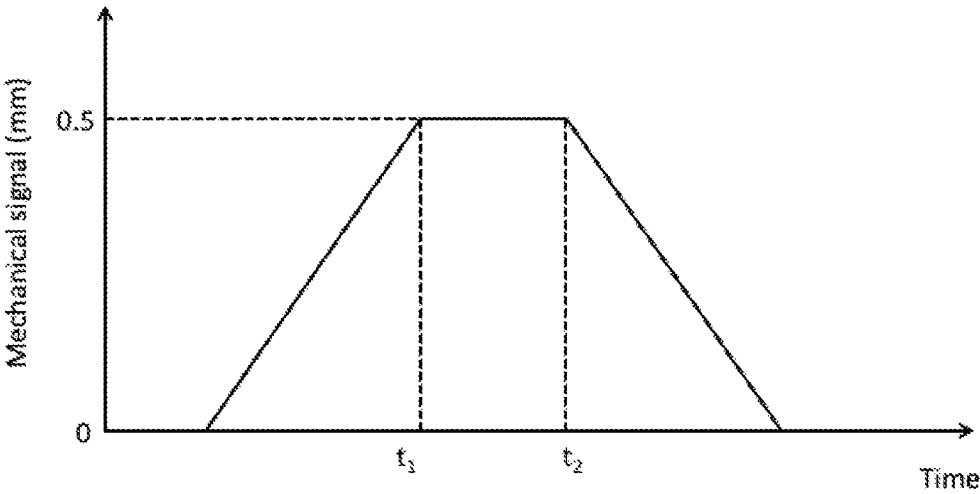


FIG. 46

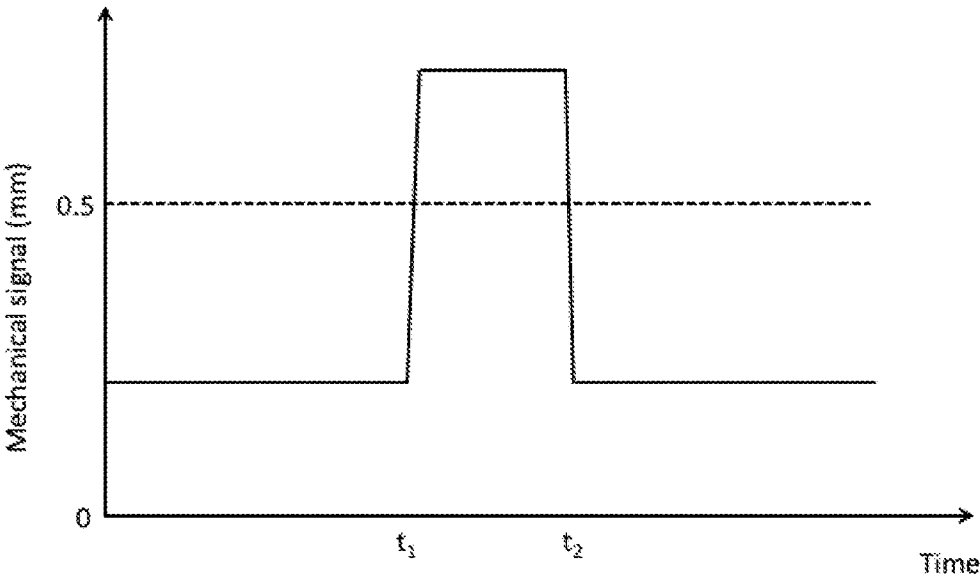


FIG. 47

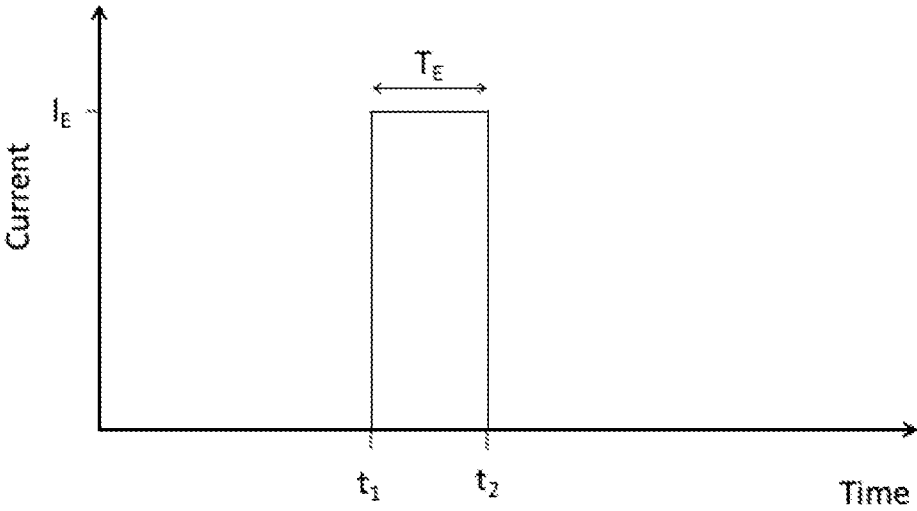


FIG. 48

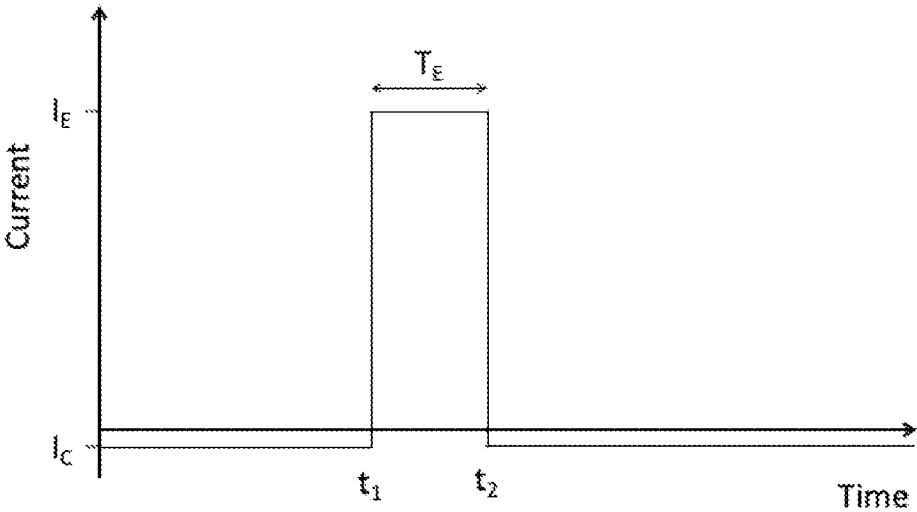


FIG. 49

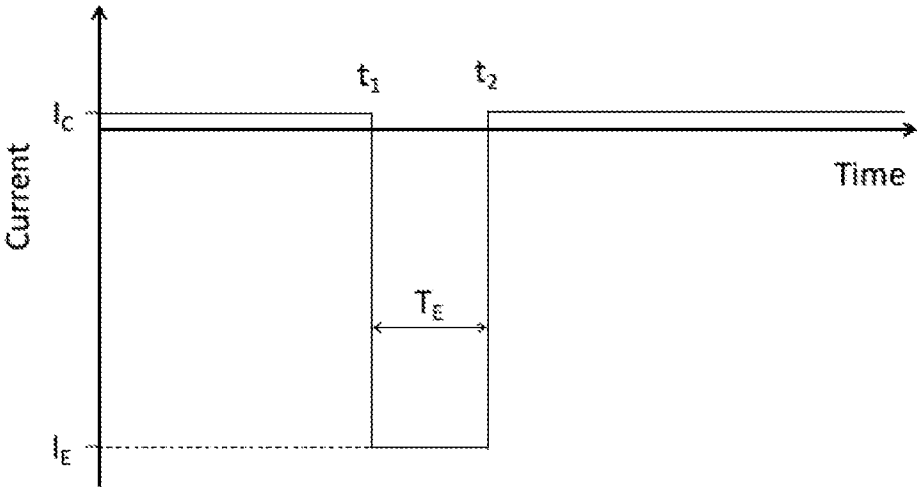


FIG. 50

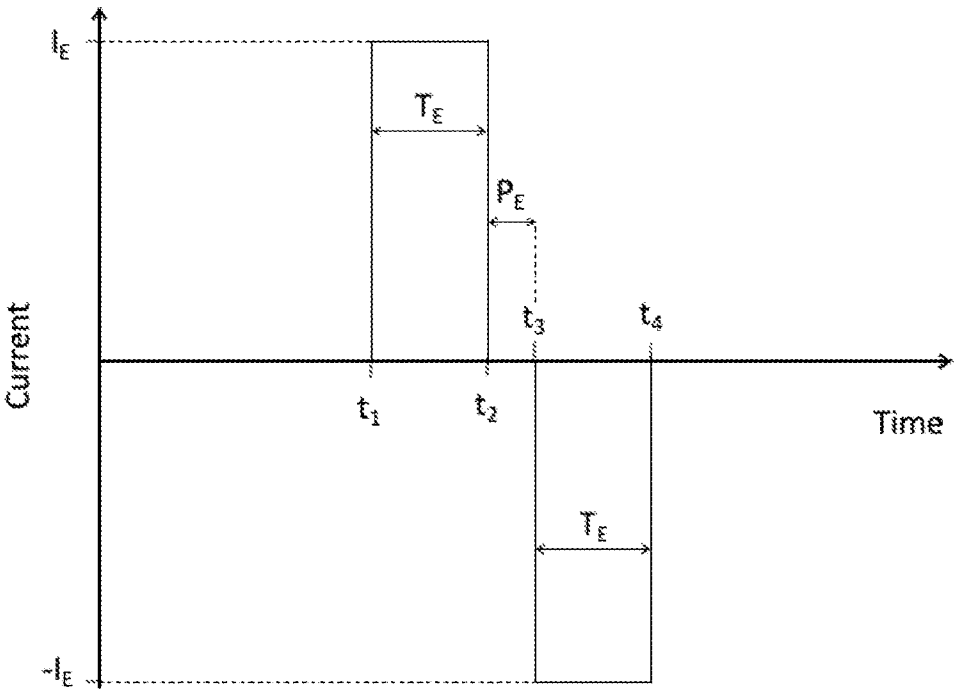


FIG. 51

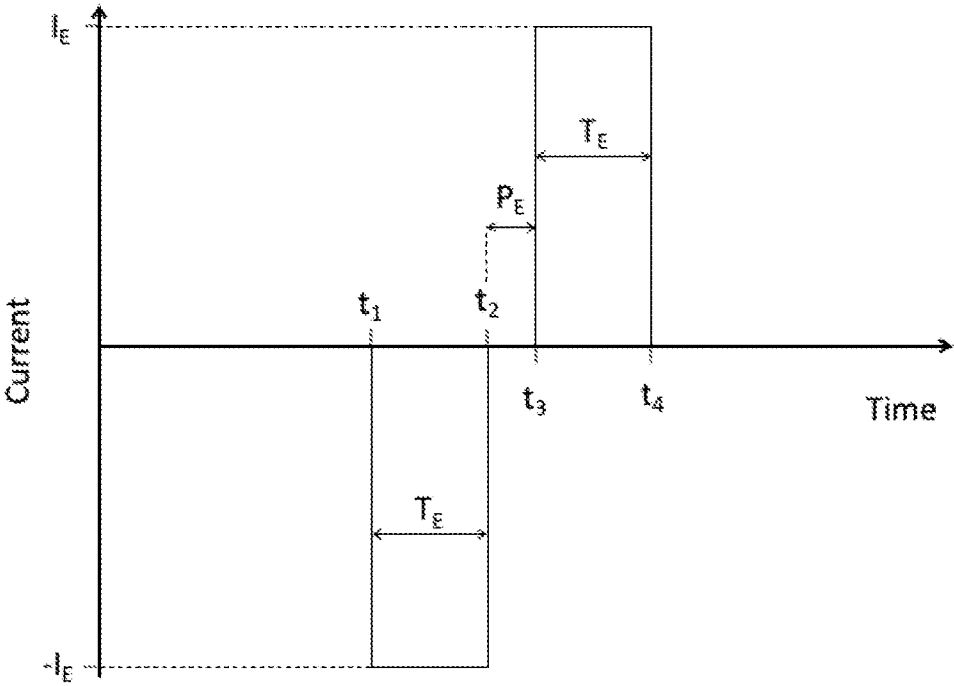


FIG. 52

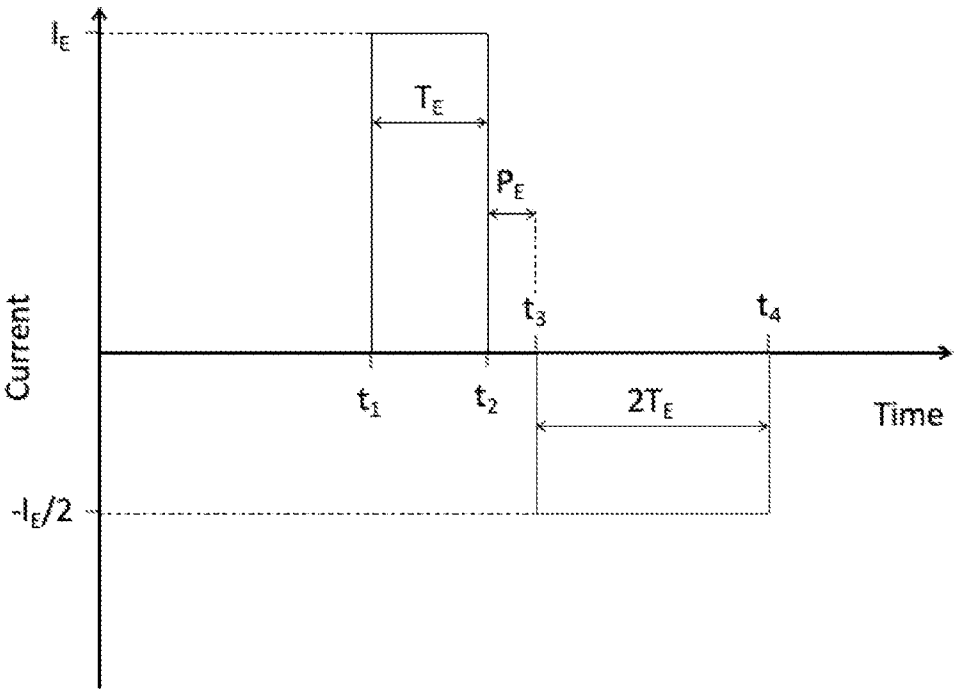


FIG. 53

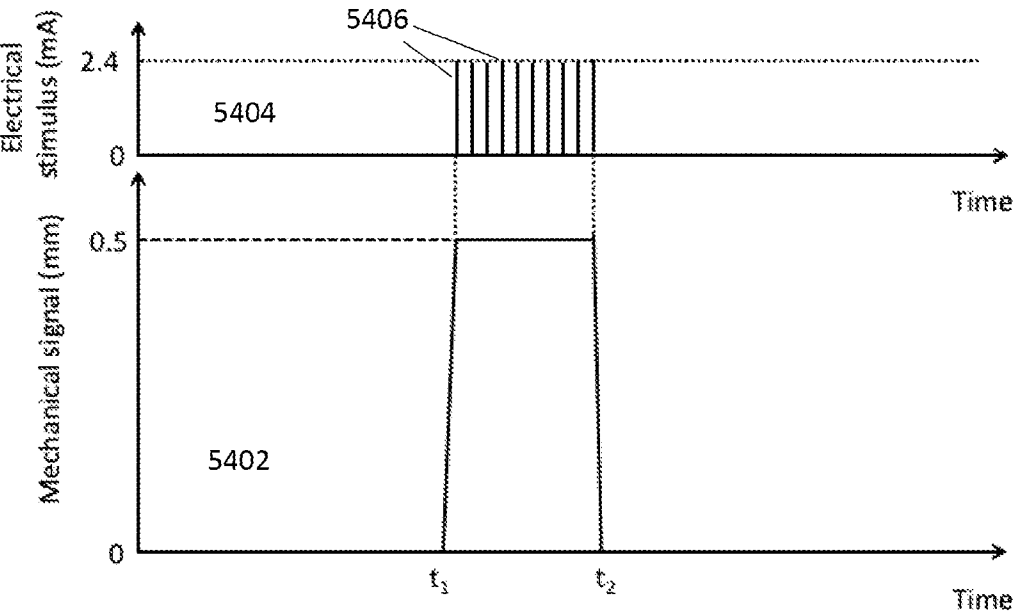


FIG. 54

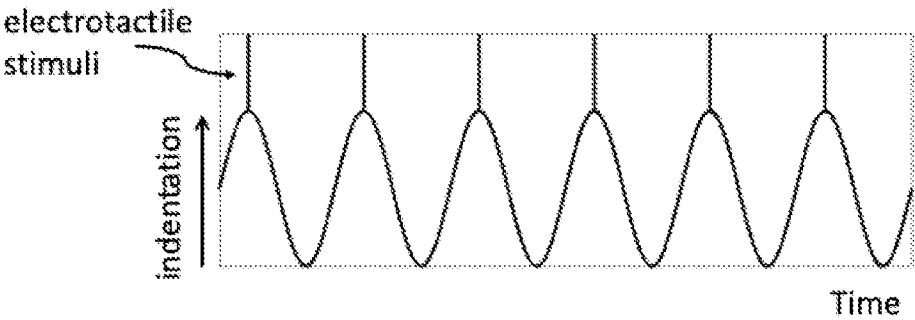


FIG. 55

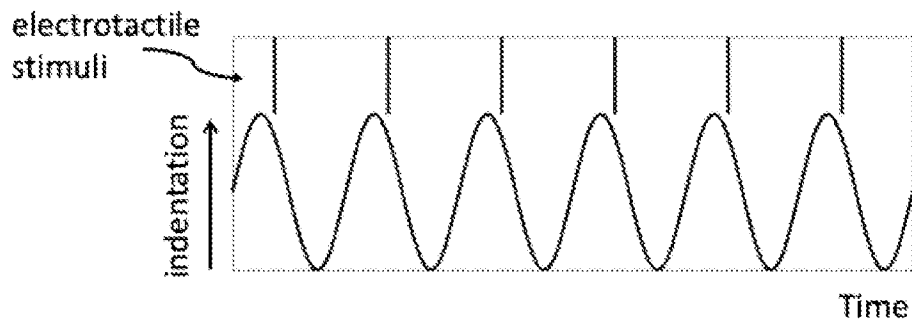


FIG. 56

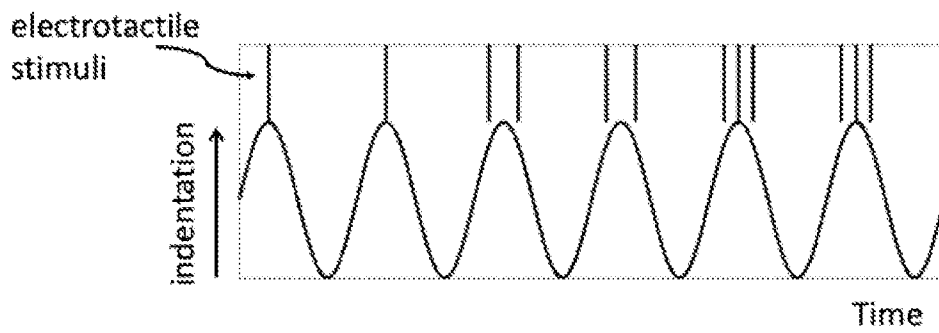


FIG. 57

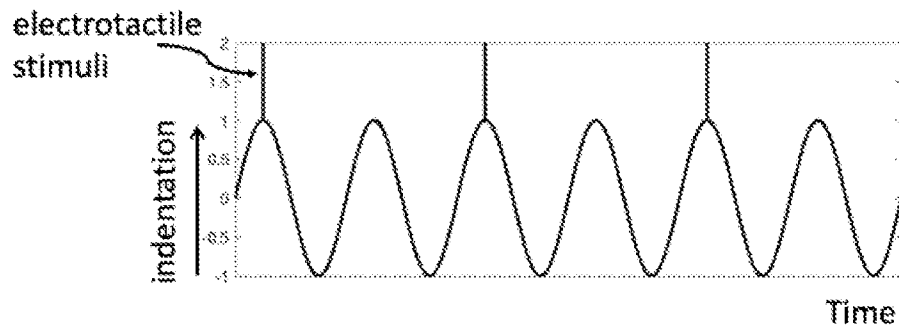


FIG. 58

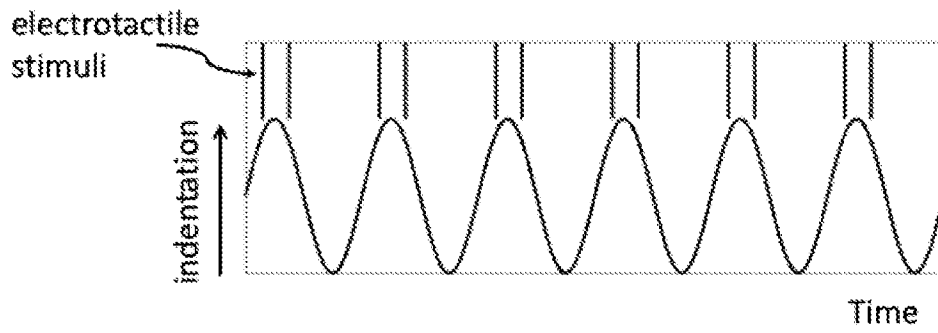


FIG. 59

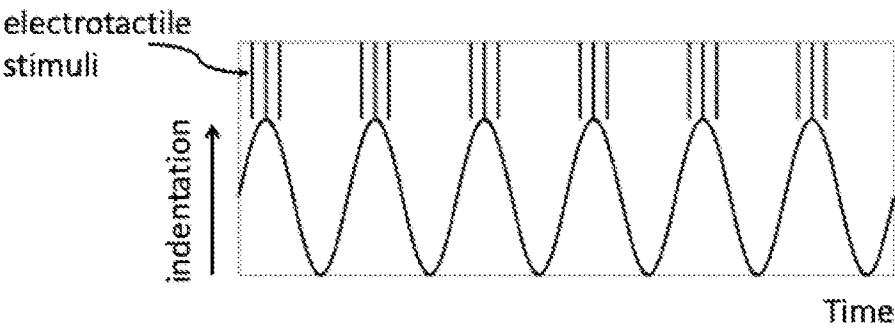


FIG. 60

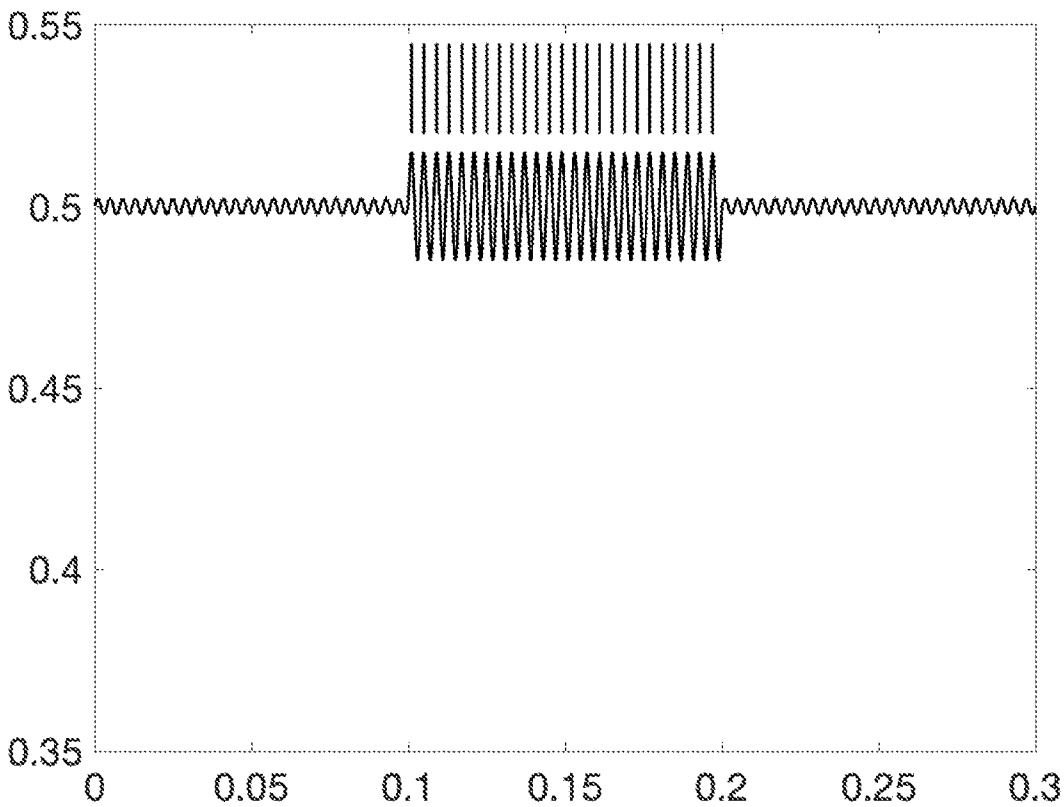


FIG. 61

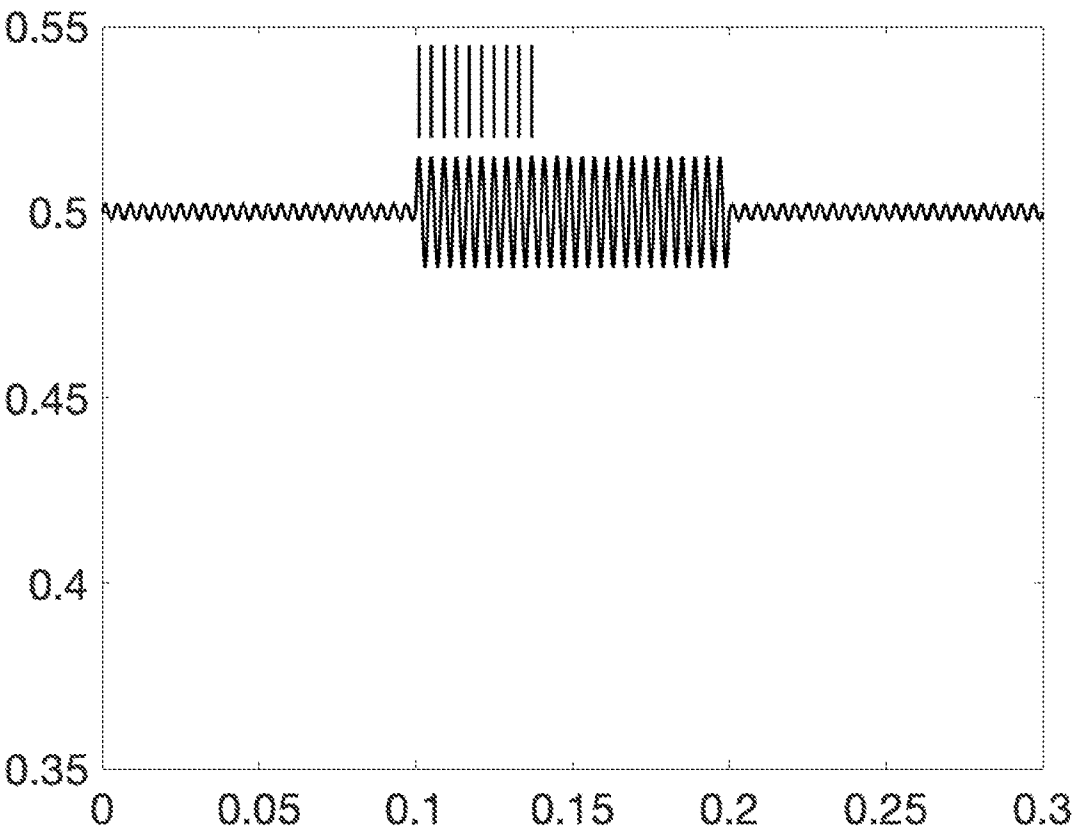


FIG. 62

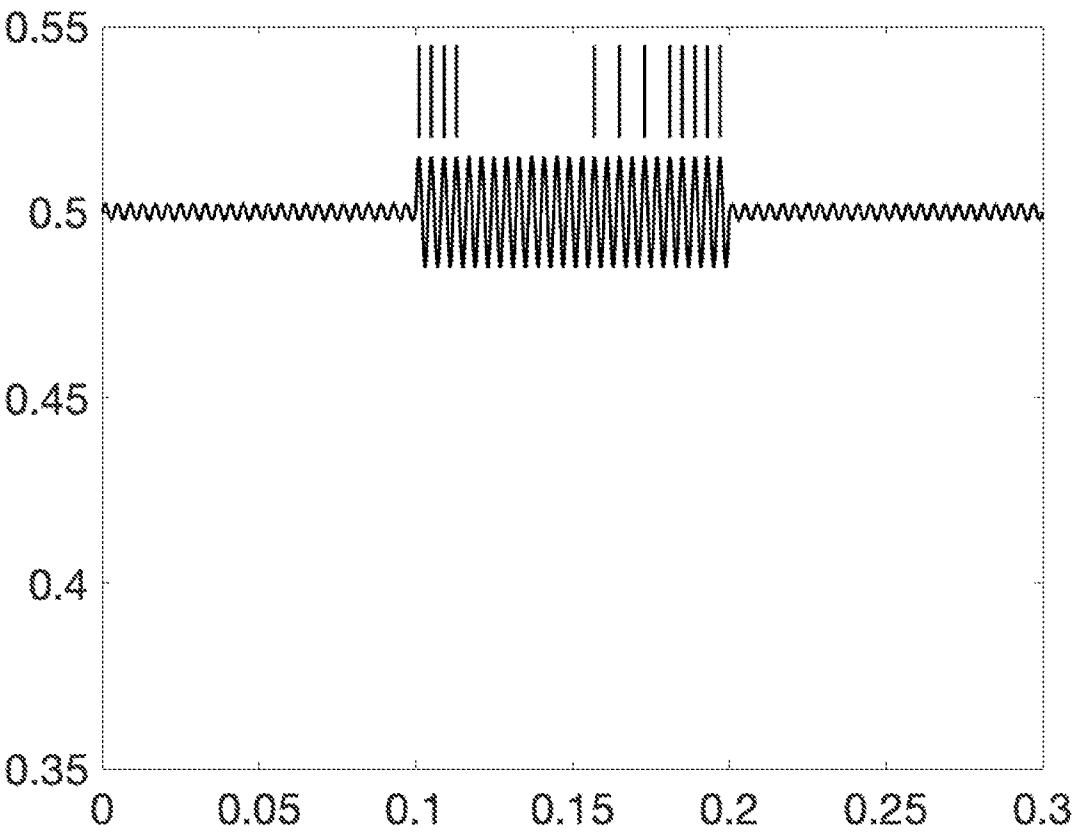


FIG. 63

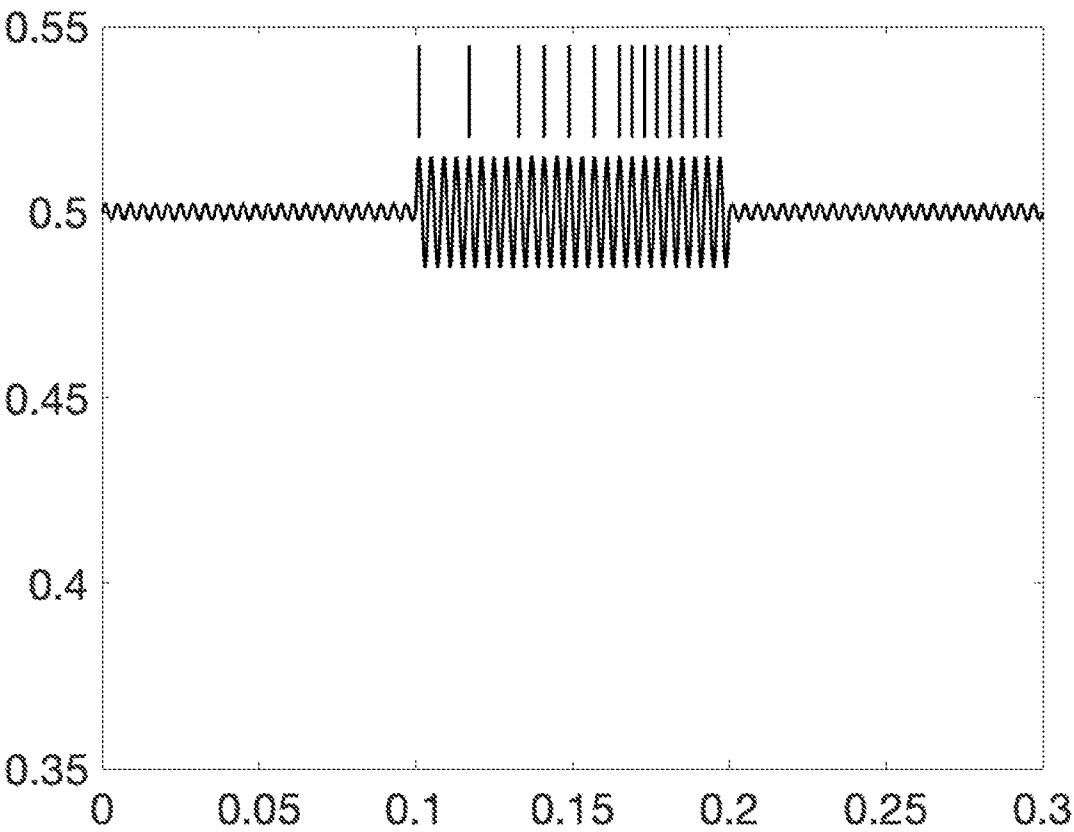


FIG. 64

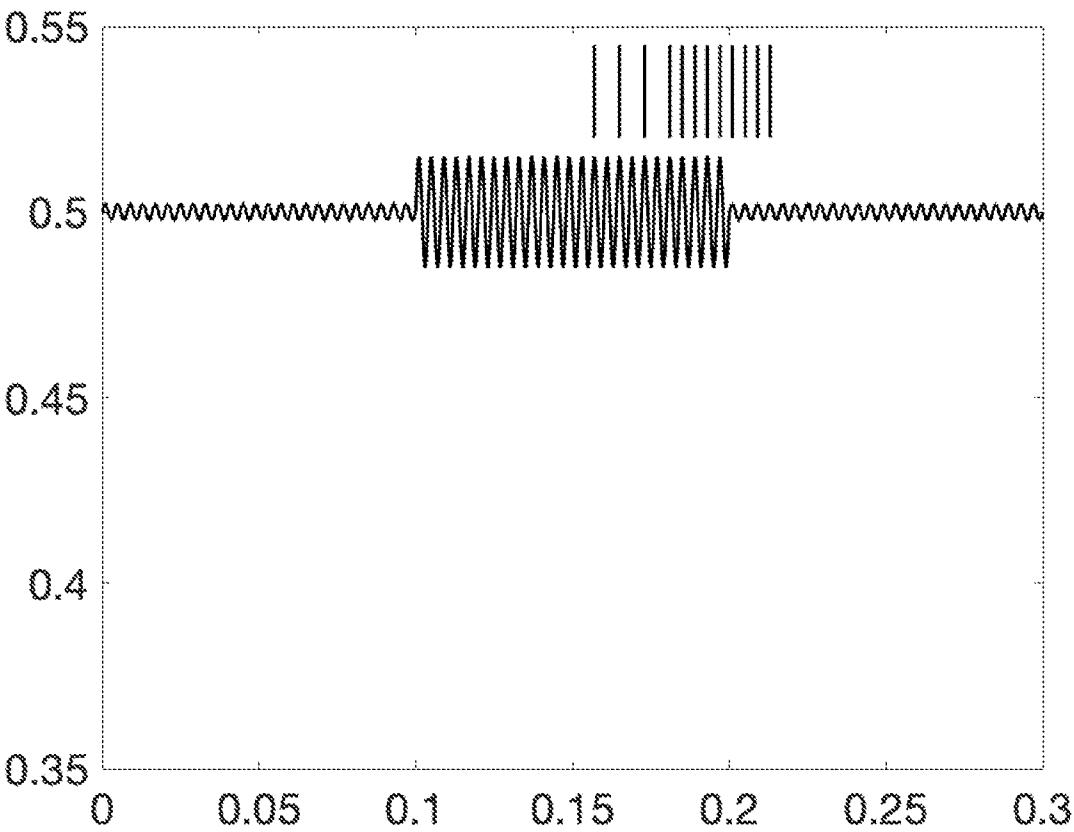


FIG. 65

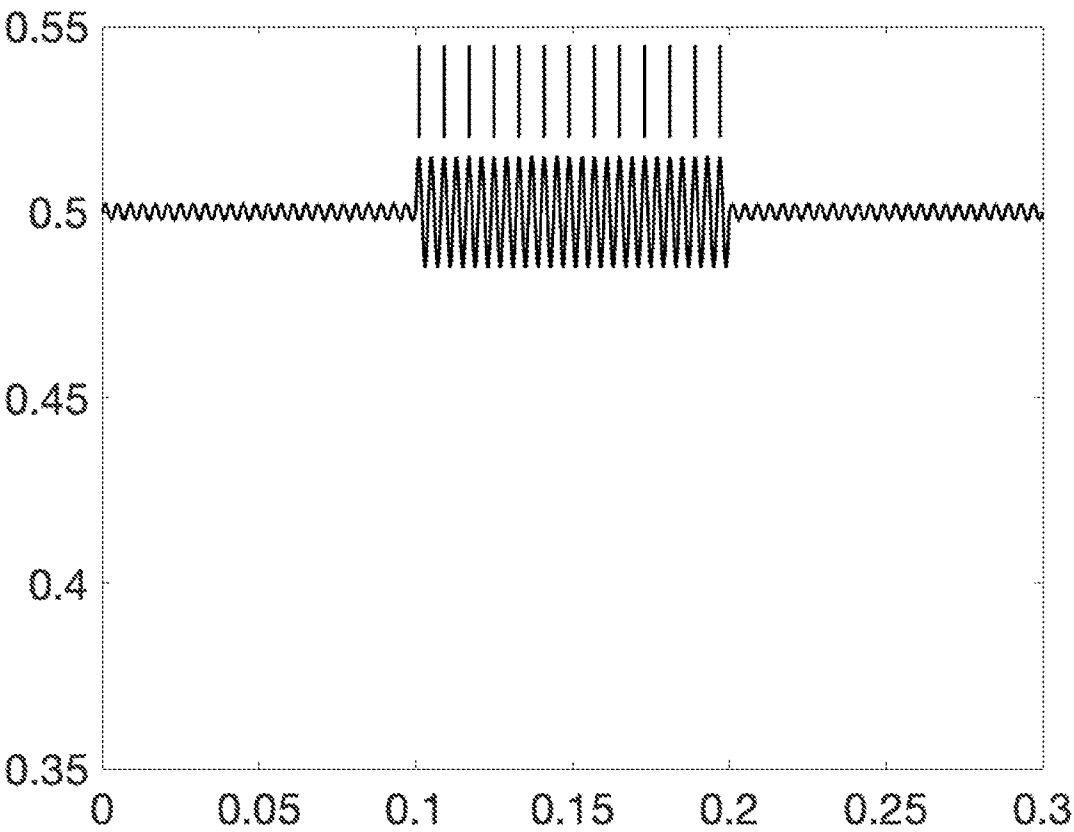


FIG. 66

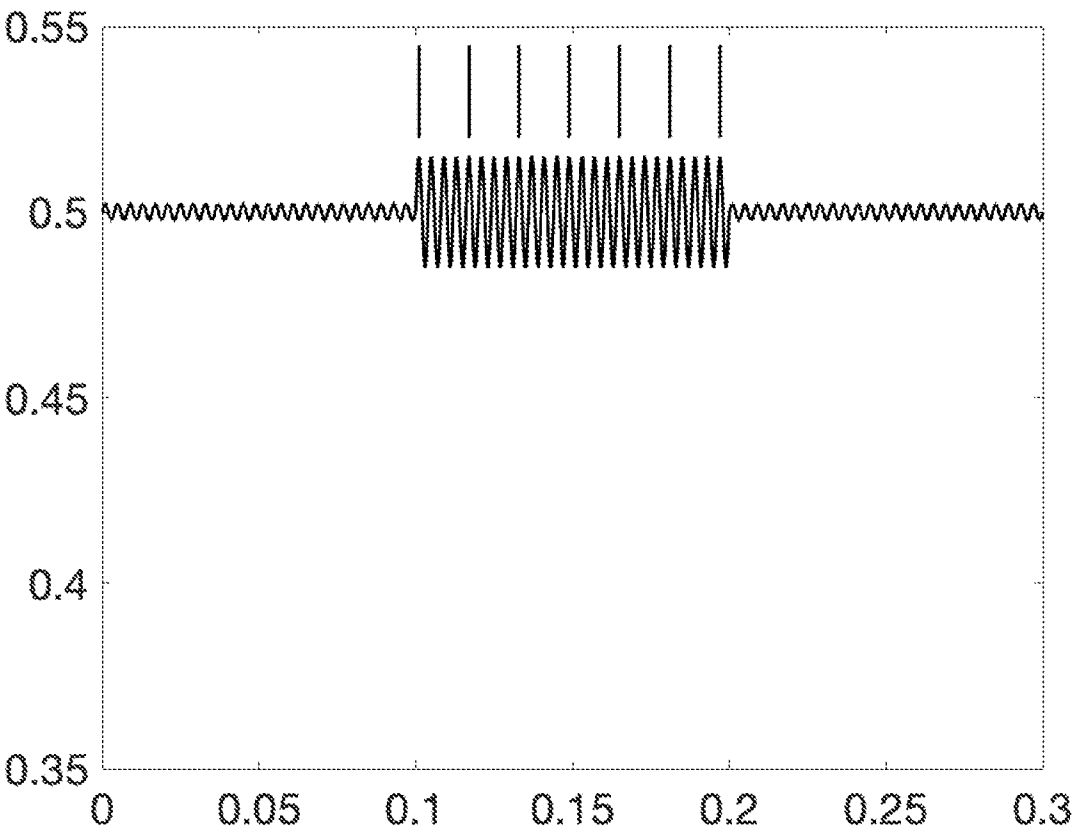


FIG. 67

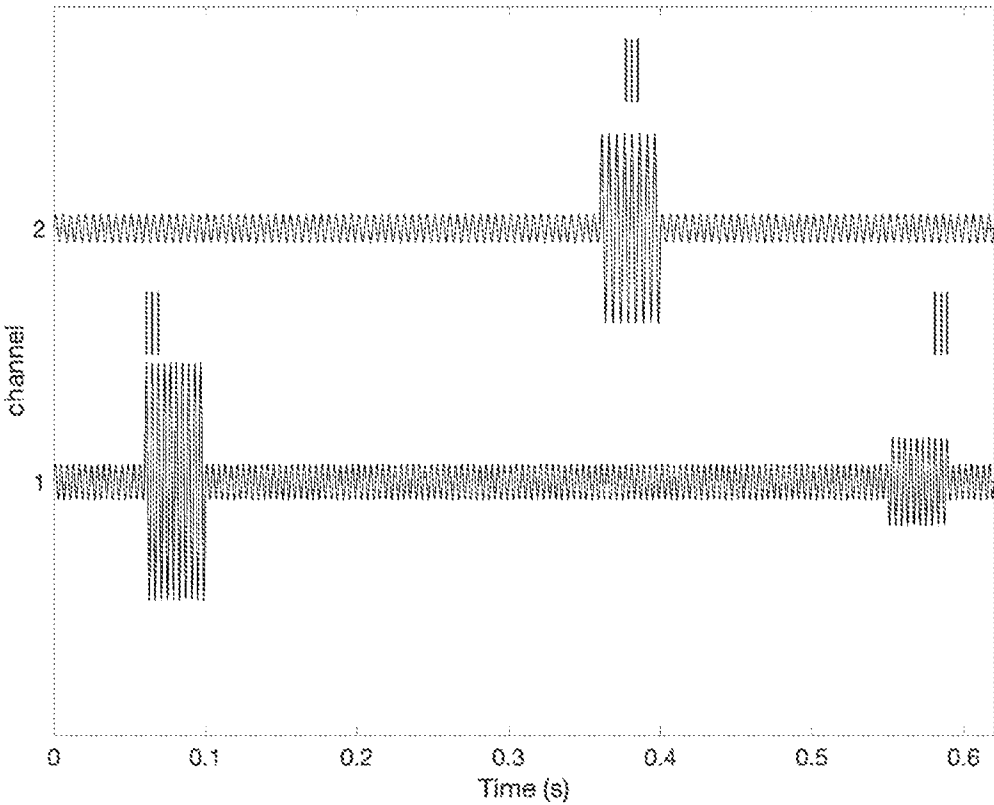


FIG. 68

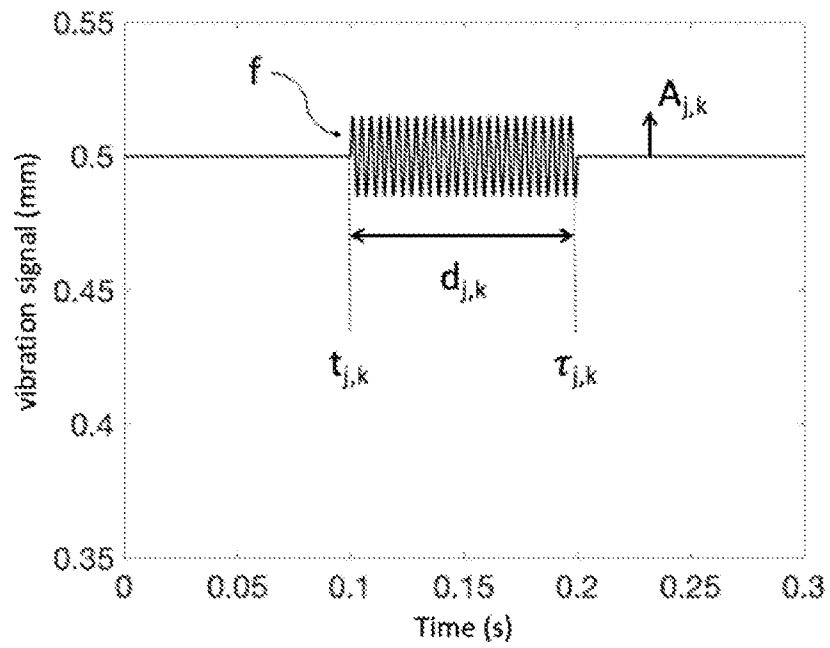


FIG. 69

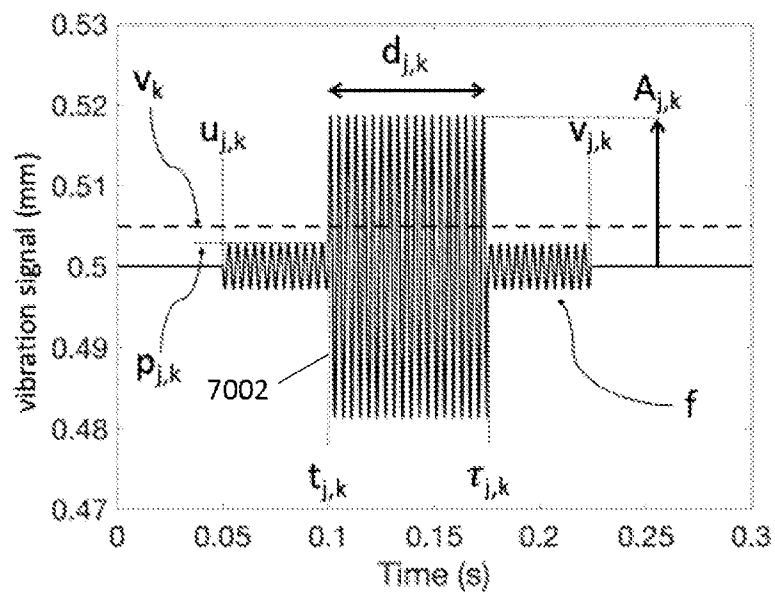


FIG. 70

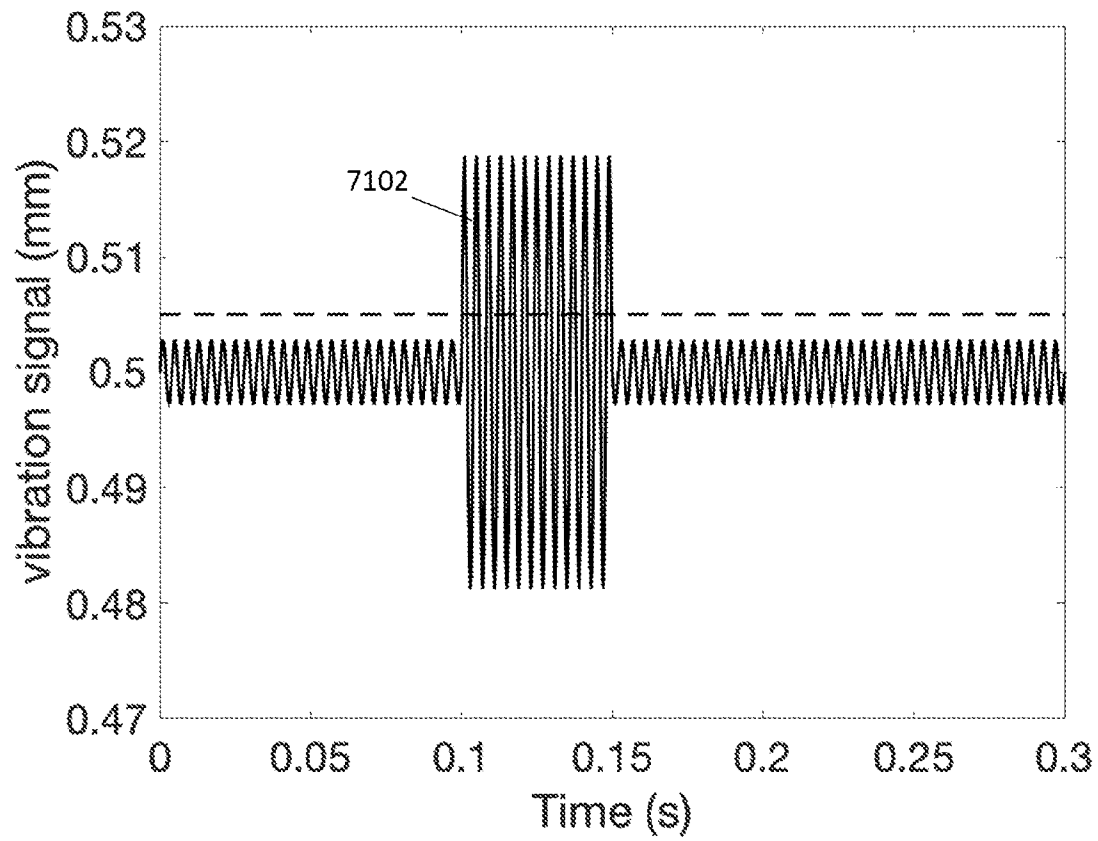


FIG. 71

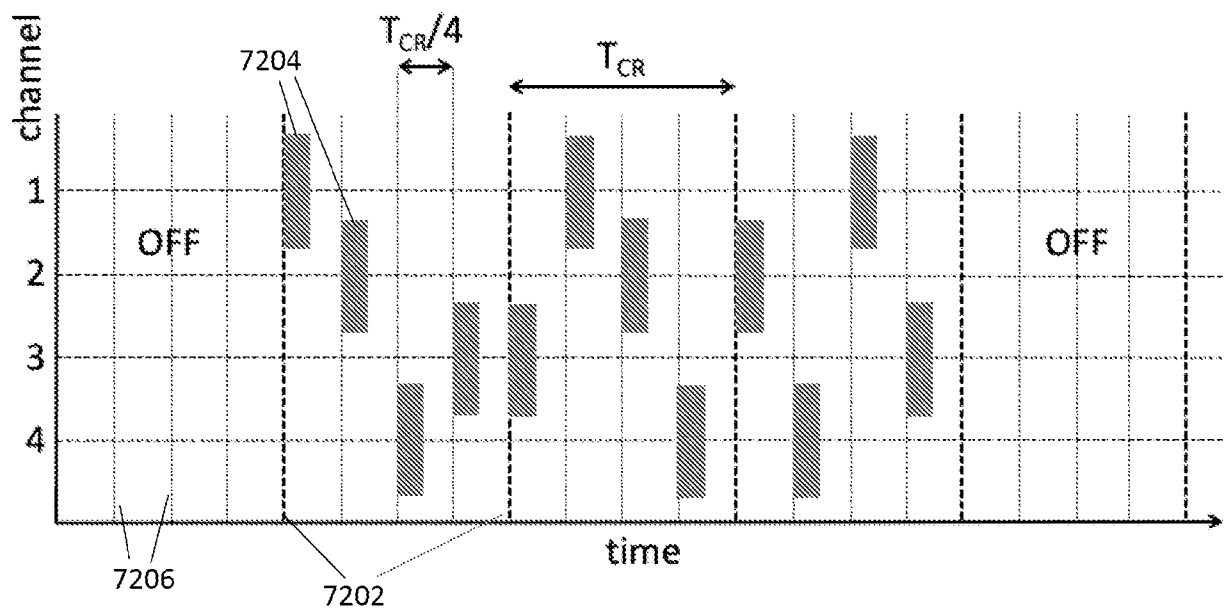


FIG. 72

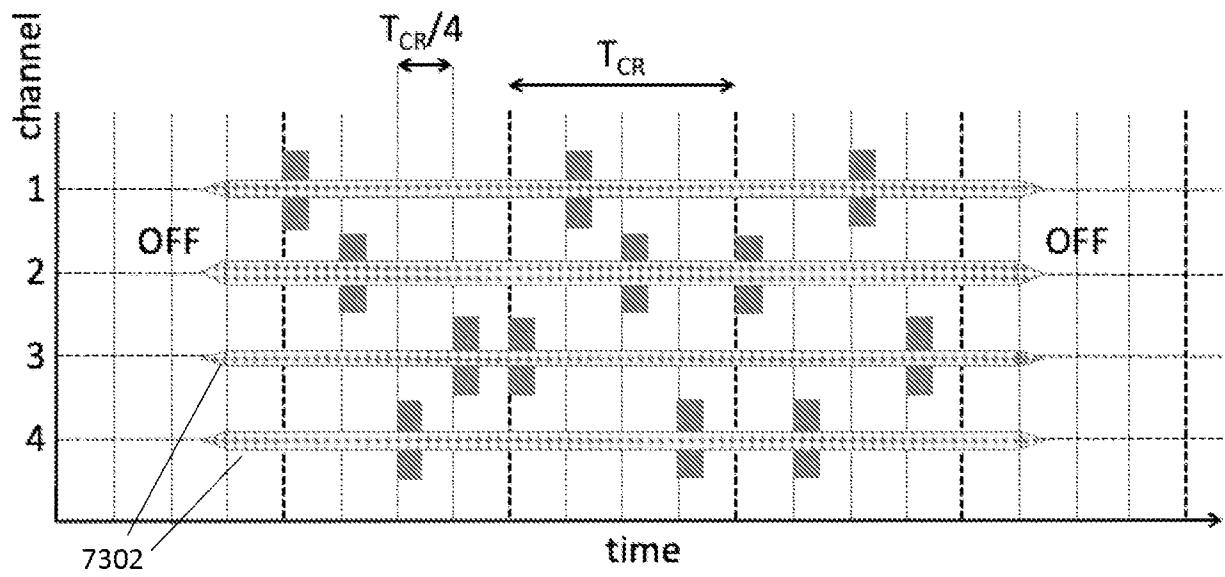


FIG. 73

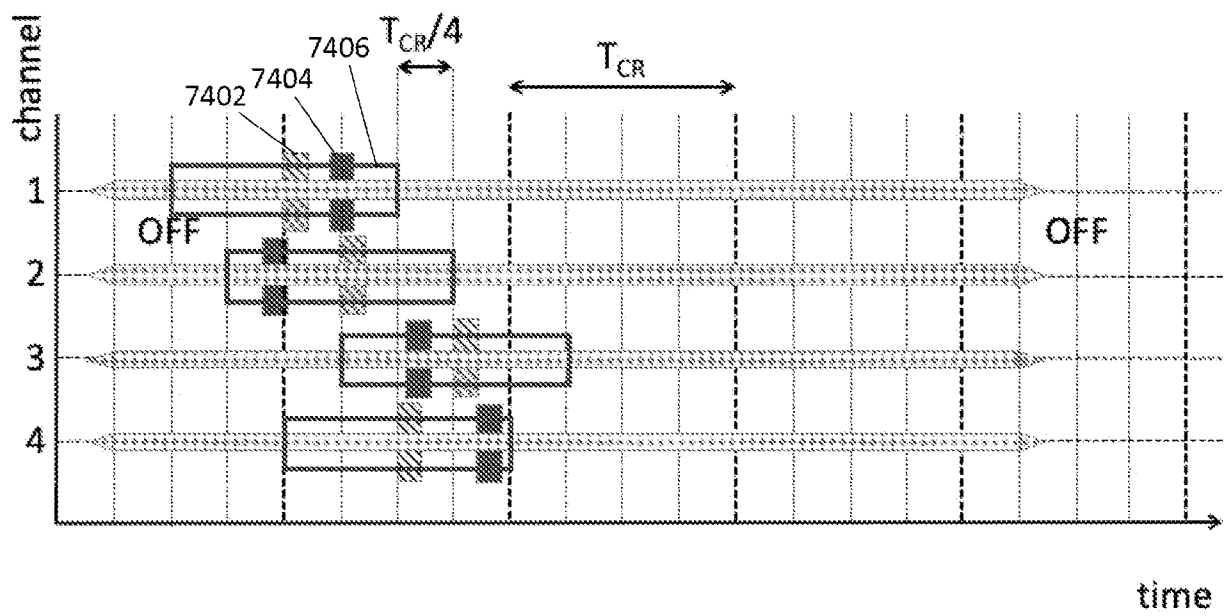


FIG. 74

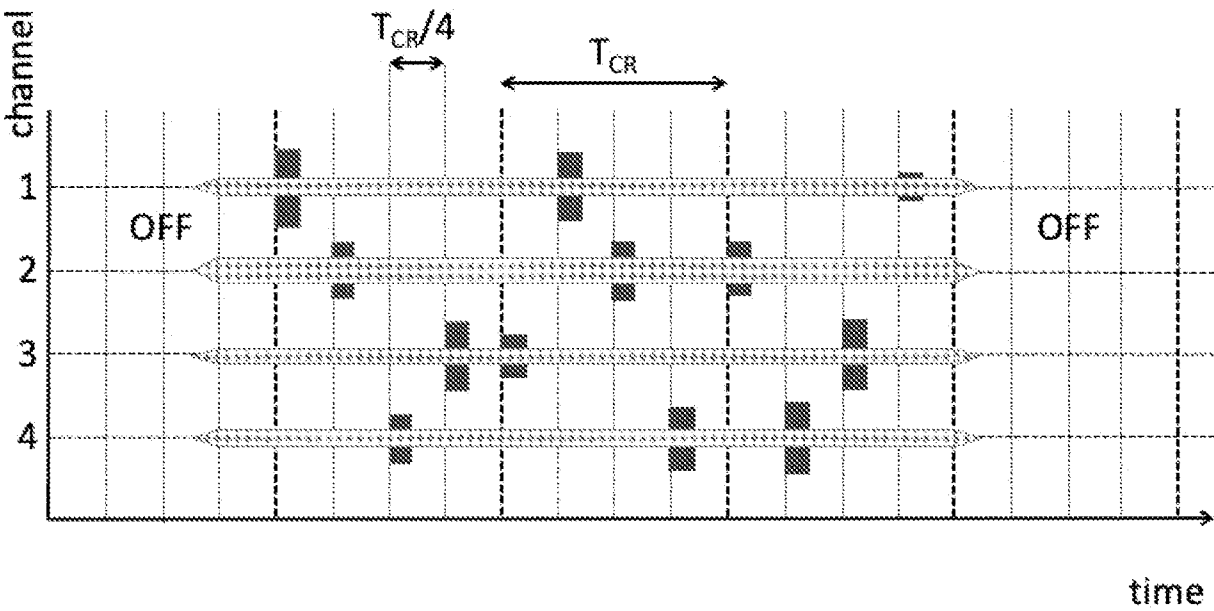


FIG. 75

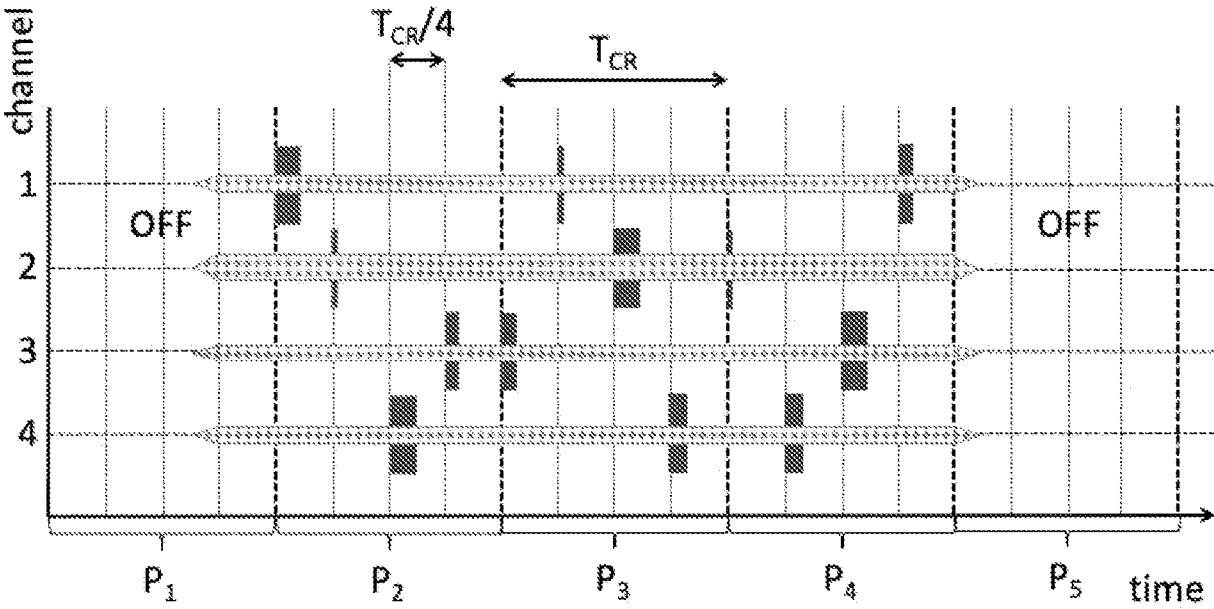


FIG. 76

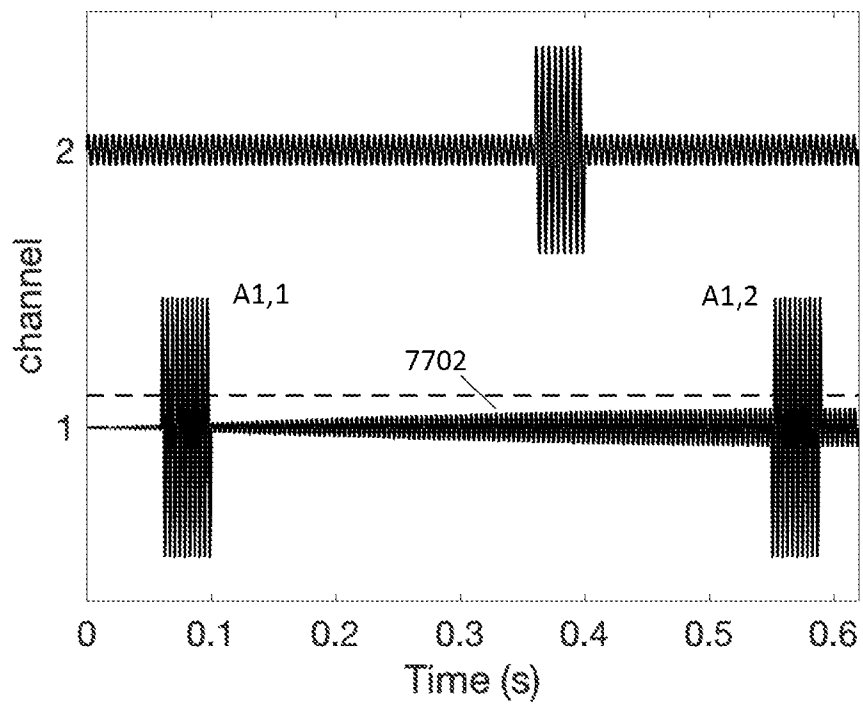


FIG. 77

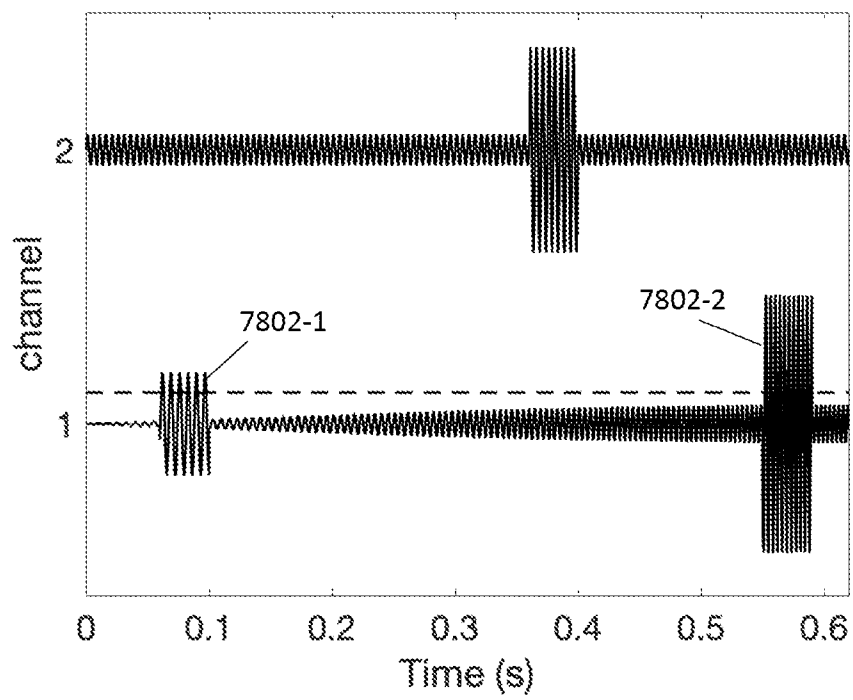


FIG. 78

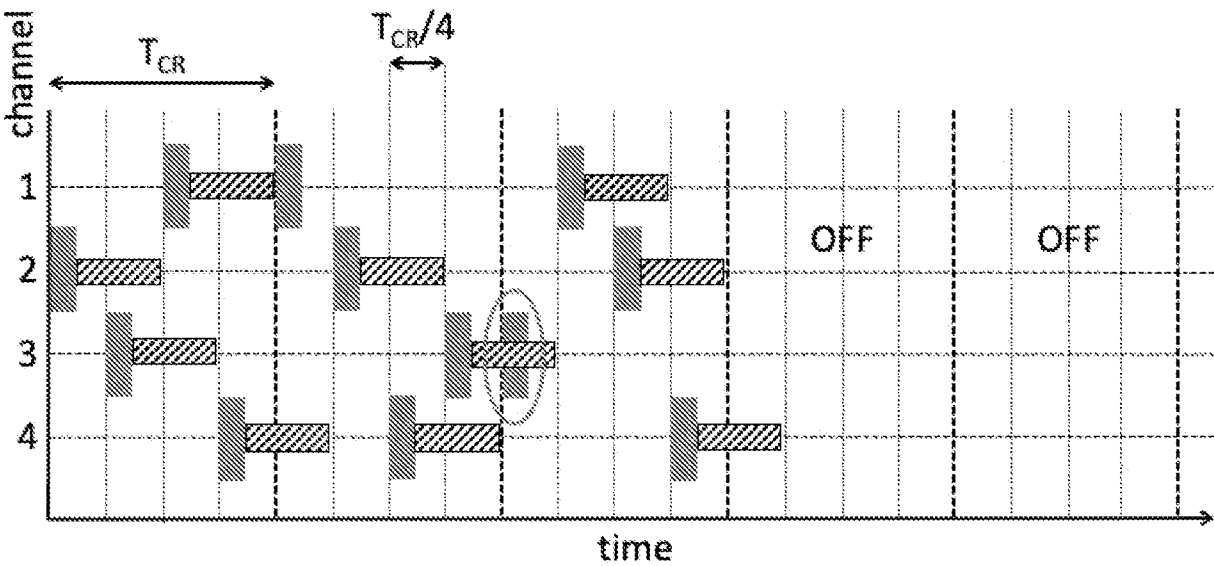


FIG. 79

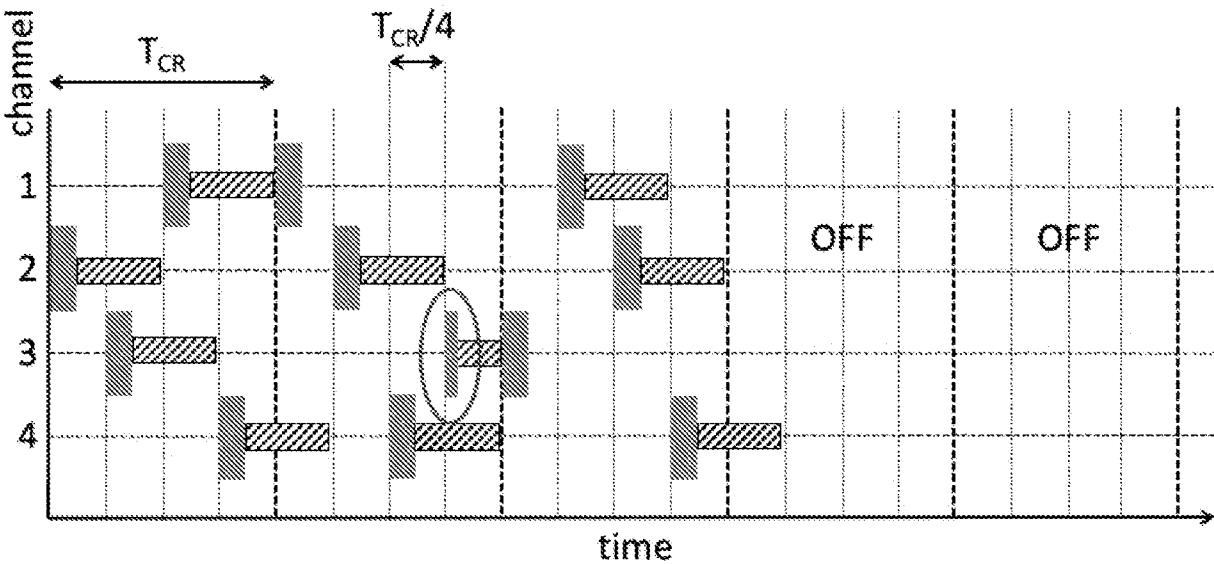


FIG. 80

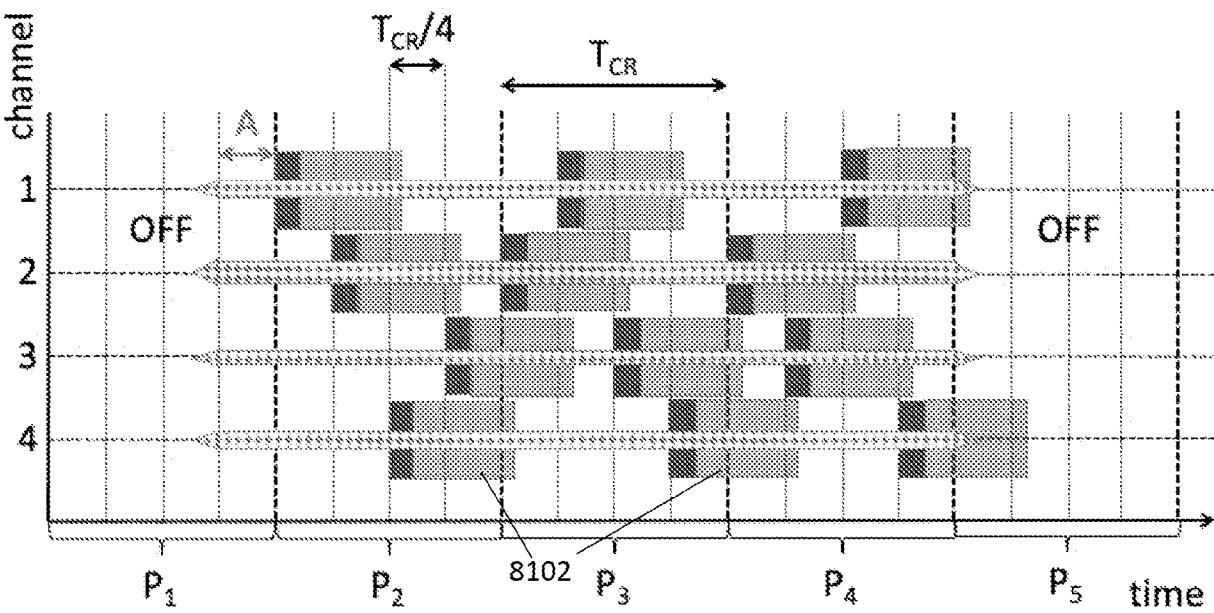


FIG. 81

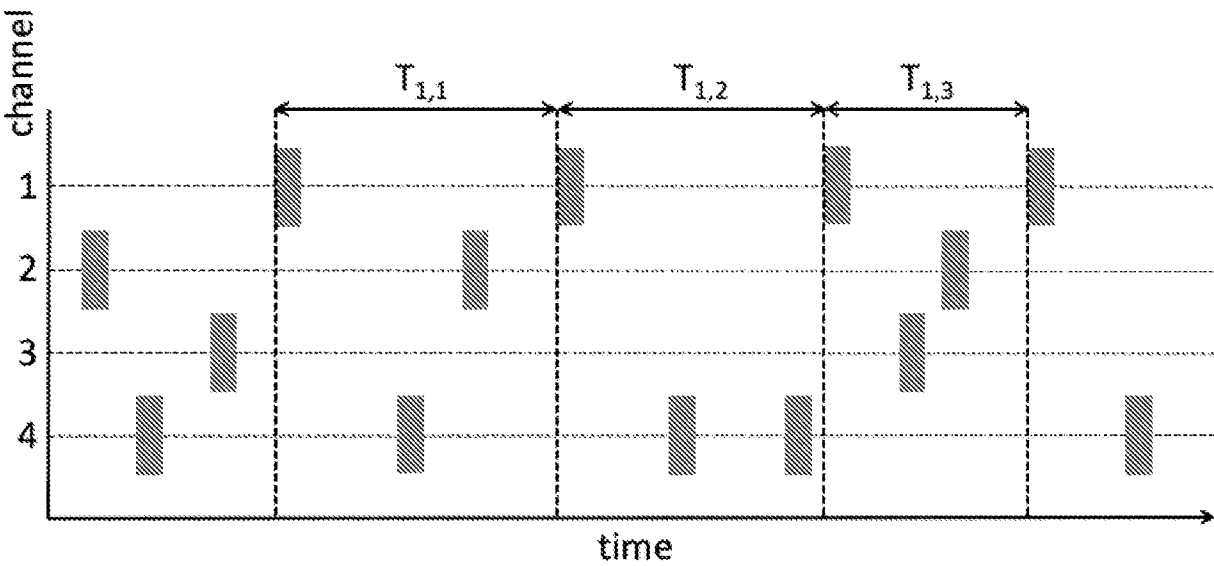


FIG. 82

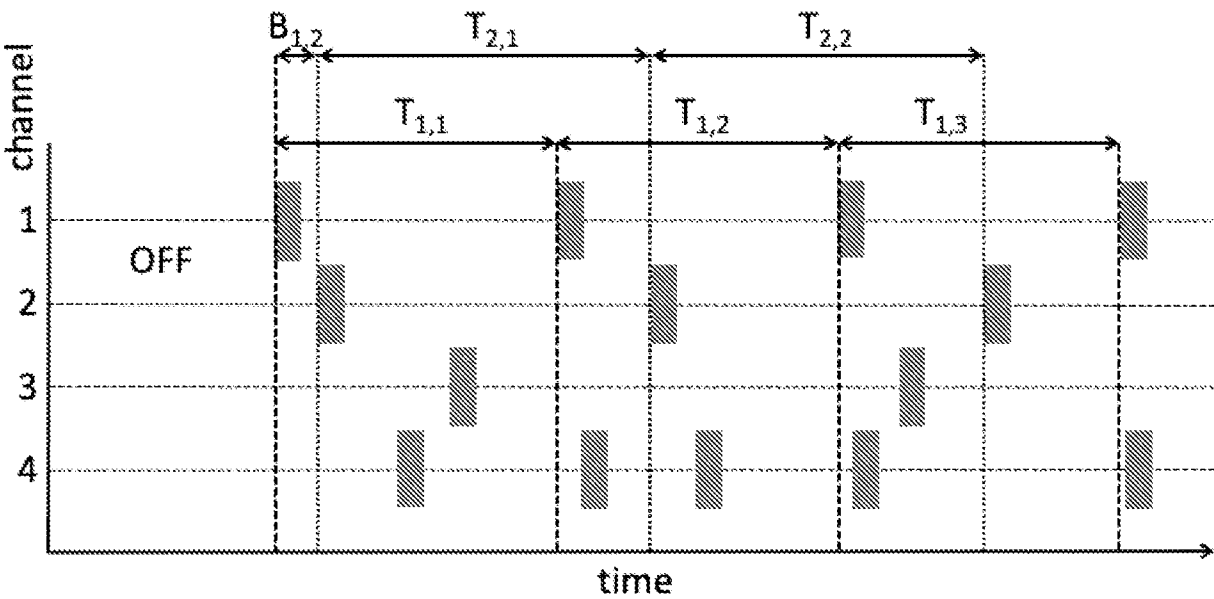


FIG. 83

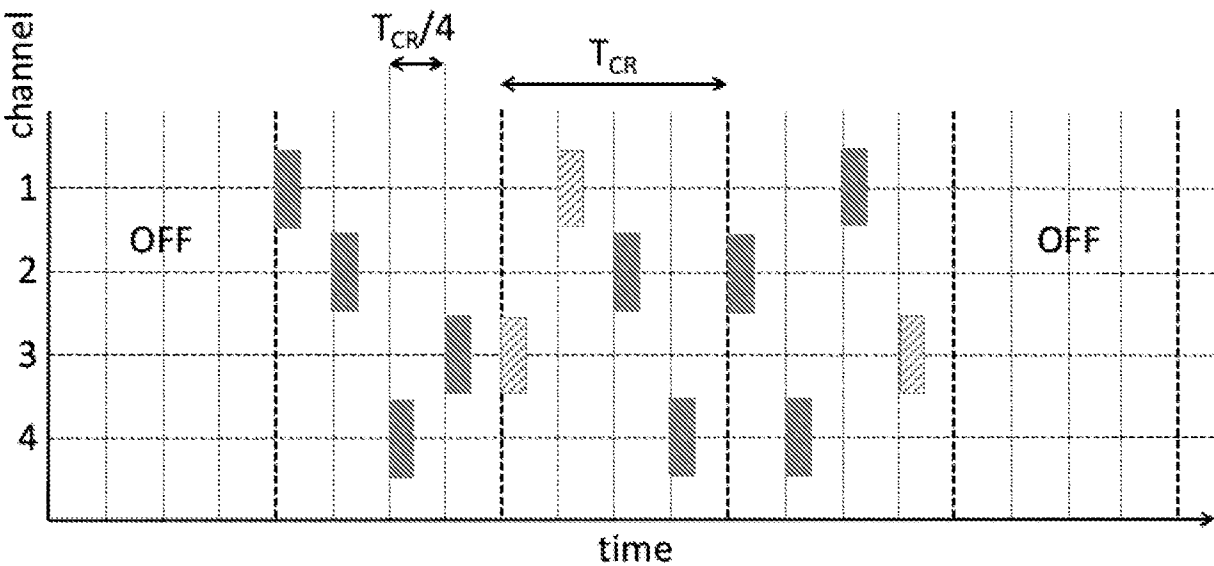


FIG. 84

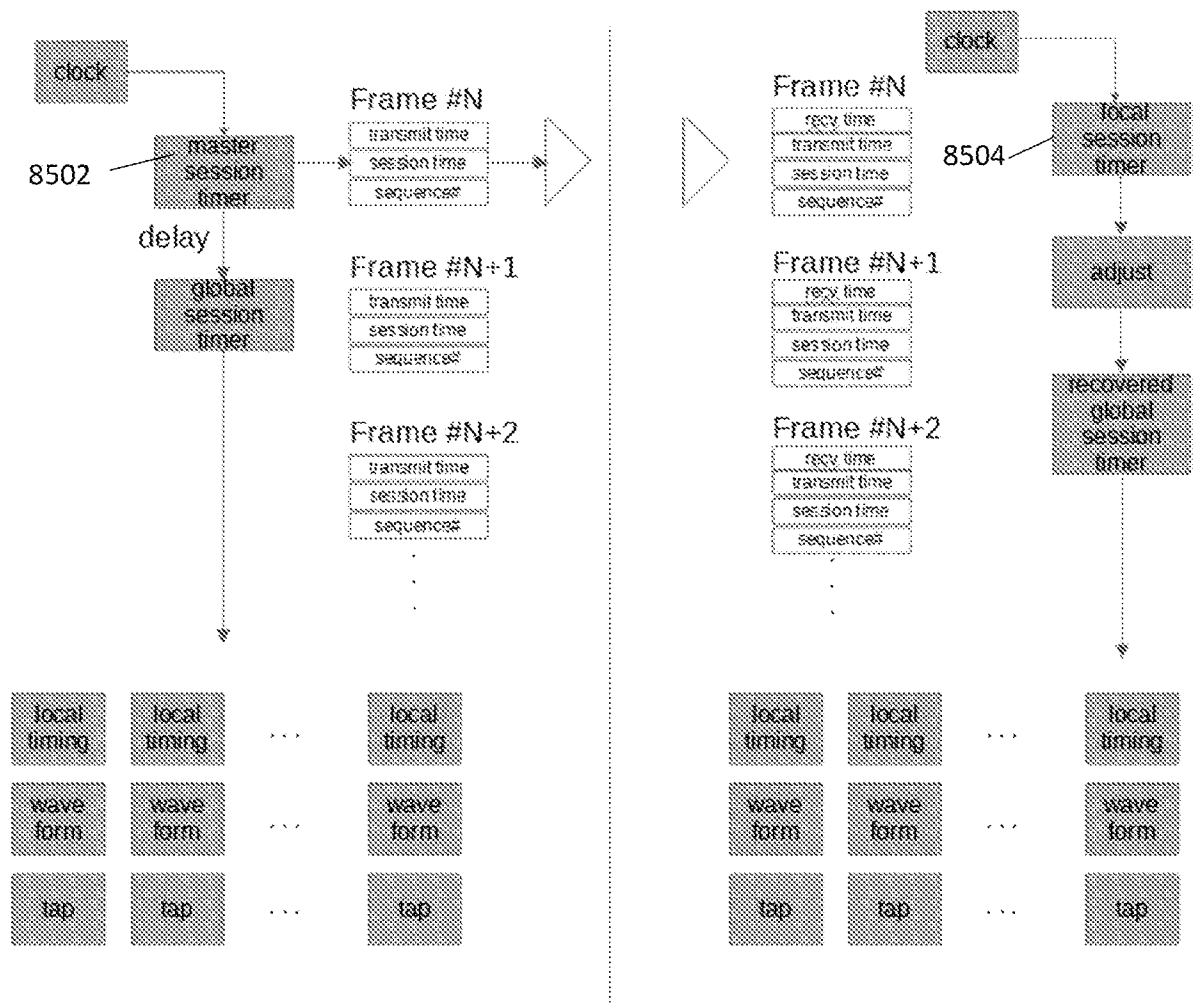


FIG. 85

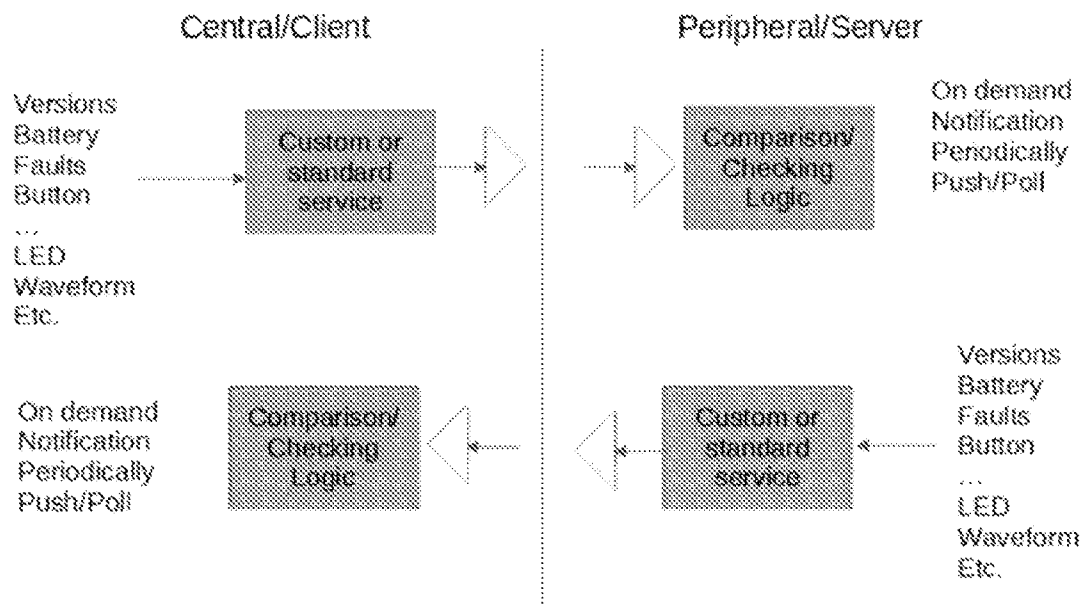


FIG. 86

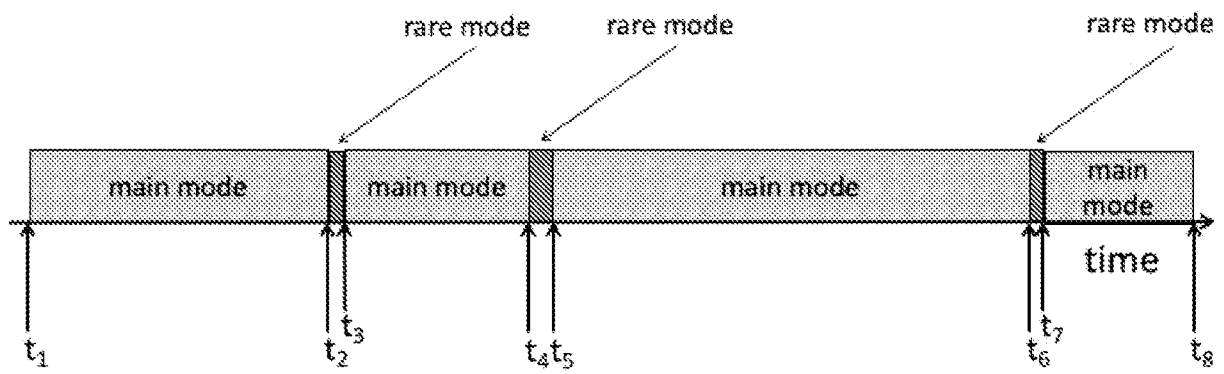


FIG. 87

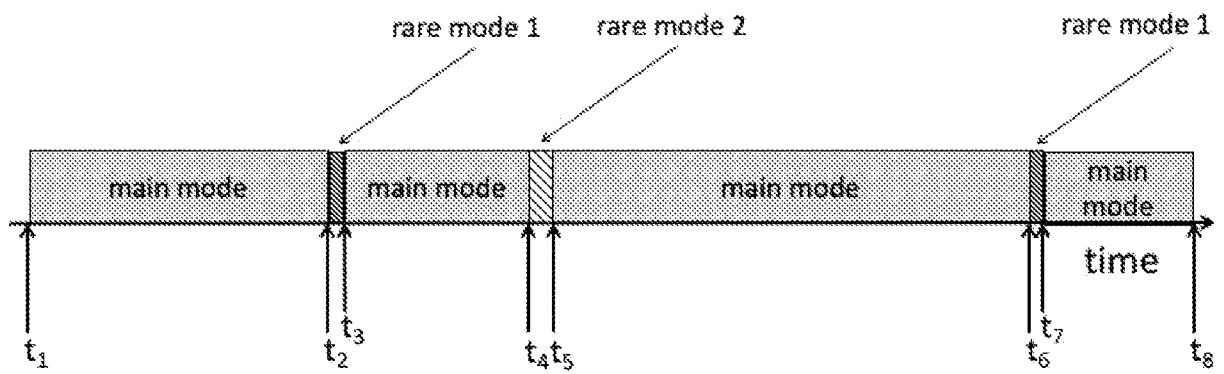


FIG. 88

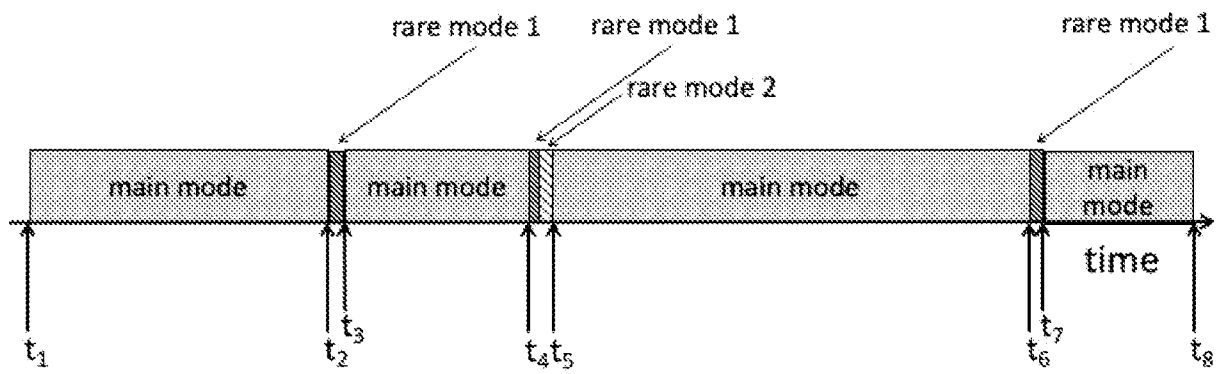


FIG. 89

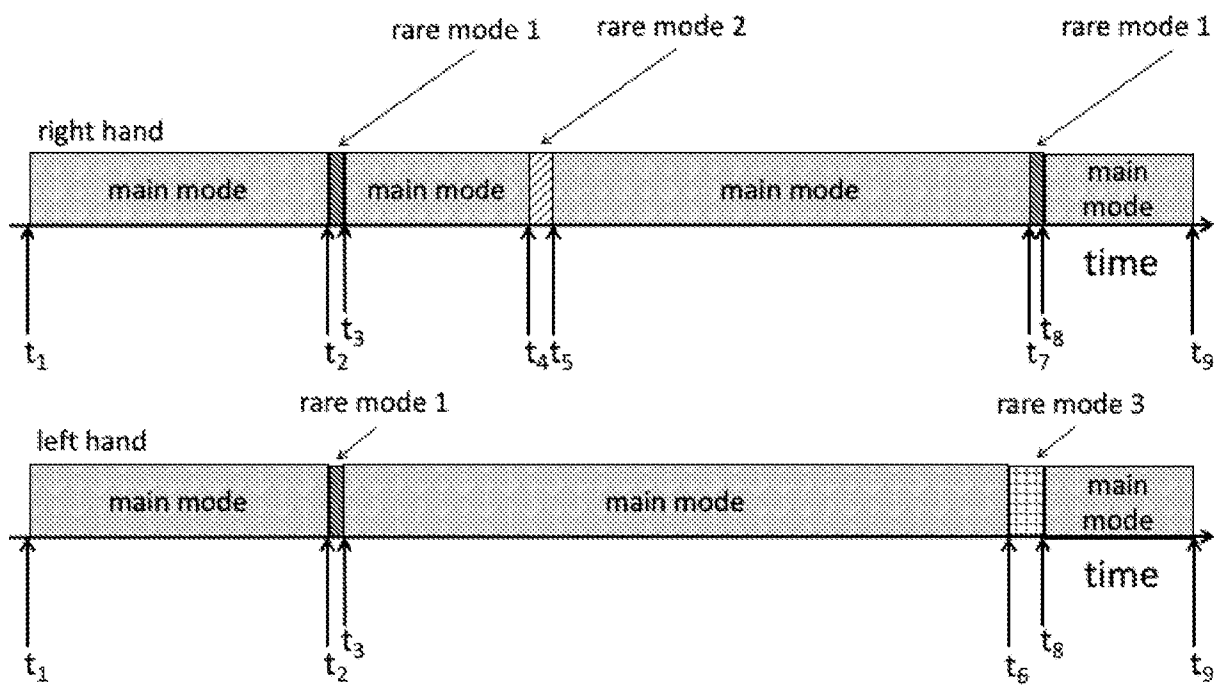


FIG. 90

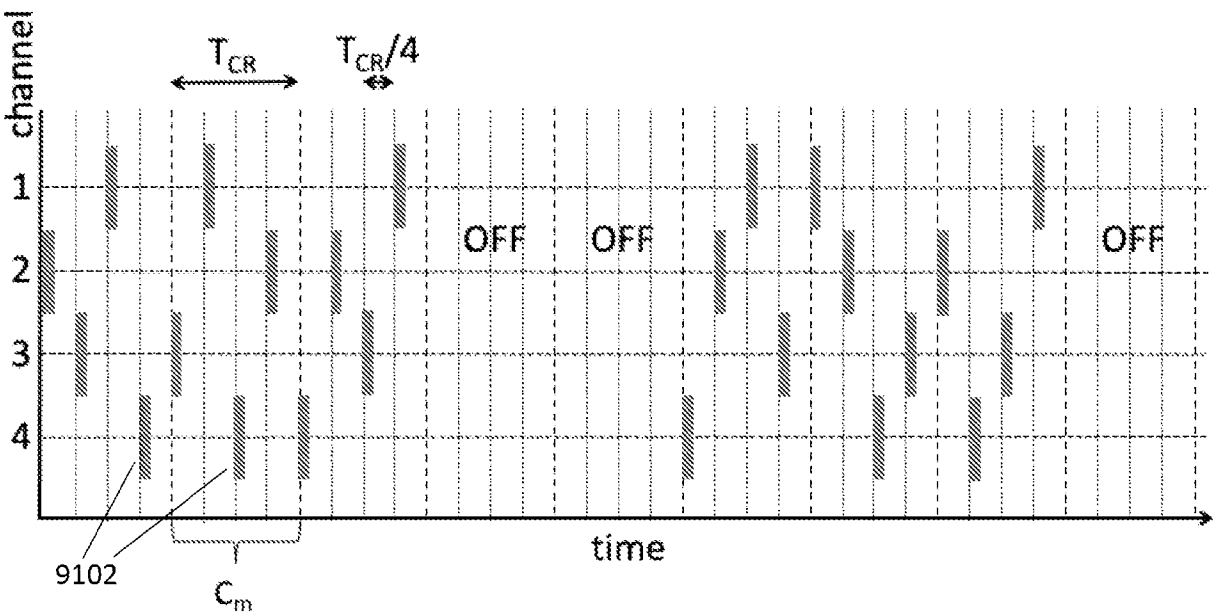


FIG. 91

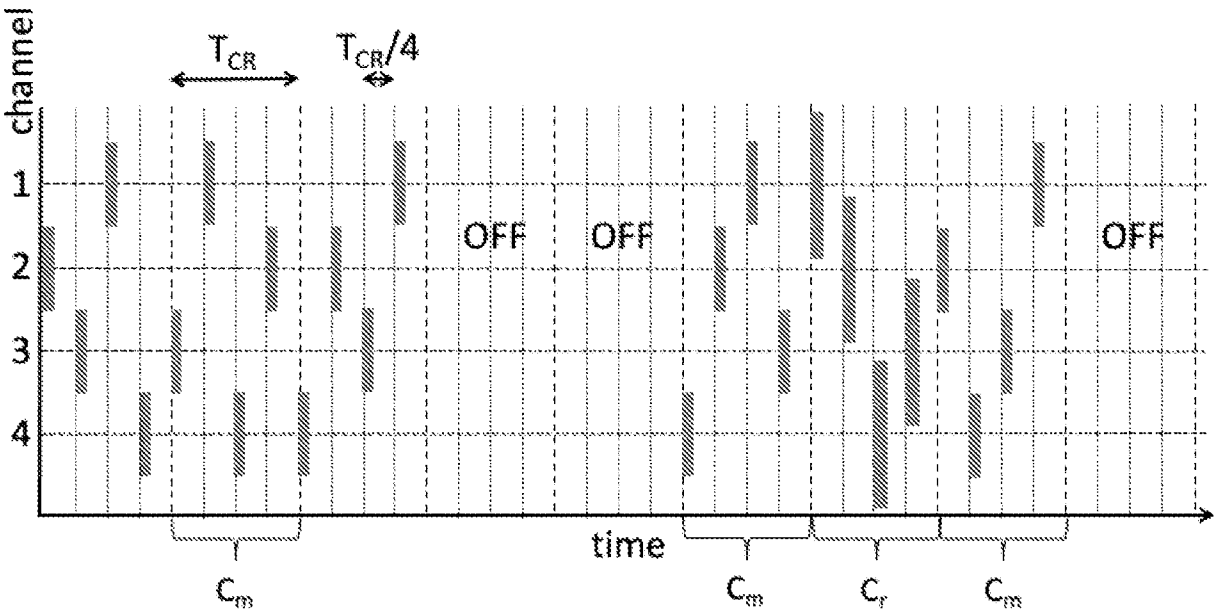


FIG. 92

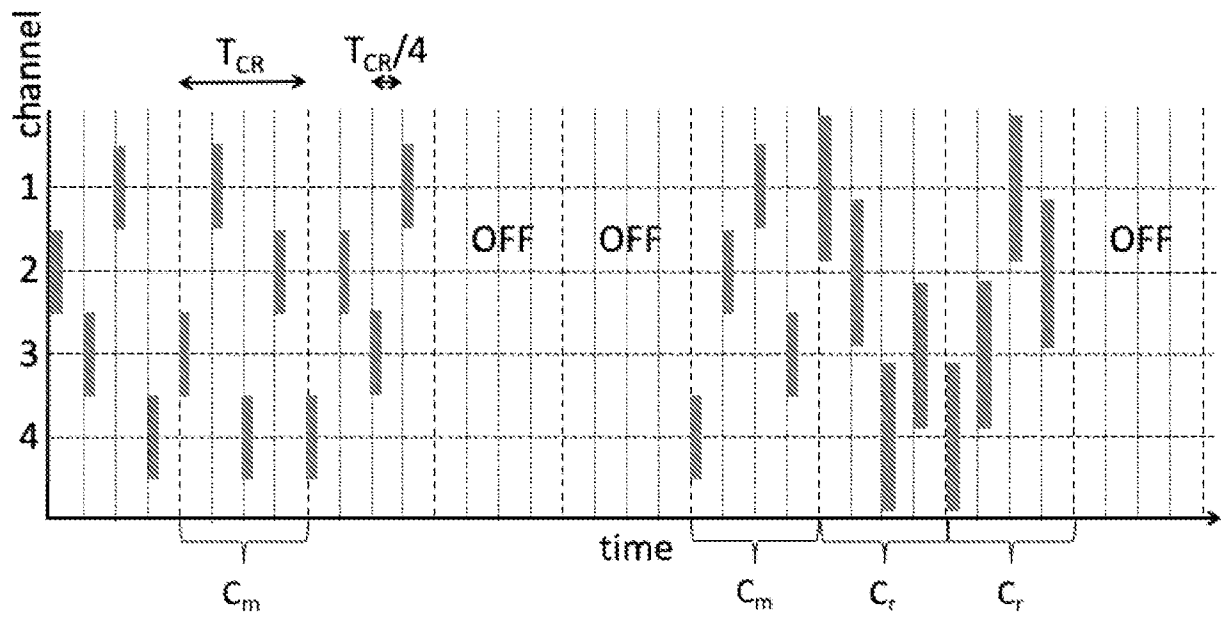


FIG. 93

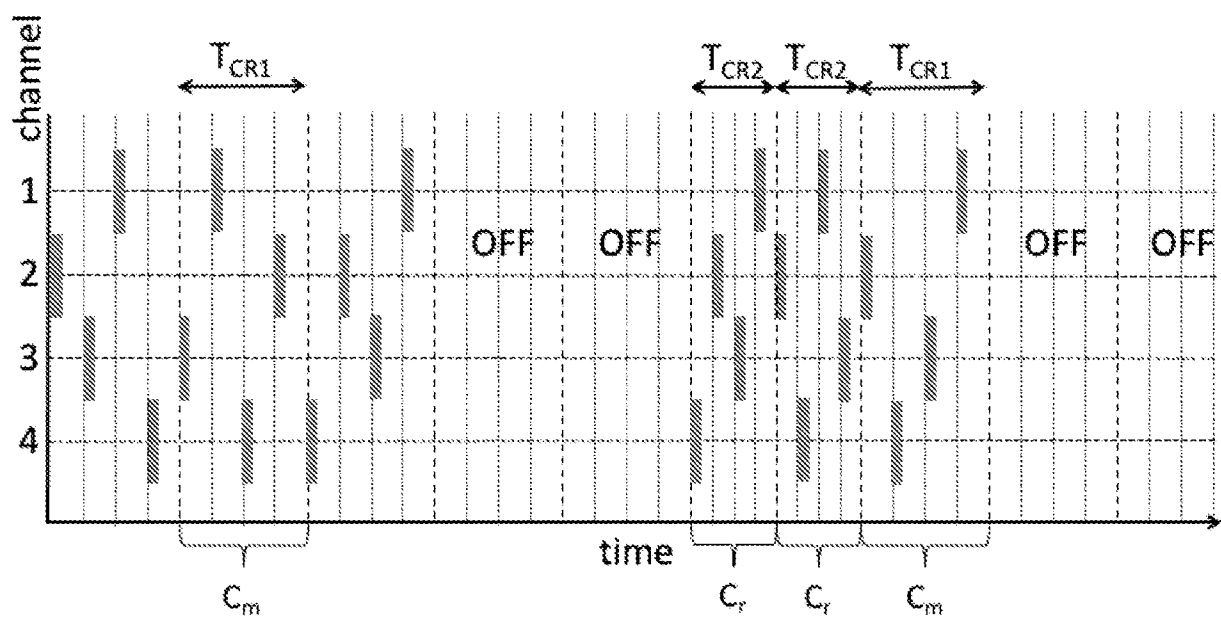


FIG. 94

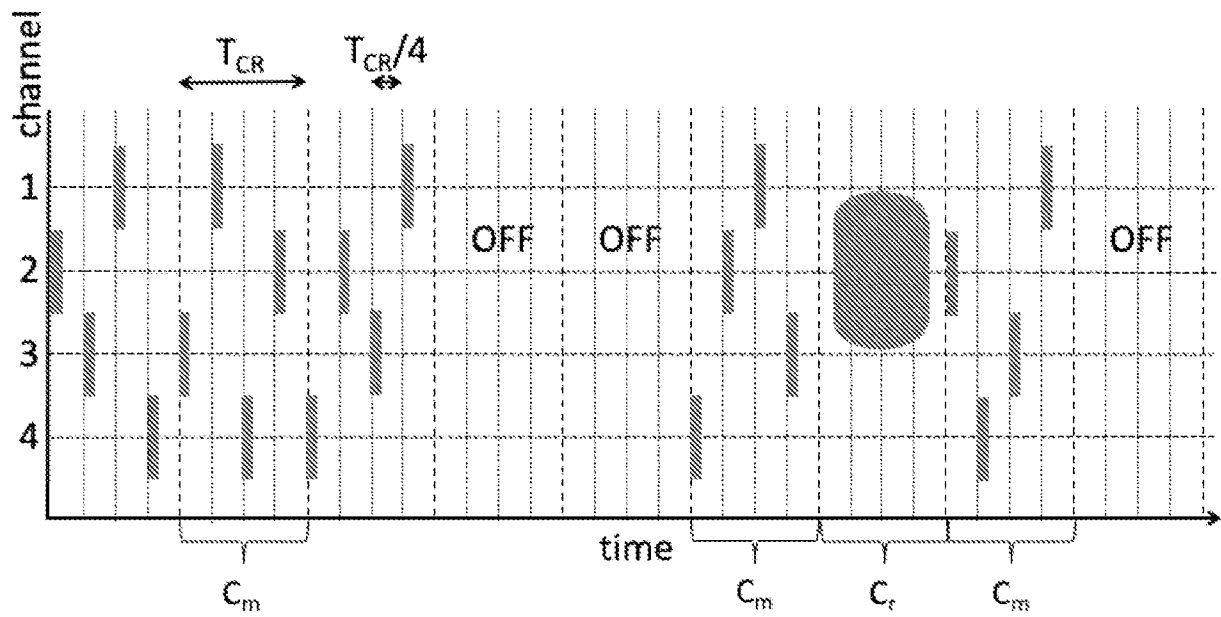


FIG. 95

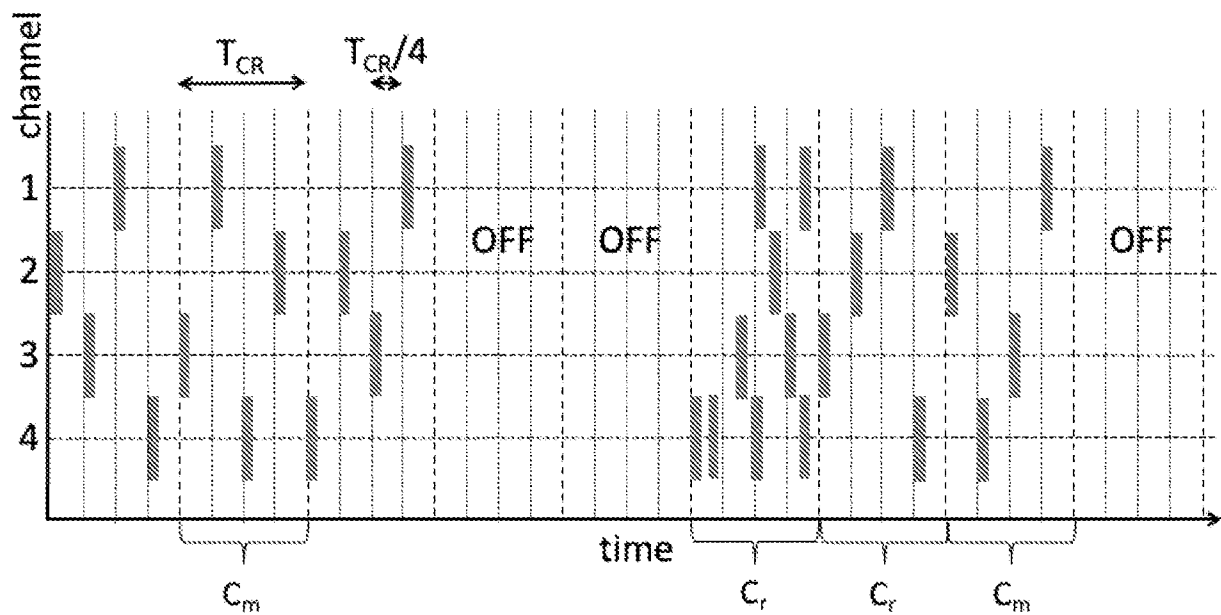


FIG. 96

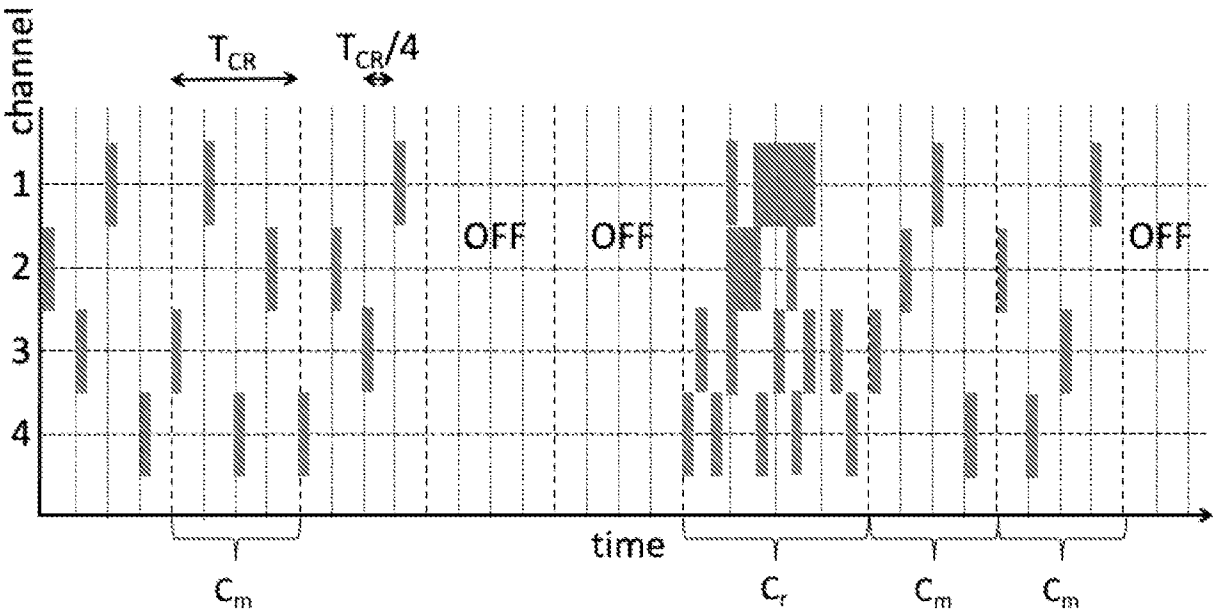


FIG. 97

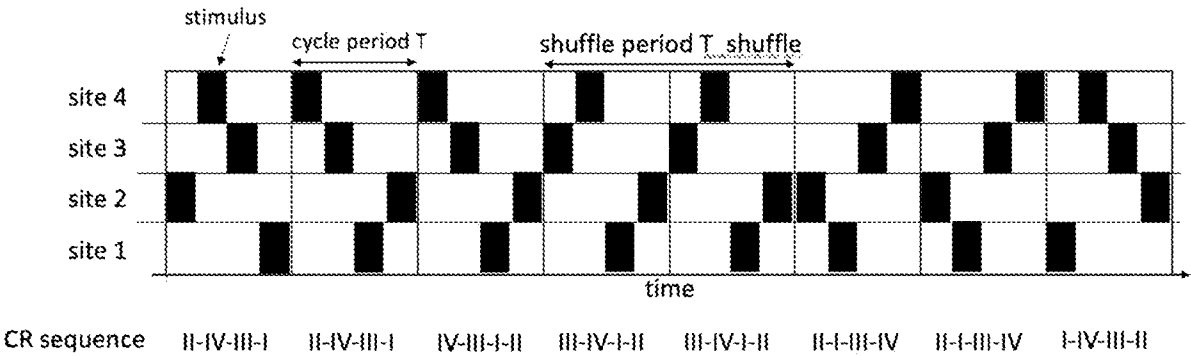


FIG. 98

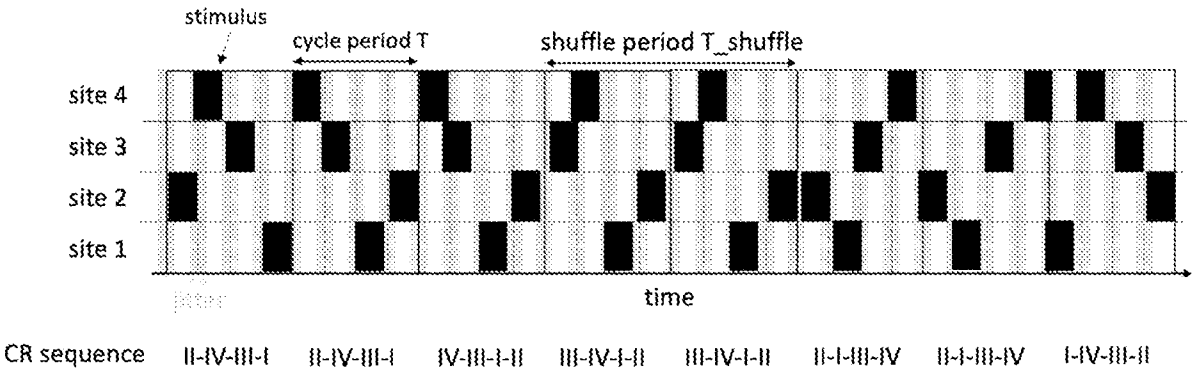


FIG. 99

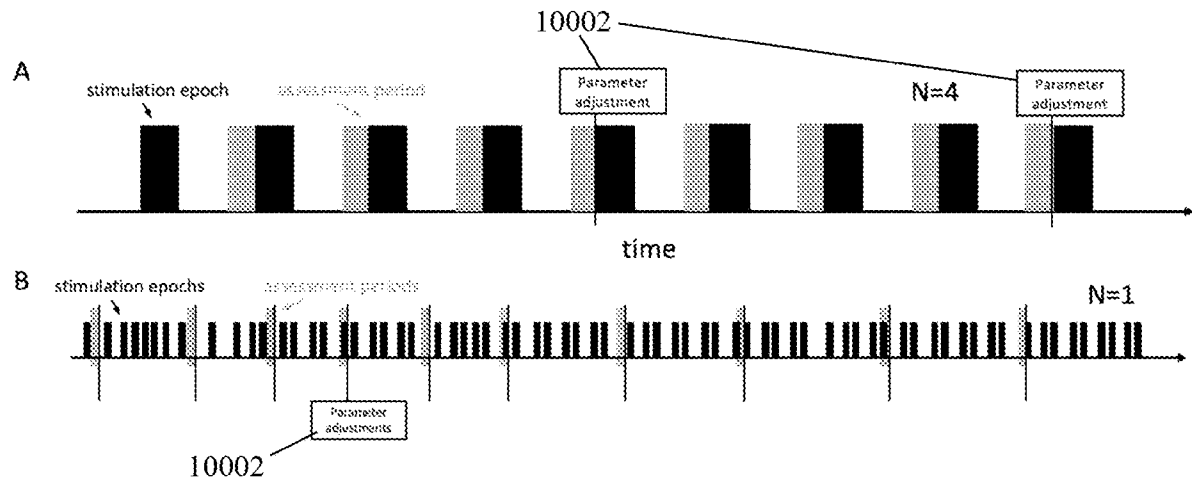
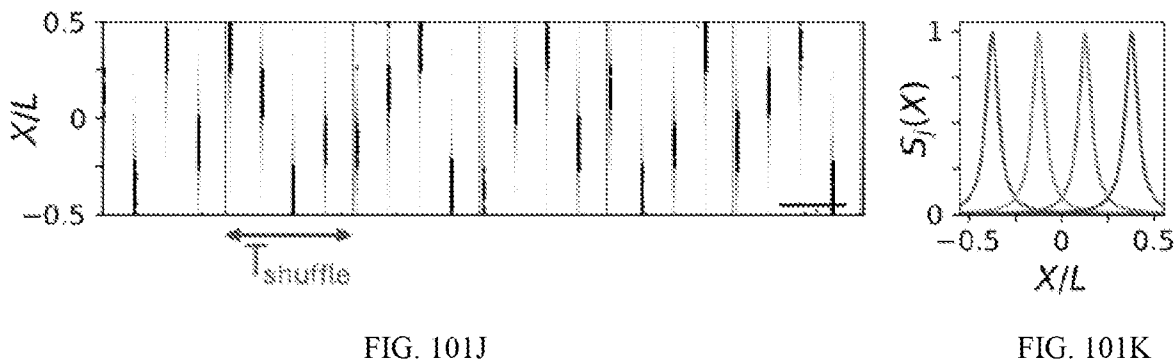
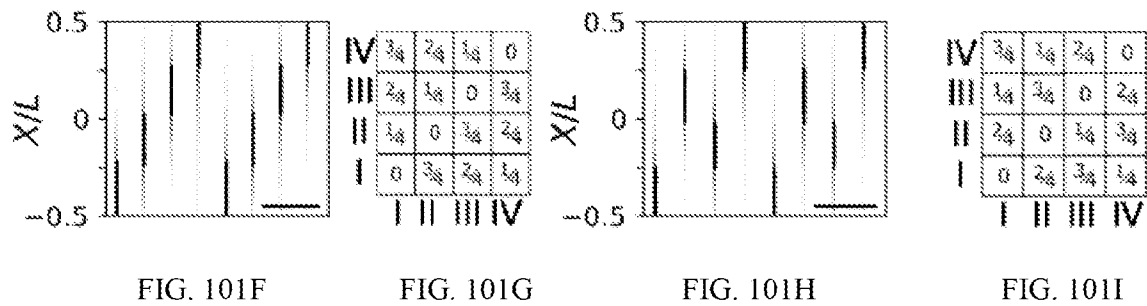
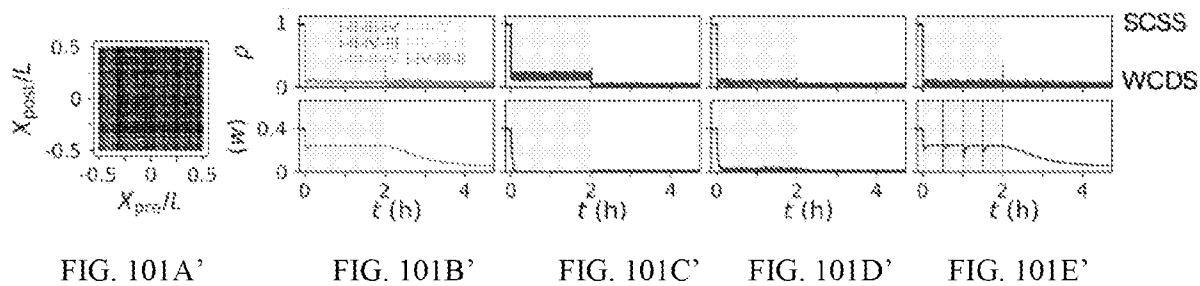
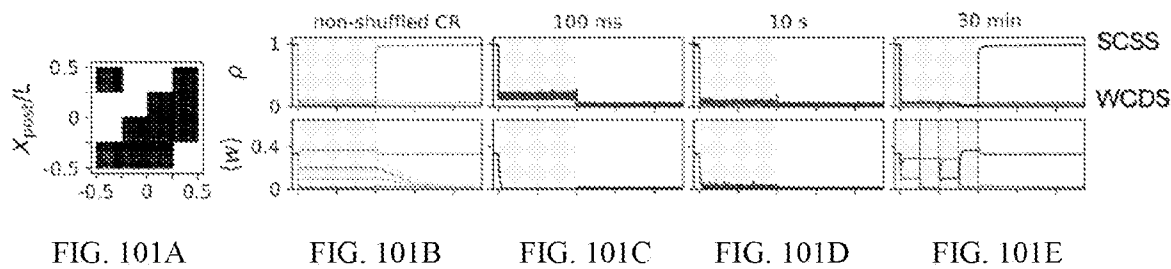


FIG. 100



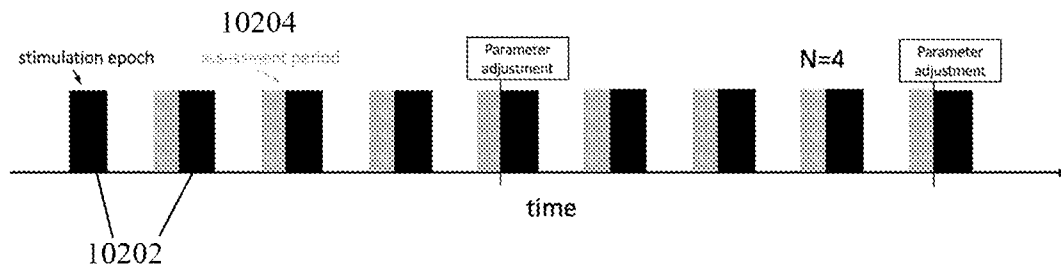


FIG. 102

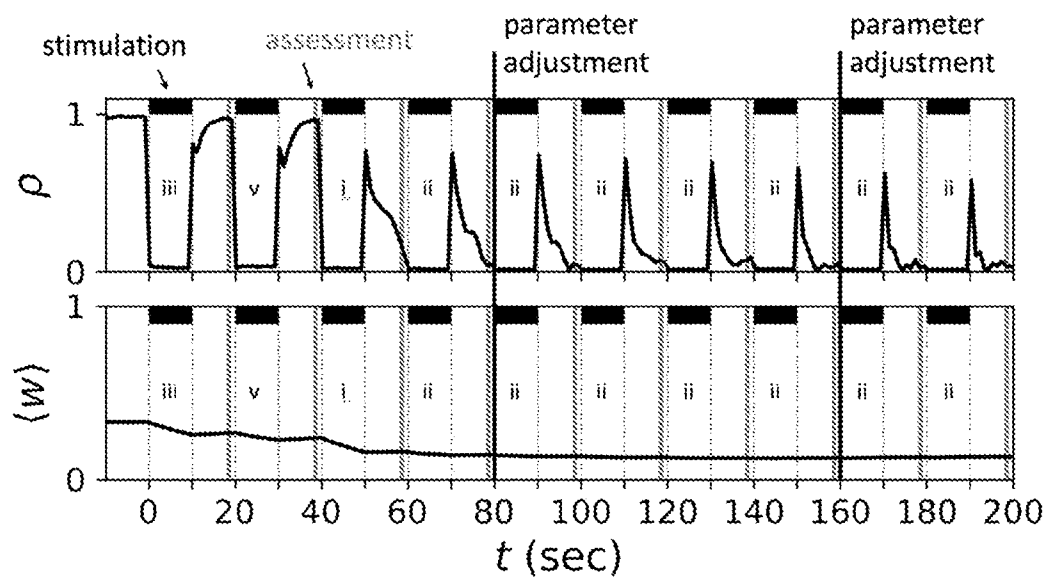


FIG. 103

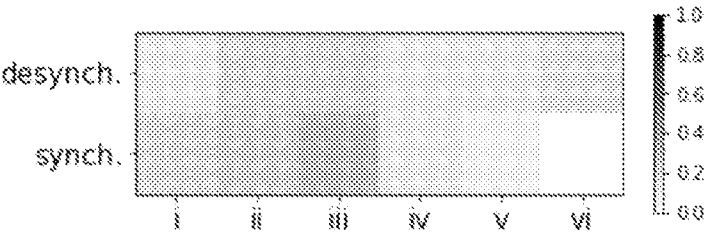


FIG. 104

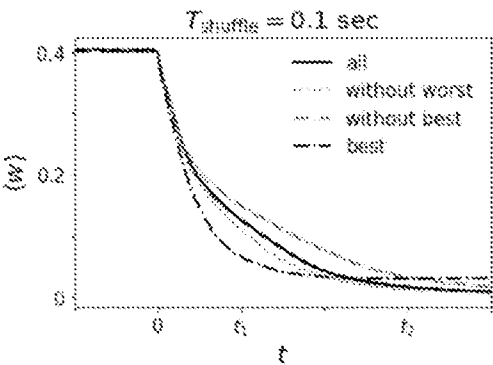


FIG. 105A

all	ON	ON	ON	ON	ON	ON
without worst	ON	ON	ON	ON	ON	OFF
without best	OFF	ON	ON	ON	ON	ON
best	ON	OFF	OFF	OFF	OFF	OFF
I-II-III-IV	I-II-IV-III	I-III-II-IV	I-III-IV-II	I-IV-II-III	I-IV-III-II	I-IV-III-II
II-III-IV-I	II-IV-III-I	III-II-IV-I	III-IV-III-I	IV-II-III-I	IV-III-III-I	IV-III-III-I
III-IV-I-II	IV-III-I-II	II-IV-I-III	IV-II-I-III	II-III-I-IV	III-II-I-IV	III-II-I-IV
IV-I-II-III	III-I-II-IV	IV-I-III-II	II-I-III-IV	III-I-IV-II	II-I-IV-III	II-I-IV-III

FIG. 105B

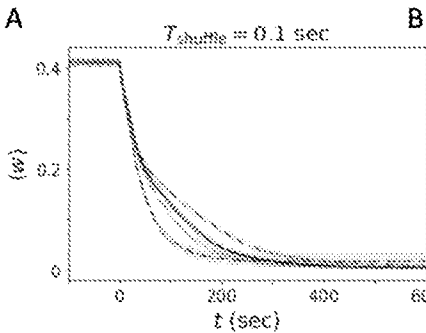


FIG. 106A

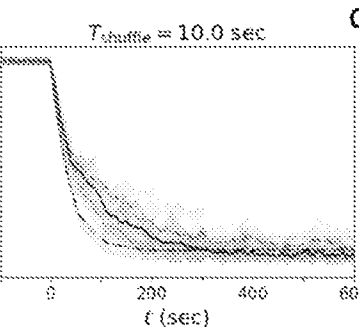


FIG. 106B

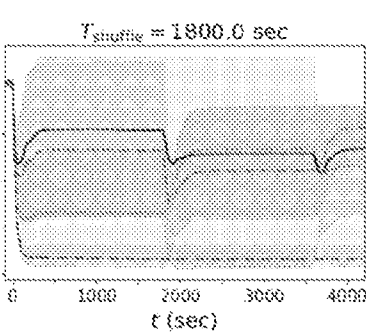


FIG. 106C

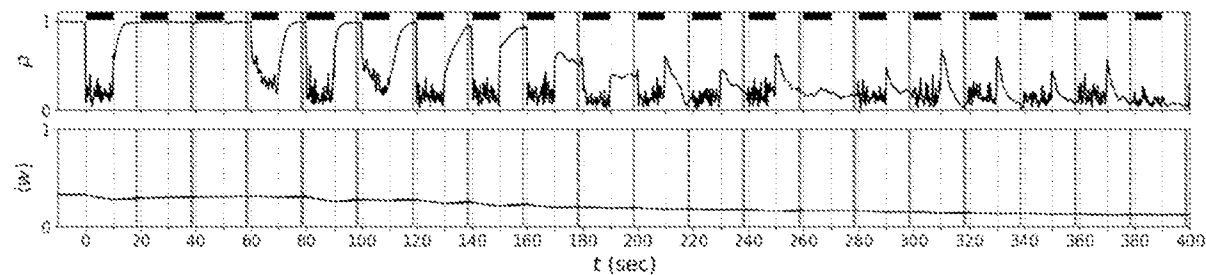


FIG. 107

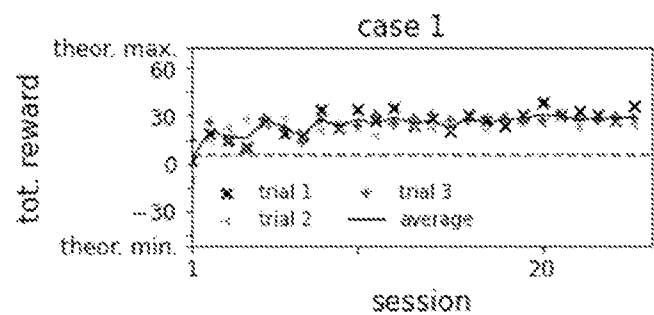


FIG. 108A

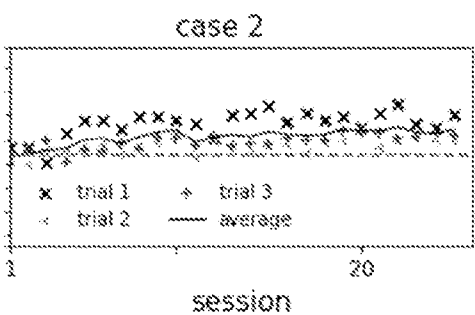


FIG. 108B

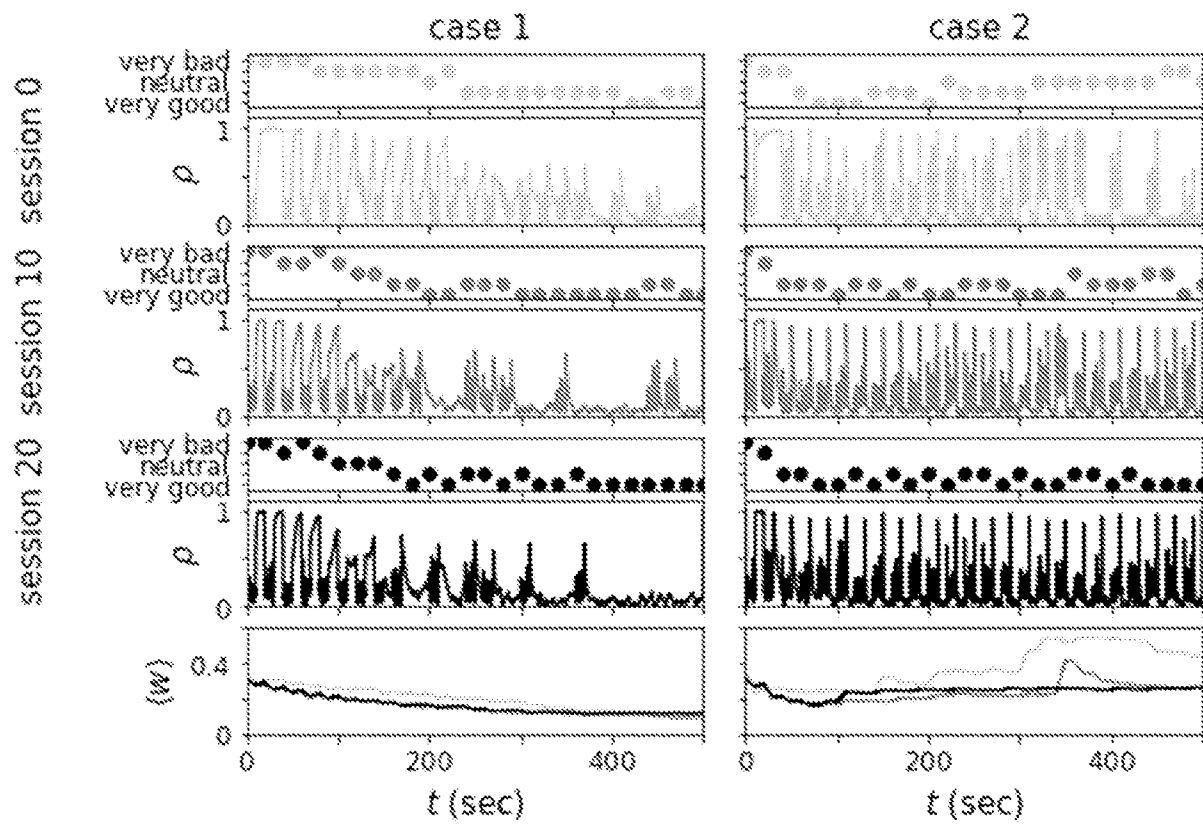


FIG. 109

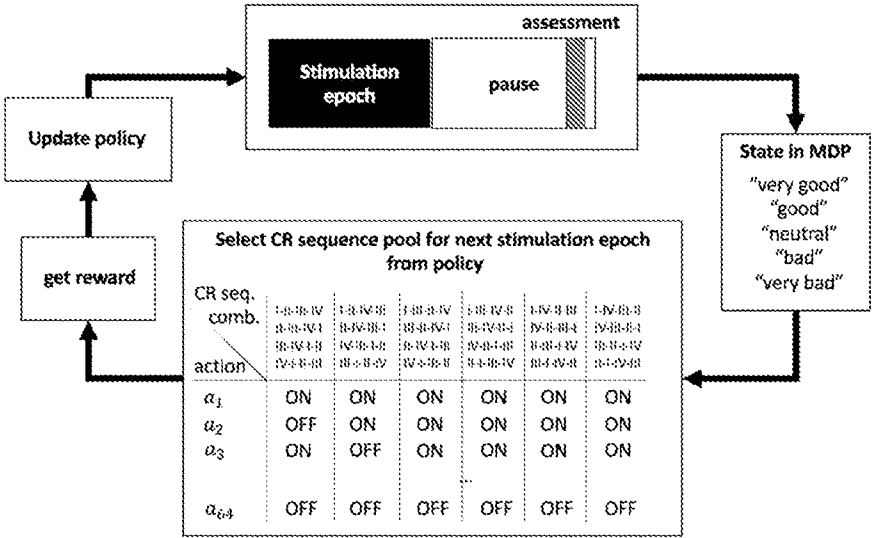


FIG. 110

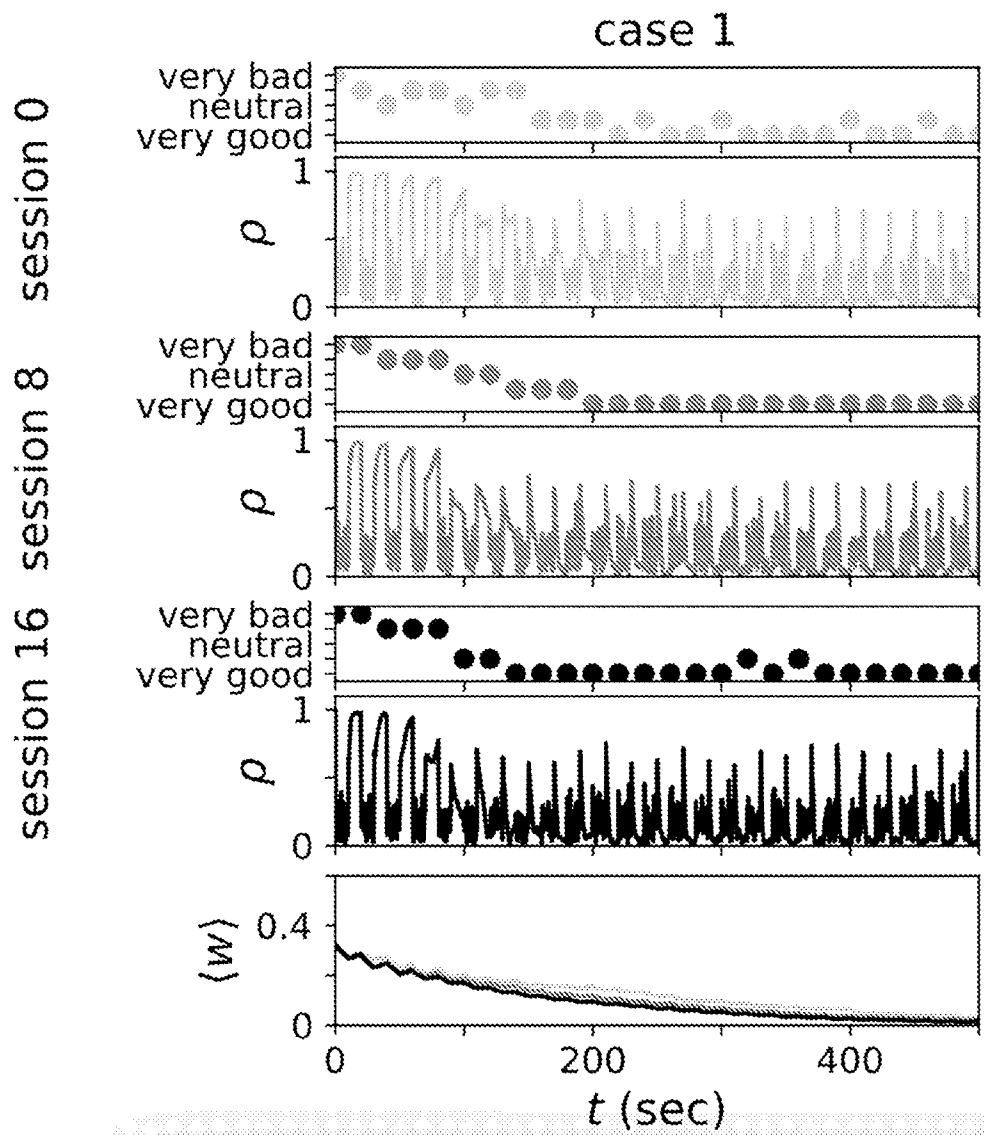


FIG. 111

FIG. 112A

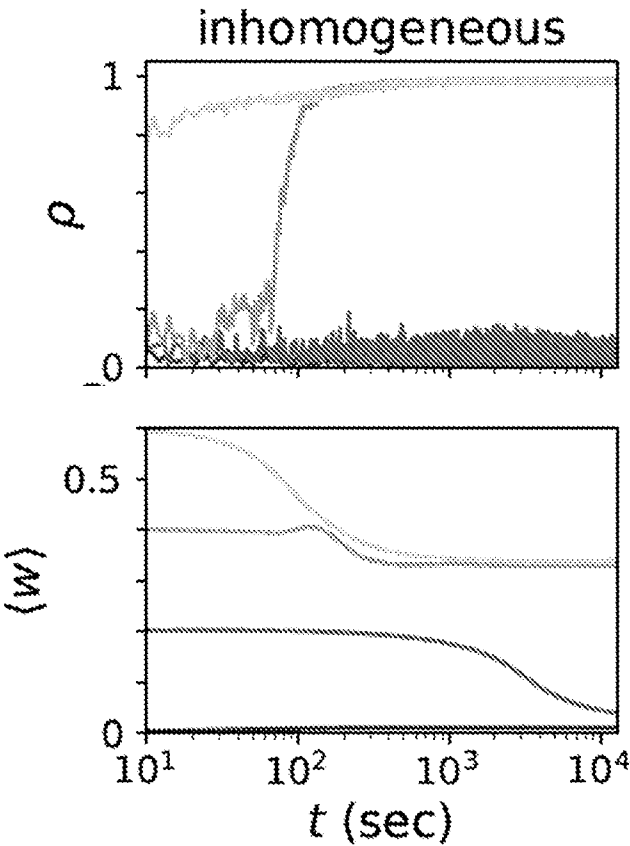


FIG. 112B

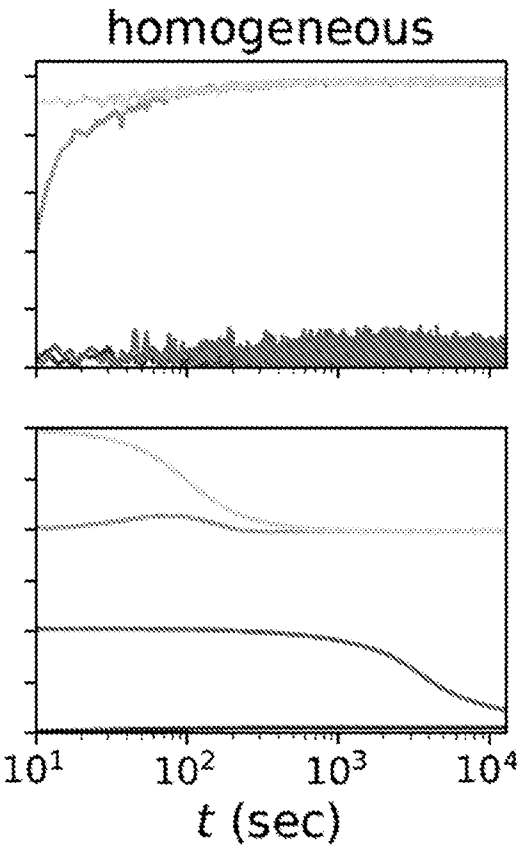


FIG. 112C

FIG. 112D

FIG. 113A

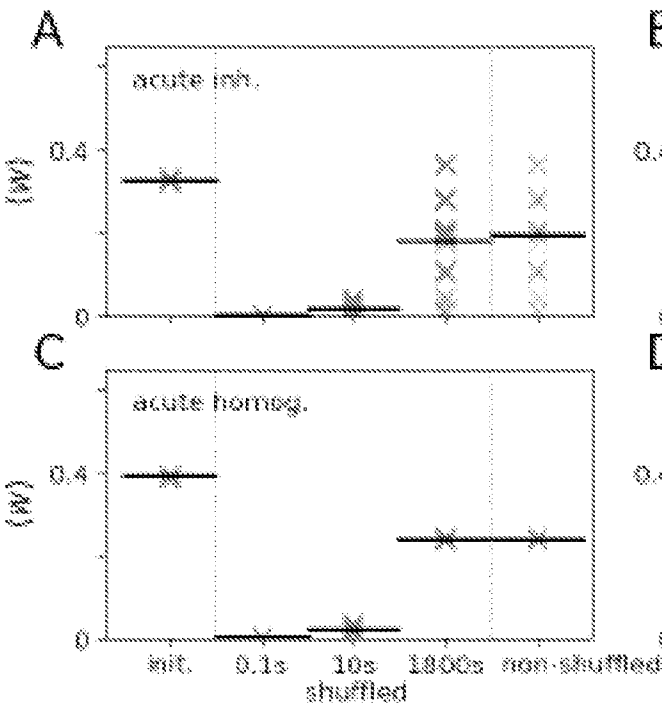


FIG. 113B

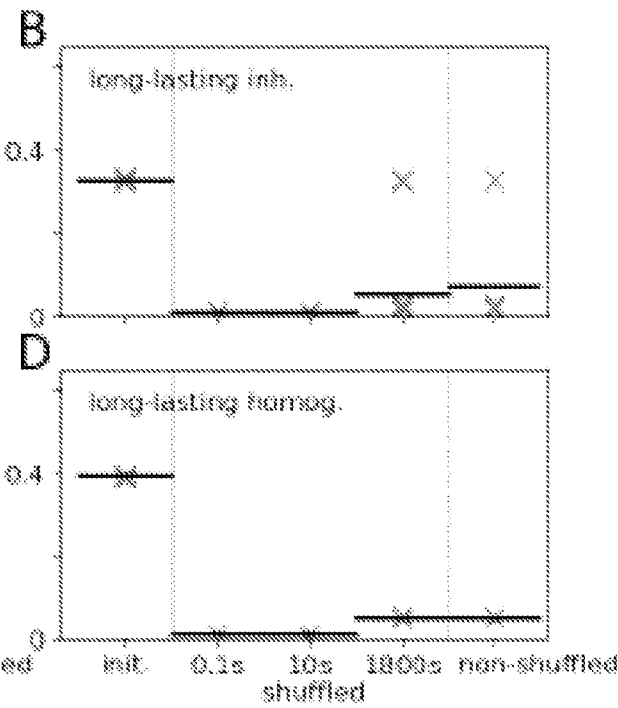


FIG. 113C

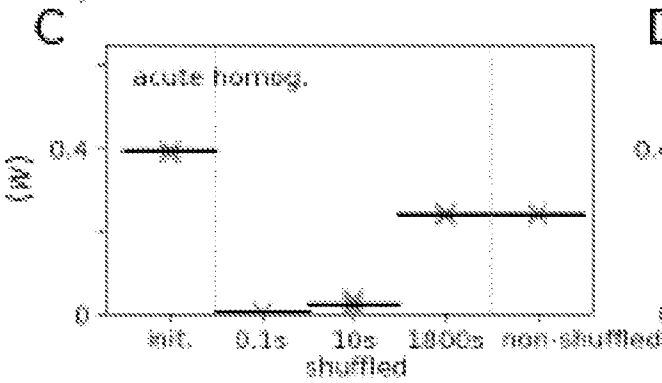
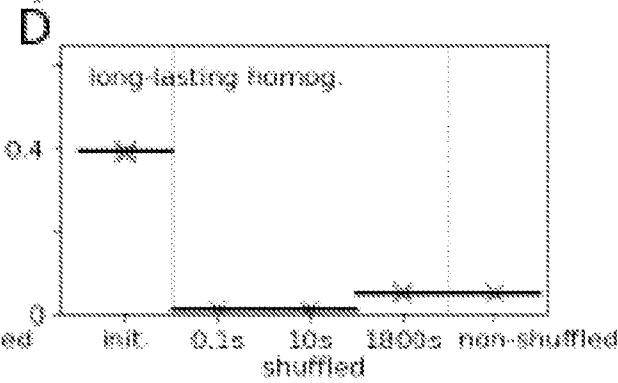


FIG. 113D



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/054294

A. CLASSIFICATION OF SUBJECT MATTER A61H 1/02(2006.01)i; A61N 1/36(2006.01)i; A61N 1/04(2006.01)i According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61H 1/02(2006.01); A61B 5/00(2006.01); A61H 1/00(2006.01); A61H 19/00(2006.01); A61H 23/02(2006.01); H01L 41/047(2006.01); H01L 41/08(2006.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean utility models and applications for utility models Japanese utility models and applications for utility models Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) eKOMPASS(KIPO internal) & Keywords: vibrotactile stimulation, non-disc-contactor, fingertip, housing		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2018-0212137 A1 (THE TRUSTEES OF DARTMOUTH COLLEGE et al.) 26 July 2018 (2018-07-26) See paragraphs [46]-[58], claims 6,15 and figures 7-12.	1,3,5,6 2,4,7,8
Y	US 2006-0015045 A1 (GARY A. ZETS et al.) 19 January 2006 (2006-01-19) See paragraphs [49],[61] and figures 1-3,6-7c.	2,4,8
Y	US 2013-0109914 A1 (JIMMYJANE, INC.) 02 May 2013 (2013-05-02) See paragraph [49] and figures 3,6-6D.	7
A	US 2014-0107542 A1 (SHAI Y. SCHUBERT et al.) 17 April 2014 (2014-04-17) See paragraph [68] and figures 2-7.	1-8
A	US 2023-0113744 A1 (NEOSENSORY, INC.) 13 April 2023 (2023-04-13) See paragraphs [48]-[50] and figures 3A-4.	1-8
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: “A” document defining the general state of the art which is not considered to be of particular relevance “D” document cited by the applicant in the international application “E” earlier application or patent but published on or after the international filing date “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) “O” document referring to an oral disclosure, use, exhibition or other means “P” document published prior to the international filing date but later than the priority date claimed “T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention “X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone “Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art “&” document member of the same patent family		
Date of the actual completion of the international search 02 April 2025		Date of mailing of the international search report 02 April 2025
Name and mailing address of the ISA/KR Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon 35208, Republic of Korea Facsimile No. +82-42-481-8578		Authorized officer LEE, Kang Ha Telephone No. +82-42-481-8463

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-8, drawn to a device for providing more effective vibrotactile stimulation comprising a vibrotactile mechanical stimulator and a housing.

Group II, claims 9-12, drawn to a method comprising providing a 3-(physiological) channel electrotactile stimulation.

Group III, claims 13-16, drawn to an apparatus comprising a contractor for providing electrotactile stimulation containing an inner and an outer electrode.

Group IV, claims 17-29, drawn to a method comprising providing stimuli that enable spatially more focal and/or shorter activation.

Group V, claims 30-39, drawn to a device to effectively reduce unwanted mechanical and proprioceptive stimulation while securely mounting controller and battery for a fingertip stimulation array.

Group VI, claims 40-42, drawn to a method comprising combining vibrotactile and electrotactile stimulation.

Group VII, claims 43, 44, drawn to a method and device that delivers non-invasive, sensory stimulation treatment in a way that counteracts habituation, including by increasing and rewarding a patient's attention, alertness, and curiosity level.

Group VIII, claims 45-48, drawn to a method comprising using hard- and firmware apparatuses to provide more precise vibrotactile and/or electrotactile stimulation by avoiding interhemispheric inhibition.

Group IX, claims 49-54, drawn to a method comprising automatically/autonomously calibrating relevant stimulation parameters.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-8**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US2024/054294

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				AU	2012-328612	A2	26 June 2014
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				WO	2012-116038	A3	27 December 2012
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				US	11497675	B2	15 November 2022
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				US	2022-0126094	A1	28 April 2022
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