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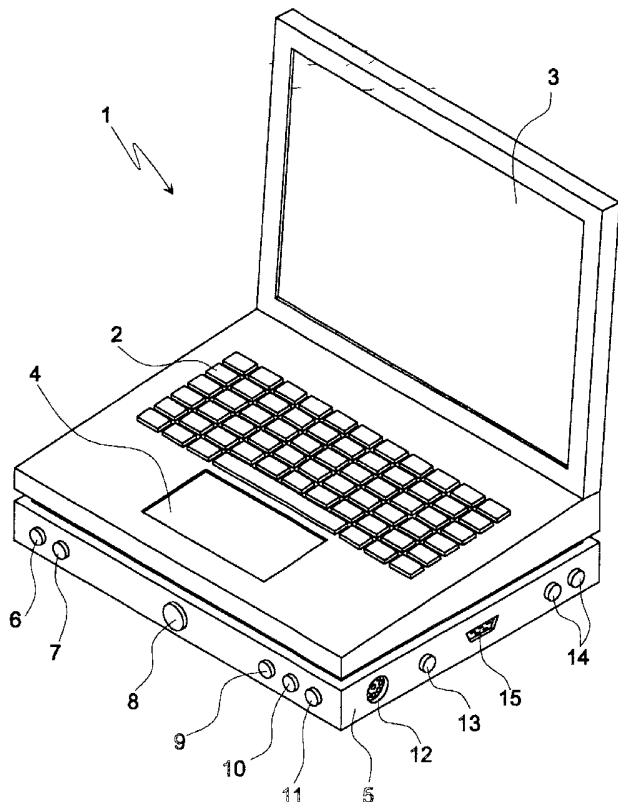
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(54) Title: SYSTEM DESIGNED TO GENERATE PROGRAMMED SEQUENCES OF STIMULI RESULTING IN CONTROLLED AND PERSISTENT PHYSIOLOGICAL RESPONSES IN THE BODY



(57) Abstract: The present invention refers to a system which induces controlled and persistent functional responses of the immune, nervous, vascular and muscular systems particularly to a system for the electric stimulation of a patient and to the relative method for providing electric stimuli to a patient. In an embodiment the system for the electric stimulation of a patient comprises: at least two electrodes able to be applied on the body of said patient; means for generating electric pulses between said at least two electrodes; said electric pulses have amplitude, width and frequency of repetition selectively variable; characterized by further comprising: a control system of said means for generating electric pulses; said control system controls said means for generating electric pulses in order to feed, automatically according to a prefixed succession, to said at least two electrodes a sequence of said electric pulses having variable width and repetition frequency in the time, said sequence include a first type of pulse having an asymmetric shape. (Fig. 2)



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"System designed to generate programmed sequences of stimuli resulting in controlled and persistent physiological responses in the body."

DESCRIPTION

5 The present invention refers to a system which induces controlled and persistent functional responses of the immune, nervous, vascular and muscular systems particularly to a system for the electric stimulation of a patient and to the relative method for providing electric stimuli to a patient.

10 The human organism has developed a complex regulatory system which involves hormonal, immune and nervous activities that have the fundamental assignment of maintaining the homeostasis, that is the internal equilibrium in rest and stress conditions. These systems, that interact between them, control the cardiovascular and respiratory systems and metabolism. For example the excessive hormones production due to the stress, such as
15 the hydrocortisone and the norepinephrine excesses alters the vasal walls, increases the arterial pressure, modifies the metabolism and the immunological defenses therefore it is harmful to the organism.

20 The consequence of the stress is hypertension, arteriosclerosis, obesity, and diabetes. In fact, the hydrocortisone excess due to the stress carries to an increase of the visceral fat, insulin excess, resistance to insulin, dislipidemia, increase of immunological substances such as the pro-inflammatory interleuchines L 1 - L 6, TNF that modify the immune defences of the body.

25 The complex control system, able to react to the stress is placed in the brain (hypothalamus). This system controls the autonomic and the hypothalamus -pituitary- adrenal systems. The immunological system is influenced by the aforesaid systems and at the same time it influences their function.

 Up today there are no pharmacological treatments for regulating stress diseases.

30 Nevertheless the Applicant has discovered that the application of

electric pulses with definite width, frequency and intensity may modify the response to the stress.

In view of the state of the art described, it is object of the present invention to induce controlled functional responses in the autonomic and central nervous systems, in the muscular, and immune and vascular systems
5 in order to reduce inflammation and to accelerate the recovery process and reduce the pain.

It is also object of the present invention to provide a system for the electric stimulation of a patient having a simple use without complicated preparation and reducing the possibility of errors that can cause serious
10 problem to the patient.

According to the present invention, such object is achieved by means of a system for the electric stimulation of a patient comprising: at least two electrodes able to be applied on the body of said patient; means for
15 generating electric pulses between said at least two electrodes; said electric pulses have amplitude, width and frequency of repetition selectively variable; characterized by further comprising: a control system of said means for generating electric pulses; said control system controls said means for generating electric pulses in order to feed, automatically according to a
20 prefixed succession, to said at least two electrodes a sequence of said electric pulses having variable width and repetition frequency in the time; said sequence include a first type of pulse having an asymmetric shape.

According to the present invention, such object is also achieved by means of a method for providing electric stimuli to a patient comprising the
25 phases of: choosing the body region where a therapy is to be applied by means of a tree structure; applying at least two electrodes on the body of said patient; generating electric pulses between said at least two electrodes;

feeding to said at least two electrodes, automatically according to a prefixed succession, a sequence of said electric pulses having width and
30 repetition frequency variable in the time.

Thanks to the present invention administering trains of pulses having temporal width variable in the time and with different pulse shapes, allows the effect to be not short-lived but long lasting. Such effect is even increased by repeating pulses at variable frequencies.

5 The long-lasting effects of the therapy seem due to a reset of the immunological and neuro-endocrine functions, which means that a new equilibrium is reached. For example vasal obstruction caused by arteriosclerosis induces an ischemic stress, the administration of precise fréquences of pulses re-establish a normal microcircle function, the pain
10 and the cutaneous lesions regress and general conditions of the patient improve. As the administration of stimuli is able to control haemorrhage this suggests that the sequences action is not due to a simple increase or decrease of the local flow, but, to a reset of the central regulating systems.

 Selecting the wanted therapy by means of a tree scheme on the
15 computer it allows to simplifying the application procedure. A further simplifying of the procedure and reduction of errors is obtained thanks to the showing of the electrode connection points on the computer.

 The features and the advantages of the present invention will be made more evident by the following detailed description of a particular
20 embodiment, illustrated as a non-limiting example in the annexed drawings, -wherein:

 Figure 1 shows a system for the electric stimulation of a patient according to the present invention;

 Figure 2 shows a block scheme of the electronic circuits of a system for
25 the electric stimulation of a patient according to the present invention;

 Figures 3a, 3b and 3c show some waveforms of electric pulses according to the present invention;

 Figure 4 shows a graph of the amplitude of a signal picked on the palm of the hand, at the varying of the time before the application of a base
30 sequence;

Figure 5 shows a graph of the spectral power of the signal of figure 4;

Figure 6 shows a graph of the spectral power of a signal picked on the palm of the hand after the application of a base sequence.

5 All the results described are reached because the apparatus object of the present invention is able to send sequences of selective and specific pulses to nerves, vessels, muscles and immune system.

At the same time the present invention reaches a new equilibrium of the neuro-immune-endocrine functions which allows the therapeutic effect to be persistent.

10 The electric and/or magnetic stimulation of the nervous system "in vivo" activates the nervous functions. Such activation may be performed in any central or peripheral area of the body.

Functional nerve activation occurs only when the following conditions are met:

15 a) currents superior to excitation threshold should be applied for the various topographical districts and subject to wide variations, as related to prior functional activity;

b) specificity of the functional response in relation to the size of the stimulated area, to the functional specialisation of the stimulated area, to the
20 direction of the stimulus, to the anatomical connections of the stimulated nervous-area, the latter condition must take into account the general properties of the pulse propagation through the nervous fibres and the synapses;

c) relationship between the stimulus characteristics (width, intensity,
25 frequency, shape of the pulse) and the conditions of the nervous tissue at the moment of the stimulation.

The exploitation of these properties in the last 70 years has permitted to improve the techniques of both clinical and experimental nervous system investigations arousing many physiological questions and demonstrating
30 functional changes in human pathology.

The idea of using the nervous system for inducing functional responses with a therapeutic purpose has given place to different approaches, which go from the electro-convulsive therapy in psychiatric contexts, to the electric stimulation of the nervous peripheral system with healing purpose (recovery of the muscular trophism and of the segmentary strength after nerve damage), to the insertion of stereotactics stimulators in proximity of specific neuronal circuits for activating or inhibiting sourcing of noise (for instance the electrostimulation of basal ganglia for extrapyramidal disorders and vagal nerve stimulation for epilepsy). Many of these applications are no longer experimental but are becoming standard therapeutic practices.

One major functional component of the nervous system is the so-called autonomic, or vegetative. Its knowledge is exponentially growing from its initial simple conception, based on Sherrington's reflex model, the physiology of the autonomous nervous system is today progressively invading other fields of medicine for its complexity and pervasivity; besides nervous regulation of the extracellular environment, inflammatory and immune response, local vasoconstriction or dilatation, and other vital functions: oxygenation, nutrition and reproduction, the innervation of a complex multi-cellular system participates to co-ordination of the endocrine activity, to the processes of cellular differentiation, and in general to the adaptation of the organism to life.

Therefore, it is clear that the perspective of modulating the activity of the autonomic nervous system through direct stimulation, similarly to what is currently done with somatic nervous system, would open boundless possibilities in the therapy of many illnesses.

The present invention refers to a neuromuscular electric-stimulator based on frequency modulation which evokes electric potentials on tissue cell membranes.

The first general property on which this machine bases its function is that each excitable tissue (nerve or muscle) responds to electric stimulation

according to an intensity-duration curve (I.D.).

The curve that derives is characteristic for each tissue: the higher is the tissue excitability, the more the I.D. curve shifts to the left. In the past these principles were used to evaluate the degree of muscle and nerve lesions.

5 This property is extensible to all biological tissues, i.e. for every type of tissue exists an I.D. curve describing its response to electric stimulation.

For instance, to stimulate a nervous fibre, being the ID curve shifted to the left, the adequate stimulus has short duration, while, at equal intensity, a smooth muscle will be stimulated for a longer duration to obtain the same
10 response. Less excitable tissues, like the connective tissue, will be elicited at higher intensity and longer duration.

The second general property is that a weak stimulus evokes a low membrane potential stimulation while the same stimulus repeated frequently become more intense due to a temporal summation of membrane potential.

15 Also the second property of excitable tissues physiology (nerve and muscle), can be extended, as a general property, to all biological membranes.

The combination of the two properties allows substituting in the I.D. scale, intensity values with frequency values. In this way curves of
20 frequency-duration (F.D.) similar to those of intensity- duration (I.D.) can be obtained.

Another important property of this machine is the information system used, consisting in sequences of high fidelity synchronised digital signals selected for their action on major functional component of the autonomic
25 nervous system.

Autonomic activity may be measured through the analysis of spectra obtained from recording heart beat, blood pressure, galvanic skin response, pupillar motility in response to postural change, psycho-physical stress, pain, etc.). Other methods to evaluate the autonomic system comprise: sympatho-
30 cutaneous reflexes, gastro-intestinal motility recording, urine bladder

motility, the analysis of micro-circle with laser-doppler flow and of the late cortical potentials after laser stimulation.

Despite of many methods do not enjoy wide standardisation, their combined use allows to quantitatively and reliably assess autonomic system functions, without considering that the microneurography, even if expensive
5 and relatively invasive, allows the direct recording of the peripheral electric activity related to autonomic functions.

Now with reference to the figure 1, that shows a system for the electric stimulation of a patient in accordance to the present invention, it is possible
10 to note a computer 1 preferably portable, composed of a body having a keyboard 2, a screen 3, and means for the movement of the cursor 4. To the computer 1 is associated a container 5 that contains the circuits devoted to the generation of the electric pulses.

The container 5 comprises a lamp or led 6 indicating that the therapy is
15 in course, a lamp or led 7 indicating that the therapy is over; a knob 8 for increasing or decreasing the value of the intensity of the pulses; a starting button 9 of the therapy, a stopping button 10 of the therapy, and a button 11 for interrupting the sound of a buzzer 12 which is used to indicate the stopping of the therapy. The container 5 also comprises a tap 13 for the
20 connection of a controlling device comprising the commands for a remote control system, one or more exit taps 14 able to connect the electrodes to the system, and a connector 15, preferably of the RS 232 type to allow the connection of the circuits placed in the container 5 to the computer 1.

Now with reference to the figure 2, that shows a block scheme of the
25 electronic circuits of a system for the electric stimulation of a patient according to the present invention it is possible to note the computer 1 connected through an interface 21 preferably serial of the RS 232 type, to a microprocessor (CPU) 22. The microprocessor 22 is preferably of the type Z180.

30 To the microprocessor (CPU) 22 is connected to a RAM memory 23 of

32Kb, to a FLASH memory 24 of 128 Kb, to a digital analogical converter (D/A) 25, to a timer circuit 26, and to a circuit of input/output 27.

The digital analogical converter (D/A) 25 and the timer circuit 26 are connected, in turn, to a pulse generator 28, which furnishes the pulses to the terminals 30, that are, in turn connected, to the exit taps 14. An oscillator 29 is connected to the pulse generator 28.

The lamp 6, the lamp 7, the knob 8, the buttons 9, 10, 11, and the buzzer 12 are connected to the input/output circuit 27. The knob 8 could be alternatively replaced with two buttons, one for incrementing the amplitude of the pulse and one for decrementing the amplitude of the pulse.

The microprocessor 22 receives from the computer 1 the sequence of the therapy that must perform and the abilitation to the therapy execution. It sends to the computer 1 an indication if the therapy is in course or in stand by, the remaining time and the number of the phase in course, the time remained for the completion of the therapy, the present value of the intensity of the pulses, and an indication if the therapy is over.

The microprocessor 22 interfaces and interacts with the other circuits by means of an internal bus. The FLASH memory 24 contains the program code for the management of the circuits and for the execution of the selected therapy. The RAM memory 23 is that in use for the operations of the microprocessor 22 and it will contain the parameters of the selected therapy.

The timer circuit 26 generates the sequence of the pulses. For each phase of the therapy, it receives from the microprocessor 22 the parameters of the pulses that must be generated (kind of waveform, pulse timing, repetition frequency, and total duration of the train of pulses) and it provides them at logical digital level, coherently to the received parameters, toward the pulse generator 28. The pulses are sent out only during the phase in which the therapy is in course. At the end of a possible temporary interruption, the pulses will restart from the point of therapy interruption.

The digital analogical converter (D/A) 25 generates the reference

voltage for the intensity value of the pulse. This voltage could vary between 0 and 3.6 Vdc and it is used for generating the amplitude voltage of the pulse. It could be increased or decreased at pleasure through the knob 8, only during the phase of therapy in course. At the beginning of the therapy, this voltage always starts from 0 Vdc and is brought again to this value at the end of the therapy and to the request of a temporary interruption. At the restart the voltage of the therapy could be brought again to the wanted value always through the knob 8.

The oscillator 29 generates a fixed frequency signal that is used as base synchronism for the generation of the pulses.

The pulse generator 28 generates the pulses to be sent to the patient. The amplitude of the voltage of the pulses comes from the digital analogical converter (D/A) 25.

The therapy is selected on the computer 1 following driven tree schemes. The therapy previously chosen is started through the starting button of the therapy 9. The operator will have the possibility of regulating the amplitude of the pulses and of suspending the therapy temporarily. The apparatus is connected to the patient through one or two cables ending each with two button clips. The clips are connected to two adhesive electrodes to be set on the body of the patient in opportune points.

The patient will have the possibility of verifying on the screen 3 the type of therapy in course, the remaining minutes for the completion of the therapy, and the value of the amplitude of the pulses.

On the computer 1 are stored all the names and the references of the scheduled therapies, the sequences of the scheduled therapies, all the instructions and the messages for performing the therapies, and all the figures of the human body showing the connection points of the electrodes to the patient for the execution of the scheduled therapies. The human body is composed of two figures in which is seen from before, and behind.

On the figures are indicated by red and black flashing points the points

where connect the electrodes. The sequences of the scheduled therapies are stored on the computer 1, in the form of tables comprising, for each phase of the therapy, the pulse kind, the pulse timing, the repetition frequency and the duration of the phase.

5 From the keyboard 2 it is possible to interrogate the computer 1 to get the instructions how to operate on the apparatus, how to connect the patient to the apparatus, how to choose the therapy, and how to get information on the developing out of the therapy.

10 In particular, at the turn on of the computer 1, a menu with a list of the main body regions (for example spine, leg, arm, etc.) where is possible to apply a therapy is showed in a window. Chosen one body region, a sub menu with a detailed list of the part of said body region (for example cervical spine, lumbar spine) will be shown. Chosen the interested part of the body, a further sub menu with a list of different kind of therapy, (for
15 example back injury, left and right chronic contracture, trapezium contracture, chronic pain with parestesia) will be shown. On another window, where different views of the human body are shown, the points where the electrodes must be applied are indicated. Then, pushing a button available on the computer the therapy is enabled. That is, the computer will
20 load the table with the pulse sequence associated at the required therapy. On two window of the computer the duration of the therapy and the voltage intensity of the pulses will shown. The amplitude of the pulse should be regulated, through the knob 8, a little under the pain threshold of the patient.

25 Placed the electrodes at the positions indicated on the computer, the therapy can start pressing the starting button 9.

On the window showing the duration of the therapy, the time will be decremented accordingly, until the time will be zero and the therapy will be finished.

30 We refer now to the figures 3a, 3b and 3c that show the preferable waveforms of single electric pulses according to the present invention. They

are preferably negative pulse, of preset amplitude, having a trailing edge with a fall time T_0 , a width T_1 in which the signal remains at the low level and a leading edge having a rise time T_2 . Such a pulse has a width, taken at 50 % of the trailing edge and at 50 % of the leading edge, equal to T_i .

5 It is possible to note that the pulse of figure 3c has a leading edge that changes slope. In this case there is a first slope of the leading edge for about the 70% of the whole edge and a second slope less steep than the first slope for the remaining (30%) of the leading edge. The width of the leading edge T_2 is so divided in T_3 and T_4 .

10 The pulses of figures 3a, 3b and 3c represent preferred pulse shapes not limitative. For instance the slope change, of the pulse of figure 3c, could be around at 90% of the whole trailing edge or there could be also the trailing edges with two slopes.

15 Now it is possible to define an example of at least three principal types of pulse with different shapes.

A pulse of alpha type with a waveform as in figure 3a and for example the following characteristics $T_0=10\ \mu\text{s}$, $T_1=20\ \mu\text{s}$, $T_2=10\ \mu\text{s}$ and $T_i=30\ \mu\text{s}$. This pulse has a symmetric waveform.

20 A pulse of beta type with a waveform as in figure 3b and for example the following characteristics $T_0=10\ \mu\text{s}$, $T_1=20\ \mu\text{s}$, $T_2=20\ \mu\text{s}$ and $T_i=35\ \mu\text{s}$. This pulse has an asymmetric waveform.

25 A pulse of gamma type with a waveform as in figure 3c, (change of slope at 70% of the whole edge) and for example the following characteristics $T_0=10\ \mu\text{s}$, $T_1=30\ \mu\text{s}$, $T_2=20\ \mu\text{s}$, $T_3=10\ \mu\text{s}$, $T_4=10\ \mu\text{s}$ and $T_i=42\ \mu\text{s}$. This pulse has a particular asymmetric shape of the leading edge: it has a first slope of width T_3 and a second slope of width T_4 .

30 The timing of above can be changed according to the necessity. For example, another interesting and useful pulse has a waveform as in figure 3c, (change of slope at 70% of the whole leading edge) having the following characteristics $T_0=1\ \mu\text{s}$, $T_1=1\ \mu\text{s}$, $T_2=21\ \mu\text{s}$, $T_3=20\ \mu\text{s}$, $T_4=1\ \mu\text{s}$ and $T_i=$

16.2 μ s. The width T3 can also change between 5 and 80 μ s, and T0, T1 and T4 can be further reduced. In this way a pulse having the shape of an upside down rectangular trapezium, or in other words, a negative rectangular asymmetric pulse is obtained. In this way the pulse reach almost
5 immediately the maximum voltage prefixed; therefore the voltage decrease partially, of about 70 % in the time T3, and then return almost immediately at 0 Volt.

The choice of the correct pulse shapes is very important in the treatment of the different pathologies. It has been found that, depending on the
10 particular therapy, some pulse shapes give better result then others. Further, improvement regarding the long lasting effects can be obtaining alternating, in same therapy, the type of the pulse shape.

Other important issues are the accurated choice of the pattern of the pulse width variations in the time and the variation of the pulse repetition
15 frequency.

Stimulation frequencies differentiated for different pathologic problems have been obtained; for instance sequences for the control of pain, sequences for vessel contraction/vessel dilation, sequences for the trophic-immune regulation, sequences for muscle tone regulation.

20 The sequence for the control of pain, have been defined with a sequence having a length of 15 minutes. In this sequence the beta type pulses with $T_i = 25 \mu$ s, ($T_0 = 10 \mu$ s, $T_1 = 10 \mu$ s, $T_2 = 20 \mu$ s) and alpha type pulses with $T_i = 20 \mu$ s, ($T_0 = 10 \mu$ s, $T_1 = 10 \mu$ s, $T_2 = 10 \mu$ s) are alternated (overlapped) with intermittent rhythm:

- 25 A. stimulation of gamma type at 100 Hz for 5 minutes,
 B. overlap of beta type at 55 Hz for the last 3 minutes of A,
 A. stimulation of gamma type at 100 Hz for 5 minutes,
 B. overlap of beta type at 55 Hz for the last 3 minutes of A,
 C. overlap of alpha type at 15 Hz for the last 2 minutes of A,
30 A. stimulation of gamma type at 100 Hz for 5 minutes.

In this way a particular pulse sequence has been created, interlacing two different kinds of pulses.

For the control of the vascular contraction/dilation, low frequency stimulation of beta type is used with different length on which trains of
 5 alpha stimuli at high and increasing frequency are added, for a total of 15 minutes. In this case, the alpha type pulse has the following characteristics $T_i = 20 \mu s$, ($T_0 = 10 \mu s$, $T_1 = 10 \mu s$, $T_2 = 10 \mu s$), and the beta type pulse has the following characteristics $T_i = 25 \mu s$, ($T_0 = 10 \mu s$, $T_1 = 10 \mu s$, $T_2 = 20 \mu s$).

- 10 A. stimulation of beta type at 1.5 Hz, for 3 minutes,
- B. stimulation of beta type at 15 Hz, for 3 minutes,
- A. stimulation of beta type at 1.5 Hz, for 3 minutes,
- C. overlap on B of alpha type stimuli at 40 Hz, for the last 15 seconds,
- D. overlap on B of alpha type at 70 Hz, for the last 5 seconds,
- A. stimulation of beta type at 1.5 Hz, for 3 minutes,
- 15 B. stimulation of beta type at 15 Hz, for 3 minutes.

For the regulation of tissue trophism and immunity, the length of treatment is 16 minutes. In this case, the alpha type pulse has the following characteristics $T_i = 20 \mu s$ ($T_0 = 10 \mu s$, $T_1 = 10 \mu s$, $T_2 = 10 \mu s$).

- 20 A. stimulation of alpha type a at 1.5 Hz, for 2 minutes,
- B. stimulation of alpha type at 15 Hz, for 2 minutes,
- A. stimulation of alpha type at 1.5 Hz, for 2 minutes,
- D. stimulation of alpha type at 15 Hz, for 2 minutes,
- B. stimulation of alpha type at 1.5 Hz, for 2 minutes,
- A. stimulation of alpha type at 15 Hz, for 2 minutes,
- 25 D. stimulation of alpha type at 1.5 Hz, for 2 minutes,
- B. stimulation of alpha type at 15 Hz, for 2 minutes.

It is possible for this therapy, instead of the alpha type pulses as above, it is possible use the gamma type pulses having the following characteristics $T_0 = 1 \mu s$, $T_1 = 1 \mu s$, $T_2 = 21 \mu s$, $T_3 = 20 \mu s$, $T_4 = 1 \mu s$ and $T_i = 16.2 \mu s$.

30 The sequences for muscle tonification with a length of 4,30 minutes, has

been defined as follows. In this case, the alpha type pulse, has the following characteristics $T_i = 20 \mu s$ ($T_0 = 10 \mu s$, $T_1 = 10 \mu s$, $T_2 = 10 \mu s$), the beta type pulse, has the following characteristics $T_i = 25 \mu s$ ($T_0 = 10 \mu s$, $T_1 = 10 \mu s$, $T_2 = 20 \mu s$), and the gamma type pulse, has the following characteristics $T_i =$
 5 $16.2 \mu s$ ($T_0 = 1 \mu s$, $T_1 = 1 \mu s$, $T_2 = 21 \mu s$, $T_3 = 20 \mu s$, $T_4 = 1 \mu s$).

- A. stimulation of gamma type at 100 Hz, for 2 minutes,
- B. overlap on A of beta type at 5 Hz, in the last minute of A,
- C. overlap on B, of stimulation of alpha type at 30 Hz, in the last 30 seconds of B,
- 10 D. stimulation of alpha type at 40 Hz, for 15 seconds,
- E. stimulation of alpha type at 70 Hz, for 10 seconds,
- F. stimulation of alpha type at 80 Hz, for 5 seconds,
- A. stimulation of gamma type at 100 Hz, for 2 minutes,
- Pause of 10 seconds.

15 The whole A, B, C, D, E, F, A and pause sequence, could be repeated up to three times in succession.

The sequence for muscle contraction and de-contraction regulation having a length of 1 –5 minutes has been defined as follows.

A continuous sequence of gamma type pulses ($T_0 = 10 \mu s$, $T_1 = 30 \mu s$,
 20 $T_2 = 20 \mu s$, $T_3 = 10 \mu s$, $T_4 = 10 \mu s$ and $T_i = 42 \mu s$), overlapping alpha pulses ($T_0 = 10 \mu s$, $T_1 = 20 \mu s$, $T_2 = 10 \mu s$ and $T_i = 30 \mu s$) after 30 seconds of the started sequence, at 1 Hz for 15 seconds, then the alpha pulses increase their repetition frequency from 1 Hz to 10 Hz for 5 seconds, then the alpha pulses increase repetition frequency from 10 Hz to 40 Hz for 5 seconds. That is, in
 25 this case, the repetition frequency is increased in linear (or also in logarithm) way meanwhile the sequence is running.

The sequences of pulses defined in these therapies are to be considered only examples, non limitative, as they are subject to variations of form and width of the pulses and of the repetition frequency according to the various
 30 pathologies and conditions.

In the treatment of the different pathologies is possible to repeat different or equal sequence types to form a complete course.

For example, in the chronic lumbosacral pain treatment a preferred order of the sequences is the following. At each sequence is associated a reference to be distinguished and for clarity.

A vascular sequence V1, an anti-inflammatory sequence A1, two vascular sequence V1+V1, a modified vascular sequence V2, a modified vascular sequence V3, a modified vascular sequence V4, a vascular sequence V1, an anti-inflammatory sequence A1, a decontracting sequence D1, a modified decontracting sequence D2, a modified decontracting sequence D3, a sequence acting on the nervous system N1.

For example, in the tendinitis treatment a preferred order of the sequences is the following.

A vascular sequence V1, a modified vascular sequence V2, a modified vascular sequence V3, a decontracting sequence D1, a modified vascular sequence V2, a modified decontracting sequence D2, a modified decontracting sequence D3, a modified decontracting sequence D4, a modified vascular sequence V2, a modified vascular sequence V3, a modified vascular sequence V4, a modified sequence acting on the nervous system N3.

For example, in the sciatic and crural neuralgia treatment a preferred order of the sequences is the following.

A modified anti-inflammatory sequence A2, an anti-inflammatory sequence A1, a modified sequence acting on the nervous system N2, a vascular sequence V1, an anti-inflammatory sequence A1, a vascular sequence V1, an anti-inflammatory sequence A1, a modified vascular sequence V2, a modified vascular sequence V3, a decontracting sequence D1, a modified decontracting sequence D2, a modified decontracting sequence D3, a modified sequence acting on the nervous system N2.

In this way, the stimulation with different kind of sequences allows

modifying body functions, it strengthens the feedback with the central regulating system and provides effective and persistent therapy.

The pattern variations of duration L , width W , and repetition frequency F of the above sequences are substantially the followings.

5 The decontracting sequences D1, D2, D3 start with pulses having short width ($W \approx 20 \mu s$), short repetition frequency ($F \approx 1-4$ Hz) and short duration ($L \approx 20$ s), then the width become wider than before ($W \approx 40 \mu s$), the repetition frequency increase linearly ($F \approx$ from 4 to 60 Hz) and the duration decrease ($L \approx 2$ s).

10 The vascular sequences V1, V2, V3, V4 have pulses with cyclic (sinusoidal) width ($W \approx 10-40 \mu s$), repetition frequency substantial fixed ($F \approx 3$ Hz) with some short peak ($F \approx 10-30$ Hz), and short duration ($L \approx 2$ s).

15 The sequences acting on the nervous system N1, N2, N3 start with pulses having short width ($W \approx 20 \mu s$), short repetition frequency ($F \approx 1-4$ Hz) and variable duration ($L \approx 2-30$ s), then the width is decreased ($W \approx 10 \mu s$), the repetition frequency is increased a lot ($F \approx 100-4000$ Hz) and the duration is reduced ($L \approx 2$ s).

20 A sequence of stimuli, as the sequences acting on the nervous system N1, is performed on the palm of the hand at 110 Hz of frequency and $T_i = 40 \mu s$, has been noted by recording the late components of the over maximal excitation of the median nerve with cutaneous electrodes.

25 A preliminary recording has been performed with the classical orthodromic technique, on the palm of the hand, and the signal obtained is the one of figure 4 (average of 80 responses). This signal has been subjected to analysis of spectrum frequency and the results are shown in figure 5, where it has been reported the signal power at different frequencies.

In the spectrum, constant peak components may be distinguished (recordings effected on five healthy subjects).

30 Applying the base sequence on the palm of the hand, with frequency 100 Hz and width $T_i = 40 \mu s$, an evident alteration of the frequency spectrum

was found as shown in figure 6.

It can be seen that the power of the peak was greatly increased and the de-synchronised components reduced. In other words the application of the stimulatory sequence seems to re-organize the frequency of the pulses from the afferent nerves and to group the bands of frequency into more synchronised values.

In the above examples forms of pulses and specific sequences of stimulations have been defined to treat some pathological conditions. They are to be considered only as a non-limitative example and susceptible of modifications in accordance to various pathologic conditions. For instance, the specific sequence for the modulation of the vessel motility presents a series of frequency increases smaller than the ones used in muscles motility, a longer periods of gamma pulses, frequency increases in the first phase and by periodical changes of repetition frequency in the second final period.

CLAIMS

1. System for the electric stimulation of a patient comprising:
at least two electrodes able to be applied on the body of said patient;
means for generating electric pulses between said at least two
5 electrodes;
said electric pulses have amplitude, width and frequency of repetition
selectively variable;
characterized by further comprising:
a control system of said means for generating electric pulses;
10 said control system controls said means for generating electric pulses in
order to feed, automatically according to a prefixed succession, to said at
least two electrodes a sequence of said electric pulses having variable width
and repetition frequency in the time, said sequence include a first type of
pulse having an asymmetric shape.
- 15 2. System for the electric stimulation of a patient according to claim 1
characterized by comprising a second type of pulse having a symmetric
shape.
3. System for the electric stimulation of a patient according to claim 1
characterized in that said first type of pulse has a shape of an upside down
20 rectangular trapezium.
4. System for the electric-stimulation of a patient according to claim 1
characterized in that said sequence of said electric pulses comprises a first
type of pulse and a second type of pulse, said first type of pulse having a
width greater then the width of the second type of pulse.
- 25 5. System for the electric stimulation of a patient according to claim 1
characterized in that said sequence of said electric pulses having width
variable in the time, allow the re-arrangement of the components of
frequency (synchronization) of the afferent nervous with an amplification of
frequency bands.
- 30 6. System for the electric stimulation of a patient according to claim 1

characterized by further comprising a computer which has stored on it a plurality of sequence each one associates to a related therapy, and each therapy is selectable by means of a tree structure presented on the screen of said computer.

5 7. System for the electric stimulation of a patient according to claim 1 characterized by providing to said patient a plurality of sequences of said electric pulses that constitute a therapy.

 8. System for the electric stimulation of a patient according to claim 7
10 characterized in that said plurality of sequence comprises decontracting sequences, vascular sequences, sequences acting on the nervous system according to a prefixed succession.

 9. Method for providing electric stimuli to a patient comprising the phases of:

15 choosing the body region where a therapy is to be applied by means of a tree structure;

 applying at least two electrodes on the body of said patient;

 generating electric pulses between said at least two electrodes;

20 feeding to said at least two electrodes, automatically according to a prefixed succession, a sequence of said electric pulses having width and repetition frequency variable in the time.

 10. Method according to claim 9 characterized in that the phase of choosing the body region where a therapy is to be applied, comprises the phase of choosing the body region among a first list of body region shown on a display.

25 11. Method according to claim 10 characterized in that after the phase of choosing the body region among a first list of body region shown on a display, there is the phase of choosing a body part within the region previous chosen, in a second list showed on said display.

30 12. Method according to claim 11 characterized in that after the phase of choosing said body part within the region previous chosen, there is the

phase to choose the kind of the therapy wanted showed in a second list on said display.

13. Method according to claim 9 characterized in that the phase of applying at least two electrodes on the body of said patient comprises the phase of showing on said display the points of the body where the electrodes must be placed.

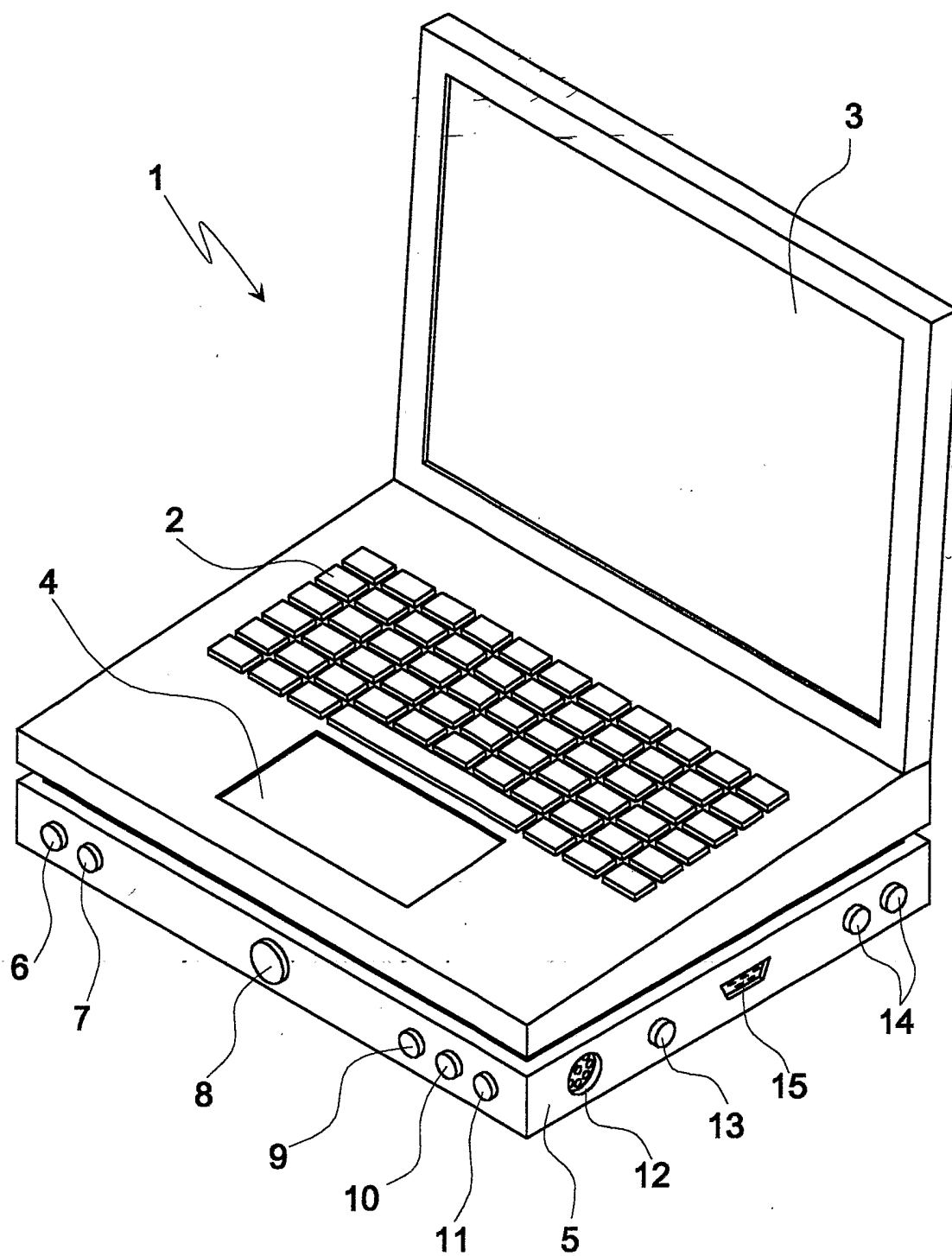


Fig.1

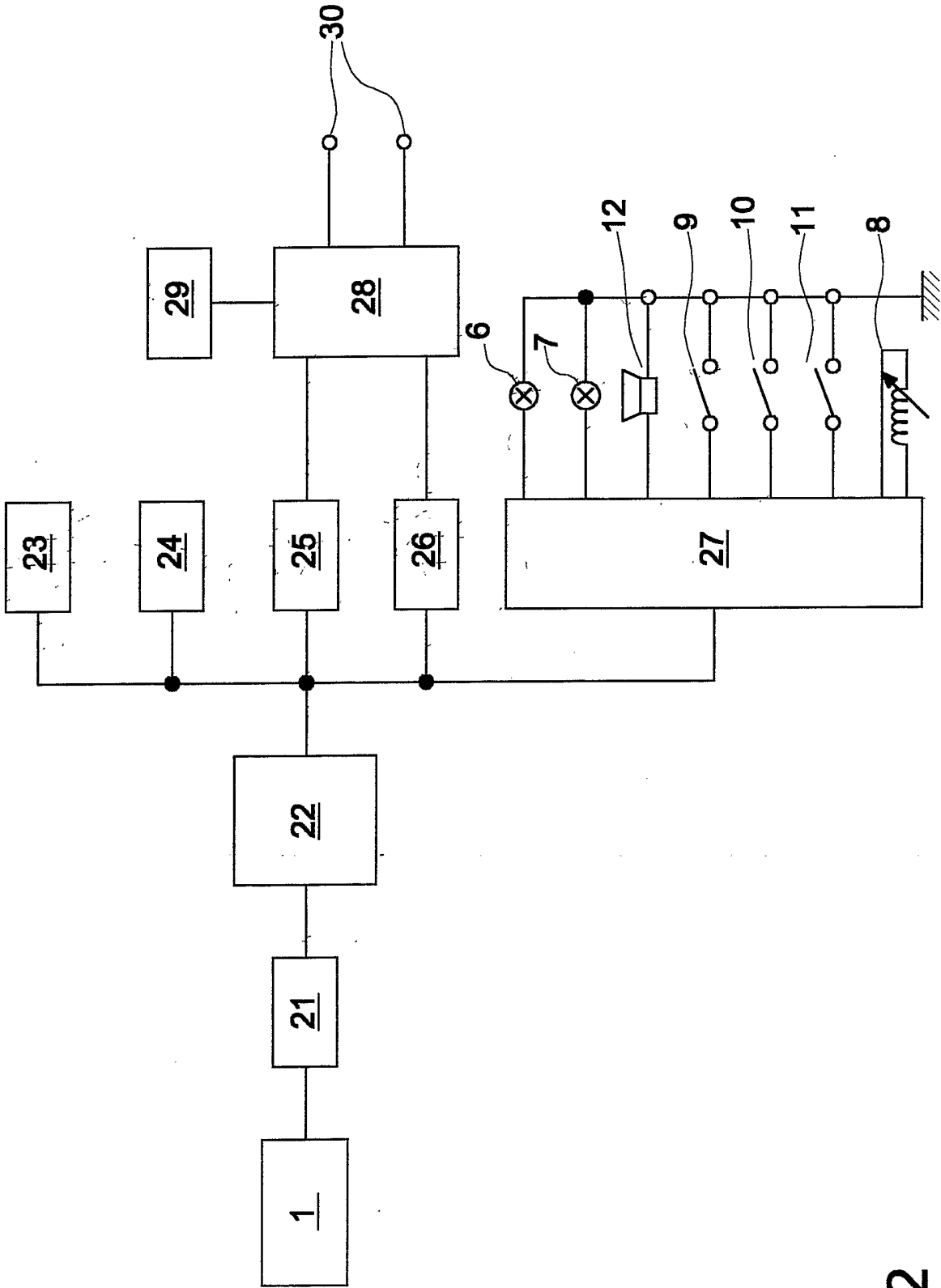


Fig.2

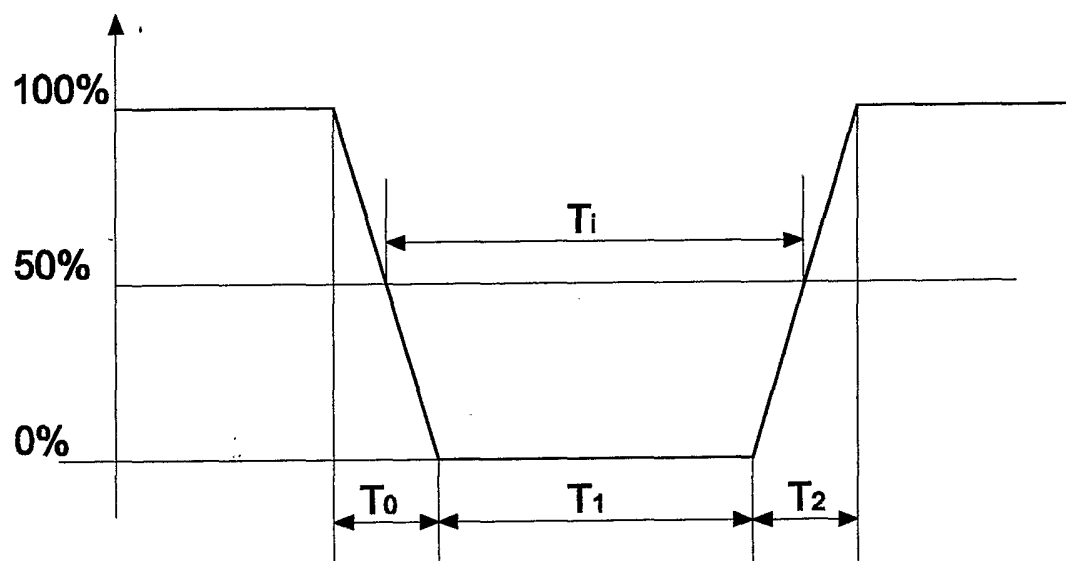


Fig.3a

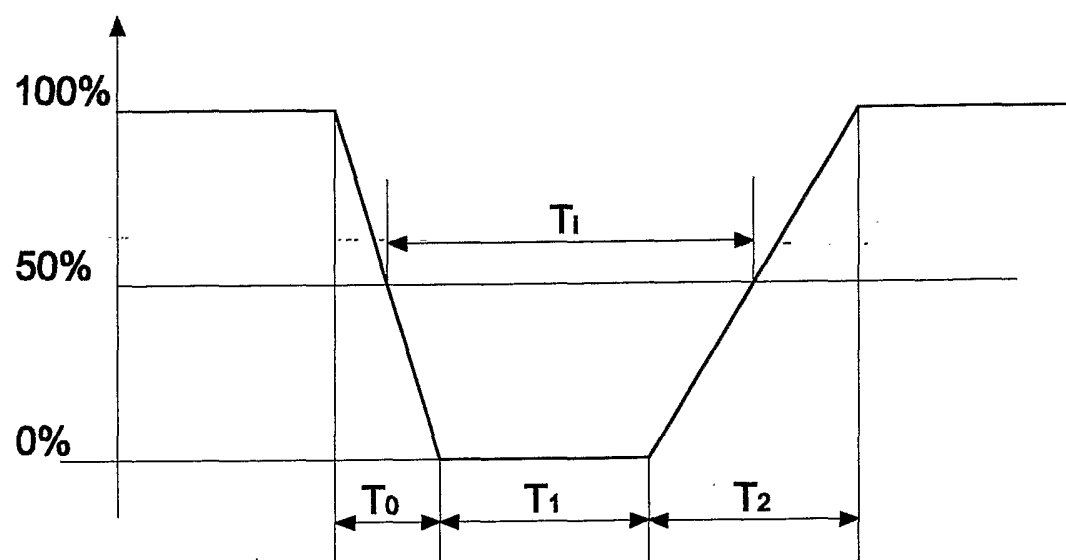
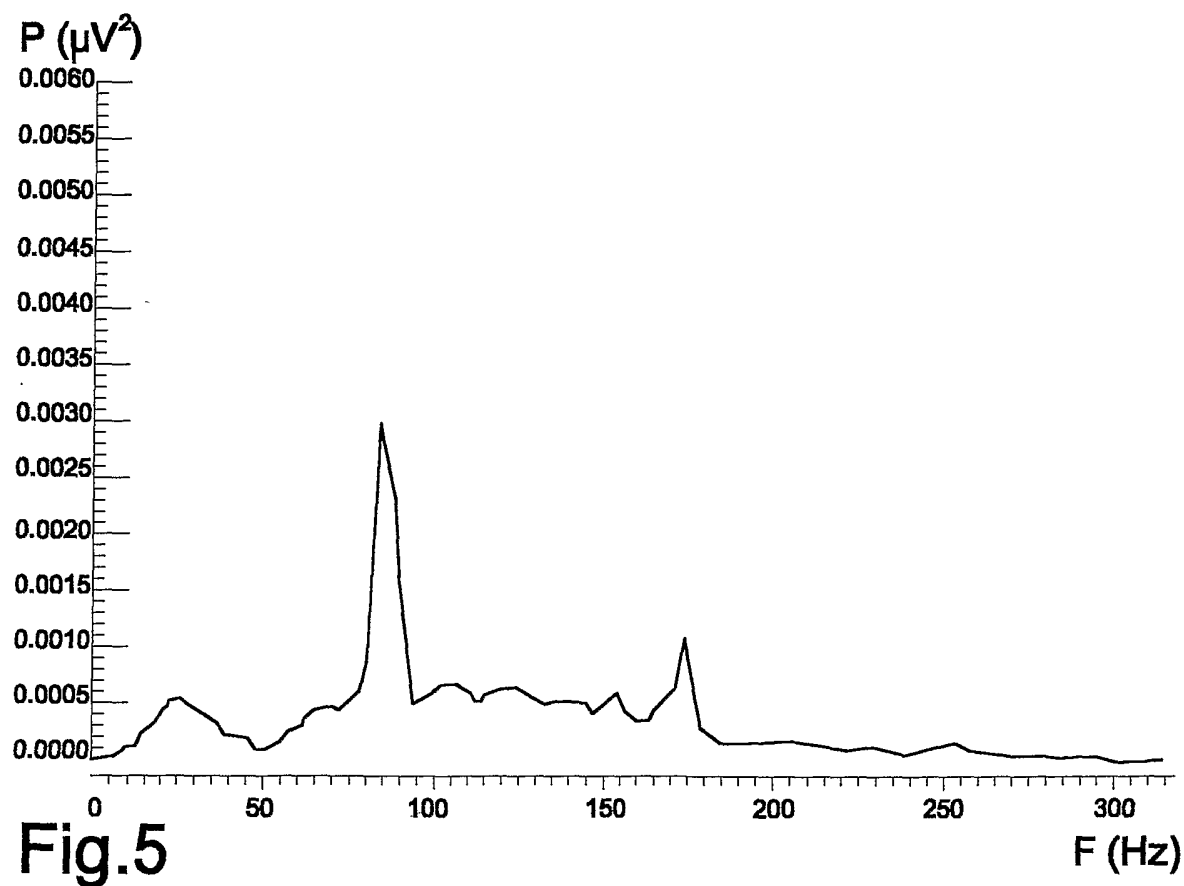
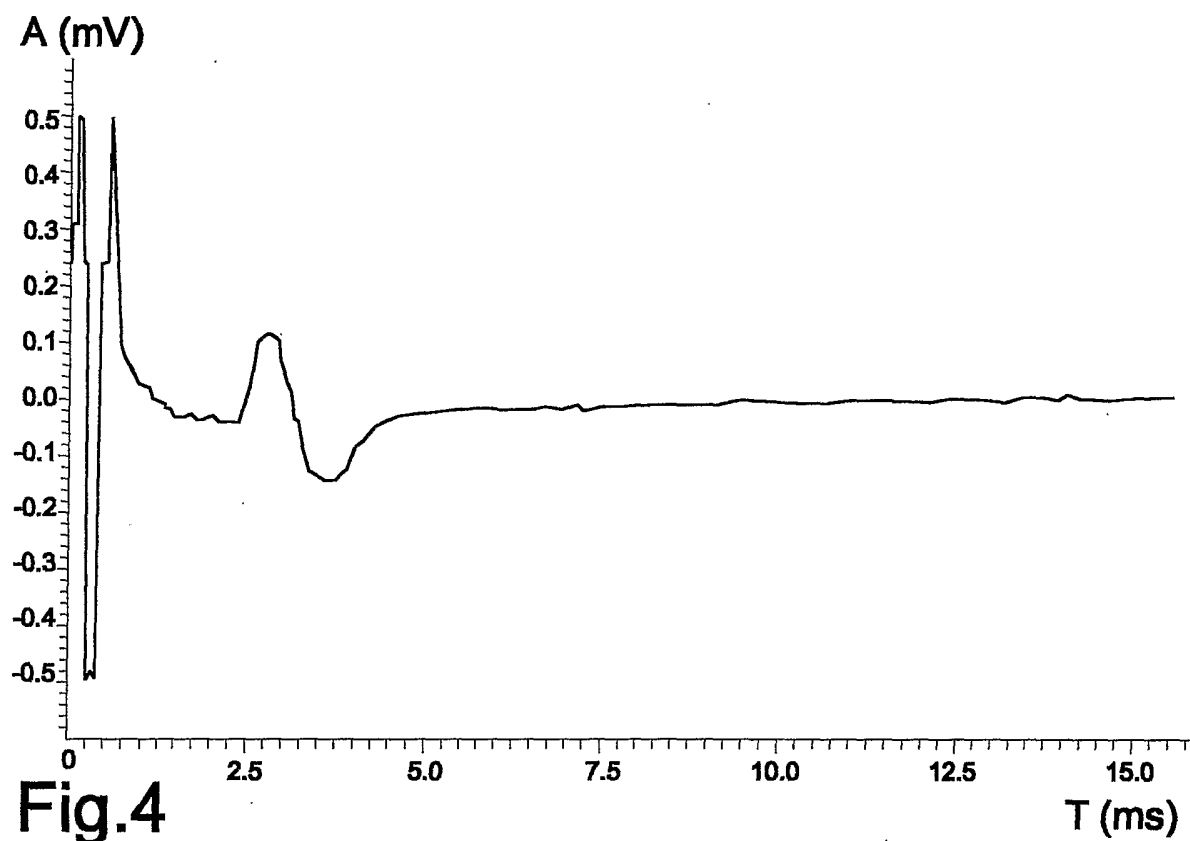


Fig.3b



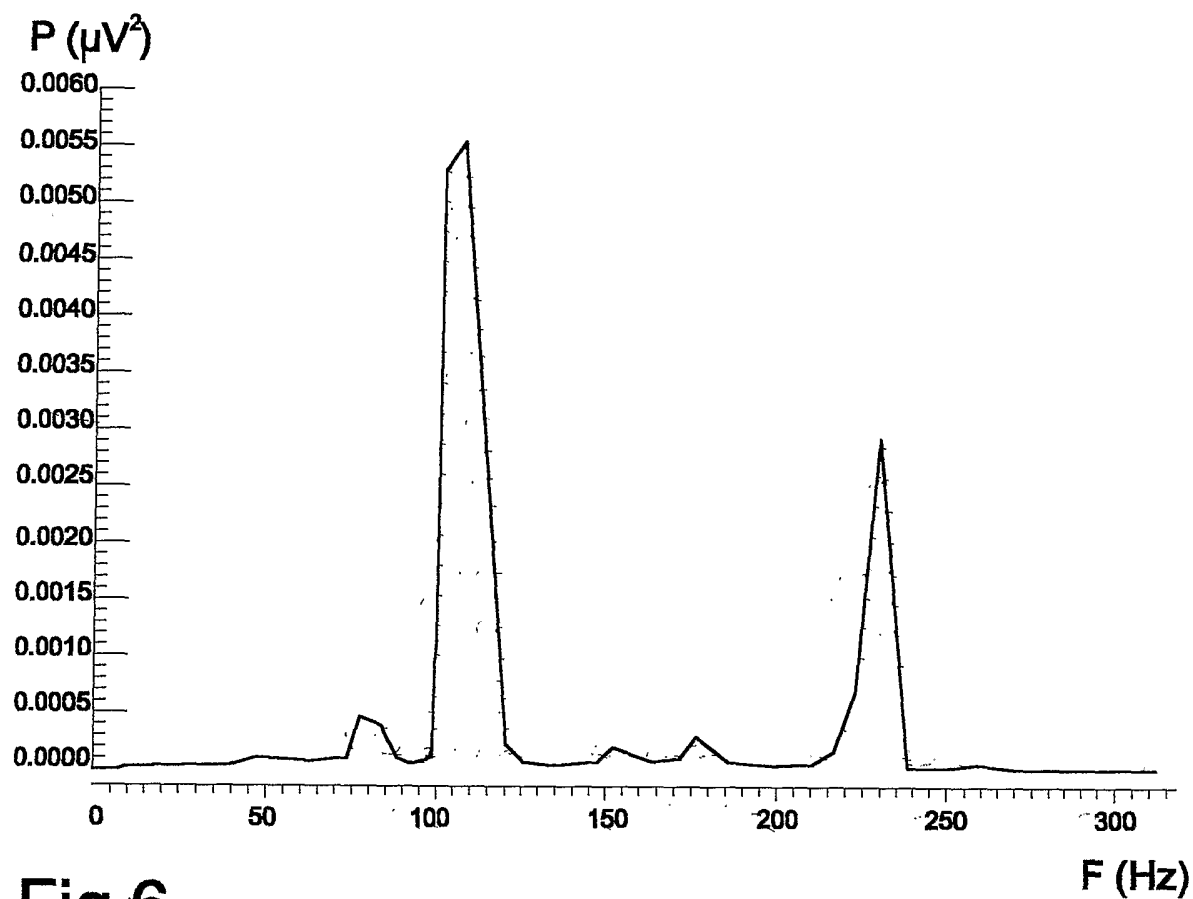


Fig.6

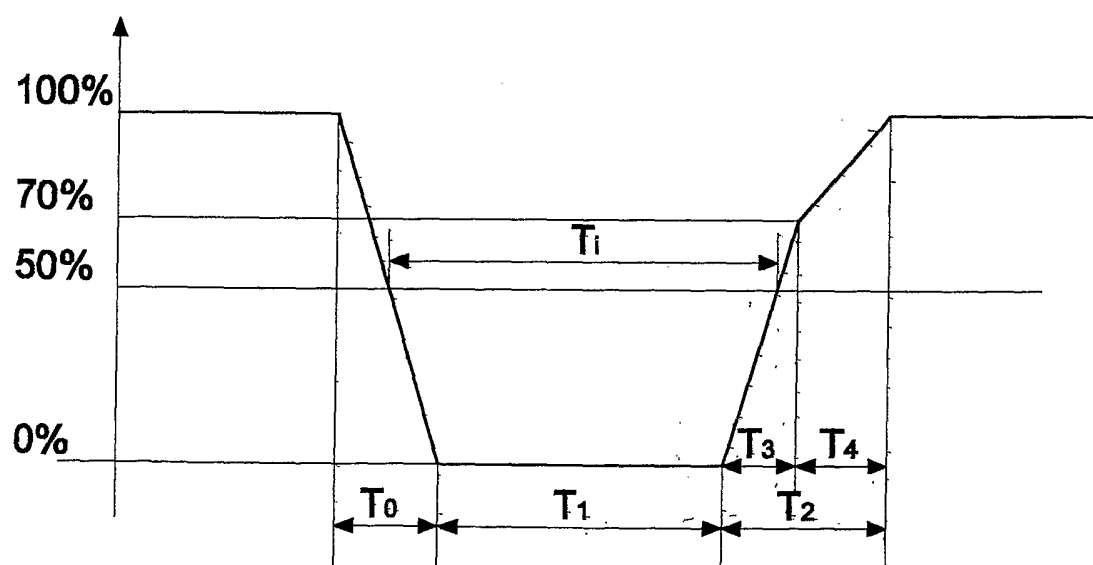


Fig.3c

INTERNATIONAL SEARCH REPORT

Internat	Application No
PCT/NL	03/00245

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61N1/36		
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) IPC 7 A61N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 524 321 A (STAODYNAMICS INC) 27 January 1993 (1993-01-27) the whole document	1
Y	---	3
X	EP 0 290 126 A (ADVANCE KK) 9 November 1988 (1988-11-09) the whole document	1,3,4
Y	---	
Y	US 4 431 000 A (MACEACHERN A WALTER ET AL) 14 February 1984 (1984-02-14) the whole document	3
A	---	
	US 5 097 833 A (CAMPOS JAMES M) 24 March 1992 (1992-03-24) the whole document	1,4

	-/--	
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document 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 17 November 2003		Date of mailing of the international search report 25/11/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Ferrigno, A

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/NL 03/00245

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 171 881 A (CODMAN & SHURTLEFF) 19 February 1986 (1986-02-19) the whole document ----	1,4
A	WO 01 87411 A (LOCKHEED CORP) 22 November 2001 (2001-11-22) abstract page 5, line 15 - line 22 ----	1
A	US 3 881 495 A (PANNOZZO ANTHONY N ET AL) 6 May 1975 (1975-05-06) the whole document -----	3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 03/00245

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **9-13**
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/NL 03/00245

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0524321	A	27-01-1993	US 5184617 A CA 2043813 A1 EP 0524321 A1 US RE35987 E	09-02-1993 06-12-1991 27-01-1993 08-12-1998
EP 0290126	A	09-11-1988	JP 6004096 B JP 63234975 A AU 593727 B2 AU 1354288 A CA 1324637 C DE 3854018 D1 DE 3854018 T2 EP 0290126 A2 KR 9003283 B1 US 4895153 A	19-01-1994 30-09-1988 15-02-1990 29-09-1988 23-11-1993 27-07-1995 02-11-1995 09-11-1988 14-05-1990 23-01-1990
US 4431000	A	14-02-1984	NONE	
US 5097833	A	24-03-1992	NONE	
EP 0171881	A	19-02-1986	BR 8502686 A DK 252585 A EP 0171881 A1 ES 8703745 A1 ES 8800610 A1 JP 60261470 A	12-02-1986 06-12-1985 19-02-1986 16-05-1987 01-02-1988 24-12-1985
WO 0187411	A	22-11-2001	AU 6164001 A CA 2408929 A1 EP 1284787 A2 WO 0187411 A2	26-11-2001 22-11-2001 26-02-2003 22-11-2001
US 3881495	A	06-05-1975	CA 1020232 A1	01-11-1977