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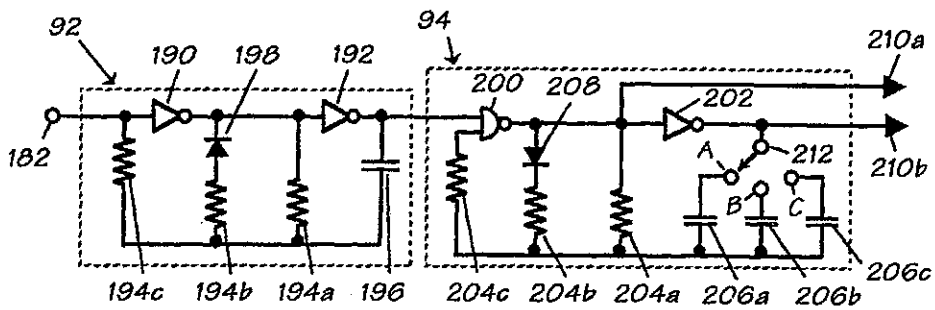
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(54) Title: APPARATUS AND METHOD FOR BIOELECTRIC STIMULATION, HEALING ACCELERATION AND PAIN RELIEF



(57) Abstract: An apparatus and method for generating an electrical signal for use in biomedical applications, including two timing blocks for generating timing intervals T_1- T_7, an interconnection block for combining these intervals into an output signal having predetermined relationships among the intervals, an output block for transmitting the output signal to a load, and, optionally, a filter for removing unwanted frequency components from the output signal and an adjustment block for selecting from among a plurality of output signals with predetermined characteristics. The output is a repeating succession of a burst of rectangular waves, an equalizing pulse (if needed) to cancel net DC bias in applications for which it is not desired, and a rest period of no signal. In applications where net DC bias is desired, the equalizing pulse may be omitted and the remaining signal features superimposed on a DC potential.

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APPARATUS AND METHOD FOR BIOELECTRIC STIMULATION, HEALING ACCELERATION AND PAIN RELIEF

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a pulsed signal generator for biomedical applications. In particular, the present invention relates to a light-weight, compact pulsed signal generator that produces an output waveform based on at least four timing intervals T_1–T_4, more preferably, a waveform based on seven timing intervals T_1–T_7.

BACKGROUND ART

Injuries, infections and degenerative conditions are major sources of pain, inconvenience, expense, lost work (and leisure) time and diminished productivity. The problems associated with these conditions grow worse with age, since an injury which would heal quickly in a young, healthy person takes much longer in one who is older, in poor health, or both. In demographically-aging societies such as now seen in most of the industrialized nations, these social and economic impacts will become increasingly magnified over the course of the next several decades.

While it is difficult to estimate the total cost of such conditions—leaving aside their impact on quality of life—the total surely amounts to many billions of dollars per year in the United States alone. For example, between five and ten million United States residents suffer broken bones every year, with many of these cases involving multiple fractures. In a young, healthy patient, many fractures need to be immobilized in a cast for six weeks or more. Even after the cast is removed, the patient's activities are frequently restricted until the healed bone regains its full strength. In the elderly, in persons with poor health or malnutrition, in patients with multiple fractures, or in patients with conditions that impact healing processes, fractures heal more slowly. In some cases, the fractures do not heal at all, resulting in the conditions known as "nonunion" or "nonunion fracture" which sometimes persists for a lifetime.

As a result, an estimated quarter-million person-years of productivity are lost in the United States due to bone fractures alone. Similar statistics can be generated not only for other classes of traumatic injury, but also for chronic conditions such as osteoarthritis, osteoporosis, diabetic and decubitus ulcers, damaged ligaments, tendonitis, and repetitive stress injuries (including the conditions commonly known as "tennis elbow" and carpal tunnel syndrome).

Since the 1960s, it has been increasingly recognized that the human body generates a host of low-level electric signals as a result of injury, stress and other factors; that these

signals play a necessary part in healing and disease-recovery processes; and that such processes can be accelerated by providing artificially-generated signals which mimic the body's own in frequency, waveform and strength. Such "mimic" signals have been shown to have many effects in the body, including helping to direct mobile cells such as fibroblasts and macrophages to sites where they are needed (galvanotaxis) and causing the release of cell growth factors such as transforming growth factor beta (TGF-β) and insulin-like growth factor (IGF). The results can include more rapid healing of skin and muscle wounds, including chronic ulcers such as those resulting from diabetes; the mending of broken bones, including most nonunion fractures; the regrowth of injured or severed nerves; and the repair of tissues damaged by repetitive motion, as in tendonitis and osteoarthritis; and the reduction of swelling, inflammation, and pain, including chronic pain for which the usual drug-based treatments do not bring satisfactory relief.

Some of the body's signals, such as the "injury potential" or "current of injury" measured in wounds, are DC (direct current) only, changing slowly with time. It has been found that bone fracture repair and nerve regrowth are typically faster than usual in the vicinity of a negative electrode but slower near a positive one, where in some cases tissue atrophy or necrosis may occur. For this reason, most recent research has focused on higher-frequency, more complex signals often with no net DC component.

While most complex-signal studies to date have been performed on bone fracture healing, the commonality of basic physiological processes in all tissues suggests that the appropriate signals will be effective in accelerating many other healing and disease-recovery processes. Indeed, specific frequency and waveform combinations have been observed to combat osteoarthritis and insomnia, stimulate hair growth, reduce swelling and inflammation, fight localized infection, speed the healing of injured soft tissues including skin, nerves, ligaments and tendons, and relieve pain without the substituted discomfort of TENS (transcutaneous electric nerve stimulation).

Figs. 1A and 1B show a schematic view of a waveform 20 which has been found effective in stimulating bone fracture healing, where a line 22 (Fig. 1A) represents the waveform on a short time scale, a line 24 (Fig. 1B) represents the same waveform on a longer time scale, levels 26 and 28 represent two different characteristic values of voltage or current, and intervals 30, 32, 34 and 36 represent the timing between specific transitions. Levels 26 and 28 are usually selected so that, when averaged over a full cycle of the waveform, there is no net DC component. In real-world applications, waveform 20 is typically modified in that all voltages or currents decay exponentially toward some intermediate level between levels 26 and 28, with a decay time constant usually on the order of interval 34. The result is represented by a line 38 (Fig. 1C).

In a typical commercially-available device for treating fracture nonunions, interval 30 is about 200 μsec, interval 32 about 30 μsec, interval 34 about 5 msec, and interval 36 about 60 msec. Alternate repetition of intervals 30 and 32 generates pulse bursts 40, each of the

length of interval 34, separated by intervals of length 36 in which the signal remains approximately at level 28. Each waveform 38 thus consists of rectangular waves alternating between levels 26 and 28 at a frequency of about 4400 Hz and a duty cycle of about 85%. The pulse bursts are repeated at a frequency of about 15 Hz and a duty cycle of about 7.5%, alternating with periods of substantially no signal. The timing of such a signal can vary broadly, since the characteristics of signals generated by bone in vivo and in vitro depend on a number of factors, including but not necessarily limited to its type, size and mineral density, and the amount of stress and its rate of application. Hence, osteoblasts are believed to be able to respond to a range of signals which differ somewhat in waveform and frequency content.

However, tissues may respond differently to markedly different frequencies and waveforms. For example, the waveform of Figs. 1A–C is effective in speeding the healing of a bone fracture but much less so in slowing the progress of osteoporosis. On the other hand, a waveform 50 (Fig. 2) consisting of single pulses 52 of polarity 26 lasting approximately 350–400 μsec each, alternating with intervals 54 of polarity 28 at a frequency of approximately 60–75 Hz, can slow or even reverse osteoporosis but has little effect on fracture repair. Again, the exact waveform and frequency for each application may vary.

The signal intensity may also vary; indeed, more powerful signals often give no more benefit than weaker ones, and sometimes less. This paradoxical relationship is shown schematically in Fig. 3, where a line 60 represents the magnitude of the healing effect at various signal intensities. For a typical signal (such as the signal of Figs. 1A–C), a peak effectiveness 62 typically falls somewhere between one and ten $\mu A/cm^2$, and a crossover point 64 at about a hundred times this value. Beyond point 64, the signal may slow healing or may itself cause further injury. Similar responses are seen in other biological processes that are responsive to electrical stimulation, including cell division, protein and DNA synthesis, gene expression, and intracellular second-messenger concentrations. For example, while conventional TENS can block pain perception with a relatively strong signal, much as a jamming signal blocks radio communication, it can also lead to progressively worsening injury since the pain's warning function has also been defeated.

The important factors for most healing applications appears to be that the high-frequency signal appears in bursts, separated by intervals of quiet or no signal, and that the waveform within these bursts is itself asymmetric. Results appear to be better when frequency components above about 50 KHz are filtered out, giving transition times on the order of five μsec. Tests using sine waves, square waves, frequencies above about 50 KHz, or waveforms generally resembling that in Fig. 1 but with duty cycles approaching 50% or with excessively fast or slow rise times, have shown much lower effectiveness at otherwise-comparable power levels.

Many different types of electrical stimulation devices are available to consumers and medical professionals, producing many different waveforms ranging from constant-current or constant voltage (DC) through low-frequency to high frequency waveforms. In general, the lower-frequency waveforms and high-frequency pulses within a low-frequency envelope tend to be aimed at tissue-healing applications, while higher-frequency waveforms are used for pain relief.

Electrical stimulation is widely used in tissue healing applications. Here, Petrofsky (U.S. No. 5,974,342) shows a microprocessor-controlled apparatus for treating injured tissue, tendon, or muscle by applying a therapeutic current. The apparatus has several channels that provide biphasic constant voltage or current, including a 100–300 μsec positive phase, a 200–750 μsec interphase, and a 100–300 μsec negative phase occurring once every 12.5–25 msec.

Pilla, et al. (U.S. No. 5,723,001) disclose an apparatus for therapeutically treating human body tissue with pulsed radio-frequency electromagnetic radiation. The apparatus generates bursts of pulses having a frequency of 1–100 MHz, with 100–100,000 pulses per burst, and a burst repetition rate of 0.01–1000 Hz. The pulse envelope can be regular, irregular, or random.

Bartelt, et al. (U.S. 5,117,826) discloses an apparatus and method for combined nerve fiber and body tissue stimulation. The apparatus generates biphasic pulse pairs for nerve fiber stimulation, and a net DC stimulus for body tissue treatment (provided by biphasic pulse trains having a greater number of negative than positive pulses). In U.S. No. 4,895,154, Bartelt, et al. describe a device for stimulating enhanced healing of soft tissue wounds that includes a plurality of signal generators for generating output pulses. The intensity, polarity, and rate of the output pulses can be varied via a series of control knobs or switches on the front panel of the device.

Gu, et al. (U.S. No. 5,018,525) show an apparatus that generates a pulse train made up of bursts having the same width, where each burst is made up of a plurality of pulses of a specific frequency. The number of pulses varies from one burst to the next; the frequency of the pulses in each burst varies from one burst to the next corresponding to the variation in the number of pulses in each burst. The pulses have a frequency of 230–280 KHz; the duty cycle of the bursts is between 0.33% and 5.0%.

Liss, et al. (U.S. No. 5,109,847) relates to a portable, non-invasive electronic apparatus which generates a specifically contoured constant current and current-limited waveform including a carrier frequency with at least two low-frequency modulations. The carrier frequency is between 1–100,000 KHz; square-wave or rectangular-wave modulating frequencies are 0.01–199 KHz and 0.1–100 KHz. Duty cycles may vary, but are typically 50%, 50%, and 75% for the three waveforms.

Borkan's tissue stimulator (U.S. No. 4,612,934) includes an implantable, subcutaneous receiver and implantable electrodes. The receiver can be noninvasively programmed after implantation to stimulate different electrodes or change stimulation parameters (polarity and pulse parameters) in order to achieve the desired response; the programming data is transmitted in the form of a modulated signal on a carrier wave. The programmed stimulus can be modified in response to measured physiological parameters and electrode impedance.

Hondeghem (U.S. No. 4,255,790) describes a programmable pulse generating system where the time periods and sub-intervals of the output pulses are defined by signals from a fundamental clock frequency generation circuit, plus a pair of parallel sets of frequency division circuits connected to that circuit. The time periods, sub-intervals, and output waveforms are variable.

Hsiang-Lai, et al. (U.S. No. 3,946,745) provide an apparatus for generating positive and negative electric pulses for therapeutic purposes. The apparatus generates a signal consisting of successive pairs of pulses, where the pulses of each pair are of opposite polarities. The amplitude, duration, the interval between the pulses of each pair, and the interval between successive pairs of pulses are independently variable.

McDonald (U.S. No. 3,589,370) shows an electronic muscle stimulator which produces bursts of bidirectional pulses by applying unidirectional pulses to a suitable transformer.

Landauer (U.S. No. 3,294,092) discloses an apparatus that produces electrical currents for counteracting muscle atrophy, defects due to poor nutrition, removing exudates, and minimizing the formation of adhesions. The amplitude of the output signals is variable.

Kronberg (U.S. No. 5,217,009, No. 5,413,596, U.S. No. 6,011,994, U.S. No. 6,321,119, and U.S. application Serial No. 09/935,007 (Filed 08/21/2001), all incorporated herein by reference) describes signal generators for biomedical applications. The generators produce pulsed signals having fixed and variable amplitude, fixed, variable, and swept frequencies, and (in some cases) optional DC biasing.

Units designed for use in transcutaneous electroneural stimulation ("TENS") for pain relief are widely available. For example, Bastyr, et al. (U.S. No. 5,487,759) disclose a battery-powered device that can be used with different types of support devices that hold the electrode pads in position. Keyed connectors provide a binary code that is used to determine what type of support device is being used for impedance matching and carrier frequency adjustment. The carrier frequency is about 2.5–3.0 KHz; the therapeutic frequency is typically on the order of 2–100 Hz.

Kolen (U.S. No. 5,350,414) provides a device where the carrier pulse frequency, modulation pulse frequency, intensity, and frequency/amplitude modulation are controlled by a microprocessor. The device includes a pulse modulation scheme where the carrier

frequency is matched to the electrode-tissue load at the treatment site to provide more efficient energy transfer.

Liss, et al. (U.S. No. 4,784,142) discloses an electronic dental analgesia apparatus and method. The apparatus generates a output with relatively high frequency (12–20 KHz) pulses with nonsymmetrical low frequency (8–20 Hz) amplitude modulation.

Bartelt, et al. (U.S. No. 5,063,929) describe a microprocessor-controlled device that generates biphasic constant-current output pulses. The stimulus intensity can be varied by the user.

Charters, et al. (U.S. No. 4,938,223) provide a device with an output signal consisting of bursts of stimuli with waxing and waning amplitudes, where the amplitude of each stimulus is a fixed percentage of the amplitude of the burst. The signal is amplitude-modulated to help prevent the adaptation response in patients.

Molina-Negro, et al. (U.S. No. 4,541,432) disclose an electric nerve stimulation device for pain relief. The device produces a bipolar rectangular signal with a preselected repetition rate and width for a first time period. Then, a rectangular signal is generated at a pseudo-random rate for a second time period, and delivery of the signal is inhibited for a third, pseudo-random period of time. This protocol is said to substantially eliminate adaptation of nerve cells to the stimulation.

Butler, et al. (U.S. No. 4,431,000) show a transcutaneous nerve stimulator for treating aphasias and other neurologically-based speech and language impairments. The device uses a pseudorandom pulse generator to produce an irregular pulse train composed of trapezoidal, monophasic pulses which mimic typical physiological wave forms (such as the brain alpha rhythm). A series of such pulses has a zero DC level; a current source in the device reduces the effects of variables such as skin resistance.

Maurer (U.S. No. 4,340,063) discloses a stimulation device which can be implanted or applied to the body surface. The amplitude of the pulse decreases with a degradation in pulse width along a curve defined by a hyperbolic strength-duration curve. This is said to result in proportionately greater recruitment of nerve fibers due to the nonlinear relationship between pulse width and threshold.

The Kosugi, et al. system (U.S. No. 4,338,945) generates pulses that fluctuate in accordance with the 1/f rule. That is, the spectral density of the fluctuation varies inversely with the frequency: pleasant stimuli often have stochastic fluctuations governed by this rule. The system produces an irregular pulse train said to promote patient comfort during the stimulation.

Signal generators are also used in hearing prostheses. For example, McDermott's receiver/stimulator (U.S. No. 4,947,844) generates a series of short spaced current pulses, with between-pulse intervals of zero current having a duration longer than that of each spaced pulse. The waveform of the stimulus current includes a series of these spaced pulses of one

polarity followed by an equal number of spaced pulses of opposite polarity so that the sum of electrical charge transferred through the electrodes is approximately zero.

Alloca (U.S. No. 4,754,7590 describes a neural conduction accelerator for generating a train of "staircase-shaped" pulses whose peak negative amplitude is two-thirds of the peak positive amplitude. The accelerator design is based on Fourier analysis of nerve action potentials; the output frequency can be varied between 1–1000 Hz.

Galbraith (U.S. No. 4,592,359) describes a multi-channel implantable neural stimulator wherein each data channel is adapted to carry information in monopolar, bipolar, or analog form. The device includes charge balance switches designed to recover residual charge when the current sources are turned off (electrode damage and bone growth are said to be prevented by not passing DC current or charge).

Despite its great healing potential, traditional Western medicine has accepted electrotherapeutic treatment only grudgingly, and to date it is used only rarely. This seems to be a legacy from early beliefs that signals would need to have high local intensities to be effective. Most electrotherapeutic apparatus now available relies either on direct implantation of electrodes or entire electronic packages, or on inductive coupling through the skin. The need for surgery and biocompatible materials in the one case, and excessive circuit complexity and input power in the other, has kept the price of most such apparatus (apart from TENS devices) relatively high, and has also restricted its application to highly trained personnel. There remains a need for a versatile, cost-effective apparatus that can be used to provide bioelectric stimulation in a wide range of applications, including healing acceleration and pain relief.

DISCLOSURE OF THE INVENTION

According to its major aspects and broadly stated, the present invention is an apparatus and method for generating an electrical signal for use in biomedical applications. The signal includes an asymmetrical, biphasic wave form consisting of intermittent bursts of quasi-rectangular waves, based on at least four timing intervals T_1–T_4; more preferably, the signal is based on seven timing intervals T_1–T_7. The apparatus includes a first timing block for generating timing intervals T_1 and T_2; a second timing block for generating timing intervals T_3 and T_4 (the timing blocks also generate intervals T_5, T_6, and T_7 if present); an interconnection block for combining these intervals into an output signal having predetermined relationships among the intervals; an output block for transmitting the output signal to a load (such as tissue being treated with the apparatus); a battery pack; and, optionally, a filter for removing unwanted frequency components from the output signal; and an adjustment block for selecting from among a plurality of output signals with predetermined characteristics. The signal has a first amplitude level L_1 during intervals T_1, T_5, and T_6, a second level L_2 during intervals T_2 and T_4, and a third level L_3 during interval T_7, where L_3 falls in the range between L_1 and L_2 inclusive.

According to a first aspect of the invention, there is provided an apparatus for generating an electrical signal including at least four timing intervals T_1-T_4, said apparatus comprising:

means for generating a set of at least four timing intervals T_1-T_4, said timing intervals having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

means for using said timing intervals to generate an electrical signal having an amplitude.

According to a second aspect of the invention, there is provided an apparatus for generating an electrical signal including at least four timing intervals T_1-T_4, said apparatus comprising:

a first timing block for generating a first timing interval T_1 and a second timing interval T_2;

a second timing block for generating a third timing interval T_3 and a fourth timing interval T_4, said intervals T_1-T_4 having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

an interconnection block operably connected between said first and second timing blocks, said interconnection block combining said intervals T_1-T_4; and

means operably connected to said interconnection block for using said timing intervals to generate an output signal with said intervals T_1-T_4, said output signal having an amplitude.

According to a third aspect of the invention, there is provided a method for generating an electrical signal, said method comprising:

generating at least four timing intervals T_1-T_4 having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

using said timing intervals to generate an electrical signal having an amplitude.

According to a fourth aspect of the invention, there is provided a system for treating tissue by application of an electrical signal, comprising:

means for generating and applying an electrical signal to tissue, said signal based on at least four timing intervals having approximately the relationships

(a) $(2 \times T_2) \leq T \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec, said timing intervals being used to generate said electrical signal.

The apparatus is lightweight, compact, self-contained, cost-effective to manufacture and maintain, and convenient to carry or wear for extended periods. It is safe for unsupervised home use without the need for special training, and able to generate the above-described output signal and deliver it efficiently through conductive pads making direct contact with the load. Since only low voltages and currents are used, the apparatus does not pose a shock hazard even in case of malfunction. Power is furnished by compact and inexpensive batteries, needing replacement only once in several weeks of use.

The apparatus may be used to provide in vivo, customizable electrotherapeutic treatment for human and animal patients, including but not necessarily limited to healing acceleration, relief of acute or chronic pain, and relief of swelling and/or inflammation. Since isolated cells or tissue cultures can also be affected by electrotherapeutic waveforms (appropriate electrical stimuli have been observed to modify the rates of cell metabolism, secretion, and replication), the apparatus may also be used for in vitro applications. In contrast to TENS-type devices, which are aimed at blocking pain impulses in the nervous system, the apparatus operates at a signal level which is below the normal human threshold level: most users do not experience any sensation during treatment apart from a steady decrease in previously existing pain. The apparatus is believed to operate directly at the treatment site by enhancing the release of chemical factors such as cytokines which are involved in cellular responses to various physiological conditions. This results in increased blood flow and inhibits further inflammation at the treatment site, thereby enhancing the body's inherent healing processes.

The output signal is an important feature of the present invention. The output signal is a waveform based on at least four timing intervals T_1–T_4 having the following relationships:

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$
(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$
(c) $T_3 \geq (10 \times T_1)$
(d) $T_4 \leq 500$ msec

where the signal has a first amplitude level L_1 during interval T_1 and a second amplitude level L_2 during intervals T_2 and T_4, where intervals T_1 and T_2 alternate through interval T_3, and where intervals T_3 and T_4 also alternate.

More preferably, the waveform is based on seven timing intervals T_1–T_7, with three different amplitude levels as described above. The timing intervals have, approximately, the following relationships:

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$
(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$
(c) $T_3 \geq (10 \times T_1)$
(d) $0 \leq T_4 \leq 500$ msec

(e) $0 \leq T_5 \leq T_1$

(f) $0 \leq T_6 \leq T_1$

(g) $0 \leq T_7 \leq 500$ msec

(h) 5 msec $\leq (T_3 + T_4 + T_7) \leq 500$ msec

In a preferred embodiment of the invention, interval T_3 includes the following sequence: an interval T_5, followed by at least one pair of intervals (T_1, T_2) and then by an interval T_6. The timing intervals and amplitude levels are variable, providing an output signal that can be adjusted for a wide range of therapeutic applications.

The apparatus for generating the signal is another important feature of the present invention. The apparatus includes timing blocks (such as oscillators or astable multivibrators) for generating the timing intervals, preferably connected so that the first timing block controls the second timing block through the interconnection block. The apparatus may include a switching block that enables the user to select from among a plurality of paired values of intervals (T_1, T_2), a plurality of paired values of intervals (T_3, T_4), and a plurality of amplitude output levels L_1–L_3. More preferably, the transition between any two of levels L_1 through L_3 has a decay time constant no greater than approximately 1/2 T_2. If desired, the apparatus may produce a waveform wherein all amplitude levels decay towards a value L_4 intermediate between L_1 and L_2. In this case, L_4 may or may not be equal to L_3, and the decay takes place with a time constant no less than approximately 10 times T_1. Thus, the output signal is adjustable in both waveform and amplitude to suit the needs of the individual user and the particular application.

Another feature of the present invention is the provision of interval T_7, during which intermediate voltage or current level L_3 is presented to the load rather than low level L_2. This feature minimizes the amount of energy which is presented to the load (such as tissue being treated with the apparatus) during this resting interval between pulse bursts.

Still another feature of the present invention is the filter, which blocks frequencies above a selected level (i.e., frequencies greater than the highest ones intentionally generated), to create a desired transition profile or to prevent interference by external high-frequency signal sources. For example, the filter may include a shunt capacitance, a resistor network, a voltage-controlled current source, or other suitable device that simultaneously slows and controls the rate of transitions, attenuates output frequency components above about 50 KHz (or other selected frequency), and prevents interference with circuit functioning by external radio-frequency signals.

Yet another feature of the present invention is the use of dual timing blocks to generate waveforms that can be combined to produce an output waveform having selected characteristics. In a preferred embodiment of the invention, one of two timing blocks is controlled by the other: that is, the output of the second block is "on" or "off" depending on whether the output of the first block is "low" or "high," respectively. This results in a circuit

that generates an output signal whose characteristics—frequency, duty cycle, amplitude—can be determined over a wide range by the particular selection of components. Two such circuits with output signals having appropriately-selected characteristics can be combined to produce the desired output waveform, with timing intervals T_1 through T_7, with a surprisingly simple overall circuit configuration.

Another feature of the present invention is the use of conventional, readily-available low-voltage batteries as a power source for the apparatus. While the invention may be used with AC (alternating current) power sources (with the addition of any suitable adapter), battery power not only reduces the size and weight of the apparatus, but also adds to its safety and ease of use for a patient undergoing treatment. Typically, the batteries need to be replaced at infrequent intervals (generally no more than once every few weeks, depending on the output signal and the particular application), simplifying patient compliance and reducing operating costs. The possibility of electrical injuries is greatly reduced, since the generator is not connected to AC line current during use, does not produce high voltages, and does not generate frequencies likely to induce ventricular fibrillation. Only low power levels, such as are required to produce therapeutic effects, are applied to the body. Thus, the generator cannot produce an electrical shock hazard even in the event of a malfunction: as a result, the invention is suitable for unsupervised home use.

Still another feature of the present invention is its versatility. The components of the apparatus are selected so as to produce an output waveform with selectable timing intervals T_1 through T_7 and output voltage (or current) levels L_1 through L_3. As noted above, tissues may respond in different ways to different signal frequencies, to a pure AC signal, or to an AC signal with a superimposed positive or negative DC component. Similarly, as shown in Fig. 3, different effects may appear at different current densities.

An apparatus with an adjustable output signal is useful for a greater variety of applications than one having a fixed output; on the other hand, medical professionals may prefer a generator having a fixed output, or an output that is adjustable only in magnitude, for outpatient use by their patients. In one embodiment of the invention, the user can select a signal for a given application by turning a dial or using a keypad to select one of a plurality of the available signals noted above.

Yet another feature of the present invention is the ability to turn off the output signal after a predetermined treatment duration, to reverse the polarity of the signal at predetermined intervals, or both. An optional timing device allows the user to thereby customize the treatment for the individual patient.

Other features and advantages of the present invention will be apparent to those skilled in the art from a careful reading of the Best Modes for Carrying Out the Invention presented below and accompanied by the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings,

Figs. 1A and 1B are schematic views of a waveform used in stimulating fracture healing, on a short and a long time scale, respectively;

Fig. 1C shows a modified form of the waveform of Fig. 1B;

Fig. 2 shows a waveform used in the treatment of osteoporosis;

Fig. 3 is a schematic view of healing effect vs. signal intensity (amplitude);

Fig. 4 illustrates a waveform according to a preferred embodiment of the present invention;

Figs. 5A–F illustrates specific embodiments of the waveform of Fig. 4;

Fig. 6 is a block diagram of an apparatus according to a preferred embodiment of the present invention;

Fig. 7 and 8 show an asymmetric oscillator circuit and a dual asymmetric oscillator circuit, respectively, both being usable with the apparatus of Fig. 6;

Fig. 9 shows a plurality of waveforms output by a particular embodiment of the apparatus of Fig. 6;

Figs. 10, 11, and 12 show a power supply, a pair of timing blocks, and a voltage switching block and filter with associated circuitry, respectively, all being usable with the apparatus of Fig. 6;

Fig. 13 is a schematic view of a pair of output waveforms;

Fig. 14 illustrates a waveform wherein the voltage levels are adjusted so as to produce a strong direct current (DC) signal component;

Fig. 15 shows an alternative form of the circuitry of Fig. 12, designed for generation of the signal of Fig. 14;

Fig. 16A and 16B illustrate a waveform with a DC component which is reversed in polarity at selected intervals;

Fig. 17 illustrates a waveform with a DC component and periodically reversed polarity which is also turned off after a preselected length of treatment; and

Fig. 18 shows an alternative form of the circuit of Figure 11, designed for generation of waveforms such as those of Figs. 15 and 16.

BEST MODES FOR CARRYING OUT THE INVENTION

In the following description of best modes for carrying out the invention, reference numerals are used to identify structural elements, portions of elements, surfaces or areas in the drawings, as such elements, portions, surfaces or areas may be further described or explained by the entire written specification. For consistency, whenever the same numeral is used in different drawings, it indicates the same element, portion, surface or area as when first used. Unless otherwise indicated, the drawings are intended to be read together with the specification, and are to be considered a portion of the entire written description of this

invention as required by 35 U.S.C. § 112. As used herein, the terms "horizontal," "vertical," "left," right," "up," "down," as well as adjectival and adverbial derivatives thereof, refer to the relative orientation of the illustrated structure as the particular drawing figure faces the reader.

The present invention is an apparatus for use in providing bioelectric stimulation in a variety of applications. The apparatus generates a waveform having approximately rectangular or quasirectangular, asymmetric pulses repeated at a chosen frequency below approximately 50 KHz, with frequencies above approximately 50 KHz filtered out (however, different cut-off frequencies may also be useful). These pulses appear in bursts which themselves are repeated at a lower frequency. The characteristics of the waveform are variable to suit differing applications or target tissues to be treated, as will be described further below.

Referring now to Fig. 4, there is shown a waveform 70 according to a preferred embodiment of the present invention. Waveform 70, indicated by line 72, has seven timing intervals T_1–T_7, indicated as intervals 74a–74g, respectively, and three levels of voltage or current L_1–L_3, indicated as levels 76a–76c. While level L_1 is shown as being above L_2 in Fig. 4, it should be understood that L_1 is not necessarily either positive or negative with respect to L_2. Intervals T_1–T_7 are related as follows:

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$

(b) $50\ \mu\text{sec} \leq (T_1 + T_2) \leq 5000\ \mu\text{sec}$

(c) $T_3 \geq (10 \times T_1)$

(d) $0 \leq T_4 \leq 500$ msec

(e) $0 \leq T_5 \leq T_1$

(f) $0 \leq T_6 \leq T_1$

(g) $0 \leq T_7 \leq 500$ msec

(h) $5\ \text{msec} \leq (T_3 + T_4 + T_7) \leq 500$ msec

That is, interval 74a (T_1) is between 2–20 times, preferably about seven times, as long as interval 74b (T_2), corresponding to duty cycles between about 5% and 33%. The sum of T_1 and T_2 lies in the approximate range of 50–5000 μsec. Intervals 74e (T_5) and 74f (T_6) range from zero to T_1 in length. Interval 74c (T_3) is at least approximately ten times interval 74a (T_1). The sum of 74c (T_3), 74d (T_4) and 74g (T_7) lies in the range from 5 msec to 500 msec, and is preferably about 70 msec. (It should be understood that these ranges are approximate; values of T_1–T_7 outside these ranges may also be useful.) Subject to these constraints, any one or combination of T_4, T_5, T_6, and T_7 may each have any length, including zero.

Intervals T_1 and T_2 form an alternating cycle T_1, T_2, T_1, T_2 and so forth, representing opposite phases of a rectangular wave whose frequency lies in the range from about 200 H_Z-20 KH_Z. Similarly, intervals T_5,T_6 and T_7 form an alternating cycle T_5,T_6,T_7,T_5,T_6

T_7 and so forth, representing successive phases in a three-phase wave whose frequency lies between approximately 5–50 Hz. Each interval T_3 is subdivided into a plurality of shorter intervals beginning with a single interval T_5, proceeding through a plurality of intervals T_1 and T_2 alternating as described above, and ending with a single interval T_6 whose end coincides with that of interval T_3, so that a representative (if atypically short) example might be T_5, T_1, T_2, T_1, T_2, T_6. Intervals T_4 and T_7, in contrast, are not so subdivided.

First and second levels L_1 (level 76a) and L_2 (level 76b) of voltage or current are opposite in polarity and define a range between them which, within tissue undergoing treatment with waveform 70, typically spans a few mV/cm (voltage) or a few $\mu A/cm^2$ (current). Within this range lie a third and optionally a fourth voltage or current level L_3 (level 76) and L_4 (level 76e), either of which may have any value within the range L_1–L_2 (for many applications, both L_3 and L_4 may be zero).

During a complete cycle of waveform 70, the voltage or current assumes level L_1 (i.e., level 76a) during intervals T_1, T_5 and T_6, level L_2 (76b) during intervals T_2 and T_4, and level L_3 (76c) during interval T_7. (Interval T_3 is subdivided as previously stated.) A transition between voltage or current levels preferably approximates an exponential decay toward the new level with a time constant t_1 less than one-sixth of T_2. More preferably, this time constant is about 5 msec so that frequency components above about 50 KHz are suppressed. Where convenient, the voltage or current after each such transition may also decay exponentially toward L_4, provided that such decay has a time constant t_2 greater than ten times T_1.

The decay time constant τ is defined as the period during which the difference between the indicated quantity and its final value drops by a factor of e, or approximately 2.71828. After a time equal to one time constant, therefore, the difference has dropped to about 27% of what it was at the start. After three time constants, the difference is down to about 5%, and the decay may be considered substantially complete. For a transition between voltage or current levels, this decay preferably takes place in about 15 μsec or one-half of T_2, whichever is shorter.

A major point of difference between the waveforms of Fig. 4 and Fig. 1 is the inclusion of output interval T_7 (74g), during which intermediate voltage or current level L_3 (76d) is presented to the output or to the tissue being treated rather than low level L_2 (76b). The purpose of this change is to minimize the amount of energy which is presented to the material being treated during this resting interval between pulse bursts.

Reference to line 38 in Fig. 1, for example, shows that a significant amount of charge remains on output capacitors or other filtering devices, and decays exponentially during interval 36 between pulse bursts. In Fig. 4, in contrast, interval T_4 (74d) defines a negative "equalizing" pulse at voltage or current level L_2 which substantially neutralizes any charge left on such devices. Once such neutralization has taken place, transition is made to level L_3 (76c)

so that no significant output current flows during interval T_7 (74g), which makes up the remainder of the timing cycle.

Note that waveform 70 as shown in Fig. 4 shows no transition between interval T_5 and the first interval T_1 within any given interval T_3, since waveform 70 has level L_1 during both T_1 and T_5. Similarly, if T_6 approaches zero within a fraction of the normal transition time, there is no transition since waveform 70 has level L_2 during both interval T_2 and interval T_4.

A special case of the above-described waveform is that in which intervals T_4, T_5, T_6 and T_7 all approach zero, making the resulting waveform a continuous pulse train alternating between voltage or current levels L_1 and L_2 for intervals of T_1 and T_2 respectively, as shown in Fig. 5A. In this case, T_3 (74c) of a waveform 80a may be considered to have any length which is an integral multiple of the sum of T_1 and T_2.

Additional specific embodiments of waveform 70 are shown in Figs. 5B–F. For clarity, the time intervals and voltage levels in each waveform shown in these Figures are not individually labeled. A waveform 80b (Fig. 5B) represents a single pulse burst in which T_1 is relatively long compared with T_3, so that the burst contains relatively few individual pulses. For comparison, a waveform 80c (Fig. 5C) represents a single pulse burst in which T_1 is relatively short compared with T_3, so that the burst contains relatively many pulses.

A waveform 80d (Fig. 5D) represents two complete pulse bursts in which T_3 is relatively short compared to T_7, so that the pulse bursts occupy only a relatively small portion of the total time. For comparison, a waveform 80e (Fig. 5E) represents two complete pulse bursts in which T_3 is relatively long compared to T_7, so that the pulse bursts occupy a relatively large portion of the total time. A waveform 80f (Fig. 5F) represents an end case in the same progression where intervals T_4, T_5, T_6 and T_7 all approach zero, making the resulting waveform the same as was shown previously in Fig. 5A. While a pulse-burst waveform such as one of waveforms 80b–80d is generally preferable, a continuous waveform such as waveform 80f using the same values of T_1 and T_2 may also be effective. The optimum treatment protocol depends on a number of factors, including the condition being treated and the time available for treatment. It will be apparent that specific embodiments of the general waveform 70 in addition to those shown in Figs. 5A–F are within the spirit of the present invention.

The above-described waveform may be configured to be "charge-balanced," that is, the interaction of T_1–T_7 and L_1–L_4, causes the summed current over an arbitrarily long period of treatment to be zero or thereabouts, since the charge leaving an electrode during all periods of negative current equals the charge which enters it over all periods of positive current. In such a charge balanced case, there is no DC component and the signal consists of substantially pure AC. Charge may be balanced, for example, either by placing DC-blocking capacitors in the output path, or by setting L_3 to zero, L_1 and L_2 equal but with opposite

polarities, and $T_4 = T_5 + T_6 +$ all T_1s - all T_2s so that equal amounts of time are spent at L_1 and L_2 in each cycle.

For any waveform 70 or 80a–80f, one or more parameters such as the sum of intervals T_1 and T_2 or the span between voltage/current levels L_1 and L_2 may be varied for particular applications. For example, L_1 and L_2 may be adjusted, preferably together so that the ratio between them is preserved, to compensate for variable user skin impedance or to activate different tissue repair processes. Similarly, the span between voltages or currents L_1 and L_2 at the output of a treatment unit may be varied so as to compensate for variable tissue cross-sections under treatment or differing optimal current densities of various tissues.

Conditions believed to be treatable with a waveform such as 70 or 80a–80f include, but are not necessarily limited to, the following: bone fractures, osteoporosis, acute pain, chronic pain, swelling, simple inflammation, and inflammatory disorders such as tendonitis (including carpal tunnel syndrome and other repetitive stress injuries) and osteoarthritis. However, it should be understood that no one set of timing intervals T_1–T_7 and voltage/current levels L_1–L_3 (or L_1–L_4) are useful for treating all (or even most) of these conditions. Accelerated healing of wounds, involving a variety of tissue types and resulting either from trauma or from degenerative conditions such as diabetes, may also be seen during treatment with waveforms 72 or 80a–80f. While not wishing to be bound by theory, it is believed that appropriate voltage/current levels and timing intervals may be used to treat a wider variety of conditions whose etiology involves improper rates or imbalances in cell metabolism, secretion or replication, or which can be relieved by suitably modifying these factors. Thus, it should be understood that the optimum waveform characteristics for each particular application are best found with a modest combination of observation and experimentation.

A waveform according to the present invention, such as waveforms 70 or 80a–80f, can be generated with an apparatus such as apparatus 90, shown in block diagram form in Fig. 6. Apparatus 90 includes a first timing block 92 which generates a succession of intervals T_1 and T_2, and optionally also T_5 and T_6; a second timing block 94 which generates a succession of intervals T_3 and optionally also T_4 and T_7; an interconnection block 96 which combines the signals from blocks 92 and 94 so that the succession of intervals T_1 and T_2 appears only during intervals T_3; a voltage or current switch 98 which generates an output signal at usable intensity; an optional adjustment block 100 for modifying the signal timing and intensity (i.e., amplitude); a filter 102 which removes unwanted signal components and preferably also sets transition and decay time constants; a connection block 104 which passes the signal out to a load 106 (cell culture, tissue, organism or part thereof, etc.); and a power supply 108 which provides energy as needed to enable the other components of apparatus 90 to perform their functions.

When present, adjustment block 100 may provide the capability of selecting from among a plurality of alternative, paired values of intervals T_1 and T_2, of intervals T_4 and T_7,

or of both sets of intervals. More preferably, such paired interval values are selected so as to change the operating frequency of apparatus 90 while maintaining a selected duty cycle, or vice-versa. For example, one such paired value set of intervals T_4 and T_7 may be one in which both intervals approach zero, thereby making the output a continuous pulse train such as waveform 80f.

Optional adjustment block 100 may also provide the capability of selecting among a plurality of alternative values of voltage or current levels L_1, L_2 and L_3 in order to establish an optimal current density within the living matter being treated (i.e., load 106), as may be needed or desired for a specific application. To this end, switch 98 may generate an output waveform 70 or 80a–80f as a voltage waveform, which is then converted to a current waveform by passage through a suitable resistor, resistor network or voltage-controlled current source making up a part of filter 102 under the control of adjustment block 100.

When a charge-balanced output is desired, filter 102 preferably includes one or more nonpolarized capacitors, or back-to-back combinations of electrolytic capacitors, connected in series with the output so as to block any direct-current component from the signal unless such a component is desired for a specific application. However, other types of devices may also be useful for filter 102.

Filter 102 preferably also includes suitable devices for blocking frequencies above a selected level (i.e., frequencies greater than the highest ones intentionally generated), to create a desired transition profile or to prevent interference by external high-frequency signal sources, as may be convenient. For example, filter 102 may include a shunt capacitance placed across the output lines after the signal has passed through the previously-mentioned resistor, resistor network or voltage-controlled current source so as simultaneously to slow and control the rate of transitions, to attenuate output frequency components above about 50 KHz, and to prevent interference with circuit functioning by any radio-frequency signals coming from the outside.

Filter 102 may also include any suitable type of rectifier for converting an otherwise biphasic output with no net DC content into a quasi-monophasic output with controlled DC content (as may be desirable for some wound-healing applications). If rectification is used, a switch may also be provided by which rectification may be turned on or off as may be needed for a specific case or phase of treatment. With rectification, it may be convenient to eliminate interval T_7, or to set output levels L_2 and L_3 relatively close together.

Blocks 92, 94, 96, 98, 100, 102, 104, 108 of Fig. 6 may be implemented in any of a wide variety of ways. For example, timing blocks 92 and 94 may both be astable multivibrators whose outputs are further processed by digital logic, constituting interconnection block 96, in approximately the manner which was described in U.S. Patent No. 5,217,009 (incorporated herein by reference). Alternatively, timing block 92 may be an astable multivibrator with timing block 94 then derived from block 92 digitally, for example, by a frequency-divider chain. Timing blocks 92 and 94 may both be derived digitally from a

common timing source, using a divider chain or microprocessor, in approximately the manner which was described in U.S. Patent No. 5,413,596 (incorporated herein by reference). In yet another approach, both timing blocks 92 and 94 may be astable multivibrators, with block 94 controlling block 92 so that block 92 runs, generating intervals T_1 and T_2, only during interval T_3 and is turned off at other times, in approximately the manner which was described in U.S. Patent No. 6,011,994 (incorporated herein by reference).

A timing block particularly well-suited for generating asymmetric, repeating waveforms such as 70 and 80a–80f is based on complementary metal-oxide-semiconductor (CMOS) logic. It is a little-known fact that a CMOS logic gate can function as either an analog or a digital device, or as both at once. This permits many signal generation and processing operations to be performed in a surprisingly effective and straightforward manner using CMOS logic gates with analog or mixed signals as inputs. A self-starting, asymmetric CMOS oscillator 120 (technically, an astable multivibrator) based on this principle, consisting of two inverting logic gates 122a and 122b and a handful of passive components, was described in U.S. Patent No. 6,011,994 and is shown in schematic form in Fig. 7. Oscillator 120 generates two complementary outputs 124a and 124b, each consisting of a succession of alternating intervals of high and low voltage, whose durations depend upon the values of capacitor 126 and resistors 128a, 128b and 128c, and the polarity of diode 130. Such an oscillator can function as either timing block 92 or timing block 94 in Fig. 6. Using the complementary outputs 124a and 124b in differential mode, rather than either of the outputs against a fixed potential, yields a peak-to-peak output voltage of nearly twice the supply voltage.

With a diode 130 connected as shown, and neglecting nonideal behavior of circuit components:

$$T_1 = 1.1 \times R_1 C,$$
$$T_2 = (1.1x\ C) / (1/R_1 + 1/R_2),$$
$$F = 1 / (T_1 + T_2), \text{ and}$$
$$D = T_1 / (T_1 + T_2)$$

where T_1 is the "high" output period of waveform 124a, T_2 its "low" output period, R_1 the value of resistor 128a, R_2 that of resistor 128b, C that of capacitor 126, F the oscillation frequency and D the duty cycle, provided that R_3, the value of resistor 128c, is large compared with R_1 and R_2. For waveform 124b, T_1 and T_2 are reversed. T_1 and T_2 are also reversed in both waveforms if the polarity of diode 130 is reversed.

Suitable values for these components may be found by first specifying a practical nonpolarized capacitor value typically in the range from about 100 pF to about 1 μF; calculating R_1 and R_2 from the equations

$R_1 = T_1 / (1.1 \times C)$, and

$R_2 = 1 / (1.1 \times C(1/T_1 + 1/T_2))$;

assigning R_3 any practical value at least twice and preferably approximately ten times R_2; then optimizing R_1 and R_2 (by a modest amount of experimentation) to compensate for the nonidealities of real-world components. Optimized values for R_1 and R_2 typically lie within approximately ± 20–30% of those calculated as described above. In no case should R_1 or R_2 be less than about 3300 Ω nor more than about 3.3 MΩ, nor R_3 greater than about 22 MΩ. If this occurs, a new value should be chosen for C in order to bring R_1, R_2 and R_3 back within these ranges.

An oscillator 120 such as this can provide virtually any desired oscillation period from several seconds down to 1 μsec or less, and any desired duty cycle within such an oscillation. Particularly useful is the fact that the oscillation frequency can be changed without substantially altering the duty cycle, simply by changing the value of capacitor 126. This feature makes it possible to select among a plurality of alternative, paired values of T_1 and T_2 while preserving a desired duty cycle, for example, through the use of a switch selecting one of a plurality of capacitors.

Two such oscillators 120 can be interconnected so that one of them, oscillating at a relatively low frequency, controls the second, which oscillates at a much higher frequency but only during a selected phase of the lower-frequency oscillation (either T_1 or T_2), thereby generating a waveform similar to that shown in Fig. 1. Such an interconnected pair of oscillators 120a, 120b, shown in Fig. 8, can function as timing block 92 and 94 of Fig. 6, with the connection between the two oscillators serving simultaneously as interconnection block 96. An advantage of this approach is that, since the power consumption of a CMOS circuit (neglecting output loading) is strongly dependent on the operating frequency, turning off the higher-frequency oscillator except during that portion of the lower-frequency oscillation when it is needed minimizes the power consumption.

Two such coupled CMOS oscillators can also be used to generate the equalizing pulse of interval T_4. More preferably, the two complementary outputs of the higher-frequency oscillator are buffered and transformed by an added, mixed analog and digital stage so that they generate output voltage or current level L_1 when in one set of opposite logic states, another voltage or current level L_2 when in the opposite set, and a third level L_3 when, at the end of interval T_4, both outputs are brought to like logic states.

In a preferred embodiment, apparatus 90 generates a plurality of specific waveforms aimed at various biomedical applications, including but not necessarily limited to fracture healing, pain relief, and osteoporosis treatment. For example, a particular embodiment of apparatus 90 may generate the six waveforms illustrated in Fig. 9, in any of a plurality of user-selectable intensities. Here, waveforms 150, 152, and 154 are pulse-burst type

waveforms, each having a different set of values for intervals T_1, T_2, T_5 and T_6; while T_3, T_4 and T_7 are the same in all three. Waveforms 156, 158 and 160 are continuous pulse-train equivalents of waveforms 150, 152, and 154, respectively, differing from them chiefly in that T_4 and T_7 are in each case are set to zero. An example of a set of timing intervals for the waveforms of Fig. 9 is given in Table 1.

Table 1. Timing intervals for waveforms 150, 152, 154, 156, 158, and 160 (Fig. 9).

	Timing Interval*						
Waveform	T_1	T_2	T_3	T_4	T_5	T_6	T_7
150	200	30	10	3	50	-	54
156	200	30	-	0	50	-	0
152	600	70	10	3	150	-	54
158	600	70	-	0	150	-	0
154	1500	170	10	3	400	-	54
160	1500	170	-	0	400	-	0

*(T_1, T_2, T_5, and T_6 are given in μsec; T_3, T_4, and T_7 are in msec)

Timing accuracy for the example of Table 1 is about ± 10% or 20 μsec, whichever is larger. An apparatus 90 with these timing intervals has been cleared by the U.S. Food and Drug Administration for use in the relief of chronic pain. Different timing intervals may also be useful for some applications.

When one CMOS oscillator of this type controls another in the manner shown, interval T_5 is the starting delay of the higher-frequency oscillator at the start of a pulse burst and is typically about one-fourth of interval T_1, while interval T_6 is simply that portion of the last interval T_1 which remains at the end of interval T_3. Hence, no attempt is made to define T_6 beyond what has already been given. Intervals T_3, T_4 and T_7 have the same values for all three pulse-burst waveforms; for the continuous waveforms, interval T_3 is undefined while T_4 and T_7 are both zero.

Intervals T_1 and T_2 are selected so that, for a pulse-burst type waveform, each burst may be divided either into approximately 6–8 pulses ("low modulation") as in waveform 150, approximately 15–32 pulses ("medium modulation") as in waveform 152, or approximately 35–72 pulses ("high modulation") as in waveform 154. The same values of intervals T_1 and T_2 are used in the corresponding continuous pulse-train waveforms.

To compensate for variable tissue cross-sections to be treated or differing optimal current densities of various tissues, preset intensities for each waveform may be provided as shown in Table 2.

Table 2. Nominal output current (total output current from connection block 104 into load 106, measured according to ANSI/AAMI Standard No. NS-4-1985. Within load 106, the current is distributed approximately uniformly across the full cross-section of the load, with local variations depending on the particular tissue types present).

	Output Current (μA)	
Setting	Pulse-Burst Mode	Continuous Mode
LOW	60	180
MEDIUM	200	600
HIGH	600	1800

In general, pulse-burst operation is recommended for treatment periods of approximately one hour or more; treatment periods up to eight hours per day or even higher are recommended for many conditions. Where available treatment time is restricted to an hour or less, however, continuous pulse-train operation may be preferred. Low modulation is recommended for treating patients with thin or moist skin, medium modulation for normal skin, and high modulation for thick or dry skin. Similarly, low intensity is recommended for use on the fingers, medium intensity on the hands and arms, and high intensity elsewhere on the body. However, the optimum combination of settings is best determined individually for each particular patient being treated; a modicum of experimentation may be applied to find the most effective combination of settings in any particular case. As noted above, waveforms 150–160 meet all the safety requirements of ANSI/AAMI NS-4-1985. As a result, an apparatus 90 with the settings set forth in Tables 1 and 2 can safely be used wherever a conventional microcurrent electrostimulator or TENS unit can be used.

An apparatus 90 with the output parameters of Tables 1 and 2 includes parts corresponding to each of blocks 92–108 of Fig. 6, examples of which will be set forth below. While specific, preferred through-hole type parts numbers are sometimes given in the following descriptions, it should be understood that different components (including surface-mount type devices) and components manufactured according to differing technologies may also be useful. Resistors are typically 1/4-watt, metal or metal-oxide film types with ±1% tolerance unless stated otherwise.

Power supply 108, shown in Fig. 10, includes a replaceable battery 172; a three-position, on/off and function selector switch 174; a steering diode 176 for function selection; a pair of blocking diodes 178a and 178b to prevent damage should battery 174 be inserted backwards; and an electrolytic bypass capacitor 180 which provides a charge reservoir for circuit operation. No adapter, socket or other device for external power input is provided. In a preferred embodiment of the invention, the battery compartment for battery 172 is designed so that apparatus 90 operates only when the compartment is closed.

Battery 172 may have a nominal output of nine volts or thereabouts. Output voltages in this range may be provided by a series stack of three 3-volt lithium coin cells with capacities of at least approximately 270 milliampere-hours each, for example, Type 2032 lithium coin cells surrounded by a heat-shrunk sleeve trimmed flush with the most positive and most negative cell faces. Such a stack powers an apparatus 90 with the particular components described below for approximately two weeks of continuous use. For longer run times, larger coin cells may be used or a plurality of such cells may be connected in parallel. Lithium cells are preferred because of their combination of small size, long shelf life, high energy density, and relatively flat discharge curve under low and approximately constant loading; however, other types of batteries may also be useful.

In the embodiment shown in Fig. 10, position "A" of selector switch 174 disables control oscillator 190 via diode 176 and output line 182, selecting continuous pulse-train mode; position "B" allows both oscillators to run, generating pulse bursts, while position "C" is "off". Positions "C", "B" and "A" of switch 176 thus correspond to "OFF", "BURST" and "CONTINUOUS" operating modes, respectively.

Diodes 178a and 178b prevent accidental damage from reversed battery insertion in switch positions "A" and "B" respectively. Capacitor 180 provides an energy buffer to minimize the effects of rising internal resistance in battery 174 near the end of the battery's useful life. Output lines 184 and 186 from capacitor 180 are respectively +9 volts nominal and ground, supplying power to the remaining circuit blocks including connections, otherwise not shown, between these lines and the CMOS logic devices in these blocks.

Switch 174 may be an on-on-on type, single-pole 3-position (SP3T) miniature slide switch, such as an NKK type SS14SDP2. Diodes 176, 178a and 178b are small general-purpose silicon rectifiers, such as Diodes Incorporated type BAV19 or a similar type of rectifier. Capacitor 180 may be any common, miniature aluminum or tantalum electrolytic type with a capacity of at least approximately 100 μF at 10 volts DC or higher.

Fig. 11 shows timing blocks 92 and 94 in the same configuration previously shown in Fig. 8. First timing block 92 includes two CMOS logic gates 190 and 192; three resistors 194a, 194b and 194c; a capacitor 196; and a diode 198. These components form an astable, asymmetric multivibrator as shown in Fig. 6. Gates 190 and 192 may be two of the four 2-input NAND gates in a CD4011B quad package, connected with lines 184 and 186 as positive and negative supply, and preferably with each gate having one input tied "high" so that it functions as a simple inverter with minimal input and supply currents. Alternatively, an inverter may be formed by tying both gate inputs together.

By way of example, resistors 194a, 194b and 194c may have values of 732 KΩ, 212 KΩ, and 2.2 MΩ, respectively, with tolerances of ±1%. Capacitor 196 may be a polypropylene or polyester film type capacitor with a value of approximately 0.100 μF at ±2% tolerance. These components yield a control signal with a relatively low duty cycle, as

shown in Fig. 5D, and a frequency of 15 Hz. Other values of resistance and capacitance may be used if other duty cycles or frequencies are desired. Exact values may also differ depending on factors such as the type of device, manufacturer, and lot number, but may be optimized as previously described. Diode 198 is a small general-purpose silicon rectifier, preferably a BAV19 or similar type.

Similarly, second timing block 94 consists of two CMOS logic gates 200 and 202; three resistors 204a, 204b and 204c; three capacitors 206a, 206b and 206c, only one of which is selected at a time; and a diode 208. These form the same type of oscillator just described, except that this one accepts a control input and generates complementary outputs in the manner which was shown in Fig. 7. Gates 200 and 202 are preferably two of the four 2-input NAND gates in a CD4011B quad package, connected with lines 184 and 186 as positive and negative supply.

Gate 200 receives as one input the output of gate 192, so that oscillator 94 is turned on when this line is "high" and off when it is "low" (this connection corresponds to interconnection block 96 of Fig. 6). Thus, when signal 192 has a low duty cycle, oscillator 94 runs only for a small fraction of the total time, thereby conserving battery power. Gate 202 has one input tied "high" in the same manner as gates 190 and 192. Gates 200 and 202 respectively feed output lines 210a and 210b with complementary pulse-burst signals in the manner which was explained with Fig. 8.

Selection among capacitors 206a, 206b and 206c is made through a three-position switch 212, which functions as a part of adjustment block 100 (Fig. 6). Capacitor 206a has the highest value of the three, and capacitor 206c the lowest. Hence, these three capacitors respectively provide the "LOW", "MEDIUM" and "HIGH" modulation settings.

For purposes of illustration, diode 208 is shown in Fig. 11 with polarity opposite that of diode 198. This arrangement causes the generation of complementary outputs (as shown in Fig. 7) with a low duty cycle on line 210a and a correspondingly high duty cycle on line 210b. Alternatively, reversing diode 208 reverses this relationship while the outputs remain complementary.

For example, resistors 204a, 204b and 204c may have values of 147 KΩ , 15.4 KΩ, and 2.2 MΩ respectively, with tolerances of ±1%. Capacitors 206a, 206b and 206c are preferably polypropylene or polyester film types with ±2% tolerances and values of .0068 μF, .0027 μF and .001 μF, respectively. These components yield pulse trains with high duty cycles and with approximately frequencies of 600 Hz, 1,600 Hz, and 4,000 Hz, respectively. Diode 208 is a small general-purpose silicon rectifier, preferably a BAV19 or close functional equivalent.*The optimum values of any circuit components provided herein as examples may differ depending on the type of device, manufacturer, lot number, and so forth, and may be found by a modest amount of experimentation for each particular application

Voltage switching block 98, filter 102, an associated part of adjustment block 100, and connection block 104 are shown together in Fig. 12. Voltage switching block 98

consists of two pull-up resistors 220a and 220b, two input protection resistors 222a and 222b, two signal coupling capacitors 224a and 224b, two bypass diodes 226a and 226b, and two CMOS inverters 228 and 230. For added current-handling capacity, each of inverters 228 and 230 may be formed by two standard CMOS logic gates of matched switching characteristics connected with inputs and outputs in parallel, and powered in common by lines 184 and 186 as positive and negative supply, rather than by a single gate. More preferably, both inverters are formed from the four 2-input NAND gates in a single CD4011B quad package or similar devices taken in pairs.

Pull-up resistor 220a and coupling capacitor 224a together form a high-pass filter which transfers fast-changing signals from line 210a to the inputs of inverter 228 with minimal distortion, but draws these inputs to logic "high" when no fast-changing signals are present. Resistor 222a and diode 226a prevent voltage or current overshoots which might damage the inverter inputs. Resistors 220b and 222b, capacitor 224b and diode 226b serve an identical function with line 210b and inverter 230. As a result, the outputs of inverters 228 and 230 reproduce the complementary outputs of gates 202 and 200 respectively when oscillator 94 is running, but both assume equal logic "low" potentials if no transitions have taken place on these lines within a specified delay time. The differential voltage between these outputs then becomes zero, midway between its positive and negative peak values, corresponding to interval T_7 in Fig. 4.

Filter 102 is made up of capacitors 240a–240d, resistors 244a and 244b, and capacitor 246. Connected in series with the output of each inverter 228 and 230 is a pair of electrolytic capacitors 240a and 240b (or 240c and 240d) with their anodes tied together, thus forming a single, effectively nonpolarized capacitor which will pass a fast-changing signal but block any direct-current component, thereby creating a charge-balanced output. Nonpolarized electrolytic capacitors made for audiophile applications may also be useful; however, these types of capacitors may have excessive leakage current for use with the present invention.

Placed in series with each such capacitor pair is a resistor 244a or 244b, beyond which both lines are bridged by capacitor 246. The function of resistors 244a and 244b and capacitor 246 is to filter out unwanted high-frequency signal components of signals leaving the inverters, while simultaneously blocking the entry of outside high-frequency signals which might interfere with device functioning. The corner frequency of the resulting filter is preferably about 50 KHz. Dividing the resistance equally between resistors 244a and 244b also enhances safety, since even if any one component should fail, the current will still be limited to a safe level.

After the end of a given pulse burst, capacitors 240a–240d discharge, as indicated by line 38 of Fig. 1 over interval 36, with a time constant which is set in part by the component values in filter 102 and the properties of load 106. When this curve reaches zero, capacitors 240a–240d hold no net charge.

At the end of the delay generated by resistors 220a and 222a, capacitor 224a and diode 226a, or by their "b" counterparts, the outputs of inverters 228 and 230 assume equal voltages, both logic "low". If this transition coincides with the passage of the capacitor discharge curve through voltage level L_2, the discharge curve is truncated at that point. Thereafter, since zero voltage is placed across the capacitors and zero charge remains on them, the output current is zero until the start of the next pulse burst. Such truncation is shown, for example, at the end of interval T4 in waveform 70 of Fig. 13.

While additional components may be needed to find the actual transition after each pulse burst, tests of the above-described apparatus 90 under typical loading conditions showed that after a 10-millisecond pulse burst, for example, the transition took place after about three more milliseconds. Since the curve is not particularly steep at this point, minor changes to component values in filter block 102 and to load 106, or to the electrical characteristics of the living tissue to which the signal is being delivered, do not substantially affect the output. Hence, values for resistor 220a and capacitor 224a (and for 220b and 224b) may be found which give near-optimal performance over substantially all expected conditions of use. The resulting delay then becomes T_4 (74d in Fig. 4) while the following, substantially current-free "rest" period becomes T_7 (74g).

Resistors 220a and 222a, capacitor 224a and diode 226a (and their "b" counterparts) serve the additional safety function of forcing the outputs of inverters 228 and 230 both to logic "zero", and thus the output current to zero, in case of oscillator failure. This feature prevents electrolytic damage to tissue which might otherwise slowly occur if the oscillator failure took place in a device whose capacitors 222a through 222d had higher than nominal amounts of DC leakage. Values for resistors 220a and 220b, based on this criterion, are 681 KΩ each; for resistors 222a and 222b, 150 KΩ each; and for capacitors 224a and 224b, 0.0068 μF each. These capacitors are preferably miniature polypropylene or polyester types with ± 2% tolerance. Capacitors 240a–240d are preferably small 10 μF aluminum or tantalum electrolytic types rated at 15 volts or higher, although each directly-connected pair may optionally be replaced with a single, nonpolarized capacitor of like value and voltage rating. Preferred practical values for resistors 244a and 244b are 332 Ω each. Diodes 226a and 226b are small general-purpose silicon rectifiers, preferably BAV19s or similar devices.

Fig. 13 illustrates the approximate waveforms 70 and 80 which are produced by the above-described circuit under pulsed and continuous operation, respectively. The voltage "droop" (that is, decay toward intermediate level L_4) is caused by the finite charge capacity of the DC-blocking capacitors.

For some applications, such as stimulation of wound healing, it may be convenient to superimpose a controlled amount of DC upon waveform 70 rather than to suppress the DC content of the output, or to provide the ability to do so as an option. Preferably, the DC bias of the waveform is shifted without diminishing its amplitude. Diode 250 provides a simple rectification device by which this can be done, while switch 252 provides the flexibility of

switching the diode into or out of the circuit to provide either charge-balanced or DC-biased operation. Where this flexibility is not desired and only DC-biased operation is to be used, the circuit of Fig. 12 may be modified by removing all components between input 210a and the junction of resistor 244a and capacitor 246; connecting this junction directly to positive supply rail 184; and replacing the combination of capacitors 240c and 240d with a short circuit. This renders levels L_2 (76b), L_3 (76c) and L_4 (76d) substantially equal while eliminating voltage droop, as in a waveform 82 (shown in Fig. 14).

The magnitude of the output current delivered to load 106 is determined in part by switch 260, which functions as a part of adjustment block 100 by selecting any one of three different resistors 262a, 262b or 262c to be placed in series with capacitors 240a and 240b and resistor 244a. Resistor 262a has the highest value of the three, and resistor 262c the lowest. The selected resistor acts in concert with resistors 244a and 244b, the series combination of the three plus the internal resistance of inverters 228 and 230 serving to limit the output current to cell culture, tissue, organism or part thereof 106. Hence, these three resistors respectively provide the "LOW", "MEDIUM" and "HIGH" output intensity settings. Resistors 262a, 262b and 262c may have values of approximately 24.1 KΩ, 3.92 KΩ, and 332 Ω, respectively.

Output block 104 consists of diodes 270 and 272, wires 274a and 274b, and conductive block 276a and 276b by which physical contact is made with the living tissue (load 106) to be treated. At least one of diodes 270 and 272 is a light-emitting diode (LED), such as a Fairchild MV8412, while the other is a small silicon rectifier such as a BAV19. The LED may be either diode 270 as shown, or diode 272. However, for DC-biased (i.e., monophasic) operation, the LED is preferably that diode of 270, 272 which shares the polarity of diode 250 with respect to the output loop. Alternatively, both diodes may be LEDs. With the diodes arranged in antiparallel manner as shown (the anode of each tied to the cathode of the other) the pair is able to pass a high-frequency signal and emit light in proportion to the current flowing. This provides an indication simultaneously that the battery is providing adequate operating voltage, that all circuit blocks which it powers are functioning correctly, and that wires 274a and 274b and conductive block 276a and 276b are connected correctly to load 106.

Wires 274a and 274b are multistranded, fatigue-resistant wires, for example, 22 AWG equivalent wires with 30/37 stranding, insulated with a tough but flexible nonconductive material such as PVC. Their lengths may be chosen as needed for a specific application. Wires 274a and 274b, or sections thereof, may optionally be made removable from the remainder of the apparatus as shown, for example, by means of appropriate, FDA-acceptable plugs and sockets. Each of the wires may terminate in a 2 mm (0.080") diameter metal pin, miniature alligator clip or other device by which easy connection may be made to conductive blocks 276a and 276b.

Conductive blocks 276a and 276b may include electrically-conductive saline solutions or gels held in appropriate structures such as disposable or reusable electrode pads, salt bridges or other appropriate structures depending upon the intended use and type of load 106 to be treated. For example, saline gel electrodes may be adhered to the skin of a human or animal patient so that the field of current flow which is established between them includes the tissues to be treated. An example of such a gel electrode is the Uni-Patch "Multi-Day" #633; however, other types of electrodes may also be useful. Alternatively, block 276a and 276b may be in whole or in part of other materials, such as silver wire or silver-plated textile fabric, used in a similar fashion.

Alternatively, an output such as that as shown in Fig. 14 can be generated more simply, yet with greater efficiency and more accurate current limiting, using a circuit 290 as shown in Fig. 15. Here, signals 210a and 210b (from the circuit of Fig. 11) are fed, via resistors 300a and 300b, to the bases of bipolar silicon transistors 302 and 304 respectively. Each of transistors 302 and 304, together with the associated passive components, forms a simple current regulator.

Current passing through a forward-biased semiconductor junction causes a voltage drop which is only weakly (i.e., approximately logarithmically) affected by the amount of current flowing. For many purposes, this voltage drop, sometimes called a "diode drop," may be assumed to be approximately constant regardless of the current. The magnitude of the voltage drop is characteristic of the material: in silicon, for example, it is typically close to 0.65 volt, while in gallium phosphide (used to make green light-emitting diodes) it is about 2.1 volt.

Thus, when voltage 210a is low, the current passing through a resistor 300a and diodes 306a and 306b sets the base of a PNP transistor 302 two diode drops, or about 1.3 volt, below positive supply rail 184. The base-emitter junction of transistor 302 cancels one diode drop of this, while the second diode drop appears between rail 184 and the emitter, in this case across a resistor 308 plus a small parasitic resistance (typically about 10 Ω) in the base-emitter path. The resulting collector current thus equals about 0.65 volt divided by the value of a resistor 308 plus 10 Ω, unless limited by other components in the current path. Transistor 302 therefore sets a maximum limit on the output current.

Similarly, when voltage 210b is high, the current passing through resistor 300b and diodes 306c and 306d sets the base of an NPN transistor 304 two diode drops above negative supply rail 186. Again, the base-emitter junction cancels one diode drop, while the other appears between the emitter and rail 186. In this case, a switch 310 allows any one of a plurality of resistors 312a, 312b, . . . to be selected. Alternatively, some combination of one or more resistors 312a, 312b, . . . might be selected, or a continuously variable resistance might be substituted. The resulting collector current is about one diode drop divided by the selected resistance plus 10 Ω, unless limited by other components.

Through the combined action of the components shown in Fig. 11 and described previously, signal line 210a is normally high (near rail 184) but pulses low (near rail 186) during each wave train, as indicated by simplified waveform diagram 230a. Similarly, line 210b is normally low but pulses high with each wave train, as indicated by diagram 230b. As a result, both transistors 302 and 304 have their base-emitter junctions forward-biased during the pulses of each wave train, allowing collector current to flow, but not during the intervals between the pulses or between the wave trains. Current is therefore provided to the output only during the pulses of each wave train.

As before, the output is through wires 274a and 274b, electrodes 276a and 276b, light-emitting diode 270, and load 106 (which may be living tissue), all of which are placed in series between the collectors of transistors 302 and 304, so that current leaving the collector of transistor 302 passes through them before entering the collector of transistor 304. The current passing through load 106 will therefore approximate the smallest of:

(1) 0.65 volt divided by the value of resistor 308 plus 10 Ω (transistor 302 dominates);

(2) 0.65 volt divided by the value of the selected resistor 312a, 312b, and so forth plus 10 Ω (transistor 304 dominates); or

(3) the voltage between rails 184 and 186, minus two silicon and one gallium phosphide diode drop totaling about 3.4 volts, the result then divided by the total resistance of resistor 308, selected resistor 312a, 312b, and so forth, wires 274a and 274b, electrodes 276a and 276b, material 106, plus 20 Ω (load dominates). In this case, the current may be arbitrarily small while, with a 9-volt supply, the voltage appearing across the load will be approximately 7–8 volts.

Preferably, the lowest-valued of resistors 312a, 312b, . . . is equal to or slightly higher than resistor 308, with the others increasing by approximately logarithmic steps. As a result, transistor 304 normally dominates unless load 106 is of low conductivity or there is a faulty connection in wires 274a and 274b or electrodes 276a and 276b, with the actual current being selected by switch 310. For three resistors 312a, 312b and 312c as shown, whose values increase in logarithmic steps, the current in load 106 therefore decreases in proportion as indicated by simplified waveform diagrams 322a, 322b and 322c respectively. Should transistor 304 fail, transistor 302 takes over and maintains current limiting at a safe, though no longer user-selectable level. Alternatively, switch 310 and resistors 312a, 312b, . . . could be connected instead to transistor 302 in place of resistor 308, or switch 310 might be a double-pole type with resistors 312a, 312b, . . . duplicated for both transistors

As described above, light-emitting diode 270 monitors the output current and signals, by its flashing, that all connections are secure, the battery is good and current is being delivered to load 106. However, since current flows in only one direction between the output terminals (out of the collector of transistor 302, through wire 274a, material 106, wire 274b,

diode 270 and into the collector of transistor 304), no antiparallel diode, such as diode 272 in Fig. 12, is needed.

As an example of the circuit of Fig. 15, transistor 302 is a small-signal PNP type such as a 2N2907 or MMBT4403LT1, transistor 304 is a small-signal NPN type such as a 2N2222 or MMBT4401LT1, diodes 306a through 306d are silicon rectifiers such as BAV19s, resistors 300a and 300b are each 10 KΩ, resistors 308 and 312a are each 130 Ω, resistor 312b is 412 Ω, and resistor 312c is 1400 Ω. All resistors have 1% tolerance.

The resulting maximum current in load 106 is about 4.2 mA with resistor 312a selected, about 1.4 mA with resistor 312b selected, and about 0.42 mA with resistor 312c selected. This current is nearly independent of the electrical characteristics of load 106, provided that the load does not dominate as explained above. With a preferred waveform timing of 200 μsec on and 30 μsec off, repeated for 10 msec 15 times per second as described above, the resulting time-averaged DC current delivered to load 106 is approximately 600 μamp with switch 310 selecting resistor 312a, 200 μamp with the switch selecting resistor 312b, or 60 μamp with the switch selecting resistor 312c.

For some applications, such as the stimulation of nerve regeneration, it may be useful not only to superimpose a DC component upon the AC waveform, but also to reverse the polarity of this DC component at regular intervals, typically each ten to sixty minutes. A waveform including such reversal is shown in Figs. 16A and 16B.

Fig. 16A shows a waveform 330 for a short interval including two pulse trains 340a and 340b as previously described, a polarity reversal 342, followed by two additional pulse trains 340c and 340d. Voltage levels 76a and 76b are set about equidistant from zero but have opposite polarities, while levels 76c and 76d are both set close to zero. For clarity, reversal 342 is shown as occurring during an interval between pulse trains, but it could as easily take place at any other point in the waveform or at different such points at different times. Note that on reversal, the voltage level during the pulses and the level during the intervals between them switch places so that the time-averaged DC component is also reversed in polarity while remaining roughly constant in amplitude.

Fig. 16B shows waveform 330 for a longer period, including three reversals 342a, 342b and 342c, illustrating how the voltage level during the pulses and the level in the intervals between them repeatedly switch places. For purposes of illustration, only five pulse trains are shown during each period between reversals. In a real application, however, the number of pulse trains between reversals would more likely be several thousands or tens of thousands.

For some applications, as in treatment during sleep in conditions for which a treatment period of less than eight hours has been found optimal, it may be useful to turn off the treatment unit after a selected length of time. Fig. 17 illustrates a waveform 332 similar to

that in Fig. 16B, but also including an automatic shutoff 344, following which the output voltage and current fall to and remain at zero.

Fig. 18 illustrates a circuit 348 capable of generating waveforms such as those shown in Figs. 14, 16A, 16B, and 17. As in Fig. 11, a control oscillator 92 generates the pulse-burst envelope and a pulse oscillator 94 then generates the bursts themselves.

All components of control oscillator 92 are as previously described, except that logic gate 192 is provided with a second control input line 350 to turn the control oscillator, and thereby the pulse oscillator also, off upon automatic shutdown so as to minimize power consumption and prolong battery life. For example, gate 192 may be a NOR gate as shown, so that a negative signal on a line 350 permits normal operation but a positive signal there turns it off. Alternatively, gate 192 may be a NAND gate, turned off by the application of a negative signal to line 350. Other control methods are also possible.

Similarly, all components of pulse oscillator 94 are as previously described, except that only one of the two possible, complementary outputs is taken, for example, through signal line 210b. Rather than feed the output filter directly, this signal is applied to one input of an exclusive-OR (XOR) gate 352. Such a gate has the property that if a steady or changing logic-level signal is fed to one of its inputs and a steady low level to the second input, the logic signal appears, faithfully reproduced, at its output. If the second input is held high instead, the signal applied to the first input appears inverted at the output. Signal polarity reversal, as illustrated in Figs. 16A, 16B and 17, may thus be accomplished simply by changing a signal 354 applied to the first input from logic high to logic low, or vice-versa.

A first output signal 356a from gate 352 is then passed through an inverter 358, creating a second output signal 356b which is complementary to first signal 356a, thus undergoing polarity reversal at the same time but in the opposite direction.

First and second signals 356a and 356b then pass to components which drive the output to zero after automatic turnoff. For DC-biased operation these may simply be a pair of logic gates 360a and 360b, of the same kind as gate 192 and fed by the same control signal 350. Such gates produce outputs 362a and 362b which are complementary in one state of signal 350 but equal, yielding a zero output, in the other. For example, using NOR gates as shown, outputs 362a and 362b are complementary so long as signal 350 remains at logic low, but both drop to zero, yielding zero output, when signal 350 changes to logic high.

Signals 362a and 362b may then be connected to additional filtering and output components, for example taking the form which was shown in Fig. 18 with the deletions suggested in the text for DC-biased operation.

For charge-balanced operation with automatic turnoff, gates 362, 358, 360a and 360b may be eliminated, control line 350 and gate 192 retained as shown in Fig. 18, and signals 210a and 210b taken from the pulse oscillator as shown in Fig. 11 and filtered as shown in Fig. 12. The simple shutdown of the control oscillator by signal 350, causing in turn a

shutdown of the pulse oscillator through the action of the components shown in Fig. 12, suffices to drive the output to zero and hold it there without any other circuit modifications.

Shutdown signal 350, polarity-reversing signal 354, or both, may be derived from the control oscillator output 370 by a conventional digital divider 372, such as a multistage binary divider chain.

For example, dividing the preferred control-oscillator frequency of 15 Hz by 2^{14} to create signal 354 yields polarity reversal at intervals of about 9.1 minutes, while division by 2^{15} yields reversal at 18.2-minute intervals. Either of these will likely suffice for many applications with no need for more elaborate divider circuitry. Alternatively, any convenient divider circuitry may be employed with the invention.

Similarly, dividing the preferred control-oscillator frequency by 2^{17} yields a shutoff signal 350 becoming active after approximately 1 hour and 13 minutes, by 2^{18} after 2 hours and 26 minutes, by 2^{19} after 4 hours and 51 minutes, and by 2^{20} after 9 hours and 43 minutes. Again, these intervals will likely suffice for many applications, although different divider circuitry (including circuitry that provides different intervals) may be used if desired. An advantage of deriving the shutdown timing from the control oscillator is that, once shutdown has occurred, the control oscillator is disabled and no further counting takes place. Thus, once shut down, the device remains that way with no need for further attention until it is manually reset. This may be done either by turning the stimulator off and then on again, or (again, if desired) by pressing a "reset" button sending an appropriate signal 374 to a reset input of divider chain 372.

Alternatively, another oscillator of the same or a different type, such as a crystal oscillator of the type used in digital watches, might be used to create shutdown signal 350, polarity-reversing signal 354, or both.

An apparatus 90, made using the component values given above and including all or any selected subset of the functions described above, may be mounted in a small, lightweight housing of molded plastic or other suitable material, preferably a housing with a pocket clip or other means for convenient mounting to a bandage, cast, wrist or other band, or article of clothing. Most preferably, the housing is no larger than necessary to hold the described devices and the circuit board or boards which bear them. Suitable housings need be no larger than approximately 5 cm x 6 cm x 2 cm (about 2.0" x 2.5" x 0.75") or thereabouts. Smaller housings may be useful if some or all of the described functions of apparatus 90 are implemented using surface-mount components, rather than the through-hole ones which have in some cases been identified in the descriptions above.

Apparatus 90 is lightweight, compact, self-contained, cost-effective to manufacture and maintain, and convenient to carry or wear for extended periods. It is safe for unsupervised home use without the need for special training, and able to generate the signals just described and deliver them efficiently through conductive pads making direct contact with the skin. Since only low voltages and currents are used, apparatus 90 does not pose a shock

hazard even in case of malfunction. Power is furnished by compact and inexpensive batteries, needing replacement only once in several weeks of use.

An apparatus according to the invention is used to provide electrotherapeutic treatment for human and animal patients, including but not limited to healing acceleration, relief of acute or chronic pain, and relief of swelling and/or inflammation. However, the apparatus need not be confined to use with intact organisms, since isolated cells or tissue cultures can also be affected by electrotherapeutic waveforms (appropriate electrical stimuli have been observed to modify the rates of cell metabolism, secretion, and replication). Isolated skin cells, for example, might be treated with selected waveforms in an appropriate medium to increase cell proliferation and differentiation in the preparation of tissue-cultured, autogenous skin-graft material. As another example, the growth of bacteria genetically engineered to produce a desirable product, such as human insulin, might be accelerated, or their secretion of the desired product increased, by treatment with a suitable waveform.

With respect to the above description of the invention, it is to be realized that the optimum dimensional relationships for the parts of the invention, to include variations in size, materials, shape, form, function and manner of operation, assembly and use, are deemed readily apparent and obvious to one skilled in the art, and all equivalent relationships to those illustrated in the drawings and described in the specification are intended to be encompassed by the present invention.

Therefore, the foregoing description is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of the invention. Thus, it will be apparent to those skilled in the art that many changes and substitutions can be made to the preferred embodiment herein described without departing from the spirit and scope of the present invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. An apparatus for generating an electrical signal including at least four timing intervals T_1–T_4, said apparatus comprising:

means for generating a set of at least four timing intervals T_1–T_4, said timing intervals having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

means for using said timing intervals to generate an electrical signal having an amplitude.

2. The apparatus as recited in claim 1, further comprising means operably connected to said generating means for changing at least one of said intervals T_1 through T_4.

3. The apparatus as recited in claim 1, wherein said generating means produces a plurality of paired values of said intervals T_1 and T_2, further comprising means for selecting one of said paired values.

4. The apparatus as recited in claim 1, further comprising means for transmitting said electrical signal to a load.

5. The apparatus as recited in claim 1, further comprising means for reversing a polarity of said electrical signal.

6. The apparatus as recited in claim 1, wherein said electrical signal is charge-balanced so that a total current delivered to a load during treatment is approximately zero.

7. The apparatus as recited in claim 1, further comprising timing means for shutting off said electrical signal after a selected period of time.

8. The apparatus as recited in claim 1, wherein said electrical signal further comprises :

a first level L_1 during said intervals T_1, and T_5; and

a second level L_2 during said intervals T_2 and T_4; , wherein L_1 and L_2 have equal amplitudes and opposite polarities.

9. The apparatus as recited in claim 1, wherein said set of at least four timing intervals further comprises at least three additional timing intervals T_5–T_7, said at least three additional timing intervals having approximately the relationships

(e) $0 \leq T_5 \leq T_1$,

(f) $0 \leq T_6 \leq T_1$,

(g) $0 \leq T_7 \leq 500$ msec, and

(f) 5 msec $\leq (T_3 + T_4 + T_7) \leq 500$ msec.

10. The apparatus as recited in claim 9, wherein said interval T_3 further comprises a sequence containing an interval T_5, followed by at least one pair of intervals (T_1, T_2), followed by an interval T_6.

11. The apparatus as recited in claim 9, wherein said intervals T_3, T_4, and T_7 form a continuous sequence of repeating intervals T_3, T_4, T_7.

12. The apparatus as recited in claim 9, further comprising means operably connected to said generating means for changing at least one of said intervals T_1–T_7.

13. The apparatus as recited in claim 9, wherein said generating means produces a plurality of paired values of said intervals T_4 and T_7, further comprising means for selecting one of said paired values.

14. The apparatus as recited in claim 9, wherein said amplitude of said electrical signal further comprises:

a first level L_1 during said intervals T_1, T_5, and T_6;

a second level L_2 during said intervals T_2 and T_4; and

a third level L_3 during said interval T_7, wherein L_3 is between L_1 and L_2.

15. The apparatus as recited in claim 14, wherein a transition between any two of said levels L_1 through L_3 has a decay time constant no greater than approximately one-half a length of said interval T_2.

16. The apparatus as recited in claim 14, further comprising a fourth level L_4, said level L_4 being intermediate said levels L_1 and L_2, wherein a transition between any of said levels L_1 through L_3 and said level L_4 has a decay time constant no less than approximately 10 times a length of said interval T_1.

17. The apparatus as recited in claim 14, further comprising means operably connected to said combining means for changing at least one of said levels L_1 through L_3.

18. The apparatus as recited in claim 14, further comprising means operably connected to said combining means for selecting among a plurality of values for said levels L_1 through L_3.

19. An apparatus for generating an electrical signal including at least four timing intervals T_1–T_4, said apparatus comprising:

a first timing block for generating a first timing interval T_1 and a second timing interval T_2;

a second timing block for generating a third timing interval T_3 and a fourth timing interval T_4, said intervals T_1–T_4 having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

an interconnection block operably connected between said first and second timing blocks, said interconnection block combining said intervals T_1–T_4; and

means operably connected to said interconnection block for using said timing intervals to generate an output signal with said intervals T_1–T_4, said output signal having an amplitude.

20. The apparatus as recited in claim 19, further comprising a filter operably connected to said generating means, said filter selectively transmitting signal components within a selected frequency range.

21. The apparatus as recited in claim 19, further comprising power supply means operably connected to said first and second timing blocks, said interconnection block, and said signal-generating means.

22. The apparatus as recited in claim 19, further comprising means operably connected to said generating means for changing said amplitude.

23. The apparatus as recited in claim 19, wherein said first and second timing blocks further comprise first and second astable multivibrators, respectively.

24. The apparatus as recited in claim 19, wherein said interconnection block uses an output of said first astable multivibrator to control said second astable multivibrator.

25. The apparatus as recited in claim 19, wherein said set of at least four timing intervals further comprises at least three additional timing intervals T_5–T_7, wherein said first timing block further comprises means for generating said intervals T_5 and T_6,

wherein said second timing block further comprises means for generating said interval T_7, and

wherein said at least four additional timing intervals have approximately the relationships

(e) $0 \leq T_5 \leq T_1$,

(f) $0 \leq T_6 \leq T_1$,

(g) $0 \leq T_7 \leq 500$ msec, and

(f) 5 msec $\leq (T_3 + T_4 + T_7) \leq 500$ msec.

26. The apparatus as recited in claim 25, wherein said interval T_3 further comprises a sequence containing an interval T_5, followed by at least one pair of intervals (T_1, T_2), followed by an interval T_6.

27. The apparatus as recited in claim 25, wherein said interconnection block divides said interval T_3 into a sequence of shorter intervals, said sequence consisting of at least one interval T_5, followed by at least one pair of intervals (T_1, T_2), followed by at least one interval T_6.

28. The apparatus as recited in claim 25, further comprising means operably connected to said generating means for changing at least one of said intervals T_1–T_7.

29. The apparatus as recited in claim 25, wherein said generating means produces a plurality of paired values of said intervals T_4 and T_7, further comprising means for selecting one of said paired values.

30. The apparatus as recited in claim 25, wherein said amplitude of said output signal further comprises:

a first level L_1 during said intervals T_1, T_5, and T_6;

a second level L_2 during said intervals T_2 and T_4;

and a third level L_3 during said interval T_7, wherein L_3 is between L_1 and L_2; and

means operably connected to said combining means for changing at least one of said levels L_1 through L_3.

31. The apparatus as recited in claim 30, wherein a transition between any two of said levels L_1 through L_3 has a decay time constant no greater than approximately one-sixth a length of said interval T_2.

32. The apparatus as recited in claim 30, further comprising a fourth level L_4, said level L_4 being intermediate said levels L_1 and L_2, an output voltage initially set at a selected one of said levels L_1 and L_2 decaying towards said level L_4 with a time constant no less than approximately 10 times a length of said interval T_1;

means operably connected to said combining means for changing said level L_4.

33. The apparatus as recited in claim 30, further comprising means operably connected to said combining means for selecting among a plurality of values for said levels L_1 through L_3.

31. The apparatus as recited in claim 19, further comprising means for reversing a polarity of said electrical signal.

32. The apparatus as recited in claim 19, wherein said electrical signal is charge-balanced.

33. The apparatus as recited in claim 19, further comprising timing means for shutting off said electrical signal after a selected time.

34. A method for generating an electrical signal, said method comprising:

generating at least four timing intervals T_1–T_4 having approximately the relationships

(a) $(2 \times T_2) \leq T_1 \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec; and

using said timing intervals to generate an electrical signal having an amplitude.

35. The method as recited in claim 34, further comprising selecting one of a plurality of predetermined, paired values of said intervals T_1 and T_2.

36. The method as recited in claim 34, further comprising the step of generating at least three additional timing intervals having approximately the relationships

(e) $0 \leq T_5 \leq T_1$,

(f) $0 \leq T_6 \leq T_1$,

(g) $0 \leq T_7 \leq 500$ msec, and

(f) $5\ msec \leq (T_3 + T_4 + T_7) \leq 500\ msec$; and

combining said additional timing intervals with said intervals T_1-T_4 to generate said electrical signal.

37. The method as recited in claim 36, further comprising the step of selecting one of a plurality of predetermined, paired values of said intervals T_4 and T_7.

38. The method as recited in claim 36, further comprising the steps of: adjusting said amplitude to a first level L_1 during said intervals T_1, T_6, and T_7; adjusting said amplitude to a second level L_2 during said intervals T_2 and T_4; and adjusting said amplitude to a third level L_3 during said interval T_7, wherein L_3 is between L_1 and L_2.

39. The method as recited in claim 38, further comprising the step of selecting among a plurality of predetermined values for said levels L_1 through L_3.

40. The method as recited in claim 34, further comprising the step of shutting off said electrical signal after a selected period of time.

41. The method as recited in claim 34, further comprising the step of charge-balancing said electrical signal so that the total current delivered to a load during treatment is approximately zero.

42. The method as recited in claim 34, further comprising the step of reversing a polarity of said electrical signal after a selected period of time.

43. A system for treating tissue by application of an electrical signal comprising:

means for generating and applying an electrical signal to tissue, said signal based on at least four timing intervals having approximately the relationships

(a) $(2 \times T_2) \leq T \leq (20 \times T_2)$,

(b) $50\ \mu sec \leq (T_1 + T_2) \leq 5000\ \mu sec$,

(c) $T_3 \geq (10 \times T_1)$, and

(d) $0 \leq T_4 \leq 500$ msec, said timing intervals being used to generate said electrical signal.

44. The system as recited in claim 43, further comprising means for selecting one of a plurality of predetermined, paired values of said intervals T_1 and T_2.

45. The system as recited in claim 43, further comprising means for generating at least three additional timing intervals having approximately the relationships

(e) $0 \leq T_5 \leq T_1$,

(f) $0 \leq T_6 \leq T_1$,

(g) $0 \leq T_7 \leq 500$ msec, and

(f) 5 msec $\leq (T_3 + T_4 + T_7) \leq 500$ msec; and

means for combining said additional timing intervals with said intervals T_1-T_4 so that said electrical signal is based on said intervals T_1 -T_4 and said additional intervals T_5-T_7.

46. The system as recited in claim 45, further comprising means for selecting one of a plurality of predetermined, paired values of said intervals T_4 and T_7.

47. The system as recited in claim 45, further comprising :

means for adjusting said amplitude to a first level L_1 during said intervals T_1, T_6, and T_7;

means for adjusting said amplitude to a second level L_2 during said intervals T_2 and T_4; and

means for adjusting said amplitude to a third level L_3 during said interval T_7, wherein L_3 is between L_1 and L_2.

48. The system as recited in claim 47, further comprising means for selecting among a plurality of predetermined values for said levels L_1 through L_3.

49. The system as recited in claim 43, further comprising means for shutting off said electrical signal after a selected period of time.

50. The system as recited in claim 43, further comprising means for charge-balancing said electrical signal so that the total current delivered to a load is approximately zero.

51. The system as recited in claim 43, further comprising means for reversing a polarity of said electrical signal after a selected period of time.