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August 20, 2004

Dr. Yoseph Bar-Cohen
Jet Propulsion Laboratory (MS 82-105)
4800 Oak Grove Drive
Pasadena, CA 91109

Re: U. S. Patent Application Serial No. 10/093,866
**TRANSCUTANEOUS SPINE TRAUMA AND DISORDERS
TREATMENT USING ULTRASONICALLY INDUCED CONFINED
HEAT (ULICH) ZONE"**
Inventors: Yoseph Bar-Cohen, et al.
Filing Date: March 7, 2002
Our Docket No. 1279-346XX/10024933

Dear Dr. Bar-Cohen:

I am enclosing a copy of an Office Action that we recently received for the subject application, along with copies of references cited by the examiner. Also enclosed is a proposed response, for your review. A reply to the Office Action is due by **October 22, 2004**. Extensions of time are available at increasing costs up to **January 22, 2005**.

Claims 1, 2, 3, 16-20, 22, 24, 25, 27 and 28 are rejected as anticipated by U.S. Patent No. 5,743,863 to Chapelon. However, Chapelon teaches an ultrasound therapy method and apparatus that provides a wideband electronic signal, as described in column 4, lines 1-57 and shown in Figures 3 and 4 of the patent. As a result, an ultrasonic wave of varying frequency is produced. Thus, rather than teaching a pulsed wave as called for in claims 1, 2, 3, 16-20, 22, 24, 25, 27 and 28, Chapelon teaches a continuous wave of varying frequency. Moreover, Chapelon discounts any use of pulsed waves by indicating that pulse methods cannot heat tissue and that pulsed waves cannot be incorporated into his invention (col. 3, lines 16-21).

Claims 1-3, 7 and 16-21 are rejected as anticipated by U.S. Patent No. 6,325,769 to Klopotek. The Klopotek patent concerns a method and apparatus for treating skin that involves the use of ultrasonic waves. Klopotek teaches the use of pulsed ultrasonic waves to create negative pressure zones in the skin (col. 9, lines 48-57). The frequency of the pulsed waves is between 1 MHz and 500 MHz, and preferably between 10 and

80 MHz (col. 8, lines 51-56). As shown in the proposed response, I suggest amending independent claims 1, 16 and 22 to recite pulsed waves greater than 500 KHz, which is described at paragraph [0024], line 6 of the patent application. This frequency range will distinguish over Klopotek and other prior art cited by the examiner. As shown in the proposed response, claims 10, 15, 24 and 29 are amended in accordance with the frequency range of amended claims 9 and 22.

Claims 1-29 are rejected as obvious over European patent application No. EP 0 872 262 of Lidgren et al. in view of U.S. Patent No. 5,413,550 to Castel. The Lidgren et al. application concerns an apparatus that incorporates two ultrasound transducers. Although, Lidgren et al. discuss ultrasonic waves of frequency 0.5 - 2.5 MHz, they do not teach or suggest the use of pulsed waves. Castel describes an ultrasound apparatus that can provide pulsed ultrasound waves. However, the pulsed waves are limited to just two frequencies, either 1 MHz or 3 MHz (col. 5, ln. 32-35; col. 5, ln. 49-55). As shown in the proposed response, I suggest arguing that neither reference teaches pulsed waves in the 500 to 900 KHz range.

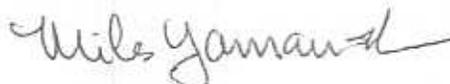
Claims 1-29 are rejected as obvious over Lidgren et al. in view of U.S. Patent No. 5,752,924 to Kaufman et al. The Lidgren et al. application is directed to the use of ultrasound to heat tissue, whereas Kaufman et al. are concerned with the use of ultrasound to alter fluid flow characteristics of bone tissue. I suggest arguing that the claims are not obvious because the references are concerned with completely different effects of ultrasound. All of this is explained in greater detail in the proposed response.

Claims 1-21 are rejected as obvious over Lidgren et al. in view of Klopotek, and claims 22-29 are rejected as obvious over Lidgren et al. in view of Klopotek and a) Kaufman et al. or b) Castel. As discussed in more detail in the proposed response, I suggest combining the arguments presented above by arguing that none of the Lidgren et al., Klopotek et al. and Castel references teach pulsed waves greater than 500 KHz, and Kaufman et al. are concerned only with the fluid flow effects of ultrasound.

Please review the proposed response and let me know if you agree with its substance. I would appreciate receiving your comments well in advance of the **October 22, 2004** due date.

In the meantime, please contact me if you have any questions or would like me to elaborate on any of the foregoing.

Very truly yours,



Miles Yamanaka

Enclosures

cc: Ms. Linda S. Stevenson

DRAFT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/093,866	Confirmation No. 2733
Applicant:	Yoseph Bar-Cohen et al.	
Filed:	March 7, 2002	
Art Unit:	3737	
Examiner:	Ruth S. Smith	
Atty. Dkt. No.:	1279-346/10024933	
Customer No.:	000167	

865 South Figueroa Street, 29th Floor
Los Angeles, California 90017-2576

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

In response to the July 22, 2004 Office Action, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of the claims in the application:

Listing of Claims:

1. (currently amended) A method of heating a tissue of the body of a life form, comprising:
 - (a) directing pulsed ultrasonic waves of about 500 to 900 KHz in frequency to a selected site of the tissue; and
 - (b) depositing at the selected site an amount of ultrasonic wave energy sufficient to heat the selected site without adversely damaging other areas of the body.
2. (original) The method of claim 1 in which the pulsed ultrasonic waves are pulsed focused ultrasonic waves.
3. (original) The method of claim 1 in which the tissue is an internal tissue.
4. (original) The method of claim 1 in which the tissue is a ligamentous tissue.
5. (original) The method of claim 4 in which the ligamentous tissue is associated with an intervertebral disc of the spine or a joint of the body.
6. (original) The method of claim 5 in which the ligamentous tissue associated with an intervertebral disc is the nucleus pulposus.
7. (original) The method of claim 1 in which the selected site is heated so that collagen crosslinking at the site is altered without adversely damaging other areas of the body.
8. (original) The method of claim 1 in which the selected site is heated so that tissue in the selected site shrinks without adversely damaging other areas of the body.
9. (currently amended) A method of treating a ligamentous tissue, comprising :
 - (a) directing pulsed focused ultrasonic waves of about 500 to 900 KHz in frequency to a selected site of the tissue; and
 - (b) depositing at the selected site an amount of ultrasonic wave energy sufficient to heat the site without adversely damaging other areas of the tissue.
10. (currently amended) The method of claim 9 in which the waves have a frequency of about ~~400KHz to about 4MHz~~ 700 to 900 KHz.
11. (original) The method of claim 9 in which the waves have a pulse duration of microseconds to seconds.
12. (original) The method of claim 9 in which wave amplitude of the pulsed focused ultrasonic waves is determined by a signal amplitude of about 1V to about 20V before amplification.

13. (original) The method of claim 9 in which the waves have a pulse rate of about 100 repetitions per second to about 1000 repetitions per second.
14. (original) The method of claim 9 in which the waves have a pulse shape in the form of a sine-wave or a square-wave.
15. (currently amended) The method of claim 9 in which the waves have ~~a frequency of about 100KHz to about 4MHz~~, a pulse duration of microseconds to seconds, a pulse rate of about 100 repetitions per second to about 1000 repetitions per second, a pulse shape in the form of a sine-wave or a square-wave, and wave amplitude of the pulsed focused ultrasonic waves is determined by a signal amplitude of about 1V to about 20V before amplification.
16. (currently amended) An apparatus for heating a tissue of the body of a life form, comprising:
 - (a) an ultrasonic source for producing pulsed ultrasonic waves;
 - (b) a lens for focusing said pulsed ultrasonic waves on a selected site of the tissue; and
 - (c) a controller for controlling wave frequency in the range of about 500 to 900 KHz and transmission parameters of said pulsed ultrasonic waves so that ultrasonic wave energy is deposited at the selected site in an amount sufficient to heat the selected site without adversely damaging other areas of the tissue.
17. (original) The apparatus of claim 16 in which the ultrasonic source is an ultrasonic transducer.
18. (original) The apparatus of claim 16 in which the lens is an ultrasonic lens.
19. (original) The apparatus of claim 16 in which the controller is a signal generator.
20. (original) The apparatus of claim 16 in which the ultrasonic transducer comprises both the ultrasonic source and the lens.
21. (original) The apparatus of claim 16 further comprising a temperature monitor for measuring the temperature of the selected site during heating.
22. (currently amended) An apparatus for treating ligamentous tissue comprising:
 - (a) a transducer assembly comprising an ultrasound transducer for producing pulsed focused ultrasonic waves, the transducer comprising a curved piezoelectric crystal;
 - (b) a signal generator for controlling wave frequency in the range of about 500 to 900 KHz and transmission parameters of said pulsed ultrasonic waves so that ultrasonic wave energy is deposited at a selected site of the tissue in an amount sufficient to heat the selected site without adversely damaging other areas of the tissue; and
 - (c) an amplifier for amplifying the signal from the signal generator; said amplifier being coupled to the output of the signal generator, said amplifier driving the ultrasound transducer.
23. (original) The apparatus of claim 22 further comprising a mounting fixture for holding the transducer assembly, and a positioning fixture for moving the transducer assembly.

24. (currently amended) The apparatus of claim 22 in which the waves have a frequency of about 100KHz to about 4MHz; 700 to 900 KHz.
25. (original) The apparatus of claim 22 in which the waves have a pulse duration of microseconds to seconds.
26. (original) The apparatus of claim 22 in which wave amplitude of the pulsed focused ultrasonic waves is determined by a signal amplitude of about 1V to about 20V before amplification.
27. (original) The apparatus of claim 22 in which the waves have a pulse rate of about 100 repetitions per second to about 1000 repetitions per second.
28. (original) The apparatus of claim 22 in which the waves have a pulse shape in the form of a sine-wave or a square-wave.
29. (currently amended) The apparatus of claim 22 in which the waves have ~~a frequency of about 100KHz to about 4MHz;~~ a pulse duration of microseconds to seconds, a pulse rate of about 100 repetitions per second to about 1000 repetitions per second, a pulse shape in the form of a sine-wave or a square-wave, and wave amplitude of the pulsed focused ultrasonic waves is determined by a signal amplitude of about 1V to about 20V before amplification.

REMARKS/ARGUMENTS

Claims 1-29 are pending.

Independent claims 1, 9, 16 and 22 are amended to clarify that the frequency of the pulsed waves is in the range of about 500 KHz to about 900 KHz. Support for this amendment is found in paragraph [0024], line 6. Accordingly, no new matter is added.

Claims 10, 15, 24 and 29 are amended to accord with the frequency range of amended claims 9 and 22. Support for the range of about 700 to 900 KHz recited in claims 10 and 24 is found in paragraph [0040], lines 11-12.

Rejections under 35 USC § 102

The rejection of claims 1, 2, 3, 16-20, 22, 24, 25, 27 and 28 under 35 USC § 102(b) as anticipated by Chapelon (U.S. Patent No. 5,743,863) is respectfully traversed. Chapelon teaches an ultrasound therapy method and apparatus that incorporates a signal generator for supplying an ultrasound transducer with a wideband electronic signal. The wideband signal provides a frequency spectrum that varies around a central frequency (col. 4, lines 1-5; Figure 4). As a result, an ultrasonic wave of varying frequency is produced, as shown in Figures 3 and 4. Thus, rather than teaching a pulsed wave as called for in claims 1, 2, 3, 16-20, 22, 24, 25, 27 and 28, Chapelon teaches a continuous wave of varying frequency (col. 4, lines 6-64). Moreover, Chapelon discounts any use of pulsed waves by indicating that pulse methods cannot heat tissue and that pulsed waves cannot be incorporated into the subject invention (col. 3, lines 16-21). Because Chapelon does not teach or suggest the use of pulsed waves to heat tissue, claims 1, 2, 3, 16-20, 22, 24, 25, 27 and 28 are not anticipated.

The rejection of claims 1-3, 7 and 16-21 as anticipated by Klopotek (U.S. Patent No. 6,325,769) is respectfully traversed. The Klopotek patent concerns a method and apparatus for treating skin that involves the use of ultrasonic waves. Klopotek teaches the use of pulsed ultrasonic waves to create negative pressure zones in the skin (col. 9, lines 48-57). The frequency of the pulsed waves is between 1 MHz and 500 MHz, and preferably between 10 and 80 MHz (col. 8, lines 51-56). In contrast, amended claims 1-3, 7 and 16-21 call for a frequency of about 500 to 900 KHz. Because Klopotek does not teach or suggest frequencies in the kilohertz range, claims 1-3, 7 and 16-21 are not anticipated.

Rejections under 35 USC § 103

The rejection of claims 1-29 as obvious over Lidgren et al. (European patent application No. EP 0 872 262 A2) in view of Castel (U.S. Patent No. 5,413,550) is respectfully traversed. The Lidgren et al. application concerns an apparatus that incorporates two ultrasound transducers to treat a tissue. Although, Lidgren et al. indicate that ultrasonic waves of frequency 0.5 - 2.5 MHz can be utilized, they do not teach or suggest the use of pulsed waves. Castel describes an ultrasound apparatus that can provide pulsed ultrasound waves. However, Castel teaches that wave frequency is restricted to two frequencies, either 1 MHz or 3 MHz, depending on the location of the target tissue (col. 5, ln. 32-35; col. 5, ln. 49-55).

As amended, claims 1-29 call for a pulsed ultrasound wave having a frequency of about 500 to 900 KHz. Lidgren et al. do not describe or even mention the use of pulsed waves of any frequency. Castel only teaches waves of 1 MHz and 3 MHz, and therefore does not teach or suggest pulsed waves in the kilohertz range. Because neither reference teaches or suggests pulsed waves in the 500 to 900 KHz range, all claim limitations are not taught. Accordingly, claims 1-29 are not obvious.

The rejection of claims 1-29 as obvious over Lidgren et al. in view of Kaufman et al. (U.S. Patent No. 5,752,924) is respectfully traversed. To establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP § 2143. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01.

As amended, claims 1-29 are directed to a method and apparatus for heating a target tissue using pulsed ultrasonic waves. According to the Office Action, it would be obvious to combine the system of Lidgren et al. with the pulsed mode of operation as taught by Kaufman et al. However, there is no motivation or suggestion to combine the references in this manner.

Lidgren et al. are concerned with heating intervertebral discs by directing two or more ultrasonic waves onto the same focal area from different directions (col. 3, ln. 12-25 and Figure 1). In such an arrangement, only the focal area receives energy from both ultrasonic waves, whereas other tissue locations receive energy from only one or the other wave. The combined heating due to both waves raises the focal area temperature higher than the surrounding tissue locations. In contrast, Kaufman et al. are concerned with the use of pulsed ultrasonic waves to alter fluid flow characteristics of bone tissue (col. 5, ln. 31-36). As pointed out by Kaufman et al., concentrating on fluid flow as the primary aspect of the ultrasonic signal leads to more effective and efficacious treatment (col. 5, ln. 36-39). Kaufman et al. do not describe or even mention heating tissue. Because Lidgren et al. are concerned with controlling one effect of ultrasonic waves, heating, while Kaufman et al. are concerned with controlling a completely different and independent effect of ultrasonic waves, fluid flow characteristics, there is no suggestion or motivation to combine the references. Accordingly, claims 1-29 are not obvious.

The rejection claims 1-21 as obvious over Lidgren et al. in view of Klopotek is respectfully traversed. As amended, claims 1-21 call for a pulsed ultrasonic wave frequency of about 500 to 900 KHz. As noted above, Lidgren et al. do not describe or even mention the use of pulsed waves of any frequency. Also, as noted above, Klopotek only teaches waves in the megahertz, not kilohertz, frequency range. Because neither reference teaches or suggests pulsed waves in the 500 to 900 KHz range, all claim limitations are not taught. Accordingly, claims 1-29 are not obvious.

The rejection of claims 22-29 as obvious over Lidgren et al. in view of Klopotek and Kaufman et al. is respectfully traversed. Amended claims 22-29 call for an ultrasonic wave frequency of about 500 to 900 KHz. As noted above, neither Lidgren et al. nor Klopotek teach or suggest pulsed waves in this frequency range. Moreover, as discussed above, there is no

suggestion or motivation to combine the Kaufman et al. patent, which deals with the effect of ultrasonic waves on fluid flow characteristics, with the Lidgren et al. application, which deals with the heating effects of ultrasonic waves. Similarly, there is no reason to combine the Kaufman et al. patent with the Klopotek patent, which deals with the shock wave effects of pulsed ultrasonic waves (col. 2, ln. 43 – col. 3, ln. 6; col. 9, ln. 48-57). Because the combination of Lidgren et al. and Klopotek does not teach every element of claims 22-29 and there is no motivation to combine these references with Kaufman et al., claims 22-29 are not obvious.

The rejection of claim 22-29 as obvious over Lidgren et al. in view of Klopotek and Castel is respectfully traversed. Amended claims 22-29 call for an ultrasonic wave frequency of about 500 to 900 KHz. As noted above, neither Lidgren et al. nor Klopotek teach or suggest pulsed waves in this frequency range. Moreover, as discussed above, Castel only teaches ultrasonic waves of 1 MHz and 3 MHz, not in the kilohertz range. Because all claim limitations are not taught or suggested, claims 22-29 are not obvious.

In view of the foregoing amendments and remarks, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Dated:

Respectfully submitted,

Miles Yamanaka
Reg. No. 45, 665



UNITED STATES PATENT AND TRADEMARK OFFICE

RB

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/093,866	03/07/2002	Yoseph Bar-Cohen	1279-346/10024933	2733

7590 07/22/2004
FULBRIGHT & JAWORSKI L.L.P.
Robert Berliner
Twenty-Ninth Floor
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Los Angeles, CA 90017-2571

EXAMINER

SMITH, RUTH S

ART UNIT PAPER NUMBER

3737

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKETED FOR
22 Aug 04
22 Sep 04
22 Oct 04
22 Nov 04
22 Dec 04
22 Jan 05

RECEIVED

JUL 26 2004

FULBRIGHT & JAWORSKI

Office Action Summary	Application No. 10/093,866	Applicant(s) BAR-COHEN ET AL	
	Examiner Ruth S Smith	Art Unit 3737	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-29 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-29 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 07 March 2002 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Notice of References Cited	Application/Control No. 10/093,866	Applicant(s)/Patent Under Reexamination BAR-COHEN ET AL.	
	Examiner Ruth S Smith	Art Unit 3737	Page 1 of 1

U.S. PATENT DOCUMENTS

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
A	US-5,752,924	05-1998	Kaufman et al.	601/2
B	US-5,413,550	05-1995	Castel, John C.	601/2
C	US-			
D	US-			
E	US-			
F	US-			
G	US-			
H	US-			
I	US-			
J	US-			
K	US-			
L	US-			
M	US-			

FOREIGN PATENT DOCUMENTS

*	Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
N					
O					
P					
Q					
R					
S					
T					

NON-PATENT DOCUMENTS

*	Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
U	
V	
W	
X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,2,3,16-20,22,24,25,27,28 are rejected under 35 U.S.C. 102(b) as being anticipated by Chapelon ('863). The claims are directly readable on Chapelon which disclose an ultrasound therapy system using pulsed focussed ultrasound waves to heat tissue. The wave parameters are within the ranges set forth in the claims.

Claims 1-3,7,16-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Klopotek ('769). The claims are directly readable on Klopotek which discloses an ultrasonic hyperthermia device which includes transmitting pulsed focussed ultrasound waves into a patient such that they are focused into a particular layer of the skin. The device includes an ultrasound source, focussing lens and controller. The device further includes means for monitoring the temperature of the selected site.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

Art Unit: 3737

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidgren et al in view of Castel. Lidgren et al disclose an ultrasound therapy system for treating disc disease. The ultrasound is focused in the intervertebral disc which includes the nucleus pulposus. The ultrasound is focused such that it does not adversely damage other areas of the body. The frequency is set between .5-2.5 MHz. The temperature in the area being treated is also monitored. With regard to claims 7,8, these limitations appear to be inherent results of using the system of Lidgren et al on a patient. Lidgren et al is silent with respect to many of the operating parameters of the system. Castel discloses an ultrasound therapy system. Castel discloses that many of the operating parameters are selected based upon the type of treatment being performed. It should be noted that while Lidgren et al is further silent with respect to the use of an amplifier, the use of such is old and well known in the art as shown for example by Castel. The use of an amplifier in the system of Lidgren et al would have been obvious in that such is a well known expedient in the art to aid in providing the desired signal effect. Castel discloses that it is well known that ultrasound therapy can be provided in a pulsed mode or continuous mode. The pulsed mode is used to reduce the average power delivered to the patient. It would have been obvious to one skilled in the art to have modified Lidgren et al such that it operates in a pulsed mode. The selection of such merely involves the selection of a known operating mode in the art

based upon the type of treatment being performed. It appears that any pulse selected would have a pulse duration that can be quantified in the second or microsecond range. Furthermore, Castel discloses that the pulse duration as well as duty factor should be selected based upon clinically tested parameters. Therefore, the operating parameters of the system, such as signal amplitude and pulse repetition rate, would have been obvious to one skilled in the art without undue experimentation based upon the desired effects of the system.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidgren et al in view of Kaufman et al. Lidgren et al disclose an ultrasound therapy system for treating disc disease. The ultrasound is focused in the intervertebral disc which includes the nucleus pulposus. The ultrasound is focused such that it does not adversely damage other areas of the body. The frequency is set between .5-2.5 MHz. The temperature in the area being treated is also monitored. With regard to claims 7,8, these limitations appear to be inherent results of using the system of Lidgren et al on a patient. Lidgren et al is silent with respect to many of the operating parameters of the system. It should be noted that while Lidgren et al is further silent with respect to the use of an amplifier, the use of such is old and well known in the art as shown for example by Kaufman et al. The use of an amplifier in the system of Lidgren et al would have been obvious in that such is a well known expedient in the art to aid in providing the desired signal effect. Kaufman et al further disclose in column 1, that it is known in the art of ultrasound therapy to use pulsed waves. The pulsed mode can be used to reduce the average power delivered to the patient. It would have been obvious to one skilled in the art to have modified Lidgren et al such that it operates in a pulsed mode. The selection of such merely involves the selection of a known operating mode in the art based upon the type of treatment being performed. It appears that any pulse selected would have a pulse duration that can be quantified in the second or microsecond range. Column 1 of Kaufman further discloses the use of a pulsed sine wave at a frequency within the range of 1.3-2.0 MHz and at a repetition rate of 100 to 1000 HZ. The selection of the operating parameters such as the signal amplitude,

frequency, repetition rate and pulse duration would have been obvious to one skilled in the art without undue experimentation based upon the desired effects of the system. The use of a wide range of such parameters are well known in the art and the selection of these is based upon the desired results of the treatment and the location of the treatment.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidgren et al in view of Klopotek ('769). Lidgren et al disclose an ultrasound therapy system for treating disc disease. The ultrasound is focused in the intervertebral disc which includes the nucleus pulposus. The ultrasound is focused such that it does not adversely damage other areas of the body. The frequency is set between .5-2.5 MHz. The temperature in the area being treated is also monitored. With regard to claims 7,8, these limitations appear to be inherent results of using the system of Lidgren et al on a patient. Lidgren et al is silent with respect to many of the operating parameters of the system. Klopotek which discloses an ultrasonic hyperthermia device which includes transmitting pulsed focussed ultrasound waves into a patient such that they are focused into a particular layer of the skin. The device includes an ultrasound source, focussing lens and controller. The device further includes means for monitoring the temperature of the selected site. It would have been obvious to one skilled in the art to have modified Lidgren et al such that it operates in a pulsed mode. The selection of such merely involves the selection of a known operating mode in the art based upon the type of treatment being performed. It appears that any pulse selected would have a pulse duration that can be quantified in the second or microsecond range. The selection of the operating parameters such as the signal amplitude, frequency, repetition rate and pulse duration would have been obvious to one skilled in the art without undue experimentation based upon the desired effects of the system. The use of a wide range of such parameters are well known in the art and the selection of any of these is based upon the desired results of the treatment and the location of the treatment.

Art Unit: 3737

Claims 22-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidgren et al in view of Klopotek ('769) and Kaufman et al or Castel. Lidgren et al disclose an ultrasound therapy system for treating disc disease. The ultrasound is focused in the intervertebral disc which includes the nucleus pulposus. The ultrasound is focused such that it does not adversely damage other areas of the body. The frequency is set between .5-2.5 MHz. The temperature in the area being treated is also monitored. With regard to claims 7,8, these limitations appear to be inherent results of using the system of Lidgren et al on a patient. Lidgren et al is silent with respect to many of the operating parameters of the system. It should be noted that while Lidgren et al is further silent with respect to the use of an amplifier, the use of such is old and well known in the art as shown for example by Castel and Kaufman et al. The use of an amplifier in the system of Lidgren et al would have been obvious in that such is a well known expedient in the art to aid in providing the desired signal effect. Klopotek which discloses an ultrasonic hyperthermia device which includes transmitting pulsed focussed ultrasound waves into a patient such that they are focused into a particular layer of the skin. The device includes an ultrasound source, focussing lens and controller. The device further includes means for monitoring the temperature of the selected site. It would have been obvious to one skilled in the art to have modified Lidgren et al such that it operates in a pulsed mode. The selection of such merely involves the selection of a known operating mode in the art based upon the type of treatment being performed. It appears that any pulse selected would have a pulse duration that can be quantified in the second or microsecond range. The selection of the operating parameters such as the signal amplitude, frequency, repetition rate and pulse duration would have been obvious to one skilled in the art without undue experimentation based upon the desired effects of the system. The use of a wide range of such parameters are well known in the art and the selection of any of these is based upon the desired results of the treatment and the location of the treatment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth S Smith whose telephone number is (703) 308-3063. The examiner can normally be reached on M-F 5:30 AM- 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Angela Sykes can be reached on (703) 308-5181. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Ruth S Smith
Primary Examiner
Art Unit 3737

RSS

INFORMATION DISCLOSURE CITATION
(Use several sheets if necessary)

Docket Number (Optional) 1279-346XX	Application Number Not Yet Assigned
Applicant(s) Yoseph Bar-Cohen	
Filing Date March 7, 2002	Group Art Unit Not Yet Assigned

1. Park
8-22-02
#5/ID

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EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILED DATE IF APPROPRIATE
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1102 U.S. PTO
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03/07/02

DUPLICATE

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REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation	
						YES	NO

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER <i>Paul J. Smith</i>	DATE CONSIDERED <i>7/04</i>
----------------------------------	--------------------------------

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

13

wherein said preselected periodic therapeutic sine modulated ultrasonic sine signal is a frequency and amplitude modulated signal with a carrier frequency having a selected value in the range between about 25 kHz and about 2 MHz, and having a sweep range between the selected value and about 2 MHz;

a modulating frequency having a selected value in the range up to about 25 kHz, and having a sweep range between the selected value and about 25 kHz;

a modulation index being up to 1000;

a pulse width being between about 0.1 ms and about 1.0 s;

a duration of a pulse and a pause for one repetition being between about 0.01 ms and about 1.0 s;

a number of pulse repetitions within a cycle being up to 5000;

a cycle duration being between about 0.2 ms and about 1.0 s;

an intensity being in the range of 20-100 mW/cm²; and a duration of exposure being between about 5 minutes and about 1 hour for 1 to 3 times a day.

8. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 7, wherein said preselected periodic therapeutic sine modulated ultrasonic sine signal is the frequency and amplitude modulated signal with:

the carrier frequency being 1.1 MHz.

the modulating frequency being 500 Hz, said modulating frequency having a sweeping range between 500 Hz and 2000 Hz;

the modulation index being 1.

the pulse width being 4 ms.

the duration of a pulse and a pause for one repetition being 8 ms.

the number of pulse repetitions within a cycle being 25, the cycle duration being 1 s, and

the intensity being 45 mW/cm².

9. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 1, wherein said thickness of said soft tissue is calculated as

$$d_s = v_s \tau$$

where d_s is the desired thickness; v_s is the velocity of ultrasound in soft tissue; and τ is a round-trip transit time for said acoustic pulse to travel from a source thereof through the soft tissue, to the bone tissue, and back through the soft tissue.

10. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 1, wherein said initial interrogating acoustic ultrasonic pulse is an exponentially damped sinusoidal signal at 1.1 MHz, with a duration of about 2 μ s.

11. A method of non-invasively therapeutically treating a bone tissue in vivo using ultrasonic signals, comprising the steps of:

(A) generating a preselected periodic therapeutic ultrasonic signal;

(B) selecting a power intensity of said therapeutic signal by virtue of

(Ba) generating an interrogating ultrasonic pulse,

(Bb) transmitting said interrogating ultrasonic pulse to

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(Bc) receiving a portion of said interrogating pulse reflected from said bone tissue.

(Bd) determining the thickness of said soft tissue using said reflected portion, and

(Be) adjusting the amplitude of said therapeutic ultrasonic signal as to ensure that a spatial-average time-average power intensity thereof reaching said bone tissue corresponds to a predetermined value; and

(C) exposing said bone tissue to said therapeutic ultrasonic signal transmitted through soft tissue overlying said bone tissue.

12. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 11, wherein said preselected periodic therapeutic ultrasonic signal is amplitude modulated and has

a carrier frequency being between about 25 kHz and about 2 MHz,

a modulating frequency being up to about 25 kHz,

a modulation index being up to 1000,

a effective duty cycle being between about 0.0001 and about 1,

an intensity being in the range of 20-100 mW/cm², and a duration of exposure being between about 5 minutes and about 1 hour for 1 to 3 times a day.

13. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 12, wherein said amplitude modulated signal has

the carrier frequency of 1.1 MHz.

the modulating frequency of 20 kHz.

the modulation index of 0.3.

the pulse width of 0.5 ms.

the cycle duration of 5 ms, and

the intensity of 45 mW/cm².

14. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 12, wherein said amplitude modulated signal has

the carrier frequency of 1.1 MHz.

the modulating frequency of 20 kHz.

the modulation index of 0.3.

the pulse width of 0.1 ms.

the cycle duration of 0.5 ms, and

the intensity of 45 mW/cm².

15. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 12, wherein said amplitude modulated signal has:

a pulse width of between about 0.1 ms and about 1.0 s,

a duration of a pulse and a pause for one repetition of between about 0.1 ms and about 1.0 s.

a number of pulse repetitions within a cycle of up to 5000, and

a cycle duration of between about 0.2 ms and about 1.0 s.

16. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 15, wherein said amplitude modulated signal has

the carrier frequency of 1.1 MHz.

the modulating frequency of 5 kHz.

the modulation index of 0.3.

the pulse width of 4 ms.

the duration of a pulse and a pause for one repetition of 8 ms.

the number of pulse repetitions within a cycle of 25.

the intensity of 45 mW/cm².

17. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 11, wherein said preselected periodic therapeutic ultrasonic signal is a frequency and amplitude modulated signal with

a carrier frequency having a selected value in the range between about 25 kHz and about 2 MHz, and having a sweep range between the selected value and about 2 MHz;

a modulating frequency having a selected value in the range up to about 25 kHz, and having a sweep range between the selected value and about 25 kHz;

a modulation index being up to 1000.

a pulse width being between about 0.1 ms and about 1.0

s, duration of a pulse and a pause for one repetition being between about 0.1 ms and about 1.0 s.

a number of pulse repetitions within a cycle being up to 5000.

a cycle duration being between about 0.2 ms and about 1.0

s, an intensity being in the range of 20-100 mW/cm², and a duration of exposure being between about 5 minutes and about 1 hour for 1 to 3 times a day.

18. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 17, wherein said frequency and amplitude modulated signal has

the carrier frequency of 1.1 MHz.

the modulating frequency of 500 Hz, said modulating frequency sweeping range of between 500 Hz and 2000 Hz;

the modulation index of 1,

the pulse width of being 4 ms.

the duration of a pulse and a pause for one repetition of 8 ms.

the number of pulse repetitions within a cycle of 25,

the cycle duration of 1 s, and

the intensity of 45 mW/cm².

19. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 11, wherein said thickness of said soft tissue is calculated as

$$d_s = v_s \tau / 2$$

5 where d_s is the desired thickness; v_s is the velocity of ultrasound in soft tissue; and τ is a round-trip transit time for said acoustic pulse to travel from a source thereof through the soft tissue, to the bone tissue, and back through the soft tissue.

10 20. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 11, wherein said initial interrogating acoustic ultrasonic pulse is an exponentially damped sinusoidal signal at 1.1 MHz, with a duration of about 2 μ s.

21. An apparatus for non-invasively therapeutically treating bone tissue in vivo comprising:

a waveform synthesizer for producing

an initial interrogating acoustic ultrasonic signal to determine the thickness of a soft tissue overlying said bone tissue, and

an excitation signal to be applied to said bone tissue, said excitation signal being a finite duration sine wave carrier signal with a frequency selected in the ultrasonic region to approximately 1.1 MHz, modulated by a modulating sine signal with a frequency selected between about 0 Hz and about 25 kHz, said excitation signal being repeated substantially in the range 1 to 5000 Hz;

an ultrasonic transducer having

a transmitting element being connected to said waveform synthesizer and adapted for acoustic coupling to nearby skin and for conveying said interrogating and said excitation signals along an ascertained path to said bone tissue,

a receiving element for receiving a reflected portion of said interrogating signal reflected from said bone tissue; and

40 a computer coupled to said transducer and said receiving element, for adjusting said excitation signal responsive to said received reflected signal.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,752,924
DATED : May 19, 1998
INVENTOR(S) : Jonathan J. Kaufman and Alessandro E. Chiabrera

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

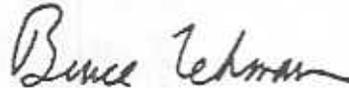
Claim 4, column 12, line 18, insert:

-- the modulation index being 0.3,
the pulse width being 0.1 ms,
the cycle duration being 0.5 ms, and
the intensity being 45 mW/cm². --

Claim 17, column 15, line 16, insert --a-- before "duration".

Claim 20, column 16, line 14, delete "," after "sinusoidal".

Signed and Sealed this
Eleventh Day of August 1998



Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks



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U. S. Patent and Trademark Office: U. S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO		<i>Complete if Known</i>	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>		Application Number	10/093866
		Filing Date	March 7, 2002
		First Named Inventor	Dr. Yoseph Bar-Cohen
		Art Unit	N/A
		Examiner Name	Not Yet Assigned
Sheet	1	of	2
		Attorney Docket Number	LA-1279-346/10024933

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Document Number		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)				
JLL	AA	6325769-			Klopotek	
	AB					

FOREIGN PATENT DOCUMENTS							
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ³
		Country Code ⁴ -Number ⁵ -Kind Code ⁶ (if known)					
D.C. # → JLL	BA	EP-88186818-2	no pub #		Scandinavia-International AB		
	BB	EP-872262	A2		" "		

¹ Applicant's unique citation designation number (optional). ² See attached Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 801.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the application number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²

Examiner Signature	<i>[Signature]</i>	Date Considered	7/04
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 509. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

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 TC 3100 MAIL ROOM



US005413550A

United States Patent [19]

[11] Patent Number: 5,413,550

Castel

[45] Date of Patent: May 9, 1995

- [54] ULTRASOUND THERAPY SYSTEM WITH AUTOMATIC DOSE CONTROL
- [75] Inventor: John C. Castel, Topeka, Kans.
- [73] Assignee: PTL, Inc., Topeka, Kans.
- [21] Appl. No.: 95,102
- [22] Filed: Jul. 21, 1993
- [51] Int. Cl.⁶ A61H 1/00
- [52] U.S. Cl. 601/2; 601/3; 607/97
- [58] Field of Search 601/2-4; 607/97; 604/22

Eighth Annual Northeast Bioengineering Conference, Cambridge Mass. 27-28 Mar. 1980 pp. 129-132.
 Castel, J. C., *Therapeutic Ultrasound*, Reprinted From "Rehab and Therapy Products Review", Jan./Feb. 1993, pp. 22-31 with reference List.

Primary Examiner—Ruth S. Smith
 Attorney, Agent, or Firm—Litman, McMahon & Brown

[57] ABSTRACT

An ultrasound therapy system with automatic dose control includes an ultrasound transducer, an ultrasound generator controllable in frequency and power output connected to the transducer, a system controller interfaced to the generator, input switches interfaced to the controller to enable the input of selected ultrasound treatment parameters, and a display interfaced to the controller. The controller is programmed to calculate an ultrasound treatment dosage in terms of frequency, ultrasound intensity, and treatment time from the entered treatment parameters. Once treatment is started, the controller tracks the accumulated dosage applied to the tissue. The clinician can vary the intensity or treatment time, and the controller will recalculate the other factor for the remaining portion of the unapplied treatment dosage.

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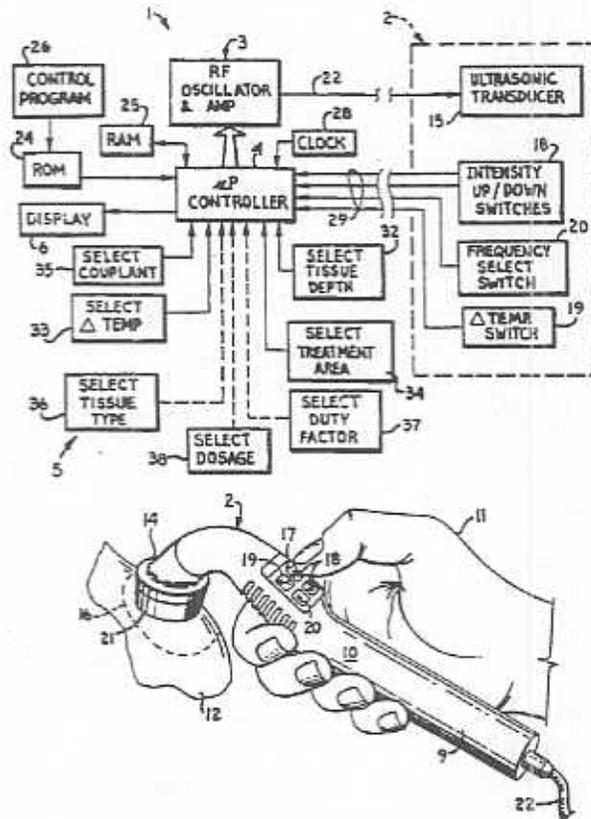
U.S. PATENT DOCUMENTS

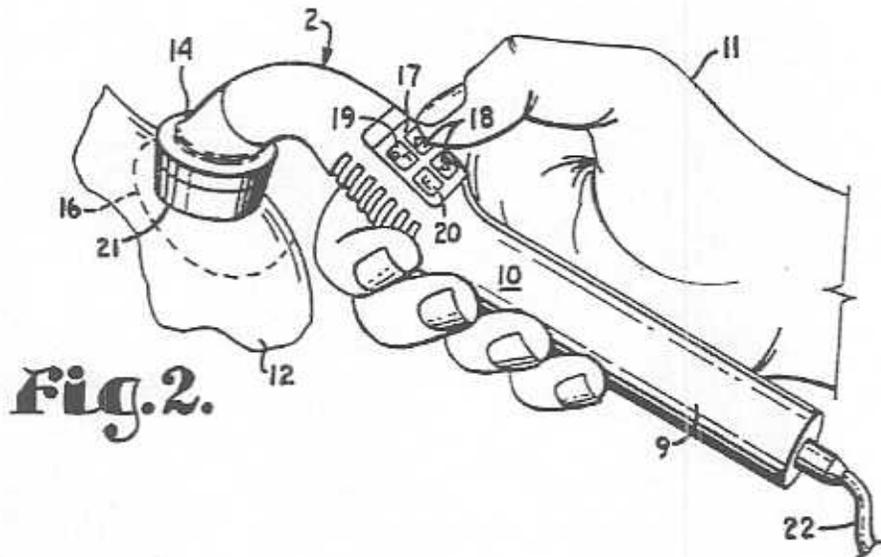
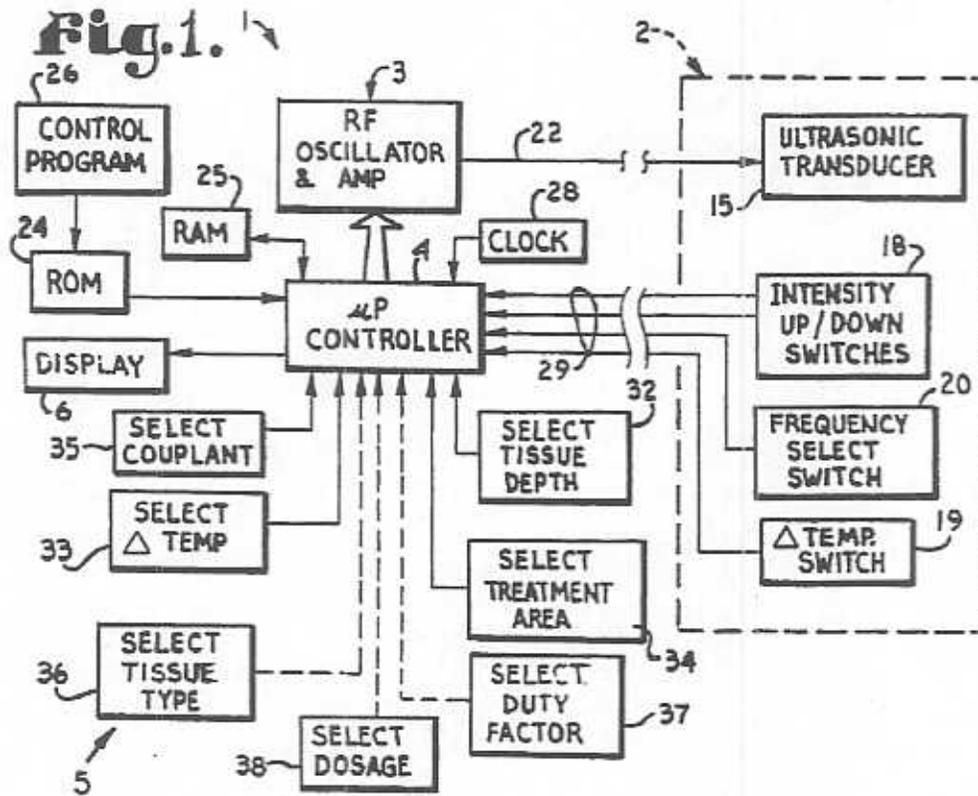
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16 Claims, 3 Drawing Sheets





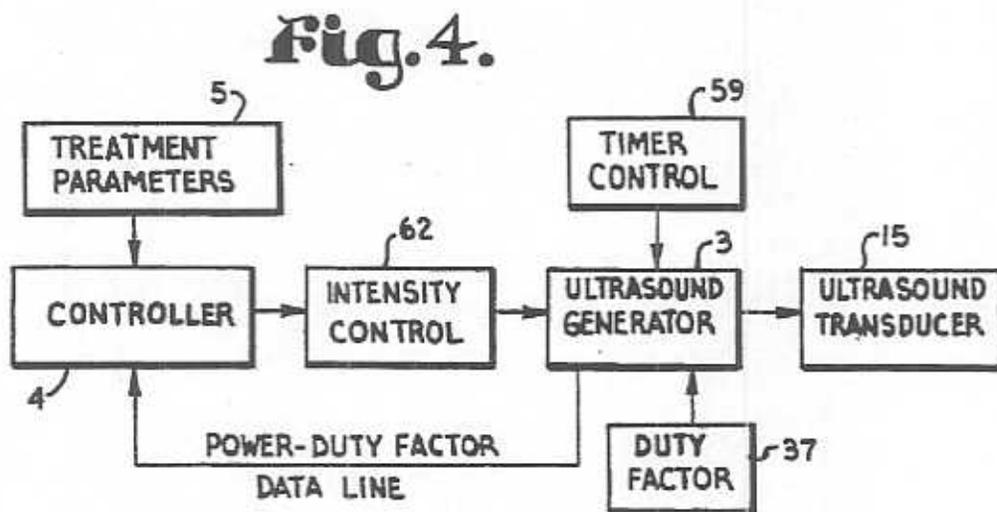
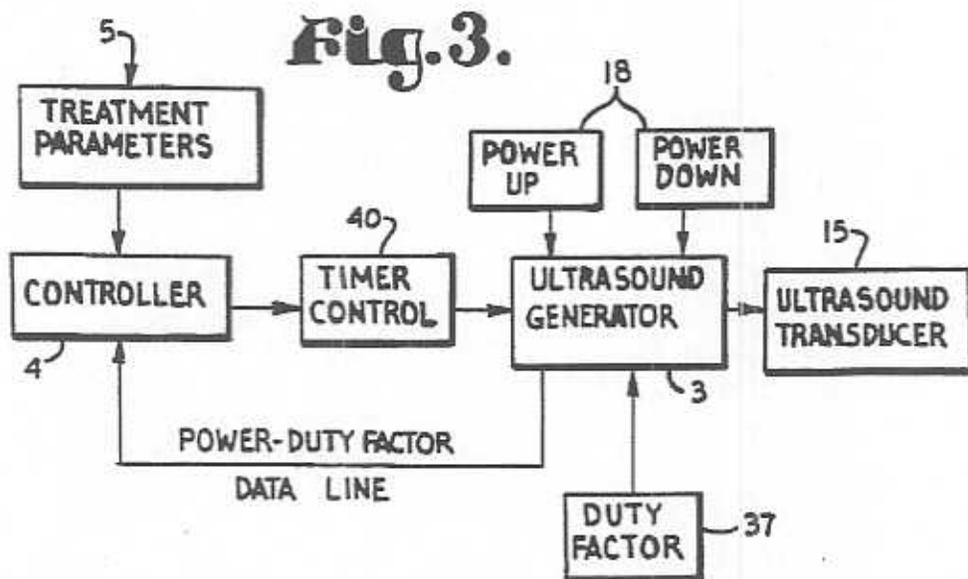
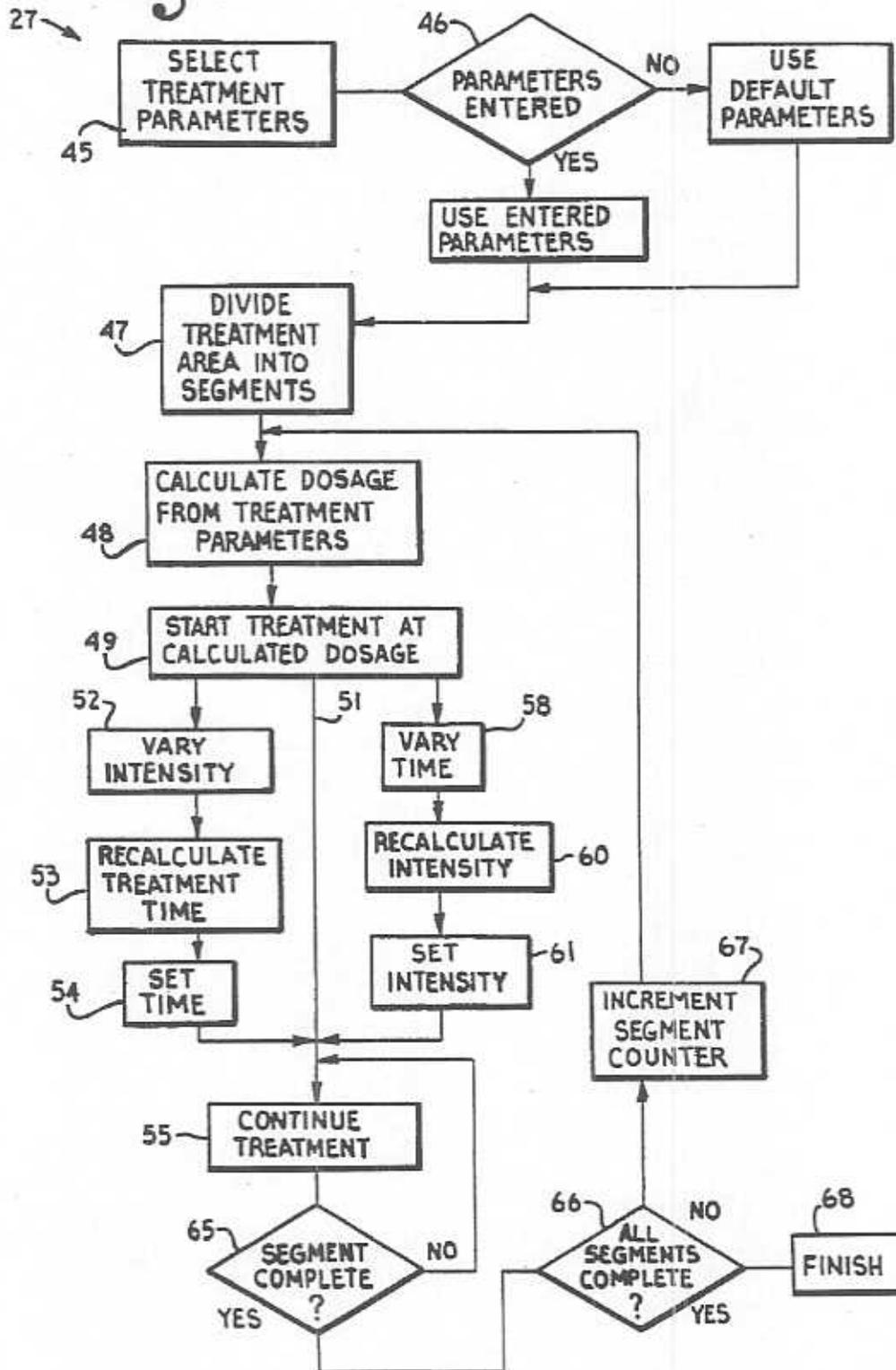


Fig. 5.



ULTRASOUND THERAPY SYSTEM WITH AUTOMATIC DOSE CONTROL

BACKGROUND OF THE INVENTION

Ultrasound has been used as a therapeutic technique in physical medicine for over forty years. By 1955, the Council on Physical Medicine and Rehabilitation of the American Medical Association recommended the technique as an adjunctive therapy for the treatment of pain, soft tissue injury, and joint dysfunction including osteoarthritis, periarthritis, bursitis, tenosynovitis, and a variety of musculoskeletal syndromes. Other applications such as acceleration of wound healing, phonophoresis of topical drugs, treatment of scar tissue, and treatment of sports injuries have been reported.

Ultrasonic therapy relies on mechanical vibration of tissue to cause thermal and nonthermal effects, using the conventional therapeutic frequency of 1 Mhz (megahertz) or the newer 3 Mhz frequency. Basically, the electrical output from the ultrasonic generator is converted into mechanical vibration through a transducer made generally of a crystalline material, such as lead zirconate titanate (PZT) or other synthetic or natural crystals. The mechanical vibration produces an acoustic wave which travels through the tissue and is absorbed in the process. The rate of absorption and, thus, the thermal effect is based on the tissue type encountered, the frequency of the ultrasound beam, and the intensity of the ultrasonic output. The energy is transferred from the transducer to the patient's tissue using a coupling medium or couplant, such as ultrasonic gel, lotion, hydrogel, or water. Output may be continuous wave or pulsed depending on the therapeutic indication. Output intensities of 0.1-3.0 W/cm² (watts per square centimeter) are typically applied for therapeutic purposes in pulsed or continuous modes with ultrasound therapy.

Power output of an ultrasonic transducer may be indicated in watts as the total power emanating from the transducer or as intensity in W/cm² which is the total acoustic power output divided by the effective radiating area or surface (ERA) of the transducer. Intensity is commonly used for therapeutic ultrasound applications. Continuous wave ultrasound output may also be measured in energy units of joules (watt-seconds) which is the amount of total delivered acoustic power applied to the tissue over the total treatment time. Continuous wave ultrasound is generally used for thermal applications.

Pulsed output is also referred to as amplitude modulated waveform operation. This means that the output turns on and off in short periodic intervals. This reduces the average power delivered to the patient, as compared to continuous output. Output power is displayed as the average power during the pulse of ultrasonic energy. In order to calculate the average power over time, the indicated power output is multiplied by a duty factor, which is defined as the on-time per period divided by the total time of the period, that is, duty factor = (time_{on})/(time_{on} + time_{off}). Pulsed outputs are generally used in pain control and tissue healing applications at non-thermal levels. Pulse durations and duty factors should be selected based on clinically tested parameters. Ultrasonic therapy systems should provide a full range of pulsed modes, allowing the clinician to treat acute as well as chronic injury.

In order to accurately portray the output characteristics of ultrasonic therapy transducers, an evaluation of

the radiating surface must be made. This can be done using sophisticated testing systems which scan each portion of the transducer with an underwater microphone known as an acoustic hydrophone. Evaluation of the radiating surface of most transducers demonstrates that in the near field (generally within 10-30 cm of the sound head surface), significant irregularities in output intensity exist. These range from little or no intensity to very high peak intensities.

The effective radiating area (ERA) of an ultrasound transducer is determined by scanning the transducer at a distance of 5 mm (millimeters) from the radiating surface and recording all areas in excess of 5 per cent of the maximum power output found at any location on the surface of the transducer. The ERA is always smaller than the actual transducer surface; thus, the apparent size of the transducer is not indicative of the effective radiating surface. For this reason, individual scans of each transducer should be performed to ensure proper calibration of intensity in W/cm² of ultrasonic output. A common mistake is to assume that the entire surface of an ultrasound transducer radiates ultrasound output. This is generally not true, particular with larger transducers, such as 10 cm². There is no point in having a large transducer with a small effective radiating surface because such an arrangement mechanically limits the coupling in smaller areas. The transducer ERA should match the physical transducer head size as closely as possible for ease of application to various body surfaces in order to maintain the most effective coupling.

The major measure of beam homogeneity of an ultrasonic transducer is the beam nonuniformity ratio (BNR). Beams from practical ultrasound transducers are not homogeneous in intensity across their wavefronts. The BNR is the ratio of the highest intensity found in the field to the average intensity, as indicated on the output display of the generator. If, for example, the BNR of a transducer is 6:1, as is typical for many ultrasonic therapy transducers, and the intensity is set at 1.5 W/cm², intensities in the order of 9.0 W/cm² would be present in the field. The high peak intensities with high BNR's are responsible for the discomfort or periosteal pain often associated with ultrasound treatment.

The higher the BNR, the more important it is to move the transducer faster during treatment to avoid hot spots and areas of tissue damage or cavitation, which refers to microbubble implosions causing small vessel and cell membrane damage. Application technique is, thus, BNR dependent. The allowable intensity of the ultrasound beam should be the lower of patient tolerance to the beam intensity or the transient cavitation threshold of 8 W/cm², which is calculated by multiplying the BNR by the output intensity. The lower the BNR, that is, the more even the spacial intensity of the beam, the slower the operator may apply the ultrasound to the treatment area without fear of periosteal burning or transient cavitation). Low BNR's provide highly uniform ultrasonic therapy fields, allowing rapid bulk heating, since the clinician is able to move slowly in the treatment area with a homogeneous beam. Accurate measurement of BNR also allows the clinician to select transducers which ensure consistent, uniform beam characteristics.

Absorption characteristics of ultrasound are unique in that the absorption coefficients for many tissues vary linearly with frequency over the range of 1.0 to 5.0

MHz. For this reason, transducers operating at both 1 and 3 MHz ultrasonic frequencies should be available to provide the clinician control the depth of beam and biological effects. Ultrasound energy at 1 MHz has a half value layer (50 per cent energy absorption layer) of 3.0 cm in muscle, whereas 3 MHz has a half value layer of 1.0 cm in muscle. The 3 MHz frequency is selected where the effect is required superficially. This would include reduction of edema in recent injuries and treatment of skin abrasions, bruising, epicondylitis, arthritis of small joints, scar tissue, periostitis, ulcers, and pressure sores. Acute injury responds well to 3 MHz ultrasound treatment, and there is a good analgesic effect. The lower frequency of 1 MHz common to most ultrasonic therapy generators is used to treat more deeply seated lesions where fibrotic or sclerotic conditions exist, widespread contractures in tendon and muscle, and large joints affected by osteoarthritis.

The biological effects of ultrasound may be categorized according to two major areas: thermal effects and nonthermal effects, including acoustic streaming, cavitation, and other mechanical effects.

In local regions of tissue subjected to an ultrasonic plane travelling wave, heat is produced at a rate per unit volume proportional to the level of intensity and the absorption coefficient of the tissue. Under stable conditions, temperature increases at a constant rate, provided the treatment area is limited to an area of approximately twice the ERA of the transducer. Treating too large of an area at a time will result in cooling effects by the normal blood flow, and an inadequate tissue temperature increase will result. Surprisingly, many therapeutic ultrasound treatments given every day in the clinic do not result in temperature increases of noteworthy value, although the clinician's intent was to provide thermal effects. This is due in part to the uneven distribution of ultrasound across the transducer surface (high BNR), the treatment of too large of an area for too short of a time, and the lack of consideration of tissue target location and coupling media.

Tissues with high collagen content most strongly absorb ultrasonic energy at the frequencies commonly used therapeutically. Most soft tissues have similar absorption coefficients. As previously described, beam penetration is a function of frequency. Thus, if one wishes deep heating, the use of 1 MHz ultrasound is indicated, as compared to surface where 3 MHz would be used.

The capability of obtaining reliable temperature increases in the tissue is the key to achieving therapeutic effects. Alterations in cell membrane diffusion, extensibility of collagen, and catalytic reactions times are specifically temperature dependent. In general, the application of therapeutic ultrasound is used to produce heating effects ranging from mild (1° C. tissue temperature increase), moderate (2° C.), or vigorous (4° C.). The higher temperature increases are useful in the treatment of chronic connective tissue and joint diseases such as contracture, chronic scars, and osteoarthritis, whereas the lower temperature increases are used in the treatment of subacute injury and to accelerate tissue repair. It has been noted that thermal levels of ultrasound induce local release of histamine, further increasing blood flow and local microcirculation. Other researchers have demonstrated that the selective heating of nerve tissue may produce temporary conduction blocks in nerve action potential propagation. This may be a factor in

blocking pain with ultrasonic therapy applied at thermal levels.

Regarding nonthermal effects, acoustic streaming is an effect produced by the ultrasonic beam within the tissue which occurs primarily at the cell membrane interface. Streaming is the unidirectional movement of tissue components exposed to the ultrasonic field. This effect has been observed by many investigators, and is thought to be responsible for affecting cellular diffusion rates, membrane permeability, and accelerated synthesis of collagen. It should be noted that these stimulatory effects generally occur at low intensity, pulsed modes of 3 MHz ultrasound and are not evident at higher intensities and different frequencies. The primary effects on collagen synthesis and healing rates appear to occur at an early stage of the regeneration process during active growth and proliferation. Reactions limited by diffusion rates including the re-absorption of exudates may be accelerated by streaming effects. These movements also contain enough energy to enhance the making or breaking of weak secondary hydrogen bonds, thus accelerating enzymatic reactions.

It has also been found that platelets exposed to ultrasonic fields release serotonin. This may help to explain pain reduction effects, since serotonin is an important neurotransmitter involved in the release of endogenous opiates, such as enkephalins and dynorphins. Increased phagocytic activity and bactericidal capacity have also been observed with five minute ultrasonic energy exposures at therapeutic levels of insonation.

Cavitation is a condition where gas bubbles form within the tissues as a result of ultrasonic radiation. These bubbles oscillate within the ultrasound field at the ultrasonic frequency. Stable bubble formation *in vivo* has been observed using acoustic imaging techniques at intensities in the therapeutic range at intermuscular interfaces. Low level cavitation and mechanical micromassage at the cellular level is thought to be responsible for cellular stimulation, edema reduction in post traumatic injury, as well as the stimulation of mechanoreceptors and the autonomic nervous system. Sympathetic, parasympathetic, and sensory stimulation by ultrasound in pulsed modes may account for the pain relieving effects often associated with ultrasonic therapy. Some researchers have demonstrated increased nerve conduction velocity following insonation of nerve tissues. It is apparent from many clinical observations that ultrasound produces significant analgesic effects in a large percentage of patients on account of both neurologic stimulation and the anti-inflammatory effects of ultrasound on tissues.

As described above, ultrasound therapy has measurable and otherwise verifiable thermal and nonthermal effects on various types of tissues depending on various parameters of the applied acoustic energy and manner of application to tissues. Thus, control of the parameters of therapeutic ultrasound would provide a clinician with the capability of treating a great variety of ailments with predictable results. However, the great majority of ultrasound treatments are applied with fixed parameters, usually 1 MHz at 1.5 W/cm² for five minutes with a relatively high BNR transducer, regardless of the area or depth of intended tissue treatment. Although some nonthermal benefits may be derived from such an approach, the thermal benefits usually intended are seldom realized from such an imprecise application of ultrasound.

While clinicians, such as osteopaths, chiropractors, and physical therapists, and others who employ therapeutic ultrasound are usually knowledgeable in their respective areas of specialty, they are usually not trained to make the necessary adjustments to therapeutic ultrasound instruments which would enable the wide variety of treatments of which the application of ultrasound is capable. Therefore, an approach which would facilitate the control of ultrasound transducer parameters in relation to the type and location of tissue to be treated and the desired effect on the treated tissue would be of considerable benefit to the patient receiving the treatment.

SUMMARY OF THE INVENTION

The present invention provides apparatus and methods for applying ultrasound to the treatment of tissues which facilitates the insonation of tissues with a precise "dose" of ultrasound energy which is calculated on the basis of treatment parameters input into the apparatus. In general the apparatus includes an ultrasonic transducer, an ultrasound generator controllable in frequency and power output connected to the transducer, an ultrasound controller including a microprocessor interfaced to the ultrasound generator, ultrasound parameter input switches interfaced to the controller, and a display interfaced to the controller. The transducer preferably has a low beam non-uniformity ratio (BNR), and the apparatus preferably includes multiple transducers having heads with different effective radiating areas to facilitate treatment of different sized areas of tissue. The ultrasound generator includes a radio frequency oscillator operable at one and three megahertz along with a radio frequency amplifier with a controllable power output.

The controller is programmed to calculate a treatment dose of ultrasound energy in terms of treatment frequency, output intensity (W/cm^2), and treatment time based on the clinician's selection of a number of treatment parameters. The treatment parameters include primarily the depth of tissue to be treated, the desired tissue temperature rise as a result of treatment, the area of tissue to be treated, and a selection of an ultrasound couplant. The treatment parameters may also include a selection of tissue type and duty factor of the ultrasound output signal. Preferably, the control program reverts to default treatment parameters if no treatment parameters are entered.

The selected tissue depth determines the frequency of the ultrasound output signal. A three megahertz signal is absorbed within a relatively shallow depth of tissue, depending on the character of the tissue. A one megahertz signal has less absorption in shallow layers and therefore penetrates to greater depths in comparison to a three megahertz signal.

The output intensity of the transducer for a given treatment is determined by the desired temperature rise of the target tissue and the type of the target tissue, the ultrasonic transmission characteristics of the coupling medium employed and of tissue intervening between the transducer and the target tissue, and the area of application of the target tissue. Thermal ultrasound treatments are characterized as mild, moderate, and vigorous, corresponding to tissue temperature increases respectively of one, two, and four degrees Celsius. The ultrasonic transmissivity of coupling media or couplants range from nearly 100% for water and 96% for aqueous gel to 68% for hydrogel. The control program of the

present invention provides for the selection of one of a number of common ultrasonic couplants. Ultrasound energy absorption in the selected couplant is factored into the determination of the amount of ultrasound energy which can be transferred to the target tissue. Various types of tissues have different ultrasound absorption characteristics, ranging from low absorption in fat, moderate absorption in muscles, higher absorption in connective tissue such as tendons and ligaments, and the highest absorption in bone tissue.

The ultrasound power output of the transducer is applied over its effective radiating area (ERA). The controller is programmed to break down a relatively large treatment area entered into a number of treatment segments consisting of a few multiples of the ERA of the transducer employed. The control program tracks the completion of each treatment segment and alerts the clinician as each segment is complete. This avoids spreading the available ultrasound energy over an area too large which would otherwise result in no effective treatment being applied. The duty factor of the output signal is a measure of the ultrasound power applied over time by a pulsed ultrasound signal and is defined as the ratio of on-time to the total period of a pulsed ultrasound signal.

After the treatment parameters have been entered and the treatment dosage has been calculated, the clinician may initiate the treatment of a first segment. In general, it is desirable to apply the maximum amount of ultrasound intensity for the shortest period of time consistent with the avoidance of tissue damage and with the comfort of the patient, to avoid cooling effects caused by increased bloodflow triggered by the increase in temperature of the treated tissue. A low BNR transducer allows the application of a high average intensity over the ERA of the transducer without the problems associated with high peaks of energy from the transducer. The control program limits the output intensity to below the transient cavitation threshold of $8 W/cm^2$. An increase in output intensity causes a decrease in the remaining treatment time to maintain the same cumulative dose of ultrasonic energy.

In practice, the clinician increases the output intensity until the patient experiences discomfort, at which point the intensity is decreased in increments. The control program tracks the cumulative energy applied and recalculates the remaining treatment time based on the new intensity level and the remaining treatment dosage to be applied. Alternatively, the clinician can vary the treatment time whereby the control program recalculates the output intensity for the remaining dosage. When treatment of the area segment is complete, the control program alerts the clinician to move to the next segment, and the process is repeated.

OBJECTS AND ADVANTAGES OF THE INVENTION

The principal objects of the present invention are: to provide an improved therapeutic ultrasound system; to provide such a system which more effectively exploits the therapeutic capabilities of ultrasound treatment than existing systems; to provide such a system which facilitates the precise use of ultrasound therapy by clinicians for more beneficial treatment of patients; to provide such a system in which an ultrasound transducer is controlled by a computer which is programmed to calculate a treatment dosage of ultrasound energy in terms of a calculated ultrasound output intensity over a

calculated treatment time based on treatment parameters entered by the clinician; to provide such a system in which the treatment dosage is calculated based on the depth of tissue to be treated, the desired tissue temperature rise in response to the treatment, the area of tissue to receive ultrasound treatment, the ultrasound coupling medium, the type of tissue to be treated, and the duty factor of the ultrasound signal; to provide such a system which tracks the cumulative dosage applied and which allows the clinician to vary either the intensity or treatment time and recalculates the other factor for the remaining portion of the treatment dosage still to be applied; to provide such a system which prevents adjustments beyond a range which might cause tissue injury from the ultrasound energy; and to provide such a therapeutic ultrasound system which is economical to manufacture, which is precise and convenient in operation, and which is particularly well adapted for its intended purpose.

Other objects and advantages of this invention will become apparent from the following description taken in conjunction with the accompanying drawings wherein are set forth, by way of illustration and example, certain embodiments of this invention.

The drawings constitute a part of this specification, and include exemplary embodiments of the present invention, and illustrate various objects and features thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram illustrating the principal components of a therapeutic ultrasound system which embodies the present invention.

FIG. 2 is a fragmentary perspective view of an ultrasound transducer unit suitable for use in the system of the present invention.

FIG. 3 is a conceptual block diagram of the ultrasound control system of the present invention in which the ultrasound intensity of a calculated treatment dosage is varied.

FIG. 4 is a conceptual block diagram of the ultrasound control system of the present invention in which the treatment time of a calculated dosage is varied.

FIG. 5 is a flow diagram of the main components of the control program of the therapeutic ultrasound system of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As required, detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely exemplary of the invention, which may be embodied in various forms. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the present invention in virtually any appropriately detailed structure.

Referring to the drawings in more detail:

The reference numeral 1 generally designates a therapeutic ultrasound system which embodies the present invention. The system 1 generally includes an ultrasound transducer unit 2, ultrasound generator circuitry 3, a system controller 4 (FIG. 1), a plurality of treatment parameter input switches 5, and a system display 6. In general, the system 1 calculates a treatment dosage of ultrasound energy to be applied by the transducer unit 2 based on treatment parameters entered by opera-

tion of the input switches 5 and maintains the calculated output intensity of the unit 2 over the calculated treatment time to achieve the calculated treatment dosage.

The transducer unit 2 (FIG. 2) includes a housing 9 forming a handle 10 for manipulation of the unit 2 by a clinician 11 to apply ultrasound energy to the tissue 12 of a patient. A distal end of the housing 9 supports a transducer head 14 having an ultrasonic transducer element 15 mounted therein. Excitation of the transducer element 15 by a radio frequency signal from the generator 3 causes ultrasonic vibration of the element 15 which is ultrasonically coupled to the tissue 12 by an ultrasonic coupling medium or couplant 16. The illustrated unit 2 has a switch panel 17 thereon with intensity up/down switches 18, a delta-temperature switch 19, and a frequency select switch 20. Further details of a representative type of ultrasonic transducer unit suitable for use in the system 1 of the present invention can be found in U.S. Pat. No. 5,086,788, issued Feb. 11, 1992, which is incorporated herein by reference.

The transducer element 15 and a radiating membrane 21 of the transducer head 14 are mutually configured to result in a low beam non-uniformity ratio (BNR) which is not greater than 4:1 and which is preferably on the order of 2:1. The use of a low BNR transducer unit allows the application of a high average intensity without exceeding the transient cavitation threshold or causing excessive patient discomfort which can result from intensity peaks present in the ultrasound beam of an transducer with a higher BNR.

The ultrasound generator circuitry 3 includes a radio frequency (RF) oscillator controllable in frequency and a power amplifier controllable in power output. Preferably, the oscillator is controllable to select either one megahertz for relatively deep tissue treatment or three megahertz for shallower treatment. The amplifier portion of the generator 3 may be controllable for output power through a continuous range or may be controllable in convenient power output increments. In other respects, the components of the ultrasound generator circuitry are essentially conventional in construction and operation. An ultrasonic drive signal is communicated from the generator circuitry 3 to the transducer unit 2 over a drive cable or drive portion of a cable 22.

The system controller 4 is essentially a microprocessor with suitable support circuitry, such as interface circuitry (not shown), read-only memory (ROM) 24, read/write memory (RAM) 25, and the like. An exemplary microprocessor for use in the system 1 is the Intel 8088, although a number of other microprocessors and microcontrollers could alternatively be employed. A control program 26 is stored in the ROM 24 and includes routines for the overall control of the system 1, including diagnostic routines, as well as an ultrasound treatment control program 27 (FIG. 5) which controls operation of the transducer 15 during ultrasound treatments. The microprocessor 4 also includes a clock circuit 28 which controls timing functions of the microprocessor 4.

The transducer housing mounted switches 18-20 are interfaced to the controller 4, and conductors 29 therefor are routed within the structure of the drive cable 22. The display 6 is preferably mounted on a console (not shown) having other portions of the system 1, other than the transducer unit 2, mounted therein. The treatment parameter input switches 5 are also mounted on such a console and are interfaced to the controller 4. The primary treatment parameter input switches 5 in-

clude a tissue depth selection switch 32, a tissue temperature increase selection or delta-temperature switch 33, a treatment area selection switch 34, and a couplant selection switch 35. Secondary treatment parameter input switches include a tissue type selection switch 36 and a duty factor selection switch 37. The secondary parameter input switches 36 and 37 are preferably included in the system 1 and increase the flexibility thereof, but are not essential to its basic operation. Alternative to entering individual treatment parameters, a clinician may simply select a desired ultrasound dosage by operation of a dosage selection switch 38. The switches 32-38 may be operated in cooperation with the display 6 to cycle through a plurality of selections for each treatment parameter.

The present invention approaches the ultrasonic treatment of tissue in terms of a "dosage" of ultrasonic energy applied to the target tissue. The treatment dosage has energy density units of joules per square centimeter (J/cm^2) which is dimensionally equivalent to watt-seconds per square centimeter ($W\text{-sec}/cm^2$). Ultrasonic output intensity is measured in watts per square centimeter (W/cm^2); thus, ultrasound treatment dosage can also be considered to be the application of ultrasound energy to tissue at a certain intensity (W/cm^2) for a required treatment time (sec). Ultrasound intensity and treatment time are referred to herein as dosage factors since the treatment dosage is the mathematical product of intensity and treatment time. In ultrasound treatments intended to cause thermal effects in the target tissue, the dosage is calculated to cause a selected temperature rise in the selected tissue, given the other treatment parameters which affect the transfer of ultrasonic energy from the transducer to the target tissue.

In general, the system 1, and the treatment control routine 27 in particular, enables the entry of various treatment parameters, calculates the frequency of operation and treatment dosage based on the entered parameters, and sets the oscillator and amplifier portions of the ultrasound generator 3 to output an ultrasound drive signal of the calculated frequency and power to the transducer 15 having a given effective radiating area (ERA) and sets a timer control 40 (FIG. 3) to the time required at the set power level to output the calculated dosage from the transducer 15 of a given ERA. Once treatment is started, the system 1 tracks the cumulative dosage applied. Either the output intensity or the treatment time can be varied during treatment, and the routine 27 will recalculate the other dosage factor for the remaining portion of the originally calculated dosage to compensate for the variation in the first dosage factor.

Referring to FIG. 5, the treatment control routine 27 is diagrammatically illustrated. At 45, the treatment parameters are entered by operation of the parameter selection switches 32-37. At 46, the routine 27 checks to see if treatment parameters have been entered. If any of the treatment parameters have not been entered, the routine 27 uses corresponding default parameters. The default parameters may, for example, be a tissue temperature rise of 4° C., deep tissue (implying 1 MHz operation), aqueous gel as a couplant, and a treatment area of 2 ERA's. The system 1 can alternatively be set up to use other default parameters.

The ultrasound energy from the transducer 15 must be applied to a definite area of tissue 12 in order to cause the desired tissue temperature rise. The entered treatment area is divided into treatment area segments at 47. To the extent possible, the treatment area is divided into

equal area segments of several ERA's each for the transducer unit 2 employed. Thereafter, the dosage is calculated individually for each segment or the total dosage for the entire treatment area can be calculated and divided into segment dosages proportional to the area of the segments. At 49, the treatment is started whereby the transducer element 15 is energized at the selected frequency and at the calculated dosage or energy density.

During treatment, time is measured by the timer control function 40 which is updated by a time signal or clock interrupt from the system clock 28. The clinician can apply the treatment at the calculated intensity for the calculated treatment time, as indicated by the default line 51. However, because heating of tissue will eventually trigger increased bloodflow in the treated area which will cause an effective cooldown, it is advantageous to increase the output intensity to the tolerance level of the patient and conduct the treatment in a minimum amount of time.

A variation in the output intensity at 52, by operation of the switches 18, causes the routine 27 to recalculate the treatment time at 53 for the remaining portion of the unapplied dosage initially calculated. The recalculated time is set into the timer control function 40 of the routine 27 at 54, and treatment continues at 55. Alternatively, the clinician can vary the treatment time at 58 by operation of a timer control 59 (FIG. 4), in which case, the routine 27 recalculates the output intensity at 60 for the unapplied dosage and sets the recalculated intensity at 61 to an intensity control function 62 of the routine 27 (FIG. 4). The intensity control function 62 is used by the routine 27 to physically adjust the power output of the amplifier section of the ultrasound generator 3. Thereafter, treatment continues at 55. Either the intensity or treatment time can be varied at any time prior to expiration of the treatment time. The routine 27 checks increases in intensity to prevent the peaks of output intensity, as determined from the BNR of the transducer unit 2 employed, from being increase beyond the transient cavitation potential of 8 W/cm^2 .

Periodically, the routine 27 polls the timer control 40 at 65 to determine if the treatment is complete for the current area segment. If not, treatment continues at 55. If treatment of the current segment is complete, the routine 27 checks a segment counter at 66 to determine if all segments have been treated. If not, the segment counter is incremented at 67, and the dosage for the next area segment is calculated at 48. Alternatively, if the segments are of equal area, control may be returned to the start treatment block 49. When all segments have been treated, the routine 27 enters a wait mode at "finish" 68, at which calculations and control for a new treatment can be initiated.

The treatment control routine 27 is an exemplary embodiment of the ultrasound therapy method of the present invention. Variations in the routine 27 are foreseen and are intended to be encompassed within the spirit of the invention. FIGS. 3 and 4 diagrammatically illustrate the control functions of the system 1 based on variation of the ultrasound output intensity in FIG. 3 and variation of the treatment time in FIG. 4.

The routine 27 has been described in terms of calculation of a treatment dosage based on a desired temperature increase in the treated tissue. For non-thermal treatments and for repetitions of treatment of a particular tissue of a patient, it might be more convenient for the clinician to enter a treatment dosage directly, by use

of the dosage selection switch 38. When the dosage is entered directly, the routine 27 calculates and maintains a default ultrasound intensity and treatment time or compensates for manual variations in the intensity or treatment time.

It is to be understood that while certain forms of the present invention have been illustrated and described herein, it is not to be limited to the specific forms or arrangement of parts described and shown.

What is claimed and desired to be secured by Letters Patent is as follows:

1. A method for automatically controlling by automatic control circuitry a therapeutic ultrasound transducer for ultrasonically treating tissue and comprising the steps of:

- (a) providing means for inputting tissue treatment parameters into automatic control circuitry operatively connected to a therapeutic ultrasound transducer;
- (b) upon tissue treatment parameters being entered, automatically calculating by said control circuitry an ultrasound treatment dosage based on input tissue treatment parameters said treatment dosage including at least two dosage factors which are mathematically related to said dosage;
- (c) upon no tissue treatment parameters being entered, automatically calculating by said control circuitry an ultrasound treatment dosage based on selected default tissue treatment parameters;
- (d) automatically controlling said ultrasound transducer by said control circuitry to maintain the calculated ultrasound treatment dosage;
- (e) manually varying a first of said dosage factors; and
- (f) automatically varying a second of said dosage factors to compensate for variation of the first dosage factor to thereby maintain the previously calculated dosage.

2. A method as set forth in claim 1 wherein said treatment dosage includes as dosage factors ultrasonic intensity of said transducer and a treatment time, and wherein steps (e) and (f) further include the steps of:

- (a) automatically tracking the percentage of the calculated dosage applied to said tissue;
- (b) prior to expiration of said treatment time, manually varying a first of said dosage factors; and
- (c) automatically varying a second of said dosage factors in inverse proportion to variation of said first dosage factor for a remaining percentage of the previously calculated treatment dosage to be applied to said tissue.

3. A method as set forth in claim 2 and including the steps of:

- (a) prior to expiration of said treatment time, manually varying said treatment time; and
- (b) automatically varying said ultrasound intensity in inverse proportion to variation of said treatment time for a remaining percentage of said calculated treatment dosage to be applied to said tissue.

4. A method as set forth in claim 2 and including the steps of:

- (a) prior to expiration of said treatment time, manually varying said ultrasonic intensity; and
- (b) automatically varying said treatment time in inverse proportion to variation of said ultrasonic intensity for a remaining percentage of said calculated treatment dosage to be applied to said tissue.

5. A method as set forth in claim 1 and including the step of:

- (a) manually inputting as a tissue treatment parameter a selection of an ultrasonic couplant between said transducer and an external surface of a part of the body having said tissue therebelow.

6. A method as set forth in claim 1 and including the step of:

- (a) manually inputting as a tissue treatment parameter a selection of a desired tissue temperature increase of said tissue in response to application of said treatment dosage thereto.

7. A method as set forth in claim 1 and including the step of:

- (a) manually inputting as a tissue treatment parameter a selection of a tissue depth of said tissue to receive ultrasonic energy by application of said treatment dosage thereto.

8. A method as set forth in claim 1 and including the step of:

- (a) manually inputting as a tissue treatment parameter a selection of a treatment area of said tissue to receive said treatment dosage.

9. A method as set forth in claim 1 and including the step of:

- (a) providing an ultrasonic transducer having a beam nonuniformity ratio (BNR) which is not greater than 4:1.

10. A method for automatically controlling by automatic control circuitry a therapeutic ultrasound transducer for ultrasonically treating tissue and comprising the steps of:

- (a) inputting a selection of a desired tissue treatment depth to automatic control circuitry operatively connected to a therapeutic ultrasound transducer;
- (b) inputting to said control circuitry a tissue temperature increase at the selected tissue depth;
- (c) automatically calculating by said control circuitry an ultrasound treatment dosage in terms of dosage factors of an ultrasound intensity applied to said tissue over a treatment time based on the input tissue temperature increase;
- (d) energizing said transducer at a frequency corresponding to the input tissue treatment depth;
- (e) automatically maintaining an output of ultrasonic energy from said transducer at the calculated treatment dosage;
- (f) prior to expiration of said treatment time, manually varying a first of said dosage factors; and
- (g) automatically varying a second of said dosage factors to compensate for variation of the first of said dosage factors to thereby maintain the originally calculated treatment dosage.

11. A method as set forth in claim 10 and wherein steps (f) and (g) further include the steps of:

- (a) automatically tracking the percentage of the calculated dosage applied to said tissue;
- (b) prior to expiration of said treatment time, manually varying said treatment time; and
- (c) automatically varying said ultrasound intensity in inverse proportion to variation of said treatment time for a remaining percentage of said calculated treatment dosage to be applied to said tissue.

12. A method as set forth in claim 11 and including the steps of:

- (a) until a patient receiving said dosage experiences discomfort:
 - (1) manually decreasing said treatment time in time increments; and

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(2) for each increment of decrease of said treatment time, automatically increasing said ultrasonic intensity to maintain said calculated dosage, to thereby apply a maximum intensity of ultrasonic energy to said tissue in a minimum of treatment time commensurate with the comfort of said patient.

13. A method as set forth in claim 12 and including the steps of:

- (a) upon said patient experiencing said discomfort:
 - (1) manually increasing said treatment time in time increments; and
 - (2) for each increment of increase of said treatment time, automatically decreasing said ultrasonic intensity to maintain said calculated dosage, to thereby return to a maximum ultrasonic intensity level which does not cause discomfort in said patient.

14. A method as set forth in claim 10 and wherein steps (f) and (g) further include the steps of:

- (a) automatically tracking the percentage of the calculated dosage applied to said tissue;
- (b) prior to expiration of said treatment time, manually varying said ultrasonic intensity; and
- (c) automatically varying said treatment time in inverse proportion to variation of said ultrasonic

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intensity for a remaining percentage of said calculated treatment dosage to be applied to said tissue.

15. A method as set forth in claim 10 and including the step of:

- (a) providing an ultrasonic transducer having a beam nonuniformity ratio (BNR) which is not greater than 4:1.

16. A method as set forth in claim 10 and including the steps of:

- (a) inputting as a tissue treatment parameter at least one of:
 - (1) a selection of one of a plurality a treatment areas of said tissue to receive said treatment dosage;
 - (2) a selection of one of a plurality of ultrasonic couplants between said transducer and an external surface of a part of the body having said tissue therebelow;
 - (3) a selection of one of a plurality of types of tissue to receive said treatment dosage; and
 - (4) a selection of a duty factor of an ultrasonic signal output to be output from said transducer from a range of duty factors; and
- (b) automatically calculating said treatment dosage based upon a selection within any tissue treatment parameter which has been input.

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United States Patent [19]

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Kaufman et al.

[45] Date of Patent: ***May 19, 1998**

[54] **ULTRASONIC BONE-THERAPY APPARATUS AND METHOD**

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Related U.S. Application Data

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[51] Int. Cl.⁶ **A61N 1/00; A61B 8/00**

[52] U.S. Cl. **601/2; 600/439; 600/449**

[58] Field of Search **601/2; 128/660.03; 607/50, 51; 600/439, 449**

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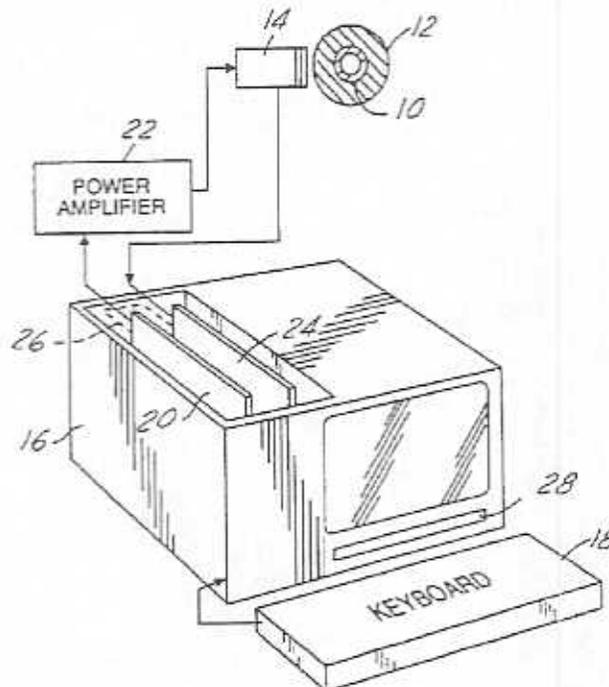
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5,088,976	2/1992	Liboff et al.	600/13
5,100,373	3/1992	Liboff et al.	600/13
5,106,361	4/1992	Liboff et al.	600/13
5,143,588	9/1992	Liboff et al.	204/155
5,259,384	11/1993	Kaufman et al.	128/600.01
5,309,898	5/1994	Kaufman et al.	601/2
5,318,561	6/1994	McLeod et al.	600/14
5,393,296	2/1995	Ratber	607/51 X
5,496,256	3/1996	Boch et al.	607/51 X
5,520,612	5/1996	Winder et al.	607/51 X
5,524,624	6/1996	Tepper et al.	607/51 X
5,547,459	8/1996	Kaufman et al.	601/2
5,556,372	9/1996	Talish et al.	607/51 X

Primary Examiner—Francis Jaworski
Attorney, Agent, or Firm—Dykema Gossett PLLC

[57] ABSTRACT

A method of ultrasonic bone-therapy subjects a bone to an ultrasonic excitation pulse signal of finite duration, supplied to a transducer next to the bone, and involving a sinusoidal signal in the ultrasonic region to approximately 2 MHz peculiarly modulated by a sinusoidal signal with frequency between about 0 Hz and about 25 kHz; the excitation signal is repeated in the range of 1 to 5000 Hz. The exposure time for therapy is chosen to be in the range of 5 minutes to 1 hour, for 1 to 3 times a day, for a period of days as necessary for healing or for promoting bone growth and ingrowth. An apparatus for implementing the above method for ultrasonic bone therapy is disclosed comprising a transducer having a transmitting and a receiving element, a special waveform signal generator, and a computer for performing the necessary operations defining a preferred treatment regime.

21 Claims, 3 Drawing Sheets



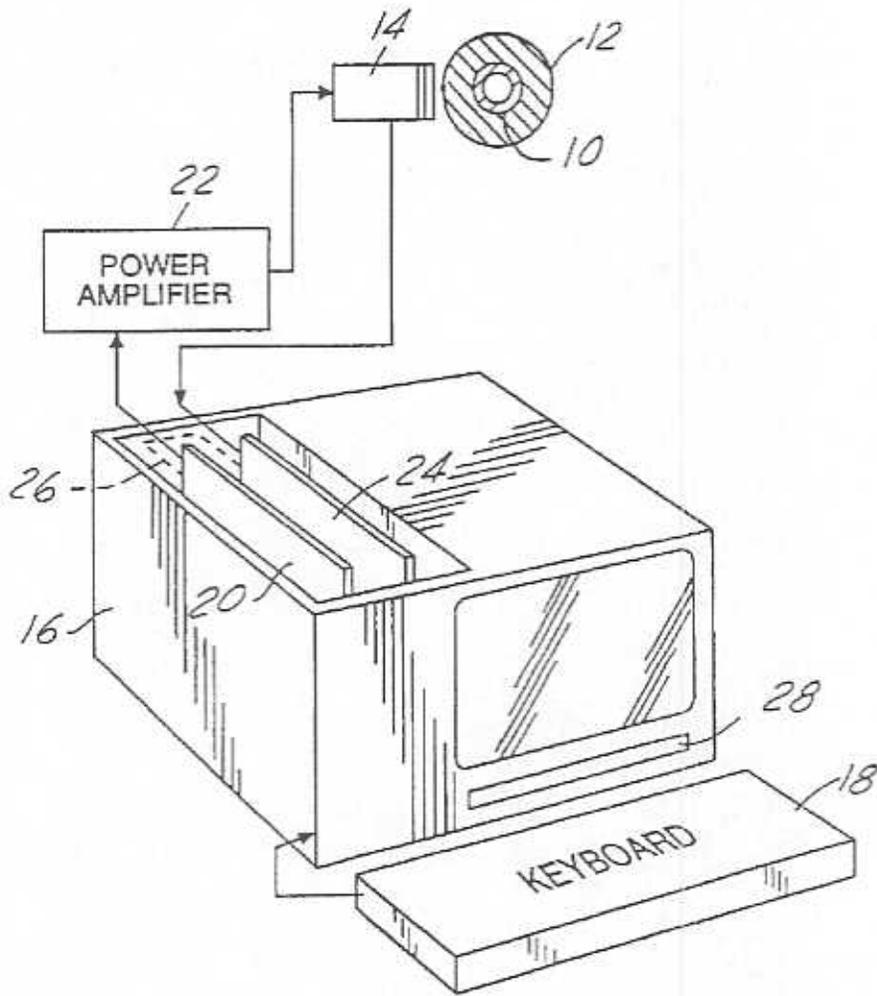


FIG. 1

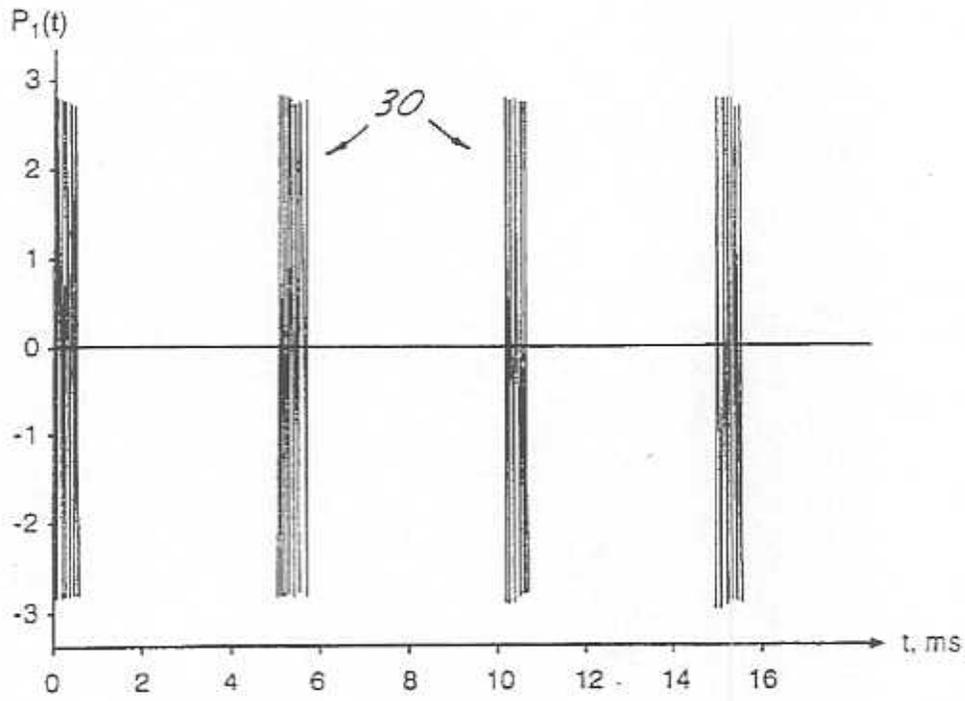


FIG.2

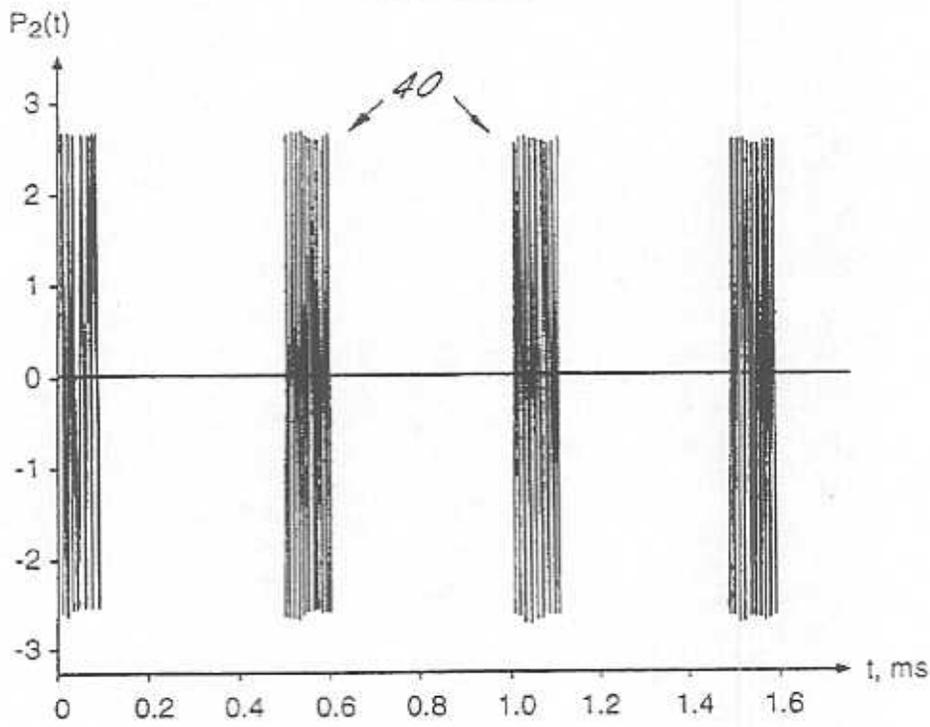


FIG.3

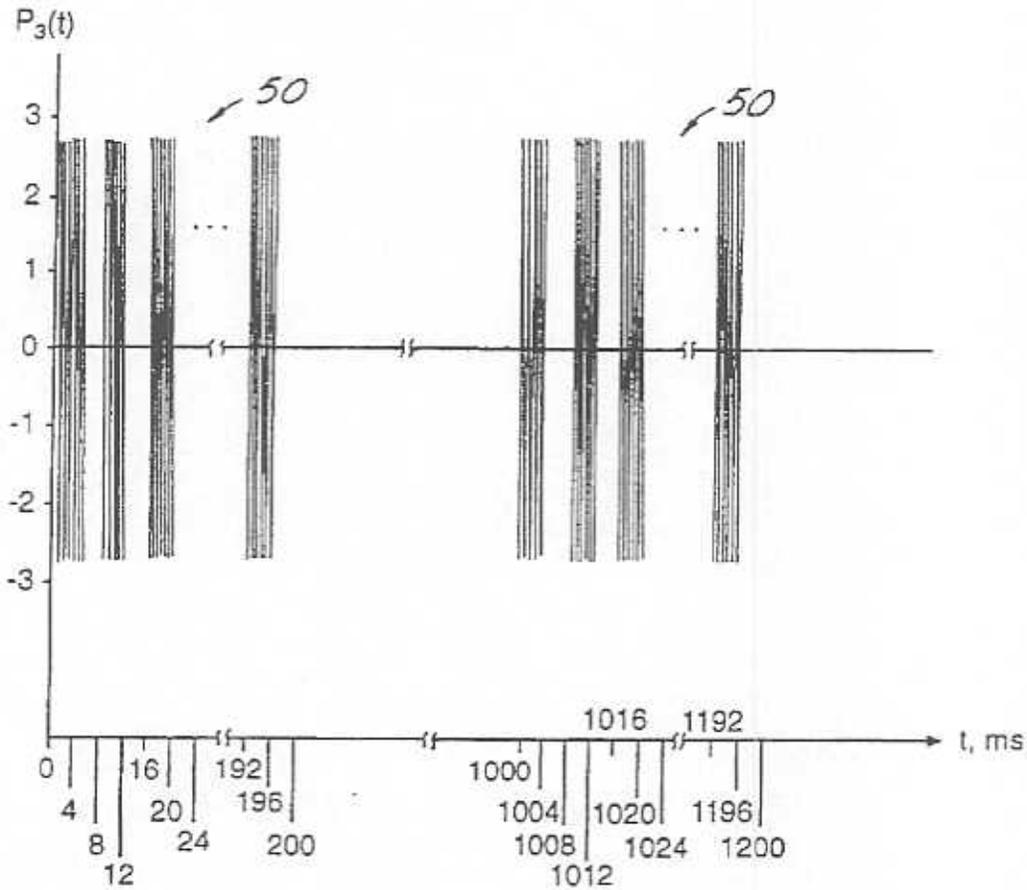


FIG. 4

ULTRASONIC BONE-THERAPY APPARATUS AND METHOD

This is a continuation of application Ser. No. 08/329,015, filed on Oct. 25, 1994, and now U.S. Pat. No. 5,547,459.

FIELD OF THE INVENTION

The invention pertains to apparatus and method for non-invasively therapeutically treating bone tissue in vivo.

BACKGROUND OF THE INVENTION

In recent years, various attempts have been made to stimulate bone growth. These approaches have been essentially ad hoc, with no consistent framework within which to identify the most effective stimulation.

Kaufman et al., U.S. Pat. No. 5,309,808 discloses an apparatus and method for therapeutically treating and/or quantitatively evaluating bone tissue in vivo. The Kaufman method includes subjecting bone to an ultrasonic acoustic signal pulse of finite duration, and involving a composite sine-wave signal consisting of plural discrete frequencies. These frequencies are spaced in the ultrasonic region to approximately 2 MHz; the excitation signal is repeated substantially in the range from 1 to 1000 Hz.

Duarte, U.S. Pat. No. 4,530,360 discloses an apparatus and a method of using ultrasonic energy for therapeutic treatment of bone tissue in vivo, using a pulsed sine wave at substantially a single frequency within the range from 1.3 to 2.0 MHz, and at a pulse repetition rate of 100 to 1000 Hz.

McLeod et al., U.S. Pat. Nos. 5,103,806 and 5,191,880 disclose methods for promoting bone tissue growth and the prevention of osteopenia, using mechanical loading of the bone tissue. In both patents, the inventors apply a mechanical load to the bone tissue at a relatively low level on the order of between about 10 and about 1000 microstrain, peak to peak, and at a frequency in the range of about 10 to 100 Hertz.

Bassett et al., U.S. Pat. No. 4,928,959 disclose a method and device for providing active exercise treatment for a patient suffering from a bone disorder. A patient is subjected to an impact load in order to stimulate bone growth, with an impact load sensor being used to monitor the treatment strength. The inventors noted that high frequency (up to 100,000 Hz) force components were important for stimulating bone growth.

Numerous other patents disclose methods for stimulating bone growth relying on the generation of electromagnetic signals. For example, Ryaby et al., U.S. Pat. Nos. 4,105,017 and 4,315,503 describe methods for promoting bone healing in delayed and nonunion bone fractures, using an asymmetric pulsed waveform. In U.S. Pat. No. 4,993,413, McLeod et al. disclose a method and apparatus for inducing a current and voltage in living tissue to prevent osteoporosis and to enhance new bone formation. They disclose the use of a symmetrical low frequency and low intensity electromagnetic signal substantially in the range of 1-1000 Hertz. In Liboff et al., U.S. Pat. No. 5,318,561 (and others), methods are disclosed that incorporate the combined use of a static and time-varying magnetic field to stimulate bone healing and growth. Specific amplitudes and frequencies are disclosed for optimal enhancement of bone growth, based on the theory of "ion-cyclotron resonance".

A recent publication by Weinbaum et al. provides a comprehensive and theoretically consistent basis to characterize the means by which bone growth occurs. The seminal

article "A model for excitation of osteocytes by mechanical loading-induced bone fluid shear stresses," may be found in the *Journal of Biomechanics*, Vol. 27, 1994, pp 339-360. In this publication, they propose that it is not strain magnitude but strain rate that is the primary relevant variable responsible for adaptive bone growth and remodeling.

The prior art, exemplified by the references that have been briefly discussed, have used primarily ad hoc approaches or empirical findings for determining exogenous stimulations used up to now for the promotion of bone growth and healing. Some have focussed on the generation of specific values of biomechanical strain in the tissue as the primary modality of action. However, this invention incorporates the realization that fluid flow induced in normal physiological loading is the critically important variable in bone healing, and moreover, includes an efficient means for generating this fluid flow in living tissues. Specifically, this invention includes a means for stimulating fluid flow at relatively high frequencies by taking unique advantage of the nonlinear characteristics of ultrasound propagation in an ionic-fluid-saturated porous medium such as bone. In addition, this invention incorporates the important features of repetitive stimulation in analogy to that found in normal physiologic loading, and of adaptive feedback control for ensuring that an optimal signal dose arrives at the desired bone tissue site.

SUMMARY OF THE INVENTION

It is an object of this invention to provide an improved method and apparatus for non-invasively therapeutically treating bone tissue in vivo, to promote bone healing and bone growth.

Another object is to meet the above object, such that bone healing and bone growth may be more efficiently and more effectively stimulated than heretofore.

A specific object is to achieve the above objects with an optimal set of ultrasonic signals chosen with respect to the specific nonlinear characteristics of their propagation within the bone tissue and with respect to the emulation of physiological loading.

A further specific object is to enable adaptive and on-line evaluation of the optimal dose of an applied exogenous ultrasonic acoustic therapeutic signal.

It is a general object of the invention to achieve the foregoing objects with apparatus components that are for the most part commercially available.

The invention in its presently preferred form achieves the foregoing objectives by subjecting bone to an ultrasonic acoustic excitation signal pulse of finite duration in the ultrasonic region of approximately 1.1 MHz, supplied to a transducer adapted for acoustic coupling to the skin surface overlying a bone; the excitation signal is repeated in the range of about 1 Hz to about 5000 Hz. The exposure time for therapy is chosen to be in the range of 5 minutes to 1 hour, for 1 to 3 times a day, for a period of days as necessary for complete healing or for promoting bone growth or ingrowth.

Before ultrasonic therapy is started, an initial interrogating acoustic ultrasonic pulse is preferably transmitted in order to determine the actual thickness of soft tissue overlying the bone treatment site. (Note that the thickness may change over time due to tissue swelling, for example.) The bone treatment site may be the zone of fracture, the interface between an implanted device (e.g., hip) and bone, or an intact bone which has reduced bone mass, as for example with osteoporosis. Using the round-trip pulse transmit time between the transducer and the near-bone surface and the nominal attenuation value associated with the soft tissue, the

input signal amplitude supplied to the transducer is adjusted to ensure that the spatial-average time-average (SATA) power density (i.e., intensity I_{SATA}) reaching the near-bone surface is approximately 45 mW/cm^2 . The received signal is also monitored during the actual treatment exposure to ensure that the patient is receiving the prescribed therapy during the prescribed treatment time.

With these and other objects and advantages in view, the present invention will be clearly understood from the ensuing detailed description in connection with the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram diagrammatically showing the interconnections of components of an apparatus of the invention.

FIGS. 2, 3 and 4, respectively, illustrate a set of acoustic ultrasonic signals used for stimulation of bone growth and healing for several of the currently preferred embodiments.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1 diagrammatically illustrates selected interconnected components for constructing an apparatus for performing methods associated with this invention, namely for non-invasively therapeutically treating bone tissue in vivo, to stimulate bone growth (ingrowth) and bone healing. These components are, in general, commercially available from different sources and will be identified as the detailed description of their total operation is provided.

Referring now to FIG. 1, the bone locale 10, such as a fracture site, an area affected by osteoporosis, or any other part of bone tissue to be treated non-invasively, is shown surrounded by soft tissue 12. Ultrasonic transducer 14 is placed near bone locale 10, adjacent soft tissue 12. By way of example, transducer 14 can be a rectangular piezoelectric transducer of approximately one by two inches placed on the surface of the skin overlying the fractured bone at approximately the site of fracture. The transducer may have a single piezoelectric element that is adapted for both transmitting and receiving, or one transmitting element and one or more receiving elements (not specifically shown). Such transducers are available from Parallel Designs, Inc., Phoenix, Ariz. As shown, transducer 14 is used for signal launching and receiving the launched signals after reflecting back from bone 10 and passing through surrounding soft tissue 12. An ultrasonic couplant (not shown) such as a gel is applied between transducer 14 and the patient's outer skin surrounding the soft tissue 12.

Basic operation is governed by a signal processing unit 16, which specifically may be a computer, and more specifically, a personal computer, such as the 66 MHz Pentium available from Gateway 2000, Inc., North Sioux City, S.Dak. As its designation suggests, this computer contains a 66 MHz clock-pulse generator, and an Intel 586 (Pentium) processor, with provision for keyboard instructions at 18. Computer 16 performs constant on-line monitoring of proper functioning of the apparatus according to the present invention. Specifically, computer 16 ensures providing a prescribed therapy to a patient by responding to and watching the reflected signals to calculate an appropriate treatment dose of ultrasonic exposure.

A sinusoidal function-generator at a card 20 is relied upon to generate an excitation signal, which is supplied to launch transducer 14, via power amplifier means 22. The power amplifier is suitably Model No. 2401, an RF power amplifier product of EIN, Inc., Rochester, N.Y. This product provides a 50 dB gain over the range 20 kHz to 10 MHz.

The excitation signal produced by the generator at card 20 is a pulsed sine wave signal in the ultrasonic range to about 2 MHz, which is sine wave modulated in the range of 0 to 25 kHz. The generator at card 20 may suitably be a commercially available waveform synthesizer, a product of Quatech, Inc., Akron, Ohio, identified by Quatech part No. WSB-100. This waveform synthesizer provides generation of analog signals independent of host computer 16, allowing full processor power to be used for other tasks, including calculation of waveform data. Card 20 preferably has the capacity to generate an output signal comprising literally thousands of points in the indicated ultrasonic frequency range.

Another card 24 is also shown installed in computer 16, for converting analog signals obtained from the receiving element of transducer 14 into digital format for further processing in computer 16. A known in the art switching element (not shown) can be used for disconnecting transducer 14 from card 20 and connecting it to card 24 which latter card may suitably contain a 100 MHz waveform digitizer, part number STR*8100, a product available from SONIX, of Springfield, Va. A connection 26 (shown by broken lines) connects signal-generator card 20 to A/D card 24, for synchronizing purposes and for the purposes of digitizing the reflected waveform, to enable computer 16 to perform a suitably compensated, continuously operative updating average of the signals received at transducer 14. A conventional reamplifier (not shown) for increasing the level of the reflected waveform before being input to card 24 can be included.

In order to obtain an estimate of the thickness of the traversed soft tissue overlying the fracture site and properly adjust the amplitude of the therapeutic ultrasonic signal, an initial interrogating acoustic ultrasonic pulse is preliminarily transmitted by card 20 via transducer 14. An exponentially damped sinusoidal signal at 1.1 MHz, with a duration of about $2 \mu\text{s}$ could be an example of such a pulse.

Transducer 14 is then used as a receiver to record the reflected signal from the near bone surface. The arrival time of the reflected signal provides a measure of the round-trip transit time, τ , for the acoustic pulse to travel from the transducer through the soft tissue to the bone surface (where it is partially reflected), and back through the soft tissue. The soft-tissue thickness, d_s , can then be calculated as

$$d_s = v_s \tau / 2$$

where v_s is the velocity of ultrasound in soft tissue and is given by $v_s = 1540 \text{ ms}^{-1}$.

Once an estimate of soft tissue thickness is obtained, it may be used for adjusting the input signal amplitude to ultrasonic transducer 14 to ensure that the optimal power intensity impinges on the fractured bone. This is preferably carried out as follows. Through a reflection measurement, an above mentioned estimate of soft tissue thickness, d_s [cm], is acquired. Then, according to, for example, Biomedical Ultrasonics, by P.N.T. Wells, Academic Press, London, 1977, a nominal value for ultrasonic attenuation at 1.1 MHz in soft tissue can be obtained as $\alpha_s = 1 \text{ dB/cm}$. Thus, for a soft tissue thickness given by d_s , the total decrease in signal amplitude, $\Delta\alpha$ in dB at the bone surface is

$$\Delta\alpha = \alpha_s d_s$$

The following formula may then be used to construct a look-up table which provides the necessary values for the

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relative amplification, A , applied to the input signal. The signal amplification is calculated from

$$A=10^{(0.0477I)}$$

For example, the associated input signal amplifications to be used may be calculated for a range of soft tissue thicknesses:

Soft Tissue Thickness [cm]	Signal Amplification
1	1.12
2	1.26
3	1.41
4	1.58
5	1.78
6	2.00

It is noted that these signal amplifications are relative to the nominal signal value used for producing the desired power density (intensity $I_{SAT}=45 \text{ mW/cm}^2$), within the near field of the ultrasound transducer in a medium of negligible attenuation, such as water. It should also be noted that for safety considerations, it may not be possible to use arbitrarily large incident power intensities (at the skin surface), which may, for example, be needed in case of excessively thick soft tissue overlying the fractured bone. In these cases, a maximum power intensity will be specified *a priori*; anything above this value will be saturated to this maximum intensity.

The therapeutic signal is specifically designed to optimally stimulate the fracture healing process. The optimal signal characteristics, which are set forth in more detail below, are derived using nonlinear wave-propagation theory and stimulate bone healing and growth through its direct effect on fluid flow. The reliance on acoustic microstreaming as the primary bio-effective aspect of the endogenous ultrasonic signal has led to a more effective and efficacious treatment for bone repair, in contrast to the prior art, which relies on, for example, the endogenous piezoelectricity of bone (see Duarte, supra), the generation of mechanical strains in the bone tissue (see Bassett et al., U.S. Pat. Nos. 4,928,959 and 5,046,484, and McLeod et al., supra), or on the induction of electrical currents in bone tissue (see Ryaby et al., U.S. Pat. No. 4,266,533).

For better understanding the fluid flow nature of the ultrasound stimulation of bone growth and repair, it should be taken into consideration that the induction of fluid flow arises out of a complex set of interactions of the externally applied ultrasonic signal with the bone tissue. The interactions can be characterized using a generalized theory of acoustics in porous media that includes the effects of an ionic fluid in the pore spaces, as exists in bone tissue. A summary of this theory given below provides the basis for which the optimal ultrasonic therapeutic signals are derived.

Fluid flow is assumed to be the fundamental entity which, when stimulated, will enhance bone growth and healing. In what follows, w is defined to be the displacement vector of the fluid relative to the solid matrix (known also as specific discharge relative to the solid) and $\xi=-\nabla \cdot w$ is the increment of the fluid content per unit volume of the medium. Here ∇ is the nabla operator, and (\cdot) is the scalar product. Therefore, $\psi_E \cdot n = (\partial w / \partial t) \cdot n$ is the Eulerian flux (ms^{-1}) of fluid crossing a unit area whose normal unit vector is n . (This flux is related to the fluid flow in acoustic microstreaming.) In this case, $\partial \xi / \partial t$ is the net fluid flux entering the unit volume (i.e., fluid influx).

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A generalized Darcy equation can be used to express the relationship between fluid flux and related quantities in the porous medium by taking into account the contribution of Maxwell's stress tensor in the fluid:

$$\left(\frac{\eta}{k_0} + \frac{\alpha_\infty \rho_f}{f_0} \frac{\partial}{\partial t} \right) \frac{\partial w}{\partial t} = -\nabla p_f + \epsilon_f (\nabla^2 \phi_f) \nabla \phi_f + \frac{\epsilon_f^2}{3\epsilon_0} \nabla (\nabla \phi_f \cdot \nabla \phi_f)$$

In this expression, η ($\text{kgm}^{-1}\text{s}^{-1}$) is the viscosity of the fluid, α_∞ is the (high frequency) tortuosity of the porous medium, k_0 (m^2) is the (low frequency) Darcy permeability, ϵ_f and ϵ_0 (Fm^{-1}) are the dielectric permittivities of the fluid and vacuum, respectively ($\epsilon_f \gg \epsilon_0$), f_0 is the volumetric porosity, and ρ_f (kgm^{-3}) is the fluid density. The function ϕ_f (V) is the scalar electric potential in the fluid that results from the perturbation of the endogenous electric potential by the exogenous acoustic exposure (i.e., the ultrasonic signal). The endogenous electric potential arises from several sources, including primarily the interaction of the ionic fluid with the charged solid matrix surface. It also should be noted that the electric field within the fluid is equal to $-\nabla \phi_f$ (Vm^{-1}). The pressure in the fluid is denoted by p_f (Nm^{-2}), and is the pressure resulting from the interaction of the exogenous acoustic exposure with the fluid-filled porous bone structure.

After some reasonable simplifying assumptions and using " $\langle \cdot \rangle$ " to denote time average, the previous equation can be used to express the time average Eulerian fluid (streaming) flux as a function of the time average fluid pressure and electric potential as:

$$\langle \psi_E \rangle = \langle \frac{\partial w}{\partial t} \rangle = -\frac{k_0}{\eta} \nabla \langle p_f \rangle + \frac{k_0}{\eta} \frac{\epsilon_f}{f_0} \left(1 + \frac{\epsilon_f}{3\epsilon_0} \right) \nabla \langle \nabla \phi_f \cdot \nabla \phi_f \rangle$$

This equation demonstrates that the average Eulerian flux of fluid in the porous medium is dependent on the electric field squared, and that the latter's spatial variation can give rise to a non-zero mean (or net) fluid flux irrespective of the time waveform of the perturbation induced by the ultrasound exposure on the electric field $-\nabla \phi_f$. Moreover, the steady component of the fluid flux occurs whether or not the applied mean pressure (i.e., time average) is zero, as may arise for example, with the ultrasonic input.

Some of the equations necessary to evaluate all the components of the acoustic field are omitted, as the details are quite cumbersome and do not add additional insight into the results presented above. It should be noted that the net average fluid flux entering the unit volume is zero, i.e.,

$$\langle \frac{\partial \xi}{\partial t} \rangle = 0$$

thus providing an alternating pulsatile fluid influx.

It should also be pointed out that the theory presented can also characterize two other sources of nonlinearity in the interaction of the ultrasonic signal with the bone tissue. The first is related to convective flow and is one source of the well-known "radiation pressure" exerted by an acoustic wave. This phenomenon arises from hydrodynamical considerations, and in the notation used may be written as

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$$\underline{\psi}_L = \frac{d\underline{w}}{dt} = \frac{\partial \underline{w}}{\partial t} + (\underline{\psi}_L \cdot \nabla) \underline{w} = \underline{\psi}_L + (\underline{\psi}_L \cdot \nabla) \underline{w}$$

where $\underline{\psi}_L$ is the material of Lagrangian fluid (streaming) flux and $(\underline{\psi}_L \cdot \nabla) \underline{w}$ is the convective nonlinearity.

Another source of nonlinearity and one which may also be incorporated into the fundamental theory arises due to the constitutive relationship between pressure and density, namely

$$P_F = P_{F0} + A \left[\frac{P_F - P_{F0}}{\rho_{F0}} + \frac{B}{2A} \left(\frac{P_F - P_{F0}}{\rho_{F0}} \right)^2 \right]$$

where ρ_{F0} and P_{F0} are the unperturbed fluid density and pressure, respectively, and A and B are the well-known nonlinear parameters of the fluid where B/A can typically be as large as 11. This relationship applies to the fluid phase. Analogously, a nonlinear constitutive relationship can also be written for the solid phase of the bone tissue, which will account for additional nonlinearities in the overall solution for fluid flux. Furthermore, the contribution of Maxwell's stress tensor to the solid matrix is another source of nonlinearity.

As may be seen readily from the describing equations, both constant and oscillatory fluid flows for promoting bone growth and repair can be stimulated through appropriate design of the applied acoustic signal that will be discussed below in more detail. The above theory clarifies that for obtaining both constant and oscillatory fluid flows at rates relevant to therapeutic bone dynamics, the leading term is the square of the applied ultrasonic signal $p(t)$, i.e., $p^2(t)$. This nonlinearity enables the "in vivo" demodulation of the exogenous ultrasonic waveform, allowing it to have maximal therapeutical effects on bone growth and healing. The signals are specifically designed to be modulated by relatively high frequencies (generally above 500 Hz) in a pulsed excitation mode, which permits the bone tissue to respond maximally during each stimulatory cycle.

The foregoing aspects of the nonlinear acoustic theory provide the underlying basis for determining and thereby inducing fluid flow by the exogenous ultrasonic therapeutic signal.

It also should be noted that the received ultrasonic signal is used as a means for providing on-line fault detection, to ensure that the required therapeutic signal is reaching the fracture site during all periods of the treatment prescribed to a patient.

General signal-processing/display/storage software for the signal processing control and operation of computer 16 is not shown but will be understood to be contained on a conventional floppy disk loaded at 28 into computer 16; this software is suitably the MATLAB-386, available from The MathWorks, Inc., Natick, Mass. Further software (not illustrated) includes the signal processing toolbox, also available from MathWorks, as well as Fortran 5.0, available from Microsoft Corporation, Bothell, Wash., and LabView, available from National Instruments Corporation, Austin, Tex.

In the presently preferred embodiments of this invention and with additional reference to FIGS. 2, 3 and 4, showing the general outlook of the signals employed, without concrete details specifically regarding frequency and power parameters thereof, bony member 10 surrounded with soft tissue 12 is placed next to ultrasound transducer 14. An ultrasound signal is transmitted from transducer 14, passes through soft tissue 12, is partially transmitted into the bony

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member, and is partially reflected from bone tissue 10 back through soft tissue 12 to be received by the receiving element (not specifically shown) of transducer 14. The transmitted ultrasound signal is generated using a finite-duration sine-wave signal, which is sine-wave modulated. A single cycle of this waveform is described by

$$p(t) = \sum_{i=0}^{N-1} p_A(t - iT), \quad (1a)$$

repeating every T seconds (1/T Hz), where $p_A(t)$ is given by the following equation:

$$p_A(t) = \begin{cases} K[1 + a \sin(2\pi f_m t)] \sin(2\pi f_c t), & 0 \leq t \leq T_p \\ 0 & \text{otherwise,} \end{cases} \quad (1b)$$

In equations 1a and 1b, the range of signal parameter values are $0 \leq f_m \leq 25$ kHz (preferably without the zero value, i.e., in most cases $f_m \neq 0$), $25 \text{ kHz} < f_c \leq 2 \text{ MHz}$, $0.2 \text{ ms} \leq T \leq 1.0 \text{ s}$ (corresponding to pulse repetition rates of 1 Hz–5 kHz), $0.1 \text{ ms} \leq T_p < 1.0 \text{ s}$, $0.1 \text{ ms} < T_p' \leq 1.0 \text{ s}$ (corresponding to a duty cycle, $\gamma = NT_p'/T$, or effective duty cycle taking into account the integrated "on-time" (the overall pulse durations) within a cycle, $\gamma = (T_{p1} + T_{p2} + \dots + T_{pN})/T$, of $0.0001 \leq \gamma < 1$), $1 \leq N \leq 10,000$. The range of the modulation index, a, is given by $0 \leq a \leq 1000$. The constant K is adjusted so that the acoustic ultrasonic wave impinging at the near bone surface has an intensity (I_{SAZTA}) in the range of 20–100 mW/cm².

In a special case (N=1), where $p(t) = p_A(t)$, this waveform is described by

$$p(t) = K[1 + a \sin(2\pi f_m t)] \sin(2\pi f_c t), \quad 0 < t < T_p$$

repeating every T seconds, for a period of time preferably ranging from 5 minutes to 1 hour. The range of parameters is: $0 \leq f_m \leq 25$ kHz (preferably without the zero value, i.e., in most cases $f_m \neq 0$); $25 \text{ kHz} \leq f_c \leq 2 \text{ MHz}$; $0.2 \text{ ms} \leq T \leq 1 \text{ s}$ (corresponding to pulse repetition rates of 1 Hz–5000 Hz) and $0.1 \text{ ms} \leq T_p \leq 1 \text{ s}$ (corresponding to a duty cycle, $\gamma = T_p/T$, of $0.0001 \leq \gamma < 1$). The constant K is adjusted such that an intensity (I_{SAZTA}) of the acoustic ultrasonic wave impinging at the near bone surface is in the range of 20–100 mW/cm².

Operating in the pulsed regime takes advantage of the acoustic nonlinearities when high amplitude waves are present. The maximum peak amplitude is $K(1+a)$, and is constrained not to exceed normal safety levels. Amplitude modulation of the carrier signal at a relatively high frequency is specifically used to generate fluid flux at relatively high rates. For the preferred embodiments of this invention, the amplitude of the signal, as noted above, is adjusted to provide I_{SAZTA} of approximately 45 mW/cm² at the fracture site.

It is noted that dynamic strains induced in the bone tissue are primarily in the ultrasonic spectral region, that is, at the nominal frequency of the applied ultrasonic signal. For the presently preferred embodiment, this frequency is 1.1 MHz, and in all cases is above 25 kHz. Additionally, the strain levels induced in the bone tissue, assuming a characteristic length of 10 centimeters, are extremely small. The peak-to-peak strain value can be reasonably well approximated from the well known equation for induced particle displacements associated with an ultrasonic input (see for example *Physical Principles of Medical Ultrasonics*, ed., CR Hill, Halsted Press, 1986, p. 57). The particle displacement, D, is given by

$$D = I / (\pi f)^2 / (\rho_0 c^2)^{1/2}$$

where I is the ultrasonic power intensity in the bone tissue, ρ_0 is the unperturbed bone density, c is the velocity of

ultrasound in the bone, and f is the ultrasonic frequency. Using values associated with bone, and for the preferred ultrasonic signal embodiments, a value of D of about 0.016 microns (at 1.1 MHz) can be obtained, and therefore the induced peak-to-peak strain is found to be less than about 0.2 microstrain.

For the purposes of the present invention, the three presently preferred embodiments include ultrasonic signals that are specified as follows:

1. As illustrated in FIG. 2, signal 30 is repeated at a repetition rate of 200 Hz ($T=5$ ms). A single cycle of the waveform is a 0.5 ms duration sine wave of carrier frequency 1.1 MHz modulated by a 20 kHz sine wave, followed by 4.5 ms of "off time", with the modulation index, $a=0.3$. This signal is described by the following equation:

$$p(t) = \begin{cases} K\{1 + 0.3\sin(2\pi \cdot 20 \cdot t)\} \cdot 10^3 \sin(2\pi \cdot 1.1 \cdot 10^6 t), & 0 \leq t \leq 0.5 \text{ ms} \\ 0, & 0.5 \text{ ms} \leq t \leq 5 \text{ ms} \end{cases}$$

repeating at 200 Hz, and K is adjusted so that $I_{SAZA}=45$ mW/cm².

2. As illustrated in FIG. 3, signal 40 is repeated at a repetition rate of 2000 Hz ($T=0.5$ ms). A single cycle of the waveform is a 0.1 ms duration sine wave of carrier frequency 1.1 MHz modulated by a 20 kHz sine wave, followed by 0.4 ms of "off time", with the modulation index, $a=0.3$. This signal is described by the following equation:

$$p(t) = \begin{cases} K\{1 + 0.3\sin(2\pi \cdot 20 \cdot t)\} \cdot 10^3 \sin(2\pi \cdot 1.1 \cdot 10^6 t), & 0 \leq t \leq 0.1 \text{ ms} \\ 0, & 0.1 \text{ ms} \leq t \leq 0.5 \text{ ms} \end{cases}$$

repeating at 2000 Hz, and K is adjusted so that $I_{SAZA}=45$ mW/cm².

3. As illustrated in FIG. 4, signal 50 is repeated at a repetition rate of 1 Hz. A single cycle of the waveform consists of 25 repetitions ($N=25$) of a 4 ms duration ($T_p=4$ ms) 1.1 MHz sine wave modulated by a 5 kHz sine wave ($f_m=5$ kHz), each such 4 ms "on time" being followed by 4 ms of signal "off time" ($T_o=8$ ms). The entire sequence of 25 sinusoidally modulated sinusoidal pulses, together with their associated 4 ms "off times", lasts for 200 ms, after which time the signal is off for 800 ms. The sequence is then repeated at 1 second intervals (1 Hz), the modulation index being $a=0.3$.

This signal is described by the following equation:

$$p(t) = \sum_{i=0}^{24} p_i(t - i \cdot 8 \text{ ms}), \text{ repeating at 1 Hz,}$$

where

$$p_i(t) = \begin{cases} K\{1 + 0.3\sin(2\pi \cdot 5 \cdot t)\} \cdot 10^3 \sin(2\pi \cdot 1.1 \cdot 10^6 t), & 0 \leq t \leq 4 \text{ ms} \\ 0, & \text{elsewhere} \end{cases}$$

and K is adjusted so that $I_{SAZA}=45$ mW/cm².

In order to synthesize the second signal of the presently preferred embodiments, the above-mentioned Quatech card is used in conjunction with another instrument, suitably a Wavetek Model No. 178 Programmable Waveform Synthesizer available from Wavetek, San Diego, Calif. In this case, the Quatech card outputs the modulating waveform as input to the Wavetek Waveform Synthesizer to amplitude modulate the 1.1 MHz carrier signal.

An enlarged class of ultrasonic therapeutic signals includes waveforms, which are frequency modulated in addition to them being amplitude modulated in order to take further advantage of the nonlinear propagation characteristics of bone tissue. In this case, sweeping not only the modulating frequency but also the carrier frequency contributes both to changing and manipulating so-called hot and cold spots in ultrasonic treating a tissue, and to bringing energy to a bone at different frequencies. These things considered, the efficiency of treating bone tissues in accordance with the present invention is additionally increased.

The waveforms of this class can be described as follows:

$$p(t) = \sum_{i=0}^{N-1} p_i(t - iT), \quad (2a)$$

repeating every T seconds, where

$$p_i(t) = K\{1 + a \sin[2\pi(f_m - (f_m^* - f_m) \cdot i/T)] \sin[2\pi(f_c + (f_c^* - f_c) \cdot i/T)]\} \sin(2\pi f_c t)$$

$0 \leq t \leq T$, where all the parameters are contained in the same ranges as defined before. f_m^* and f_c^* define the upper limit values of sweeping for modulating and carrier frequencies, respectively, with $f_m \leq f_m^* \leq 25$ kHz and $f_c \leq f_c^* < 2$ MHz.

For the purposes of the present invention, the presently preferred embodiment of this class of signals include an ultrasonic waveform that is specified as follows, with $f_c^*=f_c=1.1$ MHz, $f_m=500$ Hz, and $f_m^*=2000$ Hz:

$$p(t) = \sum_{i=0}^{24} p_i(t - i \cdot 8 \text{ ms}), \text{ repeating at 1 Hz,}$$

where

$$p_i(t) = \begin{cases} K\{1 + \sin[2\pi(500 + (2000 - 500) \cdot i/8)] \sin[2\pi(1.1 \cdot 10^6 t)]\}, & 0 \leq t \leq 4 \text{ ms} \\ 0, & \text{elsewhere} \end{cases}$$

and K is adjusted so that $I_{SAZA}=45$ mW/cm².

From the aforesaid it follows that according to the present invention the following four types of signals could be employed in its implementation, with the specific parameters discussed in the above:

- sine wave modulated sine wave signals;
- swept sine wave modulated sine wave signals;
- sine wave modulated swept sine wave signals;
- swept sine wave modulated swept sine wave signals.

For the purposes of this invention, a sine wave can be assumed to be used to denote a sinusoidal function at a single frequency or a sinusoidal function with frequency modulation, i.e., a swept sine wave. It is also appreciated that for most cases the modulating frequency in these signals is not supposed to assume the zero value. However, in some concrete instances it can begin or end at or pass through this value.

The main and important advantages of the present invention can be summarized as follows:

- the reliance on fluid flow as the primary bio-physical phenomenon related to bone growth, which is affected in a near optimal fashion by the ultrasonic signal;
- the use of an analytic model for characterizing ultrasonic wave propagation in a porous medium such as bone, in order to establish the biophysical parameters of interest (i.e., fluid flow), in comparison to the prior art, which used either experimental observations only or ad hoc approaches;
- the use of relatively high frequency (preferably greater than 500 Hz and less than 25 kHz) sinusoidal amplitude modulation as a means for directly affecting fluid flow;

- the use of a relatively low carrier frequency, allowing greater soft tissue and bone penetration due to significantly decreased signal attenuation;

- the use of a repetitive stimulation, emulating physiological loading;

- the ability to construct the device with components that are largely commercially available;

- the use of reflection measurements to estimate actual soft tissue thickness, to thereby adjust the amplitude level (i.e., dose) appropriate for each patient and to provide on-line fault detection.

It should be understood that though the apparatus and method in accordance with the present invention have been described in detail they may be subjected to modifications and other embodiments incorporating the inventive features. Specifically, the apparatus can be constructed with the use of analog components alone, in order to reduce significantly the overall cost and complexity. Accordingly, it is intended that the foregoing disclosure is to be considered as illustrating the principles of the invention as an example of those features and not as a delimiting description, which is the purpose of the claims that follow.

What is claimed is:

1. A method of non-invasively therapeutically treating a bone tissue in vivo using ultrasonic signals, comprising the steps of:

producing a preselected periodic therapeutic sine modulated ultrasonic sine signal;

exposing said bone tissue to said therapeutic ultrasonic signal transmitted through soft tissue overlying said bone tissue;

transmitting an interrogating acoustic ultrasonic pulse to said bone tissue through said soft tissue overlying said bone tissue;

receiving a portion of said interrogating signal reflected from said bone tissue;

determining the thickness of said soft tissue using said reflected portion; and

adjusting the amplitude of said therapeutic ultrasonic signal as to ensure that spatial-average time-average power intensity thereof reaching said bone tissue corresponds to a predetermined value.

2. A method of non-invasively therapeutically treating a bone tissue in vivo using ultrasonic signals, comprising the steps of:

producing a preselected periodic therapeutic sine modulated ultrasonic sine signal; and

exposing said bone tissue to said therapeutic ultrasonic signal transmitted through soft tissue overlying said bone tissue

wherein said sine modulated ultrasonic sine signal is amplitude modulated and includes

a carrier frequency being selected in a range between about 25 kHz and about 2 MHz,

a modulating frequency being selected in a range up to about 25 kHz,

a modulation index being up to 1000,

a pulse width being between about 0.1 ms and about 1.0 s,

a cycle duration being between about 0.2 ms and about 1.0 s,

an intensity (I_{SAZI}) being in the range of 20-100 mW/cm², and

a duration of exposure being between about 5 minutes and about 1 hour for 1 to 3 times a day.

3. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 2, wherein said sine modulated ultrasonic sine signal is the amplitude modulated signal having

the carrier frequency being 1.1 MHz,

the modulating frequency being 20 kHz,

the modulation index being 0.3,

the pulse width being 0.5 ms,

the cycle duration being 5 ms, and

the intensity being 45 mW/cm².

4. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 2, wherein said sine modulated ultrasonic sine signal is the amplitude modulated signal having

the carrier frequency being 1.1 MHz,

the modulating frequency being 20 kHz.

5. A method of non-invasively therapeutically treating a bone tissue in vivo using ultrasonic signals, comprising the steps of:

producing a preselected periodic therapeutic sine modulated ultrasonic sine signal; and

exposing said bone tissue to said therapeutic ultrasonic signal transmitted through soft tissue overlying said bone tissue

wherein said preselected periodic therapeutic sine modulated ultrasonic sine signal is the amplitude modulated signal with

a carrier frequency being selected in a range between about 25 kHz and about 2 MHz,

a modulating frequency being selected in a range up to about 25 kHz,

a modulation index being up to 1000,

a pulse width being between about 0.1 ms and about 1.0 s,

a duration of a pulse and a pause for one repetition being between about 0.1 ms and about 1.0 s,

a number of pulse repetitions within a cycle being up to 5000,

a cycle duration being between about 0.2 ms and about 1.0 s,

an intensity being in the range of 20-100 mW/cm², and a duration of exposure being between about 5 minutes and about 1 hour for 1 to 3 times a day.

6. The method of non-invasively therapeutically treating a bone tissue in vivo according to claim 5, wherein said preselected periodic therapeutic sine modulated ultrasonic sine signal is the amplitude modulated signal having

the carrier frequency being 1.1 MHz,

the modulating frequency being 5 kHz,

the modulation index being 0.3,

the pulse width being 4 ms,

the duration of a pulse and a pause for one repetition being 8 ms,

the number of pulse repetitions within a cycle being 25,

the cycle duration being 1 s, and

the intensity being 45 mW/cm².

7. A method of non-invasively therapeutically treating a bone tissue in vivo using ultrasonic signals, comprising the steps of:

producing a preselected periodic therapeutic sine modulated ultrasonic sine signal; and

exposing said bone tissue to said therapeutic ultrasonic signal transmitted through soft tissue overlying said bone tissue