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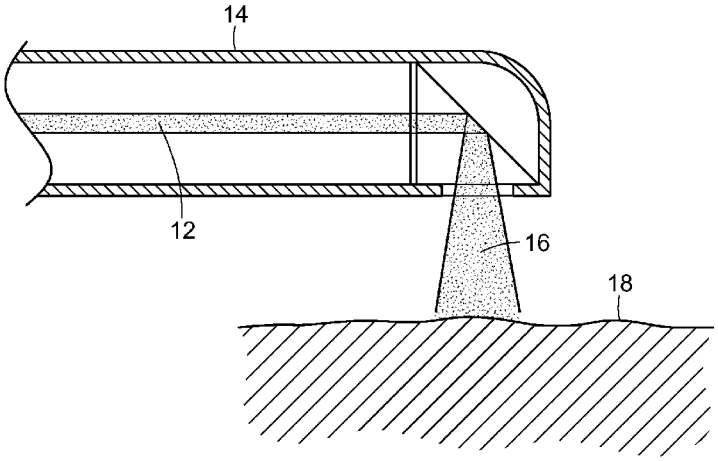

FIG. 19

(57) Abstract: A method for heat treating biological tissues includes providing a pulsed energy source having energy parameters selected so as to raise a target temperature to a level to achieve a therapeutic effect, while the average temperature rise of the tissue over a prolonged period of time is maintained at or below a predetermined level so as not to permanently damage the target tissue. Application of the pulsed energy source to the target tissue induces a heat shock response and stimulates heat shock protein activation in the target tissue so as to therapeutically treat the target tissue.

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METHOD FOR HEAT TREATING BIOLOGICAL TISSUES USING PULSED ENERGY SOURCES

DESCRIPTION

BACKGROUND OF THE INVENTION

[Para 1] The present invention is generally directed to a method for heat treating biological tissues. More particularly, the present invention is directed to a method for applying a pulsed energy source to biological tissue to stimulate activation of heat shock proteins and facilitate protein repair without damaging the tissue.

[Para 2] The inventors have discovered that there is a therapeutic effect to biological tissue, and particularly damaged or diseased biological tissue, by controllably elevating the tissue temperature up to a predetermined temperature range while maintaining the average temperature rise of the tissue over several minutes at or below a predetermined level so as not to permanently damage the target tissue. It is believed that raising the tissue temperature in such a controlled manner selectively stimulates heat shock protein activation and/or production and facilitation of protein repair, which serves as a mechanism for therapeutically treating the tissue.

[Para 3] Heat shock proteins (HSPs) are a family of proteins that are produced by cells in response to exposure to stressful conditions. Production of high levels of heat shock proteins can be triggered by exposure to different kinds of

environmental stress conditions, such as infection, inflammation, exercise, exposure of the cell to toxins, starvation, hypoxia, or water deprivation.

[Para 4] It is known that heat shock proteins play a role in responding to a large number of abnormal conditions in body tissues, including viral infection, inflammation, malignant transformations, exposure to oxidizing agents, cytotoxins, and anoxia. Several heat shock proteins function as intra-cellular chaperones for other proteins and members of the HSP family are expressed or activated at low to moderate levels because of their essential role in protein maintenance and simply monitoring the cell's proteins even under non-stressful conditions. These activities are part of a cell's own repair system, called the cellular stress response or the heat-shock response.

[Para 5] Heat shock proteins are typically named according to their molecular weight. For example, Hsp60, Hsp70 and Hsp80 refer to the families of heat shock proteins on the order of 60, 70 and 80 kilodaltons in size, respectively. They act in a number of different ways. For example, Hsp70 has peptide-binding and ATPase domains that stabilize protein structures in unfolded and assembly-competent states. Mitochondrial Hsp60s form ring-shaped structures facilitating the assembly of proteins into native states. Hsp90 plays a suppressor regulatory role by associating with cellular tyrosine kinases, transcription factors, and glucocorticoid receptors. Hsp27 suppresses protein aggregation.

[Para 6] Hsp70 heat shock proteins are a member of extracellular and membrane bound heat-shock proteins which are involved in binding antigens

and presenting them to the immune system. Hsp70 has been found to inhibit the activity of influenza A virus ribonucleoprotein and to block the replication of the virus. Heat shock proteins derived from tumors elicit specific protective immunity. Experimental and clinical observations have shown that heat shock proteins are involved in the regulation of autoimmune arthritis, type 1 diabetes, mellitus, arterial sclerosis, multiple sclerosis, and other autoimmune reactions.

[Para 7] Accordingly, it is believed that it is advantageous to be able to selectively and controllably raise a target tissue temperature up to a predetermined temperature range over a short period of time, while maintaining the average temperature rise of the tissue at a predetermined temperature over a longer period of time. It is believed that this induces the heat shock response in order to increase the number or activity of heat shock proteins in body tissue in response to infection or other abnormalities. However, this must be done in a controlled manner in order not to damage or destroy the tissue or the area of the body being treated. The present invention fulfills these needs, and provides other related advantages.

SUMMARY OF THE INVENTION

[Para 8] The present invention is directed to a method for heat treating biological tissues by applying a pulsed energy source to the target tissue to therapeutically treat the target tissue. The pulsed energy source has energy parameters including wavelength or frequency, duty cycle and pulse train duration. The energy parameters are selected so as to raise a target tissue

temperature up to 11°C to achieve a therapeutic effect, wherein the average temperature rise of the tissue over several minutes is maintained at or below a predetermined level so as not to permanently damage the target tissue.

[Para 9] The energy source parameters may be selected so that the target tissue temperature is raised between approximately 6°C to 11°C at least during application of the pulsed energy source to the target tissue. The average temperature rise of the target tissue over several minutes is maintained at 6°C or less, such as at approximately 1°C or less over several minutes.

[Para 10] The pulsed energy source energy parameters are selected so that approximately 20 to 40 joules of energy is absorbed by each cubic centimeter of the target tissue. Applying the pulsed energy source to the target tissue induces a heat shock response and stimulates heat shock protein activation in the target tissue without damaging the target tissue.

[Para 11] A device may be inserted into a cavity of the body in order to apply the pulsed energy to the tissue. The pulsed energy may be applied to an exterior area of a body which is adjacent to the target tissue, or has a blood supply close to a surface of the exterior area of the body.

[Para 12] The pulsed energy source may comprise a radiofrequency. The radiofrequency may be between approximately 3 to 6 megahertz (MHz). It may have a duty cycle of between approximately 2.5% to 5%. It may have a pulsed train duration of between approximately 0.2 to 0.4 seconds. The radiofrequency may be generated with a device having a coil radii of between approximately 2 and 6 mm and approximately 13 and 57 amp turns.

[Para 13] The pulsed energy source may comprise a microwave frequency of between 10 to 20 gigahertz (GHz). The microwave may have a pulse train duration of approximately between 0.2 and 0.6 seconds. The microwave may have a duty cycle of between approximately 2% and 5%. The microwave may have an average power of between approximately 8 and 52 watts.

[Para 14] The pulsed energy source may comprise a pulsed light beam, such as a laser light. The light beam may have a wavelength of between approximately 530 nm to 1300 nm, and more preferably between 800 nm and 1000 nm. The pulsed light beam may have a power of between approximately 0.5 and 74 watts. The pulsed light beam has a duty cycle of less than 10%, and preferably between 2.5% and 5%. The pulsed light beam may have a pulse train duration of approximately 0.1 and 0.6 seconds.

[Para 15] The pulsed energy source may comprise a pulsed ultrasound. The ultrasound has a frequency of between approximately 1 and 5 MHz. The ultrasound has a train duration of approximately 0.1 and 05 seconds. The ultrasound may have a duty cycle of between approximately 2% and 10%. The ultrasound has a power of between approximately 0.46 and 28.6 watts.

[Para 16] Other features and advantages of the present invention will become apparent from the following more detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[Para 17] The accompanying drawings illustrate the invention. In such drawings:

[Para 18] FIGURES 1A and 1B are graphs illustrating the average power of a laser source compared to a source radius and pulse train duration of the laser;

[Para 19] FIGURES 2A and 2B are graphs illustrating the time for the temperature to decay depending upon the laser source radius and wavelength;

[Para 20] FIGURES 3-6 are graphs illustrating the peak ampere turns for various radiofrequencies, duty cycles, and coil radii;

[Para 21] FIGURE 7 is a graph depicting the time for temperature rise to decay compared to radiofrequency coil radius;

[Para 22] FIGURES 8 and 9 are graphs depicting the average microwave power compared to microwave frequency and pulse train durations;

[Para 23] FIGURE 10 is a graph depicting the time for the temperature to decay for various microwave frequencies;

[Para 24] FIGURE 11 is a graph depicting the average ultrasound source power compared to frequency and pulse train duration;

[Para 25] FIGURES 12 and 13 are graphs depicting the time for temperature decay for various ultrasound frequencies;

[Para 26] FIGURE 14 is a graph depicting the volume of focal heated region compared to ultrasound frequency;

[Para 27] FIGURE 15 is a graph comparing equations for temperature over pulse durations for an ultrasound energy source;

[Para 28] FIGURES 16 and 17 are graphs illustrating the magnitude of the logarithm of damage and HSP activation Arrhenius integrals as a function of temperature and pulse duration;

[Para 29] FIGURE 18 is a diagrammatic view of a light generating unit that produces timed series of pulses, having a light pipe extending therefrom, in accordance with the present invention;

[Para 30] FIGURE 19 is a cross-sectional view of a photostimulation delivery device delivering electromagnetic energy to target tissue, in accordance with the present invention;

[Para 31] FIGURE 20 is a diagrammatic view illustrating a system used to generate a laser light beam, in accordance with the present invention;

[Para 32] FIGURE 21 is a diagrammatic view of optics used to generate a laser light geometric pattern, in accordance with the present invention;

[Para 33] FIGURE 22 is a diagrammatic view illustrating an alternate embodiment of the system used to generate laser light beams for treating tissue, in accordance with the present invention;

[Para 34] FIGURE 23 is a diagrammatic view illustrating yet another embodiment of a system used to generate laser light beams to treat tissue in accordance with the present invention;

[Para 35] FIGURE 24 is a cross-sectional and diagrammatic view of an end of an endoscope inserted into the nasal cavity and treating tissue therein, in accordance with the present invention;

[Para 36] FIGURE 25 is a diagrammatic and partially cross-sectioned view of a bronchoscope extending through the trachea and into the bronchus of a lung and providing treatment thereto, in accordance with the present invention;

[Para 37] FIGURE 26 is a diagrammatic view of a colonoscope providing photostimulation to an intestinal or colon area of the body, in accordance with the present invention;

[Para 38] FIGURE 27 is a diagrammatic view of an endoscope inserted into a stomach and providing treatment thereto, in accordance with the present invention;

[Para 39] FIGURE 28 is a partially sectioned perspective view of a capsule endoscope, used in accordance with the present invention;

[Para 40] FIGURE 29 is a diagrammatic view of a pulsed high intensity focused ultrasound for treating tissue internal the body, in accordance with the present invention;

[Para 41] FIGURE 30 is a diagrammatic view for delivering therapy to the bloodstream of a patient, through an earlobe, in accordance with the present invention;

[Para 42] FIGURE 31 is a cross-sectional view of a stimulating therapy device of the present invention used in delivering photostimulation to the blood, via an earlobe, in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[Para 43] As shown in the accompanying drawings, and as more fully described herein, the present invention is directed to a system and method for delivering a pulsed energy source, such as laser, ultrasound, ultraviolet radiofrequency, microwave radiofrequency and the like, having energy parameters selected to cause a thermal time-course in tissue to raise the tissue temperature over a short period of time to a sufficient level to achieve a therapeutic effect while maintaining an average tissue temperature over a prolonged period of time below a predetermined level so as to avoid permanent tissue damage. It is believed that the creation of the thermal time-course stimulates heat shock protein activation or production and facilitates protein repair without causing any damage.

[Para 44] The inventors of the present invention have discovered that electromagnetic radiation, in the form of various wavelengths of laser light, can be applied to retinal tissue in a manner that does not destroy or damage the retinal tissue while achieving beneficial effects on eye diseases. It is believed that this may be due, at least in part, to the stimulation and activation of heat shock proteins and the facilitation of protein repair in the retinal tissue. This is disclosed in United States patent application serial numbers 14/607,959 filed January 28, 2015, 13/798,523 filed March 13, 2013, and 13/481,124 filed May 25, 2012, the contents of which are hereby incorporated by reference as if made in full.

[Para 45] The inventors have found that a laser light beam can be generated that is therapeutic, yet sublethal to retinal tissue cells and thus avoids

damaging photocoagulation in the retinal tissue which provides preventative and protective treatment of the retinal tissue of the eye. Various parameters of the light beam must be taken into account and selected so that the combination of the selected parameters achieve the therapeutic effect while not permanently damaging the tissue. These parameters include laser wavelength, radius of the laser source, average laser power, total pulse duration, and duty cycle of the pulse train.

[Para 46] The selection of these parameters may be determined by requiring that the Arrhenius integral for HSP activation be greater than 1 or unity. Arrhenius integrals are used for analyzing the impacts of actions on biological tissue. See, for instance, The CRC Handbook of Thermal Engineering, ed. Frank Kreith, Springer Science and Business Media (2000). At the same time, the selected parameters must not permanently damage the tissue. Thus, the Arrhenius integral for damage may also be used, wherein the solved Arrhenius integral is less than 1 or unity. Alternatively, the FDA/FCC constraints on energy deposition per unit gram of tissue and temperature rise as measured over periods of minutes be satisfied so as to avoid permanent tissue damage. The FDA/FCC requirements on energy deposition and temperature rise are widely used and can be referenced, for example, at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073817.htm#attacha for electromagnetic sources, and Anastosio and P. LaRivero, ed., Emerging Imaging Technologies. CRC Press (2012), for ultrasound sources. Generally speaking, tissue temperature rises of between

6°C and 11°C can create therapeutic effect, such as by activating heat shock proteins, whereas maintaining the average tissue temperature over a prolonged period of time, such as over several minutes, such as six minutes, below a predetermined temperature, such as 6°C and even 1°C or less in certain circumstances, will not permanently damage the tissue.

[Para 47] The inventors have discovered that generating a subthreshold, sublethal micropulse laser light beam which has a wavelength greater than 532 nm and a duty cycle of less than 10% at a predetermined intensity or power and a predetermined pulse length or exposure time creates desirable retinal photostimulation without any visible burn areas or tissue destruction. More particularly, a laser light beam having a wavelength of between 550 nm-1300 nm, and in a particularly preferred embodiment between 810 nm and 1000 nm, having a duty cycle of approximately 2.5%-5% and a predetermined intensity or power (such as between 100-590 watts per square centimeter at the retina or approximately 1 watt per laser spot for each treatment spot at the retina) and a predetermined pulse length or exposure time (such as between 100 and 600 milliseconds or less) creates a sublethal, "true subthreshold" retinal photostimulation in which all areas of the retinal pigment epithelium exposed to the laser irradiation are preserved and available to contribute therapeutically. In other words, the inventors have found that raising the retinal tissue at least up to a therapeutic level but below a cellular or tissue lethal level recreates the benefit of the halo effect of the prior art methods without destroying, burning

or otherwise damaging the retinal tissue. This is referred to herein as subthreshold diode micropulse laser treatment (SDM).

[Para 48] As SDM does not produce laser-induced retinal damage (photocoagulation), and has no known adverse treatment effect, and has been reported to be an effective treatment in a number of retinal disorders (including diabetic macular edema (DME) proliferative diabetic retinopathy (PDR), macular edema due to branch retinal vein occlusion (BRVO), central serous chorioretinopathy (CSR), reversal of drug tolerance, and prophylactic treatment of progressive degenerative retinopathies such as dry age-related macular degeneration, Stargardts' disease, cone dystrophies, and retinitis pigmentosa. The safety of SDM is such that it may be used transfoveally in eyes with 20/20 visual acuity to reduce the risk of visual loss due to early fovea-involving DME.

[Para 49] A mechanism through which SDM might work is the generation or activation of heat shock proteins (HSPs). Despite a near infinite variety of possible cellular abnormalities, cells of all types share a common and highly conserved mechanism of repair: heat shock proteins (HSPs). HSPs are elicited almost immediately, in seconds to minutes, by almost any type of cell stress or injury. In the absence of lethal cell injury, HSPs are extremely effective at repairing and returning the viable cell toward a more normal functional state. Although HSPs are transient, generally peaking in hours and persisting for a few days, their effects may be long lasting. HSPs reduce inflammation, a common factor in many disorders.

[Para 50] Laser treatment can induce HSP production or activation and alter cytokine expression. The more sudden and severe the non-lethal cellular stress (such as laser irradiation), the more rapid and robust HSP activation. Thus, a burst of repetitive low temperature thermal spikes at a very steep rate of change (~ 7°C elevation with each 100µs micropulse, or 70,000°C/sec) produced by each SDM exposure is especially effective in stimulating activation of HSPs, particularly compared to non-lethal exposure to subthreshold treatment with continuous wave lasers, which can duplicate only the low average tissue temperature rise.

[Para 51] Laser wavelengths below 550 nm produce increasingly cytotoxic photochemical effects. At 810 nm, SDM produces photothermal, rather than photochemical, cellular stress. Thus, SDM is able to affect the tissue without damaging it. The clinical benefits of SDM are thus primarily produced by sub-morbid photothermal cellular HSP activation. In dysfunctional cells, HSP stimulation by SDM results in normalized cytokine expression, and consequently improved structure and function. The therapeutic effects of this "low-intensity" laser/tissue interaction are then amplified by "high-density" laser application, recruiting all the dysfunctional cells in the targeted tissue area by densely / confluently treating a large tissue area, including all areas of pathology, thereby maximizing the treatment effect. These principles define the treatment strategy of SDM described herein.

[Para 52] Because normally functioning cells are not in need of repair, HSP stimulation in normal cells would tend to have no notable clinical effect. The

"patho-selectivity" of near infrared laser effects, such as SDM, affecting sick cells but not affecting normal ones, on various cell types is consistent with clinical observations of SDM. SDM has been reported to have a clinically broad therapeutic range, unique among retinal laser modalities, consistent with American National Standards Institute "Maximum Permissible Exposure" predictions. While SDM may cause direct photothermal effects such as entropic protein unfolding and disaggregation, SDM appears optimized for clinically safe and effective stimulation of HSP-mediated repair.

[Para 53] As noted above, while SDM stimulation of HSPs is non-specific with regard to the disease process, the result of HSP mediated repair is by its nature specific to the state of the dysfunction. HSPs tend to fix what is wrong, whatever that might be. Thus, the observed effectiveness of SDM in retinal conditions as widely disparate as BRVO, DME, PDR, CSR, age-related and genetic retinopathies, and drug-tolerant NAMD. Conceptually, this facility can be considered a sort of "Reset to Default" mode of SDM action. For the wide range of disorders in which cellular function is critical, SDM normalizes cellular function by triggering a "reset" (to the "factory default settings") via HSP-mediated cellular repair.

[Para 54] The inventors have found that SDM treatment of patients suffering from age-related macular degeneration (AMD) can slow the progress or even stop the progression of AMD. Most of the patients have seen significant improvement in dynamic functional logMAR mesoptic visual acuity and mesoptic contrast visual acuity after the SDM treatment. It is believed that SDM

works by targeting, preserving, and "normalizing" (moving toward normal) function of the retinal pigment epithelium (RPE).

[Para 55] SDM has also been shown to stop or reverse the manifestations of the diabetic retinopathy disease state without treatment-associated damage or adverse effects, despite the persistence of systemic diabetes mellitus. On this basis it is hypothesized that SDM might work by inducing a return to more normal cell function and cytokine expression in diabetes-affected RPE cells, analogous to hitting the "reset" button of an electronic device to restore the factory default settings. Based on the above information and studies, SDM treatment may directly affect cytokine expression via heat shock protein (HSP) activation in the targeted tissue.

[Para 56] As heat shock proteins play a role in responding to a large number of abnormal conditions in body tissue other than eye tissue, it is believed that similar systems and methodologies can be advantageously used in treating such abnormal conditions, infections, etc. As such, the present invention is directed to the controlled application of ultrasound or electromagnetic radiation to treat abnormal conditions including inflammations, autoimmune conditions, and cancers that are accessible by means of fiber optics of endoscopes or surface probes as well as focused electromagnetic/sound waves. For example, cancers on the surface of the prostate that have the largest threat of metastasizing can be accessed by means of fiber optics in a proctoscope. Colon tumors can be accessed by an optical fiber system, like those used in colonoscopy.

[Para 57] As indicated above, subthreshold diode micropulse laser (SDM) photostimulation has been effective in stimulating direct repair of slightly misfolded proteins in eye tissue. Besides HSP activation, another way this may occur is because the spikes in temperature caused by the micropulses in the form of a thermal time-course allows diffusion of water inside proteins, and this allows breakage of the peptide-peptide hydrogen bonds that prevent the protein from returning to its native state. The diffusion of water into proteins results in an increase in the number of restraining hydrogen bonds by a factor on the order of a thousand. Thus, it is believed that this process could be applied to other diseases advantageously as well.

[Para 58] As explained above, the energy source to be applied to the target tissue will have energy and operating parameters which must be determined and selected so as to achieve the therapeutic effect while not permanently damaging the tissue. Using a light beam energy source, such as a laser light beam, as an example, the laser wavelength, duty cycle and total pulse train duration parameters must be taken into account. Other parameters which can be considered include the radius of the laser source as well as the average laser power. Adjusting or selecting one of these parameters can have an effect on at least one other parameter.

[Para 59] FIGS. 1A and 1B illustrate graphs showing the average power in watts as compared to the laser source radius (between 0.1 cm and 0.4 cm) and pulse train duration (between 0.1 and 0.6 seconds). FIG. 1A shows a wavelength of 880 nm, whereas FIG.1B has a wavelength of 1000 nm. It can be

seen in these figures that the required power decreases monotonically as the radius of the source decreases, as the total train duration increases, and as the wavelength decreases. The preferred parameters for the radius of the laser source is 1 mm-4 mm. For a wavelength of 880 nm, the minimum value of power is 0.55 watts, with a radius of the laser source being 1 mm, and the total pulse train duration being 600 milliseconds. The maximum value of power for the 880 nm wavelength is 52.6 watts when the laser source radius is 4 mm and the total pulse drain duration is 100 milliseconds. However, when selecting a laser having a wavelength of 1000 nm, the minimum power value is 0.77 watts with a laser source radius of 1 mm and a total pulse train duration of 600 milliseconds, and a maximum power value of 73.6 watts when the laser source radius is 4 mm and the total pulse duration is 100 milliseconds. The corresponding peak powers, during an individual pulse, are obtained from the average powers by dividing by the duty cycle.

[Para 60] The volume of the tissue region to be heated is determined by the wavelength, the absorption length in the relevant tissue, and by the beam width. The total pulse duration and the average laser power determine the total energy delivered to heat up the tissue, and the duty cycle of the pulse train gives the associated spike, or peak, power associated with the average laser power. Preferably, the pulsed energy source energy parameters are selected so that approximately 20 to 40 joules of energy is absorbed by each cubic centimeter of the target tissue.

[Para 61] The absorption length is very small in the thin melanin layer in the retinal pigmented epithelium. In other parts of the body, the absorption length is not generally that small. In wavelengths ranging from 400 nm to 2000 nm, the penetration depth and skin is in the range of 0.5 mm to 3.5 mm. The penetration depth into human mucous tissues in the range of 0.5 mm to 6.8 mm. Accordingly, the heated volume will be limited to the exterior or interior surface where the radiation source is placed, with a depth equal to the penetration depth, and a transverse dimension equal to the transverse dimension of the radiation source. Since the light beam energy source is used to treat diseased tissues near external surfaces or near internal accessible surfaces, a source radii of between 1 mm to 4 mm and operating a wavelength of 880 nm yields a penetration depth of approximately 2.5 mm and a wavelength of 1000 nm yields a penetration depth of approximately 3.5 mm.

[Para 62] It has been determined that the target tissue can be heated to up to approximately 11°C for a short period of time, such as less than one second, to create the therapeutic effect of the invention while maintaining the target tissue average temperature to a lower temperature range, such as less than 6°C or even 1°C or less over a prolonged period of time, such as several minutes. The selection of the duty cycle and the total pulse train duration provide time intervals in which the heat can dissipate. A duty cycle of less than 10%, and preferably between 2.5% and 5%, with a total pulse duration of between 100 milliseconds and 600 milliseconds has been found to be effective. FIGS. 2A and 2B illustrate the time to decay from 10°C to 1°C for a laser source having a

radius of between 0.1 cm and 0.4 cm with the wavelength being 880 nm in FIG. 2A and 1000 nm in FIG. 2B. It can be seen that the time to decay is less when using a wavelength of 880 nm, but either wavelength falls within the acceptable requirements and operating parameters to achieve the benefits of the present invention while not causing permanent tissue damage.

[Para 63] It has been found that the average temperature rise of the desired target region increasing at least 6°C and up to 11°C, and preferably approximately 10°C, during the total irradiation period results in HSP activation. The control of the target tissue temperature is determined by choosing source and target parameters such that the Arrhenius integral for HSP activation is larger than 1, while at the same time assuring compliance with the conservative FDA/FCC requirements for avoiding damage or a damage Arrhenius integral being less than 1.

[Para 64] In order to meet the conservative FDA/FCC constraints to avoid permanent tissue damage, for light beams, and other electromagnetic radiation sources, the average temperature rise of the target tissue over any six-minute period is 1°C or less. FIGS. 2A and 2B above illustrate the typical decay times required for the temperature in the heated target region to decrease by thermal diffusion from a temperature rise of approximately 10°C to 1°C as can be seen in FIG. 2A when the wavelength is 880 nm and the source diameter is 1 millimeter, the temperature decay time is 16 seconds. The temperature decay time is 107 seconds when the source diameter is 4 mm. As shown in FIG. 2B, when the wavelength is 1000 nm, the temperature decay time is 18 seconds

when the source diameter is 1 mm and 136 seconds when the source diameter is 4 mm. This is well within the time of the average temperature rise being maintained over the course of several minutes, such as 6 minutes or less. While the target tissue's temperature is raised, such as to approximately 10°C, very quickly, such as in a fraction of a second during the application of the energy source to the tissue, the relatively low duty cycle provides relatively long periods of time between the pulses of energy applied to the tissue and the relatively short pulse train duration ensure sufficient temperature diffusion and decay within a relatively short period of time comprising several minutes, such as 6 minutes or less, that there is no permanent tissue damage.

[Para 65] The parameters differ for the individual energy sources, including microwave, infrared lasers, radiofrequency and ultrasound, because the absorption properties of tissues differ for these different types of energy sources. The tissue water content can vary from one tissue type to another, however, there is an observed uniformity of the properties of tissues at normal or near normal conditions which has allowed publication of tissue parameters that are widely used by clinicians in designing treatments. Below are tables illustrating the properties of electromagnetic waves in biological media, with Table 1 relating to muscle, skin and tissues with high water content, and Table 2 relating to fat, bone and tissues with low water content.

[Para 66] Table 1. Properties of Electromagnetic Waves in Biological Media: Muscle, Skin, and Tissues with High Water Content

	Reflection Coefficient	
Conductivity Wavelength	Air-Muscle Interface	Muscle-Fat Interface

			σH (mho/m)	λH (cm)		r	ø	r	ø
1	30000	2000	0.400	436	91.3	0.982	+179		
10	3000	160	0.625	118	21.6	0.956	+178		
27.12	1106	113	0.612	68.1	14.3	0.925	+177	0.651	-11.13
40.68	738	97.3	0.693	51.3	11.2	0.913	+176	0.652	-10.21
100	300	71.7	0.889	27	6.66	0.881	+175	0.650	-7.96
200	150	56.5	1.28	16.6	4.79	0.844	+175	0.612	-8.06
300	100	54	1.37	11.9	3.89	0.825	+175	0.592	-8.14
433	69.3	53	1.43	8.76	3.57	0.803	+175	0.562	-7.06
750	40	52	1.54	5.34	3.18	0.779	+176	0.532	-5.69
915	32.8	51	1.60	4.46	3.04	0.772	+177	0.519	-4.32
1500	20	49	1.77	2.81	2.42	0.761	+177	0.506	-3.66
2450	12.2	47	2.21	1.76	1.70	0.754	+177	0.500	-3.88
3000	10	46	2.26	1.45	1.61	0.751	+178	0.495	-3.20
5000	6	44	3.92	0,89	0.788	0.749	+177	0.502	-4.95
5800	5.17	43.3	4.73	0.775	0.720	0.746	+177	0.502	-4.29
8000	3,75	40	7.65	0.578	0.413	0.744	+176	0.513	-6.65
10000	3	39.9	10.3	0.464	0.343	0.743	+176	0.518	-5.95

[Para 67] Table 2. Properties of Electromagnetic Waves in Biological Media: Fat, Bone, and Tissues with Low Water Content

Frequency (MHz)	Wavelength in Air (cm)	Dielectric Constant €L	Conductivity σL, (mmho/m)	Wavelength λL (cm	Depth of Penetration (cm)	Reflection Coefficient: Air-Fat Interface r	Air-Fat Interface ø	Fat-Muscle Interface r	Fat-Muscle Interface ø
1	30000								
10	3000								
27.12	1106	20	10.9-43.2	241	159	0.660	+174	0.651	+169
40.68	738	14.6	12.6-52.8	187	118	0.617	+173	0.652	+170
100	300	7.45	19.1-75.9	106	60.4	0.511	+168	0.650	+172
200	150	5.95	25.8-94.2	59.7	39.2	0.458	+168	0.612	+172
300	100	5.7	31.6-107	41	32.1	0.438	+169	0.592	+172
433	69.3	5.6	37.9-118	28.8	26.2	0.427	+170	0.562	+173
750	40	5.6	49.8-138	16.8	23	0.415	+173	0.532	+174
915	32.8	5.6	55.6-147	13.7	17.7	0.417	+173	0.519	+176
1500	20	5.6	70.8-171	8.41	13.9	0.412	+174	0.506	+176
2450	12.2	5.5	96.4-213	5.21	11.2	0.406	+176	0.500	+176
3000	10	5.5	110-234	4.25	9.74	0.406	+176	0.495	+177
5000	6	5.5	162-309	2.63	6.67	0.393	+176	0.502	+175
5900	5.17	5.05	186-338	2.29	5.24	0.388	+176	0.502	+176
8000	3.75	4.7	255-431	1.73	4.61	0.371	+176	0.513	+173 -
10000	3	4.5	324-549	1.41	3.39	0.363	+175	0.518	+174,-

[Para 68] The absorption lengths of radiofrequency in body tissue are long compared to body dimensions. Consequently, the heated region is determined by the dimensions of the coil that is the source of the radiofrequency energy rather than by absorption lengths. Long distances r from a coil the magnetic (near) field from a coil drops off as $1/r^3$. At smaller distances, the electric and magnetic fields can be expressed in terms of the vector magnetic potential, which in turn can be expressed in closed form in terms of elliptic integrals of

the first and second kind. The heating occurs only in a region that is comparable in size to the dimensions of the coil source itself. Accordingly, if it is desired to preferentially heat a region characterized by a radius, the source coil will be chosen to have a similar radius. The heating drops off very rapidly outside of a hemispherical region of radius because of the $1/r^3$ drop off of the magnetic field. Since it is proposed to use the radiofrequency the diseased tissue accessible only externally or from inner cavities, it is reasonable to consider a coil radii of between approximately 2 to 6 mm.

[Para 69] The radius of the source coil(s) as well as the number of ampere turns (NI) in the source coils give the magnitude and spatial extent of the magnetic field, and the radiofrequency is a factor that relates the magnitude of the electric field to the magnitude of the magnetic field. The heating is proportional to the product of the conductivity and the square of the electric field. For target tissues of interest that are near external or internal surfaces, the conductivity is that of skin and mucous tissue. The duty cycle of the pulse train as well as the total train duration of a pulse train are factors which affect how much total energy is delivered to the tissue.

[Para 70] Preferred parameters for a radiofrequency energy source have been determined to be a coil radii between 2 and 6 mm, radiofrequencies in the range of 3-6 MHz, total pulse train durations of 0.2 to 0.4 seconds, and a duty cycle of between 2.5% and 5%. FIGS. 3-6 show how the number of ampere turns varies as these parameters are varied in order to give a temperature rise that produces an Arrhenius integral of approximately one or unity for HSP

activation. With reference to FIG. 3, for an RF frequency of 6 MHz, a pulse train duration of between 0.2 and 0.4 seconds, a coil radius between 0.2 and 0.6 cm, and a duty cycle of 5%, the peak ampere turns (NI) is 13 at the 0.6 cm coil radius and 20 at the 0.2 cm coil radius. For a 3 MHz frequency, as illustrated in FIG. 4, the peak ampere turns is 26 when the pulse train duration is 0.4 seconds and the coil radius is 0.6 cm and the duty cycle is 5%. However, with the same 5% duty cycle, the peak ampere turns is 40 when the coil radius is 0.2 cm and the pulse train duration is 0.2 seconds. A duty cycle of 2.5% is used in FIGS. 5 and 6. This yields, as illustrated in FIG. 5, 18 amp turns for a 6 MHz radiofrequency having a coil radius of 0.6 cm and a pulse train duration of 0.4 seconds, and 29 amp turns when the coil radius is only 0.2 cm and the pulse train duration is 0.2 seconds. With reference to FIG. 6, with a duty cycle of 2.5% and a radiofrequency of 3 MHz, the peak ampere turns is 36 when the pulse train duration is 0.4 seconds and the coil radius is 0.6 cm, and 57 amp turns when the pulse train duration is 0.2 seconds and the coil radius is 0.2 cm.

[Para 71] The time, in seconds, for the temperature rise to decay from approximately 10°C to approximately 1°C for coil radii between 0.2 cm and 0.6 cm is illustrated for a radiofrequency energy source in FIG. 7. The temperature decay time is approximately 37 seconds when the radiofrequency coil radius is 0.2 cm, and approximately 233 seconds when the radiofrequency coil radius is 0.5 cm. When the radiofrequency coil radius is 0.6 cm, the decay time is approximately 336 seconds, which is still within the acceptable range of decay time, but at an upper range thereof.

[Para 72] Microwaves are another electromagnetic energy source which can be utilized in accordance with the present invention. The frequency of the microwave determines the tissue penetration distance. The gain of a conical microwave horn is large compared to the microwave wavelength, indicating under those circumstances that the energy is radiated mostly in a narrow forward load. Typically, a microwave source used in accordance with the present invention has a linear dimension on the order of a centimeter or less, thus the source is smaller than the wavelength, in which case the microwave source can be approximated as a dipole antenna. Such small microwave sources are easier to insert into internal body cavities and can also be used to radiate external surfaces. In that case, the heated region can be approximated by a hemisphere with a radius equal to the absorption length of the microwave in the body tissue being treated. As the microwaves are used to treat tissue near external surfaces or surfaces accessible from internal cavities, frequencies in the 10-20 GHz range are used, wherein the corresponding penetration distances are only between approximately 2 and 4 mm.

[Para 73] The temperature rise of the tissue using a microwave energy source is determined by the average power of the microwave and the total pulse train duration. The duty cycle of the pulse train determines the peak power in a single pulse in a train of pulses. As the radius of the source is taken to be less than approximately 1 centimeter, and frequencies between 10 and 20 GHz are typically used, a resulting pulse train duration of 0.2 and 0.6 seconds is preferred.

[Para 74] The required power decreases monotonically as the train duration increases and as the microwave frequency increases. For a frequency of 10 GHz, the average power is 18 watts when the pulse train duration is 0.6 seconds, and 52 watts when the pulse train duration is 0.2 seconds. For a 20 GHz microwave frequency, an average power of 8 watts is used when the pulse train is 0.6 seconds, and can be 26 watts when the pulse train duration is only 0.2 seconds. The corresponding peak power are obtained from the average power simply by dividing by the duty cycle.

[Para 75] With reference now to FIG. 8, a graph depicts the average microwave power in watts of a microwave having a frequency of 10 GHz and a pulse train duration from between 0.2 seconds and 0.6 seconds. FIG. 9 is a similar graph, but showing the average microwave power for a microwave having a frequency of 20 GHz. Thus, it will be seen that the average microwave source power varies as the total train duration and microwave frequency vary. The governing condition, however, is that the Arrhenius integral for HSP activation in the heated region is approximately 1.

[Para 76] With reference to FIG. 10, a graph illustrates the time, in seconds, for the temperature to decay from approximately 10°C to 1°C compared to microwave frequencies between 58 MHz and 20000 MHz. The minimum and maximum temperature decay for the preferred range of microwave frequencies are 8 seconds when the microwave frequency is 20 GHz, and 16 seconds when the microwave frequency is 10 GHz.

[Para 77] Utilizing ultrasound as an energy source enables heating of surface tissue, and tissues of varying depths in the body, including rather deep tissue. The absorption length of ultrasound in the body is rather long, as evidenced by its widespread use for imaging. Accordingly, ultrasound can be focused on target regions deep within the body, with the heating of a focused ultrasound beam concentrated mainly in the approximately cylindrical focal region of the beam. The heated region has a volume determined by the focal waist of the airy disc and the length of the focal waist region, that is the confocal parameter. Multiple beams from sources at different angles can also be used, the heating occurring at the overlapping focal regions.

[Para 78] For ultrasound, the relevant parameters for determining tissue temperature are frequency of the ultrasound, total train duration, and transducer power when the focal length and diameter of the ultrasound transducer is given. The frequency, focal length, and diameter determine the volume of the focal region where the ultrasound energy is concentrated. It is the focal volume that comprises the target volume of tissue for treatment. Transducers having a diameter of approximately 5 cm and having a focal length of approximately 10 cm are readily available. Favorable focal dimensions are achieved when the ultrasound frequency is between 1 and 5 MHz, and the total train duration is 0.1 to 0.5 seconds. For example, for a focal length of 10 cm and the transducer diameter of 5 cm, the focal volumes are 0.02 cc at 5 MHz and 2.36 cc at 1 MHz.

[Para 79] With reference now to FIG. 11, a graph illustrates the average source power in watts compared to the frequency (between 1 MHz and 5 MHz), and the pulse train duration (between 0.1 and 0.5 seconds). A transducer focal length of 10 cm and a source diameter of 5 cm have been assumed. The required power to give the Arrhenius integral for HSP activation of approximately 1 decreases monotonically as the frequency increases and as the total train duration increases. Given the preferred parameters, the minimum power for a frequency of 1 GHz and a pulse train duration of 0.5 seconds is 5.72 watts, whereas for the 1 GHz frequency and a pulse train duration of 0.1 seconds the maximum power is 28.6 watts. For a 5 GHz frequency, 0.046 watts is required for a pulse train duration of 0.5 seconds, wherein 0.23 watts is required for a pulse train duration of 0.1 seconds. The corresponding peak power during an individual pulse is obtained simply by dividing by the duty cycle.

[Para 80] FIGURE 12 illustrates the time, in seconds, for the temperature to diffuse or decay from 10°C to 6°C when the ultrasound frequency is between 1 and 5 MHz. FIG. 13 illustrates the time, in seconds, to decay from approximately 10°C to approximately 1°C for ultrasound frequencies from 1 to 5 MHz. For the preferred focal length of 10 cm and the transducer diameter of 5 cm, the maximum time for temperature decay is 366 seconds when the ultrasound frequency is 1 MHz, and the minimum temperature decay is 15 seconds when the microwave frequency is 5 MHz. As the FDA only requires the temperature rise be less than 6°C for test times of minutes, the 366 second

decay time at 1 MHz to get to a rise of 1°C over the several minutes is allowable. As can be seen in FIGS. 12 and 13, the decay times to a rise of 6°C are much smaller, by a factor of approximately 70, than that of 1°C.

[Para 81] FIGURE 14 illustrates the volume of focal heated region, in cubic centimeters, as compared to ultrasound frequencies from between 1 and 5 MHz. Considering ultrasound frequencies in the range of 1 to 5 MHz, the corresponding focal sizes for these frequencies range from 3.7 mm to 0.6 mm, and the length of the focal region ranges from 5.6 cm to 1.2 cm. The corresponding treatment volumes range from between approximately 2.4 cc and 0.02 cc.

[Para 82] Examples of parameters giving a desired HSP activation Arrhenius integral greater than 1 and damage Arrhenius integral less than 1 is a total ultrasound power between 5.8-17 watts, a pulse duration of 0.5 seconds, an interval between pulses of 5 seconds, with total number of pulses 10 within the total pulse stream time of 50 seconds. The target treatment volume would be approximately 1 mm on a side. Larger treatment volumes could be treatable by an ultrasound system similar to a laser diffracted optical system, by applying ultrasound in multiple simultaneously applied adjacent but separated and spaced columns. The multiple focused ultrasound beams converge on a very small treatment target within the body, the convergence allowing for a minimal heating except at the overlapping beams at the target. This area would be heated and stimulate the activation of HSPs and facilitate protein repair by transient high temperature spikes. However, given the pulsating aspect of the

invention as well as the relatively small area being treated at any given time, the treatment is in compliance with FDA/FCC requirements for long term (minutes) average temperature rise <1K. An important distinction of the invention from existing therapeutic heating treatments for pain and muscle strain is that there are no high T spikes in existing techniques, and these are required for efficiently activating HSPs and facilitating protein repair to provide healing at the cellular level.

[Para 83] The pulse train mode of energy delivery has a distinct advantage over a single pulse or gradual mode of energy delivery, as far as the activation of remedial HSPs and the facilitation of protein repair is concerned. There are two considerations that enter into this advantage:

[Para 84] First, a big advantage for HSP activation and protein repair in an SDM energy delivery mode comes from producing a spike temperature of the order of 10°C. This large rise in temperature has a big impact on the Arrhenius integrals that describe quantitatively the number of HSPs that are activated and the rate of water diffusion into the proteins that facilitates protein repair. This is because the temperature enters into an exponential that has a big amplification effect.

[Para 85] It is important that the temperature rise not remain at the high value (10°C or more) for long, because then it would violate the FDA and FCC requirements that over periods of minutes the average temperature rise must be less than 1°C (or in the case of ultrasound 6°C).

[Para 86] An SDM mode of energy delivery uniquely satisfies both of these foregoing considerations by judicious choice of the power, pulse time, pulse interval, and the volume of the target region to be treated. The volume of the treatment region enters because the temperature must decay from its high value of the order of 10°C fairly rapidly in order for the long term average temperature rise not to exceed the long term FDA/FCC limit of 6°C for ultrasound frequencies and 1°C or less for electromagnetic radiation energy sources.

[Para 87] For a region of linear dimension L, the time that it takes the peak temperature to e-fold in tissue is roughly $L^2/16D$, where $D = 0.00143$ cm^2/sec is the typical heat diffusion coefficient. For example, if $L = 1$ mm, the decay time is roughly 0.4 sec. Accordingly, for a region 1 mm on a side, a train consisting of 10 pulses each of duration 0.5 seconds, with an interval between pulses of 5 second can achieve the desired momentary high rise in temperature while still not exceeding an average long term temperature rise of 1°C. This is demonstrated further below.

[Para 88] The limitation of heated volume is the reason why RF electromagnetic radiation is not as good of a choice for SDM-type treatment of regions deep with the body as ultrasound. The long skin depths (penetration distances) and Ohmic heating all along the skin depth results in a large heated volume whose thermal inertia does not allow both the attainment of a high spike temperature that activates HSPs and facilitates protein repair, and the

rapid temperature decay that satisfies the long term FDA and FCC limit on average temperature rise.

[Para 89] Ultrasound has already been used to therapeutically heat regions of the body to ease pain and muscle strain. However, the heating has not followed the SDM-type protocol and does not have the temperature spikes that are responsible for the excitation of HSPs.

[Para 90] Consider, then, a group of focused ultrasound beams that are directed at a target region deep within the body. To simplify the mathematics, suppose that the beams are replaced by a single source with a spherical surface shape that is focused on the center of the sphere. The absorption lengths of ultrasound can be fairly long. Table 3 below shows typical absorption coefficients for ultrasound at 1 MHz. The absorption coefficients are roughly proportional to the frequency.

[Para 91] Table 3. Typical absorption coefficients for 1 MHz ultrasound in body tissue:

Body Tissue	Attenuation Coefficient at 1 MHz (cm^{-1})
Water	0.00046
Blood	0.0415
Fat	0.145
Liver	0.115-0.217
Kidney	0.23
Muscle	0.3-0.76
Bone	1.15

[Para 92] Assuming that the geometric variation of the incoming radiation due to the focusing dominates any variation due to attenuation, the intensity of the incoming ultrasound at a distance r from the focus can be written approximately as:

$$I(r) = P/(4\pi r^2) \quad [1]$$

where P denotes the total ultrasound power.

The temperature rise at the end of a short pulse of duration t_p at r is then

$$dT(t_p) = P\alpha t_p / (4\pi C_v r^2) \quad [2]$$

where α is the absorption coefficient and C_v is the specific volume heat capacity. This will be the case until the r is reached at which the heat diffusion length at t_p becomes comparable to r, or the diffraction limit of the focused beam is reached. For smaller r, the temperature rise is essentially independent of r. As an example, suppose the diffraction limit is reached at a radial distance that is smaller than that determined by heat diffusion. Then

$$r_{dif} = (4Dt_p)^{1/2} \quad [3]$$

where D is the heat diffusion coefficient, and for $r<r_{dif,}$ the temperature rise at t_p is

$$dT(r_{dif}, t_p) = 3P\alpha/(8\pi C_v D) \quad \text{when } r< r_{dif} \quad [4]$$

Thus, at the end of the pulse, we can write for the temperature rise:

$$dT_p(r) = \{P\alpha t_p/(4\pi C_v\}[(6/r_{dif}^2)U\{r_{dif}-r) + (1/r^2)U(r-r_{dif})] \quad [5]$$

On applying the Green's function for the heat diffusion equation,

$$G(r,t) = (4\Omega Dt)^{-3/2} \exp[-r^2/(4Dt)] \quad [6]$$

to this initial temperature distribution, we find that the temperature dT(t) at the focal point r=0 at a time t is

$$dT(t) = [dT_o/\{(1/2)+(\pi^{1/2}/6)\}][(1/2)(t_p/t)^{3/2} + (\pi^{1/2}/6)(t_p/t)] \quad [7]$$

with

$$dT_o = 3P\alpha/(8\pi C_v D) \quad [8]$$

[Para 93] A good approximation to eq. [7] is provided by:

$$dT(t) \approx dT_o\,(t_p/t)^{3/2} \quad [9]$$

as can be seen in FIG. 15, which is a comparison of eqs. [7] and [9] for $dT(t)/dT_o$ at the target treatment zone. The bottom curve is the approximate expression of eq [9].

The Arrhenius integral for a train of N pulses can now be evaluated with the temperature rise given by eq. [9]. In this expression,

$$dT_N(t) = \Sigma\, dT(t-nt_l) \quad [11]$$

where $dT(t-nt_l)$ is the expression of eq. [9] with t replaced by $t-nt_l$ and with t_l designating the interval between pulses.

[Para 94] The Arrhenius integral can be evaluated approximately by dividing the integration interval into the portion where the temperature spikes occur and the portion where the temperature spike is absent. The summation over the temperature spike contribution can be simplified by applying Laplace's end point formula to the integral over the temperature spike. In addition, the integral over the portion when the spikes are absent can be simplified by noting that the non-spike temperature rise very rapidly reaches an asymptotic value,

so that a good approximation is obtained by replacing the varying time rise by its asymptotic value. When these approximations are made, eq. [10] becomes:

$$\Omega = AN[\{t_p(2k_BT_o^2/(3EdT_o)\}\exp[-(E/k_B)1/(T_o + dT_o + dT_N(Nt_l))] + \exp[-(E/k_B)1/(T_o + dT_N(Nt_l))]] \quad [12]$$

where

$$dT_N(Nt_l) \approx 2.5\ dT_o\ (t_p/t_l)^{3/2} \quad [13]$$

(The 2.5 in eq. [13] arises from the summation over n of $(N-n)^{-3/2}$ and is the magnitude of the harmonic number $(N,3/2)$ for typical N of interest.)

[Para 95] It is interesting to compare this expression with that for SDM applied to the retina. The first term is very similar to that from the spike contribution in the retina case, except that the effective spike interval is reduced by a factor of 3 for this 3D converging beam case. The second term, involving $dT_N(Nt_l)$ is much smaller than in the retina case. There the background temperature rise was comparable in magnitude to the spike temperature rise. But here in the converging beam case, the background temperature rise is much smaller by the ratio $(t_p/t_l)^{3/2}$. This points up the importance of the spike contribution to the activation or production of HSP's and the facilitation of protein repair, as the background temperature rise which is similar to the rise in a continuous ultrasound heating case is insignificant compared to the spike contribution. At the end of the pulse train, even this low background temperature rise rapidly disappears by heat diffusion.

[Para 96] FIGURES 16 and 17 show the magnitude of the logarithm of the Arrhenius integrals for damage and for HSP activation or production as a

function of dT_o for a pulse duration t_p = 0.5 sec, pulse interval t_I = 10 sec, and total number of pulses N = 10. Logarithm of Arrhenius integrals [eq. 12] for damage and for HSP activation as a function of the temperature rise in degrees Kelvin from a single pulse dT_o, for a pulse duration t_p = 0.5 sec., pulse interval t_I = 10 sec., and a total number of ultrasound pulses N = 10. FIG. 16 shows the logarithm of the damage integral with the Arrhenius constants A = 8.71×10^{33} sec^{-1} and E = 3.55×10^{-12} ergs. FIG. 17 shows the logarithm of the HSP activation integral with the Arrhenius constants A = 1.24×10^{27} sec^{-1} and E = 2.66×10^{-12} ergs. The graphs in FIGS. 16 and 17 show that Ω_{damage} does not exceed 1 until dT_o exceeds 11.3 K, whereas Ω_{hsp} is greater than 1 over the whole interval shown, the desired condition for cellular repair without damage.

[Para 97] Equation [8] shows that when α = 0.1 cm^{-1}, a dT_o of 11.5 K can be achieved with a total ultrasound power of 5.8 watts. This is easily achievable. If α is increased by a factor of 2 or 3, the resulting power is still easily achievable. The volume of the region where the temperature rise is constant (i.e. the volume corresponding to $r=r_d = (4Dt_p)^{1/2}$) is 0.00064 cc. This corresponds to a cube that is 0.86 mm on a side.

[Para 98] This simple example demonstrates that focused ultrasound should be usable to stimulate reparative HSP's deep in the body with easily attainable equipment:

Total ultrasound power:	5.8 watts – 17 watts
Pulse time	0.5 sec
Pulse interval	5 sec

Total train duration (N=10) 50 sec

To expedite the treatment of larger internal volumes, a SAPRA system can be used.

[Para 99] The pulsed energy source may be directed to an exterior of a body which is adjacent to the target tissue or has a blood supply close to the surface of the exterior of the body. Alternatively, a device may be inserted into a cavity of a body to apply the pulsed energy source to the target tissue. Whether the energy source is applied outside of the body or inside of the body and what type of device is utilized depends upon the energy source selected and used to treat the target tissue.

[Para 100] Photostimulation, in accordance with the present invention, can be effectively transmitted to an internal surface area or tissue of the body utilizing an endoscope, such as a bronchoscope, proctoscope, colonoscope or the like. Each of these consist essentially of a flexible tube that itself contains one or more internal tubes. Typically, one of the internal tubes comprises a light pipe or multi-mode optical fiber which conducts light down the scope to illuminate the region of interest and enable the doctor to see what is at the illuminated end. Another internal tube could consist of wires that carry an electrical current to enable the doctor to cauterize the illuminated tissue. Yet another internal tube might consist of a biopsy tool that would enable the doctor to snip off and hold on to any of the illuminated tissue.

[Para 101] In the present invention, one of these internal tubes is used as an electromagnetic radiation pipe, such as a multi-mode optical fiber, to transmit

the SDM or other electromagnetic radiation pulses that are fed into the scope at the end that the doctor holds. With reference now to FIG. 18, a light generating unit 10, such as a laser having a desired wavelength and/or frequency is used to generate electromagnetic radiation, such as laser light, in a controlled, pulsed manner to be delivered through a light tube or pipe 12 to a distal end of the scope 14, illustrated in FIG. 19, which is inserted into the body and the laser light or other radiation 16 delivered to the target tissue 18 to be treated.

[Para 102] With reference now to FIG. 20, a schematic diagram is shown of a system for generating electromagnetic energy radiation, such as laser light, including SDM. The system, generally referred to by the reference number 20, includes a laser console 22, such as for example the 810 nm near infrared micropulsed diode laser in the preferred embodiment. The laser generates a laser light beam which is passed through optics, such as an optical lens or mask, or a plurality of optical lenses and/or masks 24 as needed. The laser projector optics 24 pass the shaped light beam to a delivery device 26, such as an endoscope, for projecting the laser beam light onto the target tissue of the patient. It will be understood that the box labeled 26 can represent both the laser beam projector or delivery device as well as a viewing system/camera, such as an endoscope, or comprise two different components in use. The viewing system/camera 26 provides feedback to a display monitor 28, which may also include the necessary computerized hardware, data input and controls, etc. for manipulating the laser 22, the optics 24, and/or the projection/viewing components 26.

[Para 103] With reference now to FIG. 21, in one embodiment, the laser light beam 30 may be passed through a collimator lens 32 and then through a mask 34. In a particularly preferred embodiment, the mask 34 comprises a diffraction grating. The mask/diffraction grating 34 produces a geometric object, or more typically a geometric pattern of simultaneously produced multiple laser spots or other geometric objects. This is represented by the multiple laser light beams labeled with reference number 36. Alternatively, the multiple laser spots may be generated by a plurality of fiber optic waveguides. Either method of generating laser spots allows for the creation of a very large number of laser spots simultaneously over a very wide treatment field. In fact, a very high number of laser spots, perhaps numbering in the hundreds even thousands or more could be simultaneously generated to cover a given area of the target tissue, or possibly even the entirety of the target tissue. A wide array of simultaneously applied small separated laser spot applications may be desirable as such avoids certain disadvantages and treatment risks known to be associated with large laser spot applications.

[Para 104] Using optical features with a feature size on par with the wavelength of the laser employed, for example using a diffraction grating, it is possible to take advantage of quantum mechanical effects which permits simultaneous application of a very large number of laser spots for a very large target area. The individual spots produced by such diffraction gratings are all of a similar optical geometry to the input beam, with minimal power variation for each spot. The result is a plurality of laser spots with adequate irradiance to

produce harmless yet effective treatment application, simultaneously over a large target area. The present invention also contemplates the use of other geometric objects and patterns generated by other diffractive optical elements.

[Para 105] The laser light passing through the mask 34 diffracts, producing a periodic pattern a distance away from the mask 34, shown by the laser beams labeled 36 in FIG. 21. The single laser beam 30 has thus been formed into hundreds or even thousands of individual laser beams 36 so as to create the desired pattern of spots or other geometric objects. These laser beams 36 may be passed through additional lenses, collimators, etc. 38 and 40 in order to convey the laser beams and form the desired pattern. Such additional lenses, collimators, etc. 38 and 40 can further transform and redirect the laser beams 36 as needed.

[Para 106] Arbitrary patterns can be constructed by controlling the shape, spacing and pattern of the optical mask 34. The pattern and exposure spots can be created and modified arbitrarily as desired according to application requirements by experts in the field of optical engineering. Photolithographic techniques, especially those developed in the field of semiconductor manufacturing, can be used to create the simultaneous geometric pattern of spots or other objects.

[Para 107] FIG. 22 illustrates diagrammatically a system which couples multiple light sources into the pattern-generating optical subassembly described above. Specifically, this system 20' is similar to the system 20 described in FIG. 20 above. The primary differences between the alternate

system 20' and the earlier described system 20 is the inclusion of a plurality of laser consoles, the outputs of which are each fed into a fiber coupler 42. The fiber coupler produces a single output that is passed into the laser projector optics 24 as described in the earlier system. The coupling of the plurality of laser consoles 22 into a single optical fiber is achieved with a fiber coupler 42 as is known in the art. Other known mechanisms for combining multiple light sources are available and may be used to replace the fiber coupler described herein.

[Para 108] In this system 20' the multiple light sources 22 follow a similar path as described in the earlier system 20, i.e., collimated, diffracted, recollimated, and directed to the projector device and/or tissue. In this alternate system 20' the diffractive element must function differently than described earlier depending upon the wavelength of light passing through, which results in a slightly varying pattern. The variation is linear with the wavelength of the light source being diffracted. In general, the difference in the diffraction angles is small enough that the different, overlapping patterns may be directed along the same optical path through the projector device 26 to the tissue for treatment.

[Para 109] Since the resulting pattern will vary slightly for each wavelength, a sequential offsetting to achieve complete coverage will be different for each wavelength. This sequential offsetting can be accomplished in two modes. In the first mode, all wavelengths of light are applied simultaneously without identical coverage. An offsetting steering pattern to achieve complete coverage

for one of the multiple wavelengths is used. Thus, while the light of the selected wavelength achieves complete coverage of the tissue, the application of the other wavelengths achieves either incomplete or overlapping coverage of the tissue. The second mode sequentially applies each light source of a varying wavelength with the proper steering pattern to achieve complete coverage of the tissue for that particular wavelength. This mode excludes the possibility of simultaneous treatment using multiple wavelengths, but allows the optical method to achieve identical coverage for each wavelength. This avoids either incomplete or overlapping coverage for any of the optical wavelengths.

[Para 110] These modes may also be mixed and matched. For example, two wavelengths may be applied simultaneously with one wavelength achieving complete coverage and the other achieving incomplete or overlapping coverage, followed by a third wavelength applied sequentially and achieving complete coverage.

[Para 111] FIG. 23 illustrates diagrammatically yet another alternate embodiment of the inventive system 20". This system 20" is configured generally the same as the system 20 depicted in FIG. 20. The main difference resides in the inclusion of multiple pattern-generating subassembly channels tuned to a specific wavelength of the light source. Multiple laser consoles 22 are arranged in parallel with each one leading directly into its own laser projector optics 24. The laser projector optics of each channel 44a, 44b, 44c comprise a collimator 32, mask or diffraction grating 34 and recollimators 38, 40 as described in connection with FIG. 21 above - the entire set of optics

tuned for the specific wavelength generated by the corresponding laser console 22. The output from each set of optics 24 is then directed to a beam splitter 46 for combination with the other wavelengths. It is known by those skilled in the art that a beam splitter used in reverse can be used to combine multiple beams of light into a single output. The combined channel output from the final beam splitter 46c is then directed through the projector device 26.

[Para 112] In this system 20'' the optical elements for each channel are tuned to produce the exact specified pattern for that channel's wavelength. Consequently, when all channels are combined and properly aligned a single steering pattern may be used to achieve complete coverage of the tissue for all wavelengths.

[Para 113] The system 20'' may use as many channels 44a, 44b, 44c, etc. and beam splitters 46a, 46b, 46c, etc. as there are wavelengths of light being used in the treatment.

[Para 114] Implementation of the system 20'' may take advantage of different symmetries to reduce the number of alignment constraints. For example, the proposed grid patterns are periodic in two dimensions and steered in two dimensions to achieve complete coverage. As a result, if the patterns for each channel are identical as specified, the actual pattern of each channel would not need to be aligned for the same steering pattern to achieve complete coverage for all wavelengths. Each channel would only need to be aligned optically to achieve an efficient combination.

[Para 115] In system 20'', each channel begins with a light source 22, which could be from an optical fiber as in other embodiments of the pattern-generating subassembly. This light source 22 is directed to the optical assembly 24 for collimation, diffraction, recollimation and directed into the beam splitter which combines the channel with the main output.

[Para 116] It will be understood that the laser light generating systems illustrated in FIGS. 20-23 are exemplary. Other devices and systems can be utilized to generate a source of SDM laser light which can be operably passed through to a projector device, typically in the form of an endoscope having a light pipe or the like. Other forms of electromagnetic radiation may also be generated and used, including ultraviolet waves, microwaves, other radiofrequency waves, and laser light at predetermined wavelengths. Moreover, ultrasound waves may also be generated and used to create a thermal time-course temperature spike in the target tissue sufficient to activate or produce heat shock proteins in the cells of the target tissue without damaging the target tissue itself. In order to do so, typically, a pulsed source of ultrasound or electromagnetic radiation energy is provided and applied to the target tissue in a manner which raises the target tissue temperature, such as between 6°C and 11°C, transiently while only 6°C or 1°C or less for the long term, such as over several minutes.

[Para 117] For deep tissue that is not near an internal orifice, a light pipe is not an effective means of delivering the pulsed energy. In that case, pulsed low

frequency electromagnetic energy or preferably pulsed ultrasound can be used to cause a series of temperature spikes in the target tissue.

[Para 118] Thus, in accordance with the present invention, a source of pulsed ultrasound or electromagnetic radiation is applied to the target tissue in order to stimulate HSP production or activation and to facilitate protein repair in the living animal tissue. In general, electromagnetic radiation may be ultraviolet waves, microwaves, other radiofrequency waves, laser light at predetermined wavelengths, etc. On the other hand, if electromagnetic energy is to be used for deep tissue targets away from natural orifices, absorption lengths restrict the wavelengths to those of microwaves or radiofrequency waves, depending on the depth of the target tissue. However, ultrasound is to be preferred to long wavelength electromagnetic radiation for deep tissue targets away from natural orifices.

[Para 119] The ultrasound or electromagnetic radiation is pulsed so as to create a thermal time-course in the tissue that stimulates HSP production or activation and facilitates protein repair without causing damage to the cells and tissue being treated. The area and/or volume of the treated tissue is also controlled and minimized so that the temperature spikes are on the order of several degrees, e.g. approximately 10°C, while maintaining the long-term rise in temperature to be less than the FDA mandated limit, such as 1°C. It has been found that if too large of an area or volume of tissue is treated, the increased temperature of the tissue cannot be diffused sufficiently quickly enough to meet the FDA requirements. However, limiting the area and/or volume of the

treated tissue as well as creating a pulsed source of energy accomplishes the goals of the present invention of stimulating HSP activation or production by heating or otherwise stressing the cells and tissue, while allowing the treated cells and tissues to dissipate any excess heat generated to within acceptable limits.

[Para 120] It is believed that stimulating HSP production in accordance with the present invention can be effectively utilized in treating a wide array of tissue abnormalities, ailments, and even infections. For example, the viruses that cause colds primarily affect a small port of the respiratory epithelium in the nasal passages and nasopharynx. Similar to the retina, the respiratory epithelium is a thin and clear tissue. With reference to FIG. 24, a cross-sectional view of a human head 48 is shown with an endoscope 14 inserted into the nasal cavity 50 and energy 16, such as laser light or the like, being directed to tissue 18 to be treated within the nasal cavity 50. The tissue 18 to be treated could be within the nasal cavity 50, including the nasal passages, and nasopharynx.

[Para 121] To assure absorption of the laser energy, or other energy source, the wavelength can be adjusted to an infrared (IR) absorption peak of water, or an adjuvant dye can be used to serve as a photosensitizer. In such a case, treatment would then consist of drinking, or topically applying, the adjuvant, waiting a few minutes for the adjuvant to permeate the surface tissue, and then administering the laser light or other energy source 16 to the target tissue 18 for a few seconds, such as via optical fibers in an endoscope 14, as illustrated

in FIG. 24. To provide comfort of the patient, the endoscope 14 could be inserted after application of a topical anesthetic. If necessary, the procedure could be repeated periodically, such as in a day or so.

[Para 122] The treatment would stimulate the activation or production of heat shock proteins and facilitate protein repair without damaging the cells and tissues being treated. As discussed above, certain heat shock proteins have been found to play an important role in the immune response as well as the well-being of the targeted cells and tissue. The source of energy could be monochromatic laser light, such as 810 nm wavelength laser light, administered in a manner similar to that described in the above-referenced patent applications, but administered through an endoscope or the like, as illustrated in FIG. 24. The adjuvant dye would be selected so as to increase the laser light absorption. While this comprises a particularly preferred method and embodiment of performing the invention, it will be appreciated that other types of energy and delivery means could be used to achieve the same objectives in accordance with the present invention.

[Para 123] With reference now to FIG. 25, a similar situation exists for the flu virus, where the primary target is the epithelium of the upper respiratory tree, in segments that have diameters greater than about 3.3 mm, namely, the upper six generations of the upper respiratory tree. A thin layer of mucous separates the targeted epithelial cells from the airway lumen, and it is in this layer that the antigen-antibody interactions occur that result in inactivation of the virus.

[Para 124] With continuing reference to FIG. 25, the flexible light tube 12 of a bronchoscope 14 is inserted through the individual's mouth 52 through the throat and trachea 54 and into a bronchus 56 of the respiratory tree. There the laser light or other energy source 16 is administered and delivered to the tissue in this area of the uppermost segments to treat the tissue and area in the same manner described above with respect to FIG. 24. It is contemplated that a wavelength of laser or other energy would be selected so as to match an IR absorption peak of the water resident in the mucous to heat the tissue and stimulate HSP activation or production and facilitate protein repair, with its attendant benefits.

[Para 125] With reference now to FIG. 26, a colonoscope 14 could have flexible optical tube 12 thereof inserted into the anus and rectum 58 and into either the large intestine 60 or small intestine 62 so as to deliver the selected laser light or other energy source 16 to the area and tissue to be treated, as illustrated. This could be used to assist in treating colon cancer as well as other gastrointestinal issues.

[Para 126] Typically, the procedure could be performed similar to a colonoscopy in that the bowel would be cleared of all stool, and the patient would lie on his/her side and the physician would insert the long, thin light tube portion 12 of the colonoscope 14 into the rectum and move it into the area of the colon, large intestine 60 or small intestine 64 to the area to be treated. The physician could view through a monitor the pathway of the inserted flexible member 12 and even view the tissue at the tip of the

colonoscope 14 within the intestine, so as to view the area to be treated. Using one of the other fiber optic or light tubes, the tip 64 of the scope would be directed to the tissue to be treated and the source of laser light or other radiation 16 would be delivered through one of the light tubes of the colonoscope 14 to treat the area of tissue to be treated, as described above, in order to stimulate HSP activation or production in that tissue 18.

[Para 127] With reference now to FIG. 27, another example in which the present invention can be advantageously used is what is frequently referred to as "leaky gut" syndrome, a condition of the gastrointestinal (GI) tract marked by inflammation and other metabolic dysfunction. Since the GI tract is susceptible to metabolic dysfunction similar to the retina, it is anticipated that it will respond well to the treatment of the present invention. This could be done by means of subthreshold, diode micropulse laser (SDM) treatment, as discussed above, or by other energy sources and means as discussed herein and known in the art.

[Para 128] With continuing reference to FIG. 27, the flexible light tube 12 of an endoscope or the like is inserted through the patient's mouth 52 through the throat and trachea area 54 and into the stomach 66, where the tip or end 64 thereof is directed towards the tissue 18 to be treated, and the laser light or other energy source 16 is directed to the tissue 18. It will be appreciated by those skilled in the art that a colonoscope could also be used and inserted through the rectum 58 and into the stomach 66 or any tissue between the stomach and the rectum.

[Para 129] If necessary, a chromophore pigment could be delivered to the GI tissue orally to enable absorption of the radiation. If, for instance, unfocused 810 nm radiation from a laser diode or LED were to be used, the pigment would have an absorption peak at or near 810 nm. Alternatively, the wavelength of the energy source could be adjusted to a slightly longer wavelength at an absorption peak of water, so that no externally applied chromophore would be required.

[Para 130] It is also contemplated by the present invention that a capsule endoscope 68, such as that illustrated in FIG. 28, could be used to administer the radiation and energy source in accordance with the present invention. Such capsules are relatively small in size, such as approximately one inch in length, so as to be swallowed by the patient. As the capsule or pill 68 is swallowed and enters into the stomach and passes through the GI tract, when at the appropriate location, the capsule or pill 68 could receive power and signals, such as via antenna 70, so as to activate the source of energy 72, such as a laser diode and related circuitry, with an appropriate lens 74 focusing the generated laser light or radiation through a radiation-transparent cover 76 and onto the tissue to be treated. It will be understood that the location of the capsule endoscope 68 could be determined by a variety of means such as external imaging, signal tracking, or even by means of a miniature camera with lights through which the doctor would view images of the GI tract through which the pill or capsule 68 was passing through at the time. The capsule or pill 68 could be supplied with its own power source, such as by virtue of a

battery, or could be powered externally via an antenna, such that the laser diode 72 or other energy generating source create the desired wavelength and pulsed energy source to treat the tissue and area to be treated.

[Para 131] As in the treatment of the retina in previous applications, the radiation would be pulsed to take advantage of the micropulse temperature spikes and associated safety, and the power could be adjusted so that the treatment would be completely harmless to the tissue. This could involve adjusting the peak power, pulse times, and repetition rate to give spike temperature rises on the order of 10°C, while maintaining the long term rise in temperature to be less than the FDA mandated limit of 1°C. If the pill form 68 of delivery is used, the device could be powered by a small rechargeable battery or over wireless inductive excitation or the like. The heated/stressed tissue would stimulate activation or production of HSP and facilitate protein repair, and the attendant benefits thereof.

[Para 132] From the foregoing examples, the technique of the present invention is limited to the treatment of conditions at near body surfaces or at internal surfaces easily accessible by means of fiber optics or other optical delivery means. The reason that the application of SDM to activate HSP activity is limited to near surface or optically accessibly regions of the body is that the absorption length of IR or visible radiation in the body is very short. However, there are conditions deeper within tissue or the body which could benefit from the present invention. Thus, the present invention contemplates the use of ultrasound and/or radio frequency (RF) and even shorter wavelength

electromagnetic (EM) radiation such as microwave which have relatively long absorption lengths in body tissue. The use of pulsed ultrasound is preferable to RF electromagnetic radiation to activate remedial HSP activity in abnormal tissue that is inaccessible to surface SDM or the like. Pulsed ultrasound sources can also be used for abnormalities at or near surfaces as well.

[Para 133] With reference now to FIG. 29, with ultrasound, a specific region deep in the body can be specifically targeted by using one or more beams that are each focused on the target site. The pulsating heating will then be largely only in the targeted region where the beams are focused and overlap.

[Para 134] As illustrated in FIG. 29, an ultrasound transducer 78 or the like generates a plurality of ultrasound beams 80 which are coupled to the skin via an acoustic-impedance-matching gel, and penetrate through the skin 82 and through undamaged tissue in front of the focus of the beams 80 to a target organ 84, such as the illustrated liver, and specifically to a target tissue 86 to be treated where the ultrasound beams 80 are focused. As mentioned above, the pulsating heating will then only be at the targeted, focused region 86 where the focused beams 80 overlap. The tissue in front of and behind the focused region 86 will not be heated or affected appreciably.

[Para 135] The present invention contemplates not only the treatment of surface or near surface tissue, such as using the laser light or the like, deep tissue using, for example, focused ultrasound beams or the like, but also treatment of blood diseases, such as sepsis. As indicated above, focused ultrasound treatment could be used both at surface as well as deep body tissue,

and could also be applied in this case in treating blood. However, it is also contemplated that the SDM and similar treatment options which are typically limited to surface or near surface treatment of epithelial cells and the like be used in treating blood diseases at areas where the blood is accessible through a relatively thin layer of tissue, such as the earlobe.

[Para 136] With reference now to FIGS. 30 and 31, treatment of blood disorders simply requires the transmission of SDM or other electromagnetic radiation or ultrasound pulses to the earlobe 88, where the SDM or other radiation source of energy could pass through the earlobe tissue and into the blood which passes through the earlobe. It would be appreciated that this approach could also take place at other areas of the body where the blood flow is relatively high and/or near the tissue surface, such as fingertips, inside of the mouth or throat, etc.

[Para 137] With reference again to FIGS. 30 and 31, an earlobe 88 is shown adjacent to a clamp device 90 configured to transmit SDM radiation or the like. This could be, for example, by means of one or more laser diodes 92 which would transmit the desired frequency at the desired pulse and pulse train to the earlobe 88. Power could be provided, for example, by means of a lamp drive 94. Alternatively, the lamp drive 94 could be the actual source of laser light, which would be transmitted through the appropriate optics and electronics to the earlobe 88. The clamp device 90 would merely be used to clamp onto the patient's earlobe and cause that the radiation be constrained to the patient's earlobe 88. This may be by means of mirrors, reflectors, diffusers, etc. This

could be controlled by a control computer 96, which would be operated by a keyboard 98 or the like. The system may also include a display and speakers 100, if needed, for example if the procedure were to be performed by an operator at a distance from the patient.

[Para 138] The proposed treatment with a train of electromagnetic or ultrasound pulses has two major advantages over earlier treatments that incorporate a single short or sustained (long) pulse. First, the short (preferably subsecond) individual pulses in the train activate cellular reset mechanisms like HSP activation with larger reaction rate constants than those operating at longer (minute or hour) time scales. Secondly, the repeated pulses in the treatment provide large thermal spikes (on the order of 10,000) that allow the cell's repair system to more rapidly surmount the activation energy barrier that separates a dysfunctional cellular state from the desired functional state. The net result is a "lowered therapeutic threshold" in the sense that a lower applied average power and total applied energy can be used to achieve the desired treatment goal.

[Para 139] Although several embodiments have been described in detail for purposes of illustration, various modifications may be made without departing from the scope and spirit of the invention. Accordingly, the invention is not to be limited, except as by the appended claims.

What is claimed is:

[Claim 1] A method for heat treating biological tissues, comprising the steps of:

providing a pulsed energy source having energy parameters including wavelength or frequency, duty cycle and pulse train duration, the energy parameters selected so as to raise a target tissue temperature up to eleven degrees Celsius to achieve a therapeutic effect, wherein the average temperature rise of the tissue over several minutes is maintained at or below a predetermined level so as to not permanently damage the target tissue; and

applying the pulsed energy source to the target tissue to therapeutically treat the target tissue.

[Claim 2] The method of claim 1, wherein the applying step comprises the step of stimulating heat shock protein activation in the target tissue.

[Claim 3] The method of claim 1, including the step of selecting the pulsed energy source energy parameters so that the target tissue temperature is raised between approximately six degrees Celsius to eleven degrees Celsius at least during application of the pulsed energy source to the target tissue.

[Claim 4] The method of claim 1, wherein the average temperature rise of the target tissue over several minutes is maintained at six degrees Celsius or less.

[Claim 5] The method of claim 4, wherein the average temperature rise of the target tissue is maintained at approximately one degree Celsius or less over several minutes.

[Claim 6] The method of claim 1, wherein the pulsed energy source energy parameters are selected so that approximately 20 to 40 joules of energy is absorbed by each cubic centimeter of the target tissue.

[Claim 7] The method of claim 1, wherein the applying the pulsed energy source step comprises inserting a device into a cavity of a body to apply the pulsed energy source to the target tissue.

[Claim 8] The method of claim 1, wherein the applying the pulsed energy step comprises directing the pulsed energy source to an exterior of a body which is adjacent to the target tissue or has a blood supply close to the surface of the exterior area of the body.

[Claim 9] The method of claim 1, wherein the pulsed energy source comprises laser light, microwave, radio frequency, or ultrasound.

[Claim 10] The method of any of claims 1-4 or 6, wherein the pulsed energy source comprises a radio frequency between approximately three to six

megahertz, a duty cycle of between approximately 2.5% to 5%, and a pulse train duration of between approximately 0.2 to 0.4 seconds.

[Claim 11] The method of claim 10, wherein the radio frequency is generated with a device having a coil radii of between approximately 2 and 6 mm and between approximately 13 and 57 amp turns.

[Claim 12] The method of any of claims 1-4 or 6, wherein the pulsed energy source comprises a microwave frequency of between approximately 10 to 20 GHz, a pulse train duration of approximately between 0.2 and 0.6 seconds, and a duty cycle of between approximately 2% to 5%.

[Claim 13] The method of claim 12, wherein the microwave has an average power of between approximately 8 and 52 watts.

[Claim 14] The method of any of claims 1-4 or 6, wherein the pulsed energy source comprises a pulsed light beam having a wavelength of between approximately 530 nm to 1300 nm, a duty cycle of less than 10%, and a pulse train duration between approximately 0.1 and 0.6 seconds.

[Claim 15] The method of claim 14, wherein the pulsed light beam has a wavelength of between 800 nm and 1000 nm and a power of between approximately 0.5 and 74 watts.

[Claim 16] The method of any of claims 1-4 or 6, wherein the pulsed energy source comprises pulsed ultrasound having a frequency of between approximately 1MHz and 5MHz, a train duration of between approximately 0.1 and 0.5 seconds and a duty cycle of between approximately 2% to 10%.

[Claim 17] The method of claim 16, wherein the ultrasound has a power of between approximately 0.46 and 28.6 watts.

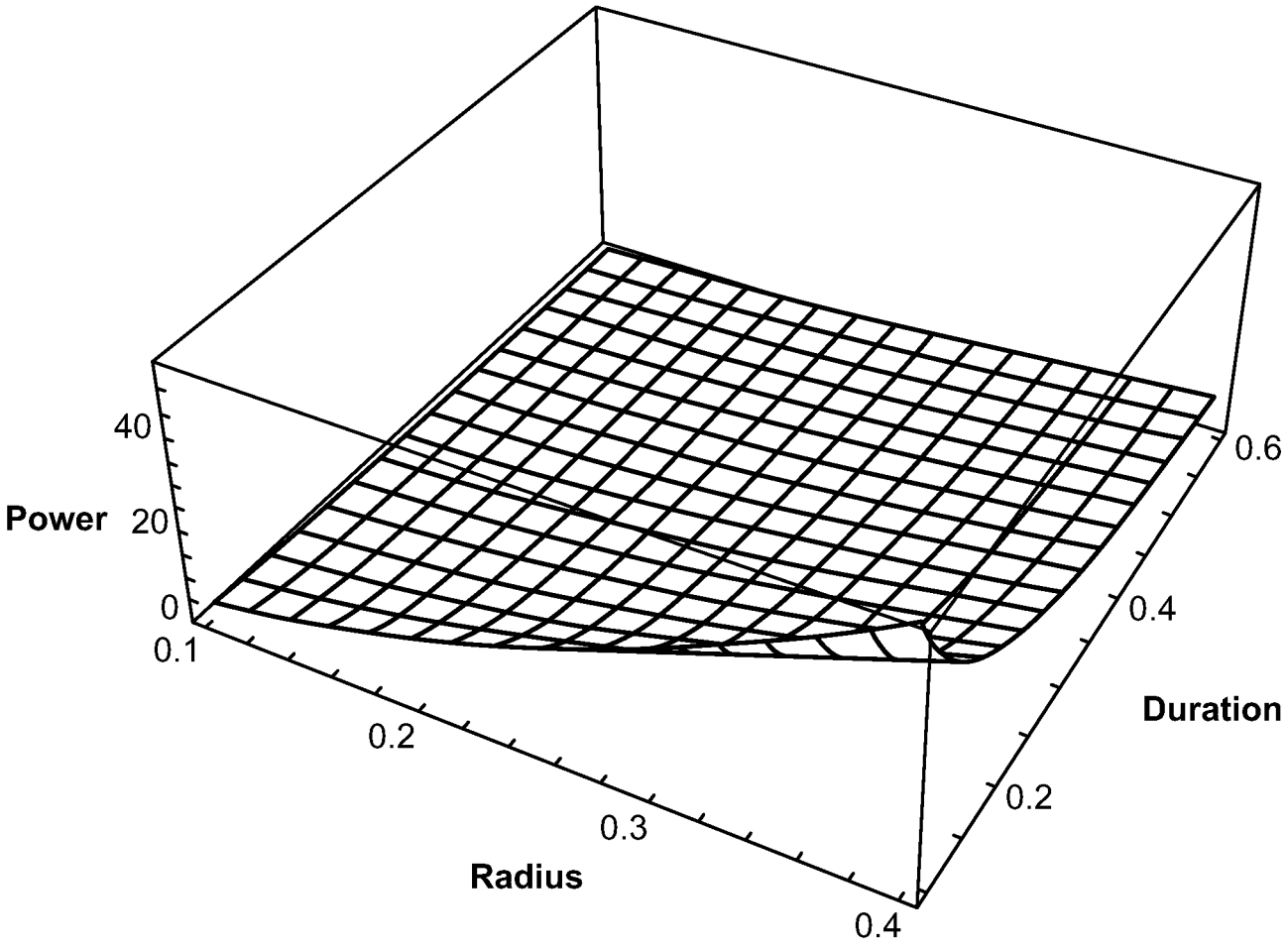


FIG. 1A

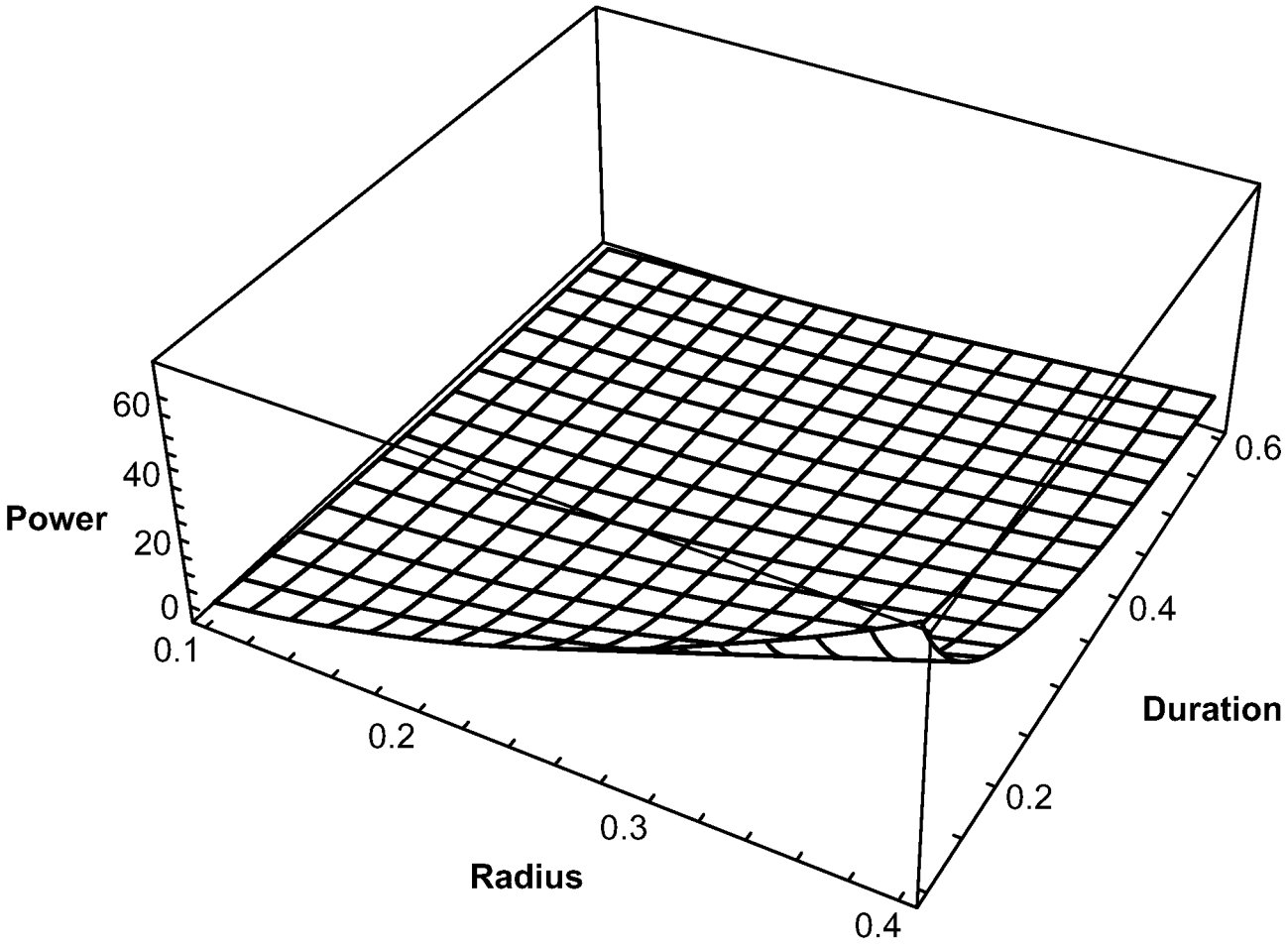
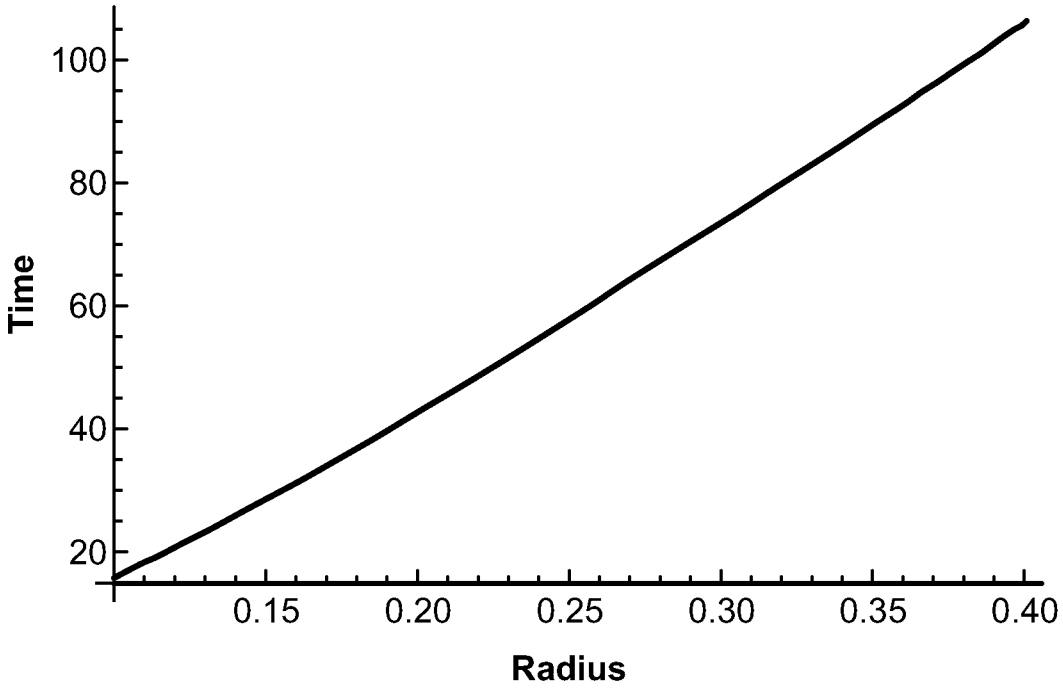


FIG. 1B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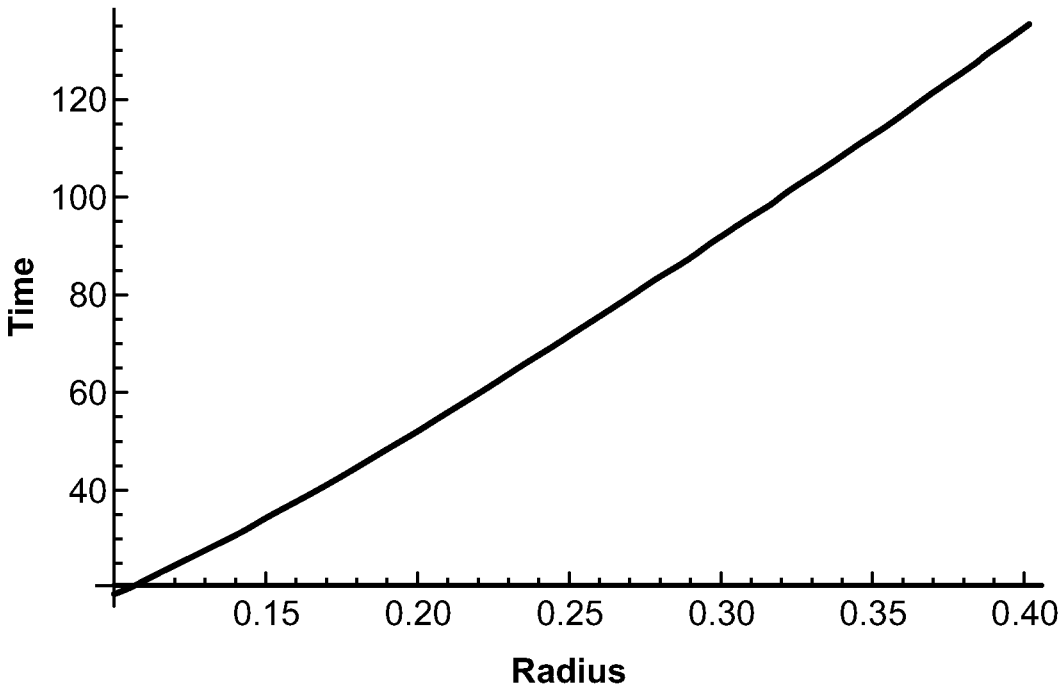
40
20
Time
0.15
0.20
0.25
0.30
0.35
0.40
Radius

FIG. 2A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60
40
Time
0.15
0.20
0.25
0.30
0.35
0.40
Radius

FIG. 2B

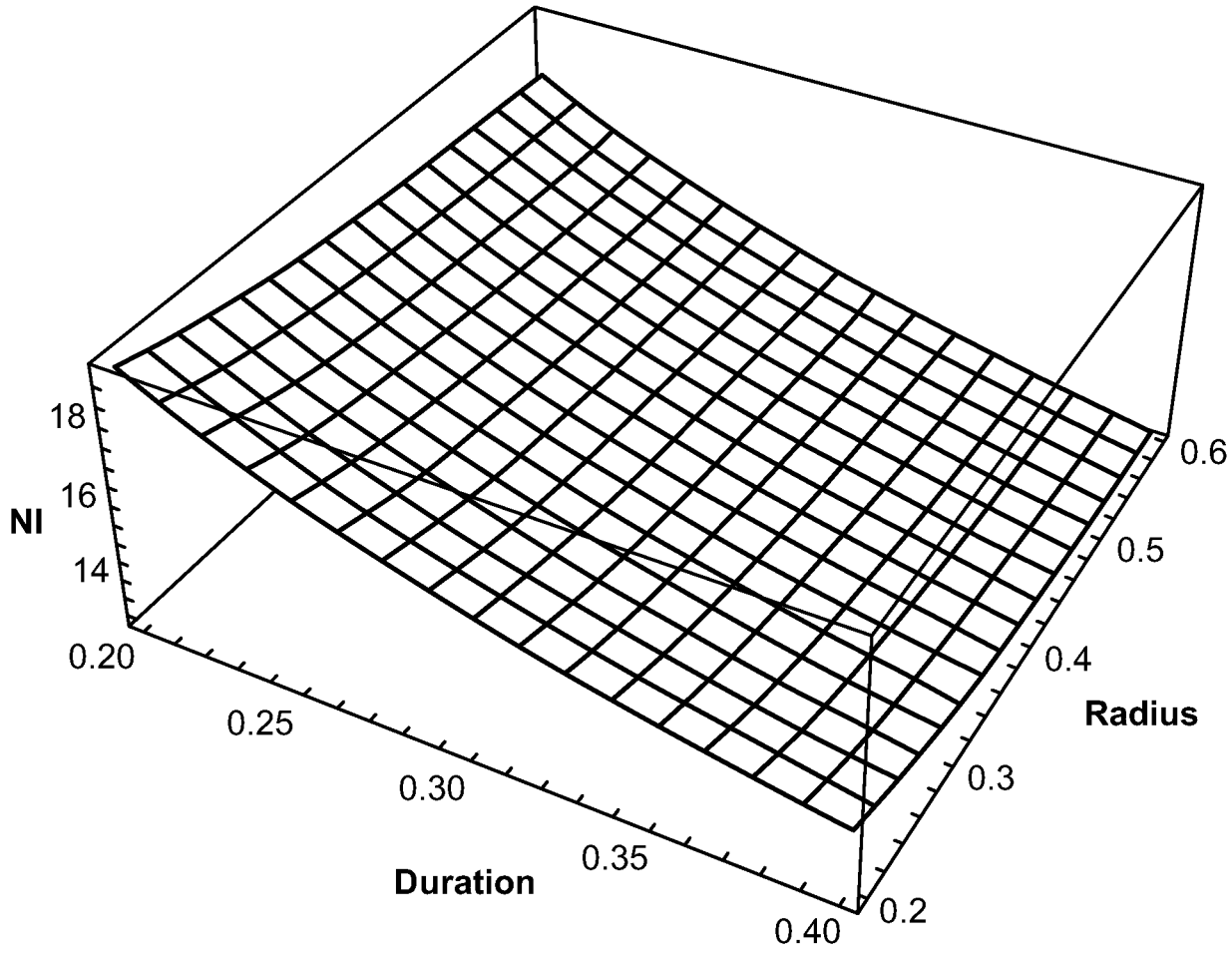


FIG. 3

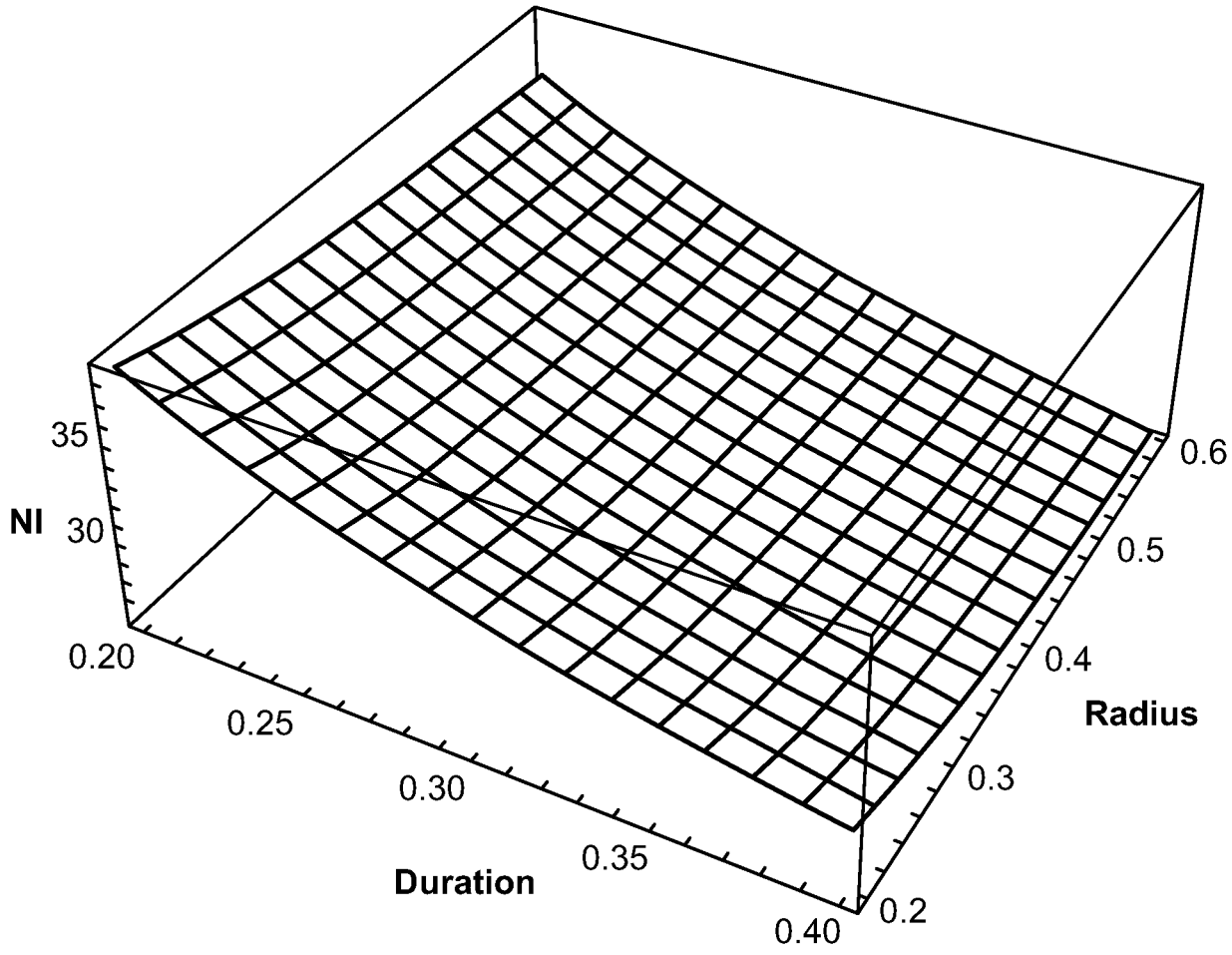


FIG. 4

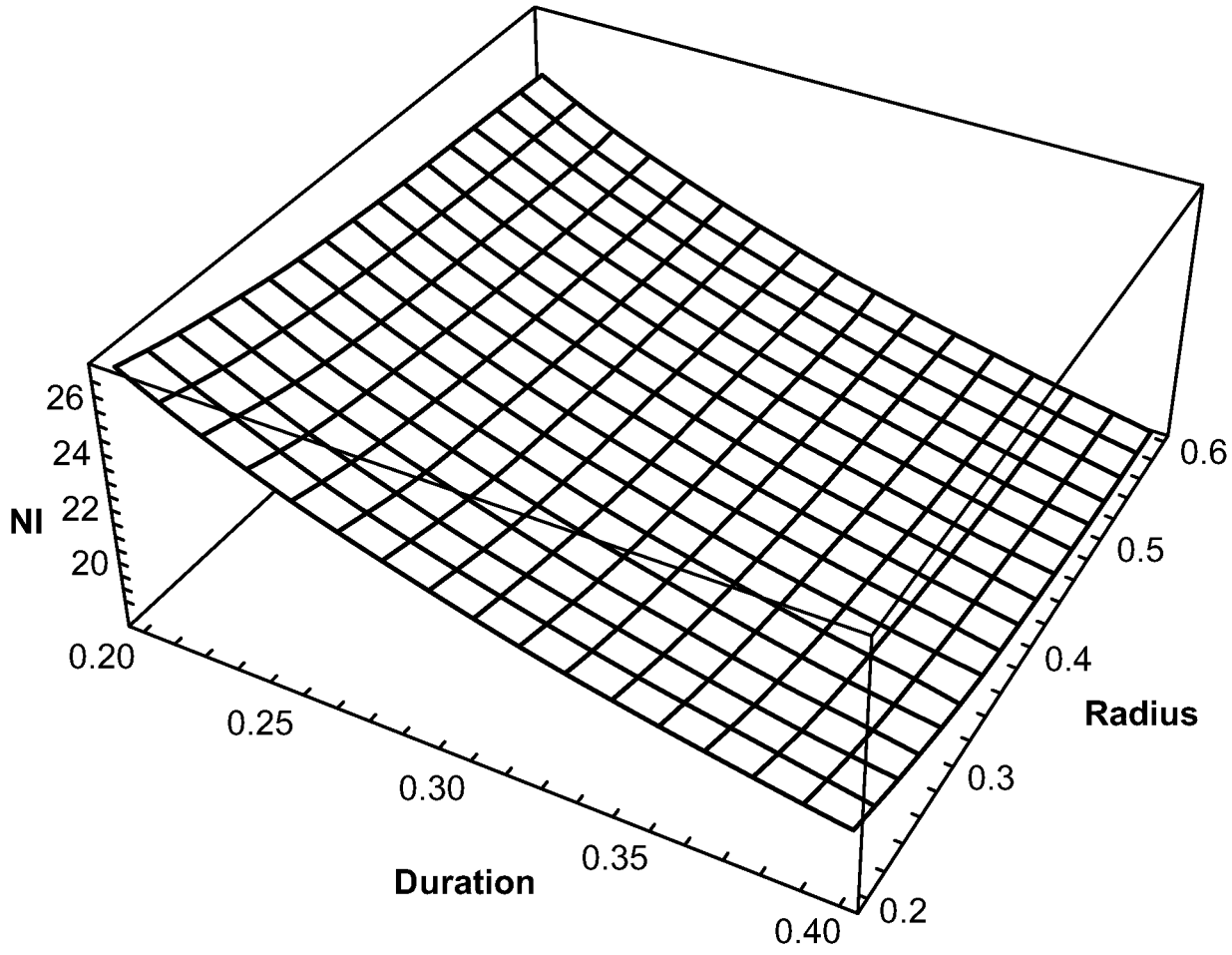


FIG. 5

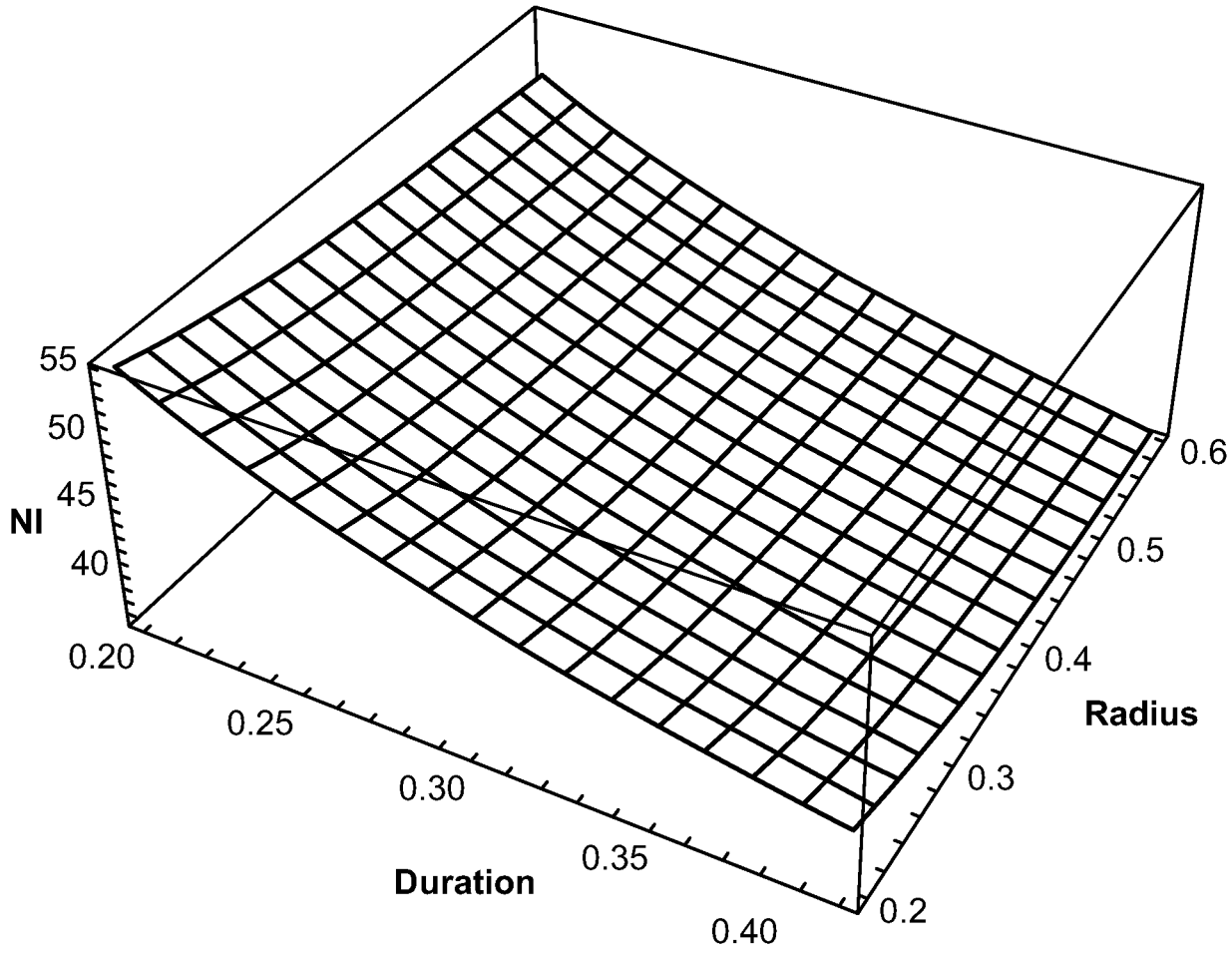


FIG. 6

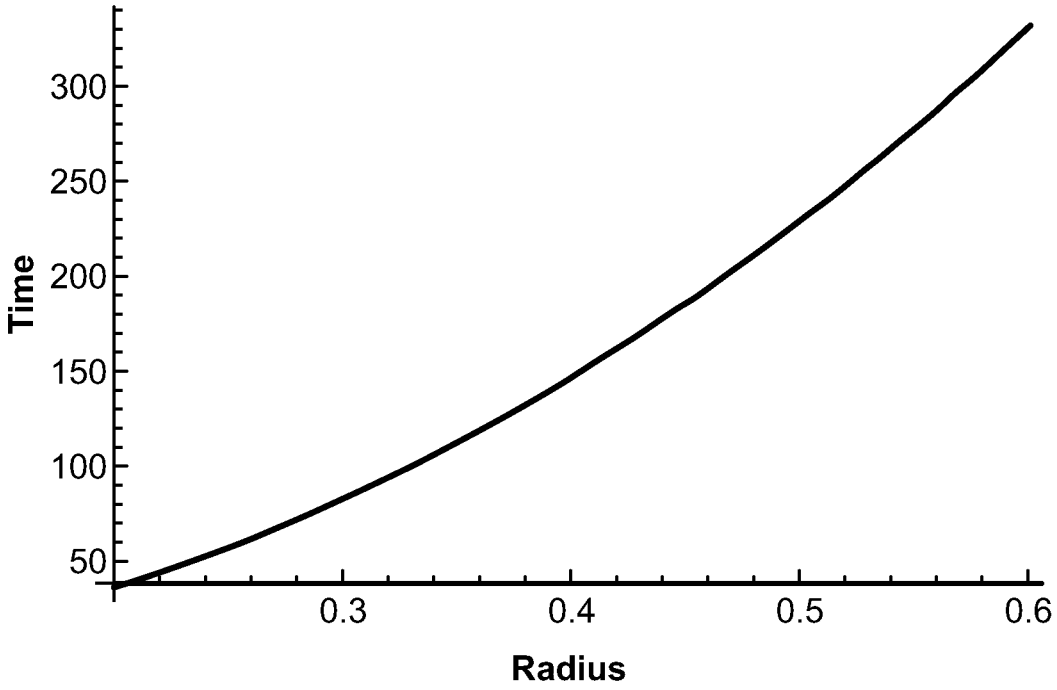


FIG. 7

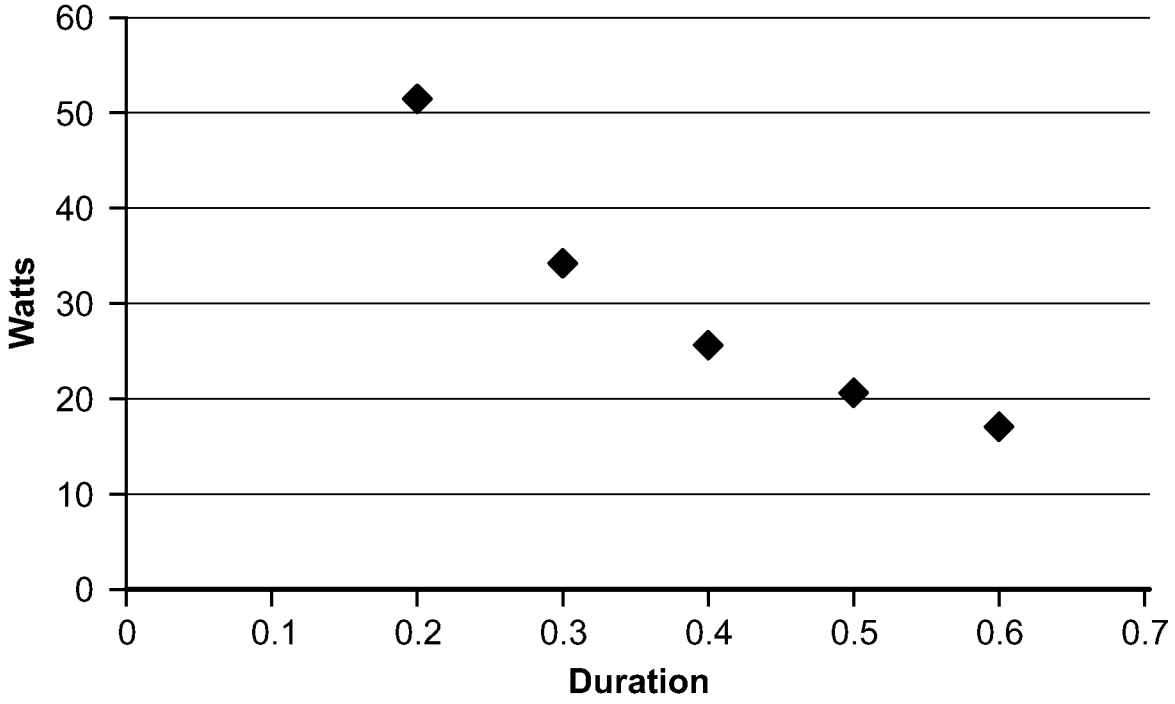
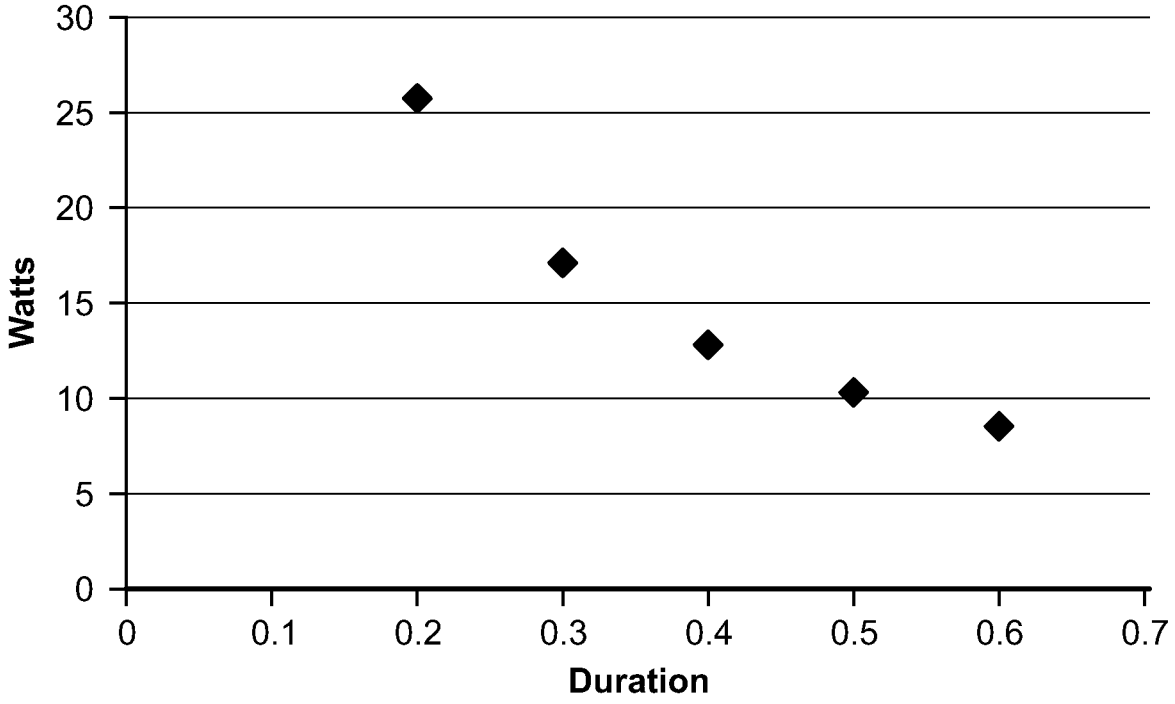

60
50
40
30
20
10
0
Watts
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Duration

FIG. 8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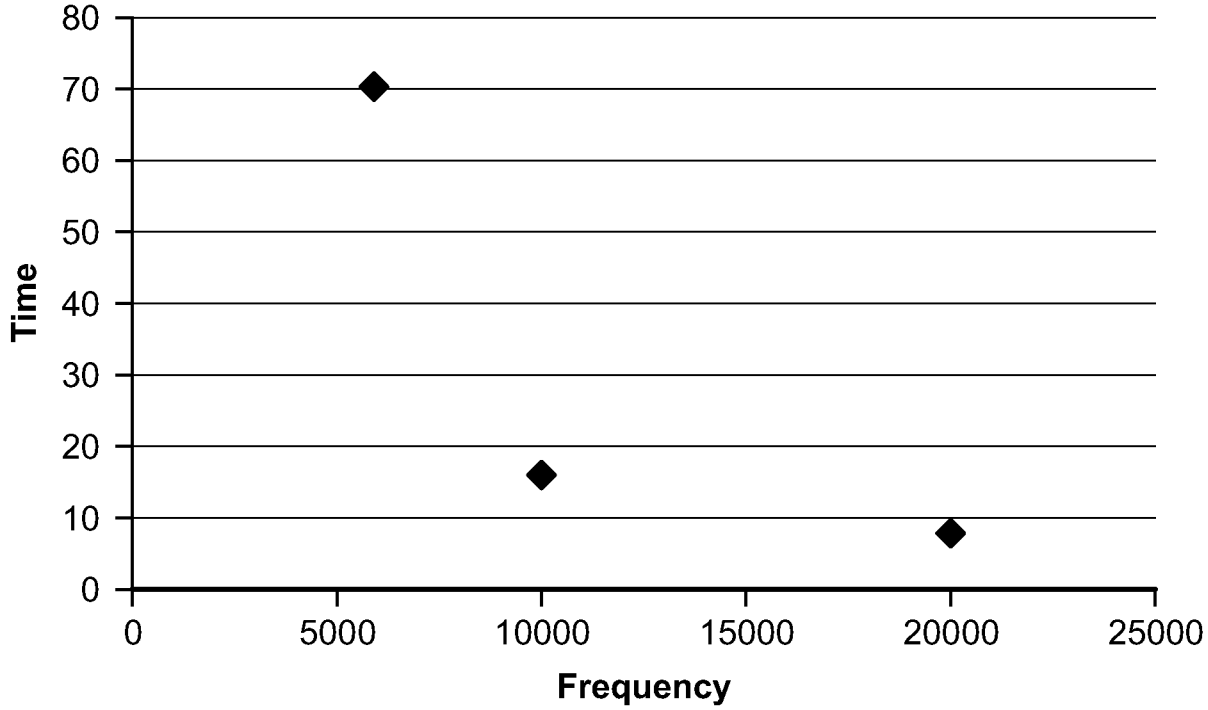
25
20
15
10
5
0
Watts
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Duration

FIG. 9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40
30
20
10
0
Time
0
5000
10000
15000
20000
25000
Frequency

FIG. 10

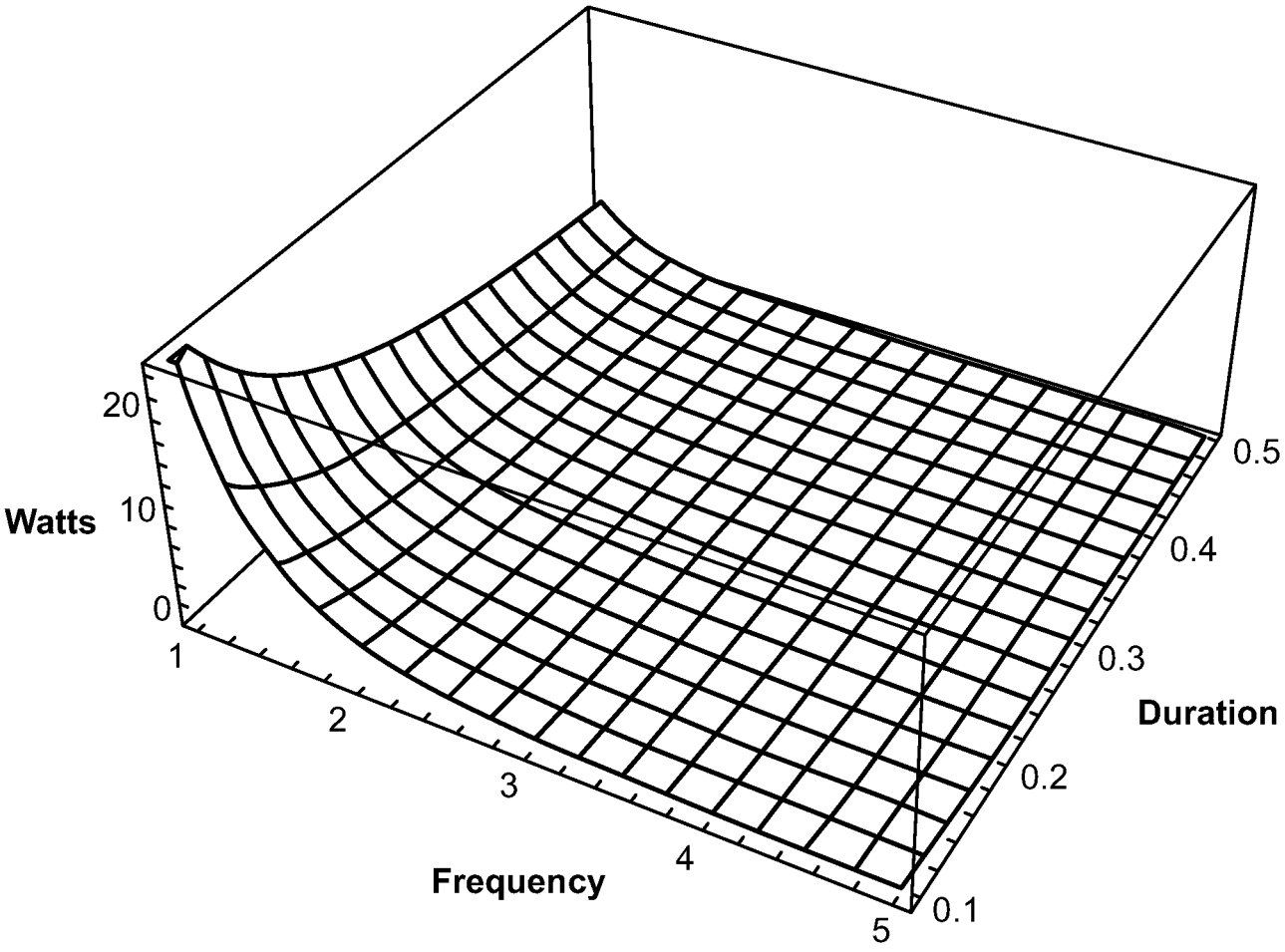

FIG. 11

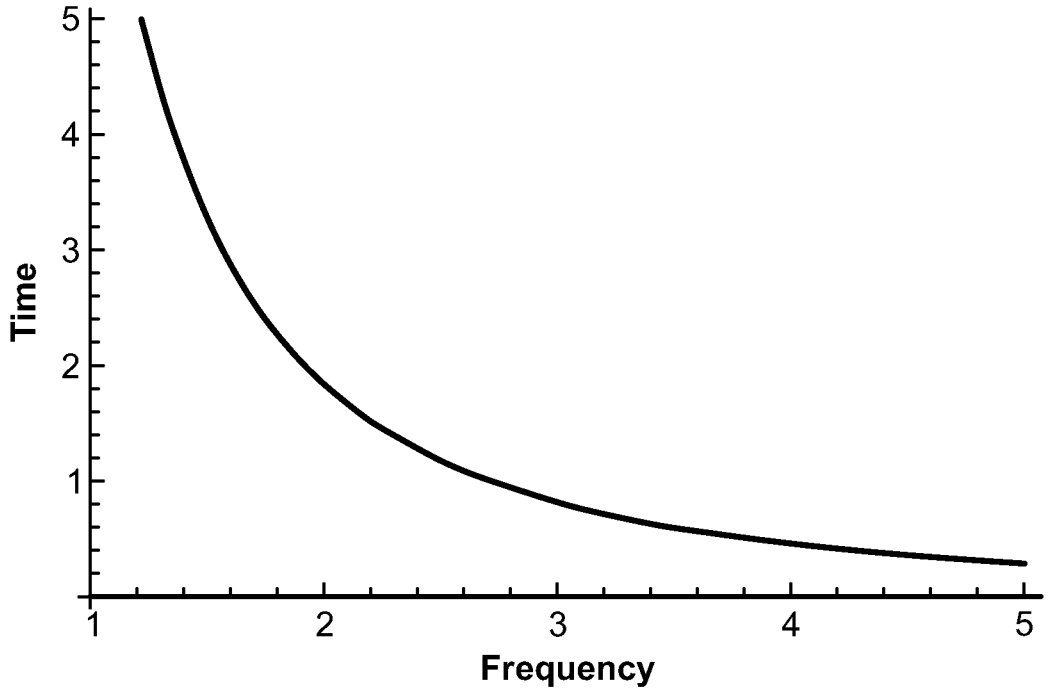
Time
5
4
3
2
1
1
2
3
4
5
Frequency

FIG. 12

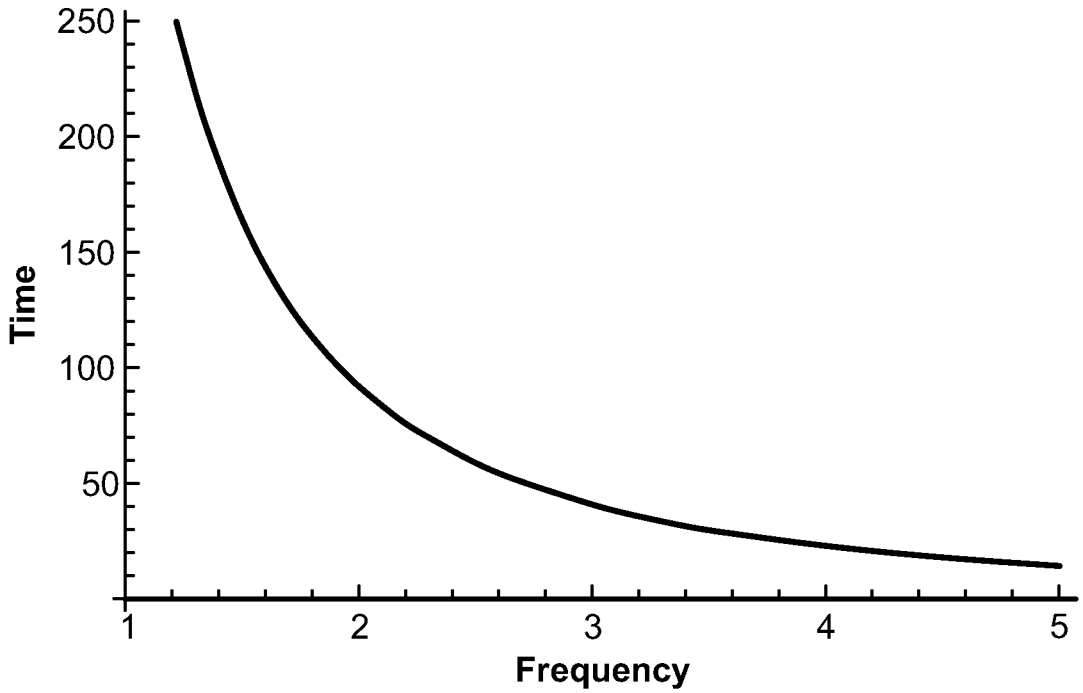
Time
250
200
150
100
50
1
2
3
4
5
Frequency

FIG. 13

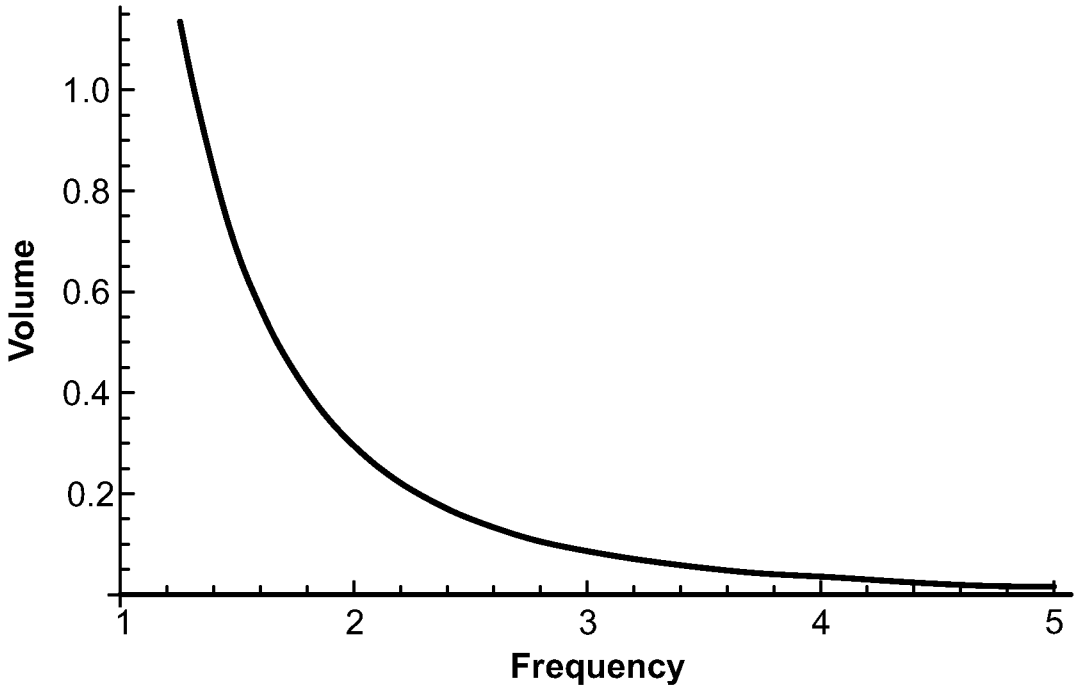
Volume
1.0
0.8
0.6
0.4
0.2
1
2
3
4
5
Frequency

FIG. 14

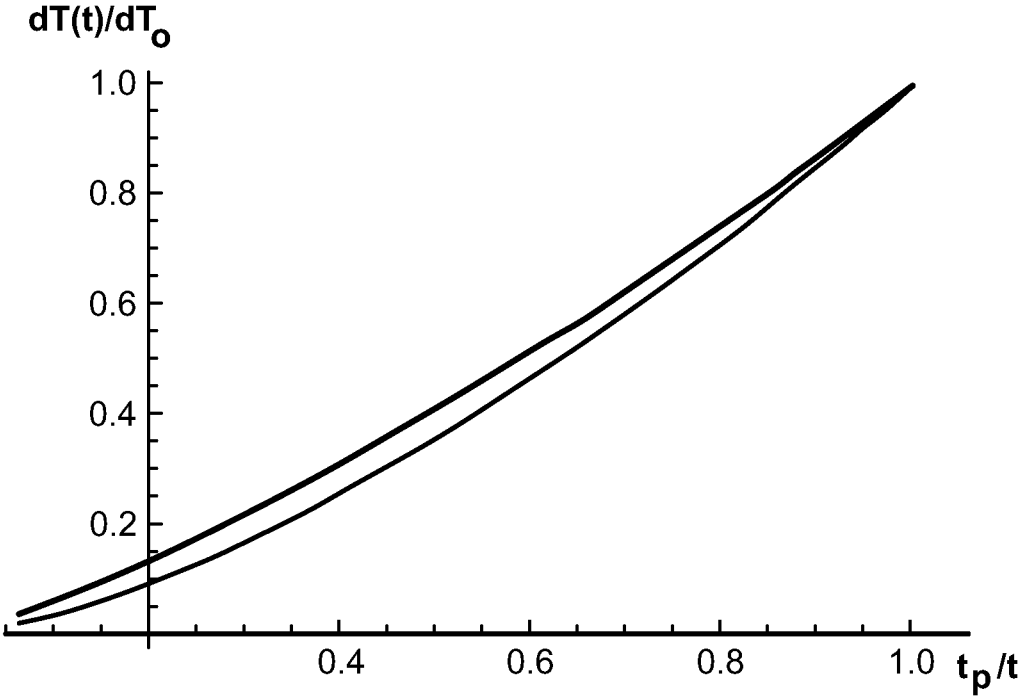
dT(t)/dT$_o$
1.0
0.8
0.6
0.4
0.2
0.4
0.6
0.8
1.0
t$_p$/t

FIG. 15

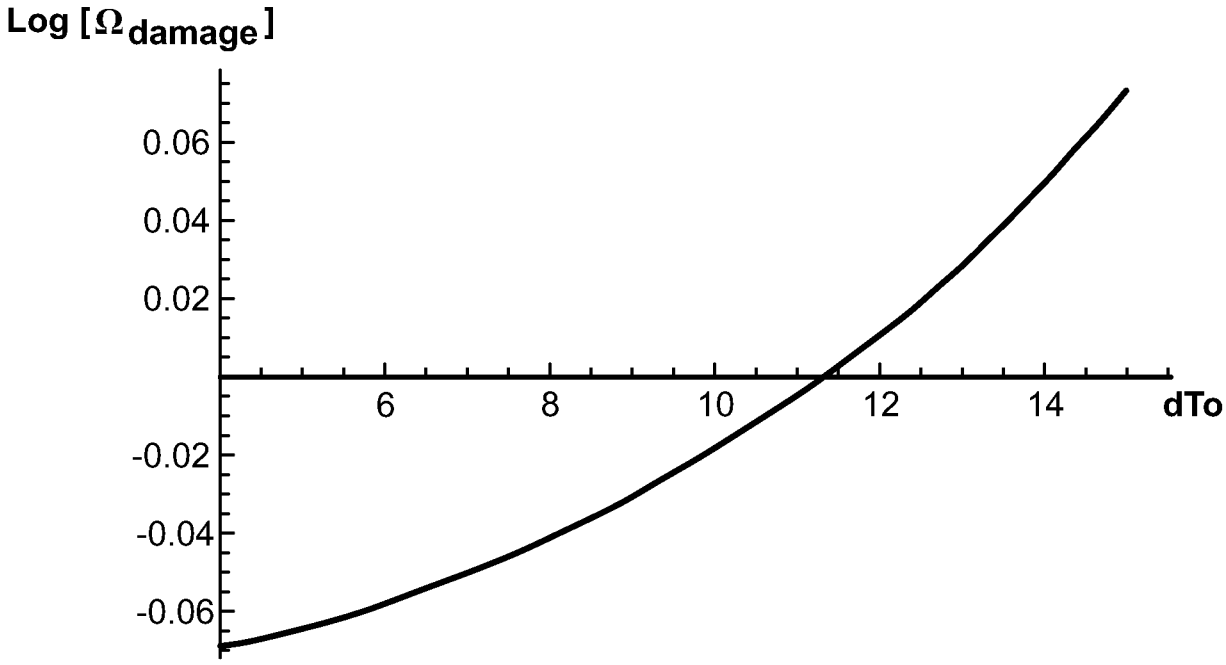
Log [Ωdamage]
0.06
0.04
0.02
-0.02
-0.04
-0.06
6
8
10
12
14
dTo

FIG. 16

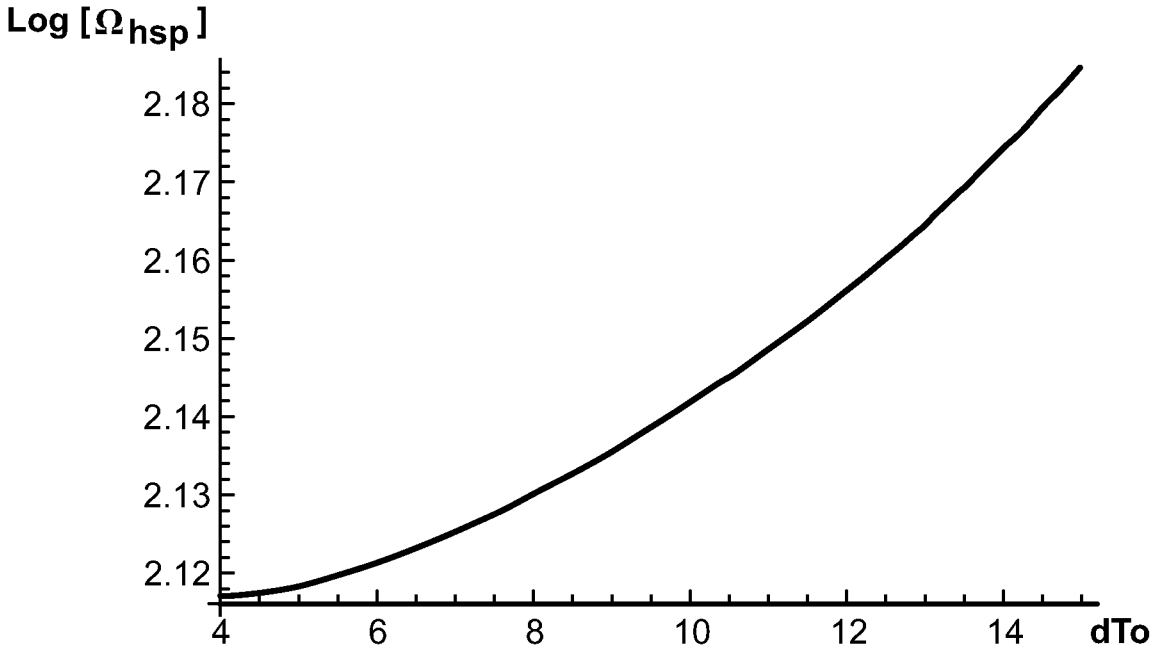
Log [Ωhsp]
2.18
2.17
2.16
2.15
2.14
2.13
2.12
4
6
8
10
12
14
dTo

FIG. 17

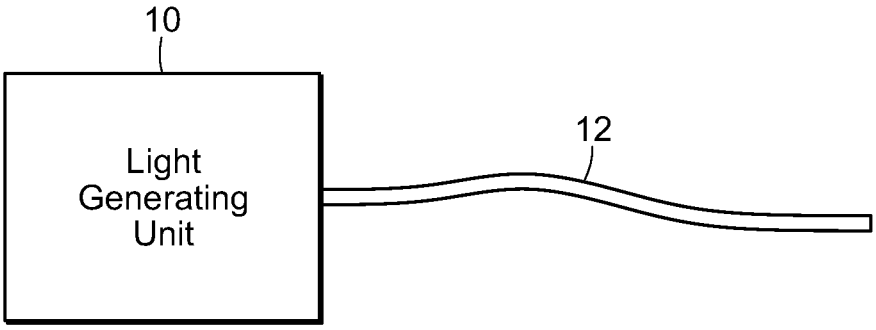

FIG. 18

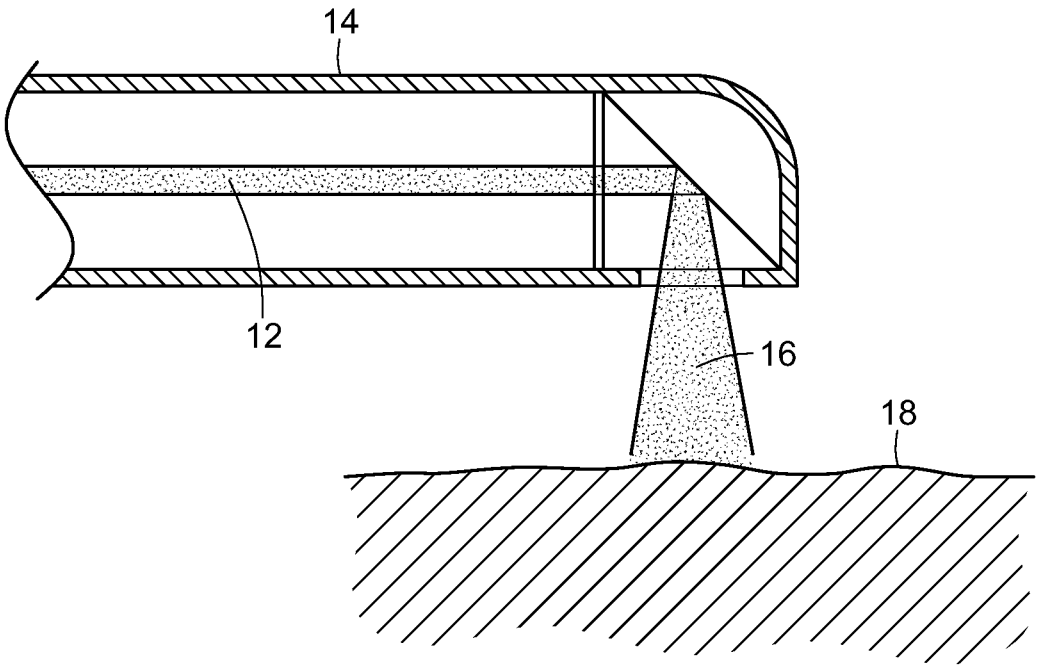

FIG. 19

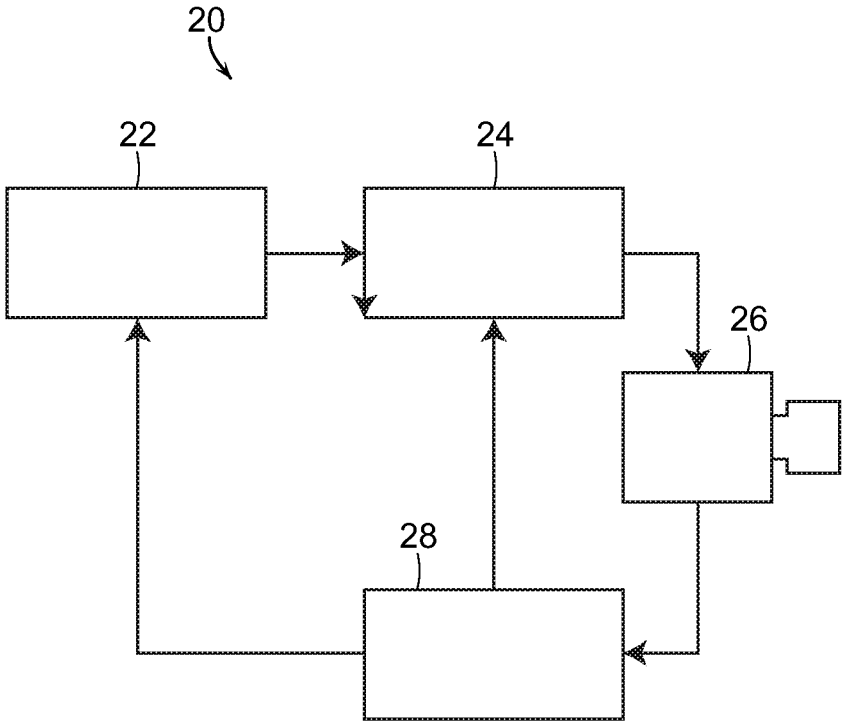

FIG. 20

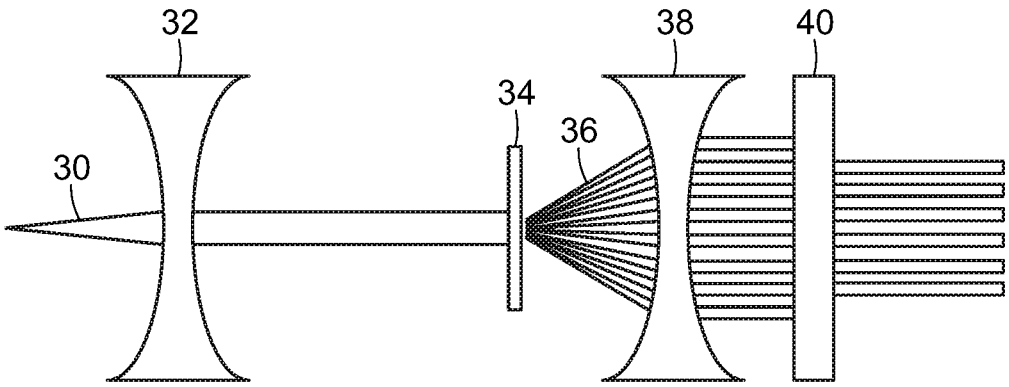

FIG. 21

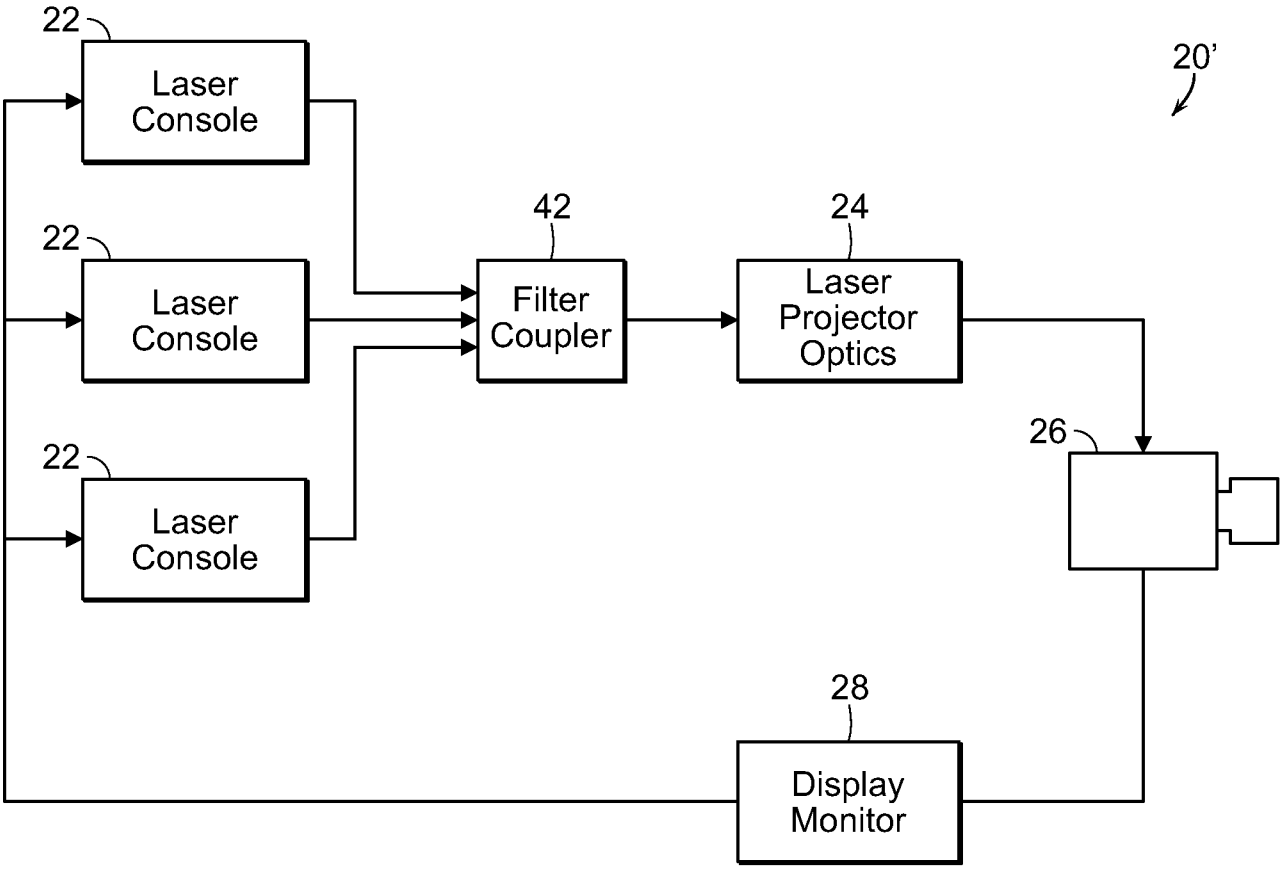
22
Laser Console
22
Laser Console
22
Laser Console
42
Filter Coupler
24
Laser Projector Optics
20'
26
28
Display Monitor

FIG. 22

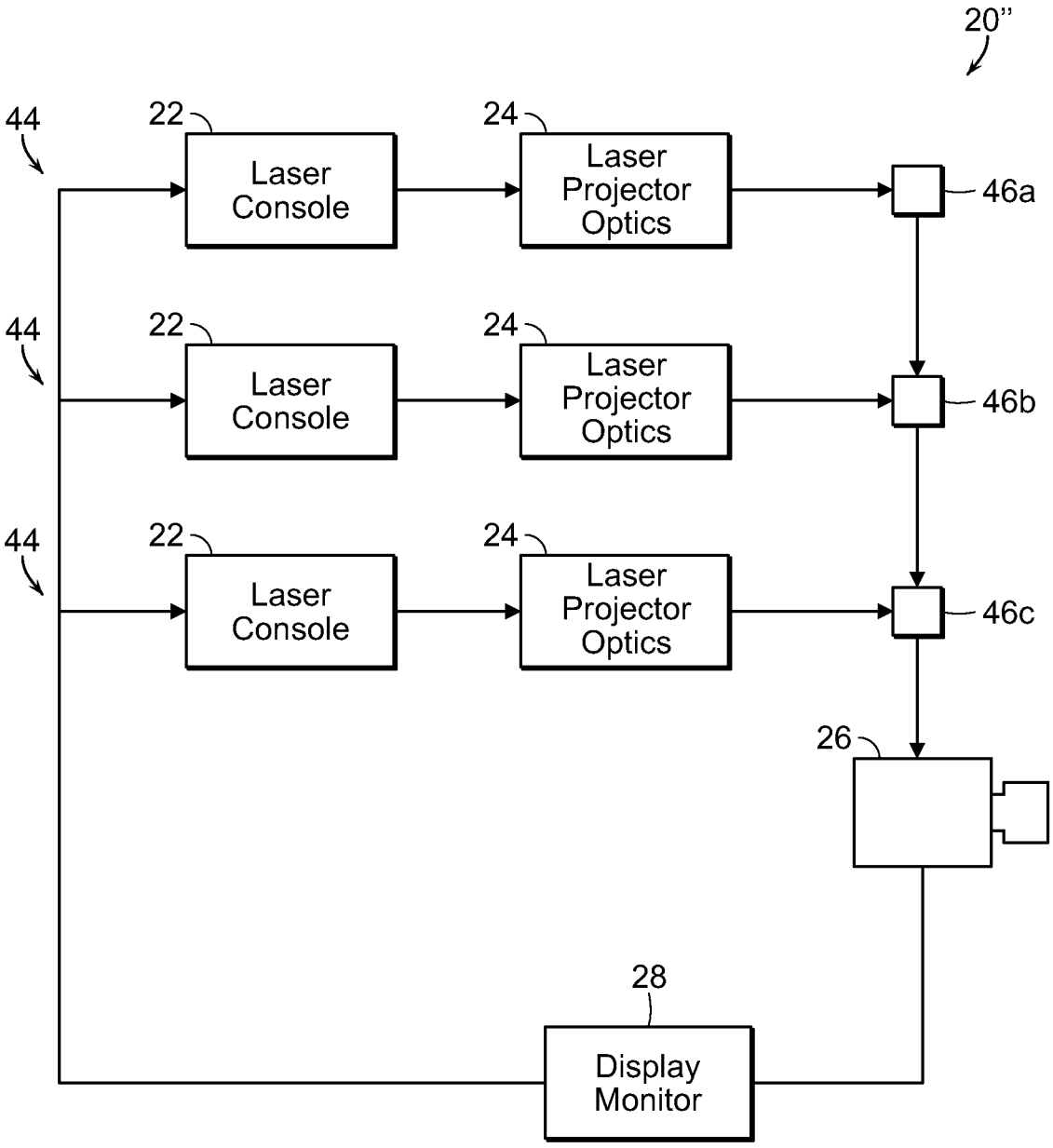
20''
44
22
Laser Console
24
Laser Projector Optics
46a
44
22
Laser Console
24
Laser Projector Optics
46b
44
22
Laser Console
24
Laser Projector Optics
46c
26
28
Display Monitor

FIG. 23

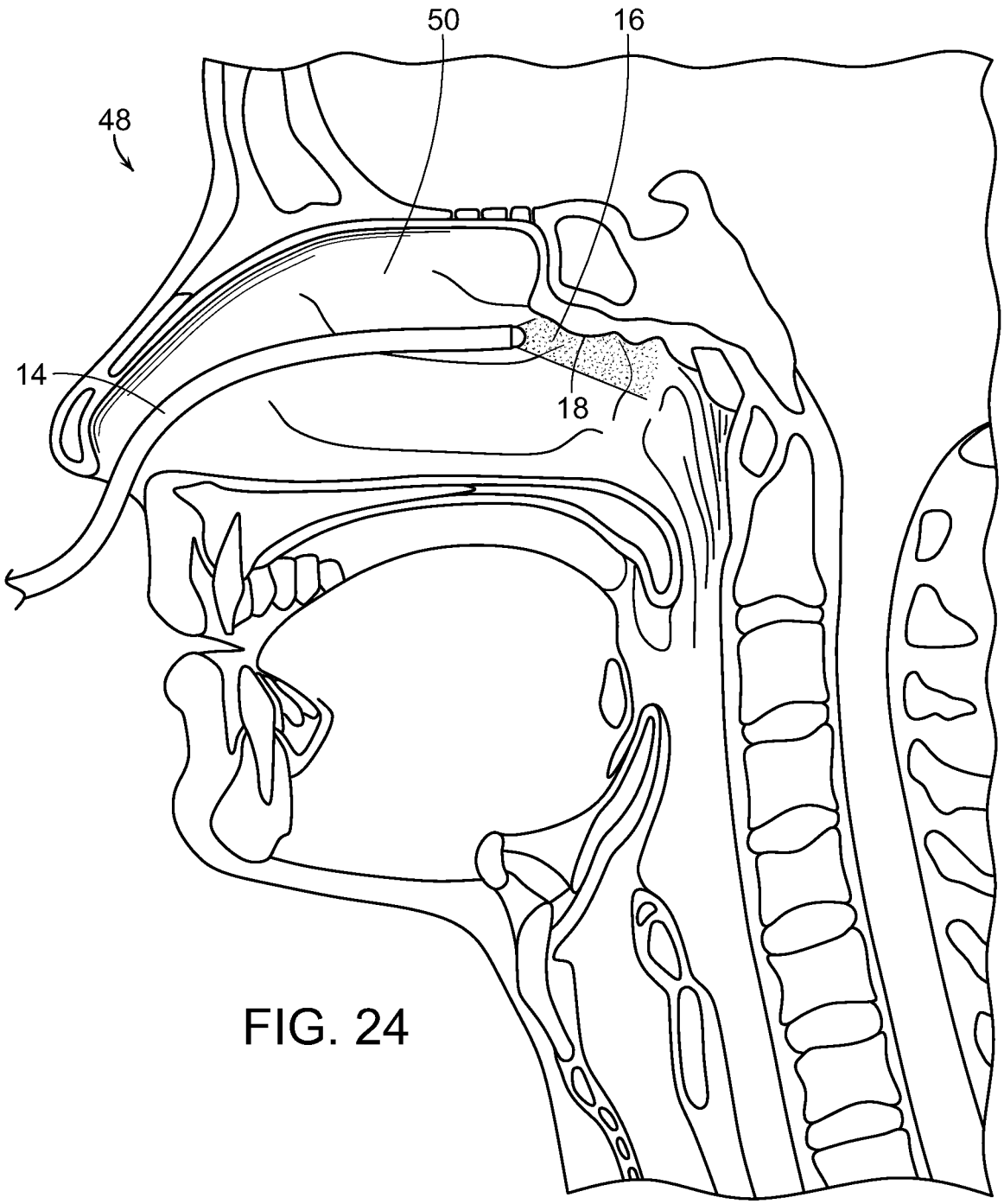

FIG. 24

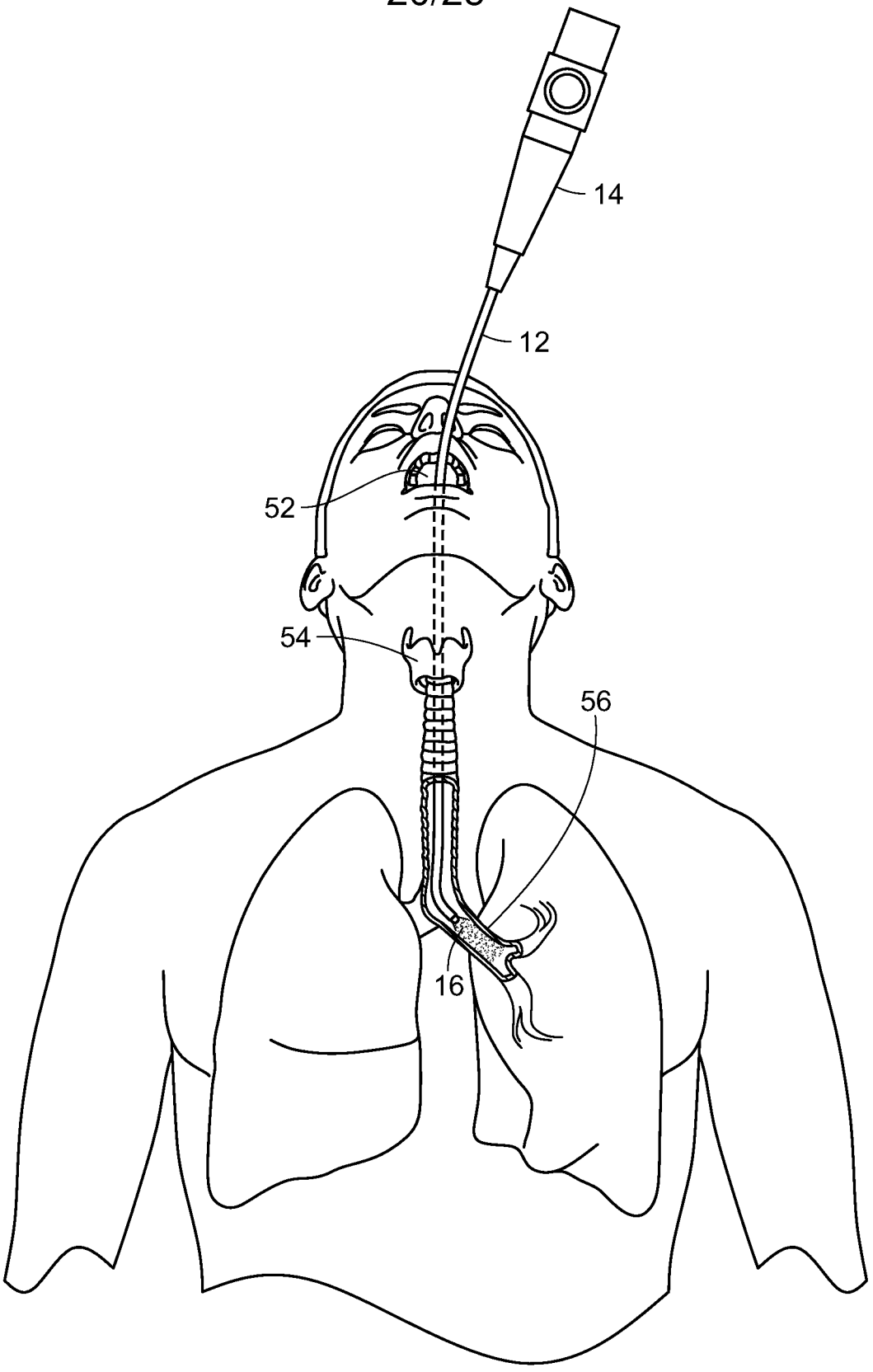

FIG. 25

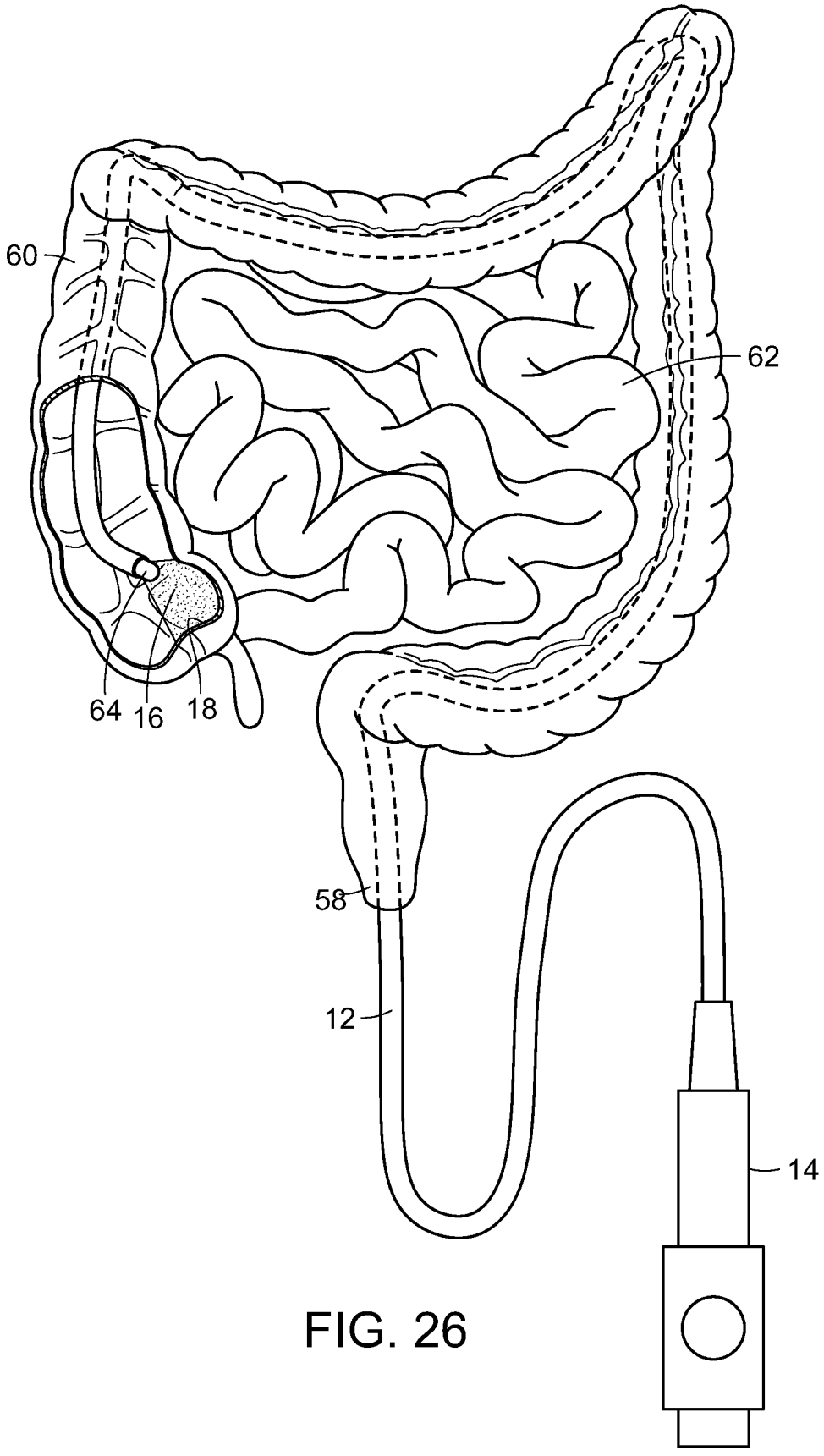

FIG. 26

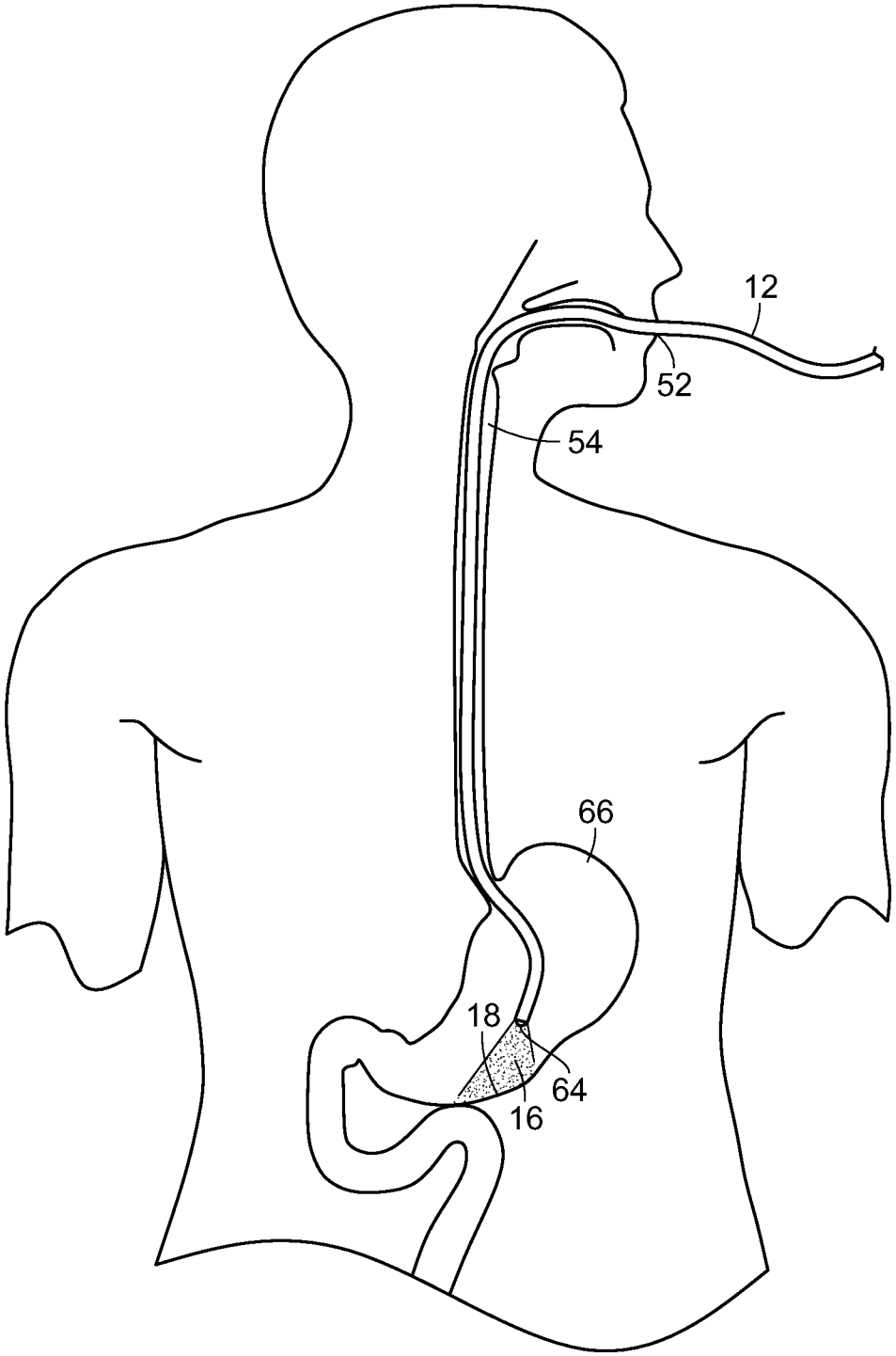

FIG. 27

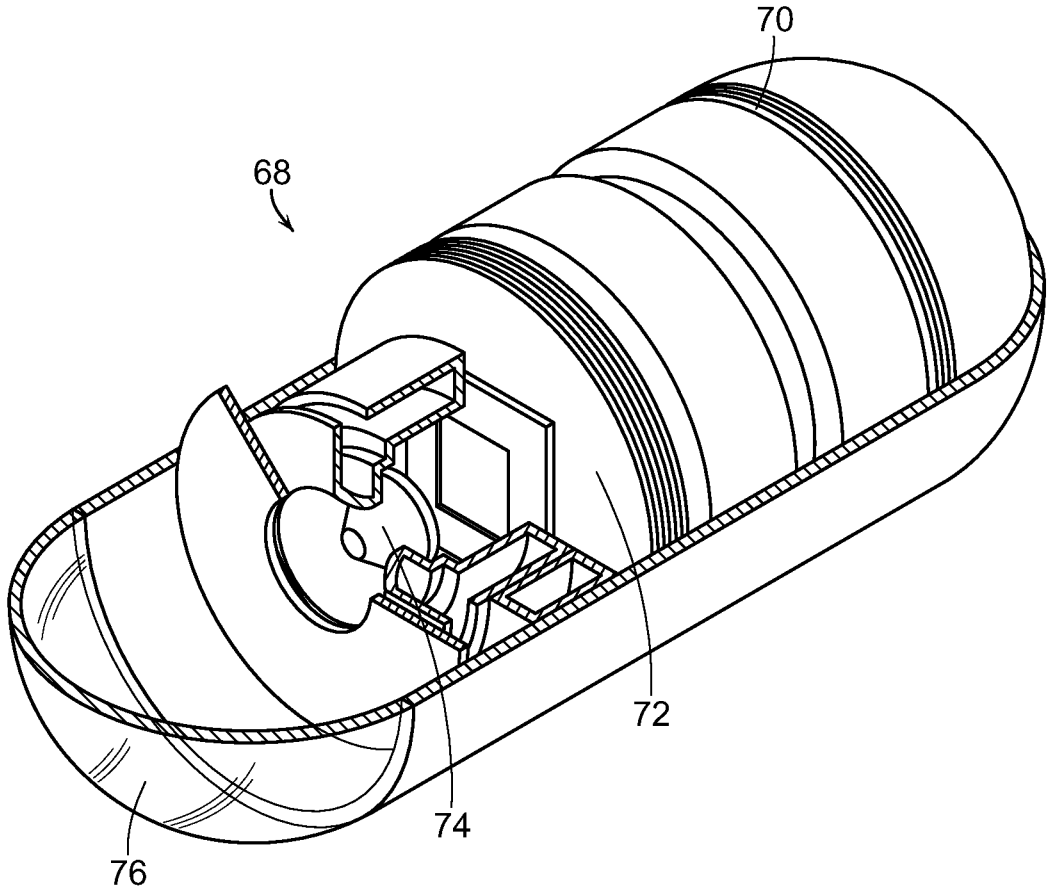

FIG. 28

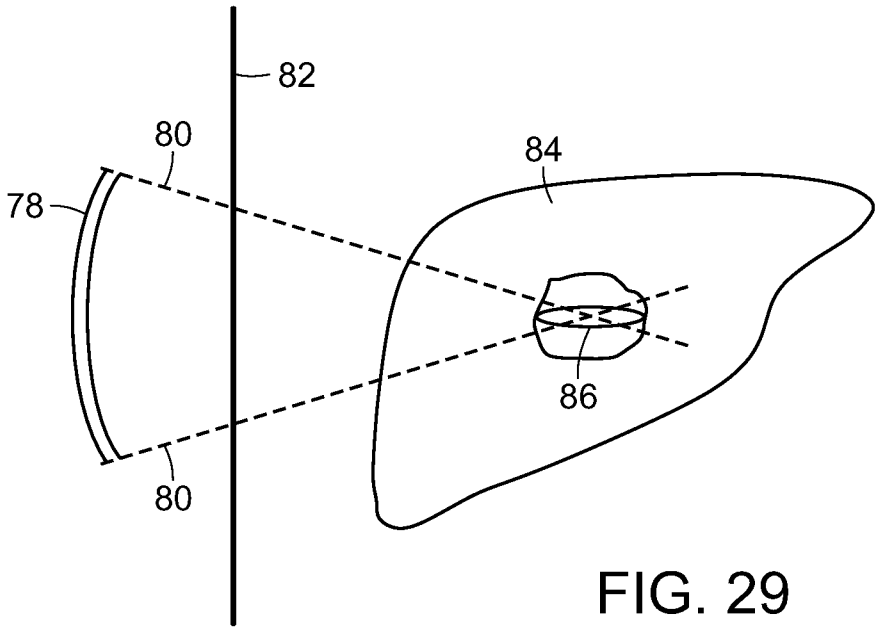
82
80
84
78
86
80

FIG. 29

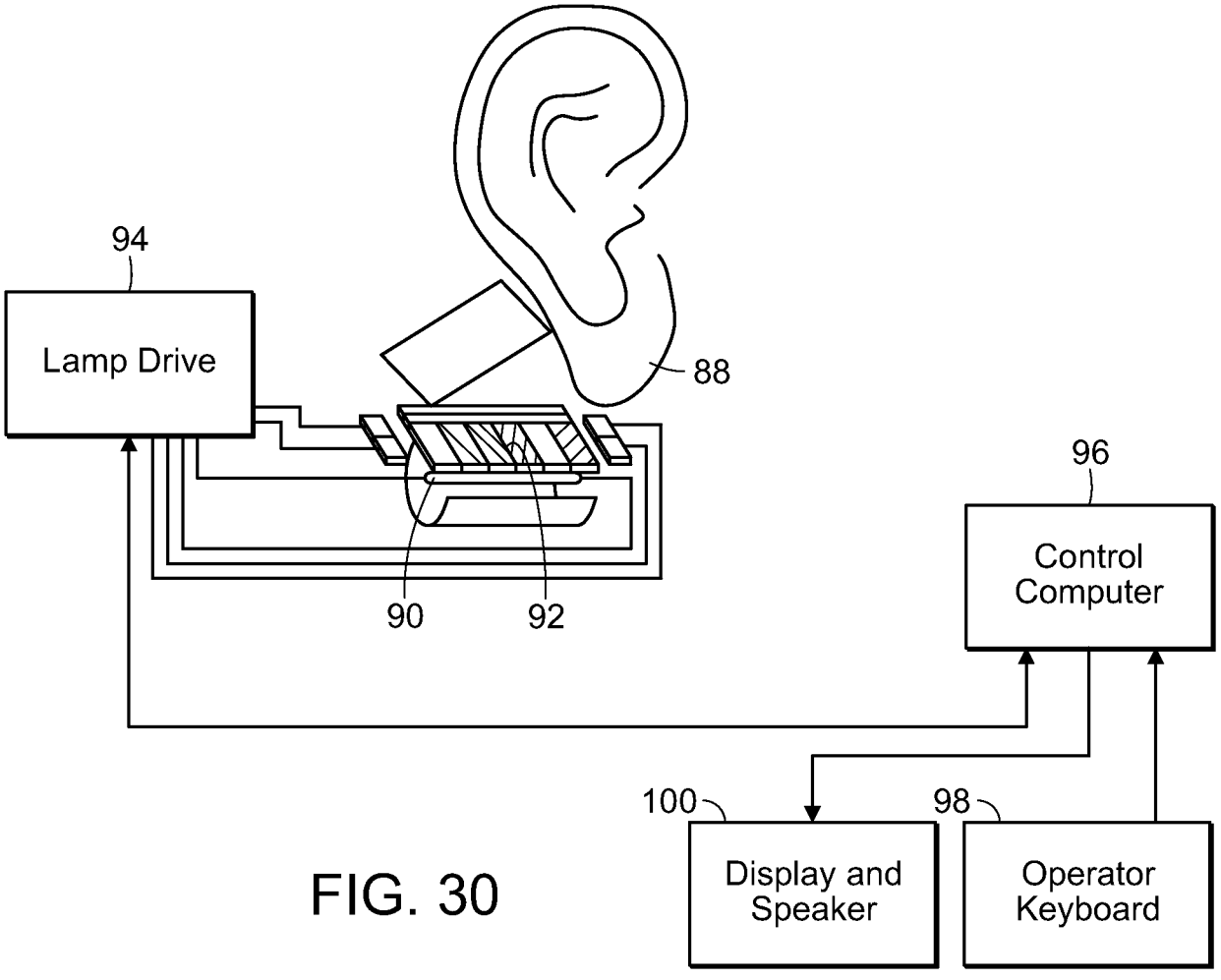
94
Lamp Drive
88
96
Control Computer
90
92
100
98
Display and Speaker
Operator Keyboard

FIG. 30

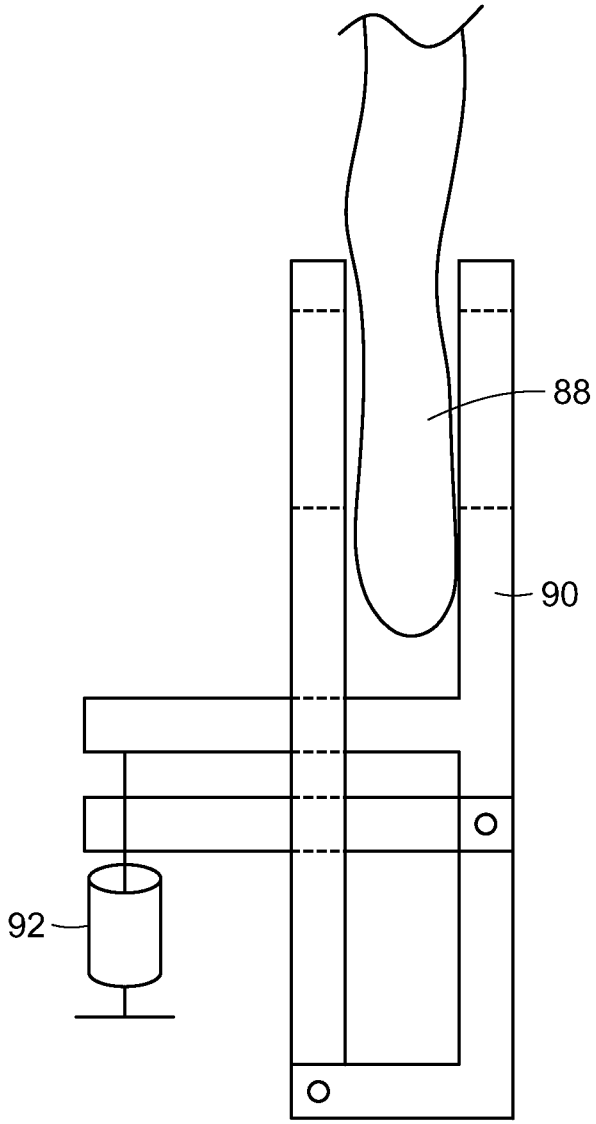

FIG. 31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/46043

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following species of the generic invention which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid

Group I: Claims 1-11, directed towards methods of applying RF energy between 3-6 MHz, 2.5%-5% duty cycle with pulse train duration of 0.2-0.4 seconds, with a specific coil radii and amp turns.
Group II: Claims 1-9, 12-13 directed towards methods of applying Microwave energy between 10-20 GHz, 2-5% duty cycle with pulse train duration of 0.2-0.6 seconds with an average power of 8-52 Watts.
Group III: Claims 1-9, 14-15 directed towards methods of applying pulsed light beams with 530-1300nm wavelength, less than 10% duty cycle, and pulse train duration of 0.1-0.6 seconds with power between 0.5-74 watts.
Group IV: Claims 1-9, 16-17 directed towards methods of applying pulsed ultrasound having a frequency between 1-5MHz, 2-10% duty cycle and train duration between 0.1-0.5 seconds with a power between 0.46 and 28.6 watts.
*Claims 1-9 are generic to groups I-IV
------ See Extra Sheet -------

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/46043

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 5/02, A61N 5/067, A61N 7/02 (2016.01)
CPC - A61N 5/025, A61N 1/403, A61N 5/0625, A61N 7/02, A61N 7/022
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61N 5/02, A61N 5/067, A61N 7/02 (2016.01)
CPC - A61N 5/025, A61N 1/403, A61N 5/0625, A61N 7/02, A61N 7/022

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
(UPC) 601/3; 607/96, 100-102 (CPC) A61N 5/02, 5/02*, 2005/02*, 5/04, 5/045; A61N 5/06, 5/06*, 2005/06*, 2005/073; A61N 7/02, 7/022, 2007/02*; A61N 7/*, 2007/* (Search term limited; see below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB, USPT, EPAB, JPAB); Google; Search Terms Used: Rf, radiofrequency, radio, frequency, mega hertz, MHz, hertz, kilohertz, KHz, pulse width, duty cycle, duration, time, length, seconds, milliseconds, microseconds, sec, millisec, joule, watt, energy, heat shock protein, without, no, low damage, non-injuring, injury, heat*, thermal*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0364924 A1 (DUNLEAVY et al.) 11 December 2014 (11.12.2014) Entire document, especially Abstract, para[0005], para[0050], para[0083]- para[0085], para[0121]- para[0124] and FIGS. 6-7.	1-6, 8-9
X	US 2010/0100162 A1 (PEYMAN) 22 April 2010 (22.04.2010) Entire document, especially Abstract, para[0026], para[0029], para[0035]- para[0040].	1-4, 7, 9
X -- Y	US 6,259,952 B1 (SLUIJTER et al.) 10 July 2001 (10.07.2001) Entire document, especially Abstract, col 2, ln 29- col 4, ln 59 and FIG. 2.	1-4, 6, 10 ---------- 11
Y	US 4,825,880 A (STAUFFER et al.) 02 May 1989 (02.05.1989) Entire document, especially col 6, line 13-15.	11
A	US 2014/0121631 A1 (BEAN et al.) 01 May 2014 (01.05.2014) Entire document.	1-11
A	US 2010/0049180 A1 (Wells et al.) 25 February 2010 (25.02.2010), Entire document.	1-11
A	US 2008/0076958 A1 (Britva et al.) 27 March 2008 (27.03.2008) Entire document	1-11
A	US 6,156,028 A (Prescott) 05 December 1998 (05.12.1998) Entire document	1-11
A	US 2010/082024 A1 (Brannan et al.) 01 April 2010 (01.04.2010) Entire document	1-11

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2016	27 DEC 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/46043

---------- Continuation of Box III: Observations where unity of invention is lacking (Continuation of item 3 of first sheet) ----------

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features
The special technical feature of each species (Groups I-IV) is provided in the group descriptions above. None of these special technical features are required in any other group.

Common Technical Features
Groups I-IV generally share the technical features of providing pulsed energy having parameters to produce a temperature increase without damaging tissue, to provide a therapeutic effect. Specifically, the contents of generic claim 1: A method for heat treating biological tissues, comprising the steps of: providing a pulsed energy source having energy parameters including wavelength or frequency, duty cycle and pulse train duration, the energy parameters selected so as to raise a target tissue temperature up to eleven degrees Celsius to achieve a therapeutic effect, wherein the average temperature rise of the tissue over several minutes is maintained at or below a predetermined level so as to not permanently damage the target tissue; and applying the pulsed energy source to the target tissue to therapeutically treat the target tissue. However, these common technical features are anticipated by US 2014/0364924 A1 to Dunleavy et al. (hereinafter: Dunleavy). Dunleavy discloses a method for heat treating biological tissues (Abstract), comprising the steps of: providing a pulsed energy source having energy parameters (para[0005]) including wavelength or frequency (para[0005]), duty cycle and pulse train duration (para[0121]-[0124], FIG. 7: note inherent to all pulsed waves), the energy parameters selected so as to raise a target tissue temperature up to eleven degrees Celsius to achieve a therapeutic effect (para[0123]), wherein the average temperature rise of the tissue over several minutes is maintained at or below a predetermined level (FIGS. 6-7, para[0121]-[0124]: pain-threshold level) so as to not permanently damage the target tissue (non-injuring para[0005]; see para[0083]-[0085]); and applying the pulsed energy source to the target tissue to therapeutically treat the target tissue (para[0005]).

Accordingly, Groups I-IV lack unity under PCT Rule 13.

(19)中华人民共和国国家知识产权局

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(22)申请日 2016.08.08

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2018.03.22

(86)PCT国际申请的申请数据
PCT/US2016/046043 2016.08.08

(87)PCT国际申请的公布数据
WO2017/074532 EN 2017.05.04

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代理人 金辉

(51)Int.Cl.
A61N 5/02(2006.01)
A61N 5/067(2006.01)
A61N 7/02(2006.01)

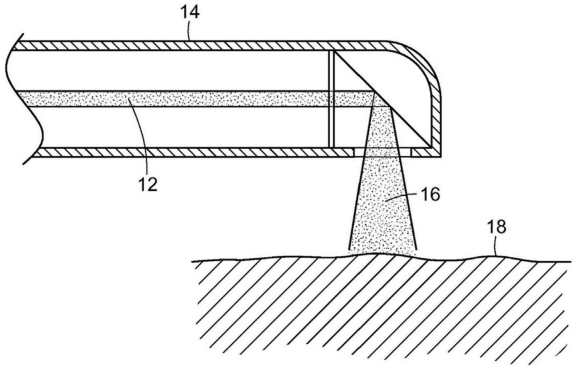
权利要求书2页 说明书18页 附图22页

(54)发明名称

使用脉冲的能量源进行生物组织热疗的方法

(57)摘要

用于热疗生物组织的方法包括提供具有选择的能量参数的脉冲的能量源，以把目标温度升高至达到治疗作用的水平，同时保持组织在长时间内平均温升在预设水平或以下，以便不会永久地损伤目标组织。把脉冲的能量源应用于目标组织引发热休克反应并刺激目标组织中的热休克蛋白活化，从而临床治疗目标组织。



CN 108136195 A

1.一种热疗生物组织的方法,包括以下步骤:

提供具有能量参数的脉冲的能量源,所述能量参数包括波长或频率、占空比和脉冲序列持续时间,选择所述能量参数以升高目标组织温度至高达11℃以实现治疗作用,其中保持组织在数分钟内平均温升在预设水平或以下,以避免永久地损伤目标组织;并且

把脉冲的能量源应用于目标组织以临床治疗目标组织。

2.如权利要求1所述的方法,其中应用步骤包括刺激所述目标组织中的热休克蛋白活化的步骤。

3.如权利要求1所述的方法,包括选择所述脉冲的能量源的能量参数的步骤,以使得在把所述脉冲的能量源应用于所述目标组织期间,目标组织温度至少升高介于约6℃至11℃之间。

4.根据权利要求1所述的方法,其中所述目标组织在数分钟内的平均温升保持在6℃或更低。

5.根据权利要求4所述的方法,其中,所述保持目标组织在数分钟内平均温升在约1℃或更低。

6.根据权利要求1所述的方法,其中选择所述脉冲的能量源的能量参数以使得每立方厘米所述目标组织吸收大约20至40焦耳的能量。

7.根据权利要求1所述的方法,其中应用脉冲的能量源的步骤包括把装置插入身体的空腔中以把所述脉冲的能量源应用于所述目标组织。

8.如权利要求1所述的方法,其中,应用所述脉冲的能量的步骤包括把所述脉冲的能量源引导至身体的外部,其与所述的目标组织相邻,或者具有靠近身体外部区域表面的血液供应。

9.根据权利要求1所述的方法,其中所述脉冲的能量源包括激光、微波、射频或超声波。

10.根据权利要求1-4或6中任一项所述的方法,其中,所述脉冲的能量源包括介于大约3至6兆赫、介于大约2.5%至5%的占空比以及介于大约0.2至0.4s的脉冲序列持续时间的射频。

11.根据权利要求10所述的方法,其中所述射频是利用线圈半径介于约2至6mm之间且安培匝数介于约13至57之间的装置产生的。

12.根据权利要求1-4或6中任一项所述的方法,其中所述脉冲的能量源包括介于大约10至20GHz之间的微波频率、介于大约0.2至0.6秒之间的脉冲序列持续时间以及介于大约2%至5%之间的占空比。

13.根据权利要求12所述的方法,其中所述微波具有介于约8瓦至52瓦之间的平均功率。

14.根据权利要求1-4或6中任一项所述的方法,其中,所述脉冲的能量源包括脉冲的光束,所述脉冲的光束具有介于约530nm至1300nm之间的波长、小于10%的占空比以及介于约0.1至0.6秒之间的脉冲序列持续时间。

15.根据权利要求14所述的方法,其中所述脉冲的光束具有介于800nm至1000nm之间的波长以及介于约0.5至74瓦之间的功率。

16.根据权利要求1-4或6中任一项所述的方法,其中所述脉冲的能量源包括脉冲的超声,所述脉冲的超声波具有介于约1MHz至5MHz之间的频率、介于约0.1至0.5秒之间的序列

持续时间以及介于约2%至10%之间的占空比。

17.根据权利要求16所述的方法,其中所述超声波具有介于约0.46至28.6瓦之间的功率。

使用脉冲的能量源进行生物组织热疗的方法

背景技术

[0001] 总体上本发明涉及一种生物组织的热疗方法。更加具体地，本发明涉及一种把脉冲的能量源应用于生物组织以刺激热休克蛋白活化并促进蛋白质修复而不损伤组织的方法。

[0002] 发明人发现，通过可控地升高组织温度至预设温度范围同时保持组织在数分钟内平均温升在预设水平或以下，以避免永久地损伤目标组织，这对于生物组织，特别是受损伤的或患病的生物组织具有治疗作用。相信以这种可控的方式升高组织温度选择性刺激热休克蛋白的活化和/或产生并促进蛋白质修复，是临床治疗组织的机制。

[0003] 热休克蛋白(HSP)是细胞响应其暴露于压力情况而产生的蛋白质家族。可以通过暴露于不同类的环境压力情况，例如感染、发炎、运动，把细胞暴露于毒素、饥饿、缺氧或缺水，而引发高水平地产生热休克蛋白。

[0004] 已知热休克蛋白在响应身体组织中大量异常情况方面起作用，异常情况包括病毒感染、发炎、恶性转变，或暴露于氧化剂、细胞毒素和缺氧环境。几种热休克蛋白起到细胞内其他蛋白质和的分子伴侣的作用，而由于它们对于保持蛋白质和简单地监控细胞蛋白质的重要作用，即便在非压力情况下，HSP家族成员以低到中等水平来表达或活化。这些活动是细胞自身修复系统的部分，称为细胞压力反应或热休克反应。

[0005] 热休克蛋白通常根据它们的分子量来命名。例如Hsp60、Hsp70和Hsp80分别指的是大约为60、70、80千道尔顿的热休克蛋白家族。它们以多种不同方式起作用。例如，Hsp70具有肽结合和ATP酶结构域，其稳定了展开和可组装状态下的蛋白质结构。线粒体Hsp60形成环状结构，从而促进蛋白质组装成天然状态。Hsp90通过与细胞酪氨酸激酶、转录因子和糖皮质激素受体结合而起到抑制调节作用。Hsp27抑制蛋白质聚合。

[0006] Hsp70热休克蛋白是细胞外的和膜结合的热休克蛋白的成员，它们涉及到结合抗原并把它们呈递给免疫系统。已发现Hsp70抑制甲型流感病毒核糖核蛋白的活性并阻止病毒的复制。来源于肿瘤的热休克蛋白引起特异性保护性免疫。实验和临床观察表明热休克蛋白涉及到调节自身免疫性关节炎、I型糖尿病、糖尿病、动脉硬化、多发性硬化和其他自身免疫反应。

[0007] 因此，相信能够在短时间内选择性且可控地升高目标组织温度至预设温度范围，同时在较长的时间内把组织的平均温升保持在预设温度是有利的。相信这引发了热休克响应，以响应感染或其他异常而增加身体组织中热休克蛋白的数量或活性。但是，这必须以可控的方式完成以避免损伤或破坏被治疗的身体组织或区域。本发明满足了这些需求，并提供了其他相关的优点。

发明内容

[0008] 本发明涉及一种热疗生物组织的方法，其通过把脉冲的能量源应用于目标组织以临床治疗目标组织。脉冲的能量源具有能量参数，包括波长或频率、占空比和脉冲序列持续时间。选择能量参数以升高目标组织温度至高达11℃以达到治疗作用，其中在数分钟内保

持组织平均温升在预设水平或以下,以避免永久地损伤目标组织。

[0009] 可以选择能量参数使得目标组织温度在把脉冲的能量源应用于目标组织的过程中至少升高大约6℃至11℃。保持目标组织在数分钟内平均温升在6℃或以下,例如在数分钟内大约1℃或以下。

[0010] 选择脉冲的能量源的能量参数以使得每立方厘米目标组织吸收大约20至40焦耳的能量。把脉冲的能量源应用于目标组织引发热休克响应并刺激目标组织中的热休克蛋白活化,而不会损伤目标组织。

[0011] 可以把装置插入身体的空腔中以把脉冲的能量应用于组织。脉冲的能量可以施加到与目标组织相邻的身体的外部区域,或者具有靠近身体外部区域表面的血液供应。

[0012] 脉冲的能量源可以包括射频。射频可以介于大约3至6兆赫(MHz)之间。它可以有介于约2.5%至5%之间的占空比。它可以有介于约0.2至0.4s之间的脉冲序列持续时间。可以利用线圈半径介于约2至6mm之间且安培匝数介于大约13至57之间的装置产生射频。

[0013] 脉冲的能量源可以包括介于10至20千兆赫(GHz)之间的微波频率,微波可以具有介于大约0.2至0.6s之间的脉冲序列持续时间。微波可以具有介于大约2%至5%之间的占空比。微波可以具有介于大约8至52瓦之间的平均功率。

[0014] 脉冲的能量源可以包括脉冲的光束,例如激光。光束可以具有介于约530nm至1300nm之间的波长,并且更优选地介于800nm至1000nm之间。脉冲的光束可以具有介于大约0.5至74瓦之间的功率。脉冲的光束具有小于10%的占空比,并且优选介于2.5%至5%之间。脉冲的光束可以具有介于大约0.1至0.6s之间的脉冲序列持续时间。

[0015] 脉冲的能量源可以包括脉冲的超声波。超声波具有介于大约1至5MHz之间的频率。超声波具有大约0.1至0.5s的序列持续时间。超声波可具有介于大约2%至10%之间的占空比。超声波具有介于大约0.46至28.6瓦之间的功率。

[0016] 结合附图,从以下的更详细的描述中,本发明的其它特征和优点将变得显而易见,这些附图举例例示了本发明的原理。

附图说明

[0017] 附图例示了本发明。在这些图中:

[0018] 图1A和1B是例示了与激光的源半径和脉冲序列持续时间相比的激光源的平均功率的曲线图;

[0019] 图2A和2B是例示了取决于激光源半径和波长的温度衰减时间的曲线图;

[0020] 图3-6是例示了各种射频、占空比和线圈半径下峰值安培匝数的曲线图;

[0021] 图7是描绘与射频线圈半径相比的温升衰减的时间的曲线图;

[0022] 图8和9是描绘与微波频率和脉冲序列持续时间相比的平均微波功率的曲线图;

[0023] 图10是描绘各种微波频率下温度衰减的时间的曲线图;

[0024] 图11是描绘与频率和脉冲序列持续时间相比的平均超声源功率的曲线图;

[0025] 图12和13是描绘各种超声频率下温度衰减时间的曲线图;

[0026] 图14是描绘与超声频率相比的焦热区域的体积的曲线图;

[0027] 图15是比较超声能量源的温度与脉冲持续时间的方程式的曲线图;

[0028] 图16和17是例示了作为温度和脉冲持续时间的函数的损伤的和HSP活化的

Arrhenius积分的对数的大小的曲线图；

[0029] 图18是根据本发明产生定时的脉冲序列的光产生单元的示意图，光产生单元具有从中延伸的光管；

[0030] 图19是根据本发明的把电磁能量传送到目标组织的光刺激传送装置的剖视图；

[0031] 图20是例示了根据本发明的用于产生激光束的系统的示意图；

[0032] 图21是根据本发明用于产生激光几何图案的光学元件的示意图；

[0033] 图22是例示了根据本发明的用于产生用于治疗组织的激光束的系统的另一个实施例的示意图；

[0034] 图23是例示了根据本发明的用于产生用于治疗组织的激光束的系统的又一个实施例的示意图；

[0035] 图24是根据本发明插入鼻腔并治疗其中的组织的内窥镜的端部的横截面和示意图；

[0036] 图25是根据本发明的支气管镜的示意性局部剖视图，该支气管镜延伸穿过气管并进入肺的支气管并对其提供治疗；

[0037] 图26是根据本发明的向身体的肠或结肠区域提供光刺激的结肠镜的示意图；

[0038] 图27是根据本发明插入胃内并对其进行治疗的内窥镜的示意图；

[0039] 图28是根据本发明使用的胶囊内窥镜的局部剖面透视图。

[0040] 图29是根据本发明的用于治疗体内组织的脉冲高强度聚焦超声的示意图；

[0041] 图30是根据本发明的用于通过耳垂向患者的血流提供治疗的示意图；

[0042] 图31是根据本发明用于通过耳垂把光刺激传送至血液的本发明的刺激治疗装置的剖视图。

具体实施方式

[0043] 如附图所示，并且如本文更充分地描述的那样，本发明涉及用于传送脉冲的能量源的系统和方法，例如激光、超声波、紫外线射频、微波射频等，其具有选择的能量参数以引起组织中的热时间过程(thermal time-course)，该热时间过程在短时间内升高组织温度至足以达到治疗作用的水平，同时在长时间保持平均组织温度低于预设水平以避免永久地损伤组织。相信创建该热时间过程刺激热休克蛋白的活化或生成，并促进蛋白质修复而不造成任何损伤。

[0044] 本发明的发明人已经发现，可以以不破坏或损伤视网膜组织并同时实现对眼疾的有益效果的方式，把各种波长的激光形式的电磁辐射应用于视网膜组织。相信这可能是至少部分地由于热休克蛋白的刺激和活化以及促进视网膜组织中的蛋白质修复。这在2015年1月28日提交的美国专利申请序列号14/607,959，2013年3月13日提交的13/798,523以及2012年5月25日提交的13/481,124中公开，其内容通过引用并入本文，如同呈现全文。

[0045] 发明人已经发现，可以产生对视网膜组织细胞治疗性而亚致死的激光光束，并由此避免损伤视网膜组织中的光凝，其中光凝对眼睛视网膜组织提供预防性和保护性治疗。必须考虑和选择光束的各种参数，以使所选参数的组合达到治疗作用，同时不会永久地损伤组织。这些参数包括激光波长、激光源的半径、平均激光功率、总脉冲持续时间和脉冲序列的占空比。

[0046] 这些参数的选择可以通过要求HSP活化的Arrhenius积分大于1(or unity)来确定。Arrhenius积分用于分析活动对生物组织的影响。例如参见Frank Kreith编辑的CRC Handbook of Thermal Engineering,Springer Science and Business Media(2000)。同时,选择的参数必须不能永久地损伤组织。因此,也可以使用损伤的Arrhenius积分,其中求得的Arrhenius积分小于1(or unity)。可选地,满足FDA/FCC关于每单位克组织的能量沉积以及在数分钟时期内测得的温升的限制,从而避免永久地损伤组织。FDA/FCC对于超声源关于能量沉积和温升的要求被广泛地使用和引用,例如参见www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073817.htm#attachaforelectromagneticsources,以及Anastosio和P.LaRivero编辑的Emerging Imaging Technologies.CRC Press(2012)。一般来说,介于6℃至11℃之间的组织温升可以如通过活化热休克蛋白而产生治疗作用,而在长时间,例如数分钟,例如六分钟,保持平均组织温度低于预设温度,如在某些情况下6℃甚至1℃或更低,不会永久地损伤组织。

[0047] 发明人已经发现,产生亚阈值的亚致死微脉冲激光束造成所需的视网膜光刺激而没有任何可见的烧伤区域或组织破坏,该亚阈值的亚致死微脉冲激光束在预设的强度或功率以及预设的脉冲长度或暴露时间下具有大于532nm的波长和小于10%的占空比。更特别地,具有介于550nm-1300nm之间的波长的激光束,并且在特别优选的实施例中,介于810nm至1000nm之间,具有大约2.5%-5%之间的占空比和预设的强度或功率(例如每平方厘米视网膜中介于100-590瓦之间,或者视网膜中每个治疗位点的每个激光点约1瓦)以及预设的脉冲长度或暴露时间(例如介于100至600ms之间或更短)造成了亚致死的、“真的亚阈值”视网膜光刺激,其保存了视网膜色素上皮细胞的暴露于激光照射的所有区域并可用于治疗。换句话说,发明人已经发现,使视网膜组织升高到至少达到治疗水平但低于细胞或组织致死水平,再现了现有技术方法的光晕效应的益处,而不破坏、烧伤或以其他方式损伤视网膜组织。这在本文中称为亚阈值二极管微脉冲激光治疗(SDM)。

[0048] 由于SDM不产生激光引发的视网膜损伤(光凝),并且没有已知的不良的治疗作用,并且已经报道为对于许多视网膜疾病(包括糖尿病性黄斑水肿(DME)增殖性糖尿病性视网膜病变(PDR)、视网膜分支静脉阻塞(BRVO)引起的黄斑水肿、中心性浆液性脉络膜视网膜病变(CSR)、药物耐受性以及进行性退行性视网膜病变(诸如干性老年性黄斑变性、Stargardts症、视锥营养不良和视网膜色素变性)的逆转)是有效的治疗。SDM的安全性使其可以在20/20视敏度的眼睛中横穿中央凹地使用,以减少由于涉及中央凹的早期DME而导致视力丧失的风险。

[0049] SDM可能凭此起作用的的机制是生成或活化热休克蛋白(HSP)。尽管存在几乎无限种可能的细胞异常,所有类型的细胞享有共同的并高度保全的修复机制:热休克蛋白(HSP)。几乎任何类型的细胞压力或损伤都会几乎立即地,在几秒至数分钟内,引起HSP。在没有致死的细胞损伤的情况下,HSP在修复活细胞和把活细胞恢复为更正常的功能状态方面非常有效。虽然HSP是短暂的,一般在数小时内达到峰值并持续几天,其效果可能会持续很长时间。HSP减少炎症,而炎症是许多疾病的共同因素。

[0050] 激光治疗可引发HSP生成或活化并改变细胞因子表达。非致死的细胞压力(如激光照射)越突然和严重,则HSP的活化越快速和强烈。因此,特别是与暴露于连续波激光的非致死性亚阈值治疗(其只能翻倍低的平均组织温升)相比,每次SDM暴露产生的变化速度非常

急剧的(每100μs微脉冲升高约7℃,或70,000℃/s)一连串重复的低温热尖峰在刺激活化HSP方面特别有效。

[0051] 550nm以下的激光波长产生增加细胞毒性的光化学效应。在810nm,SDM产生光热而不是光化学的细胞压力。因此,SDM能够在不损伤组织的情况下影响组织。因此,SDM的临床益处主要由亚病态的光热细胞的HSP活化产生。在功能失调的细胞中,通过SDM的HSP刺激导致正常化的细胞因子表达,并因此改善结构和功能。然后通过应用"高密度"激光来放大这种"低强度"激光/组织相互作用的治疗作用,通过密集/融合地治疗大的组织区域,包括所有病理的领域,以使得目标组织区域中的所有功能失调的细胞恢复健康,从而使得治疗效果最大化。这些原理确定了本文所述的SDM的治疗策略。

[0052] 由于功能正常的细胞不需要修复,因此对正常细胞的HSP刺激往往没有显着的临床效果。近红外激光(如SDM)在各种细胞类型上的作用的"病态-选择性"与SDM的临床观察结果一致,其中近红外激光影响病态细胞但不影响正常细胞。与美国国家标准协会"允许的最大暴露"的预测一致,据报道SDM在视网膜激光模式中具有独一无二的广泛的临床治疗范围。虽然SDM可能引起直接的光热作用,如熵蛋白展开和分解,对于临床上安全和有效刺激HSP介导的修复,SDM似乎是最优化的。

[0053] 如上所述,尽管HSP的SDM刺激就疾病过程而言是非特异性的,HSP介导的修复的结果是由功能失调的状态所特有的性质决定的。HSP倾向于修复任何错误的地方。因此,观察到SDM在极为不同的视网膜状况中的有效性,例如BRVO、DME、PDR、CSR、与年龄相关的和遗传性视网膜病和耐药NAMD。从概念上讲,可以认为这种设施是SDM活动的一种"重置为默认"模式。对于细胞功能吃紧的各种疾病,SDM通过HSP介导的细胞修复触发"重置"(至"出厂默认设置")以使得细胞功能正常化。

[0054] 发明人已经发现,对患有老年性黄斑变性(AMD)的患者的SDM治疗可以减缓进展甚至停止AMD的进展。大多数患者在SDM治疗后动态功能logMAR中间视敏度和中间对比视敏度有显着改善。相信SDM通过视网膜色素上皮细胞(RPE)的靶向、保全和"正常化"(移向正常)功能而起作用,

[0055] 尽管持续存在全身性糖尿病,SDM也表明可以停止或逆转糖尿病性视网膜病变的临床表现,而没有与治疗相关的损伤或不良作用。在此基础上,假设SDM可能通过在糖尿病影响的RPE细胞中引发朝向更正常的细胞功能和细胞因子表达的恢复而发挥作用,类似于点击电子设备的"重置"按钮以恢复出厂默认设置。基于上述信息和研究,SDM治疗可能通过目标组织中的热休克蛋白(HSP)活化而直接影响细胞因子表达。

[0056] 由于热休克蛋白在响应除眼组织以外的其他身体组织中的大量异常情况中起作用,相信类似的系统和方法可以有利地用于治疗这样的异常情况、感染等。如此,本发明涉及可控地把超声或电磁辐射施加到治疗可通过内窥镜或表面探针的光纤以及聚焦的电磁/声波触及的异常情况,包括炎症、自身免疫病和癌症。例如,具有最大转移威胁的前列腺表面的癌症可通过直肠镜中的光纤触及。结肠肿瘤可以通过光纤系统触及,如结肠镜检查中使用的那种。

[0057] 如上所述,在刺激眼组织中轻微错误折叠的蛋白质的直接修复方面,亚阈值二极管微脉冲激光(SDM)光刺激是有效的。除HSP活化之外,可能发生的另一种方式是因为以热时间过程形式的微脉冲引起的温度尖峰使得水在蛋白质内扩散,从而使得阻止蛋白质恢复

其天然状态的肽-肽氢键断裂。水向蛋白质的扩散导致约束氢键的数量增加了一千倍。因此，相信该过程也可以有利地应用于其它疾病。

[0058] 如上所述，必须确定和选择施加到目标组织的能量源的能量和运行参数，以达到治疗作用，同时不会永久地损伤组织。以光束能量源(例如激光束)为例，必须考虑激光波长、占空比和总脉冲序列持续时间的参数。其他可以考虑的参数包括激光源半径以及平均激光功率。调整或选择这些参数中的其中一个可能会影响至少一个其他参数。

[0059] 图1A和1B例示了显示出与激光源半径(介于0.1cm至0.4cm之间)和脉冲序列持续时间(介于0.1至0.6秒之间)相比的平均功率(瓦)的曲线图。图1A显示880nm的波长，而图1B则具有1000nm的波长。从这些图中可以看出，所需功率随着源半径减小、总序列持续时间增加以及波长减小而单调下降。激光源半径的优选参数是1mm-4mm。当激光源半径为1mm，总脉冲序列持续时间为600ms时，对于880nm的波长，功率最小值为0.55瓦。当激光源半径为4mm且总脉冲序列持续时间为100ms时，对于880nm波长，功率最大值为52.6瓦。然而当选择波长为1000nm的激光时，当激光源半径为1mm且总脉冲序列持续时间为600ms时，则功率最小值为0.77瓦，而当激光源半径为4mm且总脉冲持续时间为100ms时，则功率最大值为73.6瓦。单个脉冲期间，相应的峰值功率是通过用平均功率除以占空比而获得的。

[0060] 待加热的组织区域的体积由波长、相关组织中的吸收长度以及光束宽度确定。总脉冲持续时间和平均激光功率确定了传送给组织加热的总能量，而脉冲序列的占空比给出了与平均激光功率相关的相关尖峰、或峰值、功率。优选地，选择脉冲的能量源的能量参数以使得每立方厘米的目标组织吸收大约20到40焦耳的能量。

[0061] 视网膜色素上皮细胞中黑色素薄层的吸收长度很小。在身体的其他部位，吸收长度一般不会那么小。在400nm到2000nm的波长范围内，穿透深度和表皮的范围为0.5mm到3.5mm。穿透进入人体粘液组织的深度范围为0.5mm至6.8mm。因此，加热的体积将被限制在放置辐射源的外表面或内表面，其深度等于穿透深度，并且横向尺寸等于辐射源的横向尺寸。既然光束能量源用于治疗外表面附近或可触及的内表面附近的患病组织，半径介于1mm至4mm之间的源，当运行波长为880nm时产生大约2.5mm的穿透深度，而当运行波长为1000nm时则产生大约3.5mm的穿透深度。

[0062] 已经确定，目标组织可以在短时间内(如小于1s)加热至高达大约11℃，同时在长时间(如数分钟)把目标组织平均温度保持在较低温度范围(例如低于6℃或甚至低于1℃或更低)，以产生本发明的治疗作用。选择占空比和总脉冲序列持续时间以提供散热的时间间隔。已经发现占空比小于10％，并且优选介于2.5％至5％之间，同时总脉冲持续时间介于100ms至600ms之间是有效的。图2A和2B例示了对于半径介于0.1cm至0.4cm之间的激光源从10℃衰减到1℃的时间，其中图2A中的波长是880nm，在图2B中的波长是1000nm。可以看出，当使用880nm的波长时，衰减时间较少，而两种波长都落入为实现本发明的益处而可接受的要求和运行参数范围内，不会引起永久的组织损伤。

[0063] 已经发现，在总辐射期间，期望的目标区域的平均温升增加至少6℃并且高达11℃，优选约10℃，导致HSP活化。目标组织温度的控制是通过选择源和目标参数来确定的，以使得HSP活化的Arrhenius积分大于1，同时确保符合FDA/FCC避免损伤的保守的要求或损伤的Arrhenius积分小于1。

[0064] 对于光束和其他电磁辐射源，为了满足保守的FDA/FCC限制以避免永久地损伤组

织，任何六分钟期间目标组织的平均温升为1℃或更低。上面的图2A和图2B例示了根据温升为从约10℃到1℃，通过热扩散而降低被加热的目标区域的温度所需的典型衰减时间，如图2A所示，当波长为880nm且源直径为1mm时，温度衰减时间为16s。当源直径为4mm时，温度衰减时间为107s。如图2B所示，当波长为1000nm且源直径为1mm时，温度衰减时间为18s，而当源直径为4mm时，温度衰减时间为136s。这完全在数分钟时间内保持平均温升的时间内，例如6分钟或更短。在把能量源应用于组织期间，尽管目标组织的温度非常快速地(例如在几分之一秒内)升高(例如大约10℃)，相对低的占空比使得施加到组织的能量脉冲之间的时间段相对较长，并且相对较短的脉冲序列持续时间确保在相对较短的时间段内(包括数分钟，如6分钟或更少)有足够的温度扩散和衰减，因而没有永久地损伤组织。

[0065] 因为对于这些不同类型的能量源的组织吸收特性不同，针对各个能量源的参数有所不同，能量源包括微波、红外激光、射频和超声波。尽管不同组织类型的水含量可能不同，然而在正常或接近正常的条件下，观察到组织性质的一致性，这些条件允许临床医生在设计治疗时广泛使用的组织参数的发表。下面是例示了生物介质中电磁波特性的表格，表1涉及高含水量的肌肉、皮肤和组织，表2涉及低含水量的脂肪、骨头和组织。

[0066] 表1.高含水量的肌肉、皮肤和组织的电磁波特性

[0067]

频率 (MHz)	空气中的波长 (cm)	介电常数 €H	传导率 σH	波长 λH (mho/m)(cm)	穿透深度 (cm)	反射系数 空气-肌肉界面		肌肉-脂肪界面	
						r	ø	r	ø
1	30000	2000	0.400	436	91.3	0.982	+179		
10	3000	160	0.625	118	21.6	0.956	+178		
27.12	1106	113	0.612	68.1	14.3	0.925	+177	0.651	-11.13
40.68	738	97.3	0.693	51.3	11.2	0.913	+176	0.652	-10.21
100	300	71.7	0.889	27	6.66	0.881	+175	0.650	-7.96
200	150	56.5	1.28	16.6	4.79	0.844	+175	0.612	-8.06
300	100	54	1.37	11.9	3.89	0.825	+175	0.592	-8.14
433	69.3	53	1.43	8.76	3.57	0.803	+175	0.562	-7.06
750	40	52	1.54	5.34	3.18	0.779	+176	0.532	-5.69
915	32.8	51	1.60	4.46	3.04	0.772	+177	0.519	-4.32
1500	20	49	1.77	2.81	2.42	0.761	+177	0.506	-3.66
2450	12.2	47	2.21	1.76	1.70	0.754	+177	0.500	-3.88
3000	10	46	2.26	1.45	1.61	0.751	+178	0.495	-3.20
5000	6	44	3.92	0.89	0.788	0.749	+177	0.502	-4.95
5800	5.17	43.3	4.73	0.775	0.720	0.746	+177	0.502	-4.29
8000	3.75	40	7.65	0.578	0.413	0.744	+176	0.513	-6.65
10000	3	39.9	10.3	0.464	0.343	0.743	+176	0.518	-5.95

[0068]

[0069] 表2.低含水量的脂肪、骨头和组织的电磁波特性

	空气中的	波长			反射系数				
频率	波长	介电常	传导率σL,	λL	穿透深度	空气-脂肪界面		脂肪-肌肉界面	
(MHz)	(cm)	数€L	(mmho/m)	(cm)	(cm)	r	ø	r	ø
1	30000								
10	3000								
27.12	1106	20	10.9-43.2	241	159	0.660	+174	0.651	+169
40.68	738	14.6	12.6-52.8	187	118	0.617	+173	0.652	+170
100	300	7.45	19.1-75.9	106	60.4	0.511	+168	0.650	+172
200	150	5.95	25.8-94.2	59.7	39.2	0.458	+168	0.612	+172
300	100	5.7	31.6-107	41	32.1	0.438	+169	0.592	+172
433	69.3	5.6	37.9-118	28.8	26.2	0.427	+170	0.562	+173
750	40	5.6	49.8-138	16.8	23	0.415	+173	0.532	+174
915	32.8	5.6	55.6-147	13.7	17.7	0.417	+173	0.519	+176
1500	20	5.6	70.8-171	8.41	13.9	0.412	+174	0.506	+176
2450	12.2	5.5	96.4-213	5.21	11.2	0.406	+176	0.500	+176
3000	10	5.5	110-234	4.25	9.74	0.406	+176	0.495	+177
5000	6	5.5	162-309	2.63	6.67	0.393	+176	0.502	+175
5900	5.17	5.05	186-338	2.29	5.24	0.388	+176	0.502	+176
8000	3.75	4.7	255-431	1.73	4.61	0.371	+176	0.513	+173-
10000	3	4.5	324-549	1.41	3.39	0.363	+175	0.518	+174,-

[0071] 与身体尺寸相比，身体组织中的射频吸收长度较长。因此，加热区域由作为射频能量源的线圈的尺寸而不是由吸收长度所确定。在距线圈距离为r的远距离处，来自线圈的(近)磁场下降$1/r^3$。在较小的距离处，电场和磁场可以用矢量磁势来表示，而矢量磁势又可以用第一类和第二类椭圆积分的闭合形式表示。加热只在大小方面与线圈源本身尺寸相当的区域发生。因此，如果需要优先加热以半径为特征的区域，则选择具有相似半径的源线圈。由于磁场下降$1/r^3$，加热在半径的半球区域之外迅速下降。由于建议使用只能从外部或从内腔触及患病组织的射频，因此考虑线圈半径介于大约2至6mm之间是合理的。

[0072] 源线圈的半径以及源线圈的安倍匝数(NI)给出了磁场的大小和空间范围，而射频是把电场的大小与磁场的大小联系起来的因数。加热与传导率和电场的平方的乘积成比例。对于接近外表面或内表面的感兴趣的目标组织，传导率是皮肤和粘液组织的传导率。脉冲序列的占空比以及脉冲序列的总序列持续时间是传送多少总能量给组织的影响因素。

[0073] 射频能量源的优选参数已确定为：线圈半径介于2至6mm之间，射频范围3-6MHz，总脉冲序列持续时间0.2至0.4s，以及占空比介于2.5％至5％之间。图3-6显示了安培匝数的量如何随着这些参数的变化而变化来提供温升，该温升产生约1的HSP活化的Arrhenius积分。参考图3，对于6MHz的RF频率，介于0.2至0.4s之间的脉冲序列持续时间，介于0.2至

0.6cm之间的线圈半径以及5％的占空比，峰值安培匝数(NI)在半径0.6cm的线圈下为13，而在半径0.2cm的线圈下则为20。对于3MHz的频率，如图4所示，当脉冲序列持续时间为0.4s并且线圈半径为0.6cm、占空比为5％时，峰值安培匝数为26。然而，在同样的5％的占空比下，当线圈半径为0.2cm且脉冲序列持续时间为0.2s时，峰值安培匝数为40。在图5和图6中采用2.5％的占空比。这产生了：如图5所示，对于6MHz的射频，线圈半径为0.6cm且脉冲序列持续时间为0.4s时，安倍匝数为18；而当线圈半径仅为0.2cm且脉冲序列持续时间为0.2s时，安倍匝数为29。如图6所示，对于2.5％的占空比，3MHz的射频，当脉冲序列持续时间为0.4s且线圈半径为0.6cm时，峰值安培匝数为36，而当脉冲序列持续时间为0.2s且线圈半径为0.2cm时，峰值安培匝数为57。

[0074] 图7示出了对于线圈半径介于0.2cm至0.6cm之间的射频能量源，使温升从约10℃衰减到约1℃的时间(秒)。当射频线圈半径为0.2cm时，温度衰减时间约为37s，而当射频线圈半径为0.5cm时，衰减时间约为233s。当射频线圈半径为0.6cm时，衰减时间约为336s，这仍然在可接受的衰减时间范围内，但在其较高的范围。

[0075] 微波是根据本发明可以使用的另一种电磁能量源。微波的频率确定了组织的穿透距离。与微波波长相比，圆锥形微波喇叭的增益较大，表明在这些情况下，能量主要辐射在狭窄的正向负载。通常，根据本发明使用的微波源具有厘米数量级或更小的线性尺寸，因此源比波长小，在这种情况下，微波源可以近似为偶极天线。这种小型微波源更容易插入身体内腔，也可用于辐射外表面。在那种情况下，加热区域可以近似为半球体，其半径等于被治疗的身体组织的微波的吸收长度。由于微波用于治疗外表面或从内腔可触及的表面附近的组织，因此使用10-20GHz范围内的频率，其中相应的穿透距离仅介于大约2至4mm之间。

[0076] 使用微波能量源时组织温升由微波的平均功率和总脉冲序列持续时间确定。脉冲序列的占空比确定脉冲序列中单个脉冲的峰值功率。由于使用小于大约1cm的源半径，并且使用的频率通常介于10至20GHz之间，所以所得的脉冲序列持续时间优选为0.2至0.6s。

[0077] 所需功率随着序列持续时间的增加和微波频率的增加而单调下降。对于10GHz的频率，当脉冲序列持续时间为0.6s时，平均功率为18瓦，而当脉冲序列持续时间为0.2s时，平均功率为52瓦。对于20GHz的微波频率，当脉冲序列为0.6s时，使用8瓦的平均功率；而当脉冲序列持续时间仅为0.2s时，可以使用26瓦的平均功率。相应的峰值功率通过平均功率简单地除以占空比而获得。

[0078] 现在参考图8，该曲线图描绘了频率为10GHz并且脉冲序列持续时间介于0.2s至0.6s之间的微波的平均微波功率(瓦)。图9是类似的曲线图，但其显示微波频率为20GHz的平均微波功率。因此可以看出，平均微波源功率随总序列持续时间和微波频率变化而变化。然而，控制条件为使加热区域中HSP活化的Arrhenius积分约为1。

[0079] 参考图10，该曲线图示出了与介于58MHz至20000MHz之间的微波频率相比，温度大约从10℃衰减到1℃的时间(秒)。对于微波频率的优选范围，当微波频率为20GHz时，最小的温度衰减为8s，而当微波频率为10GHz时，最大的温度衰减为16s。

[0080] 利用超声波作为能量源允许加热表面组织以及身体中不同深度的组织，包括相当深的组织。正如其在成像中的广泛应用所证明的那样，超声波在人体内的吸收长度相当长。因此，超声波可以聚焦在体内深处的目标区域，其中聚焦的超声波束的加热主要集中在大致圆柱形的束的聚焦区域中。加热区域的体积由Airy束的焦腰和焦腰区的长度所确定，即

共焦参数。也可以使用来自不同角度的源的多个束，加热发生在重叠焦点区域。

[0081] 对于超声波，确定组织温度的相关参数是超声频率、总序列持续时间和当给出超声换能器的焦距和直径时换能器的功率。频率、焦距和直径确定了超声波能量集中的焦点区域的体积。该焦点体积包含目标治疗组织的体积。直径约为5cm且焦距约为10cm的换能器是容易获得的。当超声频率在1到5MHz之间且总序列持续时间为0.1到0.5s时，可以获得有利的焦点尺寸。例如，对于10cm的焦距和5cm的换能器直径，焦点体积在5MHz时为0.02cc，而在1MHz时为2.36cc。

[0082] 现在参考图11，曲线图示出了频率(在1MHz至5MHz之间)、脉冲序列持续时间(在0.1和0.5s之间)下的平均源功率(瓦)。假设换能器焦距为10cm，源直径为5cm。为了使得HSP活化的Arrhenius积分约为1，所需的功率随频率增加和总序列持续时间增加而单调减小。给定优选参数，对于1GHz频率和0.5s脉冲序列持续时间，最小功率为5.72瓦，而对于1GHz频率和0.1s脉冲序列持续时间，最大功率为28.6瓦。对于5GHz频率，对于0.5s的脉冲序列持续时间需要0.046瓦，而其中对于0.1s的脉冲序列持续时间需要0.23瓦。通过简单地除以占空比来获得单个脉冲期间的相应峰值功率。

[0083] 图12示出了当超声频率介于1至5MHz之间时，温度从10℃扩散或衰减到6℃的时间(秒)。图13示出了对于超声频率介于1至5MHz之间，从约10℃衰减到约1℃的时间(秒)。对于优选的10cm的焦距和5cm的换能器直径，当超声频率为1MHz时，温度衰减的最大时间为366s，而当微波频率为5MHz时，最小温度衰减时间为15s。由于FDA仅要求在数分钟的测试时间内温升小于6℃，因此1MHz时在数分钟升高1℃的366s衰减时间是允许的。如图12和13所示，6℃的温升的衰减时间比1℃的小得多，两者相差约为70倍。

[0084] 图14示出了与超声频率为介于1至5MHz之间时焦点加热区域的体积(立方厘米)。考虑到1至5MHz范围内的超声频率，这些频率的对应焦点尺寸范围介于3.7mm至0.6mm之间，而焦点区域的长度范围介于5.6cm至1.2cm之间。相应的治疗体积范围介于约2.4cc至0.02cc之间。

[0085] 给出所需的HSP活化的Arrhenius积分大于1并且损伤的Arrhenius积分小于1的参数的例子是：5.8-17瓦之间的总超声功率，0.5s的脉冲持续时间，5s的脉冲之间的间隔，在50s的总脉冲流时间内脉冲总数为10。目标治疗体积边长大约为1mm。较大的治疗体积可以通过类似于激光衍射光学系统的超声系统，通过在多个同时应用的相邻但分离和间隔的柱应用超声来治疗。多个聚焦的超声波束聚焦在身体内的非常小的治疗目标上，聚焦使得除目标处重叠光束之外的加热最小。该区域将被加热并刺激HSP的活化且通过短暂高温峰值促进蛋白质修复。然而，鉴于本发明的脉冲方面以及在任何给定时间治疗的面积相对较小，该治疗符合FDA/FCC关于长期(分钟)平均温升<1K的要求。本发明与用于疼痛和肌肉拉伤的现有治疗性加热治疗的重要区别在于，现有技术中没有高T峰值，而这对于有效活化HSP和促进蛋白质修复以提供细胞水平的治愈是必需的。

[0086] 就活化补救性HSP和促进蛋白质修复而言，相对于单个脉冲或渐变的能量传送模式，脉冲的能量传送模式具有明显的优势。此优势中有两个考虑因素：

[0087] 首先，SDM能量传送模式中活化HSP和蛋白质修复的一大优势来自于产生大约10℃的尖峰温度。这种温度的大幅上升对Arrhenius积分有很大的影响，Arrhenius积分定量地描述了活化的HSP数量和水分扩散到蛋白质中的速率，水分扩散到蛋白质中促进了蛋白质

修复。这是因为温度进入到具有很大的放大效应的指数。

[0088] 重要的是温升不长时间保持在高值(10℃或更高),因为那样会违反FDA和FCC要求,FDA和FCC要求在数分钟时间内平均温升必须小于1℃(或在超声波的情况下小于6℃)。

[0089] 通过合理地选择功率、脉冲时间、脉冲间隔和待治疗的目标区域的体积,SDM能量传送模式独一无二地满足上述两个考虑因素。之所以选择治疗区域的体积,是因为温度必须以大约10℃相当快速地从高值衰减,以使得对于超声波频率,长期平均温升不超过FDA/FCC的6℃的长期限制,而对于电磁辐射能源,不超过1℃或更低的长期限制。

[0090] 对于线性尺寸L的区域,组织中峰值温度e倍所花的时间大约为$L^2/16D$,其中D=$0.00143cm^2/sec$是典型的热扩散系数。例如,如果L=1mm,衰减时间大约为0.4s。因此,对于边长1mm的区域,由每个持续时间为0.5s、脉冲之间的间隔为5s的10个脉冲组成的序列可以实现所需的温度的瞬时高水平升高,同时平均长期温升仍然不超过1℃。以下进一步说明。

[0091] 加热体积的限制是RF电磁辐射不如超声波作为身体深部区域SDM型治疗的合适选择的原因。长的集肤深度(穿透距离)和沿着集肤深度的欧姆加热得到大的加热体积,其热惯性不同时允许获得活化HSP和促进蛋白质修复的高的峰值温度,以及满足FDA和FCC对长期平均温升的限制的快速的温度衰减。

[0092] 超声波已用于治疗性加热身体区域以缓解疼痛和肌肉劳损。然而,这种加热没有遵循SDM型协议,并且没有负责激发HSP的温度尖峰。

[0093] 然后,考虑一组指向身体深处的目标区域的聚焦的超声波束。为了简化数学运算,假设用球面形状的单一源取代光束,该球面形状聚焦在球体的中心。超声波的吸收长度可能相当长。下面的表3示出了1MHz超声波的典型吸收系数。吸收系数与频率大致成比例。

[0094] 表3.身体组织中1MHz超声波的典型吸收系数:

[0095]

身体组织	1 MHz(cm^{-1})的衰减系数
水	0.00046
血液	0.0415
脂肪	0.145
肝脏	0.115-0.217
肾脏	0.23
肌肉	0.3-0.76
骨头	1.15

[0096] 假设由聚焦引起的入射辐射的几何变化主导了由衰减引起的任何变化,距焦点距离r处的入射超声的强度可以近似写为:

[0097] $I(r)=P/(4\pi r^2)$ [1]

[0098] 其中P表示总超声功率。

[0099] 那么在r处在短的脉冲持续时间t_p结束时的温升就是

[0100] $dT(t_p)=P\alpha t_p/(4\pi C_v r^2)$ [2]

[0101] 其中α是吸收系数,C_v是比体积热容。直到r达到使得在t_p时热扩散长度与r相当的

程度，或达到达到聚焦束的衍射极限，就是这个情况。对于较小的r，温升基本上与r无关。作为一个例子，假设在径向距离处达到衍射极限，其中该径向距离小于热扩散确定的距离。那么

[0102] $r_{dif}=(4Dt_p)^{1/2}$ [3]

[0103] 其中D是热扩散系数，当$r<r_{dif}$，在t_p时的温升是

[0104] $dT(r_{dif},t_p)=3P\alpha/(8\pi C_vD)$当$r<r_{dif}$ [4]

[0105] 因此，在脉冲结束时，我们可以写出温升：

[0106] $dT_p(r)=\{P\alpha t_p/(4\pi C_v\}[(6/r_{dif}^2)U\{r_{dif}-r)+(1/r^2)U(r-r_{dif})]$ [5]

[0107] 把热扩散方程的格林函数，

[0108] $G(r,t)=(4\Omega Dt)^{-3/2}\exp[-r^2/(4Dt)]$ [6]

[0109] 应用到这个初始温度分布，我们发现在时间为t时在焦点r=0处的温度dT(t)是

[0110] $dT(t)=[dT_o/\{(1/2)+(\pi^{1/2}/6)\}][(1/2)(t_p/t)^{3/2}+(\pi^{1/2}/6)(t_p/t)]$ [7]

[0111] 而

[0112] $dT_o=3P\alpha/(8\pi C_vD)$ [8]

[0113] 方程式[7]的一个很好的近似为：

[0114] $dT(t)\approx dT_o(t_p/t)^{3/2}$ [9]

[0115] 如图15所示，图15是在目标治疗区处方程[7]和[9]的对于$dT(t)/dT_o$的比较。底部曲线是方程[9]的近似表达。

[0116] 现在可以用方程[9]给出的温升来求出N个脉冲的序列的Arrhenius积分。在这个表达中，

[0117] $dT_N(t)=\Sigma dT(t-nt_I)$ [11]

[0118] 其中$dT(t-nt_I)$是方程[9]的表达式，t用$t-nt_I$替代，其中t_I表示脉冲之间的间隔。

[0119] 可以通过把积分区间划分为出现温度尖峰的部分和没有温度尖峰的部分来大致求出Arrhenius积分。可以通过把拉普拉斯的终点公式应用于温度尖峰上的积分，简化温度尖峰上的贡献的总和。另外，注意到非尖峰温度非常迅速地上升达到渐近值，从而通过把变化的时间上升替代为其渐近值能获得良好的近似，从而可以简化没有尖峰的部分上的积分。当进行这些近似时，方程[10]变成：

[0120] $\Omega=AN[\{t_p(2k_BT_o^2/(3EdT_o)\}\exp[-(E/k_B)1/(T_o+dT_o+dT_N(Nt_I))]$

[0121] $+\exp[-(E/k_B)1/(T_o+dT_N(Nt_I))]]$ [12]

[0122] 其中

[0123] $dT_N(Nt_I)\approx 2.5dT_o(t_p/t_I)^{3/2}$ [13]

[0124] (方程[13]中的2.5是由$(N-n)^{-3/2}$中的n的总和产生的，并且是感兴趣的典型N的谐波数(N,3/2)的大小。)

[0125] 有趣的是把该表达与应用于视网膜的SDM的表达进行比较。第一项与视网膜情况中的尖峰贡献的第一项非常相似，除了对于这种3D汇聚束的情况，有效尖峰间隔减少了3倍。在视网膜情况中，涉及$dT_N(Nt_I)$的第二项则小得多。此时背景温升与峰值温升大小相当。但在汇聚束情况下，背景温升以$(t_p/t_I)^{3/2}$的比率，小得多。这指出了尖峰贡献对HSP的活化或生成和促进蛋白质修复的重要性，因为类似于连续的超声波加热情况中的背景温升与尖峰贡献相比是微不足道的。在脉冲序列结束时，这种低的背景温升甚至通过热扩散而迅速消失。

[0126] 图16和图17示出了，对于脉冲持续时间t_p＝0.5s、脉冲之间的间隔t_I＝10s以及脉冲总数N＝10的条件，对于损伤的和对于HSP的活化或生成的Arrhenius积分的对数大小，作为dT_o的函数。对于脉冲持续时间t_p＝0.5s，脉冲间隔t_I＝10s以及超声脉冲总数N＝10的条件，对于损伤的和对于HSP的活化的Arrhenius积分的对数(方程[12])是根据单个脉冲dT_o的温升(开氏温度)的函数。图16显示含有Arrhenius常数A＝$8.71x10^{33}sec^{-1}$和E＝$3.55x10^{-12}$ergs的损伤的积分的对数。图17显示含有Arrhenius常数A＝$1.24x10^{27}sec^{-1}$和E＝$2.66x10^{-12}$ergs的HSP活化的积分的对数。图16和图17中的曲线图显示在dT_o超过11.3K以前Ω_{damage}不超过1，而Ω_{hsp}在整个显示的时间间隔内大于1，这是细胞修复而没有损伤所需的条件。

[0127] 方程[8]表明，当α＝$0.1cm^{-1}$时，5.8瓦总超声功率可以实现11.5K的dT_o。这是容易实现的。如果α增加2或3倍，那么所得到的功率仍然容易实现。温度上升恒定的区域的体积(即相当于r＝r_d＝$(4Dt_p)^{1/2}$的体积)为0.00064cc。这相当于一个边长为0.86mm的立方体。

[0128] 这个简单的例子说明聚焦超声波可用于通过容易获得的装置来刺激身体深处的修复性HSP：

[0129]

总超声功率:	5.8－17 瓦
脉冲时间	0.5 秒
脉冲间隔	5 秒
序列总时长(N=10)	50 秒

[0130] 为了促进治疗更大的内部体积，可以使用SAPRA系统。

[0131] 脉冲的能量源可以指向身体的外部，其与目标组织相邻，或具有靠近身体外部的表面的血液供应。可选地，可以把装置插入身体的空腔中以把脉冲的能量源应用于目标组织。无论能量源是应用在身体外部还是体内，以及使用何种类型的装置都取决于选择的和用于治疗目标组织的能量源。

[0132] 根据本发明的光刺激可以利用内窥镜(例如气管镜，直肠镜，结肠镜等)有效地传送到身体的内表面区域或组织。它们中的每一个主要由柔性管构成，柔性管本身包含一个或多个内部管。通常，其中一个内部管包括光管或多模光纤，光管或多模光纤把光传导至镜以照亮感兴趣的区域并且使医生能够看到在照亮的端处的东西。另一内部管可以由带电流的电线构成，以使医生能够烧蚀照亮的组织。而另一个内部管可能由活组织检查工具构成，这个工具可以让医生剪掉并抓住任何照亮的组织。

[0133] 在本发明中，这些内部管中的一个用作电磁辐射管，诸如多模光纤，以传送SDM或其他输入到医生抓住端部的镜的电磁辐射脉冲。现在参考图18，光产生单元10，诸如具有所需的波长和/或频率的激光器，用于以可控的脉冲方式产生诸如激光的电磁辐射，电磁辐射通过光管或管12传送到镜14的远端，如图19所示，镜14插入到身体中，而激光或其他辐射16传送到待治疗的目标组织18。

[0134] 现在参考图20，其示出了用于产生电磁能量辐射的系统的示意图，电磁能量辐射例如是激光，包括SDM。该系统总体由标记20表示，包括激光控制台22，例如在优选实施例中的810nm近红外的微脉冲二极管激光器。激光器产生激光束，激光束根据需要穿过光学元件，例如一个或多个光学透镜或掩模24。激光投影仪光学元件24把成形的光束传送到诸如

内窥镜的传送装置26，以便于把激光束光投射到患者的目标组织上。将会理解，标记为26的框可以表示激光束投影仪或传送装置以及观看系统/相机(例如内窥镜)，或者包括使用中的两个不同元件。观看系统/照相机26向显示监视器28提供反馈，显示监视器28还可以包括必要的计算机化硬件、数据输入和控制等，以便于操纵激光器22、光学元件24和/或投影仪/观看部件26。

[0135] 现在参考图21，在一个实施例中，激光束30可以穿过准直透镜32，然后穿过掩模34。在特别优选的实施例中，掩模34包括衍射光栅。掩模/衍射光栅34产生几何对象，或更典型地同时产生的多个激光点或其他几何对象的几何图案。这由标记为36的多束激光表示。可选地，多个激光点可以由多个光纤波导产生。产生激光点的任一方法都允许在非常广泛的治疗域上同时产生非常大量的激光点。事实上，可以同时产生非常大量的、可能数百甚至数千或更多的激光点，以覆盖目标组织的给定区域，或者可能甚至整个目标组织。可能需要同时施加小型分离的激光点应用的宽阵列，就此避免与大型激光点应用有关的某些已知的缺点和治疗风险。

[0136] 使用特征尺寸与所用激光的波长同等水平的光学装置，例如使用衍射光栅，有可能利用量子力学效应，量子力学效应允许对非常大的目标区域同时施加非常大量的激光点。由这种衍射光栅产生的各个斑点都与输入光束具有相似的光学几何结构，同时每个斑点的功率变化最小。结果是具有足够辐射度的多个激光点同时对大的目标区域产生无害而有效的治疗应用。本发明还设想使用由其他衍射光学元件产生的其他几何对象和图案。

[0137] 穿过掩模34的激光发生衍射，产生与掩模34相距一定距离的周期性图案，如图21中标记为36的激光束所示。单个激光束30因此已经形成为数百甚至数千个单独的激光束36，从而产生所需的斑点或其他几何对象的图案。这些激光束36可以穿过附加的透镜38、准直器40等，以便传送激光束并形成所需的图案。这些附加的透镜38、准直器40等可根据需要进一步对激光束36进行转换和重新导向。

[0138] 可以通过控制光学掩模34的形状、间隔和图案来构建任意图案。根据光学工程领域专家的应用需求，可以根据需要任意地创建和修改图案和暴露点。光刻技术，尤其是在半导体制造领域开发的光刻技术，可用于同时创建点或其他对象的几何图案。

[0139] 图22概略地示出了把多个光源耦合到上述生成图案的光学子组件的系统。具体而言，这个系统20’与上面图20中描述的系统20类似。替代系统20’和前述系统20之间的主要区别是包括多个激光控制台，激光控制台的输出各自输入到光纤耦合器42中。光纤耦合器产生单一的输出，如在前面的系统中所述的那样，该输出输入到激光投影仪光学元件24。用本领域中已知的光纤耦合器42实现多个激光控制台22到单个光纤的耦合。其他用于组合多个光源的已知机构也可用，并且可以用来代替本文描述的光纤耦合器。

[0140] 在这个系统20’中，多个光源22遵循如在前面的系统20中所述的那样的类似的路径，即校准、衍射、再校准然后引导到投影仪装置和/或组织。在这个替代系统20’中，衍射元件必须根据通过的光的波长而不同于之前所述地发挥功能，这样得到了稍微变化的图案。该变化与衍射的光源的波长成线性关系。通常，衍射角的差异足够小，使得不同的重叠的图案可以沿着相同光路穿过投影仪装置26而引导至待治疗的组织。

[0141] 由于对于每种波长所得到的图案会略有不同，所以对于每种波长实现完全覆盖的连续偏移(sequential offsetting)将是不同的。这种连续偏移可以在两种模式下完成。在

第一种模式下，所有光的波长是同时应用的而没有相同的覆盖范围。使用偏移操控模式(steering pattern)以实现对多种波长的其中之一的完全覆盖。因此，当选择的波长的光实现对组织的完全覆盖时，其他波长的应用实现了对组织的不完全覆盖或重叠覆盖。第二模式连续地利用适当的操控模式把每个变化波长的光源应用于实现对于该特定波长的组织的完全覆盖。此模式排除了使用多种波长同时治疗的可能性，但允许光学方法为每种波长实现相同的覆盖。这避免了任何光波长的不完全覆盖或重叠覆盖。

[0142] 这些模式也可以混合和匹配。例如，可以同时应用两种波长，一种波长实现完全覆盖，另一种实现不完全覆盖或重叠覆盖，接着继续应用第三种波长并实现完全覆盖。

[0143] 图23概略地示出了本发明的系统20”的另一个替代实施例。这个系统20”通常与图20中描绘的系统20相同地配置。主要区别在于包含调谐到光源的特定波长的多个生成图案的子组件通道。多个激光控制台22平行排列，每个激光控制台22直接引导到其自己的激光投影仪光学元件24。如上面的图21所述，每条通道44a、44b、44c的激光投影仪光学元件包括准直器32、掩模或衍射光栅34和校准器38、40——针对由相应的激光控制台22产生的特定波长进行调谐的全套光学元件。然后把来自每套光学元件24的输出引导至分束器46以便与其他波长组合。本领域技术人员已知，反向使用的分束器可用于把多个光束组合成单个输出。然后从最终分束器46c的组合通道输出被引导通过投影仪装置26。

[0144] 在这个系统20”中，调谐每条通道的光学元件以产生针对该通道的波长准确的指定图案。因此，当所有通道组合并且正确对准时，可以使用单个操控模式来实现对于所有波长的组织的完全覆盖。

[0145] 系统20”可以使用与治疗中使用的光波长一样多的通道(44a、44b、44c等)和分束器(46a、46b、46c等)。

[0146] 系统20”的实现方式可以利用不同的对称性来减少对准约束的数量。例如，所推荐的网格图案在两个维度上是周期性的，并且在两个维度上进行操纵以实现完全覆盖。因此，如果每条通道的图案与指定的图案相同，则每条通道的实际图案无需针对相同的操控模式进行对齐，以实现对所有波长的完全覆盖。每条通道只需要光学对齐即可实现高效组合。

[0147] 在系统20”中，每条通道从光源22开始，就如在其他生成图案的子组件的实施例中那样，光源22可以来自光纤。该光源22指向光学元件24进行准直、衍射、再校准，然后引导到分束器，分束器把通道与主输出组合起来。

[0148] 应该理解的是，图20-23中所示的激光产生系统是示例性的。可以使用其他装置和系统产生SDM的激光源，SDM的激光源通常以具有光管等的内窥镜的形式可以功能性穿过到投影仪装置。也可以产生和使用其他形式的电磁辐射，包括紫外波、微波、其他射频波和预设波长的激光。此外，还可以产生和使用超声波以在目标组织中产生足以在目标组织细胞中活化或生成的热休克蛋白而不损伤目标组织自身的热时间过程温度尖峰。为了这样做，通常提供超声波或电磁辐射能量的脉冲源，并以提高目标组织温度的方式应用于目标组织，例如短暂地提高6℃至11℃，而长期地，例如数分钟内，仅仅提高6℃或1℃或更低。

[0149] 对于不在内孔附近的深层组织，光管不是传送脉冲的能量的有效装置。在那种情况下，可以使用脉冲的低频电磁能或优选的脉冲的超声波来在目标组织中引起一系列的温度尖峰。

[0150] 因此，根据本发明，把脉冲的超声波或电磁辐射源应用于目标组织，以刺激HSP的

生成或活化并促进活体动物组织中的蛋白质修复。通常，电磁辐射可以是紫外波、微波、其他射频波、预设波长的激光等等。另一方面，如果把电磁能用于远离天然孔的深层组织目标，则根据目标组织的深度，吸收长度把波长限制为微波或射频波的波长。然而，对于远离天然孔的深层组织目标，超声波是长波长的电磁辐射的首选。

[0151] 超声波或电磁辐射是脉冲的，以在组织中产生热时间过程，该热时间过程刺激HSP的生成或活化并促进蛋白质修复而不引起被治疗的细胞和组织的损伤。还控制和最小化被治疗的组织的区域和/或体积，以使得温度尖峰在几度的数量级上，例如大约10℃，同时保持长期温升低于FDA规定的极限，如1℃。已经发现，如果治疗过大的组织区域或体积，组织中升高的温度不能足够快地扩散以满足FDA要求。然而，限制被治疗组织的区域和/或体积以及创建脉冲的能量源实现了本发明的目的，即通过加热或以其他方式加压细胞和组织来刺激HSP的生成或活化，同时使得被治疗细胞和组织产生的任意多余热量消散在可接受的范围内。

[0152] 相信根据本发明刺激HSP的生成可以有效地用于治疗各种组织异常、疾病、甚至感染。例如，引起感冒的病毒主要影响鼻道和鼻咽部呼吸道上皮细胞的小端口。与视网膜相似，呼吸道上皮细胞是薄而清晰的组织。参考图24，其示出了人体头部48的剖视图，其中内窥镜14插入到鼻腔50中，并且把能量16(例如激光等)引导到在鼻腔50内待治疗的组织18。待治疗的组织18可以在鼻腔50内，包括鼻道和鼻咽。

[0153] 为了保证激光能量或其他能量源的吸收，可以把波长调整为水的红外(IR)吸收峰值，或者可以使用佐剂染料作为光敏剂。在这种情况下，治疗将由饮用或局部施用佐剂，等待数分钟以使佐剂渗透表面组织，以及把激光或其它能量源16例如通过内窥镜14中的光纤施用于目标组织18持续几秒钟所构成，如图24所示。为了为患者提供舒适，可以在施用局部麻醉剂之后插入内窥镜14。如有必要，这个过手术可以定期重复，例如一天左右。

[0154] 该治疗将会刺激热休克蛋白的活化或生成并促进蛋白质修复而不损伤正被治疗的细胞和组织。如以上讨论，已经发现某些热休克蛋白在目标细胞和组织的免疫反应以及健康中发挥重要作用。能量源可以是单色激光，例如810nm波长的激光，以之前引用的专利申请中描述的类似方式，但是通过内窥镜等进行施用，如图24所示。将会选择佐剂染料以增加激光吸收。尽管这包括执行本发明的特别优选的方法和实施例，但是应该理解，根据本发明可以使用其他类型的能量和传送装置来实现相同的目标。

[0155] 现在参考图25，对于流感病毒而言存在类似的情况，其中主要目标是上呼吸道的上皮细胞，其在某段的直径大于约3.3mm，即上呼吸道的上六代(the upper six generations)。薄粘液层把目标上皮细胞与气道腔分开，并且在该层中发生抗原-抗体相互作用，导致病毒失活。

[0156] 继续参考图25，气管镜14的柔性光管12通过喉部和气管54插入个人的口腔52并进入呼吸道的支气管56。在那里施用激光或其它能量的源16并传送到该区域中最上部分的组织，从而以之前图24所述的相同方式治疗组织和区域。设想选择激光或其他能量的波长，以便与驻留在粘液(mucous)的水的IR吸收峰匹配，以加热组织并刺激HSP的活化或生成并促进蛋白质修复，还有伴随的益处。

[0157] 现在参考图26，结肠镜14可以具有插入肛门和直肠58并进入大肠60或小肠62的柔性光管12，以便把所选择的激光或其他能量源16传送到待治疗的区域和组织，如图所示。这

可以用来帮助治疗结肠癌以及其他胃肠道问题。

[0158] 通常，该手术可以类似于结肠镜检查来进行，其中对肠清除所有的粪便，而患者(他/她)将侧卧，并且医生把结肠镜14的细长的光管部分12插入直肠并把其移动到结肠、大肠60或小肠64的区域以到达待治疗的区域。医生可以通过显示屏观察插入的柔性构件12的路径并且甚至观察肠内的结肠镜14的末端处的组织，以便观察待治疗的区域。使用其他光纤或光管中的一个，引导镜的末端64至待治疗的组织，并且通过结肠镜14的光管之一将激光或其他辐射的源16投递到治疗待治疗的组织区域，如上所述，以刺激该组织18中的HSP的活化或生成。

[0159] 现在参考图27，可以有利地使用本发明的另一个例子，通常称为“泄漏肠道”综合症，该综合症以胃肠道(GI tract)的炎症和其他代谢功能失调为特征。由于胃肠道易发生与视网膜相似的代谢功能失调，因此预计其将会对本发明的治疗反应良好。这可以如之前讨论的那样，通过亚阈值的二极管微脉冲激光(SDM)治疗，或者通过本文讨论的和本领域已知的其他能量源和装置来完成。

[0160] 继续参考图27，内窥镜等的柔性光管12通过喉部和气管区域54插入患者口腔52并进入胃66，在那里它的末端或端部64引导至待治疗的组织18，而把激光或其它能量的源16引导至组织18。本领域技术人员将会理解，也可以使用结肠镜并通过直肠58并进入胃66或胃和直肠之间的任何组织。

[0161] 如果需要，可以把发色团颜料口服投递至胃肠道组织，以使其能够吸收辐射。例如，如果使用来自激光二极管或LED的未聚焦的810nm辐射，则颜料在810nm处或附近具有吸收峰值。可选地，可以把能量源的波长调节为水的吸收峰处的稍长的波长，从而不需要外加的发色团。

[0162] 本发明还设想了一种胶囊内窥镜68，例如图28所示，可用于施用根据本发明的辐射和能量源。这种胶囊尺寸相对较小，例如大约一英寸长，以便被患者吞咽。当胶囊或药丸68被吞咽而进入胃并通过胃肠道时，当在适当的位置时，胶囊或药丸68可以接收功率和信号(例如通过天线70)，以活化能量源72(诸如激光二极管和相关电路)，用合适的透镜74把生成的激光或辐射通过对辐射透明的盖76聚焦到待治疗的组织上。应该理解的是，胶囊内窥镜68的位置可以通过各种方式来确定，例如外部成像、信号跟踪或者甚至借助具有灯的微型照相机，医生通过该方式可以观察药丸或胶囊68正在通过的胃肠道的图像。胶囊或药丸68可以通过其自身的能源(例如借助于电池)供能，或者可以通过天线外部供能，以使得激光二极管72或其他能量产生源产生所需的波长和脉冲的能量源，以治疗待治疗的组织和区域。

[0163] 如同在以前的申请中治疗视网膜一样，辐射将是脉冲的，以利用微脉冲温度尖峰和相关的安全性，并且可以调整功率，以使得该治疗对组织完全无害。这可能涉及调整峰值功率、脉冲时间和重复频率，以提供约为10℃左右的尖峰温升，同时保持长期温升低于FDA规定的1℃的极限。如果使用药丸68的投递形式，则该装置可以由小型可充电电池供电或通过无线感应激励等来供电。受热/压力的组织将刺激HSP的活化或生成并促进蛋白质修复，还有伴随的益处。

[0164] 从上述示例中，本发明的技术限于在身体的表面或内表面附近的通过光纤或其他光学传送装置容易触及的情况的治疗。施用SDM以活化HSP活性限于身体的表面附近或光学

可触及区域的原因是IR或可见辐射在体内的吸收长度非常短。然而，存在使得在组织或身体内更深处的症状，其可从本发明获益。因此，本发明设想使用在身体组织中具有相对较长吸收长度的超声波和/或射频(RF)以及波长甚至更短的电磁(EM)辐射，例如微波。为了活化表面SDM等不可触及的异常组织中的补救性HSP的活性，使用脉冲的超声波优于使用RF电磁辐射。脉冲的超声源也可用于表面或表面附近的异常。

[0165] 现在参考图29，利用超声波，可以通过使用一个或多个各自聚焦在目标部位上的束来具体地针对身体深处的具体区域。从而，脉冲的加热将主要仅在束聚焦和重叠的目标区域上。

[0166] 如图29所示，超声波换能器78等产生多个超声波束80，所述多个超声波束80通过声阻抗匹配凝胶与皮肤耦合，并且穿过皮肤82再穿过束80的焦点前方的未受损伤的组织而到达目标器官84，例如所示的肝脏，并且具体地到超声波束80聚焦的待治疗目标组织86。如上所述，脉冲的加热将仅在聚焦光束80重叠的作为目标的聚焦区域86处。聚焦区域86之前和之后的组织不会受到明显的加热或影响。

[0167] 本发明不仅设想治疗表面或表面附近的组织(例如使用激光等)，治疗深层组织(使用例如聚焦的超声波束等)，而且还设想治疗理血液疾病(例如败血症)。如上所述，聚焦的超声波治疗既可用于身体表面以及深部身体组织，也可应用于这种治疗血液的情况。然而，也可以设想，通常局限于上皮细胞等的表面或表面附近的治疗等的SDM和类似的治疗选择，可用于可通过相对较薄的组织层(例如耳垂)触及的区域的血液疾病的治疗。

[0168] 现在参考图30和31，血液病症的治疗仅需要把SDM或其他电磁辐射或超声波脉冲传送至耳垂88，其中SDM或其它能量的辐射源可穿过耳垂组织并进入流过耳垂的血液。可以理解的是，这种方法也可以发生在血流相对较高和/或靠近组织表面的身体的其他区域，例如指尖、口腔或喉咙内等处。

[0169] 再次参考图30和31，其显示耳垂88与配置为传送SDM辐射等的紧固装置90相邻。这例如可以通过一个或多个激光二极管92来实现，该激光二极管92把所需的脉冲和脉冲序列的所需频率传送到耳垂88。例如可以通过灯驱动器94来提供能源。可选地，灯驱动器94可以是实际的激光源，其能够通过适当的光学元件和电子元件传送到耳垂88。紧固装置90将仅用于夹紧到患者的耳垂上并且导致辐射被约束于患者的耳垂88。这可以通过镜子、反射器、扩散器等来实现。这可以通过控制计算机96来控制，该控制计算机96将通过键盘98等来操作。如果需要的话，例如，如果这个手术将由距离患者一定距离的操作者执行，则系统还可以包括显示器和扬声器100。

[0170] 所建议的使用电磁脉冲或超声波脉冲序列的治疗与包含单个短的或持续的(长的)脉冲的早期治疗相比，具有两个主要优点。首先，序列中短的(优选为亚秒的)单独的脉冲活化了细胞复位机制，如HSP活化，使得反应速率常数大于在更长(分钟或小时)程度时间的操作时的反应速率常数。其次，治疗中的重复的脉冲提供了大量的热尖峰(数量级为10,000)，这使得细胞的修复系统能够更快地越过活化能垒，该活化能垒把功能失调的细胞状态和所需的功能状态区分开。最终结果是“更低的处理阈值”，意思是可以使用较低的平均施用功率和总施用能量来实现所需的治疗目标。

[0171] 尽管为了说明的目的已经详细描述了几个实施例，但是可以在不脱离本发明的范围和精神的情况下进行各种修改。因此，除了所附权利要求之外，本发明不受限制。

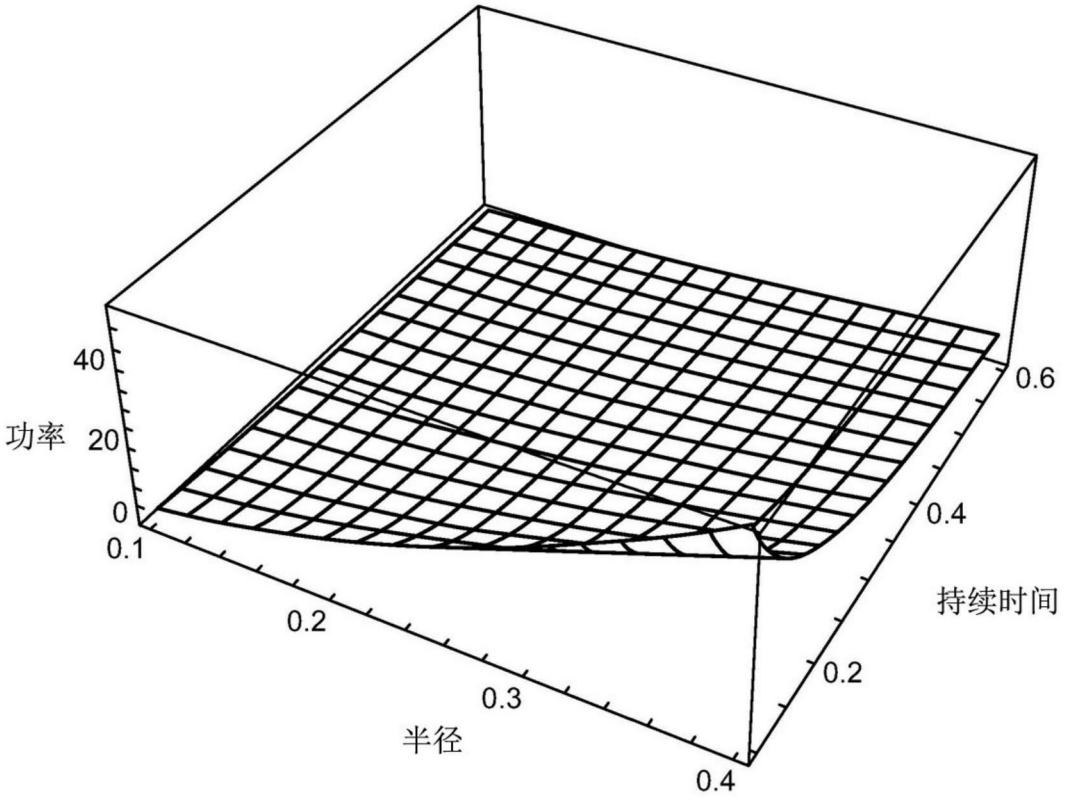


图1A

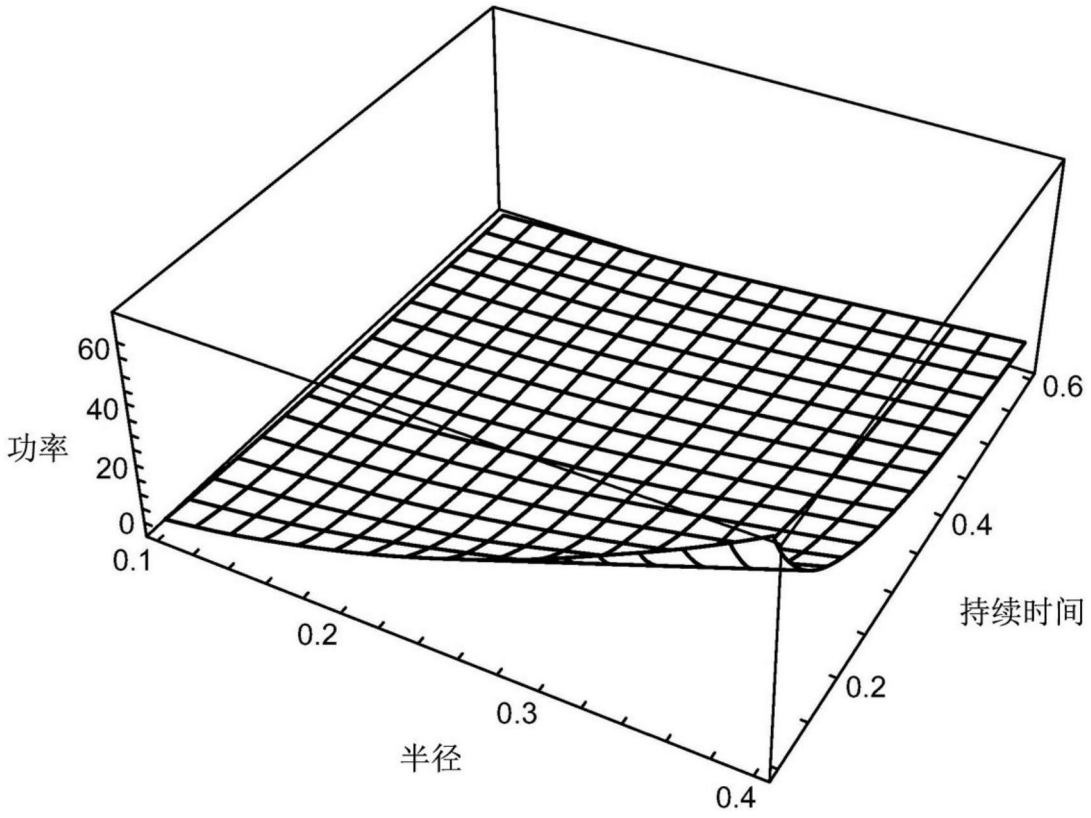

60
40
20
0
功率
0.1
0.2
0.3
半径
0.4
0.2
0.4
0.6
持续时间

图1B

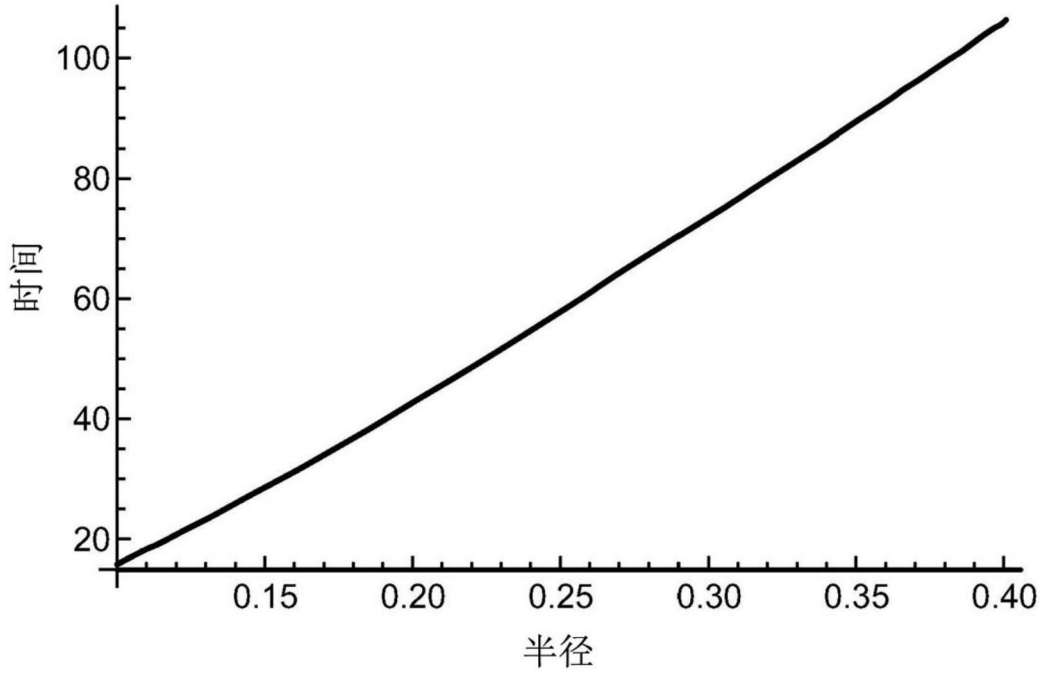

100
80
60
40
20
时间
0.15
0.20
0.25
0.30
0.35
0.40
半径

图2A

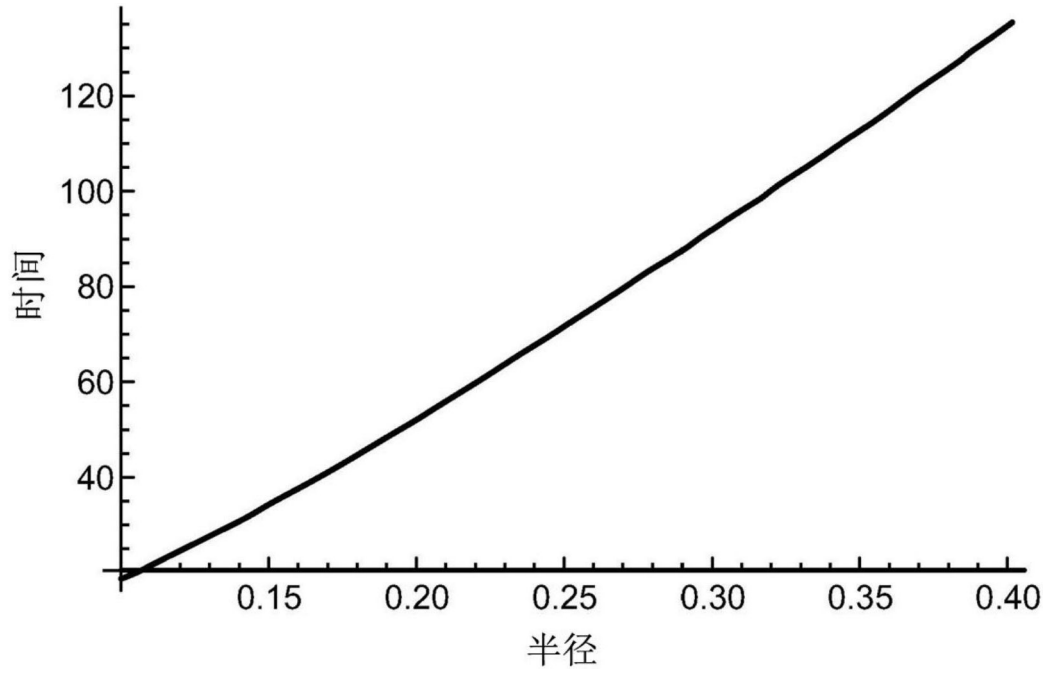

120
100
80
60
40
时间
0.15
0.20
0.25
0.30
0.35
0.40
半径

图2B

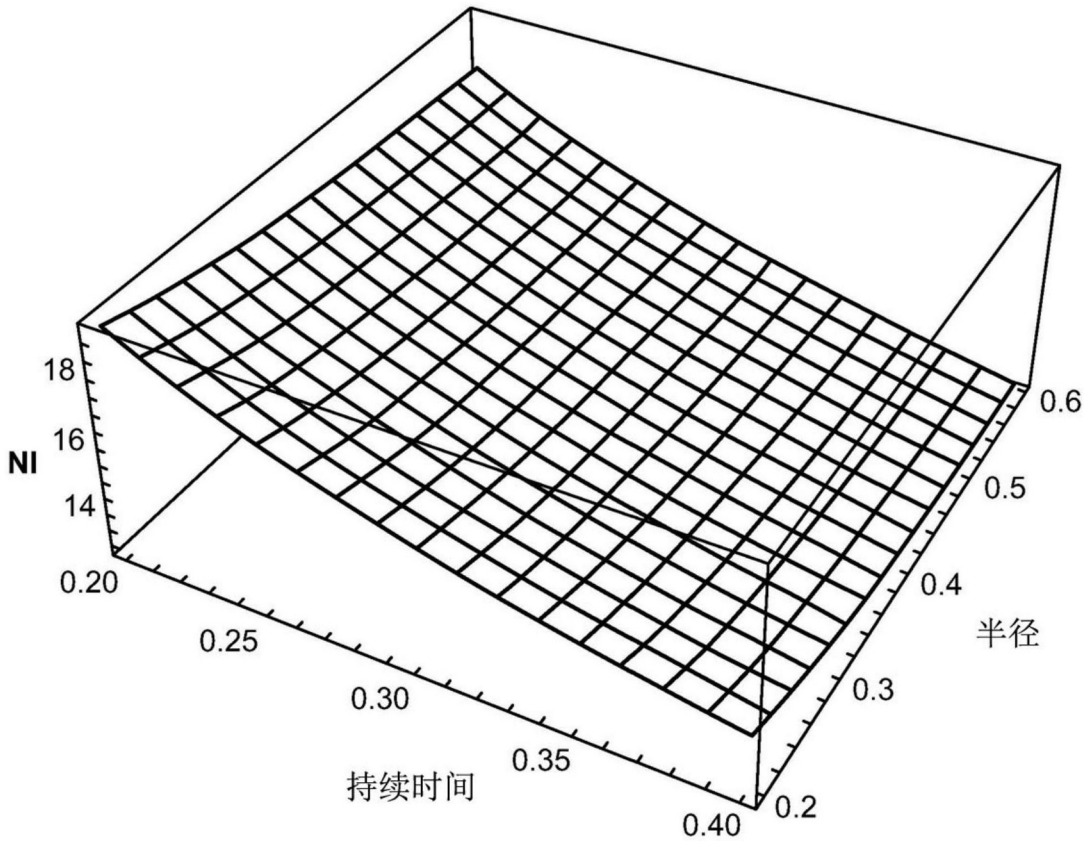

18
16
14
NI
0.20
0.25
0.30
0.35
0.40
持续时间
0.2
0.3
0.4
0.5
0.6
半径

图3

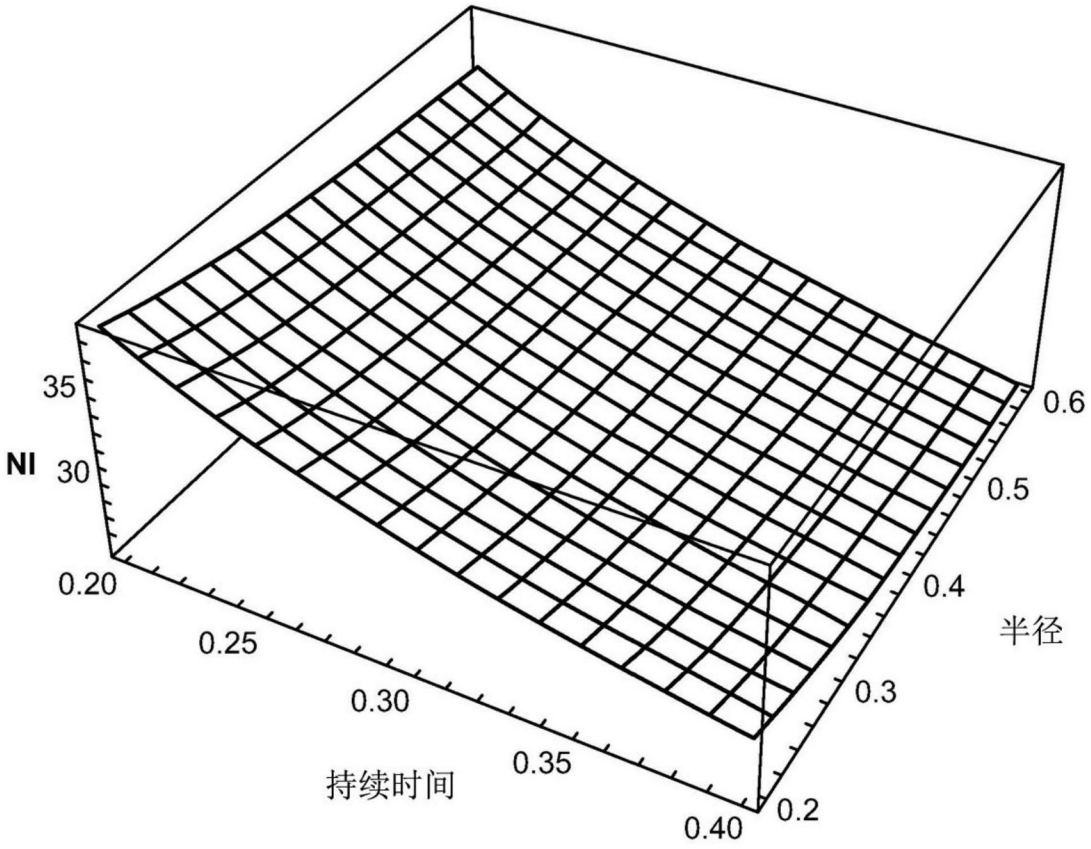


图4

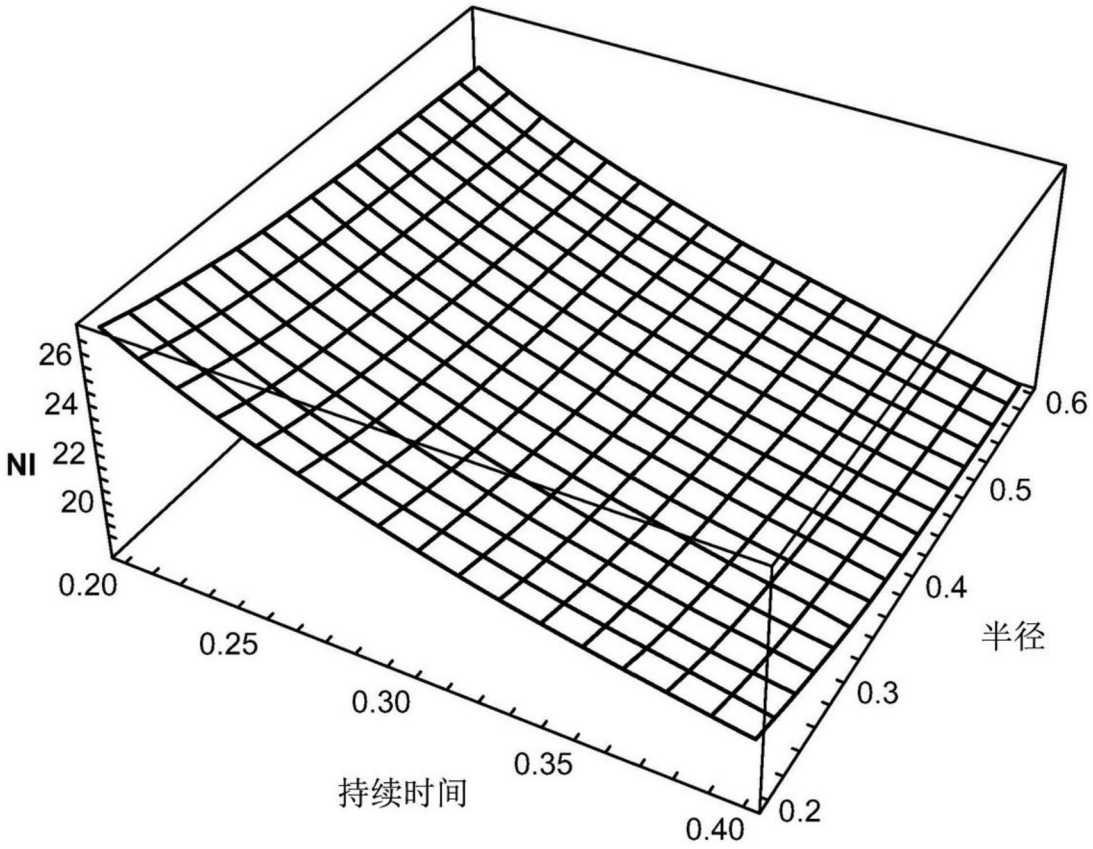


图5

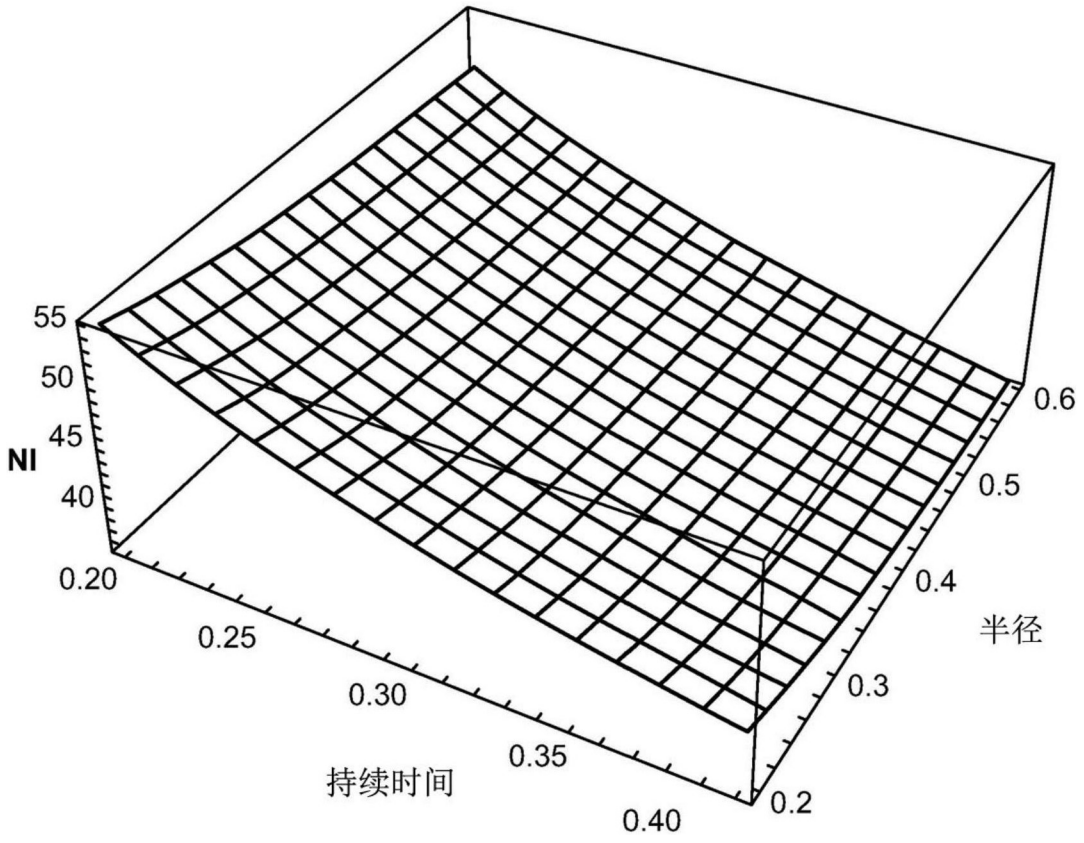

55
50
45
NI
40
0.20
0.25
0.30
0.35
0.40
持续时间
0.2
0.3
0.4
0.5
0.6
半径

图6

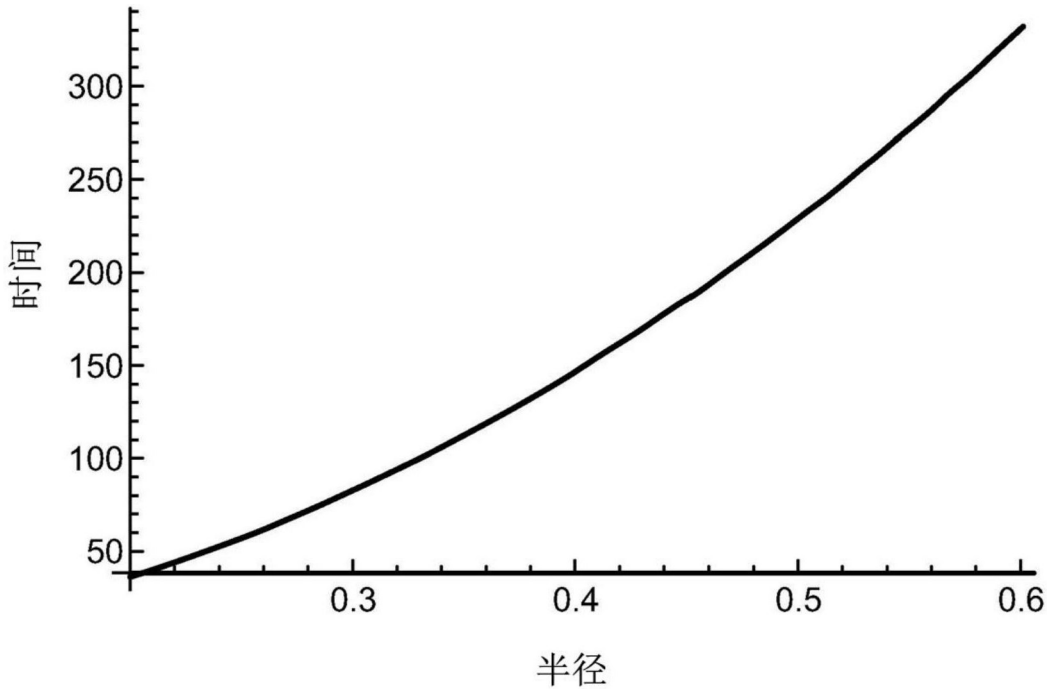

300
250
200
150
100
50
时间
0.3
0.4
0.5
0.6
半径

图7

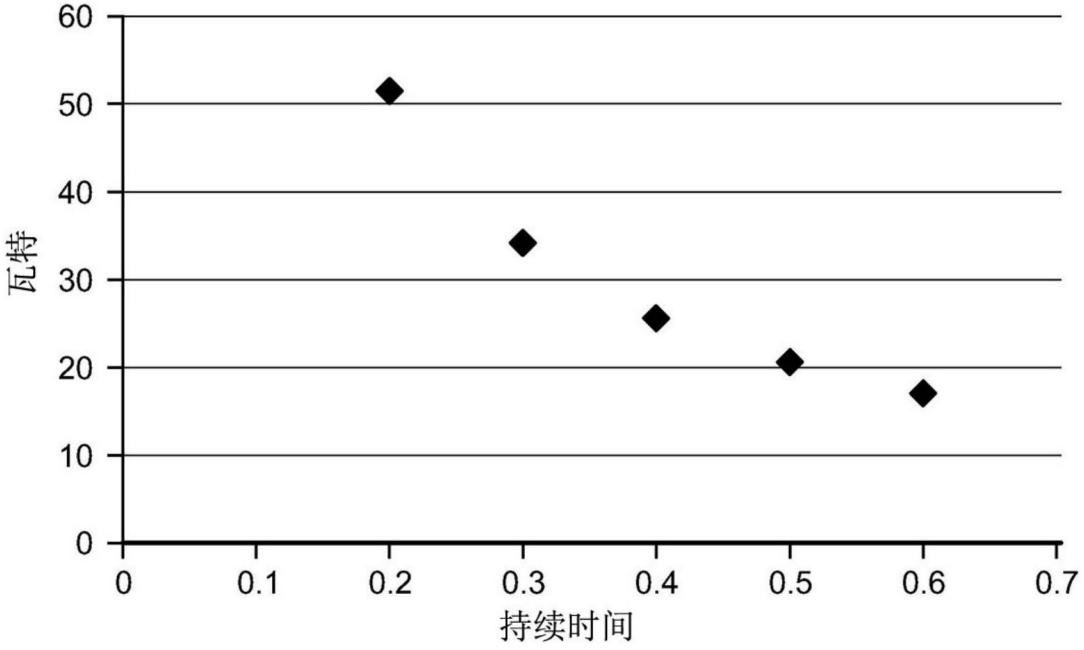

60
50
40
30
20
10
0
瓦特
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
持续时间

图8

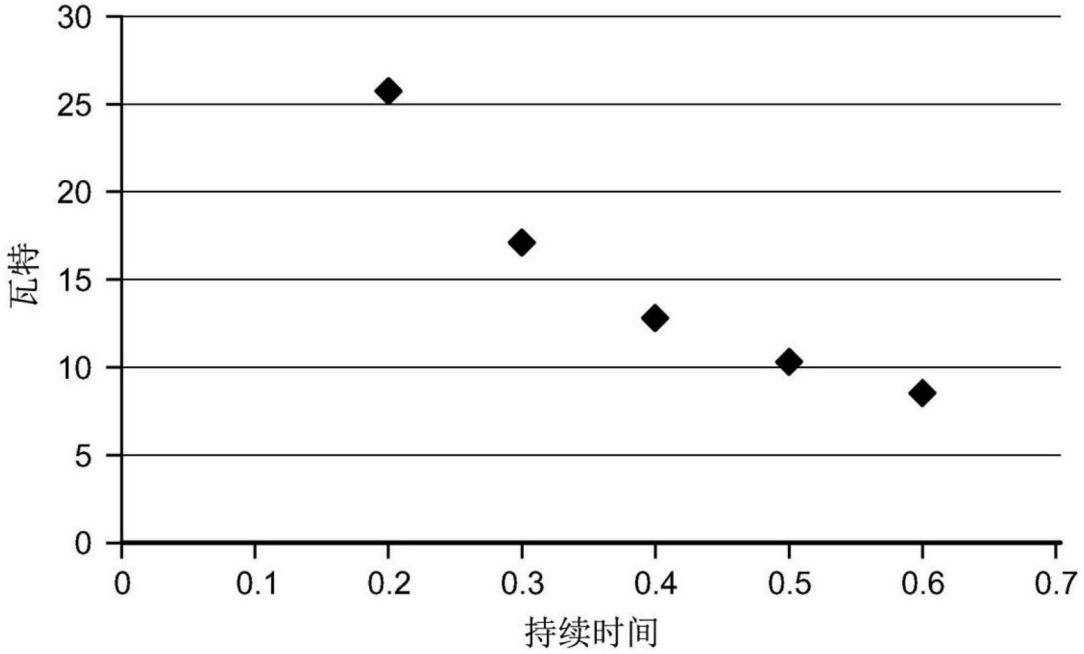

30
25
20
15
10
5
0
瓦特
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
持续时间

图9

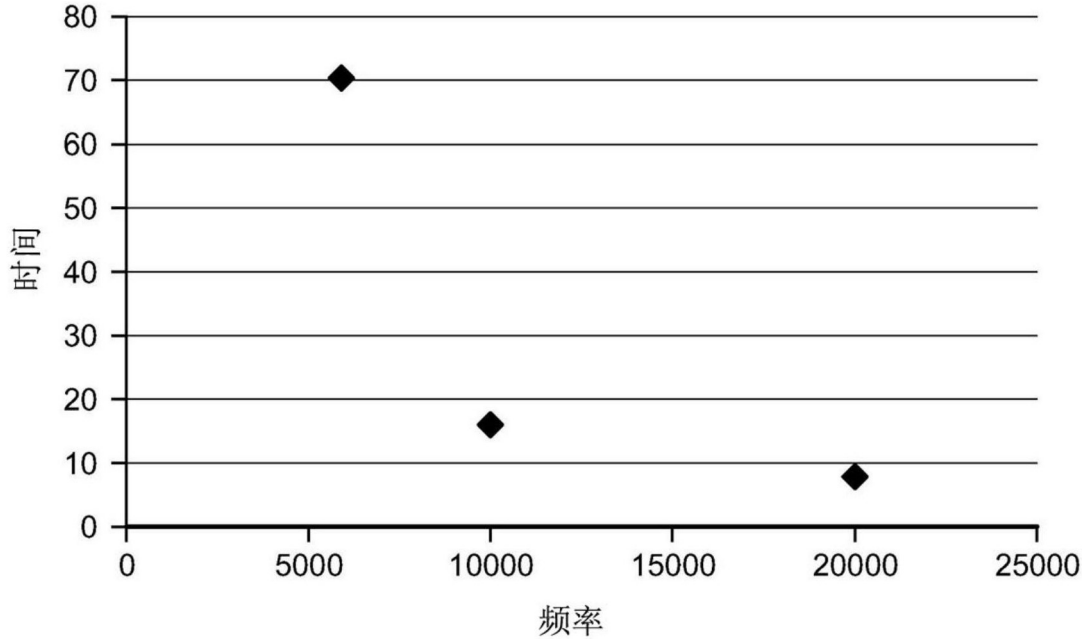

80
70
60
50
40
30
20
10
0
时间
0
5000
10000
15000
20000
25000
频率

图10

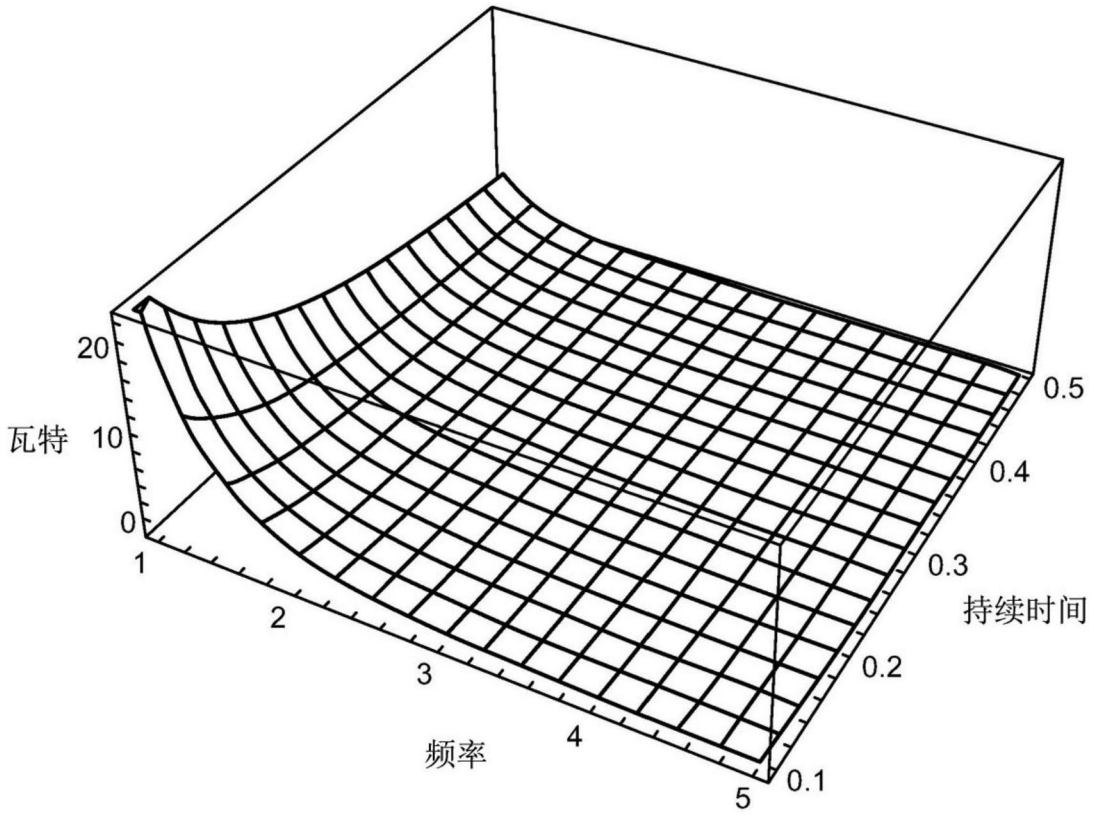

20
瓦特
10
0
1
2
3
4
5
频率
0.5
0.4
0.3
0.2
0.1
持续时间

图11

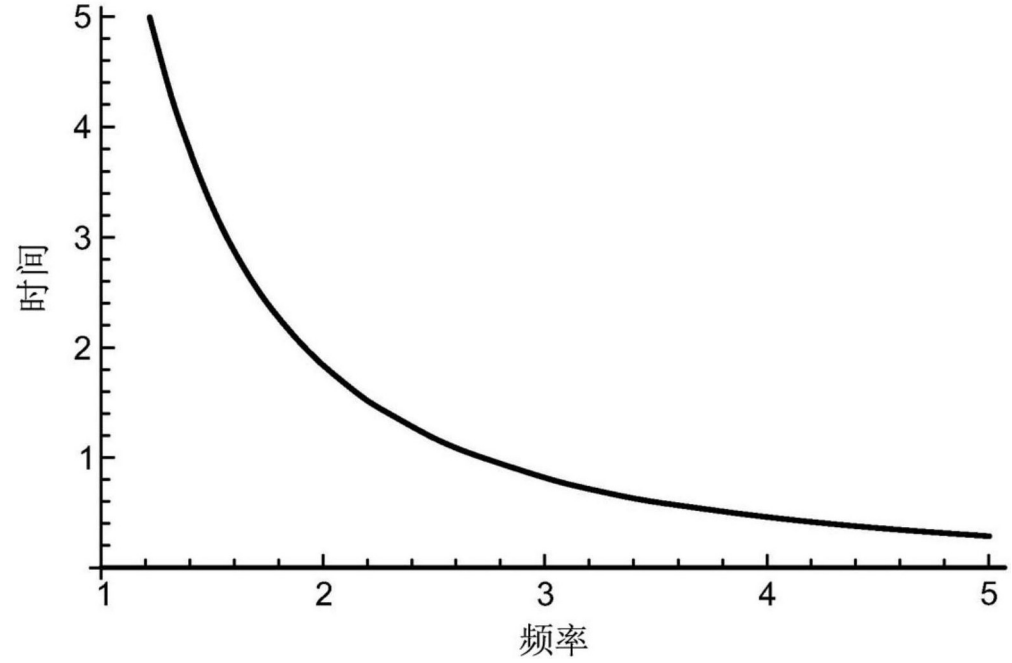


图12

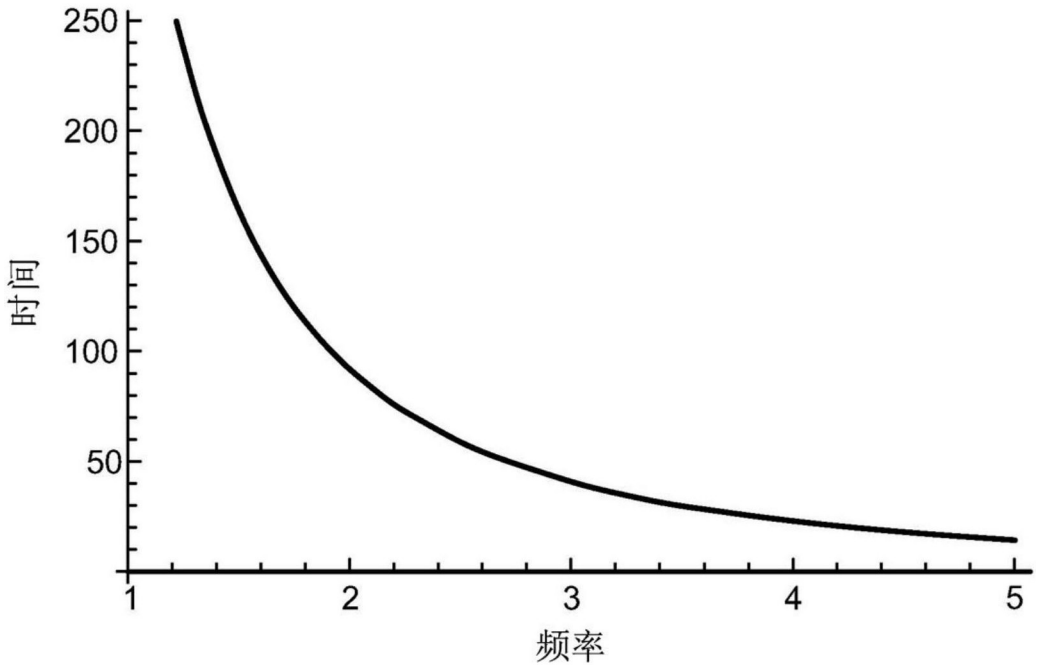


图13

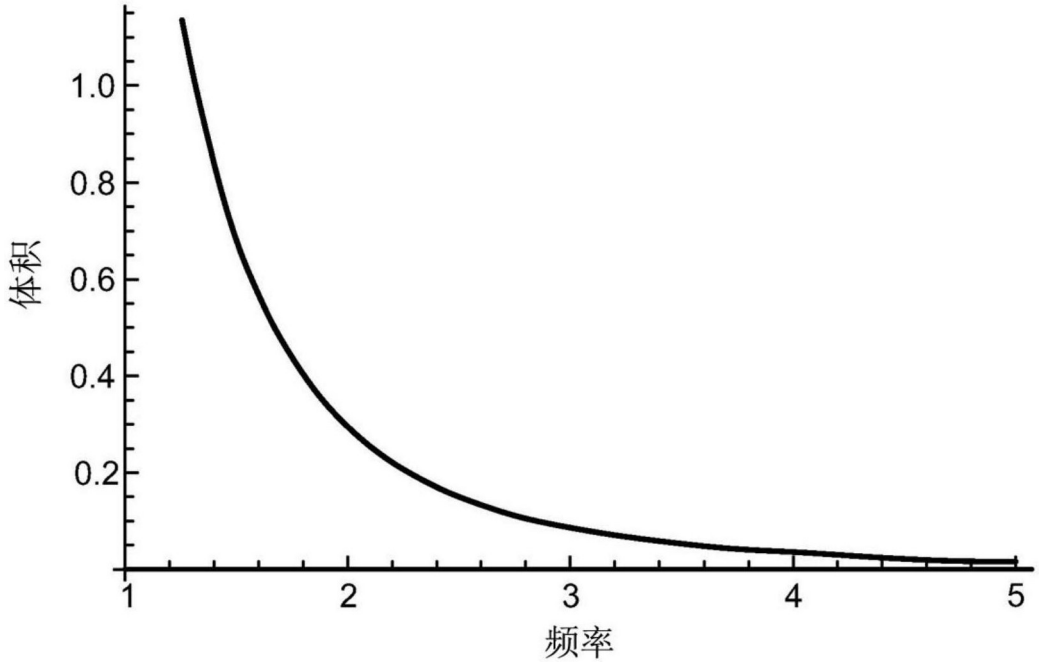


图14

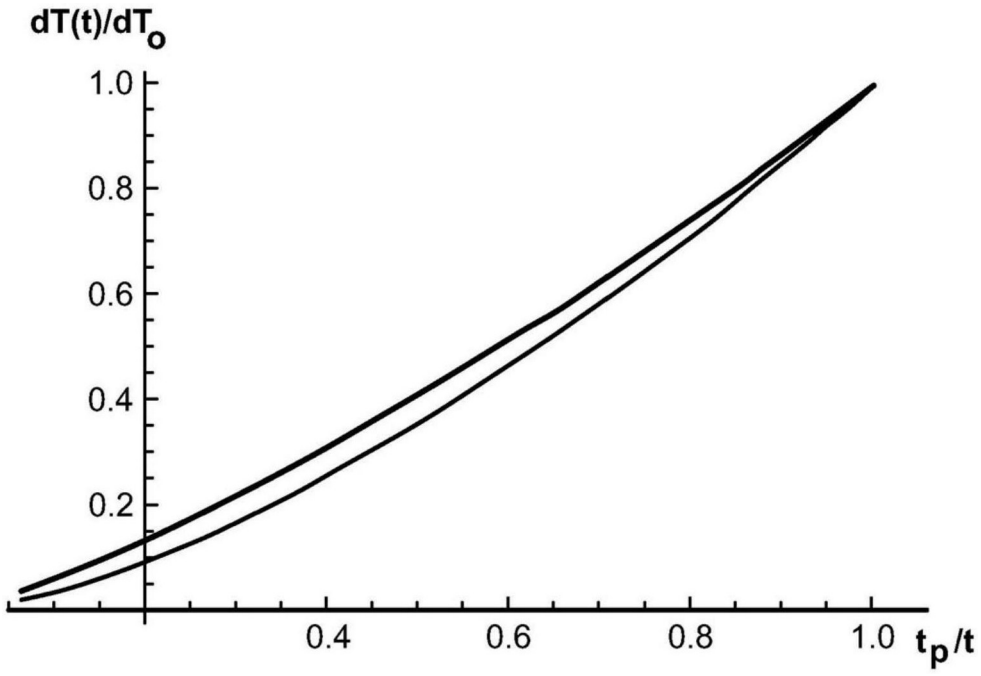


图15

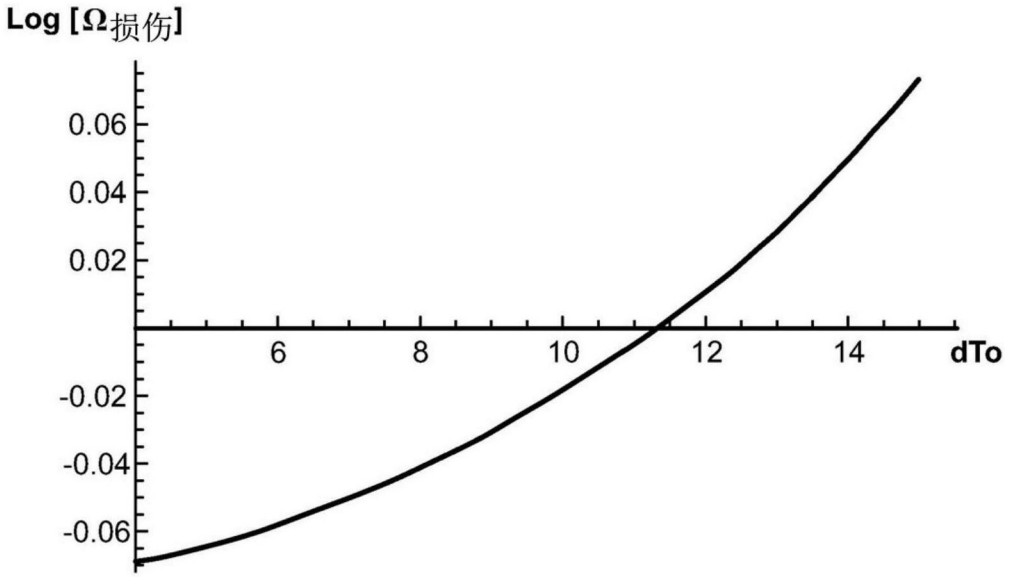

Log [Ω损伤]
0.06
0.04
0.02
-0.02
-0.04
-0.06
6
8
10
12
14
dTo

图16

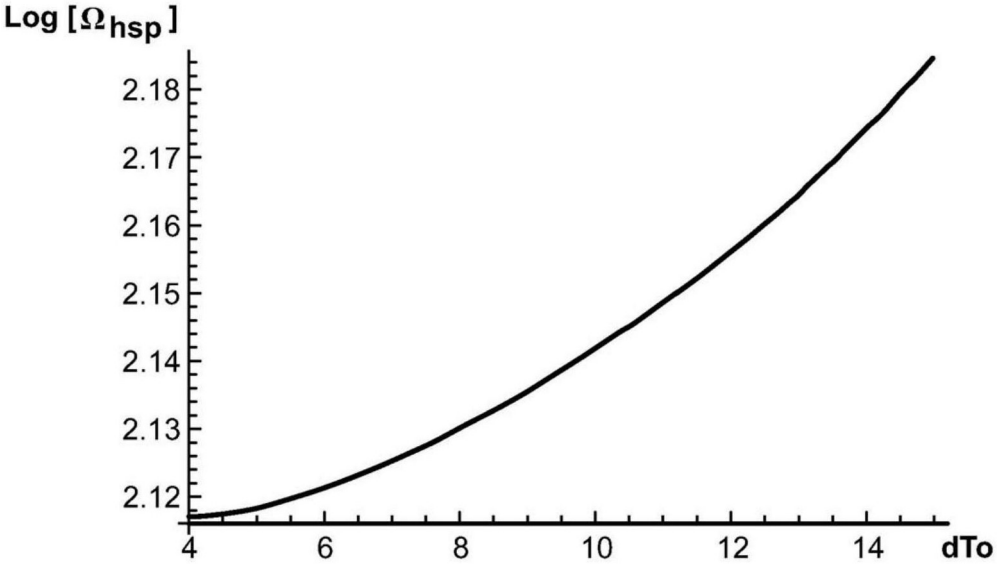

Log [Ωhsp]
2.18
2.17
2.16
2.15
2.14
2.13
2.12
4
6
8
10
12
14
dTo

图17

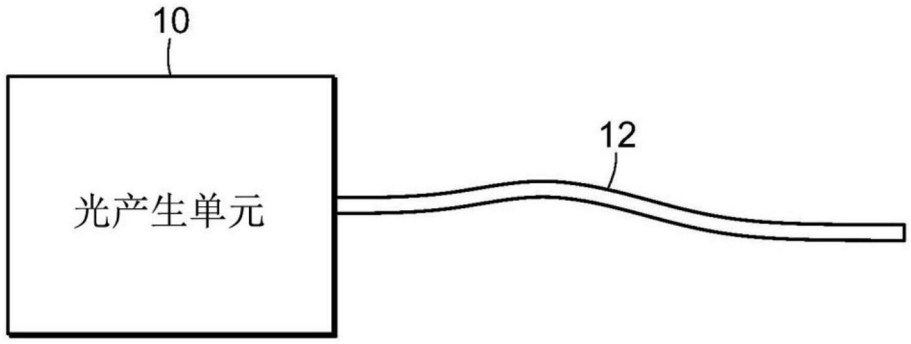


图18

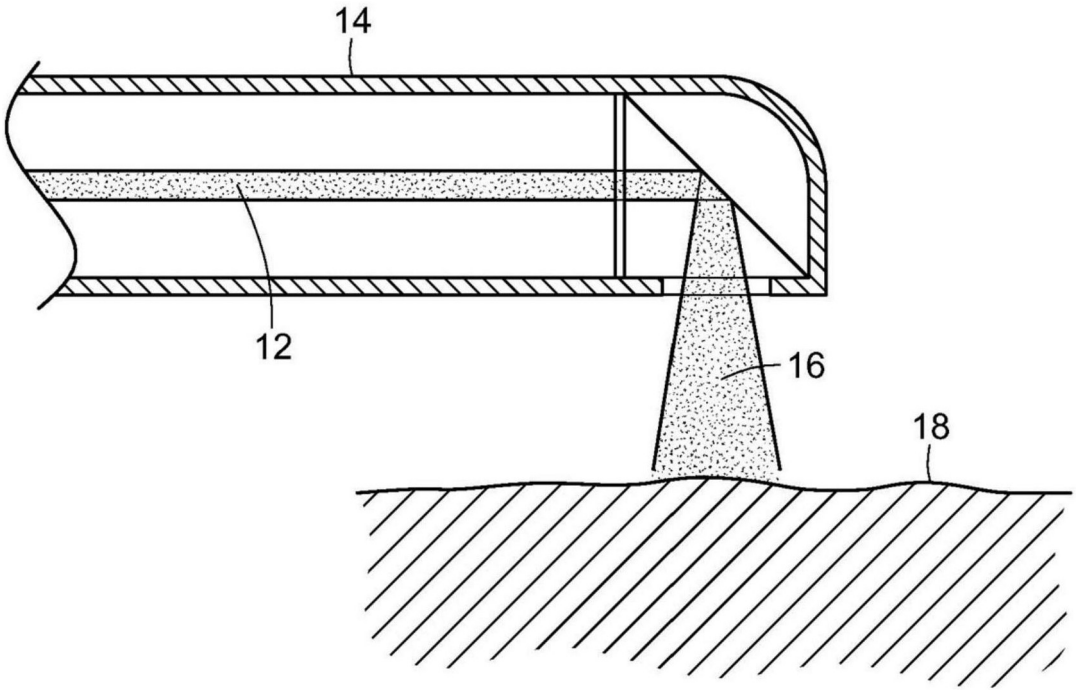


图19

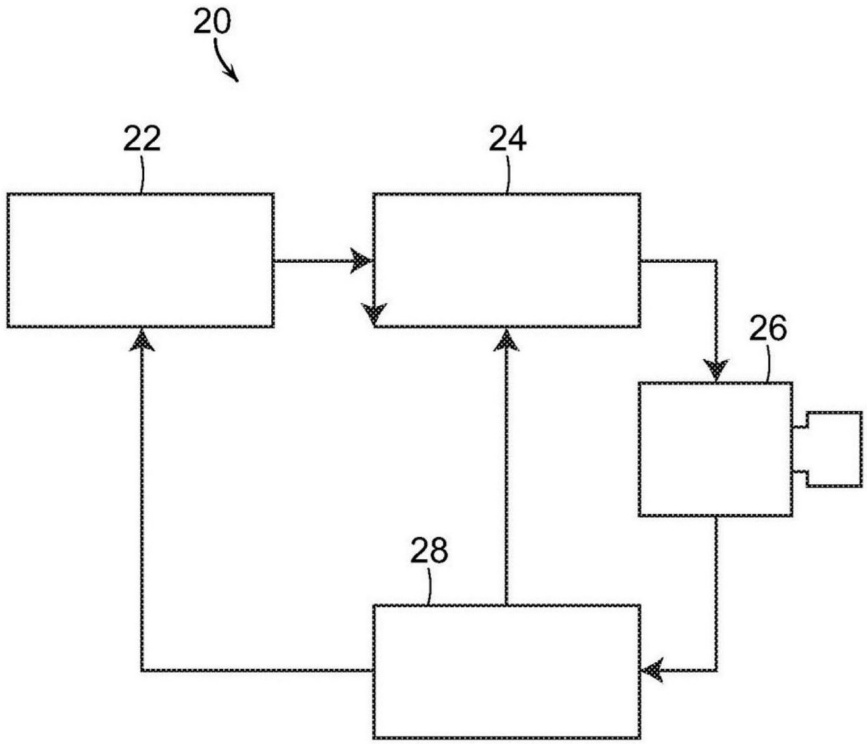


图20

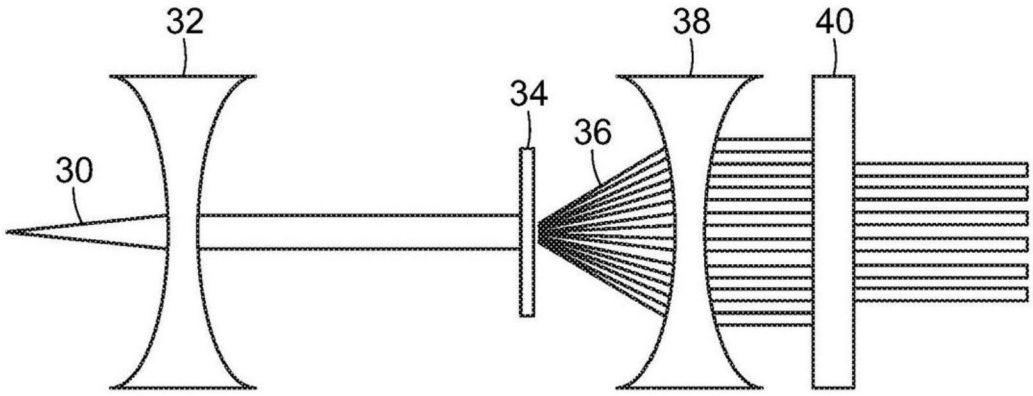


图21

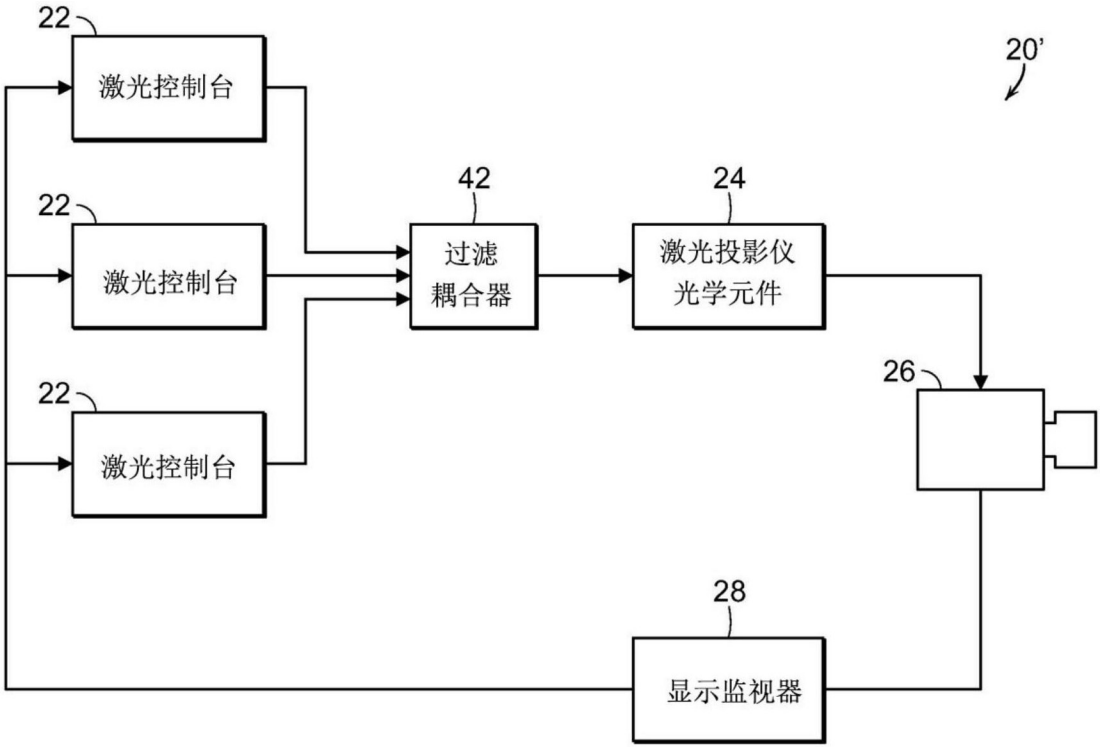

22
激光控制台
22
激光控制台
22
激光控制台
42
过滤
耦合器
24
激光投影仪
光学元件
20'
26
28
显示监视器

图22

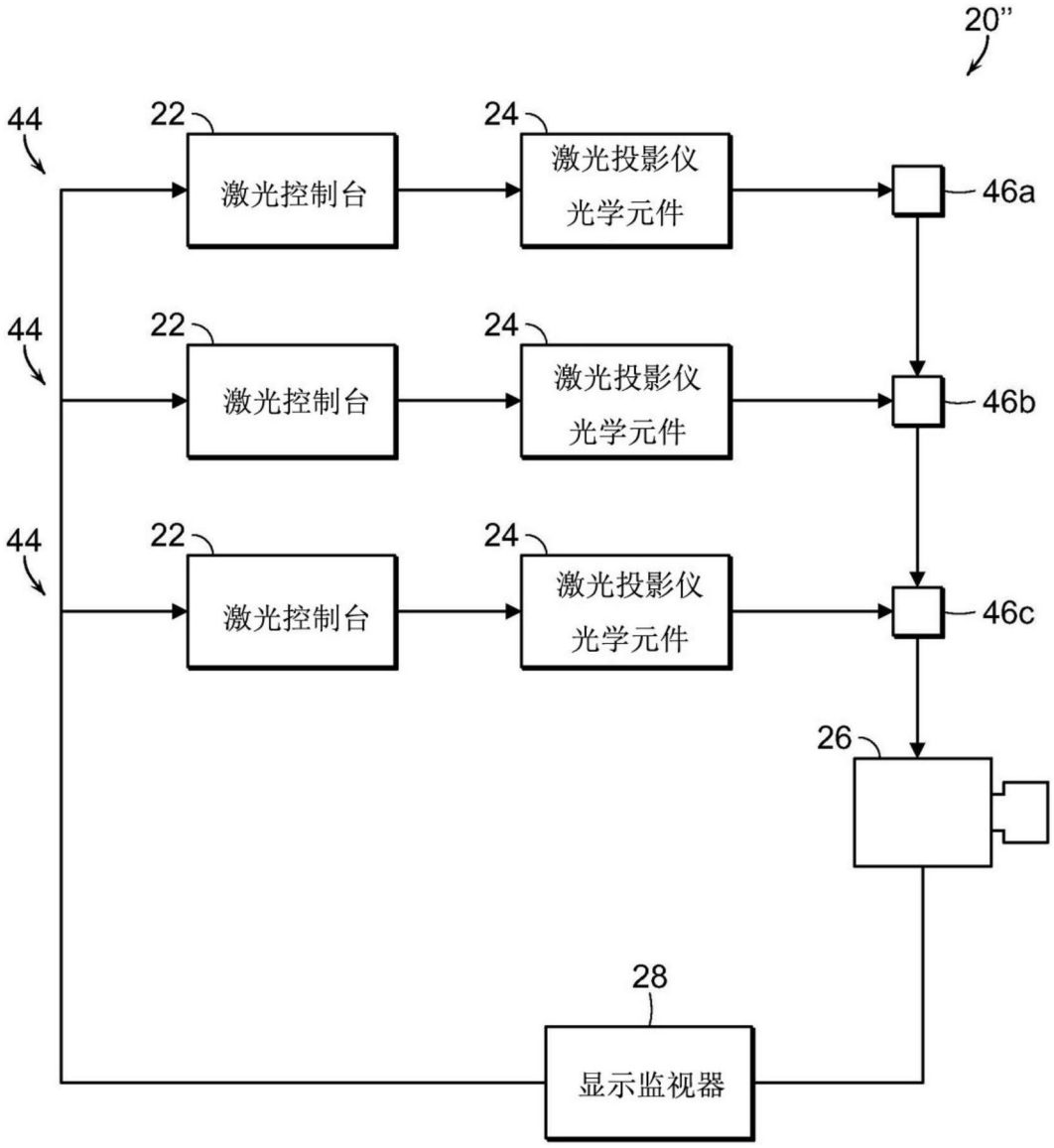

20"
44
22
激光控制台
24
激光投影仪
光学元件
46a
44
22
激光控制台
24
激光投影仪
光学元件
46b
44
22
激光控制台
24
激光投影仪
光学元件
46c
26
28
显示监视器

图23

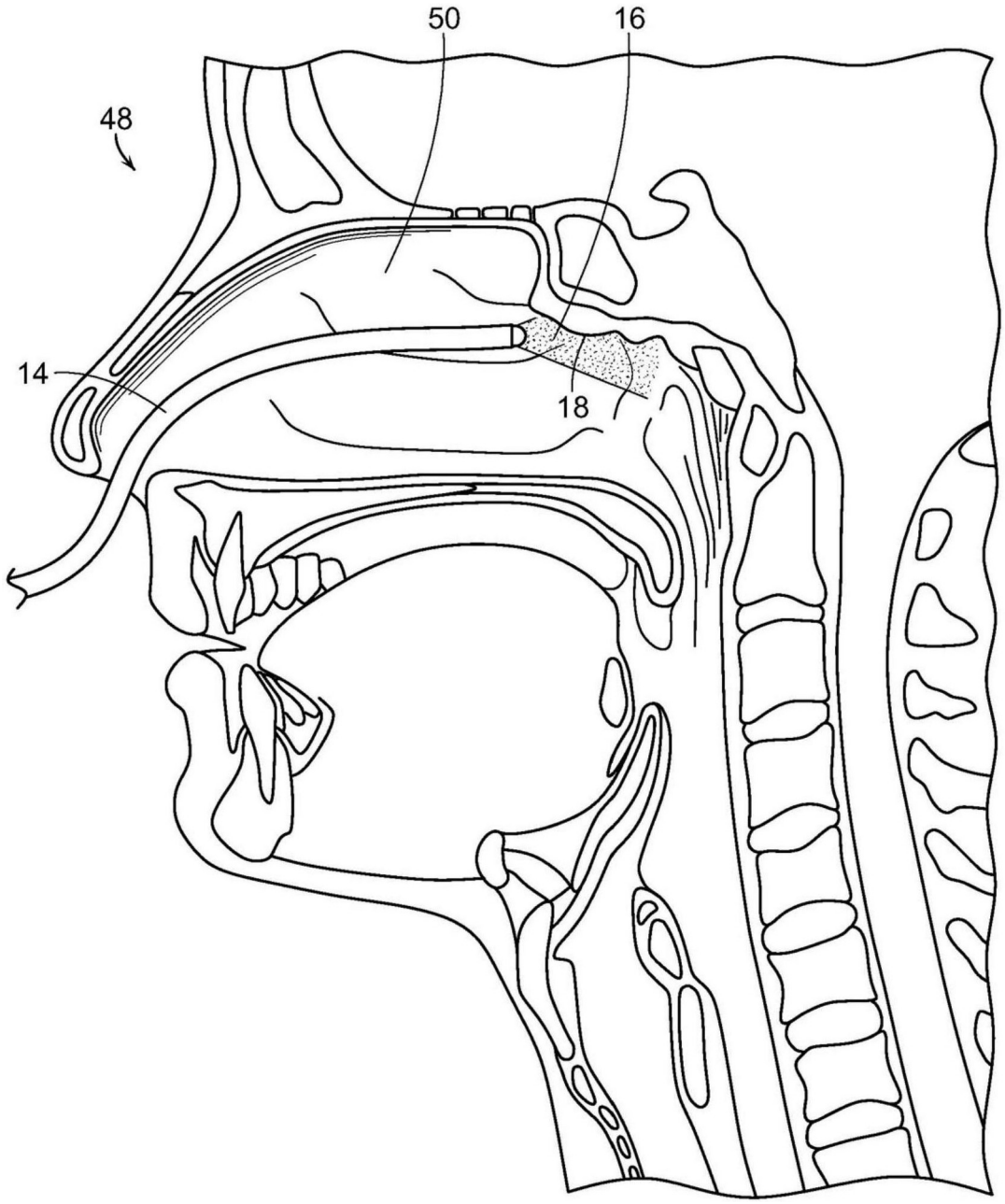


图24

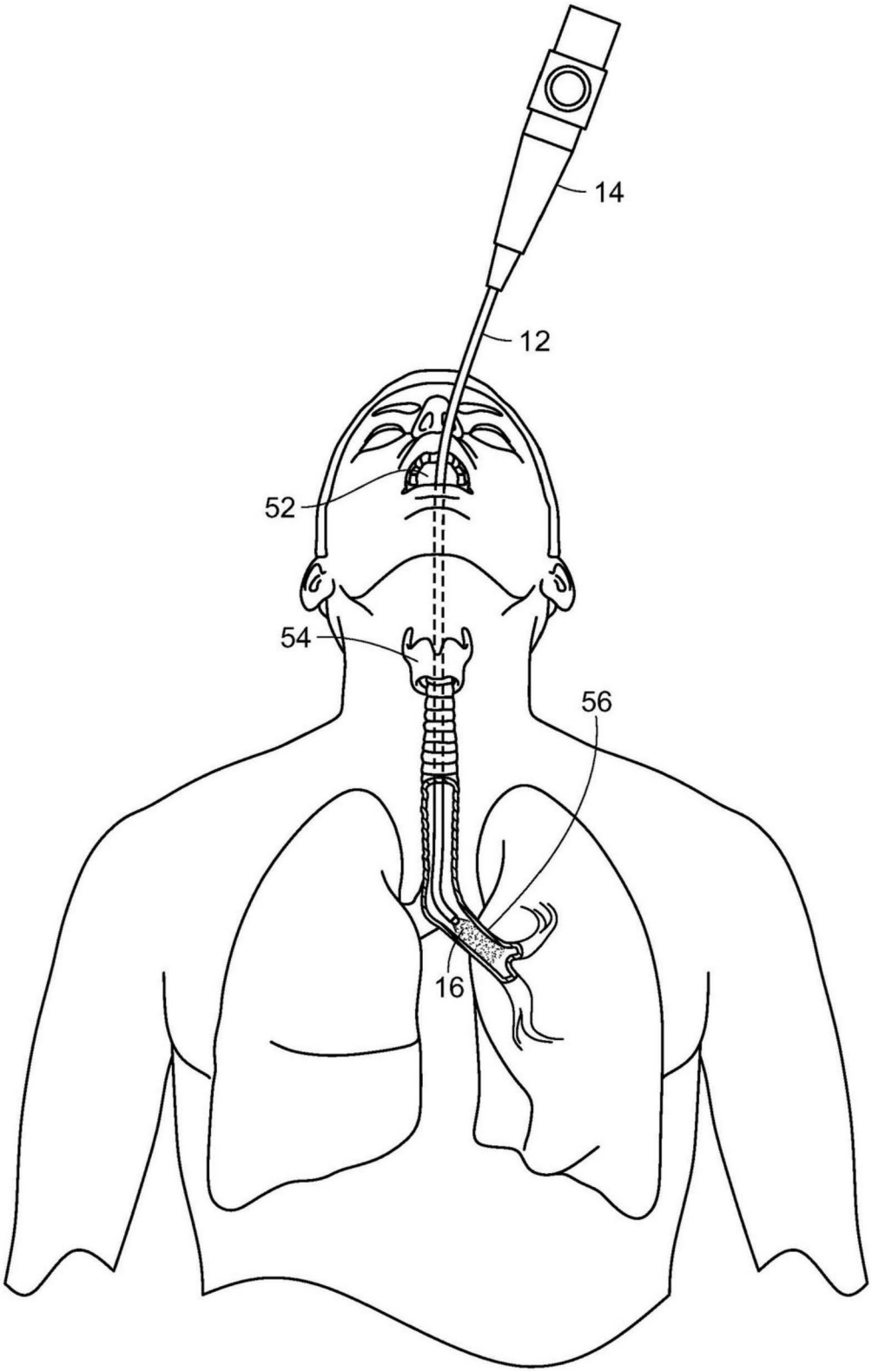


图25

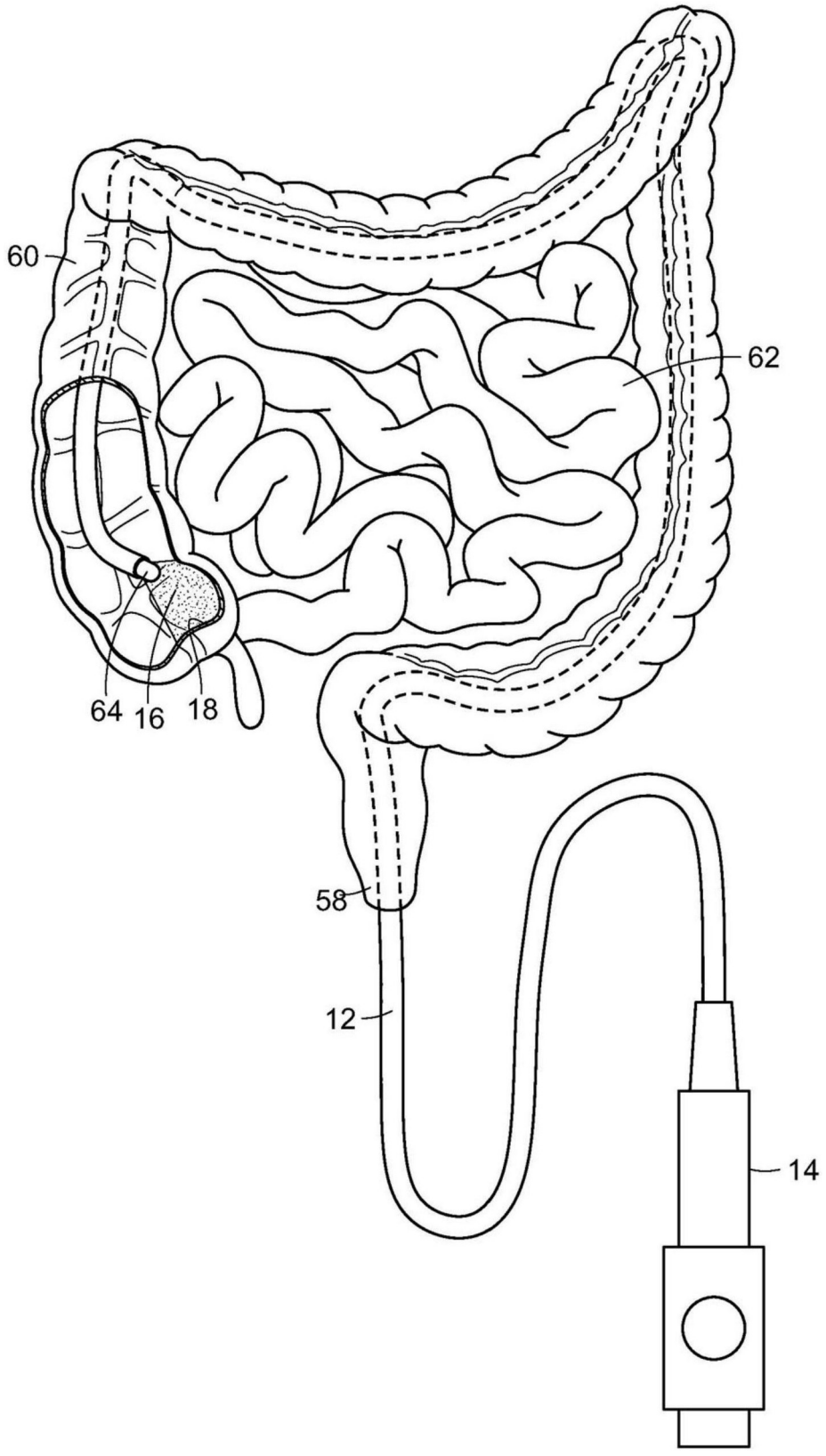


图26

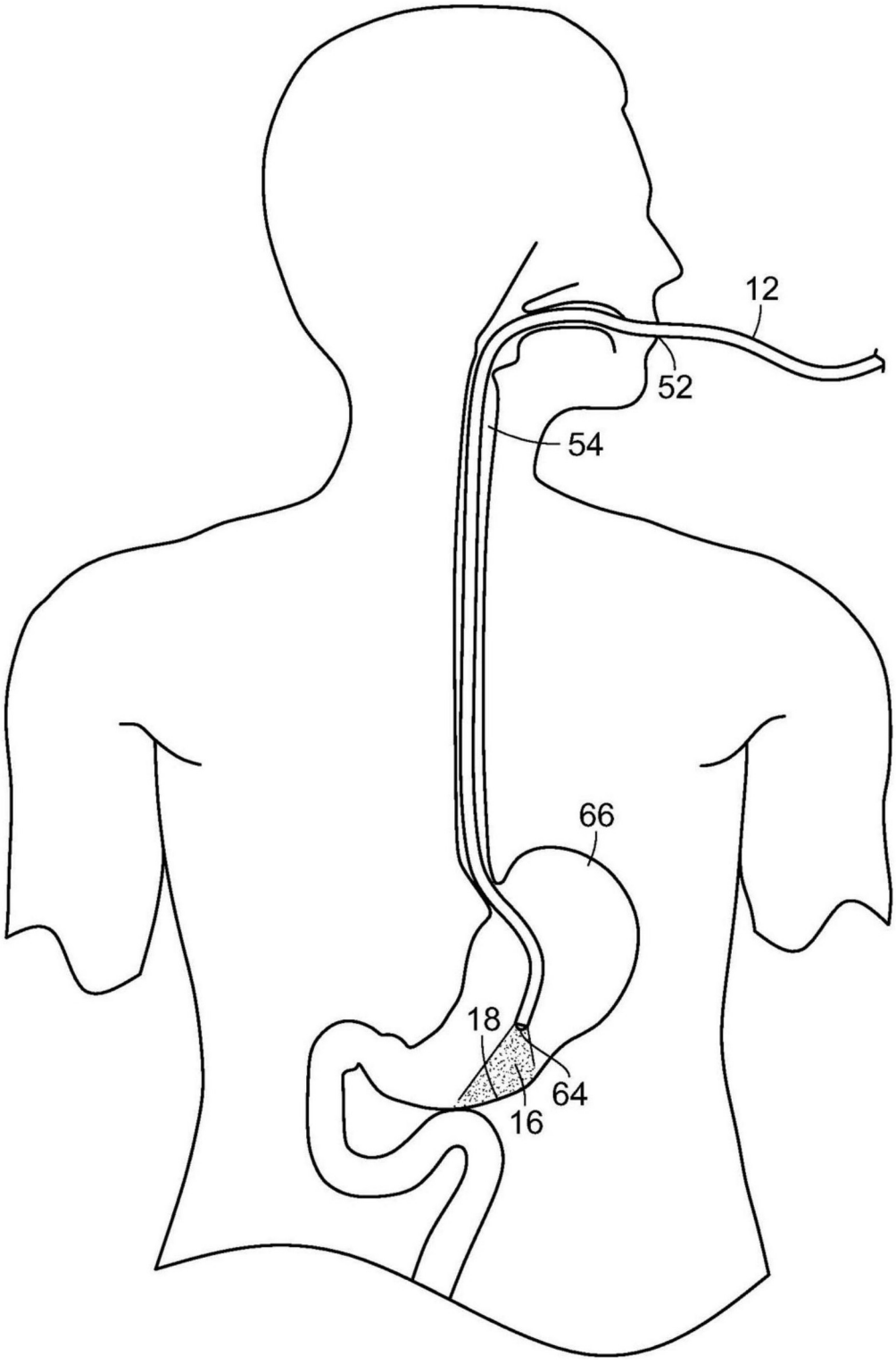


图27

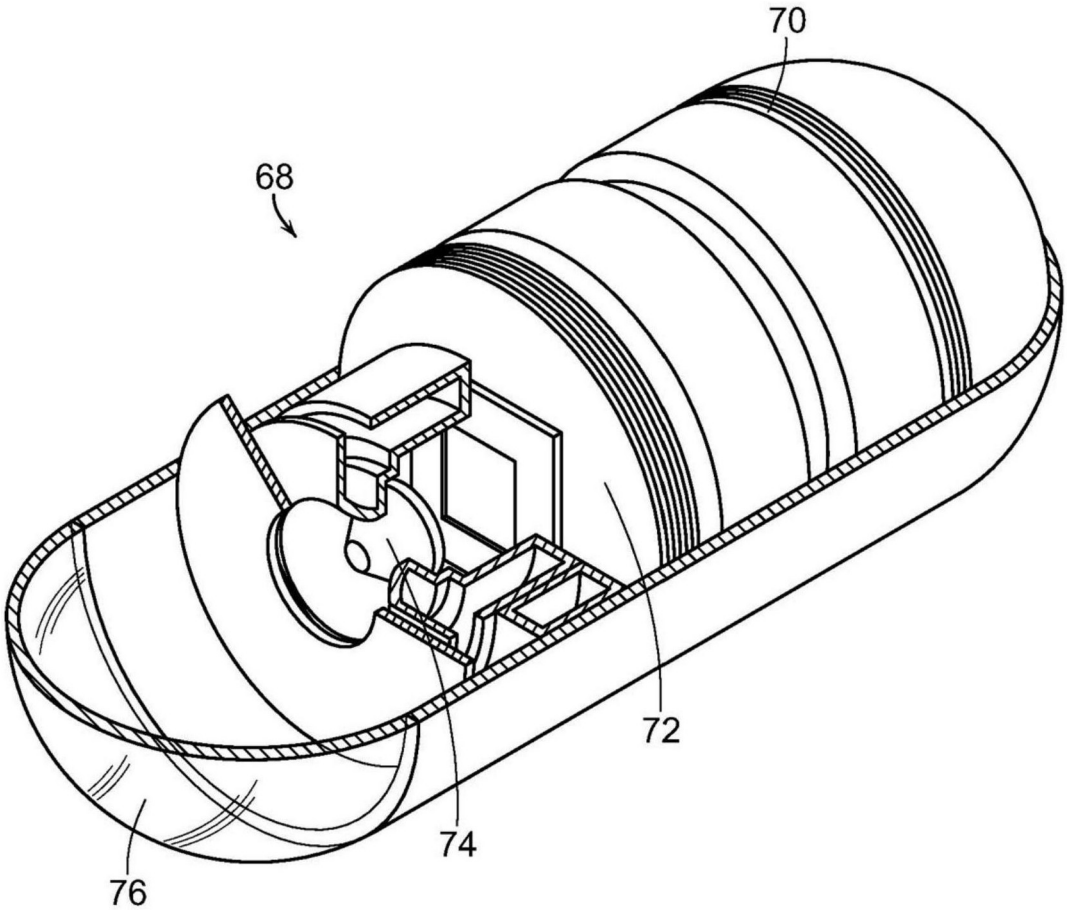


图28

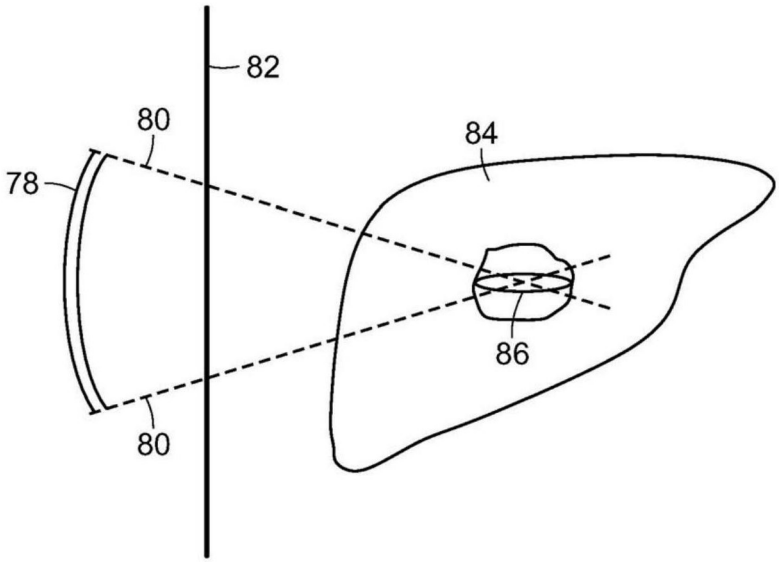


图29

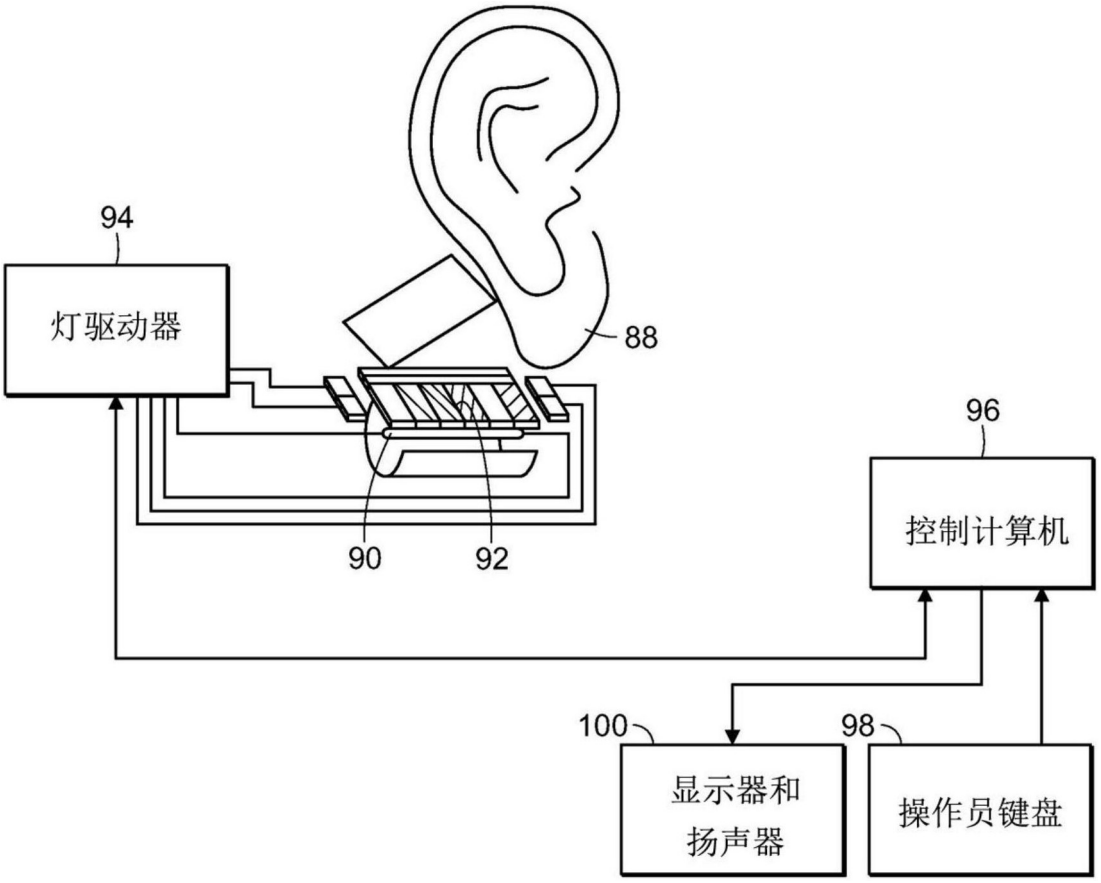


图30

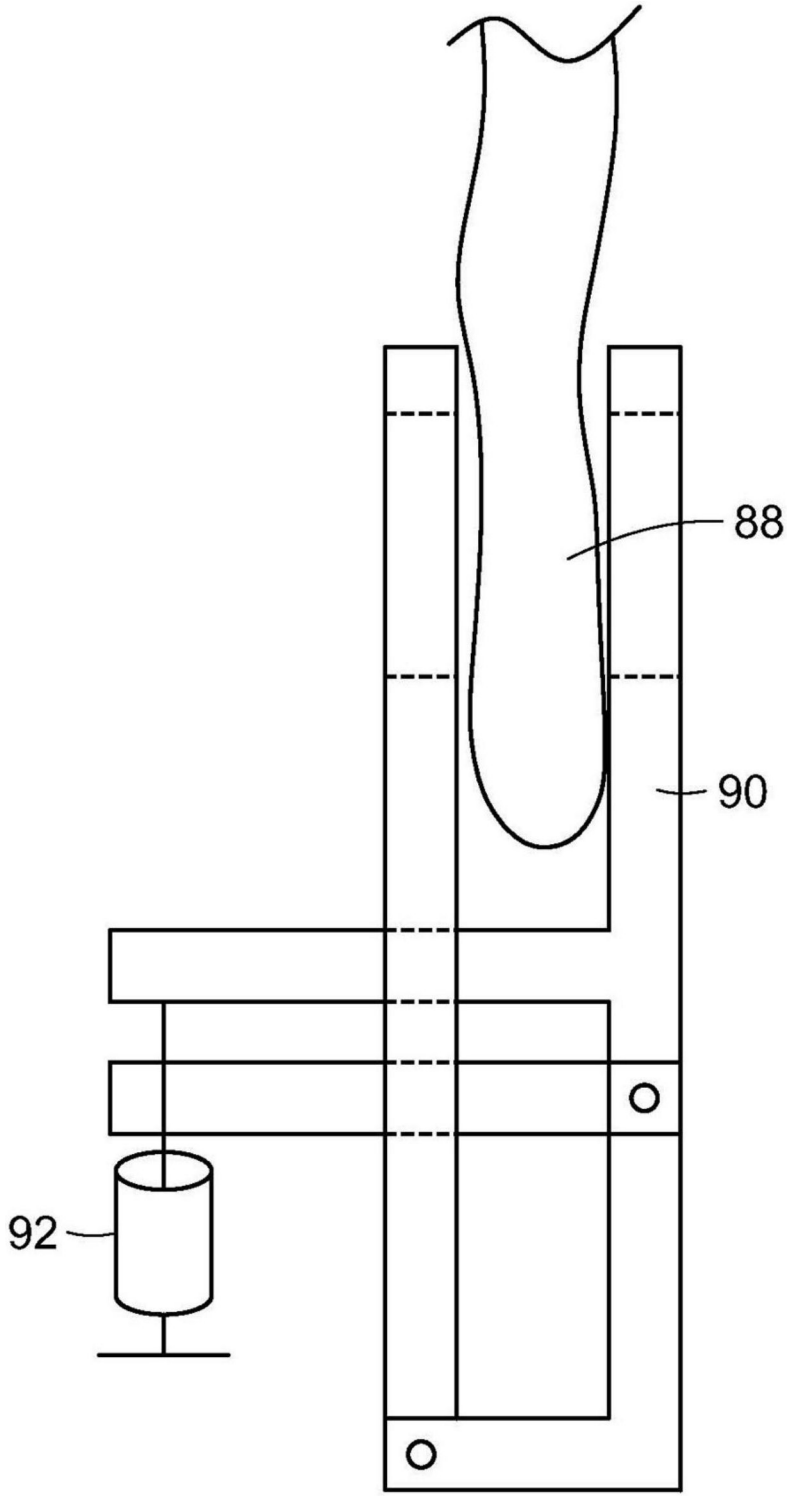


图31