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(54) **DEVICE AND METHOD FOR ASSAYING THE APPLICATION OF ENERGY TO SAMPLES IN VITRO**

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A61N 2/00 (2006.01)

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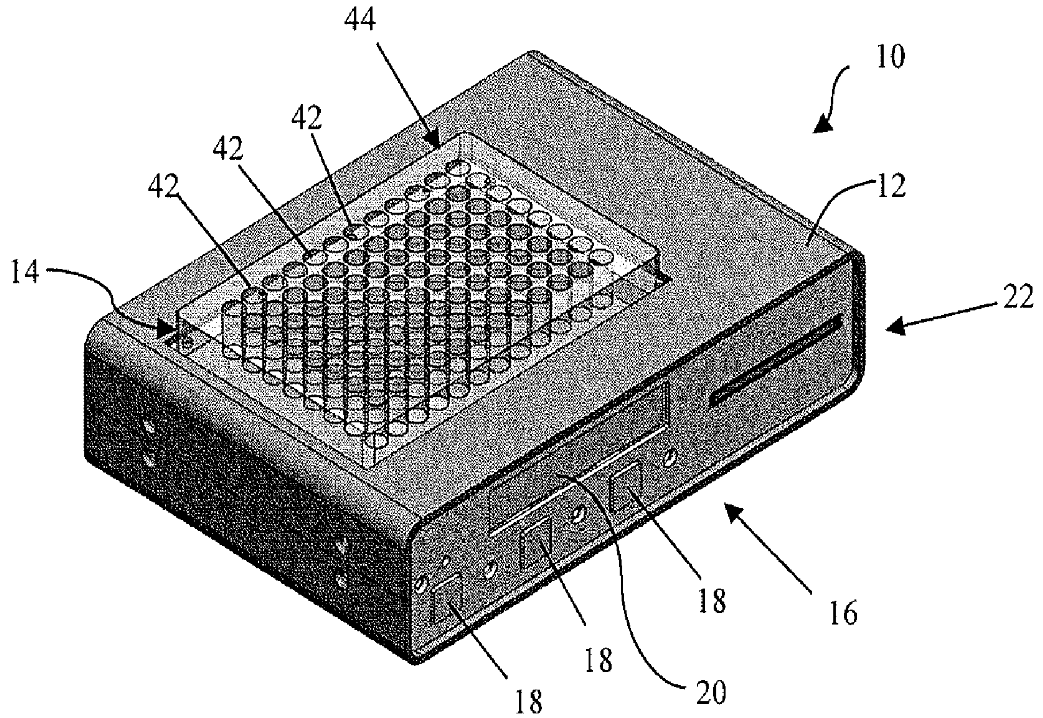
(57) **ABSTRACT**

An assay device and method of assaying the application of energy to a plurality of samples in vitro. The assay device includes a housing, an array, and a control module. The housing includes a socket sized to receive a culture plate. The array includes a plurality of emitters and is positioned within the housing adjacent to the socket so that the plurality of emitters are each aligned with at least one culture well of the culture plate when the culture plate is received in the socket. The control module is operably coupled to the array and is configured to individually drive the plurality of emitters. The control module is configured to drive at least two of the plurality of emitters at different frequencies simultaneously.



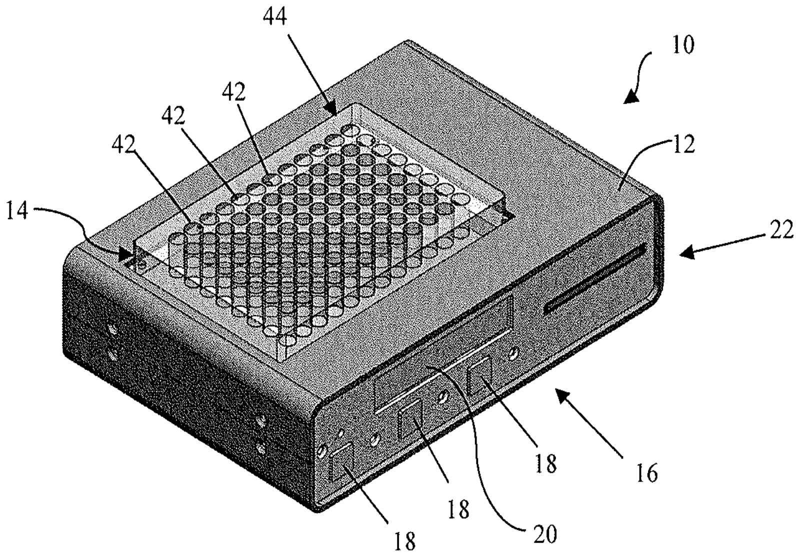

44
10
42
42
42
12
14
22
18
16
18
18
20

FIG. 1

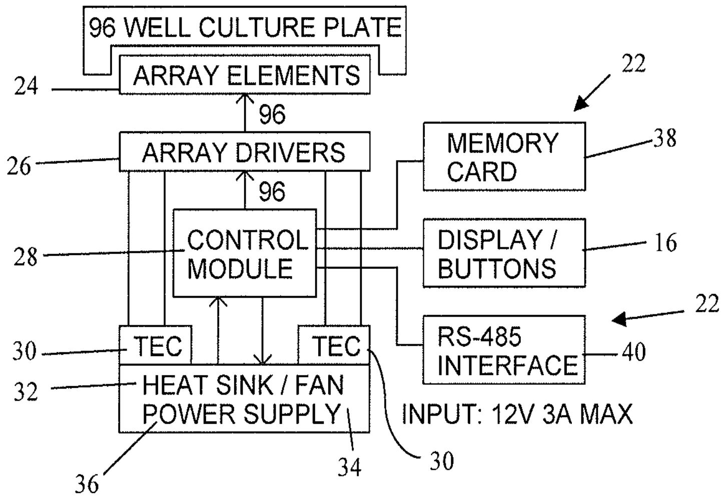

96 WELL CULTURE PLATE
ARRAY ELEMENTS
24
96
22
ARRAY DRIVERS
26
MEMORY CARD
38
96
CONTROL MODULE
28
DISPLAY / BUTTONS
16
22
TEC
TEC
30
RS-485 INTERFACE
40
HEAT SINK / FAN
32
POWER SUPPLY
INPUT: 12V 3A MAX
36
34
30

FIG. 2

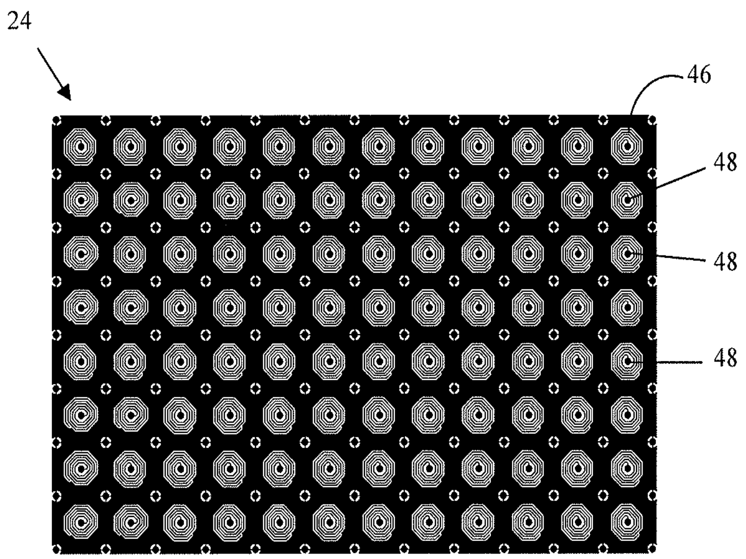

24
46
48
48
48

FIG. 3

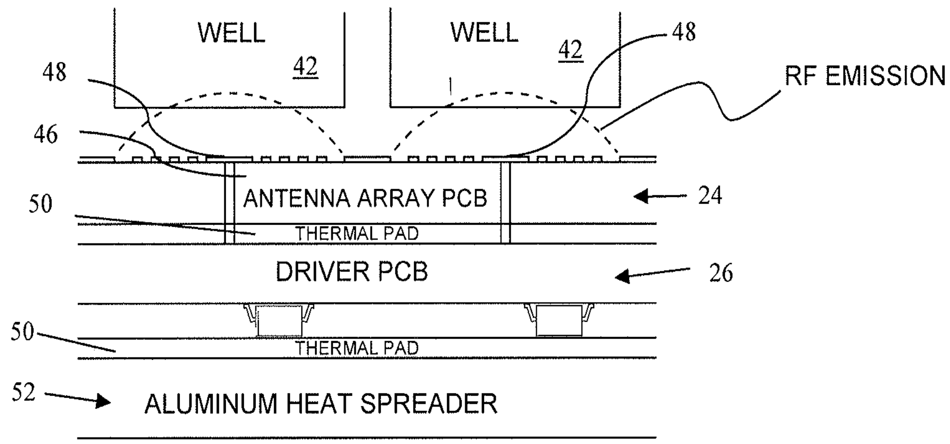

WELL
42
WELL
42
48
48
RF EMISSION
46
ANTENNA ARRAY PCB
24
50
THERMAL PAD
DRIVER PCB
26
50
THERMAL PAD
52
ALUMINUM HEAT SPREADER

FIG. 4

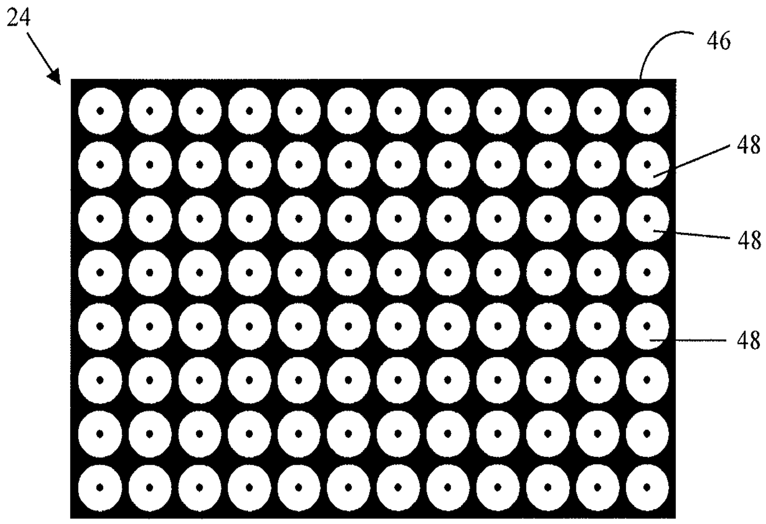

24
46
48
48
48

FIG. 5

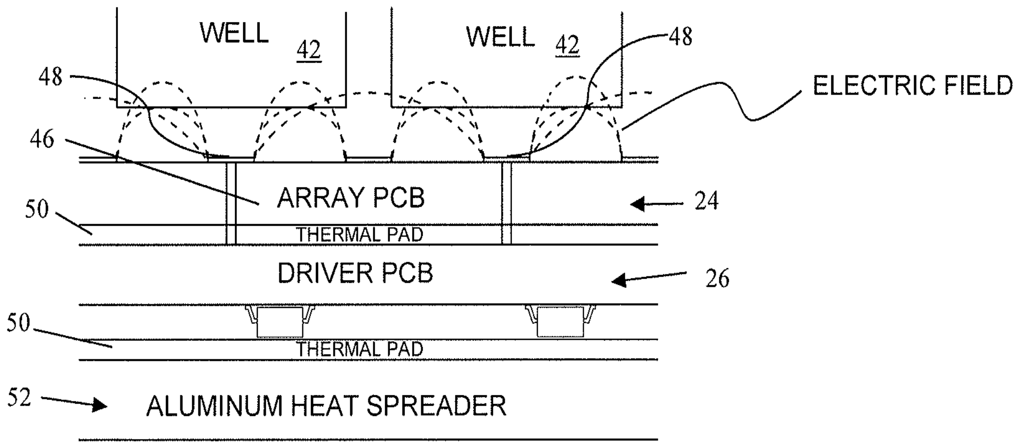

WELL 42
WELL 42
48
48
ELECTRIC FIELD
46
ARRAY PCB
24
50
THERMAL PAD
DRIVER PCB
26
50
THERMAL PAD
52
ALUMINUM HEAT SPREADER

FIG. 6

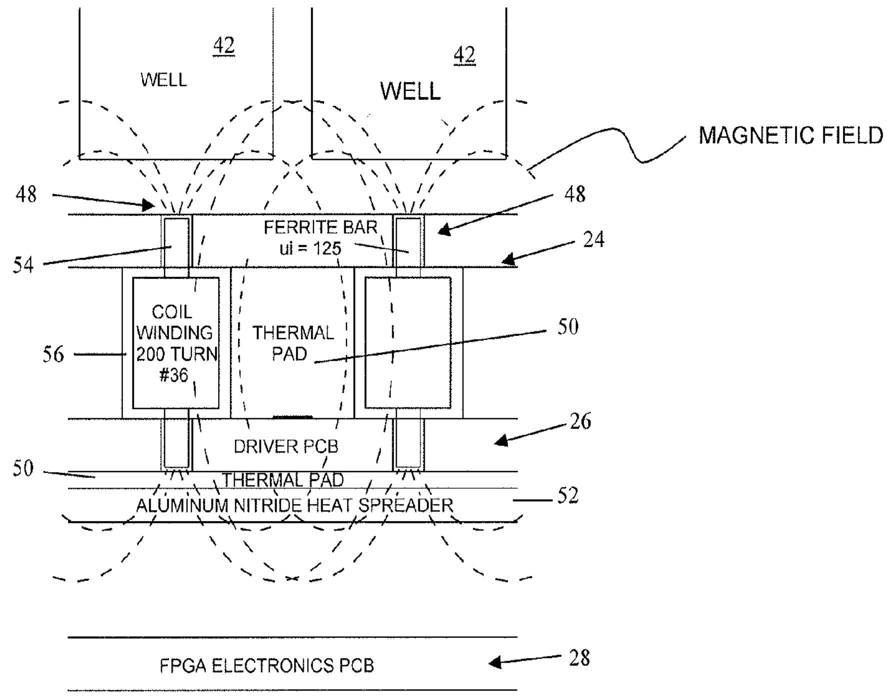

42
WELL
42
WELL
MAGNETIC FIELD
48
48
FERRITE BAR
ui = 125
24
54
COIL
WINDING
200 TURN
#36
THERMAL
PAD
50
56
26
DRIVER PCB
50
THERMAL PAD
ALUMINUM NITRIDE HEAT SPREADER
52
FPGA ELECTRONICS PCB
28

FIG. 7

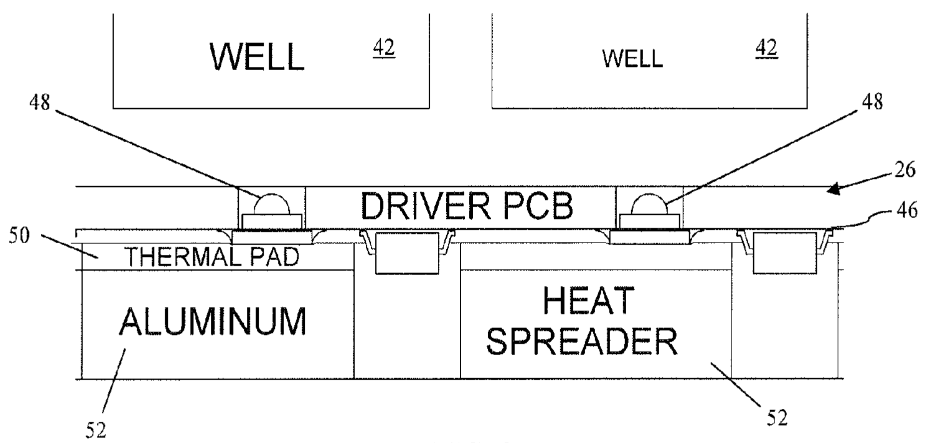

WELL
42
WELL
42
48
48
26
DRIVER PCB
46
50
THERMAL PAD
ALUMINUM
HEAT
SPREADER
52
52

FIG. 8

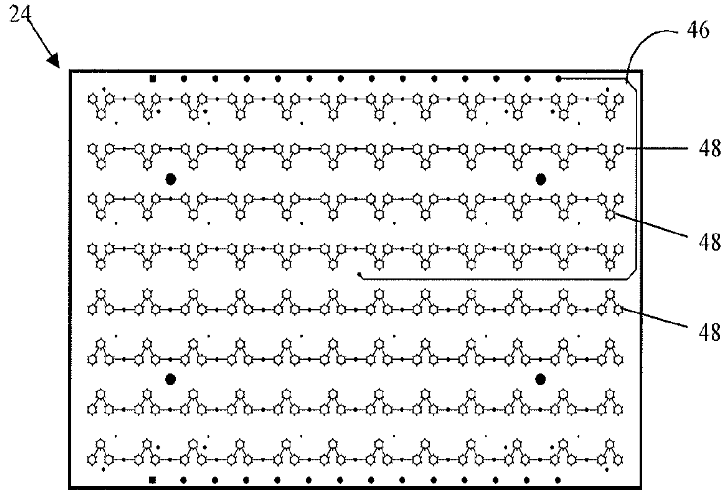

24
46
48
48
48

FIG. 9

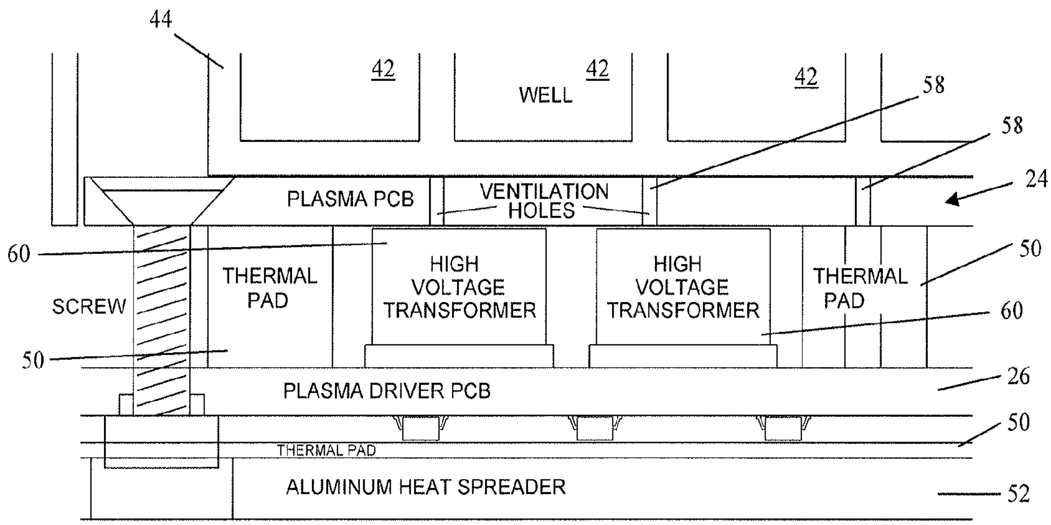

44
42
42
WELL
42
58
58
24
PLASMA PCB
VENTILATION HOLES
60
THERMAL PAD
HIGH VOLTAGE TRANSFORMER
HIGH VOLTAGE TRANSFORMER
THERMAL PAD
50
SCREW
60
50
PLASMA DRIVER PCB
26
50
THERMAL PAD
ALUMINUM HEAT SPREADER
52

FIG. 10

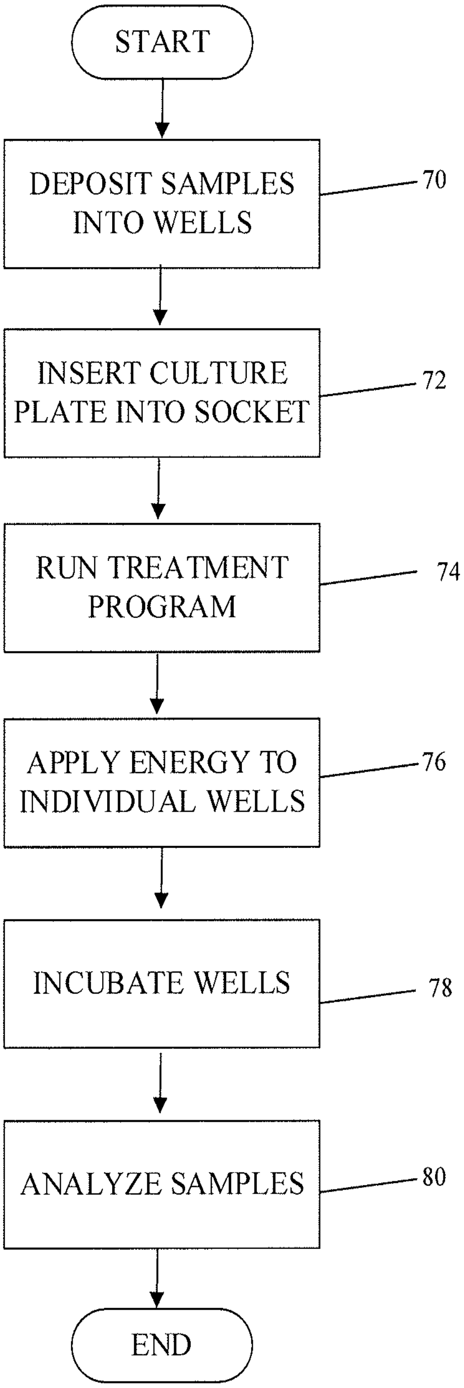

START
DEPOSIT SAMPLES INTO WELLS
70
INSERT CULTURE PLATE INTO SOCKET
72
RUN TREATMENT PROGRAM
74
APPLY ENERGY TO INDIVIDUAL WELLS
76
INCUBATE WELLS
78
ANALYZE SAMPLES
80
END

FIG. 11

DEVICE AND METHOD FOR ASSAYING THE APPLICATION OF ENERGY TO SAMPLES IN VITRO

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 62/355,543 filed on Jun. 28, 2016, the entire contents of which is incorporated herein by reference.

FIELD OF INVENTION

[0002] This invention relates to assaying the application of energy to samples. More specifically, this invention relates to a device for applying various amounts of energy, such as electromagnetic energy, to different wells of a culture plate.

BACKGROUND

[0003] Applying electromagnetic energy to living cells and tissues has been shown to have biological effects on the cells and tissues. Various types of energy have been used for treatment, such as non-thermal plasma, radio frequency, light, electrical fields, and magnetic fields. Pulsing, or modulating, the energy at different frequencies can change the effect of the treatment. However, clinical studies for determining optimum frequencies for specific treatments have been difficult to justify because the physical mechanism behind the biological interaction is not well understood. Clinical studies are also very expensive and the protocol for selecting an optimum frequency is poorly defined.

[0004] Conventionally, in vitro studies have been used to determine an optimal dosage of a medicament that causes a desired outcome. In one approach, cells or tissue samples are deposited in a multi-well culture plate and each well is dosed with a different amount of the medicament. The dosage is preferably applied with a programmed robotic device to increase speed and accuracy of the testing. The cells or tissue samples of each well may then be individually analyzed to determine the effects of the applied dosage.

[0005] While many methods and devices exist for studying medicament dosages applied to cells or tissue samples, little exist for studying energy applied to cells or tissue samples in an inexpensive and accurate manner. Thus, it would be desirable to have a device for performing in vitro studies with various types of energy.

SUMMARY

[0006] Some embodiments of the invention provide an assay device for a culture plate including a plurality of culture wells. The assay device includes a housing, an array, and a control module. The housing includes a socket sized to receive the culture plate. The array includes a plurality of emitters and is positioned within the housing adjacent to the socket so that the plurality of emitters are each aligned with at least one of the culture wells when the culture plate is received in the socket. The control module is operably coupled to the array and is configured to individually drive the plurality of emitters. The control module is configured to drive at least two of the plurality of emitters at different frequencies simultaneously.

[0007] Some embodiments of the invention provide a method of assaying the application of energy to a plurality of samples in vitro. The method includes applying the plurality of samples to individual wells of a culture plate and aligning at least one energy emitter with each individual well of the culture plate. The method also includes applying energy at a separate frequency toward each individual well via each of the at least one energy emitters for a first time period and incubating the wells for a second time period.

DESCRIPTION OF THE DRAWINGS

[0008] FIG. **1** is a perspective view of an assay device according to one embodiment of the disclosure.

[0009] FIG. **2** is a schematic diagram of the assay device of FIG. **1**.

[0010] FIG. **3** is top view of an RF array for use with one embodiment of the assay device.

[0011] FIG. **4** is a cross-sectional view of a portion of the RF array of FIG. **3**.

[0012] FIG. **5** is top view of an electric field array for use with one embodiment of the assay device.

[0013] FIG. **6** is a cross-sectional view of a portion of the electric field array of FIG. **5**.

[0014] FIG. **7** is a cross-sectional view of a portion of a magnetic field array for use with one embodiment of the assay device.

[0015] FIG. **8** is a cross-sectional view of a portion of an LED array for use with one embodiment of the assay device.

[0016] FIG. **9** is top view of a plasma emitter array for use with one embodiment of the assay device.

[0017] FIG. **10** is a cross-sectional view of a portion of the plasma emitter array of FIG. **9**.

[0018] FIG. **11** is a flow chart of a method of assaying the application of energy to a plurality of samples according to one embodiment of the disclosure.

DETAILED DESCRIPTION

[0019] Before any embodiments of the disclosure are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, it is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items. Unless specified or limited otherwise, the terms "mounted," "connected," "supported," and "coupled" and variations thereof are used broadly and encompass both direct and indirect mountings, connections, supports, and couplings. Further, "connected" and "coupled" are not restricted to physical or mechanical connections or couplings.

[0020] The following discussion is presented to enable a person skilled in the art to make and use embodiments of the disclosure. Various modifications to the illustrated embodiments will be readily apparent to those skilled in the art, and the generic principles herein can be applied to other embodiments and applications without departing from embodiments of the invention. Thus, embodiments of the invention are not intended to be limited to embodiments shown, but are to be accorded the widest scope consistent with the principles and features disclosed herein. The following detailed description is to be read with reference to the figures, in which like elements in different figures have like reference numerals. The figures, which are not necessarily to scale, depict selected embodiments and are not intended to limit the scope of embodiments of the invention. Skilled artisans will recognize the examples provided herein have many useful alternatives and fall within the scope of embodiments of the invention.

[0021] Generally, embodiments of the present disclosure provide an assay device that enables treating multiple wells of a culture plate simultaneously with different pulse frequencies of energy. The device may receive the culture plate in a socket so that the plurality of wells are aligned in close proximity to an array of energy emitters, each of which emits a different pulse frequency simultaneously. This enables many frequencies to be tested simultaneously, speeding up the search for a frequency that provides a desired outcome on samples in the culture wells.

[0022] FIG. **1** illustrates an assay device **10** according to some embodiments. As shown in FIG. **1**, the assay device **10** can include a housing **12** with a socket **14**, a user interface **16** (such as one or more push buttons **18** and a display **20**), and one or more input/output interfaces **22**. Internally, the device **10** may include an array **24**, an array driver **26**, a control module **28**, one or more thermal control devices **30**, a heat sink **32**, a fan **34**, and a power supply **36**, as shown schematically in FIG. **2**. Additionally, in one embodiment, as shown in FIG. **2**, the input/output interfaces **22** can include a memory card slot **38** and an RS-485 interface **40**. As further described below, the assay device **10** is configured to emit energy at different frequencies toward individual wells **42** of a culture plate **44** simultaneously.

[0023] As shown in FIG. **1**, the socket **14** may be sized to receive a culture plate **44** that includes a plurality of wells **42**. For example, the socket **14** may be a square or rectangular cutout in the housing **12** approximately equal to a size of the culture plate **44**. It should be noted that, while FIG. **1** illustrates the culture plate **44** with ninety-six wells **42**, it is within the scope of this disclosure to include an assay device **10** sized and adapted to receive culture plates **44** including more or less wells **42**, such as six wells, twelve wells, twenty-four wells, forty-eight wells, etc. Optionally, the socket **14** may further include a structural support (not shown) around its perimeter to support the culture plate **44**. In other embodiments, the culture plate **44** may be received within the socket **14** and rest upon a top outer perimeter of the array **24**.

[0024] Accordingly, the array **24** can be positioned within the housing **12** adjacent to (e.g., below) the socket **14**. As described in more detail below with respect to FIGS. **3-10**, the array **24** can include a board **46** with a plurality of energy emitters **48** driven by the array driver **26** to emit energy, such as radio frequency (RF), electric field, magnetic field, optical emission, and non-thermal plasma, toward the culture plate **44**. The plurality of emitters **48** may be arranged on the board **46** in an array pattern so that each emitter **48** aligns with at least one culture well **42**. As a result, one or more emitters **48** may be dedicated to emit energy at a specific frequency to a single well **42** of the culture plate **44**. Generally, in some embodiments, the number of emitters **48** may equal the number of wells **42** for which the device **10** is adapted (such as six, twelve, twenty-four, forty-eight, ninety-six, etc). However, in other embodiments, the array **24** may include more or less emitters **48** than wells **42**. For example, the device **10** may be configured so that patterns or groupings of multiple emitters **48** may be dedicated to a single well **42**.

[0025] According to some embodiments, the control module **28** can be operably coupled to the array **24** (e.g., through the array driver **26**) and can be configured to individually drive each emitter **48** at a specific frequency for a set time period. For example, the control module **28** can control the array driver **26** to drive each emitter **48** at a different frequency, or to drive groupings of more than one emitter **48** at different frequencies. The control module **28** may include an application-specific integrated circuit (ASIC), a programmable logic controller (PLC), or, preferably, a field-programmable gate array (FPGA), such as the Xilinx Artix 7. A signal generator for each emitter **48** (e.g., a square wave signal generator) can be implemented in VHDL code as a phase accumulator, or numerically controlled oscillator (NCO). In a preferred embodiment, control module output to the array driver **26** consists of the most significant bit of the phase accumulator. Using only a single bit of the output may add deterministic phase jitter, but it allows the device to define individual emitter units (e.g., up to ninety-six units) with reasonable FPGA resources. Furthermore, using a 200 MHz clock and both edges of the clock, the peak timing uncertainty can be about ±2.5 nanoseconds (ns).

[0026] The control module **28** can also be operably coupled (e.g., electrically connected) to the memory card slot **38**, the user interface **16**, the RS-485 interface **40**, the fan **34**, the power supply **36** and/or other connections (not shown). More specifically, the memory card slot **38** can be sized to receive a memory device (such as a data card) allowing, for example, the control module **28** to upload control instructions and test data from the memory card and/or download test data to the memory card. Alternatively, in some embodiments, the memory card slot **38** can be sized to receive a USB flash drive. Also, in some embodiments, the control module **28** can include internal memory accessible via one of the I/O interfaces.

[0027] In some embodiments, the control module **28** can connect to an external computer via the RS-485 interface **40**. The RS-485 interface **40** may also be used to connect multiple devices **10** (e.g., up to 128 devices) in a daisy-chain configuration, for example, using a MODBUS communication protocol. The interface can be designed so that the first device **10** in the cable chain the lowest address, and the subsequent devices **10** have sequentially higher addresses.

[0028] In some embodiments, the device **10** can include more than one RS-485 interface **40**. Additionally, it should be noted that, while the memory card slot **38** and the RS-485 interface **40** are shown and described herein, it within the scope of this disclosure to include additional input/output interfaces and/or other communications circuits. For example, the device **10** can include a power supply interface (not shown), permitting the device **10** to be connected to and powered by an external power supply.

[0029] Accordingly, the control module **28** can receive instructions via the memory card slot **38** (i.e., via an inserted memory device), the RS-485 interface **40** (i.e., via a connected external computer), or additional input/output interfaces. Furthermore, the control module **28** can receive user inputs via the user interface **16**. As shown in FIG. **1**, the user interface **16** can include one or more push buttons **18**. As such, the control module **28** can receive user input via a user pressing one of the push buttons **18**. For example, the push buttons **18** can be pressed to control power of the device (i.e., a power button), to toggle between displays or programs (e.g., via "up" and/or "down" buttons), to start a treatment program (e.g., a "start" button), to end a treatment program (e.g., a "stop" button), or for other types of device control. Additionally, in some embodiments, the device **10** can include user inputs other than push buttons, such as rotary dials, switches, or the like.

[0030] Furthermore, the user interface **16** can include the display **20**. The display **20** may be, for example, a light emitting diode (LED) display, an organic light emitting diode (OLED) display, a digital display, or another suitable display. In one embodiment, the display **20** is a 2×20-character OLED display. The control module **28** may control the display **20** to display to a user, for example, program status, on/off status, device status, present temperatures, a timer, test data, programs, or the like. In one example, the device **20** can display test data or programs in a list format, and a user can toggle the lists and/or select a desired program using the push buttons **18**. Alternatively, the control module **28** may automatically execute a program upon receiving a memory card within the memory card slot **38** and being powered on.

[0031] Internally, the control module **28** can control operation of the fan **34** as part of a thermal control system of the device **10**. More specifically, the thermal control system can include the fan **34**, the heat sink **32**, the thermal control devices **30** (such as thermoelectric coolers, TECs), and one or more temperature sensors (not shown). For example, the array **24**, the array driver **26**, and/or the control module **28** can be thermally coupled to the heat sink **32**, the TECs **30**, and the fan **34**. The heat sink **32** may act as a passive cooling device, while the fan **34** may be operated for active cooling, and the TECs **30** may be operated for heating or cooling.

[0032] The control module **28** can control operation of the fan **34** and/or the TECs **30** based on a specific treatment program (e.g., the control module **28** may operate the device **10** at a desired temperature or within a desired temperature range based on received temperature control data for a specific program). For example, during and/or after energy application to the culture wells **42**, the control module **28** can control the thermal control system (in particular, the fan **34** and the TECs **30**) to incubate the culture wells **42** for a preset time period.

[0033] More specifically, the temperature sensors can be positioned on the array **24**, the housing **12**, and/or the heat sink **32** and can be in communication with the control module **28**. The control module **28** can monitor the temperatures of these components (i.e., by retrieving a current temperature from one or more of the temperature sensors) and determine whether passive or active cooling is necessary or whether heating is necessary. That is, the control module **28** can operate the fan **34** based on input from one or more of the temperature sensors. In one embodiment, the fan **34** can draw in air from one or more bottom cutouts of the housing **12**, past the heat sink **32** and up through the socket **14** (i.e., past the culture plate **44** received in the socket **14**). Additionally, in some embodiments, the control module **28** may display an alarm (e.g., via the display **20**) if a temperature of one of the components exceeds a high or low temperature threshold for a set time period despite heating or cooling.

[0034] Furthermore, it should be noted that other thermal control devices are contemplated within the scope of this disclosure. Additionally, the heat sink **32** and all internal electronics of the device **10** can be thermally insulated from the housing **14**.

[0035] The following paragraphs describe specific arrays **24** for devices **10** configured to treat culture wells **42** with RF energy, electric fields, magnetic fields, light, and non-thermal plasma, respectively. For example, the above-described components may be common to each device **10**, with the exception of the arrays **24** and array drivers **26**, which may be specific to the type of energy emission of the device **10**. Thus, some embodiments provide different build options for an RF-specific device, an electric field-specific device, a magnetic field-specific device, a light-specific device, and a non-thermal plasma-specific device. Alternatively, in some embodiments, a device **10** can include all the above common components and can be configured to receive different arrays **24** and array drivers **26** in an interchangeable manner. Thus, such a device **10** can be used for all types of energy emissions.

[0036] FIGS. **3** and **4** illustrate an RF array **24** according to one embodiment of the disclosure. The RF array **24** comprises an RF emitter board **46** driven by an RF driver board **26**. The RF emitter board **46** can be a printed circuit board with rows and columns of individual RF emitters **48**. In one embodiment, the RF array **24** can be a 2.4 gigahertz (GHz) array. As such, an RF emitter **48** can be a resonant structure consisting of a printed spiral inductor and series capacitor, which presents a good impedance match at 2.44 GHz. While not an efficient antenna (since most of the power is dissipated in the spiral structure) the emitter **48** is meant to couple short transmissions of RF energy upward and into a culture well **42**, similar to that used in near-field communication devices. The matching is relatively narrowband, and the control module **28** can adjust the output RF frequency for each emitter **48** to determine optimum frequencies for certain treatments.

[0037] The RF driver board **26** can be a separate printed circuit board that drives the RF array **24**, as shown in FIG. **4**. A circuit for measuring the forward and reverse power on a single emitter **48** can also be included, on the assumption that all the forward and reverse power on other emitters **48** will be very similar. The RF array driver **26** can include Wilkinson power splitters, RF switches, and load resistors. The control module **28** can route digital signals to the RF driver **26** to create a distinct modulation frequency underneath each culture well **42**. The RF array driver **26** can also include a temperature compensated crystal oscillator and frequency synthesizer, as well as amplifiers and attenuators for controlling the RF level. The power into the modulation section can be −10 dBm to +17 dBm, but the maximum radiated power from the array can be about 1 mW. Additionally, as shown in FIG. **4**, the RF module (i.e., including the array **24** and the driver **26**) can further include thermal pads **50** below each of the array **24** and the driver **26** and a heat spreader **52** below the driver **26**. These components can transfer heat through the array driver **26** to the heat sink **32** or other thermal control devices.

[0038] FIGS. **5** and **6** illustrate an electric field array **24** according to one embodiment of the disclosure. The electric field array **24** comprises an electric field emitter board **46** driven by an electric field driver board **26**. The electric field emitter board **46** can be a printed circuit board with rows and columns of individual electric field emitters **48**. The electric field driver board **26** can be a separate printed circuit board that drives the electric field emitter board **46** to create an electric field flux, as shown in FIG. **6**. In one embodiment, for a driving voltage of 5 volts, peak-to-peak (Vp-p), the peak field strength can be between 1.5 volts per centimeter (V/cm) and 2.5 V/cm. In some embodiments, if a higher electric field strength is desired, the array driver voltage can be increased to 190 Vp-p up to 100 kiloHertz (kHz) using high voltage amplifiers. In some embodiments, the emitters **48** can deliver a peak electric field in a culture well **42** between about 60 V/cm and about 100V/cm. In such embodiments, the electric field array driver **26** also includes a voltage boost converter to generate the 200-volt bias for the amplifiers. Additionally, as shown in FIG. **6**, the energy field module (i.e., including the array **24** and the driver **26**) can further include thermal pads **50** below each of the array **24** and the driver **26** and a heat spreader **52** below the driver **26**. These components can transfer heat through the array driver **26** to the heat sink **32** or other thermal control devices.

[0039] FIG. **7** illustrates a magnetic field array **24** according to one embodiment of the disclosure. The magnetic field array **24** includes a magnetic field emitter board **46** driven by a magnetic field driver board **26**. The magnetic field emitter board **46** can be a printed circuit board, functioning mainly to hold the tops of magnetic field emitters **48**. More specifically, a magnetic field emitter **48** consists of a ferrite bar **54**, which in a preferred embodiment has a length of 7.5 mm and diameter of 0.8 mm. Coil winding **56** around the bar **54** can include 200 turns of #36 wire, presenting about 100 uH of inductance. The moderate permeability (ui=125) of the ferrite bar **24** will tend to efficiently couple higher harmonics generated by the driving waveform.

[0040] The magnetic field array driver **26** can be a separate printed circuit board that drives the magnetic field array **24**. In some embodiments, the duty cycle of the driving waveform can be adjusted to produce a DC bias of 2 milliamperes (mA) at 5 V. A circuit (not shown) for monitoring DC bias can be connected to a single element **48**, on the assumption that all elements **48** will have a similar bias. A calibration routine can be used to determine the required duty cycle for a given frequency. Additionally, as shown in FIG. **7**, the magnetic field module (i.e., including the array **24** and the driver **26**) can further include thermal pads **50** between the emitters **48** and a heat spread **52** below the magnetic field driver **26**, which can conduct heat past the control module **28** over to the TECs **30** (e.g., via aluminum blocks, not shown). In one embodiment, the heat spreader **52** can include aluminum nitride, which will keep metal farther away from the ends of the inductors. Also, in one embodiment, the driver PCB **26** can be positioned to maintain an area around the ferrite bars **54** with no metal for a diameter of about 0.25 inches.

[0041] FIG. **8** illustrates an optical array **24** according to one embodiment of the disclosure. The optical array **24** includes an optical emitter board **46** driven by an optical driver board **26**. The optical emitter board **46** can be a printed circuit board with light emitting diodes (LEDs) **48** mounted on it. LEDs **48** with a wide variety of wavelengths may be used in certain embodiments, for example from near infrared (NIR, around 850 nanometers (nm)) to ultraviolet (UV, around 395 nm). In one embodiment, the LEDs **48** can be in a **1206** package with lens.

[0042] The optical driver board **26** can be a separate printed circuit board that drives the optical array **24**. The LED drivers **26** can be designed to run at a fixed current, but the average power can be reduced by adjusting the duty cycle. In some embodiments, the LEDs **48** can be mounted upside down into the driver PCB **26** to create a flush surface for thermal contact with the culture plate **44**. Additionally, as shown in FIG. **8**, the optical module (i.e., including the array **24** and the driver **26**) can further include thermal pads **50** around the LEDs **48** to improve thermal transfer and a heat spreader **52** below the driver **26**. These components can transfer heat through the array driver **26** to the heat sink **32** or other thermal control devices.

[0043] FIGS. **9** and **10** illustrate a plasma array **24** according to one embodiment of the disclosure. The plasma array **24** comprises a plasma emitter board **46** driven by a plasma driver board **26**. The plasma emitter board **46** can be a printed circuit board with rows and columns of individual plasma emitters **48**. In one embodiment, the plasma emitters **48** can be those described in co-pending U.S. patent application Ser. No. 15/055,028, which is incorporated herein by reference in its entirety. The distance between the plasma dielectric and the base of the culture plate **44** may be defined by a copper and solder mask thickness of about 2 mils. To maintain constant plasma characteristics, ventilation holes **58** may be included outside the plasma areas.

[0044] The plasma array driver **26** can be a separate printed circuit board that drives the plasma array **24**. In one embodiment, the plasma array driver **26** can require multiple lines from the control module **28** to control the plasma driver **26** and high voltage transformers **60** to create a total of twenty-four drivers **26**. Each driver **26** can then be connected to a set of 4 micro-plasma arrays **24**, which sit underneath the culture wells **42**. Each set of plasma arrays **24** can present a capacitance of about 20 picofarads (pF). This capacitance resonates with the plasma drive transformer **60**, and the plasma drive frequency can be about 420 kHz. In one embodiment, the plasma modulation frequency can be adjusted by the control module **28** up to 10 kHz. The plasma tends to run at a fixed current, and a duty cycle of 10% may be used to reduce average power and extend the array life. Additionally, as shown in FIG. **10**, the plasma module (i.e., including the array **24** and the driver **26**) can further include thermal pads **50** below each of the array **24** and the driver **26** and a heat spreader **52** below the driver **26**. These components can transfer heat through the array driver **26** to the heat sink **32** or other thermal control devices.

[0045] In light of the above, embodiments of the present disclosure provide a device **10** that enables treating multiple wells **42** of a culture plate **44** simultaneously with different pulse frequencies of energy, such as RF, electric field, magnetic field, light, or plasma. FIG. **11** illustrates a method for using the device **10** according to one embodiment of the disclosure. Generally, as shown in FIG. **11**, at step **70**, a sample culture of interest, such as cells, tissues, bacteria, fungus or virus, is deposited in each well **42** of the culture plate **44**. Next, at step **72**, the culture plate **44** is inserted into the socket **14** of the device **10**. A treatment program is then selected and run, at step **74**, and energy at different frequencies is applied to each of the wells simultaneously for a time period, at step **76**. During or after the time period in step **76**, the culture wells are incubated for a second time period, at step **78**. After the time period in step **78**, the cultures in each culture well may be analyzed, at step **80**, to determine the effects of the applied energy to each well, for example to determine an optimal frequency for a desired outcome.

[0046] More specifically, at step **70**, a sample culture of interest, such as cells, tissues, bacteria, fungus or virus, is deposited in each well **42** of the culture plate **44**. For example, each well may include the same type of sample, or different wells may include different types of samples. Next, at step **72**, the culture plate **44** is inserted into the socket **14** of the device **10**. As described above, the socket **14** can be sized so that the culture plate **44** rests within the socket **14** atop the array **24**. Additionally, in some embodiments, steps **70** and **72** may be reversed (i.e., the culture plate **44** can be inserted into the socket **14** and then the samples can be deposited in each well **42**).

[0047] When the culture plate **44** is received within the socket **14**, a treatment program may be run on the device **10** at step **74**. Generally, a treatment program can include specific frequencies to apply, the first set time period, the second set time period, temperature set points or thresholds, and/or other testing parameters. For example, the device **10** may be powered on and a memory card may be inserted in the memory card slot **38** so that the control module **28** automatically executes a treatment program stored on the memory card. In another example, the device **10** may display multiple treatment program options on the display **20** and a user may select a desired treatment program for the control module **28** to run via the push buttons **18**. In yet another example, the device **10** may be connected to an external computer via the RS-485 interface **40** (or another input/output interface **22**) and a user may select a desired treatment program for the control module **28** to run via the external computer.

[0048] According to the selected treatment program, the control module **28** can control the array **26** to apply energy to the culture plate **44** at step **76**. More specifically, the control module **28** can generate a set of separate frequencies (i.e., more than one frequency) for each emitter **48** or for groups of emitters **48** to emit toward individual wells **42** of the culture plate **44** simultaneously. As discussed above, the array **24** can be configured so that a single emitter **48** is aligned under each well **42**, or so that groups of emitters **48** are aligned under each well **42**. Thus, each emitter **48** (or each group of emitters **48**) can output a different frequency simultaneously in order to test the effects of multiple frequencies on separate samples (i.e., in the separate culture wells **42**) at the same time. In one example, the control module **28** can drive at least two emitters **48** at different frequencies simultaneously. In another example, the control module **28** can generate a set of ninety-six separate frequencies simultaneously to individual control ninety-six emitters **48**. The control module **28** can apply the energy to the culture wells **42** for a first set time period according to the selected treatment program.

[0049] The control module **28** can also operate the thermal control system to incubate the culture wells **42** for a second set time period, at step **78**, according to the selected treatment program. For example, in one embodiment, the control module **28** can thermally control the temperature of the array **24** in order to incubate the wells. In some embodiments, the second set time period may be equal to the first set time period of step **76**. Additionally, in some embodiments, the second set time period may partially or completely overlap with the first set time period.

[0050] Once the second set time period is completed, the culture wells **42** may be analyzed to determine the effects of the applied energies to the samples, at step **78**. In some embodiments, the device **10** may automatically turn off once the second set time period is completed, may automatically save treatment data to memory (e.g., store frequency and temperature control data to internal memory or the memory device), or may display an alert via the display **20** to notify a user that the treatment program is complete.

[0051] In accordance with the above method, multiple samples can be simultaneously treated in vitro with different frequencies and examined to determine which sample had a desired or optimal outcome, thus allowing a determination of the optimal frequency for a specific treatment. Furthermore, the method may be repeated, for example, to see if the energy effects are repeatable. For example, the control module **28** can apply the same treatment program, but shuffle the modulation frequencies to different emitters **48**. In particular, repeating the methods and shuffling the frequencies can compensate for signal overlap between adjacent array elements. Additionally, the present methods can be applied to multiple devices **10** simultaneously using a daisy-chain configuration, as described above. Multiple tests can thus be completed quickly and accurately and both frequency and temperature data may be stored, for example, to memory devices or a database as part of a research program and to track tested frequencies.

[0052] In light of the above, embodiments of the disclosure provide a device and method for studying the application of energy at different frequencies to samples in vitro. By allowing multiple samples to be tested at different frequencies simultaneously and then incubated, the present device and method provide a standalone low-cost, quick, and accurate way to study the biological effects of samples based on the modulation frequency of RF, electric fields, magnetic fields, light, and plasma.

[0053] It will be appreciated by those skilled in the art that while the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. The entire disclosure of each patent and publication cited herein is incorporated by reference, as if each such patent or publication were individually incorporated by reference herein. Various features and advantages of the invention are set forth in the following claims.

1. An assay device for a culture plate including a plurality of culture wells, the assay device comprising:

a housing including a socket sized to receive the culture plate;

an array including a plurality of emitters, the array positioned within the housing adjacent to the socket so that the plurality of emitters are each aligned with at least one of the culture wells when the culture plate is received in the socket; and

a control module operably coupled to the array and configured to individually drive the plurality of emitters, the control module configured to drive at least two of the plurality of emitters at different frequencies simultaneously.

2. The assay device of claim **1**, wherein the plurality of emitters are configured to emit one of the following types of energy: radio frequency; electric field; magnetic field; non-thermal plasma; and light.

3. The assay device of claim **1**, wherein the array is positioned below the socket.

4. The assay device of claim **1** and further comprising an array driver, wherein the control module is operably coupled to the array via the array driver.

5. The assay device of claim **1** and further comprising a thermal control system, wherein the control module is configured to control the thermal control system based on a temperature of one of the housing, the array, and a heat sink.

6. The assay device of claim **1** and further comprising a heat sink positioned within the housing.

7. The assay device of claim **1** and further comprising a fan positioned within the housing.

8. The assay device of claim **1** and further comprising a user input in communication with the control module.

9. The assay device of claim **8**, wherein the user input includes a display and at least one push button.

10. The assay device of claim **1**, wherein the housing includes a memory card slot configured to receive a memory device, and the control module is in communication with the memory card slot.

11. A method of assaying the application of energy to a plurality of samples in vitro, the method comprising:
- applying the plurality of samples to individual wells of a culture plate;
- aligning at least one energy emitter with each individual well of the culture plate;
- simultaneously applying energy at a separate frequency toward each individual well via each of the at least one energy emitters for a first time period; and
- incubating the wells for a second time period.

12. The method of claim **11** and further comprising providing a device including an array, wherein the at least one energy emitter is positioned on the array; and positioning the culture plate adjacent to the array.

13. The method of claim **12**, wherein the step of positioning the culture plate adjacent to the array includes inserting the culture plate into a socket of the device.

14. The method of claim **12** and further comprising monitoring a temperature of the array.

15. The method of claim **12**, wherein the step of incubating the wells includes thermally controlling a temperature of the array.

16. The method of claim **11** and further comprising analyzing the samples after the second time period.

17. The method of claim **11**, wherein the first time period and the second time period overlap each other.

18. The method of claim **11** and further comprising receiving a treatment program from a memory device, the treatment program including specific frequencies to apply, the first set time period, and the second set time period.

19. The method of claim **11**, wherein the step of applying energy includes of applying one of the following types of energy: radio frequency; electric field; magnetic field; non-thermal plasma; and light

20. The method of claim **11** and further comprising storing frequency and temperature data to memory after the step of applying energy.

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摘要(译)

一种测定装置和测定体外向多个样品施加能量的方法。测定装置包括壳体，阵列和控制模块。壳体包括尺寸适于容纳培养板的插座。该阵列包括多个发射器并且位于邻近插座的壳体内，使得当培养板被接收在插座中时，多个发射器各自与培养板的至少一个培养孔对齐。控制模块可操作地耦合到阵列并且被配置为单独地驱动多个发射器。控制模块被配置为同时以不同频率驱动多个发射器中的至少两个。