

THERMAL CYCLING SYSTEM

FIELD OF THE INVENTION

[0001] The present disclosure relates to a thermal cycling system, and more particularly to a thermal cycling system applied to a polymerase chain reaction.

BACKGROUND OF THE INVENTION

[0002] The demand of fast turnaround time in quantitative polymerase chain reaction (qPCR) market becomes urgent recently. End users of qPCR systems from different fields, such as hospitals, research institutions or clinics in rural areas all eager to get the test result as soon as possible. Doctors need to get the report to identify infectious diseases that the patients might have, so the prompt treatment is necessary to save their life.

[0003] In rural areas or developing countries, ultrafast qPCR will be a solution to provide in-vitro diagnostic report in few minutes, instead of several days. However, one of the bottlenecks of ultrafast qPCR system is the speed of thermal cycling for PCR amplification. The thermal cycling technique for PCR amplification not only needs to meet the requirement of fast heating and cooling rate, but also needs to provide the precise and stable working temperature at different temperature stages during PCR amplification. However, the thermal cycling technologies for the applications mentioned above could not meet the requirement of PCR amplification. A variety of thermal cycling technologies have been developed and applied for qPCR amplification in recent years, but those technologies have different drawbacks such as slow thermal cycling speed, bulky size with heavy system, and imprecise control of temperature.

[0004] In addition, the more DNA samples tested in a system, the more difficulties the system has to maintain uniform heating. If the dimension of a conventional thermal cycler scales up for high throughput, the temperature differences among the plurality of multiple wells will become larger. Under this circumstance, it is very difficult to simultaneously perform ultrafast qPCR on a plurality of bio samples with uniform heating under the structure of a conventional thermal cycling system. On one hand, to deal with single bio sample, it causes energy waste, low heating efficiency and high cost. On the other hand, to deal with multiple bio samples, it causes short life span, complex system and complex sample preparation.

[0005] Therefore, how to develop a thermal cycling system that can solve the drawbacks in prior arts and have advantages fitting the applications, is substantially the urgent problem that must be solved right now.

SUMMARY OF THE INVENTION

[0006] It is an object of the present disclosure to provide a thermal cycling system in order to overcome the above-mentioned drawbacks encountered by the prior arts.

[0007] The present disclosure provides a thermal cycling system. Since the light emitted by the light source is magnified and collimated as an output beam, and the output beam is evenly expanded and distributed for heating a plurality of target samples received by the chamber, the target samples are uniformly heated. In addition, the target samples are continuously cooled by the cooling device, and the light source is enabled or disabled according to the thermal cycling profile for heating the target samples, such that an ultrafast thermal cycling with uniform heating and precise temperature control for target samples is implemented. As a result,

the energy is effectively used, the heating efficiency is enhanced, and the cost is lowered.

[0008] The present disclosure also provides a thermal cycling system. Since the light source, the optical element, the set of optics and the chamber attached with the cooling device are disposed along the optical path, the structure of the thermal cycling system is compact and simple. The sample preparation is simplified.

[0009] In accordance with an aspect of the present disclosure, there is provided a thermal cycling system. The thermal cycling system includes a light source, an optical element, a set of optics, a chamber and a cooling device. The light source is emitting light to an optical path. The optical element is disposed on the optical path for magnifying and collimating the light into an output beam. The output beam is evenly distributed. The set of optics is disposed behind the optical element along the optical path for evenly expanding and distributing the output beam. The chamber is disposed behind the set of optics along the optical path for receiving a plurality of target samples. The output beam is guided to the chamber for heating the target samples. The cooling device is attached to the chamber for cooling the chamber. The target samples are continuously cooled by the cooling device, and the light source is enabled or disabled according to a thermal cycling profile.

[0010] In accordance with another aspect of the present disclosure, there is provided a thermal cycling system. The thermal cycling system includes a light source, an optical element, a set of optics, a chamber, a cooling device and a temperature control unit. The light source is emitting light to an optical path. The optical element is disposed on the optical path for magnifying and collimating the light into an output beam. The output beam is evenly distributed. The set of optics is disposed behind the optical

element along the optical path for evenly expanding and distributing the output beam. The chamber is disposed behind the set of optics along the optical path for receiving a plurality of target samples. The output beam is guided to the chamber for heating the target samples. The cooling device is attached to the chamber for cooling the chamber. The temperature control unit is connected with the light source and the cooling device. The light source and the cooling device are controlled by the temperature control unit to perform a plurality of thermal cycles on the target samples.

[0011] The above contents of the present disclosure will become more readily apparent to those ordinarily skilled in the art after reviewing the following detailed description and accompanying drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 schematically illustrates a cross-sectional view of a part of a thermal cycling system according to an embodiment of the present invention;

[0013] FIG. 2 schematically illustrates a structure of a thermal cycling system according to an embodiment of the present invention;

[0014] FIG. 3 schematically illustrates the power distribution of an output beam illuminating on a chamber of a thermal cycling system according to an embodiment of the present invention;

[0015] FIG. 4 schematically illustrates a temperature-time diagram of a test result recording thermal cycles within ± 1 degree Celsius of the holding temperature implemented by a thermal cycling system according to an embodiment of the present invention;

[0016] FIG. 5 schematically illustrates a temperature-time diagram of a test result recording 40 thermal cycles that takes less than 2 minutes

implemented by a thermal cycling system according to an embodiment of the present invention;

[0017] FIG. 6 schematically illustrates the configuration of a light source, a cooling device, a sensor, a temperature control unit and a graphical user interface of a thermal cycling system according to an embodiment of the present invention;

[0018] FIG. 7 schematically illustrates a flow chart of thermal cycles implemented by a thermal cycling system according to an embodiment of the present invention;

[0019] FIG. 8 schematically illustrates a top view of a chamber of a thermal cycling system according to an embodiment of the present invention; and

[0020] FIG. 9 schematically illustrates a structure of a chamber of a thermal cycling system according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0021] The present disclosure will now be described more specifically with reference to the following embodiments. It is to be noted that the following descriptions of preferred embodiments of this disclosure are presented herein for purpose of illustration and description only. It is not intended to be exhaustive or to be limited to the precise form disclosed.

[0022] Please refer to FIG. 1 and FIG. 2. FIG. 1 schematically illustrates a cross-sectional view of a part of a thermal cycling system according to an embodiment of the present invention. FIG. 2 schematically illustrates a structure of a thermal cycling system according to an embodiment of the present invention. According to an embodiment of the present invention, a thermal cycling system 1 includes a light source 2, an optical element 3, a set of optics 4, a chamber 5 and a cooling device 6.

Light is emitted to an optical path by the light source 2. The optical element 3 is disposed on the optical path for magnifying and collimating the light into an output beam. The output beam is evenly distributed by the optical element 3. The set of optics 4 is disposed behind the optical element 3 along the optical path for evenly expanding and distributing the output beam into a bigger area. The chamber 5 is disposed behind the set of optics 4 along the optical path for receiving a plurality of target samples. The output beam is guided to the chamber 5 for heating the target samples. The cooling device 6 is attached to the chamber 5 for cooling the chamber 5.

[0023] Since the target samples are received in the chamber 5, the target samples are continuously cooled by the cooling device 6, and the light source 2 is enabled for heating the target samples or disabled according to a thermal cycling profile. In particular, according to the thermal cycling profile, the light source 2 is enabled to heat the target samples to a first preset temperature (e.g. 95 degrees Celsius for denaturation), and when the light source 2 is disabled, the target samples are cooled to a second preset temperature (e.g. 65 or 60 degrees Celsius for annealing) by the cooling device 6.

[0024] As a result, the target samples are uniformly heated, and an ultrafast thermal cycling with uniform heating and precise temperature control for target samples is implemented. The energy is effectively used, the heating efficiency is enhanced, and the cost is lowered.

[0025] On the other hand, since the light source 2, the optical element 3, the set of optics 4 and the chamber 5 attached with the cooling device 6 are disposed along the optical path, the structure of the thermal cycling system 1 is compact and simple. The sample preparation is simplified.

[0026] Please refer to FIG. 1 and FIG. 2 again. The set of optics 4 includes a beam splitter 41 and a lens group 42. The lens group 42 is

disposed behind the optical element 3 along the optical path, and the beam splitter 41 is disposed between the optical element 3 and the lens group 42. The optical element 3 is disposed between the light source 2 and the beam splitter 41. The optical element 3 is for example a light pipe, but not limited thereto. One end of the light pipe is disposed adjacent to the light source 2, and the other end of the light pipe is disposed adjacent to the beam splitter 41, but not limited thereto.

[0027] In some embodiments, a thermal cycling system 1 further includes a housing 7. The optical element 3, the set of optics 4 and the chamber 5 are disposed in the housing 7. The light source 2 and the cooling device 6 may be held by the housing 7. For example, the light source 2 is at least partially disposed in the housing 7. In other words, the light source 2 may be completely received in the housing 7, or partially protruded outside the housing 7. Similarly, the cooling device 6 is partially disposed in the housing 7.

[0028] In some embodiments, the cooling device 6 includes at least one active cooler and at least one passive cooler. The active cooler and the passive cooler are connected with each other. The passive cooler is preferably a heatsink, and the active cooler is preferably a thermoelectric cooler (TEC). Alternatively, the passive cooler may be a heat spreader, a heat pipe or a thermal interface material (TIM), and the active cooler may be a cooling fan, a blower or forced liquid coolant, but not limited thereto.

[0029] Please refer to FIG. 1, FIG. 2 and FIG. 3. FIG. 3 schematically illustrates the power distribution of an output beam illuminating on a chamber of a thermal cycling system according to an embodiment of the present invention. As shown in FIGS. 1-3, the light source 2 is preferably an infrared (IR) laser unit. Since the IR laser unit is a solid-state light-emitting element, the life span of the light source 2 is obviously longer than

the life spans of lamps of prior arts. Alternatively, the light source 2 may be a light-emitting diode (LED), a tungsten lamp or a halogen lamp, but not limited thereto. In addition, the chamber 5 may be a chamber with area equal to 30 mm x 30 mm (i.e. 900 mm²). Preferably, the light emitted by the light source 2 is finally magnified, collimated, evenly expanded and evenly distributed into an output beam with area equal to 30 mm x 30 mm (i.e. 900 mm²), such that the full area of the chamber 5 is uniformly heated. Therefore, the temperature deviation at different location of the chamber 5 is negligible at any given point. The uniformity can be defined as the Japanese Business Machine Makers Association (JBMA) uniformity. The illumination value at quadrants Q1, Q2, Q3 and Q4 and the center should be captured by photodetector as shown in FIG. 3. The calculation for uniformity is defined as below:

[0030] Uniformity (%) = {[Q1, Q2, Q3, Q4 (average, power)] / Center(average, power)} * 100%

[0031] In the present invention, the uniformity is within 5% power deviation from each quadrant (as shown in FIG. 3).

[0032] Please refer to FIG. 4. FIG. 4 schematically illustrates a temperature-time diagram of a test result recording thermal cycles within +/- 1 degree Celsius of the holding temperature implemented by a thermal cycling system according to an embodiment of the present invention. As shown in FIG. 4, 40 thermal cycles of the target samples from 65 to 95 degrees Celsius within +/- 1 degree Celsius of the holding temperature are implemented by a thermal cycling system of the present invention. It is obvious that the precise temperature control with a long duration time can be achieved by a thermal cycling system of the present invention.

[0033] Please refer to FIG. 5. FIG. 5 schematically illustrates a temperature-time diagram of a test result recording 40 thermal cycles that

takes less than 2 minutes implemented by a thermal cycling system according to an embodiment of the present invention. As shown in FIG. 5, 40 thermal cycles of the target samples from 65 to 95 degrees Celsius are implemented within 116 seconds. In other words, 40 thermal cycles would totally take less than 2 minutes (i.e. 120 seconds) which is faster than existing thermal cyclers in the market. It should be noted that in prior art, 40 thermal cycles of a bio sample usually take 30-50 minutes. The ultrafast thermal cycling is implemented by the present invention.

[0034] Please refer to FIG. 1, FIG. 2 and FIG. 6. FIG. 6 schematically illustrates the configuration of a light source, a cooling device, a sensor, a temperature control unit and a graphical user interface of a thermal cycling system according to an embodiment of the present invention. According to an embodiment of the present invention, the thermal cycling system 1 further includes a sensor 8 and a temperature control unit 9. The sensor 8 is connected with a computer for monitoring real-time temperatures respectively corresponded to the target samples and an output power of the light source 2. The temperature control unit 9 is connected with the light source 2 and the cooling device 6. The light source 2 and the cooling device 6 are controlled by the temperature control unit 9 according to the real-time temperatures and the output power sensed by the sensor 8, and the thermal cycling profile. In some embodiments, the computer may be a control system provided with a graphical user interface (GUI) 10 for being controlled by a user, but not limited thereto. The control system is connected with the light source 2 and the cooling device 6. When data measured by the sensor 8 is received by the control system, a command is sent to the light source 2 and the cooling device 6, thereby changing the reaction temperature for thermal cycling. In other words, the light source

2 is enabled or disabled according to the command sent by the control system, but not limited thereto.

[0035] In some embodiments, the control system allows on the spot adjustment of the duration and output power of the light source 2 based on a feedback signal of the sensor 8 and the set parameters. Furthermore, the graphical user interface 10 allows the user to adjust the thermal cycling profile based on the demands, such as ramping up rate and cooling rate, incubation time and incubation temperature, denaturation time and denaturation temperature, annealing time and annealing temperature, and a preset number of thermal cycles.

[0036] Please refer to FIG. 1, FIG. 4 and FIG. 7. FIG. 7 schematically illustrates a flow chart of thermal cycles implemented by a thermal cycling system according to an embodiment of the present invention. A thermal cycling profile can be configured with P, I, D control based on requirements. In other words, parameters such as PID control, holding time, laser output power, sampling time, holding temperature, ramping rate, variation of temperature, number of cycles, input power of cooling unit, ..., etc. are configurable. A flow chart of thermal cycles includes steps as follows. As shown in step S10, ramping up the temperature according to the parameters. Next, as shown in step S20, controlling the power of laser (i.e. the light source 2). Then, as shown in step S30, heating the target samples to a max temperature. Next, as shown in step S40, holding the temperature for an initial time, in which the initial time can be adjusted on demand. Then, as shown in step S50, starting thermal cycles. A thermal cycle includes step S60, step S70 and step S80. The step S60 is a step of holding the temperature (i.e. the first preset temperature) for denaturation time. The step S70 is a step of ramping down the temperature according to the parameters. The step S80 is a step of holding the temperature (i.e. the

second preset temperature) for annealing time. After a thermal cycle is done, step S90 of checking the number of thermal cycles is performed after the step S80. If the preset number of thermal cycles is not completed, step S100 of ramping up the temperature according to the parameters is performed after the step S90, and the step S60, the step S70, the step S80, the step S90 and the step S100 are repeated until the preset number of thermal cycles is completed.

[0037] Please refer to FIG. 8. FIG. 8 schematically illustrates a top view of a chamber of a thermal cycling system according to an embodiment of the present invention. FIG. 9 schematically illustrates a structure of a chamber of a thermal cycling system according to an embodiment of the present invention. As shown in FIG. 8, the chamber 5 of the thermal cycling system of the present invention includes a plurality of wells 51, so that the thermal cycling system of the present invention may be called as a thermal cycling system having multiple wells 51. A number of the target samples is equal to a number of the wells 51, each of the wells 51 has a recess 511, a first channel 512 and a second channel 513, and the recess 511 is communicated with the first channel 512 and the second channel 513 respectively. In particular, the target samples are one-to-one received by the recesses 511, each of the target samples is inputted to the corresponded one of the recesses 511 through the corresponded one of the first channels 512, and an instantaneous temperature of one of the target samples is read by a thermal reading device through the corresponded one of the second channels 513. The number of the wells can be 9 as shown in FIG. 8 and FIG. 9, but not limited thereto.

[0038] Please refer to FIG. 1, FIG. 8 and FIG. 9. FIG. 9 schematically illustrates a structure of a chamber of a thermal cycling system according to an embodiment of the present invention. As shown in FIG. 1, FIG. 8 and

FIG. 9, the chamber 5 further includes a main body 50 and a protection plate 52. The wells 51 are evenly distributed on the main body 50. The protection plate 52 is disposed on the main body 50 and disposed between the main body 50 and the set of optics 4, and the recesses 511, the first channels 512 and the second channels 513 of the wells 51 are covered by the protection plate 52. In some embodiments, the main body 50 is made of a thermally conductive and bio-compatible material, such that the target samples may be uniformly and appropriately heated and/or cooled. The biocompatibility of the main body 50 can be supported and proved by experimental data with the target samples themselves and the target samples with the main body 50. In some embodiments, the protection plate 52 is an optically transparent plate.

[0039] From the above discussion, the present disclosure provides a thermal cycling system. Since the light emitted by the light source is magnified and collimated as an output beam, and the output beam is evenly expanded and distributed for heating a plurality of target samples received by the chamber, the target samples are uniformly heated. In addition, the target samples are continuously cooled by the cooling device, and the light source is enabled or disabled according to the thermal cycling profile for heating the target samples, such that an ultrafast thermal cycling with uniform heating and precise temperature control for target samples is implemented. As a result, the energy is effectively used, the heating efficiency is enhanced, and the cost is lowered. Meanwhile, since the light source, the optical element, the set of optics and the chamber attached with the cooling device are disposed along the optical path, the structure of the thermal cycling system is compact and simple. The sample preparation is simplified.

[0040] The present disclosure can be modified by one skilled in the art as various modifications, but none of the modifications is not included within the scope of the claims.

WHAT IS CLAIMED IS:

1. A thermal cycling system, comprising:

a light source emitting light to an optical path;

an optical element disposed on the optical path for magnifying and collimating the light into an output beam, wherein the output beam is evenly distributed;

a set of optics disposed behind the optical element along the optical path for evenly expanding and distributing the output beam;

a chamber disposed behind the set of optics along the optical path for receiving a plurality of target samples, wherein the output beam is guided to the chamber for heating the target samples; and

a cooling device attached to the chamber for cooling the chamber;

wherein the target samples are continuously cooled by the cooling device, and the light source is enabled or disabled according to a thermal cycling profile.

2. The thermal cycling system according to claim 1, wherein according to the thermal cycling profile, the light source is enabled to heat the target samples to a first preset temperature, and when the light source is disabled, the target samples are cooled to a second preset temperature by the cooling device.

3. The thermal cycling system according to claim 1 further comprising a sensor and a temperature control unit, wherein the sensor is connected with a computer for monitoring real-time temperatures respectively corresponded to the target samples and an output power of the light source, the temperature control unit is connected with the light source and the cooling device, and the light source and the cooling device are controlled by the temperature control unit according to the real-time temperatures and the output power sensed by the sensor, and the thermal cycling profile.

4. The thermal cycling system according to claim 1, wherein the light source is an infrared laser unit, a light-emitting diode, a tungsten lamp, or a halogen lamp.
5. The thermal cycling system according to claim 1, wherein the set of optics comprises a beam splitter and a lens group, wherein the lens group is disposed behind the optical element along the optical path, and the beam splitter is disposed between the optical element and the lens group.
6. The thermal cycling system according to claim 5, wherein the optical element is disposed between the light source and the beam splitter.
7. The thermal cycling system according to claim 5, wherein the optical element is a light pipe, one end of the light pipe is disposed adjacent to the light source, and the other end of the light pipe is disposed adjacent to the beam splitter.
8. The thermal cycling system according to claim 1 further comprising a housing, wherein the optical element, the set of optics and the chamber are disposed in the housing.
9. The thermal cycling system according to claim 8, wherein the light source and the cooling device are held by the housing.
10. The thermal cycling system according to claim 8, wherein the light source is at least partially disposed in the housing.
11. The thermal cycling system according to claim 8, wherein the cooling device is partially disposed in the housing.
12. The thermal cycling system according to claim 1, wherein the cooling device comprises at least one active cooler and at least one passive cooler, and the active cooler and the passive cooler are connected with each other.
13. The thermal cycling system according to claim 12, wherein the passive cooler is a heatsink, a heat spreader, a heat pipe or a thermal interface material.

14. The thermal cycling system according to claim 12, wherein the active cooler is a thermoelectric cooler, a cooling fan, a blower or forced liquid coolant.

15. The thermal cycling system according to claim 1, wherein the chamber comprises a plurality of wells, a number of the target samples is equal to a number of the wells, each of the wells has a recess, a first channel and a second channel, and the recess is communicated with the first channel and the second channel respectively.

16. The thermal cycling system according to claim 15, wherein the target samples are one-to-one received by the recesses, each of the target samples is inputted to the corresponded one of the recesses through the corresponded one of the first channels, and an instantaneous temperature of one of the target samples is read by a thermal reading device through the corresponded one of the second channels.

17. The thermal cycling system according to claim 15, wherein the chamber further comprises a main body and a protection plate, the wells are evenly distributed on the main body, the protection plate is disposed on the main body and disposed between the main body and the set of optics, and the recesses, the first channels and the second channels of the wells are covered by the protection plate.

18. The thermal cycling system according to claim 17, wherein the main body is made of a thermally conductive and bio-compatible material.

19. The thermal cycling system according to claim 17, wherein the protection plate is an optically transparent plate.

20. A thermal cycling system, comprising:

 a light source emitting light to an optical path;

 an optical element disposed on the optical path for magnifying and collimating the light into an output beam, wherein the output beam is evenly

distributed;

a set of optics disposed behind the optical element along the optical path for evenly expanding and distributing the output beam;

a chamber disposed behind the set of optics along the optical path for receiving a plurality of target samples, wherein the output beam is guided to the chamber for heating the target samples;

a cooling device attached to the chamber for cooling the chamber; and

a temperature control unit connected with the light source and the cooling device, wherein the light source and the cooling device are controlled by the temperature control unit to perform a plurality of thermal cycles on the target samples.