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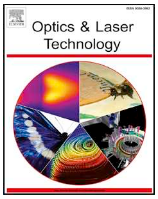

Development of a new multi-mode NIR laser system for photodynamic therapy

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HIGHLIGHTS

- Super pulse mode for reduced thermal damage and slightly deeper penetration.
- Current and temperature stability with different illumination modes.
- ARM-based TEC controller and Laser diode driver.
- Triple microprocessor for optical and electrical stability.

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ABSTRACT

Photodynamic Therapy (PDT) has been used in various fields especially in cancer treatment. In PDT, designing a light source has vital importance in order to achieve a successful treatment. Among the light sources, Lasers are important candidates for their precise wavelengths to activate the photosensitizers (PS), coherent nature and fiber-coupled usage. In order to achieve perfect PDT treatment, the Laser light sources needs to be embedded with high stability current, temperature controllers and closed loop control systems.

In this study, a novel Multi-mode PDT Laser system (MPTL) was developed with four different radiation modes. Importantly, Super Pulse Mode (SPM) was implemented for the first time among the PDT Laser systems in the open literature to minimize the thermal damage to the target tissue. The proposed system achieved high optical output stability by precise current and temperature control of the Laser resonator. The MPTL achieved high optical output stability (± 1mW) in the range of 0–1500 mW, high wavelength stability (± 1nm) at 635 nm, and high temperature stability (± 0.2 °C) in all radiation modes. The MPTL system with super pulse mode can be safely used for wide range of PDT clinical applications.

1. Introduction

Photodynamic Therapy (PDT) is currently being used for treatment in various fields such as cancer, rheumatoid arthritis, dermatological and infectious diseases. PDT uses special compounds such as photosensitizers (PS), light and oxygen for targeted treatment. Successful treatment can be applied when these compounds exist around the desired target. In PDT cancer treatment, the PS exhibits selective affinity for tumor cells [1]. When it is activated by light, tumor cells are selectively destroyed. Following the light absorption, PS is stimulated to a higher energy state and two different types of reactions may occur resulting in this excitation [2,3]. In Type 2 reaction, reactive singlet oxygen causes tissue destruction by damaging vascular endothelium and cell membranes in the target tissue [4,5]. The short life span of the excess oxygen causes localized damage, therefore nearby healthy tissue is not affected by the mechanism [6,7].

The absorption spectra of the photosensitizers are different from each other. If the wavelength of the light is compatible with the peak value in the absorption spectrum of PS, the reaction will be more effective [1]. Therefore, the PDT needs a special light source that emits

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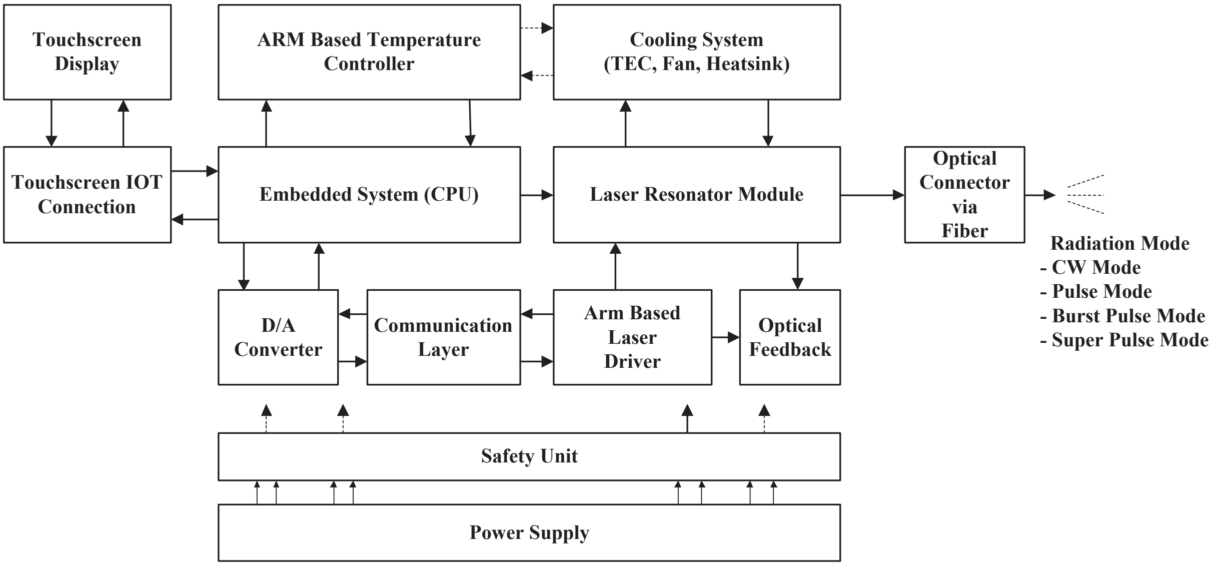

Fig. 1. The proposed MPTL for PDT.

the peak wavelength of the PS [4]. PS may vary according to the specific application. Some PS's can be harmful to the body and induce pain when injected [8–10]. There are several PS on the market that had an FDA (Food and drug administration) approval for clinic use. And among the other PS's, ALA-5 (aminolevulinic acid-5) tested and proven to be more effective and has no toxic effect, and Ala-5 can be used effectively in the areas such as; melanoma, skin cancer, colorectal cancer, breast cancer, bladder cancer and actinic keratosis [11,12].

In PDT, several light sources are used such as Lasers (Light Amplification by Stimulated Emission of Radiation), halogen, xenon, light-emitting diodes to activate the PS [13]. However, the Lasers have recently been widely used even though the higher costs over the other alternatives [14,15]. One of the main reasons is that the Laser light can easily be transmitted through the optical fiber. Therefore, it is possible for Laser light can be focused on a very small diameter of tumors with the help of the lenses placed at the end of the fiber optic cable. Laser systems can deliver the exact peak point of the PS activation spectrum [10,8]. There are several types of Lasers such as helium-neon, diode, argon and KTP (blue-green spectrum, crystal-based) Lasers that have been used in PDT. However, diode Lasers are currently preferred since they offer great convenience in terms of portability compared to other types. A diode Laser has the advantages of semiconductor technology that produces coherent projection of light in the visible to infrared range. It uses a light beam with a narrow spectrum to target specific wavelength [17,18]. However, the PDT Laser system has some design challenges. Laser diodes (LD) need to be stabilized at a certain temperature for illumination of the desired wavelength. In different radiation modes, temperature controlling system design is a challenge. However, it can be achieved by TEC (thermoelectric cooling) system with closed-loop control methods [8,16–18]. In addition to these challenges, continuous illumination during the treatment causes thermal damage to the target and LD itself. Illumination mode variations can be used to reduce irreversible thermal damage reduction and to increase oxygen concentration in tissue [4,19,20]. The optimum Laser system should be designed to prevent thermal damage due to excess accumulation of optical energy in the Laser and to provide sufficient oxygen for successful treatment [21–24]. The laser diode can maintain more stable optic power output, more narrow wavelength bandwidth, better FHWM where the delivering of the peak absorption of PS more accurately.

In this study, a novel Multi-mode PDT Laser system (MPTL) was developed. The novelty of the study was that SPM (Super Pulse Mode) was implemented for the first time among the PDT Laser systems in the open literature. The proposed system achieved high optical output stability by precise Laser current control and stabilization of the temperature in the Laser resonator. Three main parts were developed to create the MPTL. The first part consisted of the main controller, communication module and GUI on a touch-screen. The second part included the fast switching Laser controller unit. Finally, the third part had the TEC system. The MPTL system has four different radiation modes for the desired light dose. The performance of the system for optical radiation modes was evaluated by measuring the variability and stability of the optical wavelength, the optical power output, and the Laser resonator temperature. All in all, the proposed system achieved high optical output stability (± 1mW) in the range of 0–1500 mW, high wavelength stability (± 1nm) at 635 nm, and high-temperature stability (± 0.2 °C) in all radiation modes.

2. Materials and method

MPTL system was designed to produce 0 to 1500 mW stable optical output at 635 nm with LD (Intense 5200 Series, USA). A temperature controller stabilized the Laser resonator temperature at 15° C for radiation modes. The embedded photodiode transimpedance amplifier circuit was used for constantly measuring the optical power output for all radiation modes. The high accuracy and high stability of the Laser output were accomplished using digital-to-analog (D/A) and current-to-voltage (I/V) converters that produced 4096 levels between the 0 to 1500 mW Laser optical output. The ARM-based microcontroller controlled the optical radiation mode with a PID (Proportional-Integral-Derivative) controller and the optical feedback from the LD was evaluated by ARM-based Laser driver unit. The IEC 60601-2-22 standard was implemented for a graphical user interface (GUI) and security management. The main block diagram of the developed system was illustrated in Fig. 1.

2.1. System design

The Laser system was designed and developed with various parts. The system consists of a main controller, Laser driver and TEC module with implemented algorithms. The software was developed for embedded systems. GUI was developed for maximizing the user experience and implemented with the light-based dosimetric algorithm.

2.1.1. Main controller design

The embedded system based main controller consists of a touchscreen, microcomputer, communication modules, and a connection shield. The microcomputer can communicate the Laser driver system and the temperature controller unit. The GUI was developed with light dose adjustment to maximize the effect of the treatment. The developed software was controlled via touchscreen and the user can choose radiation modes, radiation time, power and mode-specific illumination parameters. Before user choice, the system calculates the total energy with the implemented algorithm. By selecting the radiation mode and adjusting the power and duration of the radiation, the user can easily generate the appropriate radiation for treatment.

2.1.2. ARM-based laser driver design

The optical output stability is one of the most important specs in Photodynamic therapy. In LD's, there is an exponential relationship between the current passing through the diode and the terminal voltages. A small change in the voltage can cause a triple fold change on the current that drives the LD according to the experimental measurements. To achieve optical power output stability, four different PID polynomial function was implemented. In the Laser driver hardware, the voltage levels were controlled with 12-bit accuracy DAC (digital-analog converter) in the range 0 to 2.6 V. The current was controlled with a precision of 1 mA. The ARM-based Laser driver circuit contains a transimpedance amplifier circuit for measuring the photodiode current inside the Laser resonator. The system constantly controls the optical output of the system. The simplified LD constant current circuit was shown in Fig. 2.

In the basic circuit given in Fig. 2, the high input impedance of the terminals of the opamp (U1) was the key point. The opamp generates the output signal for equalizing the voltage between the input terminals to 0 V with impedance matching. The current flows through the resistor (R2) depended on the value of the V_{in} (Pin-44) connected to the Ic-U3 (Pin-3). The V_{in} voltage is generated by the microcontroller. Besides, to protect the microcontroller from excess current, U4-high speed optocoupler was used for switching. The current at the drain of the Q1 MOSFET, cannot flow through the gate terminal without microcontroller's supervision. After switching, desired current and voltage drops can be seen across the LD (D1) for precise control and parameters safety observations.

The properties of Continuous Wave Mode (CW), Pulse Mode (PM), Burst Pulse Mode (BPM) and Super Pulse Modes (SPM) are considered during the Laser driver unit design. The selection of time constant and threshold time for LD illumination is quite important for pulse modes to achieve precise light dose. The switching times of the Laser driver were adjusted according to the MOSFET input capacitance and resistance (R5). The time constant of the system was chosen as 1 μs. The system was calibrated according to the 1.5 μs for clear illumination to prevent the Laser resonator failure.

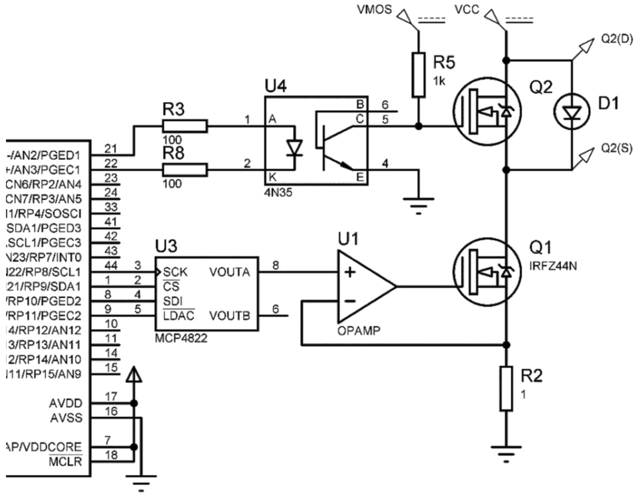

Fig. 2. The ARM-based LD constant current controller.

To produce an optical output, the current threshold of the LD was evaluated as a function of time constant for Pulse modes (Fig. 7). The current threshold was measured for nanosecond level illumination for SPM, which was the most critical parameter due to the extremely short pulse durations. The time constant of Super pulse mode was adjusted to threshold time plus illumination time for precise illumination per pulse.

2.2. Radiation modes

Radiation modes are configured according to the power value (mW) and output time (s) information to reach the desired energy level. Four different radiation mode energy levels are illustrated in Fig. 3. In pulse modes, the on/off time needs to be adjusted. The BPM is based on the PM which contains microsecond to millisecond level pulses inside of the pulses. This mode is designed to prevent thermal damage caused by the Laser's optical energy applied to the tissue. PM, BPM, SPM is capable increasing the tissue re-oxygenation [4]. In SPM, faster switching time is used for deeper penetration of the light in the tissue [21]. 200 ± 50 ns radiation at 100 ms second intervals occurs by repeating the value determined by the user. SPM aims to reach a higher penetration depth in the tissue.

The power of a light source and the delivered energy expressed are expressed Watts and Joules respectively. In PDT the power of per unit area called the irradiance and expressed in W/m^2 or mW/cm^2. For example, if an area of 5×5 cm^2 is uniformly irradiated with 2 W power, the irradiance is 80 mW/cm^2. The energy delivered to the surface in 30 min is 144 J/cm^2. The MPTL system made these calculations through the embedded algorithm and get the desired parameters from the specialist with the GUI. The controller processed the algorithm and then calculated the light dose for each radiation mode.

2.2.1. Laser driver software

The LD driver voltage was measured through the isolated input for electronic board safety measurements and the multi-region PID algorithm implemented in the ARM-based microcontroller.

The most important part related to the control of electrical parameters is the detection of P, I, and D coefficients. The transfer functions of the LD are difficult to determine, even in a simulation environment. According to the situation of LD, PID coefficients were determined by experimental methods.

The LD voltage drop was measured with a differential amplifier and read through the analog input of the microcontroller. The optical power values constantly compared with the reference value. The error was kept in a certain value (± 1% optic power) by the ARM-based Laser driver. The current is constantly adjusted by the controller according to temperature, voltage, and photodiode optical feedback.

2.2.2. TEC temperature controller

The temperature of the LD must remain constant in a narrow range for the desired radiation wavelength. The Laser output and wavelength of the diode Laser resonator can be affected by the system operation. To produce an optical wavelength at 635 nm according to the manufacturer's information, the internal temperature of the resonator should be maintained at 15 °C. Real-time measurements of temperature change requires a microprocessor integral (PID) control. Thereby, the closed-loop PID control was used for keeping the system in a specific temperature range (15 °C) [22]. The basic principle of the temperature control system was the diode that was in direct contact with the cold and hot sides of two Peltier elements (in Fig. 4). The purpose of double-sided temperature control in the system was to create the heating and cooling effect in the desired range.

Two main factors affecting the temperature control accuracy of the LD: are the effect of the temperature difference between the two ends of the TEC and the current passing through the Peltier elements. The

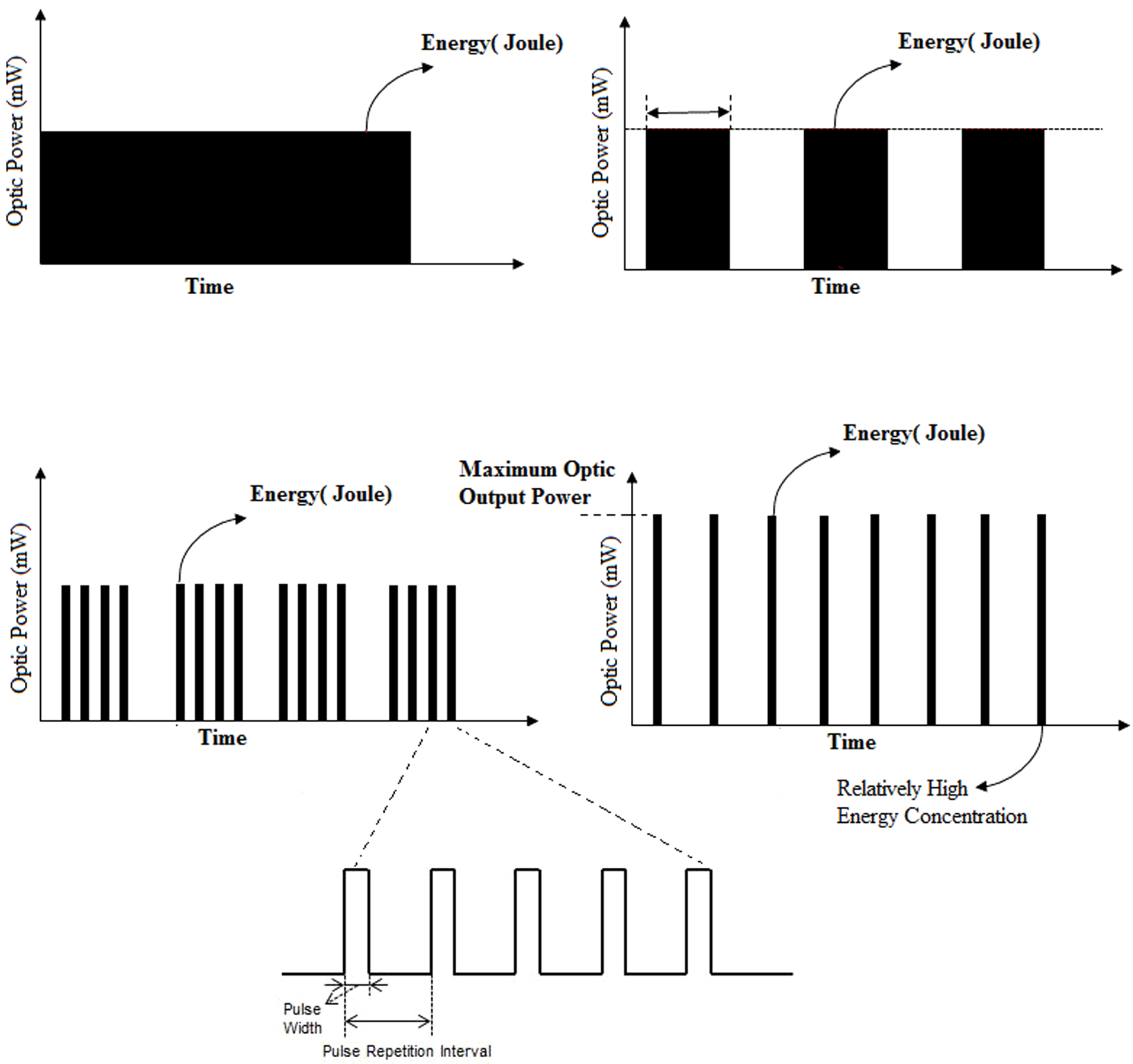

Fig. 3. Energy levels of the radiation modes of (a) CW, (b) PM, (c) BPM and (d) SPM.

temperature difference between the two ends of the TEC needs to be adjusted according to the heat produced by the LD because of the cases. In the first case, the Peltier element can reverse the direction of the heat flow between the cold and hot hands (connection points) by applying a thermocouple using an external or internal current. The physics of the Peltier effect can be defined as the tendency of the electrical current to

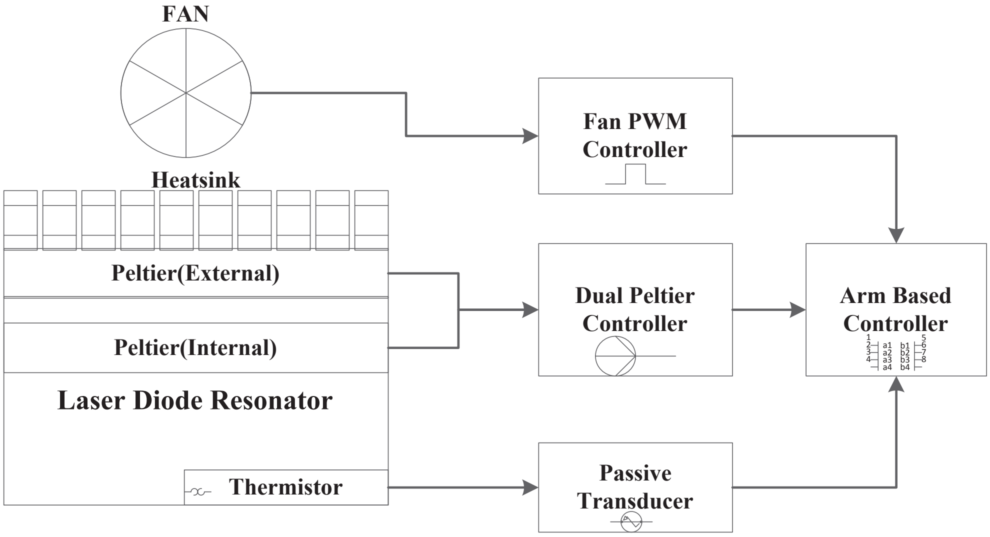

Fig. 4. The temperature control and TEC system.

drag the heat energy into a thermoelectric circuit. The current carries the internal energy of a conductor as it flows from one point to another. When an electric current passes from a material having an entropy different than another material, heat must be emitted or absorbed at the junction to neutralize the change in the energy of the carriers. In the second case, Peltier element can be damaged easily by the current. To protect the Peltier element, the current must be controlled more precisely. The current itself is a heat-producing event to prevent the Seeback, Joule and Peltier element effects. Pulse width modulation has been implemented for driving Peltier element [22–25]. TEC module driver was designed to eliminate any unwanted current spikes.

In the proposed design H-bridge circuit was used for driving the TEC module. Since the Peltier operation is directly connected to the DC; the system controls the current for both Peltier elements. Each Peltier element was controlled separately. The PID algorithm controls the direction and intensity of the current via PWM modulation with 1 mA precision, after measuring the temperature change.

2.2.3. Temperature controller software

The precise control of the TEC system is crucial for the PDT application. High stability achieved by detecting of P, I, and D coefficients of the system. Since there were two Peltier elements controlled with the same microprocessor, the PID coefficients were calculated and implemented separately according to the literature [22–26].

Temperature changes were constantly measured by the system. An error signal was sent to CPU when the temperature exceeds the desired range. After an error message, radiation was shut down by the main controller.

3. Results

The output of the MPTL was adjusted as a function of voltage-V, current-A, power-P, and temperature-°C to maintain perfect wavelength-nm and optic power-W balance for keeping radiation stable to perform successfully PDT treatment. The alteration of each parameter was recorded by keeping the other variables constant and the changes were discussed below.

3.1. Laser diode electrical control parameters and temperature stability

In experimental measurements, the variation of the current depending on voltage and relative power of the LD is shown in Fig. 5. The voltage and current measured and constantly compared to the feedback and the desired values obtained in real-time with the PID control algorithm. As shown in Fig. 5, the optical power cannot be obtained when the LD current does not reach 2.1 A. After going beyond this value, 17% LD current variation leads to 100% variation effect on the optical power. Namely, from 0 to 1500 mW optical output voltage drop was only between 1.7 and 2.6 Volts on LD. This voltage drop is continuously measured over the aluminum resistance connected in series to the internal resistance of the laser diode and compared with the reference voltage to ensure that it remains within the specified 1% error rate.

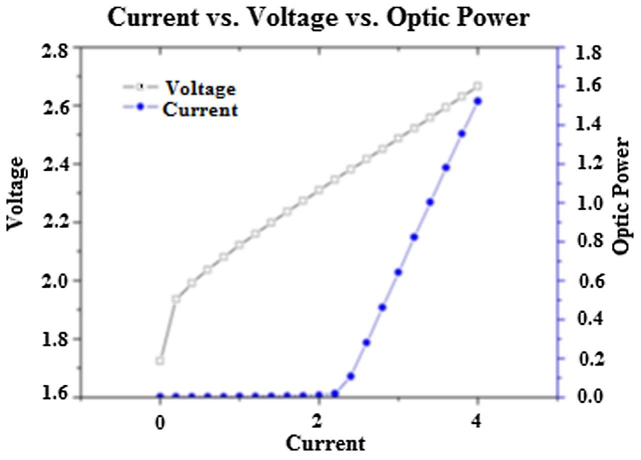

Fig. 5. LD optical output relation by current and voltage [4]

Also, the temperature stability of the system is crucial for the desired output. Optical power stability at a low output power level and wavelength stability at high output power level are considered as big problems for all PDT laser systems. TEC system, current and voltage control circuitry should work perfectly to prevent optic power oscillations and wavelength peak shifts at different powers.

The long term temperature stability graph was plotted using the values recorded for 6 h, and given in Fig. 6.a. The short term temperature stability was shown in Fig. 6.b. The LD temperature was kept constant at 15 ± 0.2 °C degree after switching current from 0 to 4 A which is a maximum change in the current for radiation. In Fig. 6.b, it is expected to stabilize the MPTL with the pre-illumination setting after the first radiation. The MPTL system was calibrated for all radiation modes after the temperature was settled within the error ± 0.2 °C. The temperature stabilization time was measured as 5 s in room temperature. The system achieved these specifications for all radiation modes. The difference in data for all modes was within the %0.01 margin. Therefore only one graph was demonstrated with the burst pulse mode averaged data.

3.2. Multiple PID regions

When a single PID region is applied to the entire system, the stable operation of the system was not possible for different power ranges. To get maximum optical power and wavelength stability, four different PID functions were implemented for four different power intervals as demonstrated in Fig. 7. There was second-order polynomial fit ($R^2 = 0.99$) for all PID regions.

3.3. Wavelength and optic power stability in radiation modes

Although the maximum clinical working time of the device is estimated as a 90 min, the data were taken for 6–12–24 h for specifying the limits of the system about stability. The spectrum stability was measured as a 635 nm ± 0.2, the temperature stability of the whole system was measured as 15 °C ± 0.2 and the optical power stability was measured as within the 1% error between 0 and 1500 mW for the proposed system.

Wavelength stability was measured as a function of time and power. The maximum optical output of the system was 1500 mW and the wavelength FWHM (Full width half maximum) was measured as 635 ± 1 nm (Fig. 8.a) for all radiation Modes. To measure the stability of the wavelength output, the system was operated at maximum power for 20 min, and as shown in Fig. 8.b, only ± 0.2 nm oscillation was observed. At low power levels, oscillation decreased to ± 0.1 nm between 0 and 400 mW. The system can supply the desired optical energy (power × time) value for four different radiation modes with a 1% error at the desired power and wavelength. All radiation modes demonstrated same wavelength stability as shown in Fig. 8 for preventing the confusion only one averaged data was shown. The same energy values for the stability of CW, PM and BPM were shown in Fig. 9a, b, and c. For SPM, the maximum optical power of the system, 1500 mW, as illustrated in Fig. 9d.

One of the biggest challenges was to produce the pulses and super pulses without harming the LD. The MPTL system needs to produce pulses without any harmful spikes. The minimum time for illumination, after switching the LD, was measured as 20 μs which constituted the time threshold. For PM and BPM, time constant was implemented in the algorithm for light dose calculation. In addition, SPM radiation was measured in the range of 200 ns ± 50 after the threshold value reached. In Fig. 10a and b oscilloscope output with spike elimination

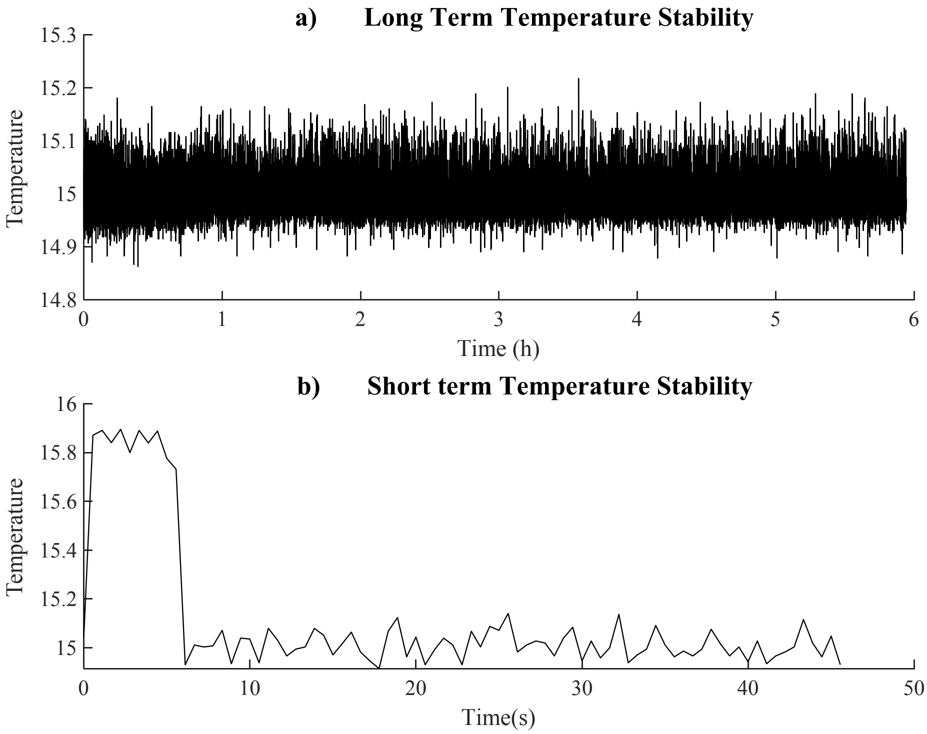

Fig. 6. (a) Overall temperature stability in 6 h working time (b) Temperature stabilizing response of the MPTL system.

process was illustrated for pulse mode. The current was exposed to sudden changes in very small time for pulse modes. Thereby, this process creates unwanted spikes. Spikes were eliminated via Laser driver design (see chapter 2.1.2 and Fig. 2) and time adjustments for all radiation modes.

In the developed system, perfect Optical output power (Fig. 9) and wavelength stability (Fig. 8) achieved over time with temperature stability (Fig. 6), different optical power output PID functions (Fig. 7) in radiation modes. After achieving the electrical and radiation stability, experiments were made in order to demonstrate the tissue thermal effect of the radiation modes. Measurements demonstrated below.

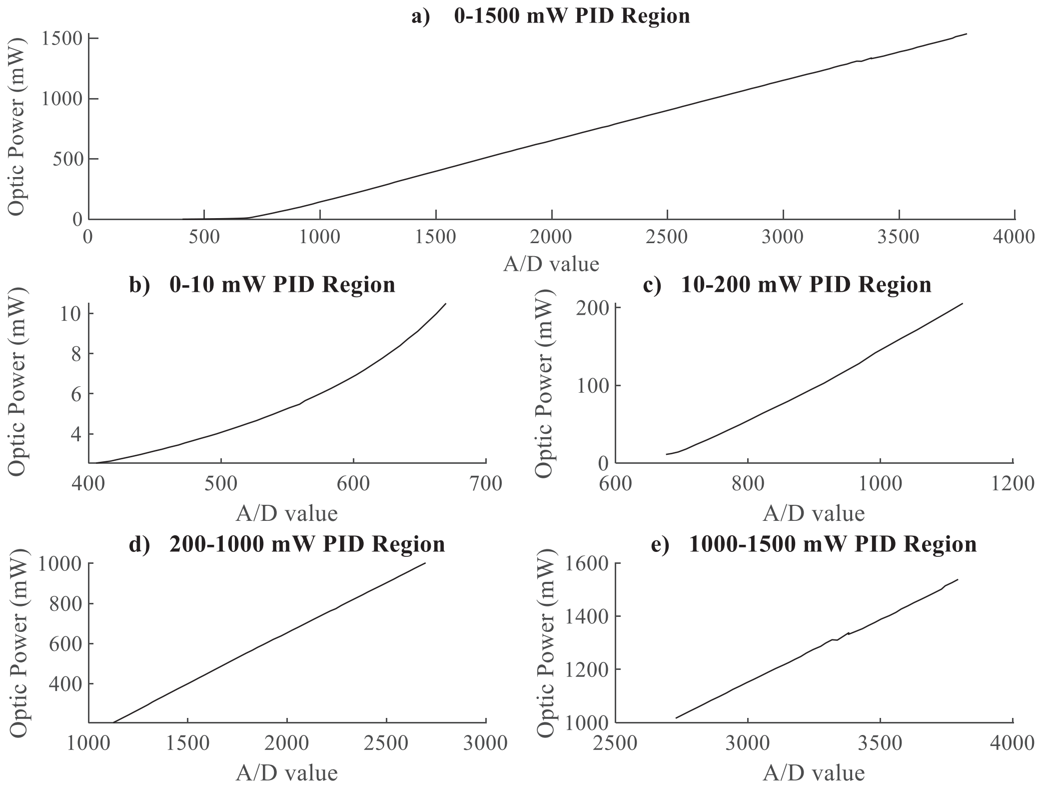

Fig. 7. (a) The optical power versus A/D value. (b) 0–10 mW, (b) 10–200 mW, (c) 200–1000 mW, (d) 1000–1500 mW.

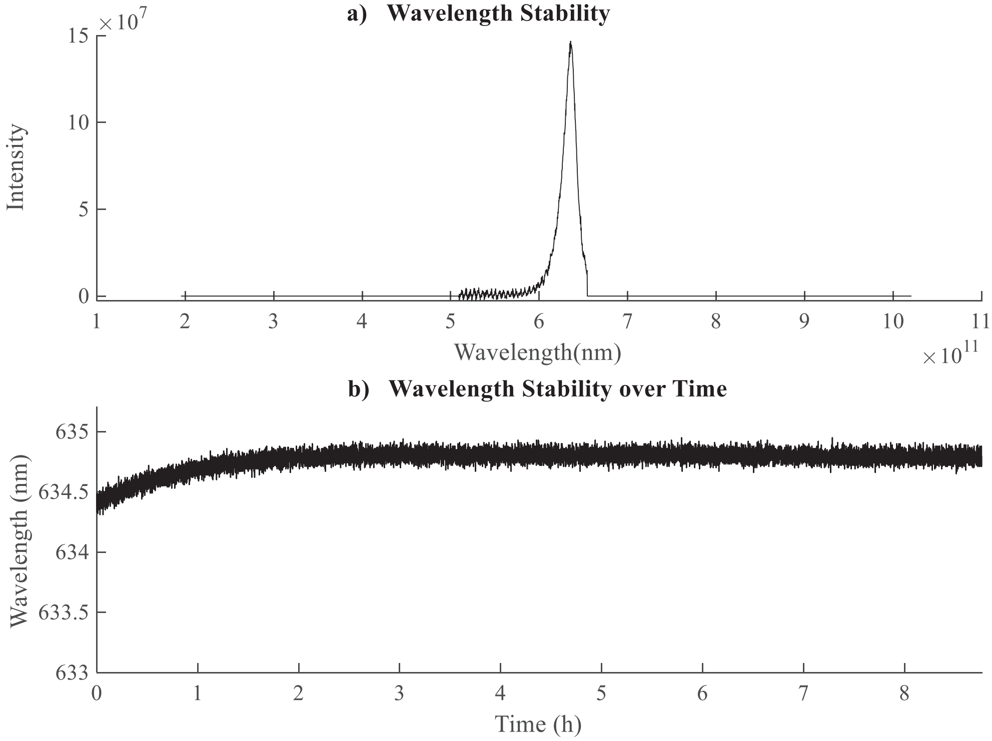

Fig. 8. All radiation modes, (a) The wavelength spectrum, (b) Laser output stability of wavelength over 10-hour time at 500 mW.

3.4. Thermal effect of irradiation modes on tissue

The used test setup to measure the temperature of the tissue surface is shown in Fig. 11. The components of the temperature measurement system are PDT Laser device (1), fiber optic cable (2), a collimator (3), temperature sensing device (4), tissue sample (5) and base (6).

The temperature changes were observed in chicken breast tissue. The target area was 2 cm^2, so the beam size adjusted to 1.5 cm^2. There is only 0. 1 °C temperature difference between the center of the target tissue and edge of the beam size. This also demonstrate the quality of the light that radiate from the MPTL system. The optical power was 100 mW/cm^2 and 300 mW/cm^2 for CW, PM, BPM and SPM. The laser

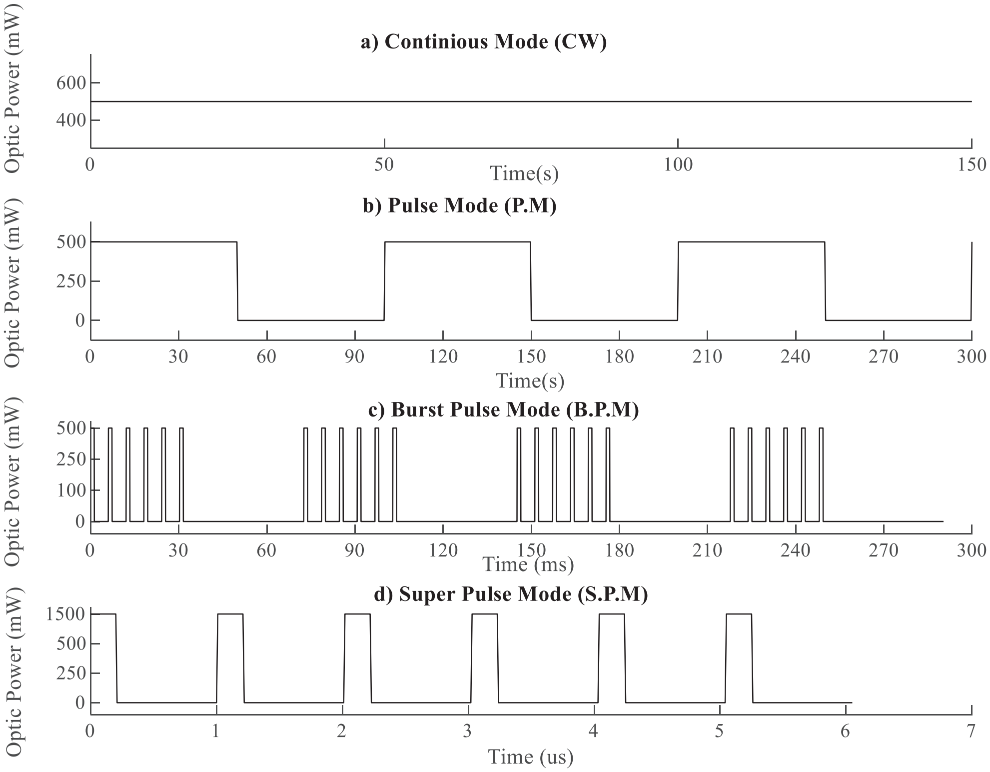

Fig. 9. Optical outputs of MPTL system: (a) CW, (b) PM, (c) BPM, (d) SPM.

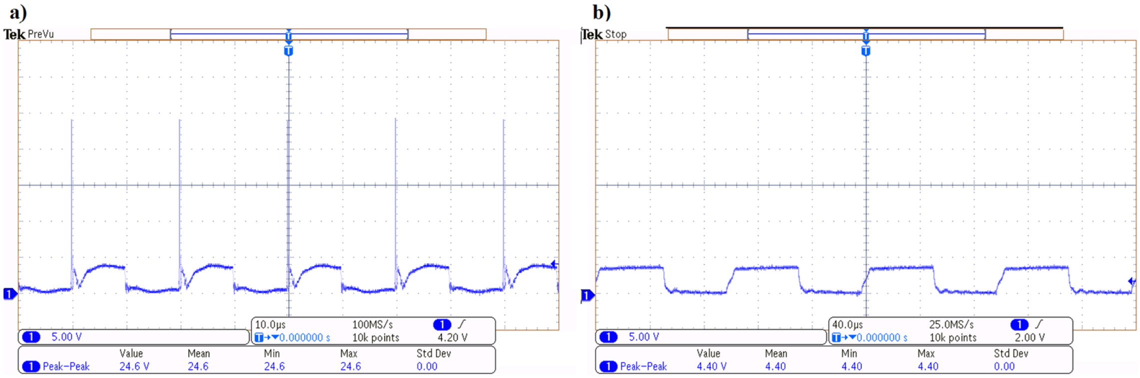

Fig. 10. (a) LD current pulses with unwanted spikes. (b) LD current pulses with eliminated spikes.

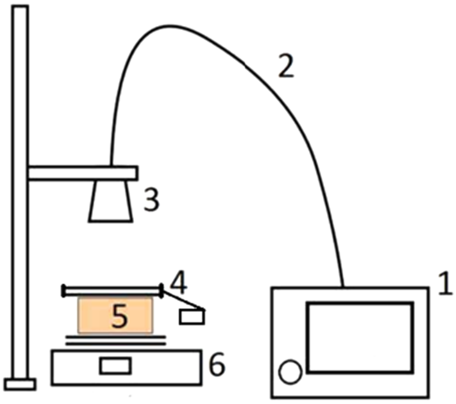

Fig. 11. The test setup used to measure the temperature of the tissue surface.

point temperature sensor (Wollex, Ultra, South Korea) was used for fast temperature measurement of the tissue. Collimator distance to the tissue was 10 cm. The exposure time was adjusted according to the Energy equation (J = watt × time). Therefore the exposure time was different for each radiation modes to deliver same amount of energy. CW, PM, BPM and SPM exposure time was 800, 1600, 1600, and 1600 s. The pulse of time was adjusted to delivering same amount of energy as shown in Fig. 9.

Temperature increments were taken per 10 J/cm^2 and are shown in Fig. 12. The temperature values reached after a total energy density of 800 J/cm^2 were measured as 46.5 °C in CW mode, 30.5 °C in pulse radiation mode, 28.5 °C in burst pulse mode and 26.8 °C in super pulse mode.

4. Discussion

Photodynamic therapy devices require precise and reliable controls for clinical and experimental applications. At the same time, it is expected that the calibration of the system will be completed in a short time for being ready to start operating. In this study, an effective photodynamic therapy laser device has been developed. The laser diode module and the irradiated tissue were protected from thermal damages by the TEC system and radiation modes. MPTL system was capable of self-calibrating by continuously measuring the optical power. The commercialized laser devices for PDT clinical applications have been examined in the literature. These systems may cause thermal damage to the tissue during treatment due to the lack of implementation of various radiation modes. H.s. Lim 2012 [4] developed the PDT device to prevent thermal damage with different modes. This PDT device was approved by Korean-FDA and has been used in the clinics. In his study, the PDT device had continuous, pulse and burst pulse modes. The study was demonstrated that the lowest thermal effect was achieved in burst pulse mode. However, the optical power cannot be continuously measured and calibrated thereby causing the optical output to oscillate. However, the MPTL device that we developed has four irradiation modes and can deliver high energy to the tissue in a very short amount of time with super pulse mode. Therefore, it creates 3.7 °C lower temperature changes on the tissue compared to the study by H. Lim 2012 [4]. Tissue temperature changes were shown in Fig. 12. Also, the MPTL system constantly calibrates all parameters to prevent oscillations of wavelength and optic power output. In order to achieve challenges about developing a laser device number of steps were followed and discussed below.

Various studies on temperature control of laser devices with TEC systems are shown in Table 1. The settling time of the temperature constant of the whole system, temperature changes of the laser diode module, optical output power and measured wavelength changes during the control were used as the comparison parameters.

The time required for the system temperature to remain constant at the reference value is one of the important parameters after system initialization. Similar studies that consist of TEC modules were examined. The temperature settling times were as shown in Table 1. In these studies, the temperature settling time was not given under which load and condition it was determined. For the MPTL system, the settling time was between 5 and 10 s for optic powers between 0 and 1500 mW with 10 W electrical system load. Importantly, this system specially designed for delivering the perfect light dose on PDT clinical applications in every radiation mode.

PDT laser systems was also examined for further discussion. Shadid et al. 2018 [30] developed a PDT laser system that consists of CW radiation mode at 635 nm peak wavelength and 2-W of optical output. However, the system was developed with one radiation mode and did not consist of self-optical calibration. In the study, wavelength, temperature stability or thermal damage was not considered. Driel et al. 2016 [31], was used a commercial PDT laser system (Modulight, 7710, Finland). The system specifications were 690 nm wavelength, CW mode, calibration before each usage. However, the system was developed with one radiation mode and a lack of self-optical calibration during PDT which can cause thermal damage, tissue re-oxygenation problems, and mistreatments. Oluwole et al. 2018 [32] used a commercial PDT laser system (Modulight, Turnkey Laser, Finland) which consists of a multi-wavelength and calibration module. However, the system developed with single-mode and optical power stability was not mentioned. Marks et al. 2000 [33] was used a PDT laser system which consists of 630 nm wavelength, fiber optic cable with the inflatable balloon. However, the system did not consist of any optical calibration, temperature calibration module or any radiation mode other than CW. Karamata et al. 2000 [34], was used a PDT laser system which consists of 690 nm wavelength for eye cataract treatment. The system had relatively low power, did not consist of any radiation modes and any optical or wavelength stability was not mentioned.

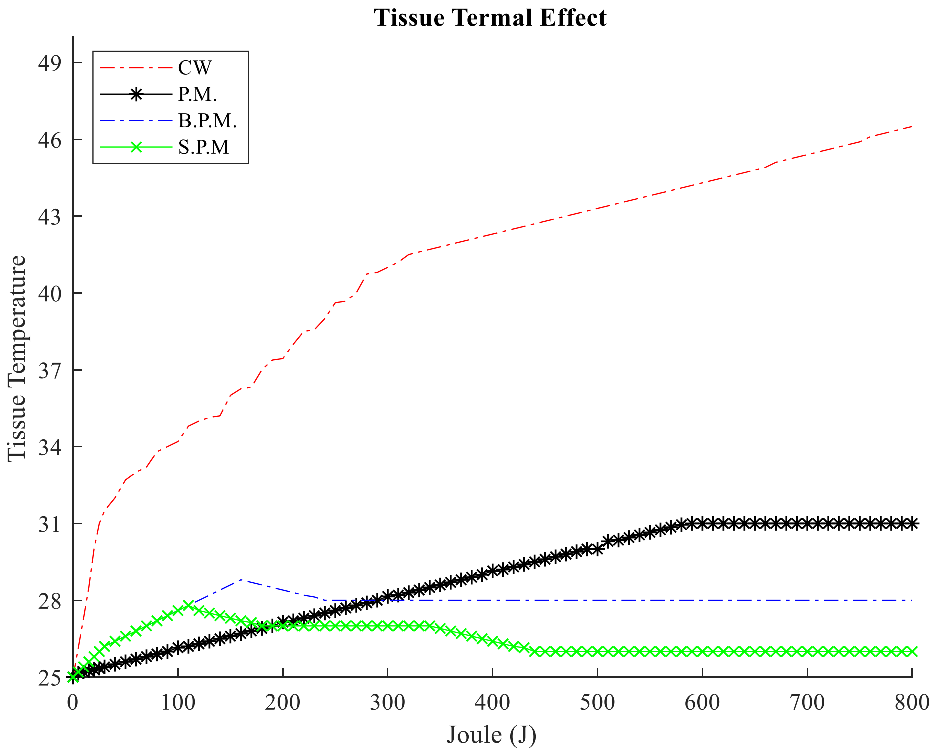

Fig. 12. Tissue temperature versus energy intensity for irradiation modes.

Table 1
Performance evaluation of TEC controller system.

System	$T_,$ (settling time)	Wavelength change	Δ°C	Watt
In this study	5 s	± 0,2%	± 0,2	1500 mW
Chengxiang [27]	15 min	< 0,5%	± 0,2	–
Hu [28]	6–7 min	–	± 0,2	–
Huang [29]	< 1 min	–	< 0,05	–
Lim [4]	10 min	± 0,2%	± 0,2%	350 mW

The importance of the short time pulse modulation has been shown by the studies in various field. Barbara et al. 2017 [35] showed the increased penetration depth of ER: YAG laser super pulses in the dermatological application. Balu et al. 2015 [36] demonstrated in human and animal tissues with a Yb-fiber laser at 1060 nm. The study demonstrated the super pulses had relatively higher tissue penetration depth. Gao et al. 2016 [37] was studied flat wart and facial black dots healed faster with super pulses. Importantly, Vladimir et al. 2016 [38] proved that the pulse modes have significant effect on re-oxygenation of the tissues during PDT. Vinnichenko et al. 2018 [39] verified the super pulse had deeper penetration effect on ablation, cut and coagulation on the tissue. There are also other fields that use super pulse for treatments. Anju et al. 2016 [40], Santo et al. 2018 [41] used super pulse for photobiomodulation and their studies demonstrated significant improvements on the wound healing and cardiopulmonary exercise tests. Silvia et al. 2009 [42] demonstrated increases osteoblast activity via super pulse. Vanessa dos et al. 2015 [43] demonstrated the thermal impact of phototherapy super-pulsed light sources on human skin. The study proves that super pulsed laser can diminish the thermal damage and discomfort after the treatment. According to the literature, The quality of the light source, light delivery technique and tissue thermal properties is an important aspect for PDT applications. Furthermore, the radiation effect to the tissues needs to be observed for every light source and radiation modes to examine tissue properties.

Tissue optical properties can affect the several components about the PDT. Knowledge about the temperature dependent changes in optical properties is needed for safer and more accurate laser treatments. Optical properties of the tissue are affected by temperature changes. The absorption and reduced scattering coefficients changes can be estimated from the reflectance and transmittance values. Ercan et al. 2018 [44] demonstrated that the total transmittance showed positive correlation with temperature while the diffuse reflectance was found to be negatively correlated. Although the absorption coefficient did not demonstrate a statistically significant change with temperature, the reduced scattering coefficient was negatively correlated. The results indicate that temperature-dependent changes in optical properties should be taken into consideration for a safer laser treatment. Therefore, the MPTL system was developed with high power, constant optical output feedback for self-calibration, fast system temperature calibration for the first operation, four different radiation modes, long term wavelength, and optical power stability to establish safer and more accurate treatment. The MPTL system could deliver SPM at high power in a short time with relatively high energy which was suitable for reducing thermal damage and improving re-oxygenation. In addition, light output of the systems can be transferred via fiber optic cable which gives an opportunity to perform minimally invasive tasks. With developed MPTL system; melanoma, skin, bladder, lung, colon, oesophagus, stomach cancer and infected tissues etc. can be treated with super pulsed laser irradiation via suitable fiber optic probes. Furthermore, PM, BPM and SPM modes can be used for clinical PDT application for reduced thermal damage and increased re-oxygenation of the target tissue which could solve the biggest challenges on PDT treatments. Besides, SPM could be used for delivering relatively high energy in a short amount of time and deeper penetration to reach deeply occurred cancerous or infectious tissues. One of the benefits of the super pulse is that it can decrease the after effect of treatment such as itchiness [44]. In addition, SPM could reduce the PDT treatment schedule by decreasing the PDT repetition rate for complete cure.

5. Conclusion

With the presented MPTL system, a reliable light source has been developed for PDT applications by optimizing the LD temperature and laser optical output with embedded systems. Importantly, with these specifications, precise parameter control prevented wavelength shifts and captured the peak absorbance point of the photosensitizers (ALA-5) for more effective treatment. Importantly, tissue thermal damage and tissue optical property changes can be minimized by the radiation modes. The results of in vitro measurements of tissue specimens indicate that the temperature increase depends on the irradiation mode of the laser system; the temperature increases for the pulsed and burst-pulsed laser irradiation modes are substantially lower than for CW laser irradiation. Consequently, this optimized PDT laser system may be used to reduce potential thermal damage during PDT in clinics through new pulse irradiation modes and controlled laser output. SPM benefits have been shown in the literature about decrement of treatment after effects, increased penetration depth, in vitro tissue experiments, and lower thermal damage to the target environment. MPTL system has an important advantage which is having relatively high energy levels while reaching relatively deeper part of the tissues. As far as we know from open literature reviews, this system is the first system that in the world that contains four different radiation mode for PDT modalities. MPTL system can play a key role to more successful PDT treatment options.

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Appendix A. Supplementary material

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References

[1] B C Wilson, M S Patterson, The physics of photodynamic therapy, Phys. Med. Biol. 31 (4) (1985).

[2] B.C. Wilson, M.S. Patterson, The physics, biophysics and technology of photodynamic therapy, Phys. Med. Biol. 53 (2008) R61–R109.

[3] F.W. Hetzel, S.M. Brahmavar, Q. Chen, S.L. Jacques, M.S. Patterson, B.C. Wilson, T. C. Zhu, The American Association of Physicists in Medicine, Photodynamic Therapy Dosimetry, AAPM Report No. 88, Medical Physics Publishing for the American Association of Physicists in Medicine, 2005.

[4] H.S. Lim, Reduction of thermal damage in photodynamic therapy by Laser irradiation techniques, J. Biomed. Opt. 17 (12) (2012) 128001(1–9).

[5] V.H. Fingar, Vascular effects of photodynamic therapy, J. Clin. Laser Med. Surg. 14 (5) (1996) 323–328.

[6] M. Panjehpour, B.F. Overholt, R.E. Sneed, R.C. DeNovo, M.G. Petersen, Comparison between pulsed and continuous wave Lasers for photodynamic therapy, Proc SPIE 1881 (1993) 319–324.

[7] K. Matthewson, P. Coleridge-Smith, T.C. Northfield, S.G. Bown, Comparison of continuous-wave and pulsed excitation for interstitial Neodymium-YAG Laser induced hyperthermia, Lasers Med. Sci. 1 (1986) 197–201.

[8] J.W. Feather, I. Driver, P.R. King, C. Lowdell, B. Dixon, Light delivery to tumour tissue through implanted optical fibres during photodynamic therapy, Lasers Med. Sci. 5 (1990) 345–350.

[9] W.M. Star, Light delivery and light dosimetry for photodynamic therapy, Lasers Med. Sci. 5 (1990) 107–113.

[10] L.H. Murrer, J.P. Marijnissen, W.M. Star, Light distribution by linear diffusing sources for photodynamic therapy, Phys. Med. Biol. 41 (1996) 951–961.

[11] C. Nathalie, R. ZeitouniAllan, OseroffSherry Shieh "Photodynamic therapy for nonmelanoma skin cancersCurrent review and update", Mol. Immunol. 39 (2003) 1133–1136.

[12] Chunping Ao, Jiajia Xie, Li Wang, Songshan Li, Junpeng Li, Lifen Jiang, Hui Liu, Kang Zeng," 5-aminolevulinic acid photodynamic therapy for anal canal condylomaacuminatum: A series of 19 cases and literature review, vol. 19, September 2017, pp. 308–344.

[13] C.P. Neckel, Comparative study on CW-mode versus pulsed mode in A1GaAs-diode Lasers, Proc. SPIE 4249 (2001) 44–49.

[14] T.S. Mang, Lasers and light sources for PDT: past, present and future, Photodiagnosis Photodyn. Ther. 1 (2004) 43–48.

[15] A. Juzeniene, P. Juzenas, L.W. Ma, V. Iani, J. Moan, Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy, Lasers Med. Sci. 19 (2004) 139–149.

[16] J.L. Sandell, T.C. Zhu, A review of in vivo optical properties of human tissues and its impact on PDT, J. Biophoton. 4 (2011) 773–787.

[17] H.S. Lim, Development and optimization of a diode Laser for photodynamic therapy, Int. J. Laser Ther. 20 (3) (2011) 195–203.

[18] H.S. Lim, Design and evaluation of excitation light source device for fluorescence endoscope, Proc. SPIE 7380 (2009) 73805A.

[19] V.C. Colussi, D.K. Feyes, H. Mukhtar, Perspectives of photodynamic therapy for skin diseases, Skin Pharmacol. Appl. Ski. Physiol. 11 (1998) 336–346.

[20] W.D. Tope, J.J. Shaffer, Photodynamic Therapy. Dermatology'de. J.L. Bolognia, J.L. Jorizzo, R.P. Rapini (Eds.), 31(4) (1986). 327–360.

[21] Jean-Luc Boulnois, Photophysical processes in recent medical laser developments: a review, Lasers Med. Sci. 1 (1986).

[22] Oguz Kaan Kazan, Ali Furkan Kamanli, Mustafa Zahid Yildiz, Halil Arslan, Hyun Soo Lim, Closed Loop Laser Diode Temperature Control System Design, in: International conference on engineering technology and innovation (ICETI), 2017.

[23] Eugènia Agut-Busquet, et al., Photodynamic therapy with intralesional methylene blue and a 635 nm light-emitting diode lamp in hidradenitis suppurativa: a retrospective follow-up study in 7 patients and a review of the literatüre, Photochem. Photobiol. Sci. 15 (2016) 1020.

[24] María E. Etcheverry, et al., Photodynamic therapy of HeLa cell cultures by using LED or Laser sources, J. Photochem. Photobiol., B 160 (2016) 271–277.

[25] R.R. Heikes, R.W. Ure, Thermoelectricity: science and engineering, Interscience Publishers, New York, 1961.

[26] G. Singh, Steady state and transient analysis of thermoelectric devices using finite element method, 2003.

[27] L. Chengxiang, Design of automatic temperature control system on laser diode of erbium-doped fiber source, in: Fourth International Conference on Intelligent Computation Technology and Automation, 2011.

[28] M. Hu, Improved PID algorithms with application to excimer laser temperature control, in: 2014 2nd International Conference on Systems and Informatics, 2014.

[29] H. Huang, Design of a small temperature control system based on TEC, in: 9th International Symposium on Computational Intelligence and Design, 2016.

[30] Muhammad Imran Shahid, Babar Hussain, Muhammad Aslam, Design and development of photodynamic therapy Laser system, Int. Res. J. Electric. Electron.Eng. 2 (1) (2015) 007–017.

[31] Pieter B.A.A. van Driel, Martin C. Boonstra, Maxime D. Slooter, Raimond Heukers, Marieke A. Stammes, Thomas J.A. Snoeks, Henriette S. de Bruijn, Paul J. van Diest, Alexander L. Vahrmeijer, Paul M.P. van Bergen en Henegouwen, Cornelis J.H. van de Velde, Clemens W.G.M. Löwik, Dominic J. Robinson, Sabrina Oliveira, EGFR targeted nanobody–photosensitizer conjugates for photodynamic therapy in a preclinical model of head and neck cancer, J. Control. Release 229 (2016) 93–105.

[32] David O. Oluwole, Fatma Aslhan Sar, Edith Dube EarlPrinsloo, Abdulcelil Yuzer, Tebello Nyokong, Mine Ince, 'Photophysicochemical properties and photodynamic therapy activity of highly water-soluble Zn(II) phthalocyanines', Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 203 (2018) 236–243.

[33] P.V. Marks, P.E. Belchetz, A. Saxena, U. Igbaseimokumo, S. Thomson, M. Nelson3, M.R. Stringer, J.A. Holroyd, S.B. Brown, Effect of photodynamic therapy on recurrent pituitary adenomas: clinical phase I/II trial Ð an early report, Br. J. Neurosurg. 14 (4) (2000) 317 ± 325.

[34] B. Karamata, M. Sickenberg, H. van den Bergh, A fibreoptic light distributor for the preventative photodynamic therapy of secondary cataract, Lasers Med. Sci. 15 (2000) 238–245.

[35] Barbara Zoreca, Dejan Škrabeljb, Marko Marincek, Damijan Miklavci, Nataša Pavšelja, The effect of pulse duration, power and energy of fractional Er:YAG Laser for transdermal delivery of differently sized FITC dextrans, Int. J. Pharm. 516 (2017) 204–213.

[36] Mihaela Balu, Ilyas Saytashev, Jue Hou, Marcos Dantus, Bruce J. Tromberg, Sub-40 fs, 1060-nm Yb-fiber Laser enhances penetration depth in nonlinear optical microscopy of human skin, J. Biomed. Opt. 20 (12) (2015) 120501–1.

[37] Jing Gao, Changbing Shen, Randy Ko, Xiadong, Zheng Zhongying, Wang Shengxiu Liu, Yongjiang Li, Mingjun Tang, Weiwei Yin, Chunjun Yang, Xuejun Zhang, Combination effect of super pulsed carbon dioxide Laser and photodynamic therapy for recalcitrant facial flat warts: a preliminary study' Journal of Cosmetic and Laser, Therapy 18 (1) (2016) 56–57.

[38] Vladimir V. Klimenkoa, Nickolay A.b. Knyazeva, Fedor, V. Moiseenko, Anatoliy A. Rusanov, Alexey A. Bogdanova, Michael V. Dubinaa, 'Pulse mode of Laser photodynamic treatment induced cell apoptosis', Photodiagn. Photodyn. Ther. 13 (2016) 101–107.

[39] V.A. Vinnichenko, A.A. Kovalenko, I.V. Yaroslavsky, G.B. Altshuler Effects of continuous wave, conventional pulse and super-pulse Tm fiber Laser on tissue: a comparison study, in: 2018 International Conference Laser Optics (ICLO) 42–8 June 2018, IEEE Xplore: 16 August 2018.

[40] Y. Anju, G. Asheesh, K.K. Gaurav, V. Saurabh, K.S. Sanjeev, B.S. Shashi, Photobiomodulatory effects of superpulsed 904 nm laser therapy on bioenergetics status in burn wound healing, J. Photochem. Photobiol., B 162 (2016) 77–85.

[41] R.M. Santo, B. Pina, D. Annunziata, B. Luigi, S. Martina, S. Giusy, P.N. Steven, CO2 laser and photodynamic therapy: study of efficacy in periocular BCC, Dermatol. Therapy 31 (2018).
[42] S. Silvia, M. Marco, M. Germana, P. Renato, A.C. Rosa, M. Giuliana, Superpulsed laser irradiation increases osteoblast activity via modulation of bone morphogenetic factors, Lasers Surg. Med. 41 (2009) 298–304.
[43] dos S. Vanessa, Et al. The thermal impact of phototherapy with concurrent superpulsed lasers and red and infrared LEDs on human skin, Lasers Med. Sci. 30(5) (2015) 1575–1581.
[44] K. Ercan, C. Inci, G. Murat, Monitoring system for investigating the effect of temperature change on optical properties", Lasers Med. Sci. 33 (2018) 1763–1768.

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