Installation for Local Hyperthermia in Crossed Laser Fluxes

Iurie NICA*, Serghei ZAVRAJNÎI, Andrei GRITZCO, Iurie TIRON, Dumitru ESHANU, Vladimir MUSTEATZA, Andrei STALBE

Institute of Electronical Engeneering and Nanotechnologies „Dumitru Ghiţu", Chişinău, MD – 2028

**e-mail: tehmed@iieti.asm.md*

***Abstract* – As is well known, on heating up the tumor over 43 – 44^{0}C the tumor cells dies, whereas healthy tissues cells remain alive up to 50^{0}C. We propose local overheating malignant morbid growth, with infrared radiation from a laser system, focused on a specific area, forming this way a powerful, dispersed in the space, source of energy. To achieve the therapeutic dose in the body at depth of 10-12 cm is necessary to be used lasers with the radiation between wavelength range of 700nm - 850nm, for which there are seen windows of transparency in biological tissues, and the total power of 5 - 15 W.**

We have developed a installation, including: a block of laser diodes with individual collimating optics, directed in a common point; multi-channel thermometer of the irradiated area; two-axis table for accurate positioning of the irradiated sample with temperature sensors fixed on it relative to the common point of crossing lasers fluxes; computer, integrating all elements of the installation in one experimental - measuring station.

The experimental results confirm the ability of the radiation with a wavelength of 808 nm to penetrate the biological tissue to a depth of up to 90 mm and deeper. The effect evaluation of addition energy in the common point of the lasers beams demonstrate that to achieve the desired temperature of the tissue up to 43-44^{0}C to a depth of 9 cm is sufficient 5 ÷ 6 lasers with power emission 4W to wavelength of 808nm. In order to avoid the burning of the surface tissues of the body is necessary to ensure the power flow density not higher than 200mW/cm^2, which requires collimators or they're systems that provide a uniform flare by each laser corresponding to the area (20cm^2, in case of 4-watt lasers).

***Keywords* – local hypertermia; diode laser; crossed rays; near infrared region.**

I. INTRODUCTION

The problem of combating cancer diseases is one of the most acute problems of the contemporary medicine, which must be solved worldwide. In combating cancer tumors are used several strategies: surgical interventions, chemotherapeutic and radiological procedures, and more recent - local or general hyperthermia and photodynamic therapy; which are used individually or in various combinations. From invasiveness point of view of the human body the most sparing

procedure is hyperthermia which benefits from a specific property of the cells (proteins) affected by the cancer namely - the death at 43-45 C, temperature that does not affect the adjacent healthy cells. The hyperthermia of the malignant malformations could be achieved through the different methods: hot water jets, electromagnetic fields, infrared rays, etc.

Hyperthermia procedures can be made relatively simple if the malformations are located on the surface of the body or organs to which we have direct access. The situation is more complicated when the tumor tissue is located deeper.

Currently in medical practice are investigated and implemented several variants of local hyperthermia using non invasive or minimum invasive methods for heating the tumors located in depth of the biological tissue. During laser-induced interstitial thermotherapy (LITT) (or interstitial laser photocoagulation) the light is delivered through flexible fibers inserted into the center of the tumor. Laser light at the tip of the fiber raises the temperature of the tumor cells and damages or destroys them. Disadvantage of this method is the possibility of treating only small volumes of the pathological tissue (1-2 cm areas diameter). The cause consists in modifications of the optical properties of the heated biological tissue located in the immediate vicinity of the radial head of the optical guide. The volume of the heated area can be increased by using a flux with a higher irradiance [1], but this may cause unpredictable consequences, for example: the tissue temperature reaches or exceeds critical value at which begins the vaporization of the intracellular liquid, which could trigger dangerous unknown processes such as boiling or carbonization of the tissue [2]

The photodynamic therapy method, which speculates the property of the malignant tumors to concentrate the photosensitive materials in the pathogenic cells, can be achieved in two ways. The most widespread - photo chemotherapy uses photo sensitizers, which molecules got stimulated when absorbing of photons initiating such effects as: destruction of the mitochondrion; substantial changes in oxygen metabolism by generating of singlet oxygen ($^1O_2$), which is extremely cytotoxic, and a large quantity of free radicals [3-5].

The second way - photo thermotherapy, involves photo sensitizers that emit a large amount of heat in the process of photons absorption. Usually these are nano-dimensional structures, such as: metallic powder, nanotubes, nanorods or nanoshells with dielectric core and metallic shell [6]. The main disadvantage of this method consists in the formation of free radicals and chemical components, the role of which, currently, is not researched enough.

II. THE HYPERTHERMIA INSTALLATION: THE FUNCTIONAL BLOCKS

Classical hyperthermia is based on fact that to temperatures of 42-45^{0}C cell's DNA suffers irreversible pathologic modifications and cells dies, while healthy cells are recovering to remove excessive temperatures. Speculating this property of tumors, in the laboratory "Medical Equipment" of the Institute of Electronics

Engineering and Nanotechnologies "D. Ghiţu" has been developed a device designed for monitored heating into malignant tumors located in depth of the tissue. The device consists from several sources (laser diodes) which radiates into infrared region of the spectrum (808 nm). Radiation with this wavelength penetrates into the tissue up to a depth of 70-120 mm for about 10 W/cm^2 irradiance [7]. But these irradiations may cause substantial photothermal damages of the superficial tissues for irradiation time longer than 50ms. Therefore, the main problem consists into irradiating the malignant tumors, without affecting the tissues between the surface and the tumor. The problem is solved by transporting the energy through the different channels to the tumor, placing the tumor in place of the intersection of the several laser beams.

The main elements of the installation are (Figure 1):
• Set of laser diodes, equipped with optical beam forming equipment and orienting it into a common point;
• Module for measuring the temperature, equipped with a set of thermal sensors able to convert the temperature into electric signal and electric signal into binary code for computer data processing. In its version of the installation, as thermo sensitive components are used thermocouples CrNi / Ni FeCu;
• The tilting table (X / Y positioning) serves for accurate positioning of the region which must be heated in the flows crossing point. Positioning is carried out by two stepper motors driven by PC.
• PC - which function is to ensure the connection between all modules of the installation, thereby creating an integral experimental system.

As a source of coherent optical radiation are used devices ATC C4000-500 MFA-808-3-F200, which main elements are diode diodes with 808nm wavelength, which have a linear dependence between optical power and the electric current intensity which flows through the laser diode (maximal optical power 4W).

Temperature measurement of the irradiation region can be accomplished by using thermocouples. The electromotor power created by thermocouples is applied to the positive terminal of the operational amplifier (CMOS). Dependence between the value of the output signal of the amplifier input signal value is linear in range of $(0\text{-}50)^0$C. The maximum possible values of the amplifier output signal is corresponding to his power supply. The analogue signal received from the operational amplifier output is transmitted to the analog-to-digital converter input - (ADC). Each converter input has a thermocouple. The data obtained from ADC are sent to the computer to be processed and displayed as an image of the thermal field.

The computer, through the RS232 serial interface controls the commands transmission to position and irradiate the object, followed by collection, storage and processing the data obtained as a result of 2D and 3D images of created thermal fields. Based on submitted orders (the temperature registered in the given point) to the control module of the optical power of the laser diodes and received data describing the temperature distribution into the sample, the computer manages the irradiation process. If the current temperature in studied area does not correspond to the expectations (the difference is more than (0.2-0.3) 0C), the microcontroller, based on comparing the amount of data containing information about the necessary temperature and amount of data containing the actual temperature, increases or decreases (by disconnecting the laser diode) the optical power until the temperature will reach the required value. This method represents the discreet method of temperature control in the region. Another method is based on continuous monitoring and correction of the thermal field with an accuracy of ± 0.10 C.

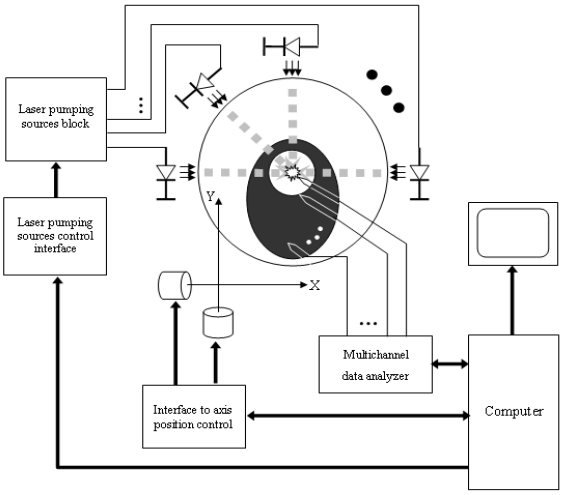


Fig. 1. Block diagram of the installation for study of local hyperthermia

Each laser diode is individually monitored by the system. The data which define the thermal regimes are transmitted through the RS232 serial interface to the executive modules, which converts the data into the optical power, producing themselves the required temperature inside the irradiated sample. The format of the data package contains the address of the module which the PC addresses to, and data about the required optical power. Creating and maintaining the working regime of the each laser diode is carried out based on comparing the data received from the computer and data obtained by the monitoring loop of the optical power. In the structure of the monitoring loop of the optical power is a photodiode, irradiated by a part of the electromagnetic flux produced by the laser diode. The signal level produced by the photodiode is directly proportional with the intensity of the radiation. The optical power control module processes the received data from the PC and monitoring loop after a specific algorithm, applying after that, an electrical signal adjusted to the sub-modules, whose function is to create the optical power corresponding to the signal.

III. THE REALIZATION OF THE LOCAL HYPERTHERMIA IN BIOLOGICAL TISSUE

3.1 Experiments purposes

1. Confirmation of the depth penetration of the biological tissues by the laser radiation with wavelength of 808 nm.
2. Monitoring and estimating the energy composition effect of the coherent infrared radiation beams which intersects in depth of the biological tissue.
3. Analyzing the possibilities of determining the constants that describe the thermal and optical characteristics of the biological tissues for thermal processes prognosis of the irradiated tissues.

3.2 Experiments Organization

An isotropic sample of biological tissue (egg white) fills the bottom of a glass cylinder with very thin walls. The cylinder has a diameter of 100 mm. In the sample are implanted the thermocouples forming a cross with perpendicular arms. The thermo sensitive peaks are in a horizontal plane parallel to the bottom of the cylinder. The

thermocouples are located on the arms of the cross at a distance of 20 mm from each other. The central thermocouple is located at the intersection point of the arms that are on the longitudinal axis of the cylinder. (Figure 2)

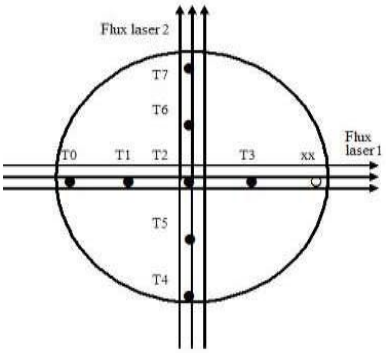


Figure 2. Fluxes emitted by the lasers are mutually perpendicular. The thermocouples are situated on the beams axis

In the experience has been used two lasers (laser diodes) with the same optical power in infrared emission (808nm) which beams propagates along those two rows of thermocouples intersecting in the position of the central thermocouple T2. The optical power emission of the W_{opt} laser diodes was 250 mW. The glass cylinder walls absorbs about 0.05% of the irradiance, so absorption can be neglected. The temperature registration regime of is shown in the description of the temperature monitoring module with 8 channels.

The lasers operated in such regimes as: intervals of absence of the radiation; irradiation of both lasers simultaneously; irradiation of one laser or another (Figure 3). For highlighting of as many nuances (details) of the process, the lasers operating intervals were quite long (30").

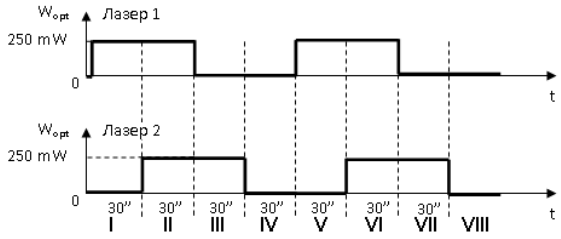


Fig. 3. The temporal charts of the alternance regimes of the laser operation

3.3 Experiments Results

In the Figure 4 is represented graphs of the time dependency of the recorded signals by thermocouples in described working lasers regimes.

The synphasic variations of the signals values registered together with the operating regimes of the lasers demonstrates the recorded influence on the sample. Is observed synphasic variations on all thermocouples, including those situated deeply in the biological sample (90 mm). This confirms the ability of deep penetration into biological tissue by the 808 nm infrared radiation.

The signal recorded by the central thermocouple (T2) illustrates composition of the infrared fluxes in the region of their intersection.

When switching the lasers, the radiation increases and decreases abruptly . . . and manifests itself in the worst case, during 25 ms, which is much faster than the variations presented in the charts. On charts, the recorded size variation from initial value to saturation value occurs in 3.75 sec, which exceeds . at about 150 times the interval of radiation increase. The same behavior occurs and in case of radiation decrease. So, the thermocouple does not register the influence of the electromagnetic field (Foucault currents).

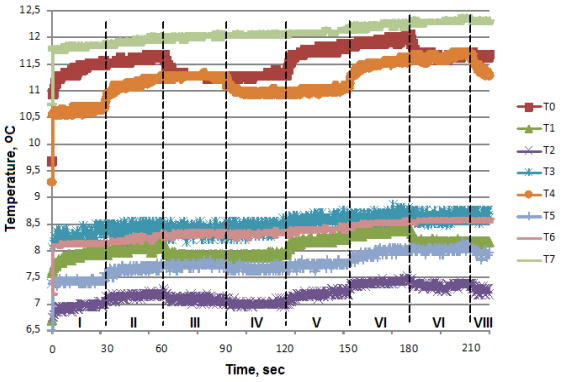


Fig. 4. Time dependence of the signals recorded by the thermocouples

Thermal inertia of the thermocouples, when measured separately (2.5 ms /° C .... 8.4 ms ° C /°) is much lower than the temporal variations shown on charts. So, the assumptions that are registered charts demonstrating the direct heating or cooling into thermocouples are not founded. Remains the conclusion that are registered temperature variations in the biological sample where are implanted thermocouples. Environmental temperature T with internal sources, which energy absorbing regions along the fluxes of radiation, described in the equation:

$$c * \rho * \frac{dT}{dt} = \beta * \nabla^2 T + D * \frac{W_0}{S} * e^{-D*r} \quad (1)$$

Where c - is the specific heat capacity of the environment, ρ - density, β - thermal conductivity, D - absorption, W_0 - The optical the power of the flow at entry into the environment, S - cross sectional area of the radiating flux, r - the module of the vectorial radius of the investigated region.

Equation (1) describes the time intervals I, II, V, VI for thermocouples T0, T1, T3 or II, III, VI, VII for thermocouples T4, T5, T6 and T7. Same equation applies for thermocouple T2 for the time intervals I, III, V and VII.For time intervals II and VI its value must be equal to the sum of the optical power of both optical lasers.

For non-irradiated areas or for times intervals when lasers don't work, so when W_0 = 0, the equation is:

$$c * \rho * \frac{dT}{dt} = \beta * \nabla^2 T \quad (2)$$

This relates for the time intervals III, IV, VII, VIII for thermocouples T0, T1, T3 or I, IV, V, VIII for thermocouples T4, T5, T6 and T7. The temperature in the region T2 is described by this equation for time intervals IV and VIII.

Is observed quick warming intervals when the temperature gradient in the observed region dV is not high and heat dissipation $\beta * \nabla^2 T * dV$ cannot match the energy accumulation which comes from released energy absorption $D * \frac{W_0}{S} * e^{-D*r} * dV$

In cases when warming the irradiated regions of the biological sample is faster than warming non-irradiated

regions, increases the temperature gradient in the irradiated regions and therefore, increases the heat evacuation from these regions. In this case we observe a pronounced decrease in growth speed of the temperature.

The decrease of the temperature that occurs when "extincting" the lasers demonstrates the redistribution process of the heat for thermal balance in the sample volume and is described very well by expression (2). Each following state of thermal balance is installed to a higher temperature than from which has started the previous warming, which demonstrates the accumulation process of the heat in biological sample.

For time intervals corresponding to the functioning of both lasers (II and VI) the curves shows a small growth (compared with the temperature growth caused by the irradiation of "its own" laser) caused by the penetration of the photons by the spreading mechanisms and the heat diffusion of an amount of energy . . . coming from nearby radiated regions. The curves erosion is caused by the dispersion . of the recorded data and determined by the resolution capacity of the entire channel . of the temperature recording ~ ± 0.05 ° C.

The different values of the initial temperatures in Figure 5.5 is caused by the distinction of the biological sample temperatures (6.5 ° C) and environment (27° C), which causes the heat transmission through the cylinder glass walls and biological sample stratification by the temperature (Figure 5).

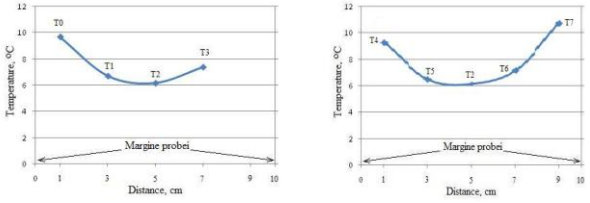


Fig. 5. The temperature field formed in the biological sample from the heat exchange with the environment. On the left- indications for thermocouples T0, T1, T2 and T3 on the right - the indications for thermocouples T4, T5, for, T6 and T7.

IV. PROCESSING AND ANALYZING THE EXPERIMENTS RESULTS

The temperature variations ΔT = T- To (To - biologic environment temperature before "switching ON" the lasers, T - biologic environment temperature at the time of measure.) at points where are situated the thermocouples, recorded in the process of biological environment radiation with radiation wavelength 808 nm are shown in Figure 6.

For analyzing of the biologic environment reaction to applied irradiation, we will explore the field distribution of temperature variations ΔT = T- To for a few characteristic temporal moments. We will choose the following items:

t1 - 1 laser works in steady state, laser 2 does not work;

t2 - both lasers works steady, at the next moment 1 laser will be "off";

t3 - 2 laser works in steady state and relaxation processes caused by "off state" of the 1 laser has ended.

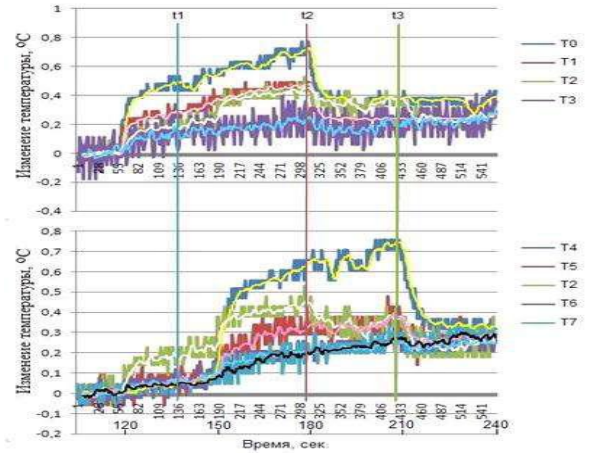
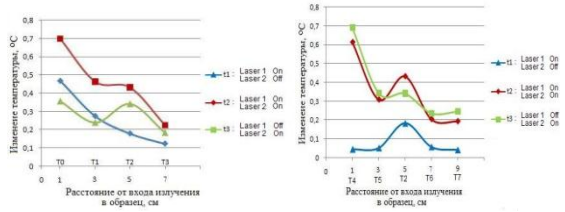


Fig. 6. The temperature variations ΔT in one cycle of irradiation of the biological sample with 808 nm infrared radiation. Top - the values along the laser beam 1, bottom- the values along the laser beam 2.



a b

Fig. 7: The distribution of the temperature variations ΔT in the biological sample in selected moments: a) along 1 laser beam, b) along 2 laser beam.

Moment t_1:

Figure 7 a*)* Exponential distribution of the temperature variations ΔT towards T0, T1, T2, T3 according with *(1)*

Figure 7 b) The temperature variation exclusively in T2 region which is common for both lasers fluxes. For points T4, T5, T6, T7 substantial variations of the temperature are not registered because laser 2 doesn't work.

Figure 7 b) The temperature variation exclusively in T2 region which is common for both lasers fluxes. For points T4, T5, T6, T7 substantial variations of the temperature are not registered because laser 2 doesn't work.

Moment t_2:

Figure 7a) Continues the exponential growth of the temperature according to (1) in the center of (T2) we observe a significant warming since W0 factor which describing energy absorbing is the

Figure 7b) Same as 7 a)

sum of the optical radiation which penetrates into the environment from both lasers

We mention, that until "switching ON" the laser 2, in the point T1 were much more warmth than in the T2. Therefore the heating process in T2 is slower compared with heating in T1. In case b) for thermocouples T5 and T2 the process is reversed. Which differences are explained on charts a) and b) in the moment T2.

Moment t_3:

Figure 7a*)* Cooling process takes place in accordance with (*2)* apart from center *(*T2) where occurs the accumulation of the heat from laser 2. Decreasing the temperature in the center (*T2)* compared with its value at time t2 explained through . the flow at reduction due to "off state" of the laser 1. Now in this region comes less radiation, and therefore is accumulated less heat. For thermodynamic balance is necessary a lower rate of evacuation of the surplus warmth, thus a lower temperature gradient.

Figure 7 b) Is shown the temperature breakdown on the direction T4, T5, T2, T6, T7 (according with temperature variation in the center. See the comments Figure 7a). For a longer regime duration of irradiating the sample, the exponential curve will keep the trend, according to (1).

V. CONCLUSIONS

Was confirmed the depth penetration of the biological tissue at the laser radiation wavelength of 808 nm. Variations of the temperature were registered by all thermocouples implanted in the biological sample, including those most distant, located at 90 mm from the beam entry location in the sample.

The signal registered by the central thermocouple T2 demonstrates the composition effect of the coherent infrared radiation beams energy intersecting in the depth of the biological tissue.

The analysis of the composition effect of the coherent infrared radiation beams energy intersecting in the depth of the biological sample suggests the need of substantial increasing of the lasers number energy characteristics equivalent to those used (250 mW) and of collimators (Øbeam = 7.14 mm) for heating with $\Delta T \sim 7 \div 100C$ at the depths of 90 mm.

When using more powerful laser diodes (4 W) can be enough 5 ÷ 6 pieces, but then to obtain the irradiation of 200mW/cm2 (supportable for the surface tissues) collimators or systems are required to ensure the uniform irradiation of the surfaces with areas of about 20 cm2.

A solution would be to use the impulsive radiation regime (50-200 ns with the frequency (ν) equal to 1-50000 Hz) with more powerful lasers.

Any approach is possible because in the development of the installation have been used the block-module concept which is very flexible and allows any reconfiguration of the installation.

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