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INTRATUMORAL TEMPERATURE MONITORING

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Deşi determinarea "in-vivo" a temperaturii ţesuturilor tumorale este o tehnică invazivă, necesitând contactul cu formaţiunea tumorală dezvoltată de pacient, această procedură oferă informaţii utile în diagnosticarea şi tratamentul multor tipuri de tumori maligne. Nivelul temperaturii poate evidenţia modificări chimice şi morfologice ale vaselor de sânge la nivelul ţesuturilor tumorale şi pre-tumorale, iar măsurarea ei poate furniza un prim indicator al acestei maladii şi respectiv al succesului medicaţiei administrate, înaintea depistării ei prin oricare altă metodă de investigaţie specifică. Lucrarea prezint o metodă şi un aparat pentru monitorizarea temperaturii, caracterizat prin rezoluţie înaltă şi sensibilitate extremă. variaţiile de temperatură înregistrate pot fi utilizate alături de semnele cele mai timpuri în evaluarea eficienţei tratamentului.

Temperature screening in tumor tissues is an invasive procedure requiring contact with the tumor zone of patient, while it offers a useful approach to the diagnosis and treatment (as therapeutic aids) of many type of cancer. Temperature screening has the ability to detect the chemical and blood vessel changes in pre-cancerous and cancerous tissues. Consequently, temperature screening can be a first indicator that therapy is efficient before the cancer can be detected by any other method. This paper presents a method, and a high-resolution and extreme sensitivity screening device temperature for living tissues.

Keywords: temperature screening, tumor tissue, cancer therapy

1. Introduction

Temperature screening in tumor tissues offers a useful approach to the diagnosis and treatment as therapeutic aids in many types of cancer. The utility of developing adequate equipment results in optimizing the treatment of the cancerous tumor. Currently, the malign tumors are detected by imaging methods. During the treatment, these are monitored by tumor markers, which provide mostly qualitative information of the tumor modifications.

In Romania, neoplasia represents approximately half, respectively 47.78% out of total reported malignant tumors. Considering the data gathered from the Cancer National Register [6], the cancer incidence exhibits a continuous growth

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(36.97/10^3 in 1996 and 43.37/10^3 in 2002). The cancer treatment by temperature monitoring method represents a new domain both in clinical activity and medical research, of important relevance in serious pathological situations when conventional therapeutic methods are exceeded. The first modern and specialized equipment using heat therapy in the treatment of cancer dates from 1898. The discovery of radiation and its inclusion in cancer therapy led to a loose of interest in thermotherapy techniques. The cancer treatment by hyperthermia combined with citostatic is of great interest in to the medical community: it is expected that remarkable results bring into attention the difficult process of cancer treatment.

In the absence of a specific cancer treatment this method is a valuable therapeutic option (adjuvant, elective or palliative), for improving the patient's condition. The equipment is intended for digestive oncology clinics as an alternative or completion in the surgical treatment of malignant tumors.

The tumor temperature is the most important parameter, which can be measured and monitored relatively easy. This parameter also reveals global information about the tumors physiological processes therefore an optimal treatment can be prescribed. Temperature real time monitoring relies on collecting quantitative information about tumor metabolic processes [7], which may lead to the improvement of the antitumor treatment such as citostatic treatment suppression, establishing administration protocols, introducing other citostatic, prescribing alternative treatments.

Currently, no intratumor temperature monitoring is performed in Romania. For the evaluation of the tumor, radiological examinations or MRI scans are analyzed within a minimum interval of 3 months, which assumes a slow feedback for the treatment modification. Conversely, by real time temperature monitoring, the treatment can be modified on a daily from one day to another. This monitoring is useful not only for prescribing the optimum treatment, but in research too, for establishing the factors that positively or negatively affect the malignant tumors.

2. Working principle and construction

The equipment for intratumor temperature monitoring is a measuring device consisting of a temperature transducer and an indicator device. It is a digital thermometer (TD) with a platinum resistance transducer (TRP) and a measured data memory function (temperature), and it can be connected to a computer. In this way the measured data can be saved and processed for long periods of time. Depending of the evolution of the intratumor temperature, an optimal treatment can be prescribed.

The temperature transducer is the thermometer part, which comes in direct contact with the measured environment (tumor tissue), and consists of a sensitive temperature element (sensor) and other different accessories, such as protection layers, insulations, connectors, connecting plugs and so on. It can be of either resistive type (thermometer with platinum electrical resistance, thermometer thermistor, and so on), or generator type (thermocouples). For this equipment is used a platinum thermo-resistance (TRP).

A sensitive Pt100 element was used, obtained by platinum coating of a ceramic support. This kind of sensitive elements provides for a better repeatability than 1 mK. It is used for its reduced dimensions (5x8 mm), its wound sensitive elements having minimum dimensions of 30 mm.

The sensitive element was artificially aged by thermal cycles at temperatures above 250 °C and less than 0 °C. This process is necessary for stabilizing the platinum and the ceramic insulating support. The endings of the sensitive element were soldered on a biocompatible, shielded four-wire cable, manufactured by Sonion, Austria. The sensitive element was coated with the biocompatible lacquer Photoplast Lacquer 3, produced by Dreve Otoplastic. The coating was performed by polymerization of the lacquer on the sensitive element surface, under the effect of UV light. This special construction is necessary to provide for biocompatibility of the temperature transducer with living tissues.

The temperature indicator device consists of an electronic device, which converts the transducer output signal into a suitable signal, a digital display for the temperature value, other ancillary devices (linear, for non-linear transducers, for thermocouples temperature compensation and so on) batteries or electric energy feeder. The device is made by SYNCHRO COMP SRL in collaboration with the National Institute of Metrology. It has internal memory, capable to execute logical functions, mathematical calculus and data storage, with a computer numerical connecting device.

3. TD calibration with TRP by fixed points method

The SIT90 temperature is determined using a deviation function:

$$W(T_{90}) - W_r(T_{90}) = a\,[W(T_{90}) - 1], \tag{1}$$

where

$$W(T_{90}) = R(T_{90})/R(273.16\ \mathrm{K}), \tag{2}$$

$$W_r(T_{90}) = C_0 + \sum_{i=1}^{9} C_i\,[(T_{90}/\mathrm{K} - 745.15)/481]^{I}. \tag{3}$$

The calibration method at the fixed points of SIT-90 consists of measuring the electrical resistance of TD with TRP at the defining fixed points temperature of SIT-90 and determining the coefficients from the interpolation relation. The coefficients are specific for each transducer and serve for interpolation between the fixed points values.

The devices used for defining fixed points are realized in conformity with the requirements of [1] document, elaborated on the basis of recommendations of the Thermometry Consultative Committee (CCT) of the "Bureau International des Poids et Mesures" (BIPM). The calibration of TD with TRP type transducer in (0...42) °C range is made at two fixed defining points:

- triple point of water (+0.01 °C) – TPW;
- melting point of Gallium (29.7646 °C);

In this domain, the deviation function is expressed in (1) with the coefficient value *a*, obtained from the measurements in the specified fixed points. The measurements of the electrical resistance of TRP at the fixed points are made as follows: $R_{0.01}$, R_{Ga}, repeating $R_{0.01}$.

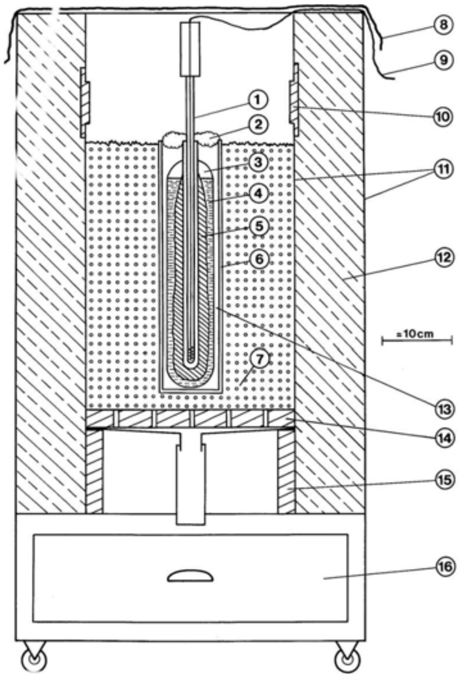
a. The experimental apparatus.

b. Triple-point cell (13)

c. Plastic container (6).

d. Transducer – coated with biocompatible lacquer.

e. Transducer – coated with varnish.



f. Schematic of the equipment.

Fig 1. Equipment used for maintaining the triple point of water.

The triple point of water is one of the most important and practical defining fixed points of SIT-90; it is the same time, the only common point between SIT-90 and Thermodynamic Scale. The temperature unit Kelvin is defined using Thermodynamic Scale, as being the fraction 1/273.16 of the thermodynamic temperature of the triple point of water. Considering this, the triple point of water is a reference point in calibration of the standard thermometers with platinum electrical resistance, for determining the ratio of the resistance $W(T_{90}) = R(T_{90})/R(273.16\ \text{K})$, which precedes the interpolation formula.

For the realization of the TPW [2] the cell must contain ice, water and vapors, all of high purity. The cell is completely immersed in a bath of crushed ice, as Figure 1 shows. The components are:

1 – standard thermometer with platinum resistance;
2 – wool glass insulation
3 – water vapors;
4 – three-distilled water;
5 – ice;
6 – plastic container;
7 – crushed ice;
8 – opaque cover;
9 – output thermometer lines
10 – insulating layer in containers' stainless steel wall
11 – stainless steel container;
12 – polystyrene insulation;
13 – air layer (maintained by plastic spacers, not shown in the figure);
14 – discharge support;
15 – support;
16 – holding tank.

Generally, the cell preparation consists of freezing a quantity of water to ensure the solid state of the water, among the existing liquid and also the gas phase. First, the inner tube is washed with distilled water then it is drained and closed with a rubber cork. The cell is immersed in the crushed ice for an hour until it cools down to 2 $^{\circ}$C.

The next step after this pre-cooling is the formation of the ice layer around the inner tube. The thickness of the ice layer varies between 4 and 8 mm, depending on the cell dimensions. The ice layer (5) builds by filling the inner tube (4) with solid CO_2 (dry ice) up to the water level. On the inferior part of the tube the layer must have a greater thickness, as figure shows. There are two options to achieve this: whether the cell is immersed in the ice before CO_2 totally sublimes, or a small quantity of CO_2 is added in the tube until the ice layer becomes thicker.

Another frosting method consists of filling the tube with alcohol by half and then adding solid CO_2. By this method the ice layer is obtained in a larger amount of time (almost an hour). If no CO_2 is available, then the ice layer is obtained by inserting a metallic bar in the inner tube that is previously cooled in liquid N_2.

The ice is first frozen few degrees Celsius below the triple point, by supercooling. When water frozen, the first fine ice needle crystals appear between the surface of the tube and the water. The tube is suddenly coated with fine needles, forming a layer of clear ice 4 to 8 mm thick. The process takes 10 to 20 minutes.

It is important to maintain permanently the tube essentially full with solid CO_2. If the solid CO_2 level diminish more than few centimeters before the refill, then the mantle brakes and the desired temperature of the triple point cannot be reached if a fissure is detected. This could expand from the surface of the tube to the surrounding water.

When the solid CO_2 is poured in the tube, a part of it falls around the cell, determining the solidification of the water in the superior part of the cell. This superior ice layer must be stopped immediately because otherwise it can break the ice. Melting can be achieved by elevating the cell and heating the region, *e.g.* by hands, while gently shaking, so that the ice surface is washed by the water inside.

3.2. Realization of the melting point of Gallium

The device for reproducing the melting point of gallium contains a crucible-cell system for the melting point and a thermometric bath with liquid (oil or water) for maintaining the gallium melting point. The thermodynamic equilibrium state of the melting point is obtained when gallium is passing from solid to liquid phase, with argon atmosphere of 101,325 Pa.

First, gallium must be in solid state. For this, we immerse the cell in a bath, which contains a mixture of ice and water, continuously monitoring the cell temperature. If the initial state of the metal is liquid, it will look like it will be subcooled, returning to the solid state, then it will drop below the temperature of solid state maintaining the appropriate temperature of water-ice mixture.

To obtain the gallium level of the melting point the following steps are necessary:

- The gallium solidifies when introduced for at least 24 hours in a Dewar vessel containing an ice-water mixture;
- The cell temperature is checked after 24 hours; if the gallium is solidified it has an appropriate temperature of the ice-water mixture;
- The solidified gallium cell is immersed into a water bath, where the temperature is maintained at 30…31 ^{o}C; it is continuously monitored with a mercury calibrated thermometer with 0.01 ^{o}C division scale; the bath temperature must be kept at a higher value then the melting point (29.7646 ^{o}C) allowing gallium to melt (no more than 32 ^{o}C).
- The temperature from the thermometric tube of the cell is continuously measured, and after 2 hours this value will reach almost the melting point temperature. At this point it starts to build a gallium layer outside the crucible, which tends to reach the bath temperature. In the thermometric tube, where the melting point is measured, the temperature

is not balanced, and yet there is no gallium along the tube to reach the equilibrium state.

4. Results

After discarding the first and last 15 % registered values, the arithmetic mean of the remained values (at least 6) was calculated, resulting R_i (PF) value, where PF is the specific fixed point and i is the number of the level at this fixed point ($i = 1, 2$).

Table 1

Measurement results

Readout	R_{Ga} [Ω]	R_{H2O} [Ω]
1	111.563	99.984
2	111.564	99.984
3	111.563	99.984
4	111.564	99.984
5	111.563	99.984
6	111.562	99.985
Mean value	111.563,17	99.984,17
$W_1(t_{Ga})$ = 1.115,808,34		
1	111.563	99.984
2	111.564	99.985
3	111.564	99.985
4	111.564	99.984
5	111.563	99.985
6	111.563	99.985
Mean value	111.563,50	99.984,67
$W_2(t_{Ga})$ = 1.115,806,09		

W_i (t_{90}) was calculated, as the ratio between the electrical resistance of TRP (measured at fixed point temperature), R_i (PF), and the electrical resistance R_i (0.01 °C) measured at the triple point of water, immediately after finishing the PF measurements. The resulting value is: $W(t_{Ga})$ = 1.115,807,21.

The mean value $W_i(PF)_{med}$ was calculated at the fixed point temperature, obtained from two measurement series. The resulting value for the coefficient of the interpolation function (1) is: $a = -2.012{,}719{,}3\times10^{-2}$.

5. Measurement model

The most important value when calibrating a TD by the fixed points method is the ratio between the electrical resistance R_{PF} determined at a PF temperature, other than TPW, and the electrical resistance $R_{0.01}$ determined at TPW temperature (0.01 ºC). The modeling function is:

$$W_{Ga} = R_{Ga}/R_{0.01}, \tag{4}$$

where:

R_{Ga}	TD calibration resistance, calculated at the melting temperature of Ga;
$R_{0.01}$	TD calibration resistance, calculated at TPW temperature;

$$R_{Ga} = R'_{Ga} + \delta R_{Ga/i} + \delta R_{Ga/h} + \delta R_{Ga/f} + \delta R_{Ga/p} + \delta R_{Ga/r} + \delta R_{Ga/m} + \delta R_{Ga/l} + \delta R_{Ga/t}, \tag{5}$$

$$R_{0.01} = R'_{0.01} + \delta R_{0.01/i} + \delta R_{0.01/h} + \delta R_{0.01/f} + \delta R_{0.01/r} + \delta R_{0.01/v} + \delta R_{0.01/m} + \delta R_{0.01/l} + \delta R_{0.01/t}, \tag{6}$$

R'_{PF}	the TD calibrated resistance at the melting point of gallium;
$\delta R_{Ga/i}$	the deviation correction of the freezing/melting temperature, considering the chemical impurities of the gallium;
$\delta R_{Ga/h}$	the variation correction of the freezing/melting temperature, considering the hydrostatic pressure;
$\delta R_{Ga/f}$	parasite heat flux correction;
$\delta R_{PF/p}$	the variation correction of the freezing/melting temperature, considering the cell gas pressure from the reference value;
$\delta R_{Ga/r}$	the resistance correction considering the finite resolution of the indicator device;
$\delta R_{PF/m}$	environment temperature effects correction on the calibrated TD displayed values;
$\delta R_{PF/l}$	TD nonlinearity correction;
$\delta R_{PF/t}$	correction of the parasite voltage and contact resistance effect from the measurement circuit;
$R_{0.01}'$	TD resistance at TPW;
$\delta R_{0.01/i}$	the variation correction of the temperature triple point, considering chemical impurities and isotopic composition;
$\delta R_{0.01/h}$	the variation correction of the triple point, considering the hydrostatic pressure;
$\delta R_{0.01/f}$	correction of the parasite heat flux;
$\delta R_{0.01/r}$	resistance correction, considering the finite resolution of the indicator device;
$\delta R_{0.01/v}$	the variation correction of the measured resistance on TPW before and after the melting point of the gallium;
$\delta R_{0.01/m}$	environment temperature effects correction on the TD displayed values;
$\delta R_{0.01/l}$	TD non-linearity correction;
$\delta R_{0.01/t}$	correction of the parasite voltage and contact resistance effect from the measurement circuit.

Considering that all the input values are not correlated, the composed standard uncertainty associated with W_{PF}, $u_c(W_{PF})$, is determined using the uncertainty propagation law for uncorrelated input values [5], which becomes

$$u_c^2(W_{PF}) = \sum_{i=1}^{18} \left(\frac{\partial f}{\partial x_i} \right)^2 u^2(x_i) + s_{WPF}^2 , \tag{7}$$

where x_1, x_2,..., x_{18} are the input estimations and f is the modeling function (4), with the analytical form expressed in (5) and (6).

6. Uncertainty budget

Table 2

Uncertainty budget

Value X_i	**Estimation** x_i **/ Ω**	**Standard uncertainty** $u(x_i)$ **/ Ω**	**Probability distribution**	**Sensibility coefficient** c_i	**Contribution on the composed standard uncertainty** $u_i(y) = c_i\, u(x_i)$
R'_{PF}	111.56317	3.07E-04	normal	0.010001584	3.074E-06
$\delta R_{PF/i}$	0	1.00E-04	normal	0.010001584	1.000E-06
$\delta R_{PF/h}$	0	1.78E-04	rectangular	0.010001584	1.777E-06
$\delta R_{PF/f}$	0	1.00E-04	rectangular	0.010001584	1.000E-06
$\delta R_{PF/p}$	0	1.50E-05	rectangular	0.010001584	1.500E-07
$\delta R_{PF/r}$	0	2.89E-04	rectangular	0.010001584	2.887E-06
$\delta R_{PF/m}$	0	1.50E-05	rectangular	0.010001584	1.500E-07
$\delta R_{PF/l}$	0	2.89E-04	rectangular	0.010001584	2.887E-06
$\delta R_{PF/t}$	0	289E-04	rectangular	0.010001584	2.887E-06
$R'_{0.01}$	99.98417	2.11E-04	normal	0.000100032	2.109E-08
$\delta R_{0.01/a}$	0	5.00E-05	normal	0.000100032	5.002E-09
$\delta R_{0.01/h}$	0	1.35E-04	rectangular	0.000100032	1.351E-08
$\delta R_{0.01/f}$	0	5.00E-05	rectangular	0.000100032	5.002E-09
$\delta R_{0.01/r}$	0	2.89E-04	rectangular	0.000100032	2.888E-08
$\delta R_{0.01/v}$	0	1.44E-04	rectangular	0.000100032	1.444E-08
$\delta R_{0.01/m}$	0	1.50E-05	rectangular	0.000100032	1.500E-09
$\delta R_{0.01/l}$	0	2.89E-04	rectangular	0.000100032	2.888E-08
$\delta R_{0.01/t}$	0	2.89E-04	rectangular	0.000100032	2.888E-08
		s_{WPF}	normal	1	1.123E-06
W_{PF}	1.115,807,21				**6.397E-06**

To express $u_c(W_{PF})$ in temperature units, the following relation is used

$$u_c^2(\Delta T_{90}) = \left(\frac{\partial T_{90}}{\partial W} \right)^2 u_c^2(\Delta W_{PF}), \tag{8}$$

where $(\partial T_{90}/\partial W)_{Ga}$= 252.989,705 8 ºC, so $u_c(T_{90}) = 0.0016$ °C.

The extended uncertainty [5] for an extension factor $k = 2$ is $U_e = 3.2$ mK.

7. Conclusions

In this paper we report the experimental model of a highly accurate intratumor temperature method and monitoring equipment that we built. The device was calibrated at the SIT 90 fixed points of, within the range (0...50) °C, with a very good accuracy. The calibration uncertainty is less than 0.005 °C.

A highly accurate and efficient temperature monitoring equipment for living tissues was developed. This equipment proves useful for the clinical research and for the verification of other medical devices aimed at monitoring the temperature of living tissues.

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