Hyperthermic Intraperitoneal Chemotherapy Approach Based on Cyber-Physical System Paradigm

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Abstract: The Cyber-Physical Medical Systems (CPMS) have emerged as an alternative to today's medical device architectures, allowing the development of high-confidence medical equipment. Architectures of high performance equipment for Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) are investigated. A cyber part based on a hierarchical embedded structure (suitable for model based development and verification) is proposed. The paper motivates that the peritoneal area surface, the volume of carrier solution and the dose of intraperitoneal chemotherapy can benefit from 3D reconstructions for estimating optimal values. The suitable architectures for temperature sensing and control blocks are analyzed and their performances are further simulated using Matlab/Simulink.

Keywords: Cyber-Physical System; Embedded systems; Sensor systems; Hyperthermic Intra-Peritoneal Chemotherapy; 3D Reconstructions.

1. INTRODUCTION

Peritoneal Carcinomatosis was first time described (1931) by Sampson in an ovarian carcinoma (Sampson, 1931), and it was associated with a 6 month median survival (Sadeghi et al., 2000). The usual treatment involves palliative surgery, systemic chemotherapy and best supportive care. John S. Spratt designed the first HIPEC device (1980), named "Thermal Infusion Filtration System" (Spratt et al., 1980) and Paul H. Sugarbaker developed the therapeutic approach based on the model of appendicular cancer (Sugarbaker et al., 1996).

The current therapeutic approach associates Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (Sugarbaker, 2012).

High performance equipment for hyperthermic intraperitoneal chemotherapy (HIPEC) can help implementing in a precise manner the concepts of cytoreductive surgery and regional chemotherapy: the intensification of the cytostatic drugs effect, through the association of hyperthermia. This would make HIPEC a technique that allows approaching in a therapeutic manner pathologies for which systemic chemotherapy is not an efficient solution, like peritoneal carcinomatosis (PC).

In the past decade, the Cyber Physical System (CPS) has emerged as a paradigm that provides the conceptual basis for architectural frameworks in many complex problems, like health-care, navigation and rescue, intelligent transportation systems (Wu et al., 2011). The CPS paradigm permits to consider in a unitary way the complex aggregate of patient physiology (including functions and pathologies of diverse organs and systems), the medical devices for diagnosis and therapeutic interventions affecting these systems, the architecture and overall control of the sensing and treatment system. The Cyber-Physical Medical Systems (CPMS) have specific features like non linearity, transport delays, spatial-temporal effects, and nontrivial aggregation of interactions, particularly due to the close interaction with the human body (Banerjeey et al., 2011), making their modelling and analysis a difficult task. In fact, there are only a few number of CPS architectures proposed for health care application (Lee, 2012).

Three-Dimensional (3D) Reconstructions are important tools in the medical field, both diagnostic and therapeutic, used in cardio-vascular surgery, orthopedic surgery, neurosurgery, prosthetic design and implantation. Most of the studies, regarding the surface area of the peritoneum and the circulated solution, are coming from Peritoneal Dialysis dedicated literature and were performed using CT-peritonegraphy (Hawkins et al., 2000), stereological (Chagnac et al., 1999), and scintigraphic method (de Forni et al., 1993). To our date, there are anthropometrical studies regarding different viscera (Carcedo, 2010; Martin et al., 2013), but no 3D Reconstruction approach to peritoneal cavity.

The medical debates about the HIPEC approach are somehow controversial: the procedures are based more on common sense than on experimental data (Macrì, 2010). Also, some of the medical controversies are related to the technical aspects of the HIPEC procedure. To our knowledge there was only

one multidisciplinary approach that addressed HIPEC, involving "L'École Nationale Supérieure des Mines de Saint-Étienne" and "Centre Hospitalier Universitaire Saint-Étienne et Lyon Sud". Significant results are related to thermal modelling of HIPEC technique (allowing to specify the appropriate flow rate and pressure, for producing a homogenous thermal distribution) (Szafnicki et al., 1998) and a real-time monitoring HIPEC (Supervision en temps-reel de la CHIP) (Ladhari et al., 2007).

The success of the HIPEC therapeutic technique depends on a deeper understanding of the complex thermal phenomena associated with HIPEC and the availability of innovative HIPEC equipment that exploits this understanding. 3D Reconstruction of Peritoneal Cavity allows characterizing each patient, permitting a customization of HIPEC process parameters.

The architectural design and the implementation of a HIPEC equipment as a high-confidence CPMS, implemented on an embedded platform is, in authors opinion, the most appropriate way to address this problem. Its functional correctness is a co-design problem: the design of the cyber part (embedded control systems and networks) and the physical part influence each other.

2. HIPEC VARIABLES AND 3D RECONSTRUCTIONS

HIPEC requires intra-peritoneal spread of cytostatic drugs, at high temperatures (42-43℃), accomplished within 30-120 minutes, during surgical interventions. There are a large number of variations in HIPEC protocols and only one consensus conference regarding colo-rectal cancer (Turaga et al., 2014).

The variables influencing the response to HIPEC are: temperature; dose of intraperitoneal chemotherapy; distribution of chemotherapy solution and heat (open vs. closed technique); timing of chemotherapy in relation to the timing of the surgical intervention; type of carrier solution; pressure; volume of carrier solution; duration of instillation; vasoactive agents; macromolecular vehicles; drug sensitivity of the tumours; size of residual tumour nodules (Sugarbaker et al., 2010).

Among those variables, volume of carrier solution and the dose of intraperitoneal chemotherapy can benefit from 3D Reconstructions as an approach to estimating optimal values. Currently, the volume of carrier solution and the surface of the peritoneal cavity are not quantified before starting the HIPEC procedure.

Different medical centres proposed a highly variable amount of carrier solutions (between 3 to 6 litters). *The volume of solution carrier should be correlated to the peritoneal surface area in contact with the solution*. Also, studies revealed large inter-individual variations between the peritoneal surface areas in contact with the carrier solution and anatomic peritoneal surface (Flessner et al., 2001; Chagnac et al., 2002). *The critical requirement for a high efficiency HIPEC is that the entire peritoneal surface area should be "washed" by the cytostatic solution.*

For the same amount of the active cytostatic drug, an increase of the carrier solution volume will increase the peritoneal contact surface area and the intraperitoneal pressure. The increased pressure associated with large volumes might be an advantage in intraperitoneal regional therapy, but it needs careful monitoring of the intraperitoneal pressure, due to hemodynamic and respiratory tolerance.

These considerations motivate why a proper model and an effective control strategy are needed to establish the optimal relation between the circulated solution volume and the peritoneal surface area in contact with. The model investigated by authors is specific to the carcinomatous ascites patients, where 3D reconstructions of the ascites can provide both the volume of ascites (i.e. circulated solution volume) and the peritoneal surface area in contact with.

The challenge related to 3D Reconstruction of the ascites is the segmentation process, a time consuming procedure when done manually (about 6 hours). The development of semiautomatic or automatic segmentations techniques can solves this issue.

In clinical practice, the dose of intra-peritoneal chemotherapy is calculated according to the Body Surface Area. The major clinical significance of increased chemotherapy dose is related to the systemic toxicity.

It is a closed relationship between the cytostatic dose and the volume of carrier solution. More dilute intraperitoneal chemotherapy concentrations retarded the clearance of chemotherapy and lead to a lesser systemic toxicity, but penetrate less into the cancer nodules. A proposed alternative was to regulate not only the chemotherapy dose but also the volume of chemotherapy solution by the patient's Body Surface Area (Sugarbaker et al., 2006). Since there is a great difference in the size of the peritoneal space for different patients, the controversies persists. If the contact area is variable, the total absorption of the drug cannot be predicted.

A 3D Reconstruction of the entire anatomic peritoneal surface (particularly the visceral one) is hardly possible, due to the proper anatomic complexities and indefinite imagistic interface with the bowels. The reliable 3D Reconstruction proposed method is to approach the parietal peritoneum. There is a scientific base for the proposal: the effective permeability of the visceral peritoneum is poor, compared with that of the parietal peritoneum (Bouchet et al., 1989; Fox et al., 1991).

The parietal peritoneum reconstruction is a facile task, even with manual segmentation and allows us to calculate the surface area involved in cytostatic absorption.

3. HIPEC DEVICES

The currently accepted (closed procedure) requires the usage of equipment that can assist in maintaining the intraperitoneal temperature of the cytostatic fluid, as well as in producing a uniform distribution of the cytostatic fluid flow.

Currently, there are several HIPEC devices on the market, based on the Spratt designed principle: pump, heat ex-

changer, thermal probes, interface and accessories (pump tubing set inflow catheters and return drains). The differences resides in user interface (digital or touch screen), number of pump (on inflow circuit +/- outflow circuit), intra-abdominal temperature probes used (usually 2-3). The most used devices are summarized in the Table 1.

Table 1. HIPEC devices

HIPEC device	Producer/ Representative	Original aspects
ThermoChem HT-2000	Therma Solutions (USA) www.thermasolutions.com	outflow catheters: Prof. Piso kit
Performer HT	RanD SRL (Italy) info@rand-biotech.com	two-stage filter for cell clusters and cell fragmentation retention
Cavitherm	Soramedical (France) www.cavitherm.com	two vortex pump head module low frequency induction heating system
SUNCHIP	GamidaTECH (France) www.gamidatech.com	FlowProtect: to reduce the risk of sticking and improve the flow-rate
EXIPER	Medica S.p.A. (Italy) www.menfis.it	high thermal efficiency heater and a miniaturized heat exchanger
Belmont Hyperthermia Pump	Belmont Instruments (USA) www.belmontinstrument.com	roller type peristaltic pump
VERATHERM	Thermal Therapeutic Systems (USA) www.thermaltherapeutics.com	Portability

Over 34 years using, there is a lack of device standardization and the differences between older and newer design are essentially reflected in user interface design and increasing prices.

The research effort behind this paper is motivated by the following problems related to the architectural/operational aspects of the currently available HIPEC equipment:

- There is no appropriate distributed temperature monitoring for providing comprehensive information regarding the intraperitoneal temperature distribution. The limited, low number of thermal sensors, randomly placed, does not allow the thermal characterization of the entire peritoneal space.
- The flow distribution is uncontrolled. The preferential circuits between the inflow and outflow catheter, permits the existence of areas with a temperature that is lower than the appropriate one.
- There are no advanced control mechanisms implemented in order to achieve homogenous temperature in the peritoneal cavity. Changing the patient position and shaking the abdomen are performed in order to homogenize the temperature in the peritoneal cavity.

4. CPS ARCHITECTURES FOR MEDICAL PLATFORMS

Many applications opportunities for CPS are suggested, both in medicine and biomedical engineering: rehabilitation, image-guided surgery, robotic surgery, proton therapy treatment; therapy, fluid flow control for medicine and biological assays; development of physical and neural prostheses; reconfigured medical devices and systems to interact with patients and caregivers in complex environments (operating rooms) (Lee et al., 2010; Baheti et al., 2011; Hu, 2014).

A CPMS is presented in European Commission Report from the Workshop on CPS (European Commission, 2013) as a collection of computing nodes distributed in a physical environment. The computing nodes are networked and interact with the physical environment. The cyber-physical interactions (see Fig. 1), can occur between computing entities and spatial regions or particular locations in the environment.

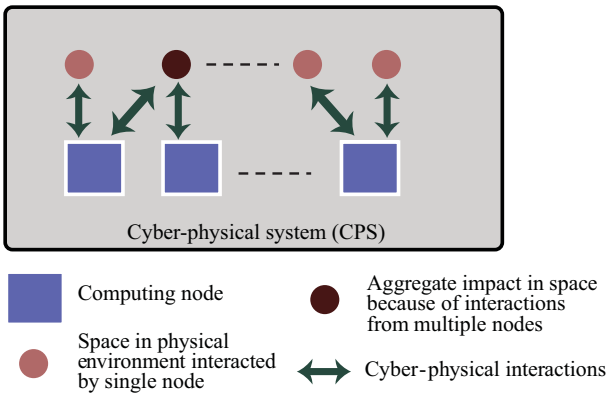

Fig. 1. Cyber-physical system architecture (European Commission, 2013).

The report „High-Confidence Medical Devices: Cyber-Physical Systems for 21st Century Health Care" (NCO/NITRD, 2009), examines the architectures, the development methods and the associated research challenges of the current medical device systems, and clearly identifies the future medical devices as High Confidence Cyber-Physical Systems. The following ideas are listed among its key findings:

- Today's medical device architectures are typically proprietary, not interoperable, and rely on professionals to provide inputs and assess outputs.
- When a patient is connected to multiple devices at once, such as in an operating room, clinicians now must monitor all devices independently, synthesize data, and act on their observations.
- While medical device architecture is beginning to include wired and wireless interfaces to facilitate networked

communication of patient data, ad hoc efforts to aggregate data across devices designed to operate separately can lead to unintended or accidental results.

- Capabilities as home health care services, delivery of expert medical practice remotely (telemedicine) and online clinical lab analysis underscores the central role of advanced networking and distributed communication of medical information in the health systems.
- Neither past nor current development methods are adequate for the high-confidence design and manufacture of highly complex, interoperable medical device software and systems.
- Today's verification and validation efforts are driven by system-life-cycle development activities that might be inadequate in the context of an increasing components and interactions complexity of the emerging medical devices and systems.

CPS architectures currently proposed for health care application consists of: a service-oriented architecture based medical CPS (Hu, 2011); a Secured Health Care Application Architecture for Cyber-Physical Systems, which utilizes WSN-cloud integrated framework (Wang et al., 2011); a modelling and analysis architecture of CPMS (Banerjeey et al., 2011). Also, it was proposed an attribute-based secure data sharing scheme for dependable and secure medical information systems (Hur et al., 2012).

The criticism of the current CPS in health care proposal, are mainly related to parameter variability, data workflow and implementation (Haque et al., 2014). Current proposals consider very few parameters or vital signs, thus limiting their possibilities.

5. SPECIFIC CPS ARCHITECTURES - CHALLENGES ASSOCIATED WITH HIPEC EQUIPMENT

First of all, it should be observed that although the cytostatic effect is proportional to the increase of the temperature, the human body is the one that sets the limits. As intraperitoneal temperatures exceeding 45℃ may induce local abdominal thermic injuries and systemic hyperthermia. The main drawbacks of the current equipment are uneven/uncontrolled distribution of the temperature in the target volume and uneven flow distribution.

A fully automated HIPEC equipment, allowing a homogeneous distribution of chemotherapy drugs and heat, able to provide optimal exposure of the patient peritoneal surface area with minimal systemic toxicity and minimal exposure of the personnel, must reside on an architecture proposed that addresses the following problems:

- complex inflow distribution system with multiple nozzles with variable flow;
- a wireless multipoint temperature measurement system;
- a thermal map of the Peritoneal Cavity (with the support of 3D Reconstructions);
- smart control algorithms for localized flow and temperature control;
- integration of the anesthesiological parameters and of the vital signs;
- hermetically sealed implementation of the devices that have to be sterilized.

The need for "Human Centric Cyber-Physical Systems" is more than relevant for the case of CPMS, since here humans will interact with the system directly, leading to the consideration of two basic issues: high-confidence operation of HIPEC-CPS and patient safety (European Commission, 2013).

A crucial condition for developing a high-confidence of HIPEC-CPS is high model fidelity (i.e. the model accurately imitates the real system). If this condition is met, there is possible to automatically synthesize the model's cyber parts using Model-Based Design methods, such that the simulated model and the behaviour of the real running system coincide.

Patient safety is a primary factor in configuring the architecture of medical devices, and was addressed by a series of standards related to medical equipment design and manufacturing. The IEC 60601 standard has a long history with the original IEC 60601-1 published in 1977. According to the 3rd edition (IEC 60601-1, published by the IEC in 2005 and known in Europe as EN60601-1:2006) medical devices will need to pass static testing, dynamic testing, and formal testing (to prove that requirements are met, that the system will be stable, and that algorithms are correctly implemented). The standard defines safety as the avoidance of unacceptable risks of hazards to the physical environment (i.e. to the patient) due to the operation of a medical device under normal or single fault condition. The concept is extended, the safety of a CPMS is defined as avoidance of risks of the computing unit or of the physical environment from harmful effects of cyber-physical interactions (Banerjeey et al., 2011).

CPMS will require a new regulatory procedure to approve their use for treating patients (Lee et al., 2010). U.S. Food and Drug Administration (FDA) approval is becoming too lengthy and will be prohibitively expensive with the increased MCPS complexity. Device manufacturers are often operating under strict time-to-market pressures and soon small, innovation-driven companies will hardly afford the effort of preparing submissions to FDA.

6. THE PROPOSED CPS HIPEC EQUIPMENT ARCHITECTURES

The following issues have to be addressed when designing the cyber part of the HIPEC-CPS:

- identify those robust embedded platforms that support capabilities such as extended built-in self-testing on the hardware platform, system-level device health monitoring, fault isolation and recovery, hardware-level security implementation, and device attestation;
- align with non-proprietary interoperability standards and provide advanced capabilities for managing the safety, security, and privacy aspects;
- specify latency and real-time, fault-tolerance, and device registration and configurability requirements.

Various agencies and standards bodies have signalled that the future of medical technology lies in medical device interoperability, emphasizing the capability to integrate information from multiple clinical sources in a context-sensitive way (Kune et al., 2012).

Such considerations were the basis for the design of an integrated HIPEC System (see Fig. 2), able to communicate via its Network Interface with a Database Server and a clinical decision support system software (PC DSS) running on a personal computer, and a set of cameras connected through a wireless access point.

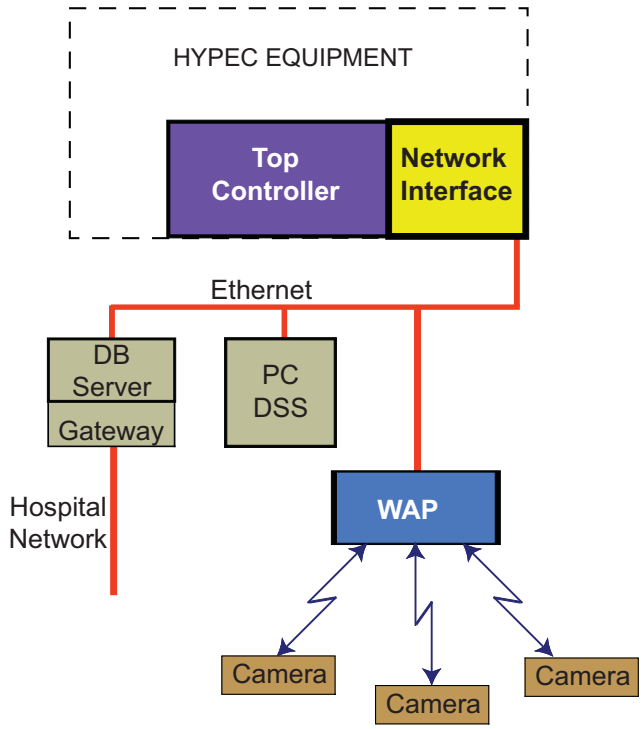

Fig. 2. The integrated HIPEC System.

The essential blocks of the proposed HIPEC equipment architecture are indicated in Fig. 3. A dedicated safety controller was included, having its own pressure and temperature sensors and a direct connection to the user interface for immediate error/alarm reporting to the medical staff, as shown in Fig. 4. The appropriate references can be prescribed to the top controller via the user interface module or through the network interface. The problem of distributed monitoring and control for flow and temperature was addressed by introducing a family of heat and flow controllers (see Fig. 4), all connected to a common bus and having defined a hierarchy with the top controller at the superior level.

This approach can accommodate for model based development and testing of heat and flow controllers as identical units, each of them implemented on an individual embedded processor. Since the local temperature sensor and the individual heater for a given flow channel are directly connected to such a controller, the physical properties (like temperature transducer inertia, heating actuator inertia, etc.) would have to be addressed by the software implemented at this level.

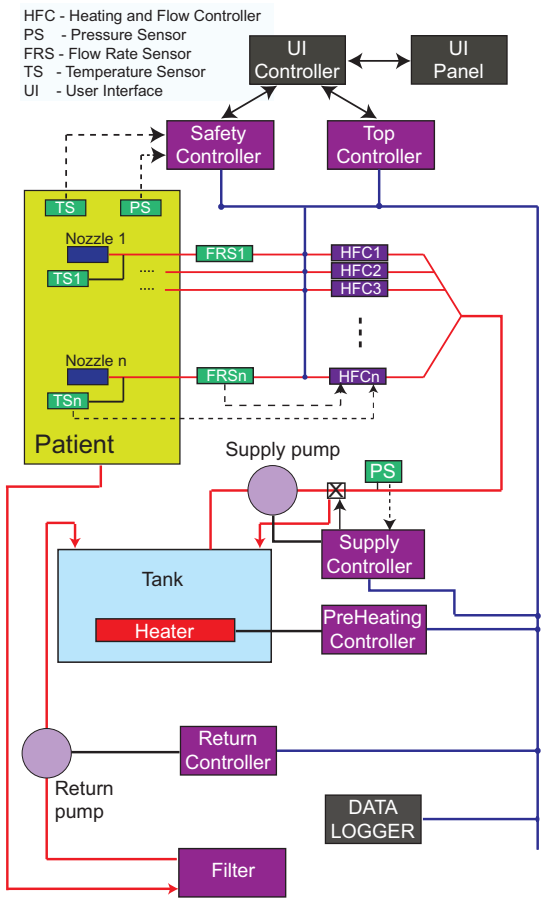

Fig. 3. The essential blocks of the proposed HIPEC equipment architecture.

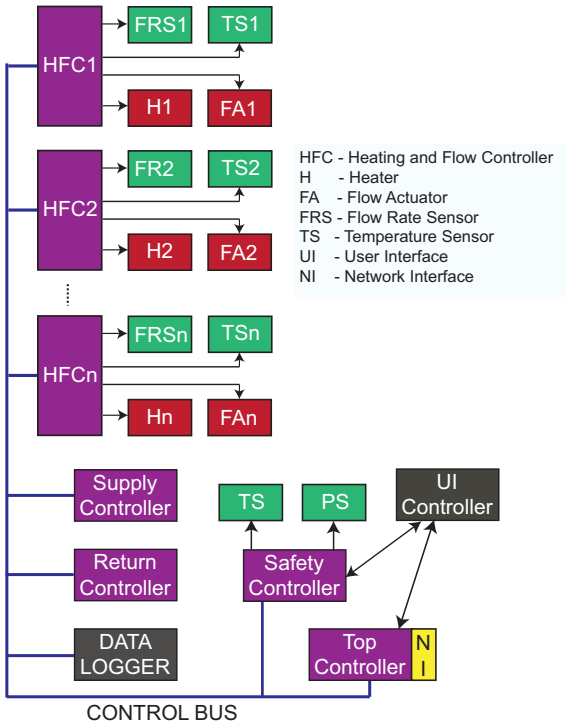

Fig. 4. Cyber part of HIPEC equipment as Cyber-Physical System.

7. TEMPERATURE MEASUREMENT SYSTEMS IN HIPEC

The measurement of the temperature is crucial for the performance of HIPEC. It must address the following issues:

- very accurate measurements are needed (errors *preferably* under 0.1C),
- multiple points (4 to 16 in our view) need to be monitored simultaneously,
- the inertia due to the temperature probe design must be minimized,
- the whole system must be hermetically sealed,
- all the components should cope with the sterilization procedures currently in use.

In this context, a sensor network integrated in a wireless system was proposed (Lungoci et al., 2014). The main design constrains are related to size (small dimensions preferred), power consumption (battery life), and sealed construction (see Fig. 5).

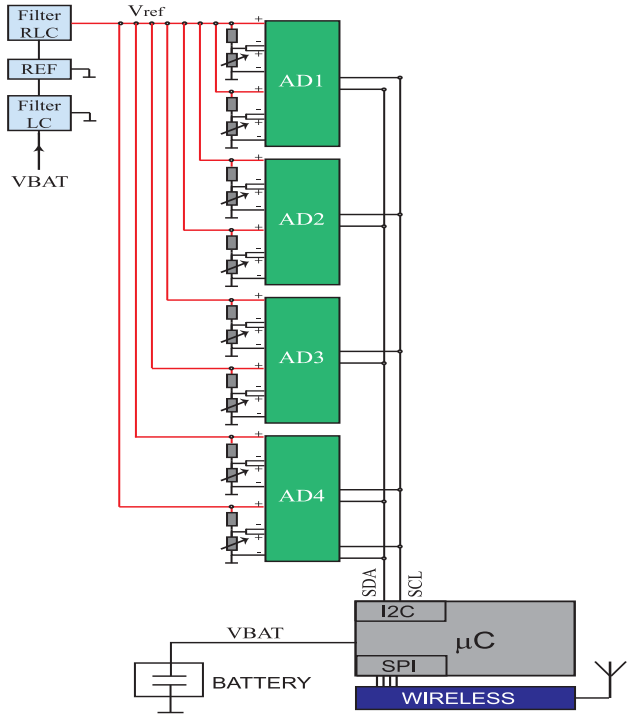

Fig. 5. Proposed wireless temperature monitoring.

Usage of AD converters imposes an analysis of the quantization error. The influence of the quantization error (maximum of ±1 LSB) on the measured temperature value is significant when the resolution is less than 12 bits (see Fig. 6).

Reducing the energy consumed by a wireless sensor using the *duty-cycling* technique, allows achieving lower average power consumption by setting the device into inactive state whenever possible. The main consumers typically encountered in a wireless sensor are the processing unit, the sensing unit and the communication unit.

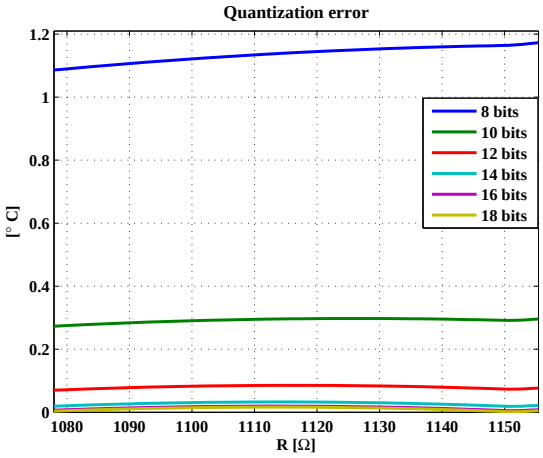

Fig. 6. Quantization error in the proposed wireless system.

Average power consumption obtained by duty-cycling can be expressed by the following equations (Bader, 2013):

$$I_\delta = \frac{I_{act}T_{act} + I_{inact}T_{inact}}{T} = \delta I_{act} + (1-\delta)I_{inact}$$

$$\delta = \frac{T_{act}}{T_{act} + T_{inact}}, 0 < \delta < 1$$

where T_{act} is the period spend by the consumer in active state, T_{inact} is the period in inactive state and $T = T_{act} + T_{inact}$.

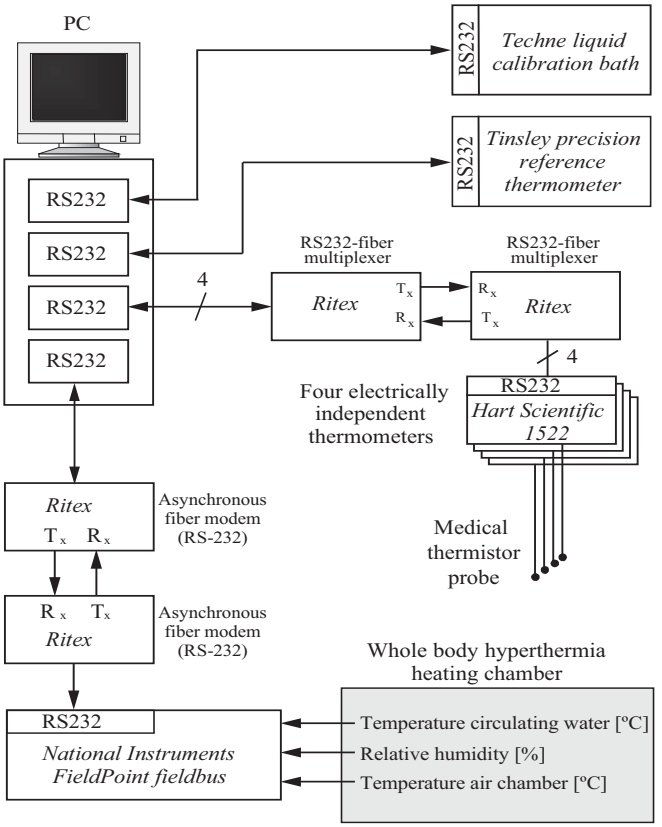

Fig. 7. Example of complex temperature monitoring system (Hjertaker et al., 2005).

Beside the technical performance, the affordability of the equipment is a key factor. The setups used in the research and investigation of the hyperthermia treatment can be quite complex. Examining the architecture of Fig. 7 can immediately give an idea about the system cost in the case of complex setups.

8. MODELS OF INTERACTION BETWEEN CYBER AND PHYSICAL PART

The proposed architecture of the CPS should consider not only the cyber part (Fig. 4), but also the physical interactions. The modelling of these interactions can serve as basis for choosing the right control algorithms. The computational effort associated with their implementation will in turn specify some performance limits and real time constrains for the embedded platform on which the implementation will be done.

In order to control the temperature of the solution from the peritoneal cavity, the control structure from Fig. 8 can be used. The structure is based on the internal model control (IMC) strategy.

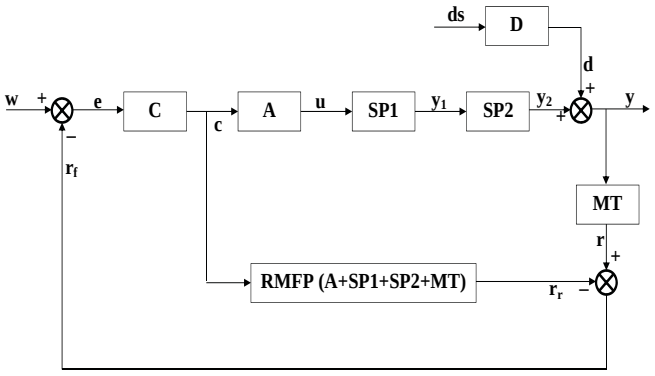

Fig. 8. The control structure based on the IMC strategy.

The significance of the notations from Fig. 8 is: SP1 and SP2 – the sub-processes 1 and 2 (they make the connection between the thermal power generated by the heating source (P_A = $u(t)$ – actuating signal) and the temperature of the solution at the input in the peritoneal cavity (T_{io} = = $y_1(t)$), respectively between $y_1(t)$ and the temperature of the solution in the peritoneal cavity ($y(t)$ – output signal); A – actuator; C – controller; MT - measurement transducer; RMFP – reference model of the fixed part of the control structure (the initial model identified for the group of elements A+SP1+SP2+MT); D – model of the disturbance propagation.

The significance of the notations associated to the signals from Fig. 8 (others than the already mentioned ones) is: $w(t)$ – reference signal in unified voltage (0-10V), $e(t) = w(t)$-$r_f(t)$ –error signal; $c(t)$ – control signal in unified voltage; $d(t)$ – disturbance signal (the effect of the patient heat absorption in temperature – negative value); $y_2(t)$ – the initial output signal (not affected by the disturbance); *ds* – the steady state value of the disturbance signal; $r(t)$ – feedback signal; $r_r(t)$ – reference feedback signal; $r_f(t) = r(t) - r_r(t)$ - final feedback signal. All *r* signals are considered unified voltage signals.

The structure of Fig. 8 was designed to work only over a limited range (temperature of the patient y_i = 36.5^{0}C). In Fig.9, the steady state value of the *w* signal is *ws*, the model of the reference propagation being W and $y_f(t)$ is the final output signal (the temperature of the solution in the peritoneal cavity). All the mentioned *y* signals besides y_i and y_f represent over-temperatures in relation to the initial conditions (body temperature y_i).

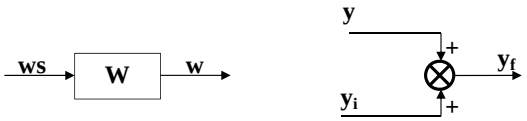

Fig. 9. The reference and the output signals.

The transfer function of the actuator is presented in (1)

$$H_A(s) = \frac{K_A}{T_A \cdot s + 1} = \frac{16}{3 \cdot s + 1}, \tag{1}$$

where the time constant is $T_A = 3\text{s}$ and the proportionality constant is $K_A = \frac{P_{A\max} - P_{A\min}}{u_{\max} - u_{\min}} = \frac{160 - 0}{10 - 0} = 16\text{A}$. The indices min and max are referring to the minimum, respectively to the maximum values of the corresponding signals. Also, *u* with the index min or max represents the domain limits of the unified voltage signals.

The transfer function identified for SP1 is presented in (2):

$$H_{SP1}(s) = \frac{K_{SP1}}{T_{SP1} \cdot s + 1} = \frac{0.0657}{5 \cdot s + 1}, \tag{2}$$

where $T_{SP1} = 5\text{s}$ and

$K_{SP1} = \frac{T_{io\max} - T_{io\min}}{P_{A\max} - P_{A\min}} = \frac{10.5 - 0}{160 - 0} = 0.0657 \frac{\text{K}}{\text{W}}$. The index *o* signifies an over-temperature.

The transfer function of SP2 is presented in (3) (Ladhari, 2007):

$$H_{SP2}(s) = \frac{K_{SP2}}{T_{SP2} \cdot s + 1} = \frac{0.9}{20 \cdot s + 1}, \tag{3}$$

where $T_{SP2} = 20\text{s}$, $K_{SP2} = 0.9$.

The transfer function of the temperature measurement transducer is indicated in (Ladhari, 2007):

$$H_{MT}(s) = \frac{K_{MT}}{T_{MT} \cdot s + 1} \cdot e^{-T_D \cdot s} = \frac{0.4255}{6.1 \cdot s + 1} \cdot e^{-2.7 \cdot s}, \tag{4}$$

where $T_{MT} = 6.1\text{s}$, the dead time constant $T_D = 2.7\text{s}$, respectively $K_{TM} = \frac{u_{\max} - u_{\min}}{T_{oo\max} - T_{oo\min}} = \frac{10 - 0}{23.5 - 0} = 0.4255 \frac{\text{V}}{\text{K}}$ (T_{oo} = $y(t)$).

The reference model of the fixed part is obtained multiplying the transfer functions of the cascaded blocks:

$$H_{RMFP}(s) = H_A(s) \cdot H_{SP1}(s) \cdot H_{SP2}(s) \cdot H_{MT}(s). \tag{5}$$

The controller is computed in order to compensate the time constants of all the elements included in the fixed part:

$$H_C(s) = \frac{(T_{MT} \cdot s + 1) \cdot (T_{SP2} \cdot s + 1) \cdot (T_{SP1} \cdot s + 1) \cdot (T_A \cdot s + 1)}{K_{MT} \cdot K_{SP2} \cdot K_{SP1} \cdot K_A \cdot (T_f \cdot s + 1)^4}. \quad (6)$$

In order to make the controller feasible, a 4th order filter with the time constant $T_f = 3\text{s}$ has to be used. A form of the controller which generates a smaller value of the control signal is proposed :

$$H_{C1}(s) = \frac{(T_{SP2} \cdot s + 1) \cdot (T_{SP1} \cdot s + 1) \cdot (T_A \cdot s + 1)}{K_{MT} \cdot K_{SP2} \cdot K_{SP1} \cdot K_A \cdot (T_f \cdot s + 1)^4}. \quad (7)$$

The power of the heating source can be calculated using the relation:

$$P_e = P_T, \quad (8)$$

where P_e is the electrical power generated by the heating source and P_T is the thermal power absorbed by the solution. This equation can be rewritten as:

$$\frac{U_A^2}{R_{HR}} = \frac{Q}{t} = \frac{m \cdot c \cdot \Delta T_{io}}{t}, \quad (9)$$

where U_A is the supply *voltage* of the heating resistance, R_{HR} is the heating resistance, m is the mass of the solution from the tube ($m = \rho \cdot V$), the volume $V = \pi \cdot \frac{d^2}{4} \cdot L = 1.4 \cdot 10^{-6}\,\text{m}^3$ (d is the tube diameter and L is the tube length; $L = 50\text{mm}$; $d = 6\text{mm}$), $c = 4000 \frac{\text{J}}{\text{kg} \cdot \text{K}}$ is the specific heat of the solution; $\rho = 1005.3 \frac{\text{kg}}{\text{m}^3}$ is the density of the solution, $\Delta T_{io} = 9\text{K}$ is the maximum increase of the over-temperature of the solution in the tube.

The flow of the solution in the tube is $F = 3.75 \cdot 10^{-6}\,\text{m}^3$, leading to a $t = \frac{V}{D} = 0.37\text{s}$ (the contact period between the heating source and the solution from the tube).

The computed value is $P_T = 136.94\text{W}$, and taking into account also a control margin, a heating source with the maximum value $P_{AMAX} = 160\text{W}$ was selected.

For the W and D elements, the following first order transfer functions are used in simulations:

$$H_W(s) = \frac{K_W}{T_W \cdot s + 1}, \quad (10)$$

where $K_W = 1$ and $T_W = 8.5\text{s}$, respectively

$$H_D(s) = \frac{K_D}{T_{DD} \cdot s + 1}, \quad (11)$$

where $K_D = 1$ and $T_{DD} = 1\text{s}$.

All the simulations are made in MATLAB/SIMULINK. The temperature evolution in time (the control system response) is presented in Fig. 10 for the case when the temperature reference is set to the value of 42^0C, neglecting all disturbance signals, and using the controller from (6).

From Fig. 10 it results that the overshoot $\sigma = 0\%$ (the imposed value), the steady state error at position $e_{stp} = 0^0$C (the imposed value), respectively the settling time $t_s = 45$s (much smaller than the imposed value – 5 min). Consequently, all the imposed performances are obtained.

In Fig. 11, the simulation is repeated with the same controller, but the disturbance with the steady state value $ds = -1^0$C occurs in the system at the moment $t_d = 50$s. The effect of the disturbance is rejected after 31s from its occurrence, moment when the response value comes back to the temperature reference value.

In the cases of Fig. 10 and Fig. 11, the maximum value of the control signal is higher than the saturation limit (10V).

The same type of simulations (as in the case of Fig. 10 and Fig. 11) are made in Fig. 12 and Fig. 13, but using the controller form indicated in (7).

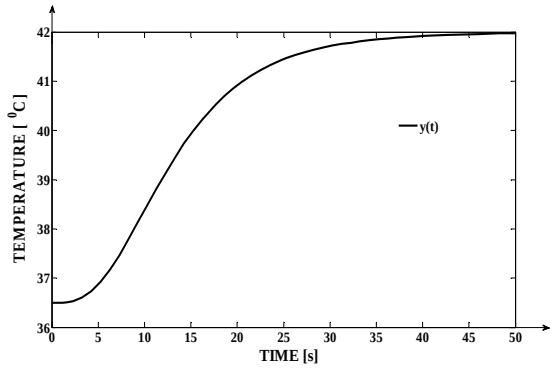

Fig. 10. The control structure response.

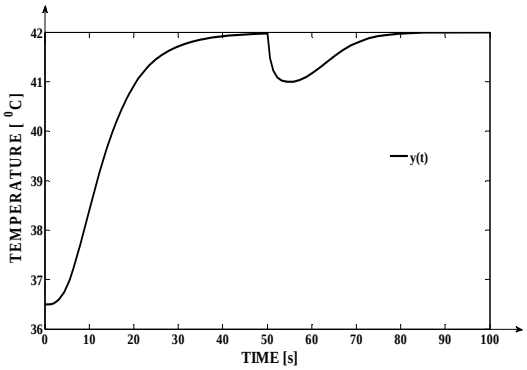

Fig. 11. The control structure response, if the disturbance occurs in the system.

In the case when $H_{C1}(s)$ controller is used, the performances decrease compared to the case of the $H_C(s)$ controller, but the control signal is smaller than the saturation limit. Also, the performances decrease is insignificant considering that the performances remain much better than the imposed ones.

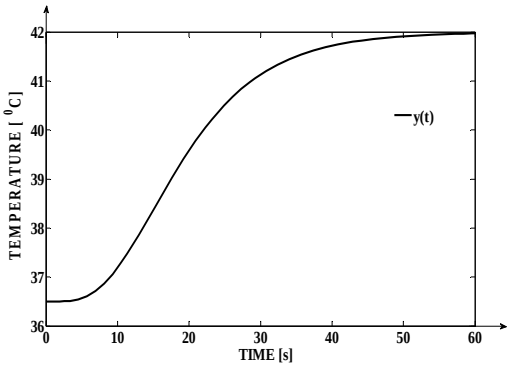

Fig. 12. The control structure response for $H_{C1}(s)$.

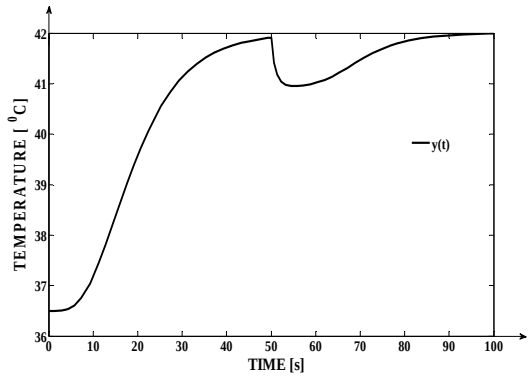

Fig. 13. The control structure response, if the disturbance occurs in the system, for $H_{C1}(s)$.

9. CONCLUSIONS

An individualized HIPEC approach can benefit from 3D Reconstruction of Peritoneal Cavity, in order to estimate the optimal volumes and from a HIPEC architecture based on the Cyber-Physical Systems Paradigm.

The implementation of a HIPEC system based on an architecture designed through the CPS paradigm can benefit from several key features: a highly modular hierarchical organization having a good degree of reuse at the level of control blocks and sensing unit, dedicated safety controller for minimizing the risks.

Matlab/Simulink modelling of the thermal transfer phenomena and of the control structures supports the appropriate selection of the cyber part parameters.

The simulation of the proposed temperature controllers showed good performances. Further developments would target the development of a combined heat/flow controller that is meant to provide similar performance in temperature control, while providing a programmable flow rate, and optimization of the wireless sensors operation in terms of sampling rate and transmission time intervals.

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