Robustness of time-multiplexed hyperthermia to temperature dependent thermal tissue properties

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Robustness of Time-Multiplexed Hyperthermia to Temperature Dependent Thermal Tissue Properties

Grazia Cappiello, Margarethus M. Paulides, Tomas Drizdal, Declan O'Loughlin, Martin O'Halloran, Martin Glavin, Gerard van Rhoon, Edward Jones

Normalized CF SAR distributions for 1W input power and simulated 3D temperature distributions obtained through the static and the selected Pareto solution for one patient. The time-multiplexed thermal distribution shows the hotspot temperature reduction. Temperature distributions are obtained using constant thermal properties of tissues.

Take-Home Messages

- A time-multiplexed hyperthermia treatment planning technique aiming at focusing the tumor heating while protecting the healthy tissue is evaluated with temperature-dependent tissue properties.
- The time-multiplexed hyperthermia via MOGA optimization can successfully intensify the heating into the target region while suppressing pre-defined hotspots when either constant thermal properties or temperature dependent tissue properties are assumed.
- The targeted medical application is hyperthermia treatment planning in order to maximize heating in the tumor while minimizing heating in surrounding tissues.
- This work demonstrates the robustness of the time-multiplexed hyperthermia approach to the variation of tissue properties due to temperature increases and ensures the clinical benefit of the method.
- This work demonstrates that time-multiplexed hyperthermia is effective, regardless of the thermal model used.

Robustness of Time-Multiplexed Hyperthermia to Temperature Dependent Thermal Tissue Properties

Grazia Cappiello, Margarethus M. Paulides, Tomas Drizdal, Declan O'Loughlin, Martin O'Halloran, Martin Glavin, Gerard van Rhoon, Edward Jones.

Abstract Microwave hyperthermia is a promising cancer treatment used in combination with radio- and chemotherapy. Typically, hyperthermia systems involve several antennas that transfer electromagnetic energy into the tissue. The principal need in hyperthermia treatment is to optimally focus the heating into the target while minimising heating in the surrounding healthy tissue. Patient-specific treatment planning is done to optimize the specific absorption rate and the resulting temperature distribution. Uncertainties associated with the thermal model used for temperature simulations represent an important challenge. Our previous work has demonstrated that the occurrence of hotspots can be reduced and target heating enhanced using time-multiplexed steering procedures. In this paper, the robustness of time-multiplexed hyperthermia against temperature dependent thermal tissue properties is investigated. Temperature simulations are used to predict the time-dependent heating achieved by multiple antenna phase and amplitude configurations that are generated by a multi-objective genetic algorithm and applied sequentially. The proposed strategy is compared with the heating obtained using one single heating setting obtained by particle swarm optimization as typically used in clinical hyperthermia. Thermal performance of the static and time-multiplexed methods are assessed by applying two thermal models, one that uses constant properties of blood perfusion and thermal conductivity of tumor, muscle and fat, and a second one that uses temperature dependent perfusion values. This study shows that time-multiplexed hyperthermia enhances target heating and limits the hotspot appearance regardless of the thermal model used in thermal simulations.

Keywords — Hyperthermia, Hyperthermia Treatment Planning, Multi-objective Genetic Algorithm, Thermal Tissue Properties

I. INTRODUCTION

HYPERTHERMIA is a cancer treatment which operates by heating cancer cells to supraphysiological temperatures between 40 °C and 44 °C for 60-90 min [1]. Hyperthermia is used as an adjuvant therapy to radiotherapy and chemotherapy for locally advanced tumors and has been shown to improve the tumor response and patient survival outcome when compared to the standard treatment alone [2], [3]. In recent years, new systems have been developed

for the application of hyperthermia to H&N cancers in clinical settings [4], [5].

Deep hyperthermia systems usually consist of a conformal multi-element antenna phased array to heat the tumor area by radiative transfer of electromagnetic energy [6]–[8]. By controlling transmission at each element of the array, energy can be focused to heat the target area through constructive interference. However, constructive interference can also occur at other, unwanted locations within the patient volume, resulting in areas of healthy tissues being over-heated, known as hotspots. Hotspots can affect the quality of the treatment and can intensify the discomfort to the patient.

To minimize hotspots and to maximize the constructive interference in the tumor area, hyperthermia treatment planning (HTP) is done before the hyperthermia treatment. The fundamental goal of hyperthermia treatment planning is to optimally distribute the electromagnetic (EM) energy and the temperature in the tissue by selecting the appropriate amplitude and phase at each element in the antenna array to maximize heating of the target while minimizing hotspots.

HTP relies on simulating the electromagnetic fields in the tissue to predict the temperature distribution. Many possibilities have been investigated for hyperthermia treatment planning:

- A variety of optimization algorithms and cost

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G. Cappiello, Declan O'Loughlin, M. O'Halloran, M. Glavin, E. Jones are with the Discipline of Electrical and Electronic Engineering, College of Engineering & Informatics, National University of Ireland Galway, University Road Galway, Ireland. M. O'Halloran and Declan O'Loughlin are also with Translational Medical Device Laboratory, Lambe Institute of Translational Research, National University of Ireland, Galway, Ireland. (e-mail: {g.cappiello1, declan.oloughlin, martin.ohalloran, martin.glavin, edward.jones}@nuigalway.ie).

M.M. Paulides, T. Drizdal, G. van Rhoon are with the Erasmus MC Cancer Institute, Department of Radiation Oncology, Section Hyperthermia, Rotterdam, The Netherlands (e-mail: {m.paulides, t.drizdal, g.c.vanrhoon}@erasmus.nl). M.M. Paulides is also with the Faculty of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands and T. Drizdal is also with the Department of Biomedical Technology, Faculty of Biomedical Engineering, Czech Technical University in Prague, nam. Sitna 3105, 272 01 Kladno, Czech Republic.

functions have been proposed [9]–[13];

- Delivery of EM energy into biological tissue using fixed amplitude and phase settings [14] or different antenna settings applied sequentially [15];
- Specific Absorption Rate (SAR) or temperature-based optimizations [16], [17].

Uncertainty still exists as to the exact thermal properties of tissues and as to whether SAR or temperature simulations are a better basis for optimization. Additionally, heat dissipation in the tissues is not always exactly known, nor are the changes in perfusion with respect to temperature well understood. Canters *et al.* [18] found that, considering these uncertainties, SAR better predicted the median temperature for hyperthermia applied in the pelvic region. In [15], we proposed a time-multiplexed hyperthermia approach which involved the application of sequential energy distributions, controlled by different antenna settings, with the aim of improving the temperature distribution. A multi-objective genetic algorithm (MOGA) was developed to obtain the time-multiplexed antenna settings (TMS) by simultaneously optimizing the Hotspot to Target SAR Quotient (HTQ) as well as a novel objective function formulated to reduce the hotspot temperature. A dataset of five H&N cancer patients treated using the HYPERcollar3D system were used to compare the method to the particle swarm optimization (PSO) currently used in clinical practice at the Erasmus MC Cancer Institute [16]. The study in [15] investigated the effectiveness of TMS with thermal simulations using constant values of blood perfusion and thermal conductivity for tumor, muscle and fat tissue, as described in [19].

In this paper, the benefits of time-multiplexed hyperthermia are further evaluated using temperature dependent thermal properties. In particular, the work evaluates the robustness of the time-multiplexed hyperthermia treatment planning algorithm from [15] using the thermal dependent perfusion model developed in [20].

II. METHODS

A. Clinical HTP Procedure

Deep-seated tumors in the head and neck (H&N) region can be treated using the HYPERcollar3D system [21], [22] developed at Erasmus MC. Before the first treatment, patient-specific HTP is conducted, consisting of generation of the patient model, modelling of the treatment set-up and SAR optimization. In the case of the HYPERcollar3D system, the VEDO software package [16], [23] is used to optimize the antenna settings. The SAR distribution can be re-optimized to change the antenna settings according to the temperatures measured during treatment, and/or patient feedback on their level of comfort. The VEDO tool currently used in the clinic is based on the Particle Swarm Optimization (PSO), followed, if necessary, by a line search method. The SAR distribution is optimized by minimizing an objective function, the Hotspot to Target SAR Quotient, which can be expressed as [16], [18]:

$$HTQ = \frac{SAR_a(VI)}{SAR_a(target)} \quad (1)$$

where $SAR_a(VI)$ ($W \cdot kg^{-1}$) is the average SAR in the volume VI and $SAR_a(target)$ ($W \cdot kg^{-1}$) is defined as the mean SAR in the target. VI is defined as the top 1% of healthy tissue volume with the highest SAR in the H&N patient model outside the target [16], [18]. The target is the radiotherapy Clinical Target Volume (CTV) which includes the tumor and the surrounding tissue at risk.

B. Time-multiplexed steering strategy

A time-multiplexed steering strategy for H&N hyperthermia was introduced in [15]. The time-multiplexed antenna settings were found by a multi-objective genetic algorithm and a novel objective function was developed to suppress a specific hotspot. MOGA optimizes two objective functions that both focus SAR into the tumor but differ in the suppression of specific hotspots.

The first objective function is the HTQ and the second one is the total Hotspot to Target SAR Quotient for a specific Hotspot, defined as:

$$HTQ_{HS} = \frac{SAR_a(V_{HS})}{SAR_a(target)} \quad (2)$$

where $SAR_a(V_{HS})$ ($W \cdot kg^{-1}$) is the mean SAR in the selected hotspot volume V_{HS} . V_{HS} is the region of the healthy tissue volume outside the CTV with the highest SAR in the H&N patient model. MOGA yields a set of Pareto optimal solutions, i.e. antenna phases and amplitudes, that produce multiple optimal SAR distributions. The SAR distributions vary in the level of energy in the CTV and in the hotspot. In this study, a Pareto optimal solution (PoptS) was identified to provide sufficient energy in the target and energy suppression in the hotspot. The time-multiplexed configuration was formed by sequentially combining multiple PoptS settings with the static settings optimized by PSO. The static settings, termed StaticS, are those that produce the optimal SAR distribution characterized by the lowest (i.e. the best) HTQ value.

C. Temperature simulations

To assess the robustness of time-multiplexed hyperthermia, temperature simulations were performed in SEMCAD-X Version 14.8.6 (Speag, Zürich, Switzerland) using the Pennes' bioheat equation (PBHE) [24]:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + \rho Q + \rho SAR - SF \rho_b c_b \rho \omega (T - T_b) \quad (3)$$

where ρ ($kg \cdot m^{-3}$) represents the density of mass, c ($J \cdot kg^{-1} \cdot ^\circ C^{-1}$) is the specific heat capacity, T ($^\circ C$) is the temperature, t (s) is the time, k ($W \cdot m^{-1} \cdot ^\circ C^{-1}$) is the thermal conductivity, Q ($W \cdot kg^{-1}$) is the metabolic heat generation rate, ω ($m^3 \cdot s^{-1} \cdot kg^{-1}$) is the volumetric blood perfusion rate, the subscript b indicates a blood property, and SF (-) is a scaling factor used to implement a temperature dependent

blood perfusion model [20], [25]. Transient thermal simulations were done using the tissue dielectric and thermal properties reported in [15]. A mix of boundary conditions was applied such that the temperature of the external air and the headrest of the treatment system were set to 20 °C and heat transfer $h = 8 \text{ W} \cdot \text{m}^{-2} \cdot ^\circ\text{C}^{-1}$ [26] was used for the boundary conditions. The tissue-waterbolus interface was modelled using $h = 292 \text{ W} \cdot \text{m}^{-2} \cdot ^\circ\text{C}^{-1}$, while $h = 50 \text{ W} \cdot \text{m}^{-2} \cdot ^\circ\text{C}^{-1}$ [26] was applied for the interfaces at tissue-lung, tissue-internal air and tissue-metal implants. Previous research has shown that the response of vasculature in tissues to heat stress depends on the temperature [25]. In this work, two different cases have been considered:

- Constant values of blood perfusion and thermal conductivity for muscle, fat and tumor tissue were developed in [19] and also used in the authors' previous work in [15]. We refer to this as the constant temperature model (CTM).
- Temperature dependent perfusion: blood perfusion for muscle was piecewise linearly scaled by a factor of 8.9, for fat by a factor of 2 and for tumor by a factor of 0.5 between temperatures of 37 °C and 45 °C as indicated in Figure 1. Temperature-dependent perfusion was modelled only for muscle, fat and tumour; for other tissues, the scaling factor is equal to 1 [27]. We refer to this as the temperature dependent perfusion model (TDPM) based on the thermal model developed in [20].

The manner in which the thermal properties vary with temperature is taken into account in the thermal behaviour of the tissue by the inclusion of the scaling factor SF in equation (3). Figure 1 shows the linear temperature dependent perfusion scaling factors for fat, muscle and tumor. The blood perfusion increases between 37 °C and 45 °C for fat and muscle. This is described by sigmoidal curves consisting of a Gaussian profile followed by a plateau for temperatures above 45 °C. In contrast, the blood perfusion in the tumor decreases with temperature.

Fig. 1. Linear Temperature dependent perfusion scaling factors for fat, muscle and tumor [27].

To evaluate the robustness of time-multiplexed hyperthermia, we compare results obtained using the CTM and the TDPM. A summary of the evaluation methodology carried out in Cappiello *et al.* [15] is presented here:

- Individual StaticS thermal simulations were run for 1200 s to calculate the total input power needed to achieve the maximum temperature of 44 °C in the healthy tissue and/or 40 °C in critical organs (eyes, brains and spinal cord).
- The hotspot was selected on the StaticS temperature distribution delineating the area with the highest temperature (44 °C). The hotspot volume varies in a range between 0.2 and 0.5 % of the healthy tissue volume among all patients. After finding the PoptS settings by MOGA, individual PoptS thermal simulations were run to obtain 44 °C in the healthy tissue and/or 40 °C in critical organs.
- Thermal simulations for time-multiplexed steering were run applying StaticS and PoptS antenna settings in a sequence over a simulation period of 1200 s, and using a steering interval of 10 s. The steering interval is the time interval for which each antenna setting is applied.

We followed same procedure to run thermal dependent perfusion simulations.

D. Hotspot delineation and localization

As described in Section II.C, the selection of the primary hotspot (Hotspot 1) was done on the static temperature distribution delineating the domain with the highest temperature. Cappiello *et al.* [15] showed that additional hotspots occurred in the healthy tissue during time-multiplexed steering, hence a second hotspot (Hotspot 2) was selected based on the time-multiplexed temperature distribution obtained by using the constant thermal model.

We first identified the highest temperature resulting from the static TDPM distribution. Hence, we identified Hotspot 1 related to CTM, (Hotspot 1-CTM) and Hotspot 1 related to TDPM (Hotspot 1-TDPM).

To verify whether Hotspot 1-TDPM occurred in the same or nearby location as Hotspot 1-CTM, we calculated the Euclidean distance between the two hotspots, using the highest temperatures in the CTM and TDPM distributions as comparison points. Lastly, we ran time-multiplexed steering using TDPM.

E. Performance Evaluation Methods: SAR and Temperature Quantifiers

The five patient models selected in our previous study [15] were also used in this study. The patient group included one neck node metastasis, one oral cavity, one parotid gland and two oropharynx tumors. Some patients had small dental implants, which have negligible impact due to their dielectric properties. All patients were treated at Erasmus MC Cancer Institute with the HYPERcollar3D system operating at a frequency of 434 MHz.

The StaticS and the PoptS solutions were evaluated based on SAR performance metrics as described in [15]. In particular, Target Coverage by 25% iso-SAR (TC_{25}) and Target Coverage by 50% (TC_{50}) were used to select the best Pareto solution which supplied a balance between providing acceptable SAR in the target and SAR reduction in the healthy tissue and these results are fully discussed in [15].

The thermal performance of the StaticS and the PoptS configurations and the robustness of the time-multiplexed steering to temperature dependent thermal tissue properties were evaluated using cumulative temperature-volume histograms and thermal indices such as the median temperature, T_{50} in the CTV, and the maximum temperature T_{max} in the hotspot, to quantify the hotspot suppression. Definitions of metrics and other quantities are summarised in Table I.

TABLE I
NOMENCLATURE

Symbol	Description
HTP	Hyperthermia Treatment Planning
HTQ	Hotspot to Target SAR Quotient
CTV	Clinical Target Volume
SAR	Specific Absorption Rate
PSO	Particle Swarm Optimization
MOGA	Multi-Objective Genetic Algorithm
TMS	Time Multiplexed antenna Setting
V_{HS}	Hotspot Volume: volume with the highest SAR in the healthy tissue
V_1	1% of the healthy tissue volume with the highest SAR
StaticS	Static Settings
PoptS	Pareto Optimal Solution
TC_x	Target Coverage: CTV volume percentage enclosed by x% iso-SAR
T_{50}	Temperature exceeded in 50% of the target volume
T_{max}	Maximum temperature in the hotspot
CTM	Constant Thermal Model
TDPM	Temperature Dependent Perfusion Model
Hotspot 1-CTM	Hotspot with the highest temperature arising from constant thermal model sims
Hotspot 1-TDPM	Hotspot with the highest temperature obtained with thermal dependent perfusion model sims
PoptS-CTM	Pareto optimal setting used with constant thermal model
$\Delta T_{StaticS - TDPM \text{ vs CTM}}$	Temperature variation arising from static constant thermal model and thermal dependent perfusion model sims
$\Delta T_{TMS-StaticS}$	Temperature variation arising from static and time-multiplexed steering

III. RESULTS

A. Hotspot distance: CTM and TDPM distributions

The StaticS and PoptS settings used to run the CTM thermal simulation were optimized in [15] for 5 patient models. PoptS was selected by ensuring sufficient focusing in the CTV, i.e. $TC_{25} \geq 75\%$ [16] and suppression of the hotspot energy, i.e. 30-60% SAR reduction compared to the SAR distribution optimized by PSO for each patient. Static temperature distributions for Patient 5 for CTM and TDPM are given in Figure 2(a) and (b) respectively.

We identified the location of the highest temperature in the static TDPM temperature distribution shown in Fig. 2(b) and we found that the Euclidean distance between the highest temperatures in CTM and TDPM is, at most, 5.4 mm, and generally much less than that. Euclidean distance values for the five patient models are reported in Table II.

Since the hotspot location does not vary significantly between CTM and TDPM over the patient population, in the following analyses the same hotspot delineation was used for both CTM and TDPM. Hence, the PoptS-CTM antenna settings were applied sequentially with the StaticS settings to run the time-multiplexing steering using TDPM.

Fig. 2. Patient 5. 3D temperature distribution on a transversal view obtained using StaticS settings with constant thermal model (CTM) ($z = 43$ mm) (a) and temperature dependent perfusion model (TDPM) ($z = 44$ mm) (b). CTV and the location of maximum temperature achieved in the healthy tissue are in the oral cavity in both cases but with a difference of 1 mm in the z -location.

TABLE II

EUCLIDEAN DISTANCE BETWEEN HOTSPOT 1-CTM (IN CONSTANT THERMAL MODEL DISTRIBUTION) AND HOTSPOT 1-TDPM (IN THERMAL DEPENDENT PERFUSION MODEL) FOR FIVE CASES TREATED WITH THE HYPERCOLLAR3D

Patient no.	1	2	3	4	5
D (mm)	3.7	5.4	2.2	2.8	1.7

B. Time-multiplexed steering speed

The temperature over time during the thermal simulation was recorded in a point in the CTV and in Hotspot 1, for TDPM. Figure 3 shows the temperature evolution for the StaticS, PoptS and time-multiplexed settings at steering intervals of 10, 20 and 120 s. Figures 3(a) and (b) refer to the point temperature in the CTV and Hotspot 1 respectively. Minor differences were observed between the three steering intervals; for consistency with Cappiello *et al.* [15], a total cycle time of 10 s was also used here.

Fig. 3. Patient 1. Point temperature (degrees Celsius) in the CTV (a) and Hotspot 1 (b) over the simulation period of 1200 s, for the temperature dependent properties. Static (magenta), Pareto optimal (yellow) and time-multiplexed thermal performance are illustrated varying the steering rate of five (red), twenty (green) and sixty (blue) seconds. Note that the differences between the three steering times are quite small, hence the plots are almost coincident.

C. Cumulative Temperature-Volume histograms and thermal indicators

Impact of TDPM on CTV: Static Thermal Performance. Static performance using CTM and TDPM were compared for the five patients through cumulative temperature-volume histograms. The temperature in the CTV and in Hotspot 1 was obtained from the static temperature distributions and the respective thermal quantifiers are

shown in Table III. The changes (ΔT_{STATIC} (TDPM vs CTM)) arising from the static CTM and the static TDPM performances are also shown in Table III. For all clinical records, the static performance obtained with TDPM provides a temperature increase of T_{50} in CTV of between 1.5 °C and 2.1 °C compared to the static CTM performance. Figure 4 is an example of the cumulative temperature-volume histogram for the static thermal performance using CTM and TDPM.

Fig. 4. CTV (red) and Hotspot 1 (violet) cumulative temperature-volume histograms for Patient 3. The static thermal performance using CTM and TDPM are shown in (a) and (b) respectively.

Robustness of TMS to Temperature Dependent Tissue Properties. Time-multiplexed performance using CTM and TDPM were compared for the five patient models. The median temperature in CTV, the maximum temperature in Hotspot 1 and the additional hotspot temperatures arising from time-multiplexed steering for Hotspot 2 and Hotspot 3 (following the definition of Hotspot 1 and Hotspot 2) are shown in Table III, together with the thermal changes resulting from static and time-multiplexed steering ($\Delta T_{\text{TMS-StaticS}}$), for both constant thermal and thermal dependent perfusion performances. Figure 5 shows an example of cumulative temperature-volume histograms for static and time-multiplexed steering using CTM and TDPM. Results obtained with time-multiplexed steering using the constant thermal model have been discussed in detail in [15]. The thermal simulations predicted an average temperature increase in the target, i.e. 0.8 °C in T_{50} and a reduction in

TABLE III

THERMAL QUANTIFIERS T_{50} THAT IS EXCEEDED BY 50 PERCENT OF ALL TEMPERATURE VALUES IN THE CTV AND $T_{\max}$ IN THE HOTSPOT FOR FIVE CASES TREATED WITH THE HYPERCOLLAR3D. TEMPERATURE VARIATIONS FROM STATICS (SINGLE SAR STEERING) TO TMS (TIME-MULTIPLEXED STEERING) OBTAINED BY CTM (CONSTANT THERMAL MODEL) AND TDPM (THERMAL DEPENDENT PERFUSION MODEL) ARE GIVEN IN BOLD

Pat. no.	Thermal model	Antenna settings	CTV	Hotspot 1	Hotspot 2	Hotspot 3
			T_{50} (°C)	$T_{\max}$ (°C)	$T_{\max}$ (°C)	$T_{\max}$ (°C)
1	CTM	StaticS	40.4	44	43.1	42
		TMS	40.7	42.9	43.9	43.5
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.3	-1.4	+0.8	+1.5
	TDPM	StaticS	42.1	42.6	42.6	41.8
		TMS	42.1	41.6	42.7	42.3
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	0	-1	+0.1	+0.5
	$\Delta T_{\text{StaticS}} (\text{TDPM vs CTM})$ (°C)		+1.7			
2	CTM	StaticS	41.7	43.7	41.3	
		TMS	42.7	42.2	43.7	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+1	-1.5	+2.4	
	TDPM	StaticS	43.2	43.5	43.1	
		TMS	43.4	42.9	44.3	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.2	-0.6	+1.2	
	$\Delta T_{\text{StaticS}} (\text{TDPM vs CTM})$ (°C)		+1.5			
3	CTM	StaticS	40.2	42.9	42.7	
		TMS	40.7	41.4	43.6	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.5	-1.5	+0.9	
	TDPM	StaticS	41.7	43.1	42.3	
		TMS	42.5	42.5	43.5	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.8	-0.6	+1.2	
	$\Delta T_{\text{StaticS}} (\text{TDPM vs CTM})$ (°C)		+1.5			
4	CTM	StaticS	40.3	43.7	43.6	
		TMS	41.5	43.1	43.7	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+1.2	-0.6	+0.1	
	TDPM	StaticS	42.4	43.7	43.7	
		TMS	42.5	42.9	43.1	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.1	-0.8	-0.6	
	$\Delta T_{\text{StaticS}} (\text{TDPM vs CTM})$ (°C)		+2.1			
5	CTM	StaticS	39.9	43.7	42	
		TMS	40.7	42.7	43.9	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.8	-1	+1.9	
	TDPM	StaticS	41.9	43.7	42.9	
		TMS	42.5	43.1	43.8	
		$\Delta T_{\text{TMS-StaticS}}$ (°C)	+0.6	-0.6	+0.9	
	$\Delta T_{\text{StaticS}} (\text{TDPM vs CTM})$ (°C)		+2			

the average maximum temperature of 1.2 °C in the healthy tissue. The time-multiplexed steering calculated with the thermal dependent perfusion model provides an increase in T_{50} of the CTV in the range of 0.1 °C and 0.8 °C for four out of five patients, and identical T_{50} is achieved for Patient 1 compared to the static TDPM performance. Also, a

hotspot reduction between 0.6 °C and 1 °C is observed for all patients studied.

As described in Cappiello *et al.* [15], the predicted temperatures in the healthy tissue cannot exceed a specified temperature limit, i.e. 44 °C. We have observed that additional hotspots arise in the healthy tissue during time-multiplexed steering leading to higher maximum temperatures in some cases as compared to the maximum temperature of the hotspots obtained in the static simulation. For example, $T_{\max}$ of Hotspot 2 and Hotspot 3 resulting from TDPM show increases in the range of 0.1-1.2 °C; however, their median temperatures are still below the CTV temperatures. While it is also possible in some cases that hotspot temperatures may exceed the specified limit of 44 °C with TMS (e.g. with Patient 2), these cases are relatively rare and the TMS method allows flexibility in controlling the steering rate to compensate for these effects if necessary. In an extreme case, if an increase in hotspot temperature was deemed to be clinically unacceptable relative to the beneficial increase in CTV, the steering rate may be set to zero so that treatment reverts to the static settings only for that patient. Further investigation of these factors will be the subject of future research. In TDPM, while the perfusion of the tumour with increasing temperature is reduced relative to CTM, the relative increase in the perfusion of muscle with increasing temperature is substantially larger, and likely dominates the thermal behaviour. Clinical experience in Erasmus MC Cancer Institute suggests that increases in CTV temperature on the order of only 0.3 degrees are beneficial [28], [29]. While the relative increase in CTV temperature using TMS is smaller with TDPM, these increases are still clinically useful in many patients.

Overall, these findings demonstrate the general robustness and utility of time-multiplexed hyperthermia to temperature dependent thermal tissue properties and the benefit both in terms of CTV coverage and hotspot suppression.

Fig. 5. CTV (red), Hotspot 1 (violet) and Hotspot 2 (green) cumulative temperature-volume histograms for Patient 3. The static (solid line) and the time-multiplexed (dash-dot line) thermal performances are illustrated using CTM (a) and TDPM (b).

IV. CONCLUSION

In this work, the robustness of a previously-developed time-multiplexed steering method for hyperthermia treatment planning for different thermal models of tissue behaviour was evaluated. In particular, the effects on the temperature simulations of assuming that the thermal properties vary with temperature, as opposed to being constant, were examined.

An increase in T_{50} , i.e. 0.2-0.8 °C and a decrease in the hotspot temperature, i.e. 0.6-1 °C were observed when applying time-multiplexed hyperthermia using temperature dependent perfusion models for four out of five patients. Previous work has suggested that time-multiplexed hyperthermia can achieve higher temperatures in the tumor and decrease temperatures in the healthy tissue when constant thermal properties are used in thermal simulations. Similarly, this work finds that time-multiplexed hyperthermia increases temperatures in the tumor and lower in the hotspot when using temperature dependent perfusion models. However, the predicted benefit of time-multiplexed hyperthermia using TDPM is smaller compared to the benefit achieved using CTM, i.e. average improvement in T_{50} is equal to 0.8 °C when using CTM and 0.3 °C when using TDPM; nonetheless, these increases can still be considered clinically useful.

The results in this work indicate that time-multiplexed hyperthermia via MOGA optimization is robust to variations in thermal properties due to temperature increases.

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