MODELLING OF TISSUE THERMAL INJURY FORMATION PROCESS WITH APPLICATION OF DIRECT SENSITIVITY METHOD

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In the paper, numerical analysis of thermal processes proceeding in a biological tissue is presented. The tissue is subjected to the external heat impulse and a 2D problem is taken into account. In order to determine the influence of variations of thermophysical parameters of the tissue on the value of tissue injury integral and the area of the lesion, a direct approach of sensitivity analysis is applied. The process of thermal injury formation is also analyzed. At the stage of numerical simulation, the boundary element method is used. In the final part of the paper, an example of numerical simulation is shown.

Keywords: bioheat transfer, Arrhenius scheme, boundary element method, sensitivity analysis

1. Introduction

The phenomenon of biological tissue damage due to external thermal factors is one of the quite frequently encountered interaction between a living organism and its surroundings. It may be either an accidental case, as in thermal burns, or a fully-controlled case, as in the treatment using thermal effects. The impact of this type of damage on the living organism is dependent on its extent and depth. It should be pointed out that an elevated temperature in a biological tissue does not always lead to irreversible changes. When the influence of temperature is moderate (37°-45°C), the main response of the tissue is dilatation of blood vessels, which is not accompanied by the tissue injury. Of course, an important factor is the exposure time of the thermal pulse, because the interaction with a suitably long (approximately 6 hours) temperature of 42°C may lead to epidermis necrosis (Henriques, 1947; Torvi and Dale, 1994). Therefore, one can conclude that if the tissue damage exceeds some threshold value, the tissue injury becomes irreversible, otherwise the tissue has the ability to return to its original, healthy state. It should be emphasized that the change in the area of the tissue thermal injury (its expansion or withdrawal) may occur even some time after the cessation of external heat impulse. Thus, determination of the time after which the wound reaches its final size may be associated with certain difficulties.

In the numerical analysis of the tissue thermal damage process one of the most commonly used approaches is the so-called Arrhenius injury integral, which allows one to determine the degree of tissue damage, and furthermore, to define some of the thermophysical parameters of tissue as dependent of the tissue injury. It is worth to mention the work by Abraham and Sparrow (2007) in which the perfusion coefficient is expressed by a polynomial function reflecting the initial increase in blood flow resulting in vasodilatation as well as blood flow decrease as the vasculature begins to shut down, whereas Glenn *et al.* (1996) used exponential functions to model changes in scattering coefficient during laser-tissue interaction.

The classic definition of the tissue injury integral implies that even at a small local increase in temperature damage of the tissue is irreversible. In the current paper, the algorithm proposed by Jasiński (2013) is used as a model of tissue damage withdrawal at those points of the domain analyzed, in which the value of the injury integral does not exceed a certain damage threshold.

The injury formation process analysis (IFPA algorithm, Jasiński, 2012) is applied in order to determine the time after which the lesion is fully formed and the area of different stages of tissue damage is based on the Arrhenius integral as well.

One of the problems connected with the application of the mathematical model is the sensitivity of the solution with respect to the parameters appearing in the governing equations. The sensitivity information may be used, among others, to analyze the influence of the change of parameters on the final solution of the problem being considered. Such a kind of problems was by Davies *et al.* (1997) and Jasiński (2009), while Majchrzak and Jasiński (2004) presented sensitivity analysis of the skin burns prediction model proposed by Henriques (1947).

2. Governing equations

The transient heat transfer in the 2D domain of a homogeneous biological tissue of rectangular shape (Fig. 1.) is described by the Pennes equation in form (Majchrzak *et al.*, 2011; Mochnacki and Piasecka-Belkhayat, 2013)

$$\mathbf{x} \in \Omega : \quad c\dot{T} = \lambda T_{,ii} + Q_V \tag{2.1}$$

where λ [Wm^{-1}K^{-1}] is the thermal conductivity, c [Jm^{-3}K^{-1}] is the volumetric specific heat, Q_V [Wm^{-3}] is the internal heat source, while $T = T(\mathbf{x}, t)$ and $\dot{T}$ denotes temperature and its time derivative.

The component Q_V comprises the information of the internal heat sources and is described as

$$Q_V = Q_{perf} + Q_{met} = c_B G_B (T_B - T) + Q_{met} \tag{2.2}$$

where G_B [(m$^3_{blood}$/s)/(m$^3_{tissue}$)], c_B [Jm^{-3}K^{-1}] and T_B correspond to the perfusion coefficient, the volumetric specific heat of blood and the artery temperature, respectively, while Q_{met} [Wm^{-3}] is the internal metabolic heat source (Majchrzak *et al.*,2003; Torvi and Dale, 1994).
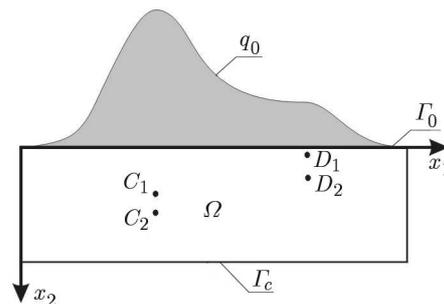

Fig. 1. The considered domain

Equation (2.1) is supplemented by appropriate boundary conditions:
— on the external surface of tissue (Γ_0)

$$\mathbf{x} \in \Gamma_0 : \quad q(\mathbf{x}, t) = \begin{cases} q_0 & t \leqslant t_{exp} \\ \alpha(T - T_{amb}) & t > t_{exp} \end{cases} \tag{2.3}$$

— on the remaining parts of the boundary (Γ_c)

$$\mathbf{x} \in \Gamma_c : \quad q(\mathbf{x}, t) = 0 \tag{2.4}$$

where q_0 [Wm^{-2}] is the known boundary heat flux, α [Wm^{-2}K^{-1}] is the convective heat transfer coefficient and T_{amb} is the temperature of surroundings, while t_{exp} is the exposure time. The initial distribution of temperature is also known.

It should be pointed out that the heat flux along the boundary Γ_0 is assumed to be irregular as in the majority of non-controlled cases of high temperature-biological tissue interactions. In this paper, it is assumed as a polynomial function of the 7th degree with the distribution of the heat flux visible in Fig. 1.

The damage of a biological tissue resulting from temperature elevation is usually modeled by the so-called Arrhenius injury integral defined as (Abraham and Sparrow, 2007; Oden *et al.*, 2007)

$$\theta(\mathbf{x}) = \int\limits_0^{t^F} A \exp\Big(-\frac{\Delta E}{RT}\Big)\, dt \tag{2.5}$$

where A is the pre-exponential factor [s^{-1}], ΔE is the activation energy [J mole^{-1}], R is the universal gas constant [J mole^{-1}K^{-1}], and $[0, t^F]$ is the considered time interval, while the criterion for tissue necrosis is

$$\theta(\mathbf{x}) \geqslant 1 \tag{2.6}$$

According to the necrotic changes in tissue, the blood perfusion coefficient is defined as (Abraham and Sparrow, 2007)

$$G_B = G_B(\theta) = \begin{cases} G_{B0} & \theta = 0 \\ (1 + 25\theta - 260\theta^2)G_{B0} & 0 < \theta \leqslant 0.1 \\ (1 - \theta)G_{B0} & 0.1 < \theta \leqslant 1 \\ 0 & \theta > 1 \end{cases} \tag{2.7}$$

where G_{B0} is the initial perfusion coefficient. The values of coefficients for the interval from 0 to 0.1 correspond to the increase in the perfusion coefficient caused by vasodilatation up to the value $\theta = 0.05$ (maximum of the function) and the beginning of narrowing of blood vessels (between 0.05 and 0.1). The interval 0.1 to 1 reflects the blood flow decrease as the vasculature going to shut down.

On the basic on the injury integral in form (2.5), the damage fraction F_D is calculated as (Glenn *et al.*, 1996; Oden *et al.*, 2007)

$$F_D(\mathbf{x}) = 1 - \exp(-\theta) \tag{2.8}$$

3. Modeling of the thermal damage of tissue

The assumption of the Arrhenius scheme is that the damage of the tissue is irreversible. In order to consider that the tissue could get back to its native state after the thermal impulse is ceased, the following algorithm is proposed (Jasiński, 2013), see Fig. 2.

Let us assume that for the time interval $[0, t^F]$ being under consideration and divided into F subintervals $[t^{f-1}, t^f]$ (where $f = 1, 2, \ldots, F$), the values $T^0(\mathbf{x}), \ldots, T^f(\mathbf{x})$ as well as $\theta^0(\mathbf{x}), \ldots, \theta^{f-1}(\mathbf{x})$ at the point $\mathbf{x} \in \Omega$ are known. At the same time, the recovery threshold θ_{rec} is accepted.

If the injury integral at the point $\mathbf{x}$ for time t^f achieves the value equal or greater than θ_{rec} then the injury of the tissue becomes irreversible. Otherwise, the function denoted as $\theta_{app}(\mathbf{x}, T)$
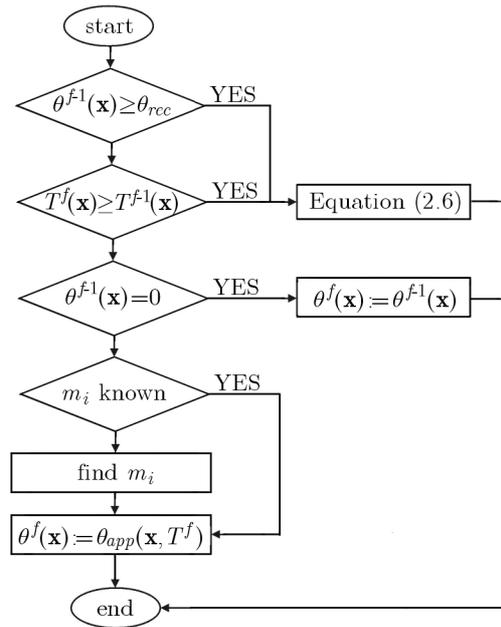
Fig. 2. The proposed algorithm of tissue injury calculation

is introduced in order to model the withdrawal of the tissue injury. In current paper, it is assumed as a linear one between (T^0, θ^0) and (T^{f-1}, θ^{f-1})

$$\theta_{app}(\mathbf{x}, T) = m_1 + m_2 T \qquad (3.1)$$

For the time t^{f+1}, if $T^{f+1} < T^f$ and $\theta^f < \theta_{rec}$, again the function θ_{app} defined for the time t^f is used.

The damage fraction F_D (Eq. (2.8)) is used in the thermal injury formation process analysis (IFPA) algorithm. In this algorithm, five intervals of values for F_D (denoted as tha) have been distinguished:

- tha 1: $[0, 0.01)$,
- tha 2: $[0.01, 0.05)$,
- tha 3: $[0.05, 0.63)$,
- tha 4: $[0.63, 0.99)$,
- tha 5: $\geqslant 0.99$.

The values in the intervals are interpreted as:

- 0.01: up to this value, the tissue is in its normal state, so the value could be named as the border of thermally untouched tissue,
- 0.05: the border of vasodilatation – arises from the polynomial function for G_B (c.f. Eq. (2.7)); at this value of F_D the perfusion coefficient has its maximum value,
- 0.63: corresponds to the criterion of tissue necrosis (c.f. Eq. (2.6)),
- 0.99: could be treated as the criterion of complete tissue destruction.

In Fig. 3, the concept of IFPA algorithm is presented. At first, the comparison of tha intervals achieved on an element of the domain considered for two successive time steps is made. Next, only the elements which have changed the intervals are selected. Finally, the bar chart with the number of elements achieving the individual interval is drawn.
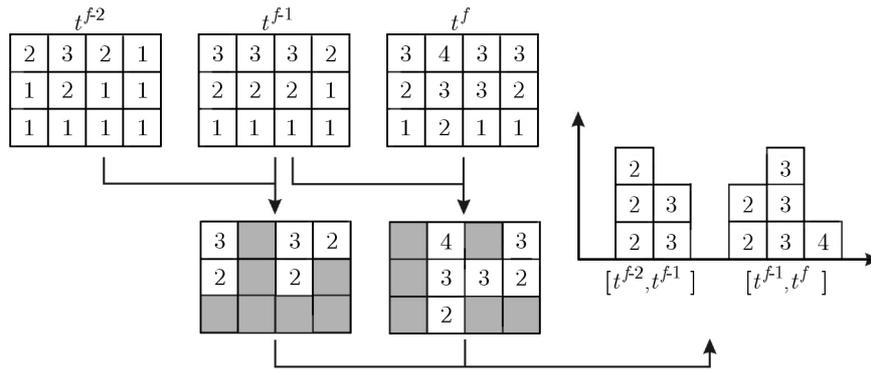
Fig. 3. The concept of the IFPA algorithm

It should be pointed out that if we add up the number of elements which have swapped from one interval to another in successive time intervals, we can obtain the knowledge of dynamics of the thermal injury formation process. Additionally, changes of the sum of elements with tha interval greater than 1 give information about the proliferation of the lesion.

4. Sensitivity analysis

To determine the influence of thermophysical parameters on the value of the injury integral, a direct approach of the sensitivity analysis has been applied (Dems, 1986; Kleiber, 1997).

According to the rules of the direct method, Eq. (2.1) is differentiated with respect to the parameter p_s, where $s = \lambda, c, G_{B0}$ or Q_{met}. So, the number of additional sensitivity tasks corresponds to the number of parameters to which the sensitivity analysis is done (Majchrzak and Jasiński, 2002; Majchrzak and Kałuża, 2006). If we denote

$$U^s = \frac{\partial T}{\partial p_s} \tag{4.1}$$

as a sensitivity function, then one can write, c.f. Eq. (2.1), (Mochnacki and Majchrzak, 2003)

$$\mathbf{x} \in \Omega: \quad c\dot{U}^s = \lambda U^s_{,ii} + Q^s_V \tag{4.2}$$

where

$$\dot{U}^s = \frac{\partial U^s}{\partial t} \qquad U^s_{,ii} = \frac{\partial T_{,ii}}{\partial p_s} \tag{4.3}$$

while

$$
\begin{aligned}
Q^s_V = &\left[\frac{c_B G_{B0} f(\theta)}{\lambda}\frac{\partial \lambda}{\partial p_s} - c_B f(\theta)\frac{\partial G_{B0}}{\partial p_s} - c_B G_{B0}\frac{\partial f(\theta)}{\partial p_s}\right](T - T_B) \\
&- c_B G_{B0} f(\theta)U^s + \left(\frac{c}{\lambda}\frac{\partial \lambda}{\partial p_s} - \frac{\partial c}{\partial p_s}\right)\dot{T} - \frac{Q_{met}}{\lambda}\frac{\partial \lambda}{\partial p_s} + \frac{\partial Q_{met}}{\partial p_s}
\end{aligned}
\tag{4.4}
$$

The variation of θ is calculated as (c.f. Eq. (2.5))

$$\frac{\partial \theta}{\partial p_s} = \int\limits_0^{t^F} A\frac{\Delta E U^s}{RT^2} \exp\left(-\frac{\Delta E}{RT}\right) dt \tag{4.5}$$

The change of the injury integral due to changes of the parameters p_s can be estimated using the following formula

$$\Delta\theta(\mathbf{x}) = \sqrt{\sum_{s=1}^{n}\Big(\frac{\partial\theta(\mathbf{x})}{\partial p_s}\Delta p_s\Big)^2} \qquad (4.6)$$

Finally, using Eq. (4.6), the value of Arrhenius integral is calculated as

$$\theta(\mathbf{x}, p_s \pm \Delta p_s) = \theta(\mathbf{x}, p_s) \pm \Delta\theta(\mathbf{x}) \qquad (4.7)$$

5. Boundary element method

The primary and also the additional problems resulting from the sensitivity analysis have been solved using the 1st scheme of the BEM for 2D transient heat diffusion problems (Brebia and Dominquez, 1992). So, the following equation will be considered

$$\mathbf{x} \in \Omega: \quad c\dot{F} = \lambda F_{,ii} + S \qquad (5.1)$$

where $F = F(\mathbf{x}, t)$ denotes the temperature or functions resulting from the sensitivity analysis (c.f. equations (2.1) and (4.2)), while $S = S(\mathbf{x}, t)$ is the source function (c.f. Eqs. (2.2) and (4.4)).

For the time grid with a constant time step Δt, the boundary integral equation corresponding to the transition $t^{f-1} \rightarrow t^f$ is of the form

$$B(\boldsymbol{\xi})F(\mathbf{x}, t^f) + \frac{1}{c}\int\limits_{t^{f-1}}^{t^f}\int\limits_{\Gamma} F^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t)J(\mathbf{x}, t)\, d\Gamma\, dt = \frac{1}{c}\int\limits_{t^{f-1}}^{t^f}\int\limits_{\Gamma} J^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t)F(\mathbf{x}, t)\, d\Gamma\, dt$$

$$+ \frac{1}{c}\int\limits_{t^{f-1}}^{t^f}\iint\limits_{\Omega} F^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t^{f-1})F(\mathbf{x}, t^{f-1})\, d\Omega\, dt + \frac{1}{c}\int\limits_{t^{f-1}}^{t^f}\iint\limits_{\Omega} S(\mathbf{x}, t)F^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t)\, d\Omega\, dt$$

$$(5.2)$$

In equation (5.2), F^* is the fundamental solution

$$F^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t) = \frac{1}{4\pi a(t^f - t)}\exp\Big[-\frac{r^2}{4a(t^f - t)}\Big] \qquad (5.3)$$

where r is the distance from the point under consideration $\mathbf{x}$ to the observation point ξ, while

$$J^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t) = -\lambda F^*(\boldsymbol{\xi}, \mathbf{x}, t^f, t)_{,i}n_i \qquad (5.4)$$

and $B(\boldsymbol{\xi})$ is the coefficient from the interval $(0,1)$.

In this paper, constant boundary elements have been used. Details concerning numerical realization of the BEM can be found, among others, in Majchrzak (2013) and Piasecka-Belkhayat (2011).

6. Results

A domain of rectangular shape (c.f. Fig. 1) of dimensions $0.05\,\mathrm{m} \times 0.015\,\mathrm{m}$ is considered. The interior of the domain has been divided into 6000 internal constant cells, while the external boundary into 320 constant elements.

In computations, the following values of thermophysical tissue parameters have been assumed: $\lambda = 0.3\,\mathrm{Wm^{-1}K^{-1}}$, $c = 3.647\,\mathrm{MJm^{-3}K^{-1}}$, $G_{B0} = 0.00125\,(\mathrm{m^3_{blood}/s})/(\mathrm{m^3_{tissue}})$, $Q_{met} = 245\,\mathrm{Wm^{-3}}$, while for the blood $c_B = 3.9962\,\mathrm{MJm^{-3}K^{-1}}$ and $T_B = 37°\mathrm{C}$. The parameters of the Arrhenius injury integral are: $A = 3.1 \cdot 10^{98}\,\mathrm{s^{-1}}$, $\Delta E = 6.27 \cdot 10^5\,\mathrm{J\,mole^{-1}}$, $R = 8.314\,\mathrm{J\,mole^{-1}K^{-1}}$ and $\theta_{rec} = 0.05$.

In the boundary condition (c.f. Eq. (2.3)), the maximum value of the heat flux q_0 is assumed as $20\,\mathrm{kWm^{-2}}$, the exposure time is $30\,\mathrm{s}$, while $\alpha = 10\,\mathrm{Wm^{-2}K^{-1}}$ and $T_{amb} = 20°\mathrm{C}$ (Jasiński, 2012).

The coordinates of the points are (c.f. Fig. 1): $C_1(0.01575, 0.001875)$, $D_1(0.03475, 0.000625)$, $C_2(0.01575, 0.003125)$ and $D_2(0.03475, 0.000875)$, the time step equals to $\Delta t = 1\,\mathrm{s}$.

As has been previously mentioned, the sensitivity analysis is performed with regard to thermal conductivity, volumetric specific heat, initial perfusion coefficient and metabolic heat source. It is assumed that for all parameters $\Delta p_s = 0.1 p_s$.

Figure 4 shows courses of the temperature as well as courses of the injury integral θ. At two of these points, C_1 and D_1, the value of the injury integral is above the recovery threshold θ_{rec}. At the point C_1, the value of the injury integral is much greater than 1, so the tissue is fully damaged, while at the point D_1 the value of injury integral is 0.168 which means partly damaged tissue. The Arrhenius integral value at points C_2 and D_2 have not reached the recovery threshold, so the functions θ_{app} (see the algorithm in Section 3) are defined for the stage of temperature lowering.
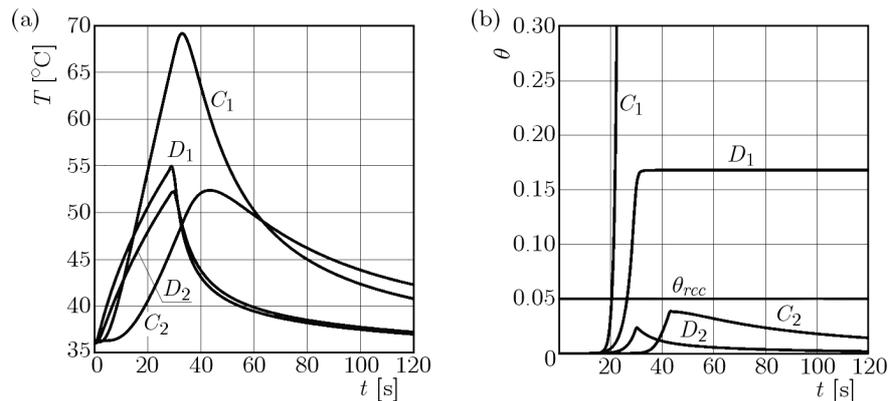

Fig. 4. Courses of temperature and the injury integral θ

In Fig. 5, courses of the Arrhenius integral found on the basis of sensitivity analysis are shown (c.f. Eq. (4.7)). It is clearly visible that at every point the courses for $\theta - \Delta\theta$ are very close to zero, so one can say that the tissue is not destructed in this case.

One can note that at the point D_2 for the case $\theta + \Delta\theta$, some values calculated on the basis of formula (4.7) are above the recovery threshold and then decrease. Although these results are correct from the sensitivity analysis point of view, the "real" course of the injury integral should correspond to the dashed line inthe right-hand side figure. This is due to sensitivity calculation without taking into account that according to the algorithm of Arrhenius injury calculation presented in Section 3, the value of integral cannot be reduced when it is above the recovery threshold.

Figure 6 presents courses of the perfusion coefficient G_B (c.f. Eq. (2.7)) obtained on the basis of sensitivity analysis of the Arrhenius integral. It is clearly visible that according to the necrotic changes in the tissue domain, the perfusion coefficient is changing, decreasing to zero for the point C_1 in which the injury integral is greater than 1. At the point D_2 marked by the dashed line, it corresponds, as previously, to the non-reduced value of the injury integral. The effect of vasodilatation is visible for all four points.
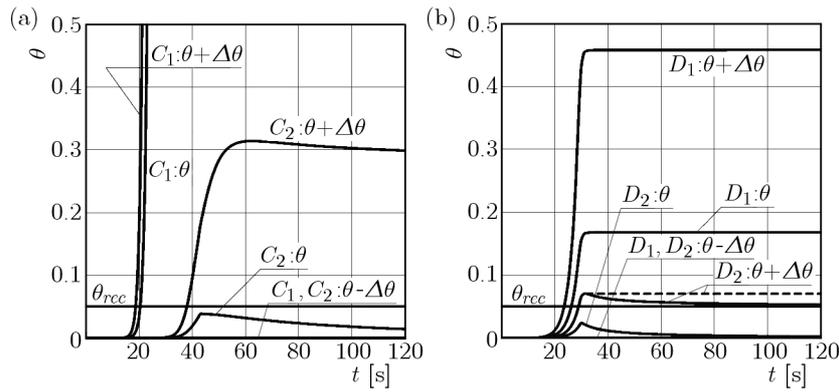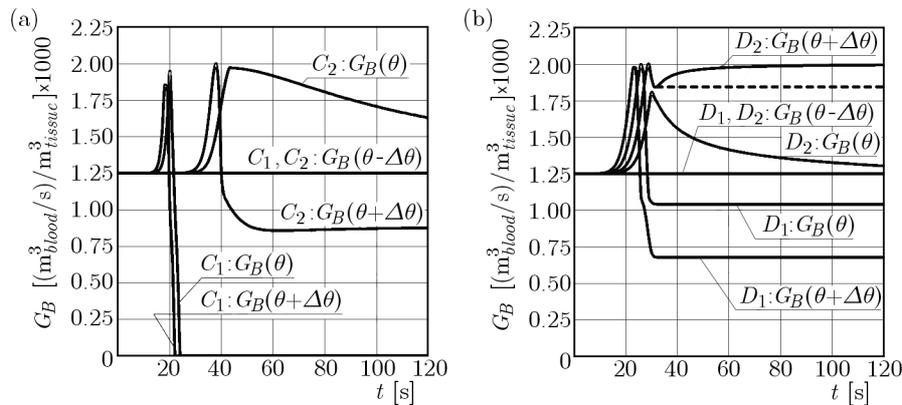
Fig. 5. Courses of the injury integral

Fig. 6. Courses of the perfusion coefficient G_B

The differences in values of the injury integral (and in consequence, the damage fraction – c.f. Eq. (2.8)) visible in Fig. 5 are substantial from the point of view of the thermal injury formation process analysis (c.f. Section 3). The results obtained by this approach are shown in Fig. 7. The results are presented for two cases: the Arrhenius integral calculated for the basic thermophysical parameters (LHS) and for sensitivity analysis case $\theta + \Delta\theta$ (RHS). One could see that for $t > t_{exp}$ some elements are classified into tha 1 (so, they go back into the healthy state) only in the first one.
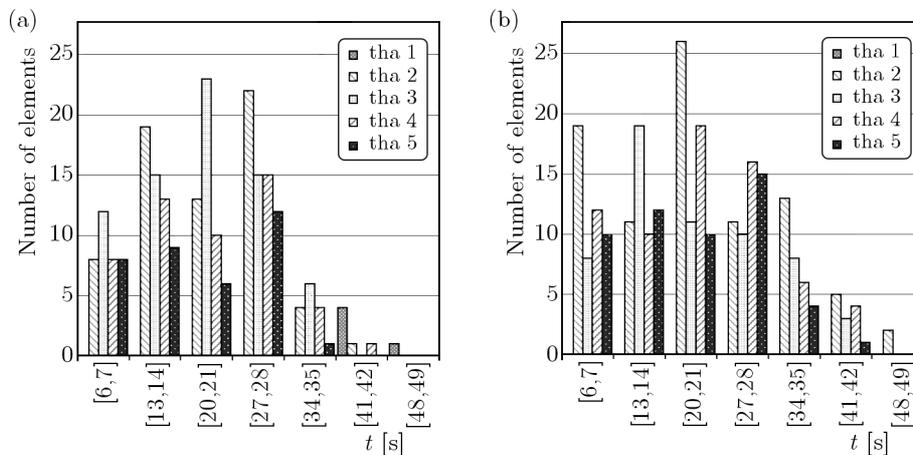

Fig. 7. The number of elements achieving individual intervals (LHS: basic values of thermophysical parameters, RHS: sensitivity analysis, $\theta + \Delta\theta$)

In Fig. 8, courses of the thermal injury proliferation process are shown. The curves are obtained by adding the number of elements which are in tha interval greater than 1. The recovery stage, that means the process of reducing the lesion area is the best visible for the case of the injury integral calculated directly. The figure is scaled in the number of elements, but it should be pointed out that these data could be very easily recalculated in the cross-section area of the lesion using the field of single internal element (for the geometrical grid assumed in the paper: $1.25 \cdot 10^{-7}\,\mathrm{m}^2$).
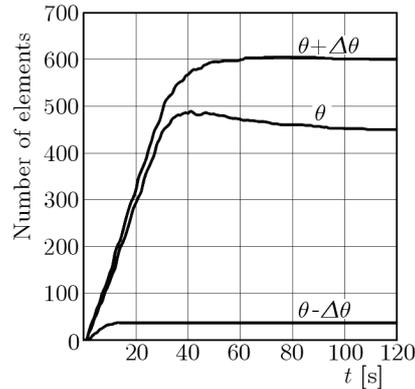

Fig. 8. Proliferation of the thermal injury

7. Conclusion

The proposed method of tissue injury calculation is closer to the real conditions of the interaction between the tissue and a high-temperature impulse. Its main advantage is the possibility of estimation of the tissue recovery area, which plays an important role in the case of modelling of the fully controlled case of the interaction.

In the sensitivity analysis, the direct approach has been used. The impact of a 10% change in the values of tissue thermophisical parameters to the Arrhenius integral has been examined.

It has turned out that in some points of the domain considered, the sensitivity parameter $\Delta\theta$ may vary by much greater than 1, what e.g. at the point C_1 determines the difference between the irreversibly damaged tissue and the totally destructed tissue (from the point of view of the IFPA algorithm, the difference between tha 4 and tha 5). The value of $\Delta\theta$ obtained at the point D_2 (approximately 0.05) causes that the point could be classified into different tha interval depending on the value calculated on the base of Eq. (4.7). It is clearly visible in Fig. 5. Furthermore, the whole algorithm of tissue injury calculation should be taken into account, otherwise the results of sensitivity analysis could give misleading information about tissue recovery at the point, in which the injury integral value is above the recovery threshold.

It is also important due to the course of the perfusion coefficient, expressed in the present paper as a polynomial function of the Arrhenius integral (c.f. Fig. 6), its value increases or decreases in accordance with the increasing or decreasing injury integral.

The tissue returns to the native state at two points considered (calculations for the basic values of thermophysical parameters, c.f. Fig. 5): at the point C_1 after 383 seconds, while at point D_2 after 197 seconds.

The process of proliferation of the thermal injury shows that the most distinct recovery stage occurred for the basic value of the injury integral (c.f. Fig. 8). The maximal area of the lesion is 489 elements and decreases down to 437 elements after 157 seconds. The results of the sensitivity analysis show that for the case $\theta - \Delta\theta$ the lesion area is very small (37 elements) and

achieved after 13 seconds, while for the $\theta + \Delta\theta$, the maximal area is 605 elements between 76 and 81 seconds, then reduces to its final area equal to 591 elements.

The sensitivity analysis in combination with tha intervals and the new algorithm of tissue injury calculation seems to be a quite convenient means of analysis of the thermal injury formation process and could give more precise data about the depth and cross-section area of injury. It could be very important, especially in cases of a controlled coagulation process like, e.g., in some thermotherapies.

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