Nonlinear higher-order transient solver for magnetic fluid hyperthermia

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The article is devoted to numerical methods for transient solution of Pennes’ bioheat equation as required for Magnetic Fluid Hyperthermia (MFH) modeling. Special attention has been paid to the role of non-linearity of blood perfusion and its influence on temperature distribution. The authors show that the higher-order time integration algorithms are highly advised for this type of problem, which should be classified as a stiff one. Popular low-order solvers give very different solutions. Furthermore, the application of adaptive time stepping scheme reduces calculation time and raises the efficiency of the simulation software.

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1. Introduction

One of the most important aims of heat transfer modeling in living tissues is to be able to predict and control the level and the area of potential damage caused to tissues by extreme temperature. During, for example, hyperthermia treatment the damage should be limited to the cancer area, while the rest of the tissues should be left below the temperature of 45 °C. On the other hand, the modeling of heat transfer in soft tissues is also necessary for an accurate assessment of energy dissipation rate in joints, and for thermal analysis of the first stages of cryosurgical protocols (before freezing, when the effects of blood circulation are observed) [1]. In order to control the temperature during hyperthermia different types of thermometers are used, for instance: thermistors, thermocouples or infrared sensors [2]. The real measurements are more trustworthy, but numerical simulations are more flexible and often more convenient.

Magnetic fluid hyperthermia (MFH) is one of the most modern and extensively investigated temperature rise methods. In MFH the amount of energy provided to the body can be precisely controlled by the strength of magnetic field, the size of magnetic particles and their volume fraction in the tumor [3–7]. That is why, the investigation of bioheat-transfer phenomenon in living biological tissues requires the temporal and spatial estimation of temperature distribution.

Since Pennes’ work [8], almost every model of temperature distribution in a human body is based on the bioheat transfer equation:

\[ \rho c_p \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) - \rho_b c_b \omega (T - T_b) + Q_{\text{met}}, \]

where \( \rho \) is the tissue density, \( c \)—the tissue specific heat, \( \rho_b \)—the density of blood, \( c_b \)—the blood specific heat, \( \kappa \)—the tissue thermal conductivity, \( \omega \)—the blood perfusion rate, \( T_b \)—the arterial blood temperature, \( Q_{\text{met}} \)—the metabolic heat source, and \( T \) is the local tissue temperature.

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Pennes’ equation (1) describes the ability of a tissue to remove heat by both passive conduction and perfusion of the tissue by blood, in general. Pennes in his work assumed a constant-rate blood perfusion in the form of $\omega = V\rho_b$, where $V$ and $\rho_b$ are the perfusion rate per unit volume of tissue and the density of the blood, respectively. In this case, the temperature of venous blood is in equilibrium with the local temperature ($T$), and the arterial blood temperature ($T_b$) is constant. That means Pennes’ original model describes blood perfusion with acceptable accuracy if there are no large vessels nearby, for example, liver [9]. However, the vascularized tissue often experiences increased perfusion as temperature increases and it is necessary to consider a more general form of (1) in which the blood perfusion $\omega$ is a function of temperature $T$ (see for example [10–12]). Thus, the perfusion rate is the key parameter in calculating the heat transfer.

In this paper we have considered a more general form of Pennes’ bioheat transfer formula, taking into account nonlinear blood mass flow, and external source of thermal energy provided to the body:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (\kappa \nabla T) - c_b W(T - T_b) + Q_{\text{met}} + Q_{\text{ext}},$$

(2)

where $W$ is the mass flow rate of blood per unit volume of tissue in units of $(\text{kg/s/m}^3)$, $Q_{\text{ext}}$ is the external power density deposited in a tissue by the use of MFH.

An important factor of hyperthermia is also cooling associated with heat exchange with environment. It can be described by the convection boundary condition:

$$\kappa \frac{\partial T}{\partial n} = H(T_{\text{amb}} - T)$$

(3)

where $H$ is the skin heat transfer coefficient and $T_{\text{amb}}$ is the ambient temperature.

Among different technologies used for the increase of the body temperature, MFH is a special one, because it is based on superparamagnetic heat phenomenon. In this case superparamagnetic nanoparticles are injected into the cancerous tissue and then exposed to external magnetic field. The external low frequency magnetic field is passing through the body without interferences, only the area with nanoparticles is excited. The power density generated from nanoparticles can be understood as the internal source of heat.

In previous works [13], the authors have shown that the power losses from conductive heating based on eddy currents induced in the living tissues are negligible compared with the power dissipated from nanoparticles. This means that the external power ($Q_{\text{ext}}$) in (2) is purely dependent on superparamagnetic heat phenomenon. In the current paper we are assuming that $Q_{\text{ext}}$ is known from previous calculations, as presented in [13].

The choice of the discussed model was determined by our previous works connected with magnetic fluid breast cancer treatment (see Fig. 1). Though, now only two types of tissues are considered (breast fat and tumor), the presented investigation gives the general idea of the temperature distribution problem in low conducting lossy material.

The research is focused on the numerical methods, which can be applied to solve Pennes’ equation. The main attention has been paid to the transient state solution and to the influence of tissue parameters, expressed as diffusion coefficient $D$ and nonlinear perfusion function $E$ (see Eq. (6)) on the solution. We have implemented the numerical time integration methods of different order showing their advantages and constraints when applied in real tissue coefficients of Pennes’ equation with MFH excitation.
Table 1
Material properties of tissues at frequency 150 kHz [14].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Thermal conductivity $\kappa$ (W/m°C)</th>
<th>Electric conductivity $\sigma$ (S/m)</th>
<th>Density $\rho$ (kg/m³)</th>
<th>Specific heat $c$ (Ws/kg°C)</th>
<th>Mass flow rate $W$ (kg/s/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>0.210</td>
<td>0.0251</td>
<td>911</td>
<td>2348</td>
<td>$W_{\text{fat}}$ (4)</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.490</td>
<td>0.3730</td>
<td>1090</td>
<td>3421</td>
<td>$W_{\text{tumor}}$ (5)</td>
</tr>
</tbody>
</table>

Fig. 2. The models of temperature-dependent blood perfusion for (a) fat tissue and (b) tumor [11,4].

2. Tissue parameters

Most of the material properties of the involved tissues were taken from ITIS database [14] (see Table 1). Those values are not the subject of variation in a range from 37 to 45 °C. Special attention has been paid to the blood perfusion coefficient since this parameter has a strong impact on the temperature values and it is definitely nonlinear in the domain of solution.

For the temperature dependence of blood perfusion the curves based on the ones presented by Lang at el. [11] were used:

\[
W_{\text{fat}} = 0.36 + 0.36 \exp \left( -\frac{(T - 45.0)^2}{12.0} \right),
\]

(4)

\[
W_{\text{tumor}} = 0.416 + 0.417 \exp \left( -\frac{(T - 37.0)^4}{220} \right).
\]

(5)

Eqs. (4) and (5) are valid only up to 45 °C, but have the advantage of being differentiable, what is handy for nonlinear Newton solver. In this case it is assumed that vasculature is not destroyed, and healthy tissues are always below 45 °C.

Temperature-dependent blood perfusion curves in fat and tumor tissue are visualized in Fig. 2. As one can see, healthy and tumorous tissues have the opposite type of nonlinearity. Hence, blood cooling factor grows when healthy fat tissue is heated, tumor has higher normal perfusion rate, which drops when the temperature increases. This effect has great importance and a positive influence on the effectiveness of the therapy.

For comparison, constant-rate perfusion rate was also modeled. Then Eqs. (4)–(5) were replaced by single values [11]. The mean perfusion value was used for fat $W_{\text{fat}} = 0.54$ kg/s/m³, and maximal for tumor $W_{\text{tumor}} = 0.83$ kg/s/m³.

3. Numerical model

From the mathematical point of view a generalized form of Pennes’ equation (2) could be seen as an extended diffusion equation:

\[
\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) - E(u)u + f,
\]

(6)

where $u$ is the unknown function defined as the relative temperature $u = T - 37$, $D$ is the diffusion coefficient:

\[
D = \frac{\kappa}{\rho c},
\]

(7)

$E(u)$ is the nonlinear function derived from perfusion approximation:

\[
E(u) = \frac{c_b W(u)}{\rho c},
\]

(8)
and $f$ is the source term (combined internal and external):

$$f = \frac{Q_{\text{ext}} + Q_{\text{net}}}{\rho c}. \quad (9)$$

For simplicity reasons, in Eq. (6) it was assumed that the blood temperature, external temperature and initial condition are known and equal to zero. These parameters are not in the subject of interests of the presented investigation. Then the convection boundary condition formulated in (3) should be rewritten as a simple Robin’s condition:

$$- \frac{\partial u}{\partial n} = -Hu. \quad (10)$$

Partially differential equation (6) with boundary condition (10) and initial condition $u = 0$ will be solved using variational approach and finite element method (FEM). The aim is to find $u \in V$ such that

$$F(u, v) = 0, \quad \forall v \in V, \quad (11)$$

where $V$ is the variational space defined by finite element approximation, $v$ is the test function and $F(u, v)$ the nonlinear variational form. Diffusion problem in strong form (6) is defined in time domain, so variational form $F$ has to be also in the time function. Standard finite element approach (multiplication by test function and integration over domain $\Omega$ bounded by $\Gamma$) was taken to obtain the weak form of equation:

$$\int_{\Omega} \frac{\partial u}{\partial t} v dx = F(u, v, t) \quad (12)$$

$$F(u, v, t) = - \int_{\Omega} D \nabla u \cdot \nabla v dx - \int_{\Gamma} Huv ds - \int_{\Omega} E(u)uv dx + \int_{\Omega} f v dx. \quad (13)$$

Since none of the coefficients $(D, H, E(u), f)$ is a function of time, the steady state solution usually exists. In such a case, a simple nonlinear equation $F(u, v, t) = 0$ has to be solved. In some cases it is enough [15], but the authors of this paper are interested in transient state solution. Our aim is to verify how different integration schemes influence the values of temperature before the steady state is reached.

To solve transient nonlinear problem, numerical solver based on finite element library FEniCS [16] was created. The package makes extensive use of scripting language Python, where weak forms can be naturally expressed by the use of special language, Unified Form Language (UFL). A wide range of finite elements and linear solvers are easily accessible for the user. FEniCS is rapidly developing open-source software, but unfortunately it does not support time-domain problems. Time integration schemes have to be implemented by the user, or an external package could be applied.

Time integration for Ordinary Differential Equations (ODE) is one of the basic topics in students’ numerical analysis course. There are many advanced high-order methods, adaptive time-step algorithms widely applicable to reduce error in complicated physical problems. On the other hand, MFH is thought to be a simple, stable problem with high time constant and well known steady state solution. Hence classical 1-st order backward Euler with fixed step is often thought to be enough [17,5]. Other authors are not bothered by the used algorithms, trusting the commercial simulation packages [4,18].

According to the best of the authors’ knowledge, the problem of accuracy for transient temperature distribution during MFH has not been addressed yet. In this paper two groups of integration methods will be compared. The first ones are simple 1-order Euler with fixed time step schemes. The second group are high-order methods from the Runge–Kutta algorithm family.

### 3.1. Euler methods

A straightforward approach to time-dependent PDEs is to discretize the time derivative by a finite difference approximation, which turns the transient problem into a set of repetitive stationary problems.

For simplicity reasons we decided to implement three basic integration schemes based on the Euler method for Eq. (12):

$$\int_{\Omega} \frac{u^k - u^{k-1}}{\delta t} v dx = \theta F^k + (1 - \theta)F^{k-1}, \quad (14)$$

where $\theta$ is the coefficient, which for forward Euler explicit scheme is 1, for backward Euler (implicit) is 0, and for Crank–Nicolson is 0.5. After rearranging Eq. (14) could be expressed in a form of variational functional:

$$- \int_{\Omega} u^k v dx + \int_{\Omega} u^{k-1} v dx + \delta_t \theta F^k + \delta_t (1 - \theta) F^{k-1} = 0, \quad (15)$$

which is suitable for FEniCS package implementation (see Python code snippet below).
The above code is mostly self-explaining. The nonlinear problem in each time step is solved by the Newton solver. It is noteworthy that FEniCS function (derivative()) provides a method for analytical linearization of weak forms described in UFL [16]. It defines a flexible interface for choosing finite element spaces and defining expressions for weak forms in a notation close to mathematical notation.

3.2. ESDIRK solver

There are number of higher order integration schemes worth considering. They can be grouped in two categories: one-step Runge–Kutta methods and linear multistep methods. The representatives of multistep methods, such as Backward Differentiation Formula (BDF), require to store $n$ previous solutions, which makes them more memory consuming.

Runge–Kutta family is widely used for transient PDE problems [19]. Using Butcher tableau one can easily describe any type of higher-order one-step solver. Special popularity was gained by Singly Diagonally Implicit Runge–Kutta methods (SDIRK). It is efficient and has excellent stability properties of implicit Runge–Kutta methods.

In 2004 SDIRK scheme was extended by Anne Kvarno, who proposed explicit first stage modification (ESDIRK) improving robustness of the approach [20]. In this paper higher-order transient solver is based on ESDIRK 4-th order method as implemented in Gryphon library [21]. Gryphon is a highly specialized module which provides error estimators and adaptive time stepping algorithms. Basic use of the library is simple (see code below).

As presented above, nonlinear weak form functional $F$ (Eq. (12)) is directly passed to the ESDIRK solver, which can automatically handle time integration. However it should be underlined, that for real problems special effort is required to tune solver parameters.

4. Simulations

The final aim of the paper is to compare lower and higher-order time integration schemes (see Fig. 3) for MFH modeling. As it turns out, the higher-order solver is needed and we conducted several experiments to understand the problem more deeply. One part of those investigations is devoted to the solver (order of integration, step size, adaptivity), and the other one to equation coefficients which make problem stiff.

4.1. Realistic MFH model

If one wants to investigate experimentally the heating profile of, for example, a magnetic nanoparticles sample, like magnetite, there is a need to validate experimental data with theoretical predictions. In the case of magnetic nanoparticles subjected to an AC magnetic field, they show the heating effects caused by losses during their magnetization reversal process. Although a number of effects occur in the magnetic nanoparticles, the heat generation is mainly through the following phenomena: hysteresis loss, Neel relaxation loss, Brown relaxation loss, losses due to friction in viscous suspension, all of which can be determined by the physical theory [6,22] and validated by computer simulation.

It is worth noticing that magnetic nanoparticles which can produce significant amounts of heat in low volumes are often characterized experimentally by, for example, Specific Loss Power (SLP), Specific Absorption Rate (SAR) or Intrinsic Loss of Power (ILP). These values of the magnetic material depend on the initial slope of the time dependent temperature curve $dT/dt$. That is why the proper knowledge of the curve profile (transient temperature distribution) is so important.

In our case the model of magnetic fluid hyperthermia applied to the breast cancer was created. As illustrated in Fig. 4(b) small inclusion consisting of magnetic fluid was placed in the center of circular breast fatty tissue. Fine, uniform discretization generates finite element mesh presented in the upper left corner of the drawing.
Fig. 3. Transient maximum value of temperature in a function of time. Comparison between 1-st order backward Euler solver and 4-th order ESDIRK.

Fig. 4. (a) Comparison between different perfusion models: linear, nonlinear, no perfusion; (b) steady state solution.

Table 2
Initial and steady state values of $E$ coefficient in Eq. (6).

<table>
<thead>
<tr>
<th>Subdomain</th>
<th>Nonlinear model</th>
<th>Linear model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial value</td>
<td>Steady state</td>
</tr>
<tr>
<td>Fat</td>
<td>$6.1 \cdot 10^{-4}$</td>
<td>$7.7 \cdot 10^{-4}$</td>
</tr>
<tr>
<td>Tumor</td>
<td>$8.0 \cdot 10^{-4}$</td>
<td>$6.6 \cdot 10^{-4}$</td>
</tr>
</tbody>
</table>

Then the material parameters (see Table 1) were recalculated to make them suitable for Eq. (12). The diffusivity $D$ was set to $9.8210^{-8}$ for fat and $1.3210^{-7}$ for tumor. The nonlinear perfusion $E(u)$ has been described by Eq. (8), where $W_{fat}$ has been scaled by the factor of $1.710^{-3}$ for fat. Analogously, the $W_{tumor}$ has been scaled by $0.9710^{-3}$ for tumor. Lastly, the source term $f$ has been set to $0.810^{-2}$, and the convection $H$ to 9.5. The justification of these values was discussed in previous authors’ work [13].

In Fig. 3 two methods of integration were compared. As one can see there is a tremendous difference between 1-st order backward Euler scheme and 4-th order ESDIRK one in the first seconds of stimulation. Higher order method shows that after excitation is switched, the temperature jumps nearly immediately by $2^\circ$C. This effect is not present when lower-order method is used, which suggests that we are dealing with a stiff transient field problem.

However, the steady state solution in both methods of integration is the same, and reaches $5^\circ$C above normal body temperature. The value of the source term $f$ has a direct and simple impact on steady state value, so if we increase $f$, higher tumor temperature will be achieved. Heating tissues by $5^\circ$C is the minimal curable temperature rise.

The influence of perfusion type and its value is presented in Fig. 4(a). A hypothetical case without perfusion term is also shown. In such a case the temperature grows to much higher values because only skin convection boundary condition limits the maximum value. The difference between linear and nonlinear model of perfusion is not so spectacular, but it is definitely noticeable.

Table 2 contains values of perfusion coefficient function $E(u)$ calculated using Eq. (8) and tissues properties described in Section 2. It explains why the nonlinear model gives higher maximal temperature. As one can see, the steady state value for nonlinear tumor is $6.6 \cdot 10^{-4}$, whereas the same value in linear model is $8.1 \cdot 10^{-4}$. The higher value of perfusion means that
the tissue is more efficiently cooled. That is why the steady state for linear model is below steady state of nonlinear model, as observed in Fig. 4(a).

4.2. Solvers

The realistic results presented in the previous subsection have shown that widely used Backward Euler scheme is not applicable in this case. The authors raise the question whether 1-st order method can be right, and what assumptions have to be made to be allowed to use implicit Euler scheme. For that reason we have created a model with dummy coefficients $D = E = H = f = 1$.

At the beginning we decided to verify whether a smaller time step for the backward Euler gives a more accurate solution. In Fig. 5 it can be observed that reducing the time step (from 1.0 to 0.01 s) gives a steeper initial slope. Higher accuracy in transient state is achieved, but the steady state is unchanged.

Next, we presented the comparison of three solvers: backward Euler, Crank–Nicolson, and ESDIRK scheme (see Fig. 6). The explicit Euler plot is not included in the figure because it is completely unstable. The other solvers give the same steady state results, and also very similar results in the transient state. This confirms that solver implementation is correct and that, when the dummy coefficients are used, the simple 1-st order method is applicable. Nevertheless, higher order solver is more accurate and efficient. Steady state is achieved in the second step by ESDIRK method, where backward Euler needs five steps.

The last experiment is to verify the usefulness of adapting time stepping. From Fig. 7 one can conclude that adaptivity allows to reduce the number of calculations in this group of problems, especially when the steady state is reached. Another important advantage of adaptivity is that accuracy on the steep slope is automatically ensured.

4.3. Equation coefficients

In the previous subsection we have demonstrated that the developed solver works correctly for the simplified equation with the dummy coefficients. On the basis of this observation we have decided to investigate how the equation coefficients influence the solution.
The results of experiments are presented in Fig. 8. Each plot is devoted to one of the coefficients: upper-left to diffusivity $D$, upper-right to $E$, lower-left to $H$, and lower-right to source $f$. Initially the values of each coefficient were set to 1.0, then for each plot different coefficient values were disturbed. The values of $D$ and $f$ were decreased from 1.0 to 0.1, while the values of $E$ and $H$ were increased from 1.0 do 10.1. This comparative analysis has been done for varying coefficients values while the rest of them were constant and set to 1.0.

Let us start the discussion of the results from plots placed in the lower row in Fig. 8. Both coefficients $E$ and $H$ are related to cooling process so, not surprisingly, higher values of them give lower steady state solution. But more interesting, from our point of view, is the observation that the initial jump of temperature is nearly not influenced by them. One can conclude that both $E$ and $H$ coefficients do not change the short-time response of the system, but have an impact on long-term stable solution.
A different conclusion should be formulated when looking at the upper plots in Fig. 8. It is expected that lower value of source $f$ results in lower steady state solution. Whereas, diffusivity has the opposite influence, that is lower $D$ means that heat energy provided to the area is less actively spread over the surrounding domain, which results in higher temperature.

Finally, it is important to realize that the initial slope of solutions presented in Fig. 8 (the upper row) is strongly influenced by the $D$ and $f$. The initial jump of the solution is clearly observed, even though in those trials maximal ratio $D/f$ is only 10. In a real MFH model this ratio is about $10^4$. This makes the solution presented in Fig. 3 more understandable.

5. Conclusions

The nonlinear higher-order time domain solver for Magnetic Fluid Hyperthermia has been developed, tested and demonstrated. The simulations for realistic values of human tissue parameters lead into a stiff problem, which has tremendous impact on the transient state solution. We show that widely used simple backward Euler method gives the incorrect solution. The obtained results showed that adaptive time stepping is strongly advised, since it can save a lot of computational time when the steady state is reached.

The paper is mainly focused on numerical methods supporting MFH modeling. Taking advantage of new solver features we were able to predict that the nonlinear model of blood perfusion leads to higher temperature in the tumorous tissue. That means that lower stimulation is required.

Further research should consider reducing computational complexity by introducing adaptive mesh refinement scheme. It should be quite straightforward since problem parameters are not the function of time. There is also an indisputable need for precise measurement verification of the temperature distribution in the transient state. That is not a technically trivial task, but special effort has to be made to confirm the new shapes of higher-order temperature time plots i.e. the initial slope. According to the presented results the temperature rise is reached much faster, which could have serious consequences for therapy planning.

References