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**ФІЗИКА І ХІМІЯ ТВЕРДОГО ТІЛА**
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# Theoretical modelling of temperature changes during induction heating of magnetite suspensions

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Although now it is customary to use magnetic hyperthermia in the treatment of oncological diseases as an auxiliary method, detailed modeling of the tissue heating process with parameters close to real ones will allow this method to be included in the main ones. Modelling of liquid heating with evenly distributed identical energy sources was presented. It allows choosing the optimal modes of using hyperthermia in real conditions. The model is based on experimental data and explains the dependence of the temperature of magnetite particles' aqueous suspension versus the time. Newton's law equations were used for modelling of dependence of body temperature versus time at a constant temperature $T_{env}$. It was hypothesized that the overheating problem could be avoided by using controlled concentrations of magnetite. The obtained results show that about 40 mg/cm$^3$ of magnetite is required to avoid overheating.

**Keywords:** magnetite, magnetic hyperthermia, heating processes simulation.

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## Introduction

Nowadays, hyperthermia is a well-known method of adjuvant cancer therapy, especially in addition to standard radiotherapy [1, 2], although the induction heating of substances has long been thoroughly studied [3-10]. Scientific papers showed that hyperthermia improves the killing of tumor cells known to be radioresistant [11] and the combination of radiotherapy with hyperthermia increases cytotoxic effects [12]. Recent developments based on the thermoradiobiological rationale of hyperthermia indicate it to be a potent radio- and chemosensitizer and, moreover, being devoid of any additional significant toxicity [13]. Various magnetic materials based on ferromagnetic nanoparticles have different structural, thermal, and magnetic characteristics, which determines the importance and necessity of taking into account the mutual influence of particle parameters and the working environment of a living organism. Detailed modelling of the tissue heating process using parameters that are close to real ones will allow the magnetic hyperthermia method to be included in the main ones.

The first requirement for the nanoparticles, which can be used in biomedicine, is their narrow size distribution. It should be the consistency of nanoparticle size distribution with the sizes of biological objects that these particles should affect or not affect. In particular, typical sizes of cells are from 10 to 100 μm, viruses – from 20 to 450 nm, capillaries – 60 nm, genes – 10-100 nm in length, and 2 nm in cross-section [14].

Hyperthermia therapy uses elevated temperatures for therapeutic purposes and can be subdivided into three diapasons by the combinations of temperatures, used times, and the induced responses (physical, biological, and physiological): physiological hyperthermia (37-42 °C), which treats aches, pains, strains, and sprains; destructive therapies (uses high temperatures from 50 to 100 °C for very short times); adjunctive or synergistic hyperthermia therapy, which is placed between the physiologically based and destructive therapies, and uses temperatures of 41–50 °C, applied for ranges from hours to minutes [1, 5].

The second requirement is the maximal safety of temperatures and energies. The highest safe local temperature for the human body is 43 °C [6] and the

permissible dose of thermal energy for example for rodents is 586 kJ/mol [7].

In addition, there is a requirement to generate a certain amount of heat per gram of magnetic material (magnetite), called the specific absorption coefficient (SAR) [8]. This value must be controlled, as well as the degree and rate of heating. SAR depends on the size, shape, chemical composition, the concentration of magnetic nanoparticles, the viscosity of the solution, and the frequency of the applied magnetic field [9, 14].

The above requirements determine the basis of the presented mathematical model of liquid heating with evenly distributed identical energy sources, which allows choosing the optimal modes for using hyperthermia in real conditions. This model is also focused on the physical aspects of the magnetic hyperthermia processes in living tissues.

The aim of this paper is to perform the theoretical modelling of temperature versus the time for an aqueous suspension of magnetite particles, which can be used in magnetic hyperthermia. The used experimental data have been obtained in the work [15]. The modelling highlights the most essential features of the investigated object, correctly reflecting the main regularities of the phenomenon and hypothesizing new information about it. The importance of the study is determined by the presence of a sufficient number of partial results and leads to obtaining a new and deeper understanding of the described phenomena.

## I. The simulation of body heating in the presence of internal heat sources

The temperature changes have been described using the system model of rather small dimensions with the uniformity of temperature distribution in its volume. The time dependence of the temperature T(t) of such system at constant temperature $T_{env}$ is determined by Newton's law equation (1):

$$dT/dt = -(T - T_{env})/\tau_{env}, \quad (1)$$

where $\tau_{env}$ is the characteristic time of temperature change, which depends on the surface state and the system shape.

If the heat sources with temperature $T_{ins}$ are distributed evenly inside the system then the law of body temperature change is similar to that shown above and described by equation (2):

$$dT/dt = -(T - T_{ins})/\tau_{ins}, \quad (2)$$

where $\tau_{ins}$ is the characteristic time depending on the surface state, geometry, and shape of the coolant.

Both heat transfer processes are described by the following equation (3):

$$dT/dt = -(T - T_{env})/\tau_{env} - (T - T_{ins})/\tau_{ins}, \quad (3)$$

which can be transformed into a simplified form:

$$dT/dt = -(T - T^*)/\tau^*, \quad (4)$$

where $1/\tau^* = 1/\tau_{env} + 1/\tau_{ins}$ and $T^* = (T_{env}/\tau_{env} + T_{ins}/\tau_{ins})\tau^*$ are effective characteristics of the system.

If the initial value $T(0) = T_0$, then the solution of the equation is as follows:

$$T(t) = T^* + (T_0 - T^*)e^{-t/\tau^*}, \quad (5)$$

where heating constant $\lambda = 1/\tau$ can also be used instead of the characteristic time $\tau$.

## II. Magnetic hyperthermia measurements

Magnetic hyperthermia measurements have been performed in work [15]. In brief, induction heating of the magnetite samples was studied using an induction coil (100 kHz, 1 kW, 5 cm in diameter). The two samples of magnetite have been used for experiments: $Fe_3O_4$-peel (the magnetite, synthesized using grape peel extract) and $Fe_3O_4$-pulp (the magnetite, synthesized using grape pulp extract). Water suspension of $Fe_3O_4$ samples was placed into an induction coil made from copper. The sample temperature was registered using an IR thermometer. The induction coil was cooled with water to maintain a constant temperature of 10–15℃ during the measurements. Hyperthermia measurements for magnetite samples were performed for 40 minutes with a step of 0.1 s. The dependences of the temperature change versus the heating time (electromagnetic field is on) and cooling time (electromagnetic field is off) were recorded. The changes in temperature depending on sample concentration provide heating parameters important for magnetic hyperthermia applications [15]. The approximated induction heating curves, obtained in this work, for $Fe_3O_4$-peel and $Fe_3O_4$-pulp samples are shown in Fig. 1a and 1b, respectively.

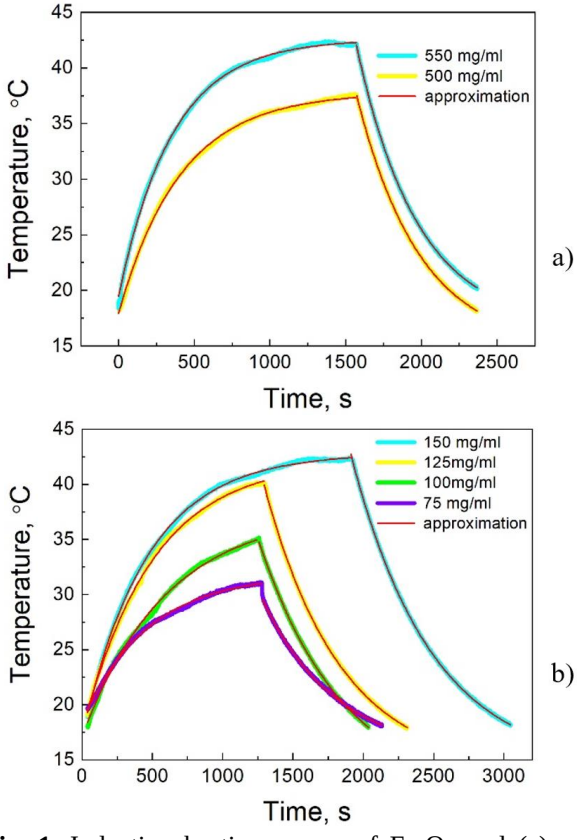



**Fig. 1.** Induction heating curves of $Fe_3O_4$-peel (a) and $Fe_3O_4$-pulp (b) samples water suspensions. The red line is an approximation of the experimental data curve.

## III. Results

Table 1 summarizes the approximation parameters and calculated parameters.

Table 1 showed that the initial temperature $T_0$ at around 17 – 19 ℃ and the temperature of the external environment $T_{env}$ at around 12-17 ℃ were supported. The effective temperature T* changes from 31 to 43 ℃ with increasing in magnetite mass. The difference and excess of the characteristic cooling time $\tau_{env}$ over the effective heating time τ* is observed, which indicates the adequacy of the proposed model. The calculated heating times $\tau_{ins}$ exceed $\tau_{env}$ and τ* by approximately an order of magnitude. This excess of heating times indicates a similar excess of the source temperature above the effective heating temperature T* and the temperature of the external environment $T_{env}$. Discarding the values of $T_{ins}$ and $\tau_{ins}$, which seem implausibly large, it is possible to determine the source temperature of $T_{ins}$ ~ 200 ℃ and the heating time of $\tau_{ins}$ ~ 5000 s. Thus, it can be seen that the temperature estimated in this way is sufficiently high and dangerous for use in living organisms.

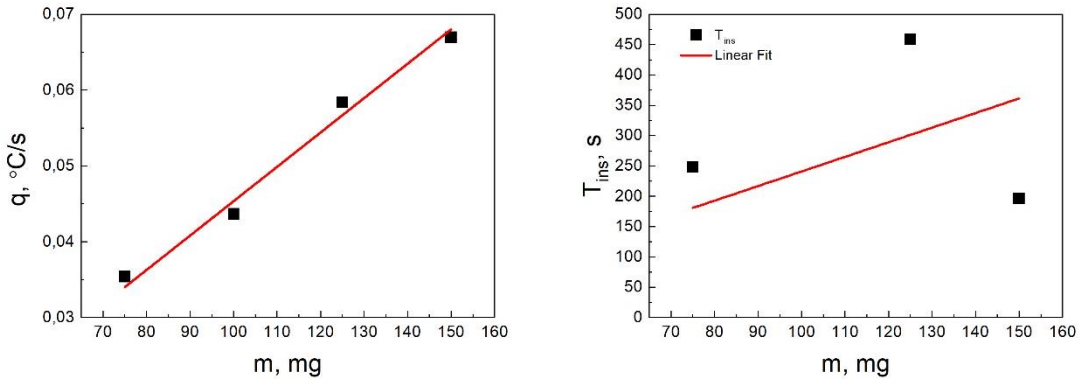
According to the data in Table 1, the characteristics of the heat source, the initial heating rate $q_{ins} = (T_{ins} – T_0)/\tau_{ins}$, and the heating temperature $T_{ins}$ were calculated for different values of the magnetite mass, as shown in Fig. 2. It is demonstrated (Fig. 2a) that the rate of temperature change $q_{ins}$ is proportional to the mass of magnetite and the time characteristic of magnetite $\tau_{ins} = T_{ins}(m) /q_{ins}(m)$ = 5590 s does not depend on temperatures if the heating temperature $T_{ins}$ is approximated by a directly proportional dependence (Fig. 2b).

The other algorithm has been used to confirm the independence of $\tau_{ins}$ from the magnetite mass. Due to the dependence of the content of magnetite on the characteristic cooling time of the compounds $\tau_{env}$ and τ*, the values $1/\tau^*$ and $1/\tau_{env}$ are fairly well approximated by a linear dependence on the mass of magnetite with

**Table 1**

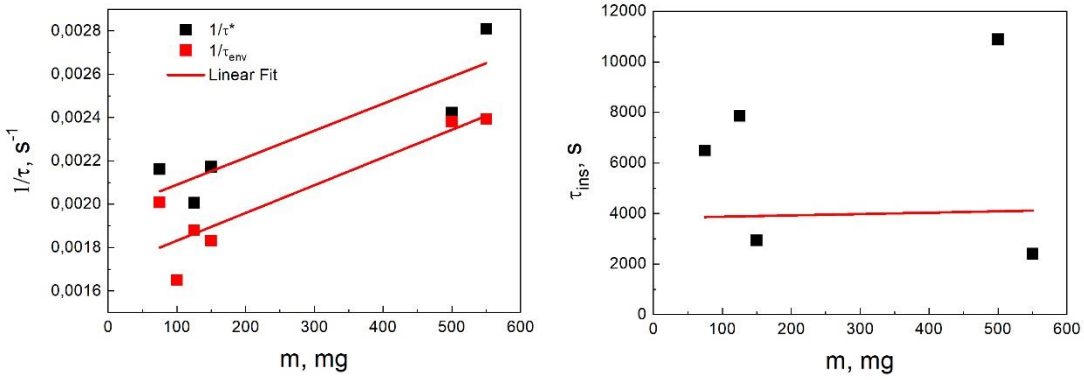
Approximation parameters and the calculated values which are extracted from the proposed model.

| m, mg | $T_0$, $^0$C | T*, $^0$C | τ*, s | $T_{env}$, $^0$C | $\tau_{env}$, s | $T_{ins}$, $^0$C | $\tau_{ins}$, s |
|---|---|---|---|---|---|---|---|
| 75 | 18.45 | 31.86 | 462.5 | 15.27 | 498 | 248 | 6490 |
| 100 | 17.12 | 37.50 | 596.3 | 11.64 | 606 | 1627 | 37200 |
| 125 | 17.48 | 42.15 | 498.3 | 13.95 | 532 | 459 | 7860 |
| 150 | 17.20 | 42.81 | 460.2 | 14.22 | 546 | 196 | 2930 |
| 500 | 17.96 | 37.80 | 404.4 | 14.73 | 420 | 636 | 10900 |
| 550 | 19.42 | 42.57 | 356.1 | 16.68 | 418 | 192 | 2400 |




(a) (b)

**Fig. 2.** Heating rate $q_{ins}$ (a) and temperature $T_{ins}$ (b) versus magnetite mass. The markers are obtained from the proposed model; the lines are their approximation.




(a) (b)

**Fig. 3.** Times τ*, $\tau_{env}$ (a) and $\tau_{ins}$ (b) versus magnetite mass. The markers are obtained from the proposed model; the lines are their approximation.

practically the same slopes (Fig. 3a). Therefore, calculated from these linear dependencies, $\tau_{ins}$ versus magnetite mass is almost horizontal at level 4000 s (Fig. 3b).

Note that $1/\tau_{env}$ = 0.00170 for magnetite mass m = 0 corresponds to the cooling constant of water, which is simply verification by experiment.

To further correspond to clinical conditions (the effective temperature T* = 43 ℃, the initial temperature $T_0$ = 36.6 ºC, and the temperature of the environment $T_{env}$ = 36.6 ℃) we presented the time dependence of the current temperature T(t). First, to obtain a fixed value of the magnetite mass for a fixed value of the effective temperature, we calculated the dependence of an effective temperature T* versus the magnetite mass due to the mass dependence of the characteristics of the heat source and cooler. Fig. 4 showed two dependencies for two values of the characteristic time of the source: $\tau_{ins}$ = 4000 s and $\tau_{ins}$ = 5000 s. The magnetite masses of 35 and 45 mg correspond to the temperature T* = 43 ℃. Then, for these values, the magnitudes $\tau^*$ = 501 s and $\tau^*$ = 511 s have been calculated and the time dependences of the current temperature have been plotted, as shown in Fig. 5. As can be seen from Fig. 5, the two curves are practically equivalent.

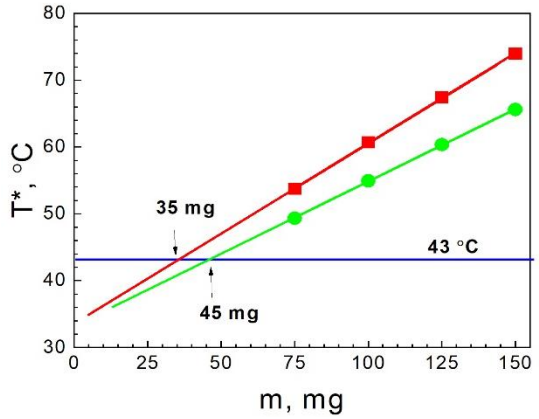



**Fig. 4.** Effective temperature as a function of mass. $T_{env}$ = 36.6 ℃, $\tau_{ins}$ is equal 4000 s (red line) and 5000 s (green line), $T_{ins}$ = 2.4084 m, $\tau_{env} = 1/(1.28\ 10^{-6}\ m + + 1.7\ 10^{-3})$.

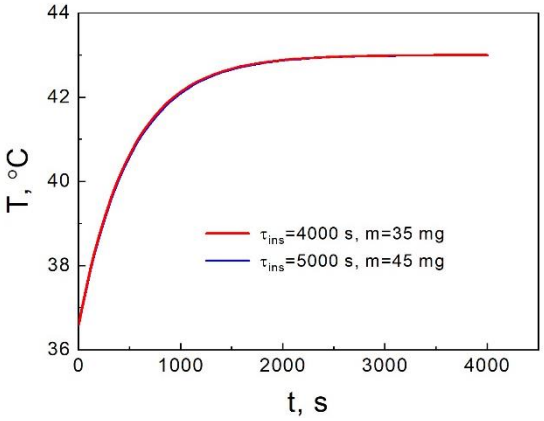



**Fig. 5.** The function of temperature versus time: m = 35 mg (red line), m = 45 mg (blue line), $T_0$ = 36.6 ℃.

## IV. Discussion

As mentioned above, one of the essential problems is the problem of uncontrolled overheating of disease tissues to high temperatures, which can destroy healthy tissues. This problem, for example, can be solved by using materials with a Curie temperature in the range of 42–45°C. The magnetic particles are expected to be heated only to this temperature by the alternating magnetic field, and thus the risk of tissue overheating is greatly reduced. For example, the iron-doped manganites with the general composition $La_{1-x}Sr_xMn_{1-y}Fe_yO_3$ have been proposed as promising mediators for self-controlled magnetic hyperthermia in the work [16]. The Curie temperature can be controlled by the iron content in a given range.

Based on the fact that the Curie temperature of magnetite is quite high $T_C$ = 585 °C [17], the probability of tissue overheating is also high. However, we suggest a possibility to avoid this problem by controlling the maximum temperature of tissue heating by selecting the magnetite concentration. For example, the suspensions of doped magnetite with concentrations of 20-75 mg/ml are needed to exactly quantify the maximum heating temperature.

Another important problem is the uniformity of nanoparticles distribution. Having established that the optimal mass concentration of magnetite is about 40 mg/ml or 40 mg/cm$^3$, we have estimated the number of nanoparticle agglomerates per one cell of an organism. If the volume of a cell with a size of 10 μm is $10^{-9}$ cm$^3$, then the mass of magnetite in it is $40 \cdot 10^{-9}$ mg. For magnetite density of 5.175 g/cm$^3$, its volume was estimated at 7.7 $10^{-12}$ cm$^3$. If the size of nanoparticles agglomerate is 0.1 μm [15], then its volume represents $10^{-15}$ cm$^3$. Thus, one cell includes 7.700 agglomerates evenly distributed. However, an effective method that realized the given uniformity of distribution of nanoparticles throughout the cell is unknown.

It is known [8] that heat generated by nanoparticles placed in an AC magnetic field is largely caused by three major mechanisms: hysteresis loss, Néel relaxation, and Brownian relaxation. According to the work [4], for particles > 30 nm in size, the Brownian mechanism is dominant, for which the viscosity of the medium is important. Therefore, it is necessary to confirm or refute the statement about the predominance of the Brownian relaxation mechanism for substances with a viscosity close to living tissues' viscosity.

In addition, the estimation of an effective characteristic of the heating process is interesting for reducing the overheating risk. Consider, as an example, the following relations between characteristic values for the heater and the cooler $T_{env}/\tau_{env} \approx T_{ins}/\tau_{ins}$ and $\tau_{ins} >> \tau_{env}$, that approximately correspond to the obtained values. Then we obtain $\tau^* \approx \tau_{env}$, $T^* \approx 2T_{env}$ for the effective characteristics. Therefore, the characteristic times of heating and cooling are close, and the effective temperature, which is reached under these conditions, is approximately twice higher than the temperature of the environment and depends slightly on the heater temperature.

## Conclusions

A model of the heat exchange process in the presence of an internal heater and an external cooler has been proposed. The characteristics of the heating and cooling process were obtained. A method of using magnetite in clinical conditions has proposed which prevent unwanted tissue overheating. To experimentally confirm the predicted results, it is proposed to investigate the time dependence of the samples temperature versus the initial temperature, which corresponds to the temperature of the human body $T_0$ = 36.6 ℃. In addition, in the following studies, we recommend thermally insulating the samples with a medium insensitive to inductive heating, similar to tissue with a constant temperature, which also corresponds to the human body temperature. It would be interesting to investigate the dissolution of magnetic nanoparticles using substances with a viscosity similar to that of living tissues, which would provide knowledge about the relaxation mechanism. Finally, we note that the transfer of the results of experiments performed under conditions far from the specified ones to clinical conditions leads to the risk of practical use of the ultra-fine and effective procedures described above.

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Я.П. Салій, І.М. Ліщинський, Т.Р. Татарчук

# Моделювання температурних змін у розчині магнетиту при індукційному нагріванні

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В даний час магнітну гіпертермію прийнято використовувати в лікуванні онкологічних захворювань як допоміжний метод, проте детальне моделювання процесу нагрівання живих тканин з параметрами, наближеними до реальних, дозволить віднести цей метод до основних. У статті представлено моделювання нагріву рідини з рівномірно розподіленими ідентичними джерелами енергії, що дозволяє підібрати оптимальні режими використання гіпертермії в реальних умовах. Модель пояснює часову залежність температури водної суспензії частинок магнетиту при постійній температурі оточуючого середовища $T_{env}$, базується на експериментальних даних і використовує рівняння закону Ньютона. Згідно з отриманими результатами припущено, що проблеми перегріву можна уникнути, використовуючи контрольовані концентрації магнетиту близько 40 мг/см$^3$.

**Ключові слова:** магнетит, магнітна гіпертермія, моделювання процесів нагрівання.