

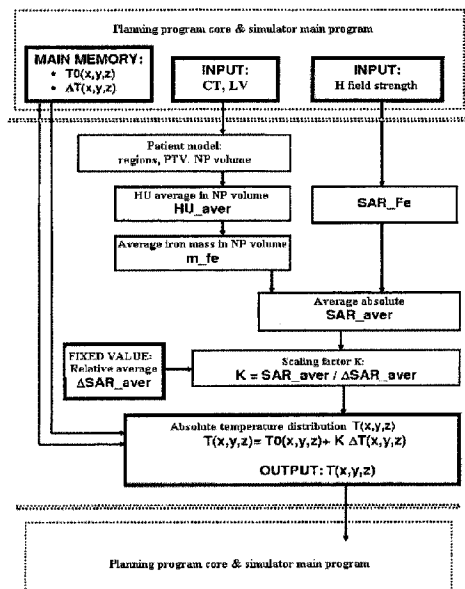


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(54) **Titre : OUTIL DE SIMULATION ASSISTE PAR ORDINATEUR DESTINE A AIDER UN UTILISATEUR LORSQU'IL PLANIFIE UNE THERMOTHERAPIE**

(54) **Title: COMPUTER-AIDED SIMULATION TOOL FOR PROVIDING ASSISTANCE IN THE PLANNING OF THERMOTHERAPY**



(57) **Abrégé/Abstract:**

The invention relates to a computer-aided simulation tool, in particular to computer-aided simulation methods, for providing assistance in the planning of thermotherapy, and to suitably configured computer equipment. The thermotherapy comprises hyperthermic treatment of a tumour volume within a volume of a human body. The hyperthermic treatment comprises the application of a magnetic field within a treatment volume by means of a magnetic field applicator. In at least one depot volume, thermal energy can be introduced by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body, by power absorption in the applied magnetic field. Field strength values and optionally calculated temperature distributions are provided for assisting the user in the planning of the thermotherapy.

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[Fortsetzung auf der nächsten Seite]

(54) Title: COMPUTER-AIDED SIMULATION TOOL FOR PROVIDING ASSISTANCE IN THE PLANNING OF THERMOTHERAPY

(54) Bezeichnung : COMPUTERGESTÜTZTES SIMULATIONSWERKZEUG ZUR UNTERSTÜTZUNG BEI DER PLANUNG EINER THERMOTHERAPIE

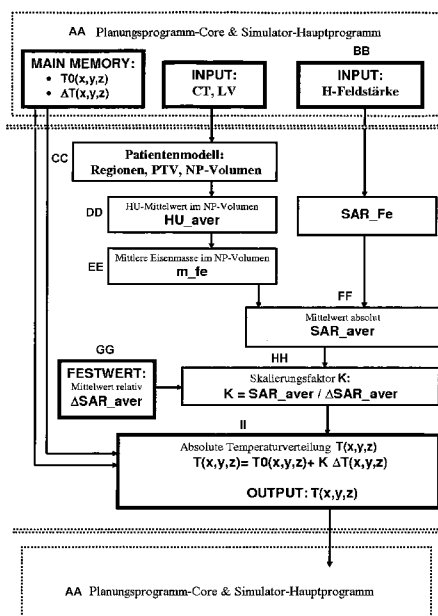


Fig. 9

AA Planning program core & simulator main program
 BB INPUT: H-field strength
 CC Patient model: Regions, PTV, NP volume
 DD HU mean value in NP volume
 EE Mean iron mass in NP volume
 FF Absolute mean
 GG CONSTANT VALUE: relative mean
 HH Scaling factor K:
 II Absolute temperature distribution

(57) Abstract: The invention relates to a computer-aided simulation tool, in particular to computer-aided simulation methods, for providing assistance in the planning of thermotherapy, and to suitably configured computer equipment. The thermotherapy comprises hyperthermic treatment of a tumour volume within a volume of a human body. The hyperthermic treatment comprises the application of a magnetic field within a treatment volume by means of a magnetic field applicator. In at least one depot volume, thermal energy can be introduced by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body, by power absorption in the applied magnetic field. Field strength values and optionally calculated temperature distributions are provided for assisting the user in the planning of the thermotherapy.

(57) Zusammenfassung: Die Erfindung betrifft ein computergestütztes Simulationswerkzeug, insbesondere computergestützte Simulationsverfahren zur Unterstützung einer Thermotherapie-Planung sowie entsprechend ausgebildete Computereinrichtungen. Die Thermotherapie umfasst eine Hyperthermie-Behandlung eines Tumervolumens in einem Körpervolumen eines menschlichen Körpers. Die Hyperthermie-Behandlung umfasst das Applizieren eines Magnetfeldes in einem Behandlungsvolumen mittels eines Magnetfeld-Applikators. In mindestens einem Depotvolumen ist mittels im Körper deponierter magnetischer, paramagnetischer und/oder superparamagnetischer Nanopartikel durch Leistungsabsorption im applizierten Magnetfeld Wärmeenergie einbringbar. Es werden Feldstärkewerte und optional berechnete Temperaturverteilungen zur Unterstützung des Anwenders bei der Planung der Thermotherapie bereitgestellt.

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Erklärungen gemäß Regel 4.17:

— hinsichtlich der Berechtigung des Anmelders, die Priorität einer früheren Anmeldung zu beanspruchen (Regel 4.17 Ziffer iii)

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Computer-aided simulation tool for providing assistance
in the planning of thermotherapy

5 The invention relates to a computer-aided simulation
tool for providing assistance in the planning of
thermotherapy, and to be more precise to a computer-
aided simulation method for providing assistance in
thermotherapy planning and to computer devices of
appropriate design.

10

PRIOR ART

Gneveckow *et al.*, "Description and characterization of
the novel hyperthermia- and thermoablation-system MFH®
15 300F for clinical magnetic fluid hyperthermia", Med.
Phys. 31(6), June 2004, 1444 ff., describe, inter alia,
the metrological determination of characteristic curves
which indicate the relationship between the values of
the magnetic field strength ("H field strength values"
20 in kiloamps per meter, kA/m) and of the power
absorption rates based on iron mass SAR_{Fe} ("Specific
Absorption Rate of Iron", in watts per gram, W/g) for
particular magnetic fluids. Further aspects of hyper-
thermia treatment on the basis of magnetic fluids are
25 described (abstract; pages 1445-1446, section
"II. Methods"; page 1447, section "IIIB. Power
Absorption" in conjunction with figure 5; page 1448,
section "IIID. Thermal distribution in the quasi-steady
state"; pages 1449-1450, section "IV. Discussion").

30

Wust *et al.*, "Magnetic nanoparticles for interstitial
thermotherapy - feasibility, tolerance and achieved
temperatures", Int. J. Hyperthermia, December 2006,
22(8), 673-685, describe a concept for hyperthermia
35 treatment on the basis of magnetic fluids. The magnetic
fluid contains iron oxide nanoparticles, dispersed in
water. The magnetic fluid needs to be distributed in
the tumor and is subsequently heated by the application
of a magnetic alternating field by means of an

applicator. Resultant temperature distributions are analyzed. Resultant values for the specific absorption rate in tissue (SAR) are ascertained from the particle distribution determined by means of computed tomography (CT) in combination with specific H field strength values in kA/m. The temperature distribution in the tumor area is calculated numerically by using a bioheat transfer equation (subsequently BHTE). The calculated temperature distribution is matched to directly measured temperature values at reference points in or close to the target area by means of a suitably chosen, average perfusion rate. (Abstract; page 675, section "Magnetic fluid"; page 677, section "Post-implantation analysis (PIA) and Thermotherapy").

Maier-Hauff et al., "Efficacy and safety of intra-tumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme", J. Neurooncol. DOI 10/2007/s11060-010-0389-0, published online on September 16, 2010, describe intratumoral thermotherapy methods using magnetic nanoparticles. A density of the nanoparticles after introduction is ascertained by means of CT methods. On the basis of the density distribution of the nanoparticles, the SAR thereof and an estimated perfusion rate within the tumor area, the generation of heat within the target tissue is determined as a function of a magnetic field strength by using a BHTE. The magnetic field strength (subsequently also called "H field strength" or just "field strength") should be chosen such that a temperature of 43°C is not exceeded outside a border of 2 cm around the tumor. During treatments, direct temperature measurements were taken in a thermometry catheter positioned in advance. This monitors the observance of the limit temperature (abstract; page 3, figure 1 and left-hand column and right-hand column, 1st paragraph).

Nadobny et al., "Evaluation of MR-Induced Hot Spots for

Different Temporal SAR Modes Using a Time-Dependent Finite Difference Method With Explicit Temperature Gradient Treatment", IEEE Transactions on Biomedical Engineering, Vol. 54, No. 10, October 2007, pages 1837 ff., describes the numerical solution to a non-linear BHTE in the time domain, which contains a temperature-dependent perfusion, and this is taken as the basis for performing numerical simulations for the temperature distribution in the human body (abstract; page 1837, section "I. Introduction"; page 1838, section "II. Time-Dependent BHTE"; pages 1840-1841, section IIIC: Thermal Simulation Procedures"; pages 1845-1846, sections "V. Discussion", "VI. Conclusion"). Inter alia, Nadobny *et al.* described a method (called a "decomposition way") according to which the BHTE is numerically solved by using the finite differences (FD) method to split the temperature distribution into a basal and an SAR-dependent part (page 1841, left-hand column, equations 5a, 5b and 6).

20

GENERAL ILLUSTRATION OF THE INVENTION

It is an object of the present invention to propose a tool for preparing thermotherapy which provides a doctor or other medical personnel with a comprehensive overview of different therapy options in order to facilitate a decision in favor of a particular option.

This object is achieved by an inventive computer-aided simulation tool for providing assistance in the planning of thermotherapy, and to be more precise by an inventive computer-aided simulation method for providing assistance in thermotherapy planning and also by computer devices of appropriate design.

35

The invention proposes a computer-aided simulation method for providing assistance in thermotherapy planning. The thermotherapy comprises (local/regional) hyperthermia treatment of a tumor volume in the body

volume of a human body. The hyperthermia treatment comprises the application of a magnetic field in the treatment volume by means of a magnetic field applicator. In this case, thermal energy can be introduced into at least one "deposit volume", i.e. into a volume which contains nanoparticles, by power absorption in the applied magnetic field - by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body beforehand.

10

Accordingly, hyperthermia treatment within the context of the present invention is used generally to denote therapy by means of raised temperature. In the case of relatively small temperature rises up to approximately 45°C, this results in an increase in the effectiveness of chemotherapy and/or radiotherapy, hyperthermia in the narrower sense (Hildebrandt, B., et al. (2002). "The cellular and molecular basis of hyperthermia." Critical Reviews in Oncology Hematology 43(1): 33-56). In the case of temperature rises to more than 45°C, (tumor) cells die off directly, called thermoablation (Jordan, A., et al. (2006). "The effect of thermo-therapy using magnetic nanoparticles on rat malignant glioma." J Neurooncol. 78(1): 7-14. Epub 2005 Nov 29).

25

It is desirable for the deposit volume or the deposit volumes to be situated fully or at least in part within the treatment volume, preferably the tumor volume. This should have been ensured by the preceding instillation of the nanoparticles. The tumor volume or the tumor volumes should be situated fully or in part in the treatment volume, according to the aim of therapy. Hence, the treatment volume is the volume which is meant to be heated by the hyperthermia primarily. Whether and to what extent this aim can probably be achieved is predicted by the inventive simulation method.

35

The inventive method is considered to be a simulation

method for providing assistance in the planning and -
optionally - control of thermotherapy, because it
simulates the temperature distributions in the body
which arise during treatment with the magnetic field
5 applicator without such treatment actually being
performed. The method thus requires no calibration, for
example, by measured values which are measured for a
treatment that is currently taking place. The results
which are delivered by the inventive simulation tool
10 can be used to draw conclusions about treatment
parameters for a subsequent actual treatment, e.g. in
relation to the field strength value or H field
strength value that needs to be chosen.

15 The user of the inventive method or simulation tool may
be a doctor, e.g. a radiologist or a radiotherapist,
personnel with technical and/or medical training who
have been trained to use a magnetic field applicator,
or other users.

20 The nanoparticles may generally be particles which
interact in some way with a magnetic field such that
(following instillation of the particles into the body)
tissue is heated. By way of example, they may be
25 magnetic, paramagnetic or superparamagnetic nano-
particles, e.g. iron oxide nanoparticles with or
without a coating. The particles may have any spatial
forms, and may be at least essentially spherical,
spheroidal, ellipsoidal, prismatic or parallelepipedal
30 in shape, for example. Although the particles are
called 'nanoparticles' here, this term is meant to
cover not only particles having dimensions (e.g.
smallest or largest radius or diameter) in the nano-
meter range but also particles having other dimensions,
35 for example particles having dimensions in the micron
range. Preference is given to iron oxide nanoparticles
having a diameter (determined under an electron
microscope) of up to 100 nm.

The inventive simulation method comprises the following steps: in a first calculation step, also called "T selection" ("T" stands for temperature), calculation of a field strength value or H field strength value that needs to be set on the applicator on the basis of a geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment; in an optional second calculation step, also called "H controller" ("H" stands for magnetic field strength) or "fast H controller" depending on the embodiment, calculation of a (resultant) temperature distribution that is to be expected for at least some of the body volume for each H field strength value from a plurality of prescribed H field strength values, and/or a user-defined H field strength value, preferably, in an optional third calculation step ("H selection"), automatic calculation of a temperature distribution that is to be expected for a maximum admissible H field strength value when the H field strength value calculated in the first calculation step is greater than this maximum admissible H field strength value; and provision (for the user) of the calculated H field strength value that needs to be set on the applicator and optionally of at least one calculated resultant temperature distribution, e.g. that associated with the aforementioned H field strength value, in order to provide assistance for the user in planning the thermotherapy.

30

In particular variants of the inventive simulation method, the prescribed temperature limit value or one of a plurality of prescribed temperature limit values relates to a maximum temperature or a temperature maximum only within the treatment volume that is to be heated. By way of example, the prescribed temperature limit value may relate to a temperature maximum in a range from 60°C to 100°C, preferably 70°C to 90°C, particularly 80°C, in the treatment volume.

In addition or as an alternative, the prescribed temperature limit value or one of a plurality of prescribed temperature limit values may relate to a temperature maximum outside the treatment volume that is to be heated. By way of example, the prescribed temperature limit value may relate to a temperature maximum in a range from 40°C to 45°C, particularly 43°C, outside the treatment volume.

10

In some embodiments of the inventive simulation method, two prescribed temperature limit values which each relate to different volumes are used in the first calculation step. By way of example, one prescribed temperature limit value within the treatment volume may relate to a temperature maximum of 80°C and another prescribed temperature limit value outside the treatment volume may relate to a temperature maximum of 43°C. In this case, the two prescribed temperature limit values can preferably be used simultaneously in the first calculation step.

A third calculation step ("H selection") may involve a temperature distribution that is to be expected being calculated for an H field strength value that is defined as maximum admissible. The H field strength value defined as maximum admissible may relate to an H field strength value that can be set as a maximum on the applicator, for example, or to an H field strength value for a patient that is defined as maximum admissible. The third calculation step can, on the basis of the calculation result of the first calculation step (T selection), be performed automatically when the H field strength value calculated in the first calculation step is greater than the H field strength value defined as maximum admissible.

In particular variants of the inventive simulation

method, no temperature limit value is used in the calculations in the second calculation step (H controller; fast H controller) and/or in the third calculation step (H selection). During these
5 calculations, the possibly resultant simulated temperature distributions may therefore exceed the limit value(s) considered in the first calculation step. For example, temperatures higher than 43°C may thus occur outside the treatment volume and/or
10 temperatures higher than 80°C may thus occur inside the treatment volume. This allows the doctor to have a more comprehensive overview of the effects of the planned thermal therapy than if he had only strictly temperature-limit-value-based results for the
15 calculation from the first calculation step.

The calculations in the second calculation step can be performed for a plurality of prescribed H field strength values that can be set on the applicator,
20 preferably between 3 and 20 H field strength values, particularly between 5 and 10 H field strength values. In addition or as an alternative, the calculations in the second calculation step can be performed for a plurality of prescribed H field strength values that
25 can be set on the applicator, preferably between 3 kA/m and 20 kA/m, particularly preferably between 5 kA/m and 10 kA/m (H controller).

The second calculation step (H controller; fast H
30 controller) can be initiated after the first calculation step (T selection) and possibly the third calculation step (H selection) only by a user input. If the user requires no further orientation after the output of the initial resultant temperature distri-
35 bution with the associated initial H field strength value (in this case, "initially" means the result of the first or possibly the third calculation step), the user can dispense with a user input and in this way it is possible to save or otherwise use resources of the

computer device on which the inventive simulation method is implemented.

Particularly in the case of the calculation of the H field strength value that is to be set in the first calculation step (T selection), variants of the inventive simulation method do not perform numerous iterations on the basis of the "trial and error" principle which involve resultant temperature distributions from chosen field strength values being calculated by means of a numerical solution to the BHTE so as to iteratively arrive at the sought H field strength value. Such iterations in which a BHTE is numerically solved each time require very many resources in terms of computation power, computation time and memory requirement and are therefore not suitable for a simulation tool which is intended to provide a user with an overview of planned therapy options. Instead, the BHTE is numerically solved just exactly twice in the first calculation step, as explained further below.

In one embodiment of the inventive simulation method, the H field strength value is calculated in the first calculation step (T selection) on the basis of a prescribed characteristic curve - for example derived from a reference measurement - which indicates a relationship between (reference) power absorption rate and H field strength.

In one specific variant of this embodiment, the first calculation step has the following steps: calculation of an average power absorption density (or of an equivalent variable) in the applicator magnetic field in the deposit volume, wherein the relative power absorption density (or an equivalent variable) is calculated on the basis of a measured geometric distribution of the nanoparticles, a BHTE describing the model is numerically solved precisely once in order

to obtain a basal temperature distribution without power absorption, and a BHTE describing the model is numerically solved precisely once in order to obtain a relative temperature increment distribution on the basis of the relative power absorption density; and wherein the relative power absorption density is scaled by a temperature-based scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution; calculation, on the basis of the calculated average power absorption density and the calculated mass of the nanoparticles, of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, usually based on the mass of the nanoparticles in W/g; and calculation of an H field strength value on the basis of the calculated reference power absorption rate and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between reference power absorption rate and applied H field strength; furthermore, as an option, calculation of the resultant temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the temperature-based scaling factor.

The basal temperature distribution calculated in the first calculation step and/or the relative temperature increment distribution can be provided for at least one further use beyond the first calculation step, for example can be stored in the main memory and/or on a hard disk. By way of example, the use may relate to the fast calculation, in the second calculation step (for the "fast H controller" embodiment), of a resultant temperature distribution on the basis of an H field strength value that has been input by the user, without the BHTE needing to be numerically solved again in

order to obtain the temperature distribution and/or the relative temperature increment distribution.

5 In the second calculation step in the "fast H controller" embodiment, regardless of the number of prescribed and/or user-defined H field strength values, a provided (previously calculated in the first calculation step) basal temperature distribution and/or provided (previously calculated in the first
10 calculation step) relative temperature increment distribution can be used, for example the aforementioned temperature distributions (basal and relative incremental) which are provided from the first calculation step. Hence, it is possible to prevent the
15 BHTE from being numerically solved again - which is intensive in terms of memory and computation time - for the calculation of the basal and/or relative incremental temperature distribution.

20 In particular embodiments of the inventive simulation method ("H controller" embodiment), the second calculation step is designed such that the basal temperature distribution and the relative incremental temperature distribution are not used from the main
25 memory or from the hard disk but rather need to be recalculated as part of the second calculation step by numerically solving the BHTE. In this case, regardless of the number of prescribed and/or user-defined H field strength values, the BHTE is numerically solved no more
30 than twice, namely once to calculate the basal temperature distribution and once to calculate the relative temperature increment distribution.

In variants of the inventive simulation method, in the
35 second calculation step (H controller, fast H controller) the resultant temperature distribution that is to be expected is calculated by means of power-absorption-based scaling ("K") of a calculated or provided relative temperature increment distribution.

Specific embodiments of the simulation method comprise the following steps in the second calculation step (H controller, fast H controller): calculation of a relative power absorption density distribution (or of an equivalent variable) and a relative average power absorption density (or an equivalent variable) on the basis of a measured geometric distribution of the nanoparticles; provision of a basal temperature distribution on the basis of a numerical solution to a BHTE describing the model without power absorption, and provision of a relative temperature increment distribution on the basis of a numerical solution to a BHTE describing the model with the calculated relative power absorption density distribution [the provision is made by reading in the previously stored distributions (for the "fast H controller") or by numerically solving the BHTE again (for the "H controller")]; performance of the following steps for each H field strength value from the plurality of prescribed H field strength values and/or the user-defined H field strength value: calculation of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective H field strength value and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between reference power absorption rate and applied H field strength; calculation, on the basis of the reference power absorption rate and the calculated mass of the nanoparticles in the deposit volume, of an average power absorption density; power-absorption-based scaling, i.e. calculation of a power-absorption-based scaling factor on the basis of the respective average power absorption density and the relative power absorption density; calculation of a respective resultant temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the power-

absorption-based scaling factor.

According to the invention, a further computer-aided simulation method (T selection) for providing
5 assistance in thermotherapy planning is proposed. The thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body. The hyperthermia treatment comprises the application of a magnetic field in a treatment volume by means of a
10 magnetic field applicator. Thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The simulation method
15 relates to the calculation of an H field strength that needs to be set on the applicator on the basis of a geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment
20 (T selection). The H field strength value is calculated on the basis of a prescribed characteristic curve - for example derived from a reference measurement - which indicates the relationship between power absorption rate and H field strength.

25 In one particular embodiment, the simulation method has the following steps: calculation of an average power absorption density (or of an equivalent variable) in the applicator magnetic field in the deposit volume,
30 wherein a relative power absorption density is calculated on the basis of a measured geometric distribution of the nanoparticles, a BHTE describing the model is numerically solved precisely once in order to obtain a basal temperature distribution without
35 power absorption, and a BHTE describing the model which is numerically solved precisely once in order to obtain a relative temperature increment distribution on the basis of the relative power absorption density; and wherein the relative power absorption density is scaled

by a temperature-based scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution;

5 calculation, on the basis of the calculated average power absorption density and the calculated mass of the nanoparticles, of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nano-

10 particles, for example; calculation of an H field strength value on the basis of the calculated reference power absorption rate and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between

15 reference power absorption rate and applied H field strength; preferably, calculation of the resultant temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the temperature-based

20 scaling factor; and provision of the calculated H field strength value and optionally the resultant temperature distribution associated with said H field strength value, calculated as described above, in order to provide assistance for the user in planning the thermo-

25 therapy.

The invention proposes yet a further computer-aided simulation method (H controller; fast H controller) for providing assistance in thermotherapy planning. The

30 thermotherapy comprises hyperthermia treatment of a tumor volume in the body volume of a human body. The hyperthermia treatment comprises the application of a magnetic field in a treatment volume by means of a magnetic field applicator. Thermal energy can be

35 introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The simulation method relates to the calculation, for each H field strength

value from a plurality of prescribed H field strength values and/or a user-defined H field strength value, of a temperature distribution that is to be expected for at least some of the body volume (H controller). The

5 temperature distribution that is to be expected is calculated by means of power-absorption-based scaling of a calculated or provided relative temperature increment distribution.

10 In particular variants, regardless of the number of prescribed and/or user-defined H field strength values, e.g. in order to avoid numerically solving the BHTE again, a previously calculated (in the T selection step) basal temperature distribution and/or a

15 previously calculated (in the T selection step) relative temperature increment distribution is/are used (fast H controller). In addition or as an alternative, it is possible - regardless of the number of prescribed and/or user-defined H field strength values - for a

20 BHTE describing the model to be numerically solved never (fast H controller), once (H selection) or no more than twice (H controller) in order to subsequently determine the resultant temperature distribution. In the "never" case (fast H controller), the resultant

25 temperature distribution is compiled from the basal temperature distribution - previously calculated (earlier calculation steps) by means of BHTE - and the previously calculated relative temperature increment distribution by means of power-absorption-based

30 scaling. In the "once" case (H selection), the resultant temperature distribution is numerically calculated directly, i.e. without splitting into basal and incremental components, by solving the BHTE. In the "twice" case (H controller), the basal and incremental

35 temperature distributions are numerically calculated in this (second) calculation step individually by solving the BHTE and are then compiled to produce the resultant temperature distribution by means of power-absorption-based scaling.

In particular embodiments, the simulation method has the following steps: calculation of a relative power absorption density distribution (or of an equivalent variable) and a relative average power absorption density (or an equivalent variable) on the basis of a measured geometric distribution of the nanoparticles; provision of a basal temperature distribution on the basis of a numerical solution to a BHTE describing the model without power absorption, and provision of a relative temperature increment distribution on the basis of a numerical solution to a BHTE describing the model with the calculated relative power absorption density distribution; performance of the following steps for each H field strength value from the plurality of prescribed H field strength values and/or the user-defined H field strength value: calculation of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective H field strength value and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between reference power absorption rate and applied H field strength; calculation, on the basis of the reference power absorption rate and the calculated mass of the nanoparticles in the deposit volume, of an average power absorption density; power-absorption-based scaling, i.e. calculation of a power-absorption-based scaling factor on the basis of the respective average power absorption density and the relative power absorption density; calculation of the respective resultant temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the power-absorption-based scaling factor; provision of the calculated temperature distributions in order to provide assistance for the user in planning the

thermotherapy.

The invention also proposes a computer program which prompts the execution of one of the simulation methods described herein when the computer program is executed on a programmable computer device, for example a computer in a clinic or doctor's practice. The computer program may be stored or present in stored form on a machine-readable data storage medium, for example a permanent or rewritable medium in or associated with a programmable computer device or a CD-ROM, DVD or a USB stick. In addition or as an alternative, the computer program can be provided for download onto a programmable computer device, for example via a data network such as the Internet or a communication link such as a telephone line and/or a wireless connection.

Furthermore, the invention provides a computer device which is designed to provide assistance in thermotherapy planning. In this case, the thermotherapy comprises hyperthermia treatment of a tumor volume in the body volume of a human body, wherein the hyperthermia treatment comprises the application of a magnetic field in the treatment volume by means of a magnetic field applicator. In this case, thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The computer device has the following components: a first calculation component which is designed to calculate an H field strength value that needs to be set on the applicator on the basis of a geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment; a second calculation component which is designed to optionally calculate a temperature distribution that is to be expected for at least some of the body volume for each

H field strength value from a plurality of prescribed H field strength values, and/or a user-defined H field strength value; an optional third component designed to calculate a temperature distribution that is to be expected for a maximum admissible H field strength value when the H field strength value calculated in the first calculation step is greater than this maximum admissible H field strength value; and a component for providing (the user with) the calculated H field strength value that needs to be set on the applicator and optionally at least one calculated temperature distribution (e.g. associated with the aforementioned H field strength value) in order to provide assistance for the user in planning the thermotherapy.

A further inventive computer device ("T selection") is designed to provide assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body and wherein the hyperthermia treatment comprises the application of a magnetic field in a treatment volume by means of a magnetic field applicator. In this case, thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The computer device has a component which is designed to calculate an H field strength that needs to be set on the applicator on the basis of a geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment. In this case, the component has a module for calculating the H field strength value on the basis of a prescribed characteristic curve - for example derived from a reference measurement - wherein the characteristic curve indicates a relationship between power absorption rate and H field strength. In one preferred inventive variant of the computer device,

the computer device has the following modules: a module for calculating an average power absorption density in the applicator magnetic field in the deposit volume, wherein a relative power absorption density is
5 calculated on the basis of a measured geometric distribution of the nanoparticles, a BHTE describing the model is numerically solved precisely once in order to obtain a basal temperature distribution without power absorption, and a BHTE describing the model is
10 numerically solved precisely once in order to obtain a relative temperature increment distribution on the basis of the relative power absorption density; and wherein the relative power absorption density is scaled by a temperature-based scaling factor which is obtained
15 on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution; a module for calculating, on the basis of the calculated average power absorption density and the calculated mass of the
20 nanoparticles, a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example; a module for calculating an H field strength value on the basis of the calculated reference
25 power absorption rate and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between reference power absorption rate and applied field strength; optionally, a module for calculating the
30 resultant temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the temperature-based scaling factor; a module for providing the calculated field strength value in order to provide
35 assistance for the user in planning the thermotherapy; and optionally a module for providing the resultant temperature distribution associated with the calculated H field strength value in order to provide assistance for the user in planning the thermotherapy.

A further inventive computer device ("H controller", "fast H controller") is designed to provide assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body and wherein the hyperthermia treatment comprises the application of a magnetic field in a treatment volume by means of a magnetic field applicator. In this case, thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body. The computer device has a component which is designed to calculate, for each field strength value from a plurality of prescribed field strength values and/or a user-defined field strength value, a temperature distribution that is to be expected for at least some of the body volume. In this case, the component has a module for calculating the temperature distribution that is to be expected by means of power-absorption-based scaling of a calculated or provided temperature increment distribution. Preferably, the component is designed to calculate the temperature distribution that is to be expected in order to use, regardless of the number of prescribed and/or user-defined H field strength values, a provided (previously calculated in the T selection step) basal temperature distribution and/or a provided (previously calculated in the T selection step) relative temperature increment distribution (fast H controller).

With further preference, the component for calculating the temperature distribution that is to be expected is designed to calculate, regardless of the number of prescribed and/or user-defined field strength values, no more than two temperature distributions (H controller), namely a basal temperature distribution and/or a relative temperature increment distribution.

With further preference, the inventive computer device has the following modules ("H controller", "fast H controller"): a module for calculating a relative power
5 absorption density distribution and a relative average power absorption density on the basis of a measured geometric distribution of the nanoparticles; a module for providing a basal temperature distribution on the basis of a numerical solution to a BHTE describing the
10 model without power absorption, and providing a relative temperature increment distribution on the basis of a numerical solution to a BHTE describing the model with the calculated relative power absorption density distribution; a module for performing the
15 following steps for each H field strength value from the plurality of prescribed H field strength values: calculation of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles,
20 for example, wherein the calculation is based on the respective H field strength value and a prescribed characteristic curve - for example derived from a reference measurement - which relates to a relationship between reference power absorption rate and applied H
25 field strength; calculation, on the basis of the reference power absorption rate and the calculated mass of the nanoparticles in the deposit volume, of an average power absorption density; power-absorption-dependent scaling, i.e. calculation of a power-
30 absorption-based scaling factor on the basis of the respective average power absorption density and the relative power absorption density; calculation of a respective resultant temperature distribution on the basis of the basal temperature distribution, the
35 relative temperature increment distribution and the power-absorption-based scaling factor; and a module for providing the calculated temperature distributions in order to provide assistance for the user in planning the thermotherapy.

Furthermore, the invention proposes a system which comprises a computer device as outlined above and a magnetic field applicator or the parts thereof. The inventive computer device may be designed for use with the magnetic field applicator, for example by virtue of the use of, by way of example, an H field strength that can be set on the applicator as a maximum and/or metrological input data, such as a characteristic curve derived from a reference measurement, for example, for the power absorption on the basis of the H field strength. The magnetic field applicator can be matched to the inventive computer device by virtue of the applicator accepting data from said applicator, such as an H field strength value that needs to be set (for example after the end of the simulations as a default value and/or by the instigation of the user). For this embodiment, the computer device can also be used for planning or control.

The invention also proposes a system which comprises a computer program as outlined above, a data storage medium as outlined above, a computer device as outlined above or a system as outlined above, and which also comprises a magnetic fluid which contains magnetic nanoparticles. The inventive computer program may match the use of the magnetic fluid by virtue of the power absorption v. H field strength for this specific characteristic curve being used for the simulations. The computer program may be designed for the use of a plurality of magnetic fluids; in this case, the user would need to input the fluid that is actually to be used before the start of the simulations, for example by selecting from a menu in a GUI of the computer device.

Instead of in a magnetic fluid, the nanoparticles could, in principle, also be instilled into the body of the patient in another form of presentation. All forms

of presentation are intended to be covered by the invention.

A further subject of the invention comprises a method
5 for controlled heating of an organ or tissue, having
the following steps: introduction of magnetic, para-
magnetic and/or superparamagnetic nanoparticles into an
organ volume or tissue volume; ascertainment of the
10 nanoparticle quantity and/or distribution in the organ
volume or tissue volume; calculation of an H field
strength that needs to be set on the basis of one of
the appropriate methods outlined above or of a
resultant temperature distribution on the basis of one
of the appropriate methods outlined above; and
15 deposition of thermal energy by means of application of
a magnetic field, wherein the applied H field strength
is set, which corresponds to the calculated field
strength or to the field strength derived from a
calculated temperature distribution, in each case with
20 a deviation of $\pm 10\%$, preferably $\pm 5\%$, particularly
 $\pm 1\%$. This method can be performed *in vitro* if
appropriate.

A method for treating a tumor in a patient contains the
25 following steps: introduction of a suitable quantity of
magnetic, paramagnetic and/or superparamagnetic nano-
particles into a tumor volume; ascertainment of the
nanoparticle quantity and/or distribution in the tumor
volume; calculation of a field strength that needs to
30 be set on the basis of one of the appropriate methods
outlined above or of a resultant temperature
distribution on the basis of one of the appropriate
methods outlined above; deposition of thermal energy by
means of application of a magnetic field, wherein the
35 applied field strength is set, which corresponds to the
calculated field strength or the field strength derived
from a calculated temperature distribution, in each
case with a deviation of $\pm 10\%$, preferably $\pm 5\%$,
particularly $\pm 1\%$.

Suitable methods for treating tumors or for controlled heating of an organ or tissue by means of suitable nanoparticles and application of a magnetic field that are able to be improved by the inventive simulation methods are known from the prior art. For example, Maier-Hauff et al. (2010, supra) describe a successful study on 66 patients with brain tumors, 59 of them with glioblastoma. Furthermore, similar methods were successfully performed on prostate carcinoma patients (Johannsen, M., et al. (2007), Eur Urol. 52(6): 1653-61. Epub 2006 Nov 17; Johannsen, M., et al. (2010), Int J Hyperthermia 26(8): 790-5.) and also in a study in which patients with various tumors, namely chondrosarcoma, rectal carcinoma, cervical carcinoma, rhabdomyosarcoma, parapharyngeal sarcoma and prostate carcinoma, were included and treated (Wust, P., et al. (2006), Int J Hyperthermia. 22(8): 673-85.). Clinical data from suitable methods are summarized in Thiesen, B. and A. Jordan (2008, Int J Hyperthermia. 24(6): 467-74). Further methods for the treatment of tumors or for the controlled heating of an organ or tissue by means of suitable nanoparticles and application of a magnetic field are known from US 20080268061, US 20110052609, WO 2009/100716 and WO 2011/082796.

Solid tumors are preferred, particularly local and locally advanced tumors, or systemic tumor diseases, which cause local problems such as inoperable metastases. Examples are brain tumors, e.g. glioblastoma and astrocytoma, brain metastases, prostate cancer, pancreatic cancer, hepatocellular carcinoma, throat and neck tumors, cancer of the bladder, stomach cancer, intestinal cancer, renal cell carcinoma, ovarian carcinoma, cervical carcinoma, sarcomas, basal cell carcinoma and melanoma.

The inventive methods for the controlled heating of an organ or tissue can be used for the treatment of

arthrosis, arthritis and other rheumatic joint diseases, for example. The treatment of these diseases by means of similar methods is known from WO 01/13949, for example.

5

ADVANTAGES OF THE INVENTION

The invention provides the user with extensive opportunities for obtaining an overview of various
10 therapy options and the effects thereof and planning the therapy accordingly. To this end, the inventive simulation tool automatically provides a temperature distribution which has been calculated on the basis of a maximum field strength, but taking account of
15 prescribed/input temperature limit values. The invention allows two (or more) limit values to be taken into account, e.g. a maximum temperature outside the treatment area, in order to look after the healthy tissue, and/or maximum temperature inside the treatment
20 area, in order to destroy the tumor but nevertheless to limit an input of power into the body of the patient. In principle, it is conceivable to prescribe a geometric temperature limit value distribution which takes account of special features specific to tissue,
25 for example.

The inventive simulation tool may be "intelligent" in the sense that it rejects the resultant field strength value if it is greater than a maximum settable value on
30 the applicator/for a given patient, for example. In this case, the simulation tool calculates a new temperature distribution afresh on the basis of the maximum settable field strength value.

35 The user can decide whether he wishes to use the field strength value resulting therefrom without performing further simulations. As a result, the inventive simulation tool provides the experienced user with the opportunity to terminate the planning without wasting

resources. It is then already possible to use the simulation tool for the next patient, for example.

5 The user can also decide to obtain a more extensive overview. In this case, the simulation tool can calculate temperature distributions for a plurality of field strength values, for example. These calculations can be performed in the background as soon as the user has made an appropriate input (if applicable, the
10 simulation tool can also be configured such that it automatically starts these calculations in the background after the initial temperature distribution has been provided). It is therefore already possible for the user to work with the results from the first
15 calculation step without delay.

These temperature distributions do not take account of the temperature limit values discussed above. Hence, the user is in this case provided with an extensive
20 decision basis by means of the effects of particular field strength settings and, depending on the aim of the therapy, the severity of the disease, the tissue that is possibly affected, etc., may under some circumstances decide upon a therapy option in which the
25 temperature limit value or the limit values are not observed everywhere.

In addition or as an alternative, the simulation tool accepts a field strength value that is input by the
30 user and calculates the resultant temperature distribution for said field strength value. In particular embodiments of the invention, this is accomplished in time-saving fashion without numerically solving the BHTE again, which means that the result is
35 available to the user essentially without any waiting time, for example after just one second or less.

By means of the inventive simulation tool, the aim of therapy and possible side effects can thus be predicted

better and more easily and can thus also be controlled better and more extensively.

In this case, the inventive simulation tool requires -
5 both for calculating the temperature distribution using
prescribed temperature limit values (first calculation
step, see below temperature selection or "T selection")
and for calculating a scale of temperature
distributions or a user-defined field strength value
10 (second calculation step, see below H field strength
controller, "H controller" or "fast H controller") -
precisely two numerical solutions to a BHTE with
subsequent scaling, that is to say manages without
iterative trial and error approximations (by means of
15 recurrently restarted numerical solutions to the BHTE)
to the sought field strength value in the first step
and calculate the relevant temperature distributions by
means of simple scaling for an arbitrary number of
field strength values, in principle, in the second
20 step. As a result, the simulation tool is user friendly
because the calculation results are available extremely
precisely and nevertheless quickly. The inventive
simulation tool requires only a fraction of the CPU
computation time in comparison with an iterative trial
25 and error approach and therefore makes a clinically
feasible application possible in the first place, even
using computers which are older/have limited resources.

BRIEF DESCRIPTION OF THE FIGURES

30

Further aspects and advantages of the invention will
now be described in more detail with reference to the
appended figures, in which:

35 Figure 1 shows a flowchart for a general program cycle
from a first exemplary embodiment of an
inventive simulation tool having the
following main steps: "patient data", "image
fusion", "segmentation", "temperature simul-

ation" and "therapy plan". In the main step, "temperature simulation", the "temperature simulator" program package (called "simulator" for short) is called. In the first exemplary embodiment (figure 1 to figure 5), the simulator package contains three autarkic simulator (execution) programs (.exe), but the simulator can also be executed as a linkable program library having three main subroutines ("mainsubroutines") (see second exemplary embodiment figure 6 to figure 9);

Figure 2 shows a flowchart for a program cycle from a first exemplary embodiment of an inventive simulator, having a stipulated sequence of calls to the simulator programs;

Figure 3 shows a flowchart for a program cycle from the simulator from figure 2 in what is known as mode 2 (execution program "sim_h.exe": selection of the H field strength, "H selection" for short;

Figure 4 shows a flowchart for a program cycle from the simulator from figure 2 in mode 1 (execution program "sim_t.exe": temperature selection, "T selection" for short);

Figure 5 shows a flowchart for a program cycle from the simulator from figure 2 in mode 3 (execution program "sim_hr.exe": what is known as an H field strength controller, "H controller" for short);

Figure 6 shows a flowchart for a program cycle from a second exemplary embodiment of an inventive simulator, having a stipulated sequence of calls to the simulator main subroutines;

Figure 7 shows a flowchart for a program cycle from one of the three main subroutines of the simulator from figure 6 in mode 2, namely
 5 "mainsubroutine sim h voxel win"
 (H selection);

Figure 8 shows a flowchart for a program cycle from one of the three main subroutines of the simulator from figure 6 in mode 1, namely
 10 "mainsubroutine sim t voxel win"
 (T selection); and

Figure 9 shows a flowchart for a program cycle from one of the three main subroutines of the simulator from figure 6 in mode 3, namely
 15 "mainsubroutine sim hr voxel win" (what is
 known as a "fast H controller").

20 EXEMPLARY EMBODIMENTS OF THE INVENTION

The text below describes a first exemplary embodiment of an inventive simulation tool in more detail. Figure 1 shows a schematic representation of a program cycle
 25 from an inventive simulation method in the form of a piece of simulation software which has been developed with the aim of providing assistance in NanoTherm® therapy.

30 The software provides the treating doctor (neurosurgeon, radiologist) with orientation assistance during thermotherapy for malignant tumors, such as brain tumors, in order to estimate the treatment temperatures and the magnetic field strength required
 35 therefor on the basis of a BHTE that describes the model.

In order to estimate the therapy field strength, the software provides the opportunity to import and

register image data in DICOM format, e.g. from MRI and CT scans. It is likewise possible to perform contouring operations on all image files used (segmentation).

- 5 The software takes the user to the result in steps by querying the required parameters. This involves firstly 3D visualization, which reveals the contoured areas such as a tumor, a catheter and nanoparticle deposits. Secondly, an estimate of the temperature distribution
10 in the denoted areas on the basis of field strength and therapy time is shown. This is particularly important for areas which can be treated only to a restricted degree, such as in the head on a frontobasal basis in the area of the optic chiasma (hypothalamus), the
15 sylvian fissure, in which the vascular tree of the middle cerebral artery runs, the corpus callosum or the brain stem.

- The data that are input and the simulations that are
20 produced can be stored and printed, and various scenes can be produced per patient. The simulation tool thus provides assistance for the doctor or user in preparing the therapy plan. By way of example, the therapy plan is released by a signature from the doctor who is
25 responsible on the printed therapy proposal. The simulation results presented in the therapy proposal can be used for orientation purposes and do not need to make any particular demands on accuracy.

- 30 The simulation software can be operated on a customer's own hardware, and appropriate minimum requirements need to be met. The ambient conditions correspond to those of an environment for the application of medical software.

35

Overview of the first exemplary embodiment

As a program package, the software comprises a "temperature simulator" (subsequently also called "simulator" for short). Following the introduction of

magnetic fluid into a tumor, the simulator allows simulation of the temperature distribution in the body area on the basis of the magnetic field strength of the therapy appliance (applicator). The simulator
 5 calculates a particular field strength as part of a nonbinding recommendation. To perform the therapy, it is additionally possible to take temperature measurements during the therapy, as a result of which simulation results and temperature measurements
 10 together can form the basis for assessment of the therapy by the doctor, said temperature measurements preferably being influential. Naturally, the simulation results are neither a prerequisite for therapy being able to be performed nor binding for performance.

15 Figure 1 shows the main steps of a program cycle. The "simulator" program package is called in a main step "temperature simulation". The following main tasks are performed by the simulator:

- 20 • Simulation of the three-dimensional temperature distribution which probably results from the application of the magnetic field to superparamagnetic or ferrimagnetic nanoparticles, for example, on the assumption of a simplified physical model
 25 (this is described more precisely below); and
- estimation of the H field strength, for example on the basis of particular temperature selections for the patient model.

30 The simulator package is not directly part of the core of the simulation software, but rather is linked to the core by means of a firmly defined external I/O interface as part of external SOUP ("Software of
 35 *Unknown Provenance*").

The simulator package comprises three independent simulator programs `sim_t`, `sim_h` and `sim_hr`, which are described in FORTRAN77 (execution programs "`sim_t.exe`",

"sim_h.exe" and "sim_hr.exe"). The order of the calls to the simulator programs and the management of the simulator data are undertaken by the core of the simulation software, in this case called the "main program core". The main program core also manages all other main steps which have been shown in figure 1, such as image fusion, segmentation, inter alia. In this first exemplary embodiment, the data interchange between the core and the simulator, including the output of program termination messages, is effected by reading/writing from/to a hard disk directory.

The "temperature simulation" program main step in detail

The time sequence of the calls to the simulator programs in the "temperature simulation" main step is controlled or managed from the main program core and can take place on the basis of a scheme as shown in figure 2.

20

It is stipulated that after a respective change of user in the GUI ("Graphical User Interface") upon a change from the segmentation menu to the temperature simulation menu, the T selection program sim_t.exe starts first in this menu (mode = 1). This program automatically (i.e. without any input by the user) has the following two limit temperature selections to comply with:

- 43°C maximum outside the PTV ("non-PTV 43°C limit")
- 80°C maximum everywhere else, i.e. *de facto* inside the PTV ("whole-body 80°C limit").

In this case, PTV ("planning target volume") denotes the treatment area/treatment volume, i.e. the volume that is to be treated or to be heated. This can be stipulated by the user in the segmentation main step (the simulation software can, for example on the basis of manually performed tumor contouring, make a proposal for the treatment volume, for example tumor volume plus

border, which can be accepted or altered by the user, that is to say can be restricted or expanded, for example). A temperature value of 43°C is implemented as a threshold temperature, above which damage to the healthy tissue can increasingly occur, which needs to be avoided as far as possible. A temperature value of 80°C is implemented as a general temperature limit which must not be exceeded throughout the body, that is to say not even in the tumor volume, for example; this simultaneously limits the power absorption by the body as a whole. Of the two limit conditions, the one which occurs at the lower H field strength becomes effective.

However, it should be noted that the limit values of 43°C and 80°C are applied to the treatment of tumors in a body volume such as the human head, for example. Hyperthermia treatments relating to other body volumes, such as the prostate area, may be oriented to the observance of other limit values. By way of example, the limit value in the PTV may be 100°C instead of 80°C for thermotherapy on a prostate tumor.

Following the execution of `sim_t.exe`, the simulation software first of all examines internally, i.e. without the user being notified of the values by GUI, what the level of the H field strength value that is output internally as a `sim_t` output is. If this value is greater than 15 kA/m (kiloamps per meter), a pass of `sim_h.exe` (mode 2) starts automatically (without the user needing to make any input) with the selection 15 kA/m (H selection), where 15 kA/m is the maximum H field strength value that can be set on the magnetic field applicator.

If the `sim_t.exe` output value is less than or equal to 15 kA/m, it is not necessary for a `sim_h.exe` program run to be automatically started, and the next step follows directly.

In this next step, the temperature distribution and the following values are output graphically to the GUI:

- the H field strength recommendation (the output from `sim_t.exe` or 15 kA/m from the automatic `sim_h.exe` run); this output is provided in the GUI window; and
- the maximum temperature reached outside the PTV, and also the maximum temperature reached in the treatment area, and also possibly further output variables; this output is provided in a popup window.

10

There may be cases in which the prescribed temperature of 43°C, for example, outside the PTV is not reached, specifically when the limit condition of 80°C in the PTV has already been reached at a lower H field strength value.

15

On the basis of the output of the initial result as described above, the user can prompt the "H controller" or field strength controller `sim_hr.exe` (mode = 3) to be started (in other exemplary embodiments, the field strength controller can also be started automatically). The system performs these calculations in the background, so that the user has the opportunity to look at the initially ascertained temperature distribution in the meantime. Optionally, the user can skip the start of the H controller, or can terminate the calculation in due fashion.

25

In the configuration example described here, the H controller calculates ten temperature distributions for the following fixed values of the H field strength (multiple H selection): 5 kA/m, 6 kA/m, 7 kA/m, 8 kA/m, 9 kA/m, 10 kA/m, 11 kA/m, 12 kA/m, 13 kA/m and 14 kA/m. This covers the entire range of settings for the applicator used in this example in steps of 1 kA/m. When the pass has taken place, the user is provided with the opportunity to look at the temperature distributions for these H field strength values by means of the setting of a position on the relevant bar.

35

The indicated list of H field strength values relates to the treatment of glioblastomas in the head, for example. Other values can be prescribed for treatments
5 in other body areas or volumes. By way of example, for the treatment of prostate tumors, a step size of just 0.5 kA/m can be prescribed for values between 2 kA/m, 2.5 kA/m, ..., 8 kA/m.

10 The H controller has no kind of limits for the temperatures reached (other than `sim_t.exe` in the initial run). Therefore, there may be cases in which the temperatures reached are higher (or lower) than 80°C in the calculation area and/or higher (and/or
15 lower) than 43°C outside PTV.

If the user wishes to obtain yet a further review besides the field strength recommendation of `sim_t.exe` and possibly the ten results for the H controller, he
20 has the option of manually typing the desired input H field strength value in a GUI window. The calculation then starts in the H selection mode (`sim_h.exe`). He can repeat this as desired.

25 In the H selection mode, there are no kind of limits in respect of the temperatures reached (other than `sim_t.exe` in the initial run). Therefore, there may be cases in which the temperatures reached are higher (or lower) than 80°C in the calculation or treatment area
30 and/or higher (and/or lower) than 43°C outside the PTV.

Furthermore, the user can return to the segmentation step at any time in order to make corrections on the PTV or other segmentation corrections. In this case,
35 the simulator changes to the initial state. As soon as a new segmented data record (what is known as a "labeled volume" or LV data record, see below) is available and the user changes from the segmentation step to the temperature calculation menu, the whole

procedure is repeated, i.e. the simulator starts with the sim_t.exe initial run.

General technical approach

5 The production of the temperature rise by nanoparticles in the magnetic field is notionally split into two steps:

1. In a first step, the nanoparticles in the magnetic
10 field prompt a local power absorption, indicated by a power absorption density (W/m^3) or rate (W/kg), in this case denoted generally by SAR ("Specific Absorption Rate");

15 2. In a second step, this SAR acts as a (main) source of the temperature rise.

The simulation of temperatures which are obtained from values of the H field strength is split into two main
20 steps in the simulator:

1. Ascertainment of an SAR distribution for a given H field strength by what is denoted here as an "SAR solver" (i.e. an appropriate calculation component or a
25 calculation module); and

2. Ascertainment of the temperature distribution ("T distribution") from the SAR distribution (in what is known as the "T solver").
30

In the SAR solver introduced above, the SAR is determined from metrological data, for example on the basis of a CT (computed tomography) data record with marked magnetic fluid deposits (see below) and a
35 metrologically ascertained dependency of the iron core SAR on the H field strength. Physical approximations can be used for implementation, as are presented in Gneveckow et al. 2004, for example.

In the T solver, a time-dependent BHTE is numerically solved using finite differences by taking account of particular circumstances of the application with magnetic fluids. The T solver can use explicit
5 temperature gradients, as are described in Nadobny et al. 2007, appendix, for example.

In the simulator package, the SAR solver and the T solver do not form separate program units, but rather
10 are merged to form a joint program, with the SAR and T solver components being "mixed" in different ways among one another in the program cycle depending on the selection mode. This is described more precisely below.

15 The geometric shape of the SAR distribution (and consequently of the temperature distribution) is highly dependent on the geometric positions of the nanoparticles or deposits of the magnetic fluid ("nanodeposits", "deposit volumes") which are latched
20 in the tissue. These nanoparticle positions need to be communicated to the simulator as an input in order to determine the SAR. To this end, a segmented (e.g. binary) three-dimensional data record (in this case denoted as "LV.raw", LV standing for "labeled volume",
25 see below) with marked nanoparticles which is produced on the basis of the planning CT needs to be made available to the simulator in the preceding main step "segmentation". Furthermore, the values of the Hounsfield units at the locations of the nanoparticles
30 need to be known. This is accomplished by reading in the binary CT file CT.raw.

The power absorption of the nanoparticles in the magnetic field can be represented in the simulator in
35 different ways. A specific power absorption can be quantified by a power absorption rate ("Specific Absorption Rate", SAR) in units of watts per kilogram or gram (W/kg or W/g), the mass which needs to be set in this case being the magnetically effective mass,

that is to say the mass of the magnetic fluid (in this case the SAR is usually indicated in W/kg) or the iron mass in the case of nanoparticles with an iron core (in this case the SAR is usually indicated in W/g), for example. Instead of using a rate, a specific power absorption can also be indicated via a power absorption density in units of watts per cubic meter or cubic centimeter (W/m^3 or W/cm^3). If a specific power absorption density is involved, the volume would be approximately the volume of the magnetic fluid.

A specific reference power absorption rate or density can relate to the (measured) power absorption of a magnetic fluid with a carrier (for example water) and the nanoparticles "dissolved" therein, for example. In this case, the quantity of the nanoparticles in the carrier is known extremely precisely for such a reference measurement (e.g. in molar mass). The reference statement thus relates to a magnetic fluid in the reference state prior to instillation. The iron core SAR "SAR_{fe}" used here is one such reference statement which is usually based on the iron mass and is indicated in W/g.

The actual power absorption ("Absorbed Power Rate" or "Absorbed Power Density", APD, in W/m^3) in the tissue is dependent on the density of the magnetically effective (masses of the) nanoparticles which is present in said tissue. Hence, the actual or tissue-specific power absorption in the tissue is altered in comparison with the specific reference power absorption in this manner on the basis of density; in general, the nanoparticles in the tissue are present in a lower density than the reference magnetic fluid (they are "diluted"). In order to limit the amount of terms used, the use of APD should be avoided. Even for the actual power absorption, we therefore continue to refer to the SAR or a spatial SAR distribution SAR (x,y,z), for example, even if, strictly speaking, the unit W/m^3

should be used. The language use is justified insofar as the conversion from SAR to APD or vice versa is a simple matter for the simulator: the actual density of the (iron mass of the) nanoparticles per voxel is known, being derived from the CT data (e.g. grayscale values in HU). The (specific/actual) power absorption rate and power absorption density can also each be converted into one another by a density factor (magnetically effective mass density in the magnetic fluid/in the tissue following instillation). In this sense, we also refer to a volume SAR in this case. Hence, the terms "SAR" and "volume SAR" are equivalent to the term power absorption density, and the issue of the form in which the data are kept by the simulator is one of numerical optimization, unlike in the case of the "(reference) power absorption rate", e.g. the SAR_{fe}, which is based on the mass of the nanoparticles in W/g.

In other words, the term "power absorption density" as used here relates to a (volume) SAR, while the term "(reference) power absorption rate" relates to a reference variable that is determined metrologically outside the body (*in vitro*), like SAR_{fe}.

A volume SAR can thus be understood to mean either a power absorption rate in W/kg that is deposited in the body or a power absorption density in units of W/m³ (watts per cubic meter), for example, that is deposited in the body. In addition, a (reference) SAR rate or (reference) power absorption rate is also used which is indicated in units of W/kg (watts per kilogram), W/g (watts per gram), etc., for example.

According to general language use, the supplementary "distribution" is occasionally omitted. A statement may thus be a location-dependent distribution, that is to say SAR (x,y,z), or a location-independent value, for example an average power absorption density such as the

volume SAR SAR_aver. Whether or not a distribution is present is evident to a person skilled in the art from the general context.

5 Re the functionality of individual components or modules in the first exemplary embodiment

Depending on the input or selection mode, the simulator execution program "sim_t.exe", "sim_h.exe" or "sim_hr.exe" is called from the main program of the
10 simulation software in a particular order in time. Possible orders have already been discussed above.

The simulator provides two ways or options for ascertaining (simulating) an absolute temperature
15 distribution:

- Using the "H selection" ("H" symbolizes H field strength). The absolute value of the field strength H is prescribed (typically in kA/m). The temperature distribution $T(x,y,z)$ (in °C) is sought.
20
- Using the "T selection" ("T" stands for temperature). Temperature limit values T_{limit} (in °C) are prescribed, and the field strength value H (in kA/m) and the associated temperature distribution $T(x,y,z)$
25 (in °C) are sought.

The T selection is implemented using the execution program "sim_t.exe", and the H selection is implemented using the execution program sim_h.exe. The third
30 program module, sim_hr.exe, also uses a (multiple) H selection. sim_t.exe and sim_h.exe each calculate one temperature distribution, while ten temperature distributions are ascertained in one cycle for ten values of the H field strength in the case of
35 sim_hr.exe (the "H controller").

A transfer parameter (or input value from the point of view of the simulator) "MODE" having the value MODE=1, the "H selection" (sim_h.exe) MODE=2 and the "H

controller" (sim_hr.exe) MODE=3 is assigned to the calculation type "T selection" (sim_t.exe).

5 The text below provides a more precise description, by way of example, of the three simulator program modules (which can each also be available as standalone programs) with their functionalities.

H selection (MODE=2, sim_h.exe)

10 A schematic illustration of the cycle of the program module sim_h.exe is shown in figure 3. The absolute value of the H field strength H is prescribed. The temperature distribution $T(x,y,z)$ is sought.

15 First, the nanodeposit volume (deposit volume) or nanoparticle volume ("V_NP") and an average HU value "HU_aver" from all the values $HU(x,y,z)$ in V_NP are formed from the evaluation of the geometric nanoparticle distribution (read in via LV.raw) and
20 comparison of the Hounsfield units (" $HU(x,y,z)$ ", read in via CT.raw).

Next, the average iron concentration is estimated from the average "HU_aver", and from this the iron mass
25 "m_fe" (more generally: the particle mass) in the V_NP is estimated, it being assumed in this case that the nanoparticles have an iron core as the magnetically effective component. This approach is thus based on multiple approximations: m_fe is estimated from the
30 average iron concentration, which is in turn estimated from the average HU value. The concentration of the nanoparticles following instillation into the patient is determined from the CT data. Only approximately 50% of the instilled particles remain in the body and are
35 present in the "nanodeposit" in concentrations or distributions which are difficult to foresee.

Independently of this, the simulator derives the iron core SAR "SAR_fe" from the H field strength. This is a

reference power absorption rate in units of W/g, for example, based on the iron mass, which indicates a measured power absorption for the nanoparticles in an undiluted reference state, that is to say the power
 5 absorption rate of an undiluted magnetic fluid (undiluted batch) containing the nanoparticles prior to instillation into a patient, for example.

The nanoparticles may be magnetic (that is to say
 10 ferromagnetic or ferrimagnetic, for example), paramagnetic and/or superparamagnetic. Depending on parameters such as material, size distribution, etc., there may be a mixture of different magnetic properties.

15 The SAR_{fe} is calculated by applying a nonlinear characteristic curve $SAR_{fe} = f(H)$, determined metrologically beforehand for the magnetic fluid. The characteristic curve is determined for a specific
 20 applicator and specifically used nanoparticles (magnetic fluid). It is assumed that the treatment area is situated centrally between pole pieces of the applicator (e.g. in an area of ± 10 centimeters), so that, in a good approximation, the same (maximum) H
 25 field strength value can be used everywhere in that area. In order to avoid a complex tabular representation, the characteristic curve $SAR_{fe} = f(H)$ can be approximated by three fitting factors a,b,c, so that it can assume a form

$$30 \quad SAR_{fe} = aH^b + c \quad (1)$$

with the units SAR_{fe} in W/g (watts per gram) and H in kA/m.

35 m_{fe}, SAR_{fe} and V_{NP} are now used to estimate an average "SAR_{aver}" for the volume SAR(x,y,z) based on the tissue mass in W/kg (or, equivalently: multiplied by the specific local density in W/m³ or W/cm³) in the

nanodeposit. This is thus an average power absorption density in the deposited state of the nanoparticles.

Next, a location-dependent volume SAR distribution is formed, and the invention assumes with good approximation that in V_{NP} the SAR values are proportional to the HU values, i.e.

$$SAR(x,y,z)=HU(x,y,z)*SAR_{aver}/HU_{aver} \quad \text{in } V_{NP} \quad (2),$$

10

$$SAR(x,y,z)=0 \quad \text{outside } V_{NP} \quad (3).$$

All the values $HU(x,y,z)$ are positive in V_{NP} , which means that no physically impossible negative SAR values can arise.

15

With the location-dependent power absorption "density" distribution $SAR(x,y,z)$ as the source of the temperature, a BHTE $T(x,y,z) = f(SAR(x,y,z))$ is then numerically solved, e.g. on the basis of Nadobny et al. 2007, equations (1)-(2), and in this case a finite difference method with explicit temperature gradient calculation based on Nadobny et al. 2007, equations (8)-(15), is applied.

25

The BHTE describing the model is dynamic, i.e. time-dependent. After some time, a steady state condition is reached, in which the supply of heat by power absorption in the applied magnetic field is the same as the heat dissipation for the blood flow, cooling in the environment, perfusion terms. On the basis of experience, such a condition is reached after approximately 20 min. It may be prescribed in the simulator that, taking account of an appropriate safety margin, the steady state condition is meant to be deemed to have been reached after 30 min (minutes), for example (hyperthermia treatment can take between 1 hour and 1.5 hours, for example). In principle, the user may also be treated in the initial phase (before a steady

35

state is reached). The simulator operates in a time domain, and can therefore also model and provide (output) any times before a value of 20 min or 30 min.

- 5 The H selection option (sim_h.exe) (MODE=2) requires just a single pass in order to numerically solve the BHTE $T(x,y,z) = f(\text{SAR}(x,y,z))$.

The invention proposes that in the case of the H selection the temperature is not limited, i.e. depending on the level of the H field strength, any temperatures can arise in the body which may also be above the usual temperature limit values (e.g. 43°C in healthy tissue).

15

T selection (MODE=1, sim_t.exe)

Figure 4 schematically shows a program cycle for the simulator in T selection mode. Temperature limit values $T_{\text{limit}}(x,y,z)$ are prescribed, and the field strength value H and the associated temperature distribution $T(x,y,z)$ are sought.

First of all, the nanoparticle distribution is read in from LV.raw and the Hounsfield units are read in via CT.raw - as in the case of sim_h.exe. Next, the iron concentration (generally the magnetically effective particle concentration) is determined and from this the iron mass m_{fe} (generally the magnetically effective particle mass) is determined, as in the case of sim_h.exe. These variables are independent of an acquired H field strength.

Further progression of sim_t.exe is different than in the case of sim_h.exe, however, since the absolute value of the field strength is not prescribed, but rather is now sought. The procedure comprises the calculation of an appropriate volume SAR (in W/kg, or optionally as a power absorption density in W/m³) which "fits" the prescribed limit temperature, and also

finding the H field strength from the calculated volume SAR.

The limit temperature selections $T_{\text{limit}}(x,y,z)$ that
 5 need to be observed simultaneously and with equal
 authorization in the example described here are as
 follows:

- for the "non-PTV region" (for a Boolean operation,
 "body volume minus PTV"), a maximum admissible
 10 temperature value (= temperature limit value)
 $T_{\text{limit}}(\text{non-PTV})$ is prescribed. By way of example,
 this value may have been set to 43°C by default in
 the main program of the simulation software and
 transferred to the simulator thus, i.e. $T_{\text{limit}}(\text{non-PTV})$
 15 = 43°C. The "non-PTV" region corresponds roughly
 to the healthy tissue or the tissue that is not to be
 treated.
- The temperature everywhere in the body volume is
 20 meant to be no more than 80°C. This value may have
 been stipulated internally in the simulator, for
 example. In interaction with the above limit value,
 on the basis of which the non-PTV is meant to be at
 no more than 43°C, this is a limit for the treatment
 25 area PTV, and therefore $T_{\text{limit}}(\text{PTV})=80^\circ\text{C}$.

The resultant field strength H must observe both
 selections, i.e. it is meant to be low enough for all
 the temperatures $T(x,y,z)$ to be less than or equal to
 30 80°C in the PTV and at the same time less than or equal
 to 43°C outside the PTV. In other words, of two field
 strength values which each observe one of the two T
 selections, the lower is output.

35 To observe these T selections, it would theoretically
 be possible to start `sim_h.exe` multiple times and to
 recurrently readjust the input field strength, so that
 the T selections would be observed at the end of such
 an iterative process. This iterative and accordingly

imprecise and complex path (cf. "iterative way" in Nadobny et al. 2007, page 1841) is not pursued in this case.

5 The procedure according to the invention is different in this case in order to determine the H field strength value directly, in a resource-saving manner and nevertheless precisely. In this case, it should be borne in mind that the statement of problem is in no way trivial, since the SAR (and hence temperature) is dependent on the H field strength in a nonlinear manner. However, a linear relationship can be indicated at least for some of the statement of problem, specifically between the SAR and the temperature (cf. 10 "decomposition way" in Nadobny et al. 2007, page 1841, equations (5a), (5b), (6)). Thus, the temperature distribution $T(x,y,z)$ is first of all split into a basal component $T_0(x,y,z)$, which is obtained without SAR, and into a temperature rise component 20 $T_{\text{rise}}(x,y,z) = K \cdot \Delta T(x,y,z)$, with the result that:

$$T(x,y,z) = T_0(x,y,z) + K \cdot \Delta T(x,y,z), \quad (4)$$

and for the SAR the following is true

25

$$SAR(x,y,z) = K \cdot \Delta SAR(x,y,z). \quad (5)$$

K is a scalar scaling factor (in MODE=1, we refer to "temperature-based" scaling factor), $\Delta T(x,y,z)$ is the relative temperature increment and $\Delta SAR(x,y,z)$ is the relative SAR distribution, which can also be called the relative power absorption density or is equivalent thereto. Unlike in the case of sim_h.exe, an absolute value SAR_aver is not determined from SAR_fe, but 30 rather an arbitrary (relative) test average " ΔSAR_{aver} " for the relative volume SAR $\Delta SAR(x,y,z)$ is prescribed internally. By way of example, this test average may be set as $\Delta SAR_{\text{aver}} = 100 \text{ W/kg}$ in the simulator. In a manner similar to that in equation (2), the invention 35

approximates the location-dependent $\Delta\text{SAR}(x,y,z)$ values therefrom as follows:

$$\Delta\text{SAR}(x,y,z) = \text{HU}(x,y,z) * \Delta\text{SAR_aver} / \text{HU_aver} \text{ in } V_NP, \quad (6)$$

5

$$\Delta\text{SAR}(x,y,z) = 0 \quad \text{outside } V_NP. \quad (7)$$

Next, two passes for numerically solving the BHTE are started in succession: once for $T_0(x,y,z)$ (with SAR(x,y,z)=0) and once for the relative temperature increment $\Delta T(x,y,z) = f(\Delta\text{SAR}(x,y,z))$. Next, the temperature-based scaling factor is found using a minimum search over all support points or voxels x,y,z :

$$K = \text{Min}(T_limit(x,y,z) - T_0(x,y,z)) / \Delta T(x,y,z), \quad (8)$$

where $T_limit(x,y,z) = 80^\circ\text{C}$ in the non-PTV and 43°C in the PTV.

When the temperature-based scaling factor K has been found, it is immediately possible to indicate the absolute SAR(x,y,z) and $T(x,y,z)$ using equations (5) and (4) without the BHTE needing to be numerically solved once again. For the average of SAR(x,y,z), the following is likewise true:

$$\text{SAR_aver} = K * \Delta\text{SAR_aver}. \quad (9)$$

Next, the invention performs the initial steps from sim_h.exe in inverse order: first, the iron core SAR SAR_fe is determined from the average SAR_aver and the previously determined iron mass m_fe. The last step is the application of a generally nonlinear characteristic curve $\text{SAR_fe} = f(H)$ in the inverse sense, i.e. the value SAR_fe is used to ascertain the H field strength value, which is then finally communicated - in addition to the temperature distribution $T(x,y,z)$ - to the user as an output.

H controller (MODE=3, sim_hr.exe)

Figure 5 schematically shows a program cycle for the simulator in H regulator mode. In a call, the simulator program sim_hr.exe immediately simulates a plurality of
 5 temperature distributions for a multiple H selection, i.e. for different absolute values of H which are made available as input values.

In the example described here, a set of ten temperature
 10 distributions is determined for a set of ten firmly prescribed field strength values (5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 kA/m). However, the H controller is not simply a sim_h.exe executed ten times in succession with ten passes for numerically solving the BHTE. In
 15 order to save computation time, instead only two passes - in a manner similar to that in sim_t.exe - are required, namely likewise for $T_0(x,y,z)$ and $\Delta T(x,y,z)$.

First of all, the evaluation of the geometric nano-
 20 particle distribution (read in via LV.raw) and comparison of the Hounsfield units (read in via CT.raw) are used - in a manner similar to that in the case of sim_h.exe - to determine the average HU value HU_aver, from this the average particle or iron concentration
 25 and from this the particle or iron mass m_fe. These values are the same for all H values.

Next, for a relative value of $\Delta SAR_{aver}=100$, ΔSAR_{aver} is estimated and $\Delta SAR(x,y,z)$ is approximated - as in
 30 sim_t.exe - on the basis of equations (6) and (7) above.

In a manner similar to that in sim_t.exe, two passes are next performed for the purpose of numerically
 35 solving the BHTE for $T_0(x,y,z)$ and $\Delta T(x,y,z)$.

Next, a loop having i=10 repetitions starts. Each time, the relative H field strength value H(i) is read in, that is to say 5...14 kA/m in 1 kA/m steps, for example.

By applying the characteristic curve $SAR_{fe}=f(H)$ based on equation (1), the value is used - as in the case of `sim_h.exe` - each time to calculate the relevant value $SAR_{fe}(i)$, and this value (and the initially determined iron mass m_{fe}) is used to estimate the absolute average of the volume SAR, $SAR_{aver}(i)$.

Hence, for each loop repetition, a scaling factor $K(i)$ can be determined according to the invention from (according to the invention, we refer in `MODE=3` to "power-absorption-based" scaling factor):

$$K(i) = SAR_{aver}(i) / \Delta SAR_{aver}. \quad (10)$$

With the power-absorption-based scaling factor $K(i)$, an absolute temperature distribution is obtained for each i :

$$T(x,y,z,i) = T0(x,y,z) + K(i) * \Delta T(x,y,z), \quad (11)$$

and is then output. Hence, ten absolute (scaled) temperature distributions are output in succession, although only two passes were required for numerically solving the BHTE.

It is pointed out that the power-absorption-based scaling (power-absorption-based scaling factor K as per equation 10) performed in the case of the H controller (`MODE=3`) is based on the specific power absorption rate (SAR) and is therefore fundamentally different than the scaling which is performed in the T selection (`MODE=1`) on a (limit) temperature basis (temperature-based scaling factor K as per equation 8). In addition, it is noted that the power-absorption-based scaling factor K , in the case of the H controller (equation 10), cannot simply be formed by forming a ratio of H values, as is explained by the generally present nonlinearity of the characteristic curve $SAR_{fe}=f(H)$.

Binary input file CT.raw

This 3D data record can represent a regular 3D grid, the elements (pixels) of which have associated CT density values (Hounsfield units, as "short" numbers). The geometric reference to the position (x,y,z) of an element in the CT grid is obtained via the x,y,z index and the statements relating to the bounding box which are additionally transferred to the simulator. The x coordinate is the fastest changing (inner loop), and the z coordinate is the slowest (outer loop). The CT data record must correspond to the postoperative planning CT and contain nanoparticles (following instillation of the magnetic fluid). The simulator is interested particularly in the CT values in the nanoparticle pixels. For these values, the simulator derives the information about the current iron concentration (that is present following the instillation in the body), which is relevant to the calculation of the SAR and/or the temperature.

20 Binary input file LV.raw

This data record (LV stands for "labeled volume") can likewise represent a regular 3D grid, the elements of which have associated coded labels ("byte" numbers). The geometric reference to the 3D position (x,y,z) of an element in the LV grid is obtained via the index and the statements relating to the bounding box. The bounding box of LV.raw may be identical to that of CT.raw. The data record LV.raw is produced in the previous program main step "Segmentation", for example on the basis of the planning CT. The labels are used to describe/code the following three types of regions:

- Geometric-anatomical regions (exterior, "head", tumor): This information is required in order to perform the calculation of the temperature distribution. By way of example, the simulator models the thermal interface between the body and the exterior, and therefore the relevant geometry must be known. It is also expected that the doctor plots the

tumor, even though the simulator can also calculate without a segmented tumor. A distinction is drawn between body (part) volumes, that is to say "head", for example, treatment volumes (PTV), that is to say
 5 "tumor + border around the tumor", for example, and deposit volumes, that is to say one or more (many) voxels containing nanoparticles. "non-PTV" would thus be "head minus tumor (incl. border)" in the example.

10 • Nanoparticle areas (source volumes): Geometric positions (marked as labels) of the nanoparticles or deposits of the magnetic fluid which are latched to the tissue ("nanodeposits", deposit volumes). These nanoparticle positions need to be communicated to the
 15 simulator as an input in order to determine the SAR. The SAR is produced only in the positions of the nanoparticles. The nanoparticle areas can overlap the geometric-anatomical regions and the thermal limit condition regions. The geometric distribution of the
 20 nanoparticles inside the deposit volume or the deposit volumes is important for the calculations, for example in the T solver or H controller.

• Thermal limit conditions regions: Regions or organs
 25 where particular temperatures $T_{\text{limit}}(x,y,z)$ are not meant to be exceeded. By way of example, a distinction is drawn between the treatment area ("PTV", "planning target volume") and the rest of the head for the healthy tissue ("non-PTV region", i.e.
 30 region outside the treatment area). The limit condition regions can overlap the geometric-anatomical regions and the nanoparticle areas. As a standard option, the segmentation editor provides the tumor plus a tumor border of 1 cm as PTV.

35

The coding of LV.raw is implemented such that, for each 8-bit label, 6 bits are used for coding the geometric-anatomical information, and 1 bit is used for coding

the nanoparticles (YES/NO) and the PTV (YES/NO), respectively.

5 A second exemplary embodiment of the inventive simulation tool is described more precisely below. A program package implements a temperature simulator (occasionally also called just "simulator" below) which is part of a piece of simulation software which has been developed with the aim of providing assistance in
10 cancer therapies. Like the first exemplary embodiment described above, the second exemplary embodiment is also provided for simulations in the head area.

As a result of the introduction of the magnetic fluid
15 into the tumor area ("instillation" or "implantation"), what are known as "nanoparticle deposits" or "nanodeposits" can be found in this area. During the therapy, these nanoparticles can be activated by means of high-level low-frequency external magnetic fields,
20 i.e. the influence of the magnetic field can result in a local temperature rise. On the basis of the CT data, the simulator produces a simulation (prediction) of the temperature distribution in the head area on the basis of the magnetic field strength of the therapy appliance
25 (magnetic field activator). This occurs after the instillation but before the therapy. The results provided by the simulator are neither a prerequisite for therapy being able to be performed nor binding for the performance of said therapy, for example in
30 relation to a particular application field strength calculated by the simulator. By way of example, the performance of the therapy can be influenced by a temperature measurement carried out during the therapy. This temperature measurement is more crucial in nature
35 for the doctor than simulation results. Simulation results and - crucially - temperature measurement can provide the doctor with pointers for assessing the therapy.

In a manner similar to that in the first exemplary embodiment, the simulator performs the following main tasks, inter alia:

- 5 - simulation of a three-dimensional temperature distribution, as is probably obtained through the application of the magnetic field to nanoparticles on the assumption of a simplified physical model;
- 10 - estimation of a magnetic field strength (H field strength) on the basis of particular temperature selections for the patient model.

In a manner similar to that in the first exemplary embodiment, the simulator is not part of a main program core in this case, but rather is linked to the main program core as part of an external SOUP ("Software of Unknown Provenance"). However, the data interchange between the simulator and the main program core no longer takes place via an external rigid directory interface (complete writing out and reading in of the data via hard disk), but rather the simulator is linked as a program library and therefore the data interchange takes place via main memory. Important changes which arise as a result of this different software structure or architecture include:

- 25 - linking of the simulator as a program library instead of execution programs such as sim_t.exe, sim_h.exe and sim_hr.exe;
- 30 - introduction of the "fast H controller" instead of the "H controller";
- dynamic memory location management for the FORTRAN arrays.

35

The modification of the H controller is described in detail further below. Furthermore, the linking as a program library will now be dealt with briefly.

In the case of the first exemplary embodiment, the simulator comprised three separate FORTRAN execution programs "sim_t.exe", "sim_h.exe" and "sim_hr.exe", and each program was responsible for a particular selection mode (modes 1, 2 and 3). Accordingly, a transfer parameter (or input value from the point of view of the simulator) "MODE" with the value MODE=1 was transferred to the calculation type "T selection" ("T" for "temperature"; sim_t.exe program), MODE=2 was transferred to the "H selection" ("H" stands for "magnetic", i.e. selection of an H field strength; sim_h.exe program), and MODE=3 was assigned to the "H controller" (multiple desired field strength values, sim_hr.exe program).

In the second exemplary embodiment which is discussed here, the basic split of the program into three modes is retained (MODE=1, MODE=2 and MODE=3), with MODE=3 having been modified in terms of software (cf. further below). However, the simulator no longer comprises three separate exe programs, but rather acts as a program library. Hence, the communication or the data interchange between the main program core and the simulator no longer takes place via external directory interfaces, but rather takes place via main memory. Advantages of this solution are, inter alia, that it is no longer necessary for large volumes of data to be read out and in via external directories (i.e. from or to a hard disk), and thus the program execution speeds are increased and/or possible sources of error are eliminated.

The simulator implemented as a program library can be called from the main program core. The main program of the program library forms an interface to the main program core, that is to say takes on the tasks of the external interface in the first exemplary embodiment - which interface ensures the provision of CT.raw, LV.raw in said embodiment - at the "SOUP end".

All the main programs in the first exemplary embodiment, i.e. `sim_t.exe` (for `MODE=1`, T selection), `sim_h.exe` (for `MODE=2`, H selection) and `sim_hr.exe` (for `MODE=3`, H controller), are provided as FORTRAN (main) subroutines in the second exemplary embodiment which are then all called sequentially (depending on the `MODE`) by the main program. These customized main subroutines are referred to here as "mainsubroutines".

The order in which the simulator modes are called and the simulator data are managed continues to be controlled and managed from the main program core.

The following main subroutines exist:

- "mainsubroutine_sim_t_voxel_win" (for `MODE=1`, T selection),
- "mainsubroutine_sim_h_voxel_win" (for `MODE=2`, H selection), and
- "mainsubroutine_sim_hr_voxel_win" (for `MODE=3`, fast H controller).

The CT data and the segmented label data are not, as in the first exemplary embodiment, written to the hard disk by the main program core as binary data records `CT.raw` (CT data record) and `LV.raw` (data record with coded labels) and then read in by the hard disk again as a binary input for the simulator. Instead, these data are in this case transferred as arrays in the main memory via the simulator.

A text file `SimInput.txt` (this provides the input for the first exemplary embodiment of the simulator) is not needed in this case. All the input parameters are carried in argument lists from the main program core to the main program of the simulator and on to the three mainsubroutines. This relates to the following input parameters, inter alia: `MODE` (1,2,3), desired H field strength (H = magnetic field strength, indicated in kA/m), desired maximum temperature in the non-PTV area,

molarity and fitting factors a,b,c (profile of the characteristic curve $SAR_{fe}=f(H)$), all the CT file dimension parameters (number of elements, bounding box, statements relating to the coordinate system used (m, cm, mm), number of regions).

There are also no output temperature data records written from the simulator to the hard disk and then read into the main program core again in this case.

10 Instead, appropriate arrays are transferred from the main program of the simulator to the main program core via main memory.

All the output parameters calculated in the first exemplary embodiment of the simulation program and then written to the output file SimOutput.txt are in this case transferred from the simulation program via argument lists from the mainsubroutines to the main program of the simulator and on to the main program

15 core via main memory. The most important output parameters are: MODE (1,2,3), resultant H field strength, resultant maximum temperature in the non-PTV area, resultant maximum temperature in the PTV area, percentage share tumor with resultant temperatures >39

20 degrees, nanoparticle volume, tumor volume, resultant average volume SAR, resultant average Hounsfield unit value in the nanoparticle volume, average iron core SAR.

30 The following additional parameters are transferred in the argument lists of the mainsubroutines to the main program of the simulator: error messages, and parameters which monitor the order of the calls to the mainsubroutines (MODE=3 must not be called before

35 MODE=1, see below).

Overview of the cycles in the second exemplary embodiment

The simulator provides the user with two options for ascertaining the absolute temperature distribution:

- by means of the H selection: The absolute value of the H field strength is prescribed (in kA/m); the temperature distribution $T(x,y,z)$ (in °C) is sought; and
- by means of the T selection: the temperature limit values T_{limit} are prescribed (in °C), and the field strength value H (in kA/m) and the associated temperature distribution $T(x,y,z)$ (in °C) are sought.

The T selection (MODE=1) is implemented by means of the call to the mainsubroutine mainsubroutine_sim_t_voxel_win. The H selection (MODE=2) requires the other mainsubroutine mainsubroutine_sim_h_voxel_win to be called. The fast H controller (MODE=3), which is also an H selection in principle, is implemented by means of the call to the mainsubroutine mainsubroutine_sim_hr_voxel_win, but requires at least one call to mainsubroutine_sim_t_voxel_win beforehand, since it uses the output from mainsubroutine_sim_t_voxel_win as input.

The chronological sequence of the calls to the simulator programs is controlled or managed from the main program core and is effected on the basis of a fixed scheme, which is shown in figure 6.

It is imperatively stipulated that after a changeover from the GUI segmentation editor to the GUI temperature simulation editor, the MODE=1 is always automatically started first, i.e. the T selection subroutine mainsubroutine_sim_t_voxel_win, i.e. without this requiring or needing an input by the user. This program observes two fixed limit temperature selections:

- maximum 43°C outside the PTV ("non-PTV 43°C limit"), and

- maximum 80°C everywhere else, i.e. *de facto* inside the PTV ("whole-body 80°C limit").

In relation to the non-PTV 43°C limit, it is noted that
 5 this value is regarded as a threshold temperature, above which damage to the healthy tissue can increasingly occur. The whole-body limit of 80°C can also be chosen differently, for example a value in the range between 50°C and below 100°C, preferably between
 10 60°C and 90°C, can be chosen. Of the two limit conditions, the one which occurs at the lower H field strength becomes effective.

After the performance of the first, i.e. automatic,
 15 pass in MODE=1, the main program core examines internally (without an output being provided by means of GUI) what the level of the H field strength value that is output internally as an output from the main program of the simulator program library is. If this
 20 value is greater than 15 kA/m, a pass in MODE=2 again starts automatically with the H selection 15 kA/m, or generally the physically maximum settable H field strength value on the magnetic field activator. If the output value from MODE=1 is less than or equal to
 25 15 kA/m, it is not necessary for a program run to be started in MODE=2, and the next step follows directly.

Following the termination of the automatic passes as described above, the following data are output to the
 30 GUI:

- temperature distribution;
- H field strength recommendation, i.e.
 - o the output from MODE=1 when $H < 15$ kA/m, or
 - o the value 15 kA/m (limiting pass in MODE=2 was
 35 performed),
- maximum temperature reached outside PTV, maximum temperature reached in the whole calculation area, and further variables.

There may be cases in which the maximum temperature outside the PTV is lower than the maximum admissible temperature (e.g. 43°C), specifically when the limit condition of, by way of example, 80°C has been reached
5 in the PTV.

After considering this initial result (the result from the automatic passes) on the monitor, the user decides whether he is satisfied with the result. If this is not
10 the case, he can type in any desired H field strength value and start a fast calculation of the temperature distribution in MODE=3 (fast H controller) for this value as often as desired.

15 The fast H controller has no limitations at all in respect of the temperatures reached, unlike the T selection in the initial pass. Therefore, there may be cases in which the temperatures reached are higher (or lower) than 80°C in the calculation area and/or higher
20 (and/or lower) than 43°C outside PTV.

The user can return to the program main step "segmentation" at any time in order to make segmentation corrections, such as corrections on the
25 PTV. In this case, the simulator changes to the initial state. As soon as there are new LV data present as the output for the segmentation and the user changes from the program main step "segmentation" to the temperature calculation editor, the procedure described above is
30 repeated, i.e. the simulator starts with the initial pass "T selection", etc. Alternatively, the initial pass in MODE=1 can be initiated without returning to the segmentation editor by using a GUI button "Restart automatic temperature simulation". In this case too,
35 the procedure in which the simulator starts with the initial pass "T selection", etc., is repeated.

The three simulator modes are described below according to their aims and functions.

MODE=2 (H selection, call goes to
mainsubroutine sim h voxel win)

5 The absolute value of the H field strength is prescribed. The temperature distribution $T(x,y,z)$ is sought, cf. the cycle shown schematically in figure 7. First of all, the patient model is generated. This is based on the combination of two data records (arrays):

10 - CT data record (array), which is read in by the simulation program as part of patient data that are to be read in (in this regard cf. figure 3; in this fundamental cycle, the first and second exemplary embodiments are very similar);

15 - LV data record (array) ("LV" stands for "labeled volume"), i.e. a coded label array, which is produced by the simulation program during segmentation (cf. figure 3).

20 The basis used for the patient model is the LV elements ("labels"), in which the following information is coded on a voxel basis:

- 25 - the geometric-anatomical regions ("head", "tumor", etc.);
- the thermally relevant regions (treatment area, also called PTV, "planning target volume");
- geometric distribution of the nanoparticles (NP).

30 The evaluation of the NP distribution results in the ascertainment of the NP volume V_{NP} . The comparison with the CT data record then takes place, with the average Hounsfield unit (HU) value "HU_aver" being determined by forming an average for those values of
 35 HU(x,y,z) which fall into the V_{NP} .

Next, the average HU_aver is used to estimate the average iron concentration, and for this the average iron mass m_{fe} in the V_{NP} .

Independently, e.g. in parallel with these steps, the simulator derives the iron core SAR ("SAR_fe") from the H field strength. This is accomplished by applying a generally nonlinear characteristic curve $SAR_{fe}=f(H)$ that has been determined experimentally for the magnetic fluid used. In this case, it is assumed that the treatment area is situated centrally between the pole pieces of the magnetic field applicator, where there is the same (maximum, constant) H field strength to a good approximation. In order to avoid a complex tabular illustration, the characteristic curve $SAR_{fe}=f(H)$ can be approximated by three fitting factors a,b,c as follows, for example:

$$SAR_{fe}=a H^b+c \quad (12)$$

with SAR_{fe} in W/g (watts per gram) and H in kA/m (kiloamps per meter).

m_{fe} , SAR_{fe} and V_{NP} are now used to estimate the average "SAR_aver" of the volume $SAR(x,y,z)$ in the nanodeposit, cf. equation (2) in Gneveckow et al. 2004, for example.

Next, the location-dependent volume SAR distribution is formed, it being assumed that in V_{NP} the SAR values are proportional to the HU values, i.e.

$$SAR(x,y,z)=HU(x,y,z)*SAR_{aver}/HU_{aver} \text{ in } V_{NP} \quad (13)$$

$$SAR(x,y,z)=0 \text{ outside } V_{NP}. \quad (14)$$

All values $HU(x,y,z)$ are meant to be positive in V_{NP} so that no physically impossible negative SAR values occur. This can be ensured as early as in the segmentation editor, for example, by means of appropriate filtering or threshold setting and can possibly be checked again in the simulator.

With the location-dependent $SAR(x,y,z)$ as the source of the temperature, the BHTE $T(x,y,z)=f(SAR(x,y,z))$ is then numerically solved, cf. Nadobny et al. 2007, equations (1)-(2). This can be solved by using a finite difference method with explicit temperature gradient calculation, as described in Nadobny et al. 2007, equations (8)-(15), for example.

Unlike in $MODE=1$ and $MODE=3$, $MODE=2$ the BHTE describing the model is solved for absolute values of the SAR which are derived from the absolute H selection value. The H selection option $MODE=2$ therefore requires - unlike in $MODE=1$ and $MODE=3$ - just a single pass for numerically solving the BHTE $T(x,y,z)=f(SAR(x,y,z))$.

In the case of the H selection, the temperature is not limited, i.e. depending on the H field strength it is possible for any temperatures to arise in the body, which are also above the usual temperature limit values (e.g. $43^{\circ}C$ in healthy tissue).

$MODE=1$ (T selection, call goes to:
mainsubroutine sim t voxel win)
 Temperature limit values $T_limit(x,y,z)$ are prescribed, and the field strength value H and the associated temperature distribution $T(x,y,z)$ are sought, cf. the schematic illustration in figure 8. In contrast to the T selection in the first exemplary embodiment, particular data records are output for the later call for $MODE=3$ (fast H controller) and are temporarily provided in the main memory.

First of all, the patient model is produced - as in $MODE=2$ - from the LV and CT data and then HU_aver and m_fe are determined for the NP volume (these variables are independent of the applied H field strength). The remainder of the cycle in $MODE=1$ is different than in the case of $MODE=2$, however, since the absolute value of the field strength is not prescribed but rather is

sought. A procedure for ascertaining an appropriate volume SAR which corresponds to the prescribed limit temperature also has an additional step added for the application of nanoparticles, namely the calculation of
 5 the H field strength from the volume SAR.

The limit temperature selections $T_{\text{limit}}(x,y,z)$ which need to be observed simultaneously and with equal authorization are:

- 10 - the "non-PTV" region corresponds approximately to the healthy tissue or the tissue that does not need to be treated. For this non-PTV region, which in the Boolean sense is "body minus PTV" or "head minus PTV", a maximum admissible temperature value
 15 (= temperature limit value) $T_{\text{limit}}(\text{non-PTV})$ is prescribed. This value may be able to be altered by the user, or else may be firmly prescribed. The value may also have been set to 43°C by default, i.e. $T_{\text{limit}}(\text{non-PTV})=43^{\circ}\text{C}$.
 20
- The temperature in the body is not meant to exceed a maximum value of 80°C, for example, anywhere. This value may be firmly prescribed in the simulator, for example. Since the non-PTV is meant
 25 to be at no more than 43°C at the same time, the second limitation is effective for the treatment area PTV, i.e. $T_{\text{limit}}(\text{PTV})=80^{\circ}\text{C}$.

The resultant field strength H must observe both
 30 selections, i.e. it is meant to be low enough for all the temperatures $T(x,y,z)$ to be less than or equal to 80°C in the PTV, and at the same time to be less than or equal to 43°C outside PTV. Of the two field strength values which each observe one of the two T selections,
 35 the lower is output.

To observe these T selections, it would be possible to start MODE=2 multiple times, with the input field strength being repeatedly readjusted, so that the T

selections would be observed at the end of such an iterative process. This iterative and accordingly imprecise or complex path (cf. "iterative way" in Nadobny et al. 2007, page 1841) is not pursued in this case.

The procedure according to the invention is different in this case in order to determine the H field strength value directly, in a resource-saving manner and nevertheless precisely. In this case, it should be borne in mind that the statement of problem is in no way trivial, since the SAR (and hence temperature) is dependent on the H field strength in a nonlinear manner. However, a linear relationship can be indicated at least for some of the statement of problem, specifically between the SAR and the temperature (cf. "decomposition way" in Nadobny et al. 2007, page 1841, equations (5a), (5b), (6)). Thus, the temperature distribution $T(x,y,z)$ is first of all split into a basal component $T_0(x,y,z)$ (as would be obtained without SAR) and into a temperature rise component $T_{\text{rise}}(x,y,z)=K*\Delta T(x,y,z)$, with

$$T(x,y,z)=T_0(x,y,z)+K*\Delta T(x,y,z), \quad (15)$$

where the following is true for the SAR:

$$SAR(x,y,z)=K*\Delta SAR(x,y,z). \quad (16)$$

K is a scalar scaling factor - that needs to be ascertained - (we refer to "temperature-based" scaling factor in MODE=1), $\Delta T(x,y,z)$ is the relative temperature increment and $\Delta SAR(x,y,z)$ is the relative SAR distribution.

In contrast to the first exemplary embodiment, the output for a mainsubroutine_sim_t_voxel_win comprises not only the actual temperature distribution $T(x,y,z)$ but also distributions $T_0(x,y,z)$ and $\Delta T(x,y,z)$. These

temperature distributions are characterized in detail as follows:

- $T(x,y,z)$: Absolute resultant temperature distribution, which corresponds to a particular absolute SAR which is necessary in order to comply with particular constraints, e.g. in $\text{MODE}=1$ the limit temperatures are such constraints. $T(x,y,z)$ is also output in the simulation program in accordance with the first exemplary embodiment.
 5 $T(x,y,z)$ belongs to the data which are visualized in the GUI ("graphical user interface") of the simulation program.
- $T_0(x,y,z)$: Absolute "basal" temperature distribution, as obtained without SAR; initial temperature and basal temperature for numerically solving the time-dependent BHTE are identical as for the solution based on $T(x,y,z)$. This temperature distribution is temporarily stored in the main memory and is then available as an input for the fast H controller.
 15
 20
- $\Delta T(x,y,z)$: The distribution of the relative temperature rise (= temperature increment), said distribution being obtained for an arbitrary, firmly prescribed and/or user-defined SAR level ("fixed value" in figure 8). Since it is not the temperature but rather the temperature increment that is simulated in this case, initial temperature and basal temperature for numerically solving the time-dependent BHTE are equal to zero. This temperature distribution is likewise temporarily stored in the main memory and is then available as an input for the fast H controller.
 25
 30

35

Unlike in $\text{MODE}=2$, an absolute value SAR_{aver} is not determined from SAR_{fe} , but rather an arbitrary (relative) test average " $\Delta\text{SAR}_{\text{aver}}$ " for the relative volume SAR $\Delta\text{SAR}(x,y,z)$ is prescribed internally as a

"fixed value" (constant, cf. figure 8) (in the simulator, this test average is set as $\Delta\text{SAR}_{\text{aver}}=100 \text{ W/kg}$). In a manner similar to that in equation (13), this is used to approximate the location-dependent $\Delta\text{SAR}(x,y,z)$ values as follows:

$$\Delta\text{SAR}(x,y,z)=\text{HU}(x,y,z) * \Delta\text{SAR}_{\text{aver}}/\text{HU}_{\text{aver}} \quad \text{in } V_{\text{NP}}, \quad (17)$$

$$\Delta\text{SAR}(x,y,z) \text{ outside } V_{\text{NP}} \quad (18)$$

10

Next, two passes for numerically solving the BHTE are started in succession: once for $T_0(x,y,z)=f(\text{SAR}=0)$ and once for the relative temperature increment $\Delta T(x,y,z)=f(\Delta\text{SAR}(x,y,z))$. The scaling factor is then found using a minimum search over all support points (voxels) x,y,z ("temperature-based scaling factor"):

$$K=\text{Min}(T_{\text{limit}}(x,y,z)-T_0(x,y,z))/\Delta T(x,y,z) \quad (19)$$

20 with $T_{\text{limit}}(x,y,z)=80^\circ\text{C}$ in Non_PTV and 43°C in PTV.

When the temperature-based scaling factor K has been found, the absolute SAR (x,y,z) and $T(x,y,z)$ can immediately be specified using equations (16) and (15) without having to numerically solve the BHTE again. For the average of $\text{SAR}(x,y,z)$, the following is likewise true:

$$\text{SAR}_{\text{aver}}=K*\Delta\text{SAR}_{\text{aver}}. \quad (20)$$

30 The initial steps from $\text{MODE}=2$ are then performed in inverse order: i) the iron core SAR SAR_{fe} is determined from the average SAR_{aver} and the previously determined iron mass m_{fe} ; ii) the nonlinear characteristic curve $\text{SAR}_{\text{fe}}=f(H)$ (cf. Gneveckow et al. 2004, figure 5) is applied in the inverse sense, i.e. the H field strength value is ascertained from the value SAR_{fe} . Said H field strength value is transferred as an output from mainsubroutine `sim_t_voxel_win` to the main program of

the program library and on to the main program core or to the GUI. Although the three data records $T(x,y,z)$, $T_0(x,y,z)$ and $\Delta T(x,y,z)$ form the output of mainsubroutine_sim_t_voxel_win, only $T(x,y,z)$ is passed
 5 on to the GUI. $T_0(x,y,z)$ and $\Delta T(x,y,z)$ are temporarily stored in the main memory in order subsequently to be provided as an input for mainsubroutine_sim_hr_voxel_win in MODE=3.

10 MODE=3 ("fast H controller", call is made to mainsubroutine sim hr voxel win)

In MODE=3, a temperature distribution is ascertained for arbitrary H selection in a matter of seconds without needing to solve the BHTE, for example using a
 15 finite difference program. The prerequisite is that $T_0(x,y,z)$ and $\Delta T(x,y,z)$ are read in as an input for mainsubroutine_sim_hr_voxel_win. These temperature data records should already be present in the main memory, i.e. MODE=1 has already been successfully called and
 20 terminated at least once, for example, for a given patient model, cf. figure 9.

First of all, the patient model is produced - as in MODE=1 or MODE=2 - from the LV and CT data. Next,
 25 HU_aver and m_fe are determined for the NP volume. These variables are independent of the applied H field strength. The average iron mass m_fe has already been calculated in MODE=1 (T selection). As an alternative to recalculation, it is also conceivable for the
 30 average iron mass m_fe to be kept in the main memory following calculation in MODE=1 (T selection) for access by MODE=3 (fast H controller). Since the underlying patient model is always the same regardless of the MODE, a calculation such as that for the average
 35 iron mass m_fe could also be relocated entirely, for example to the segmentation step (cf. figure 1). However, local calculation of such variables may be advantageous, for example in respect of aspects such as

a modular structure for the program package, performance of software tests, etc.

Independently of the calculation of the average iron
 5 mass, a field strength value H that has been input by
 the user in the GUI is read in - in a manner similar to
 that in the case of $\text{MODE}=2$ - and the relevant value of
 the iron core SAR SAR_{fe} is calculated by applying the
 characteristic curve $\text{SAR}_{\text{fe}}=f(H)$. From this value and
 10 from the previously determined iron mass m_{fe} , the
 absolute average of the volume SAR, SAR_{aver} , is then
 ascertained. At the same time, a relative fixed value
 of $\Delta\text{SAR}_{\text{aver}}=100 \text{ W/kg}$ is prescribed - as in $\text{MODE}=1$ -,
 the fixed value $\Delta\text{SAR}_{\text{aver}}$ in $\text{MODE}=3$ needing to be
 15 identical to the fixed value $\Delta\text{SAR}_{\text{aver}}$ in $\text{MODE}=1$.

The invention therefore allows the scaling factor K to
 be determined from (according to the invention, in
 $\text{MODE}=3$ we refer to the "power-absorption-based" scaling
 20 factor):

$$K = \text{SAR}_{\text{aver}} / \Delta\text{SAR}_{\text{aver}}. \quad (21)$$

The calculated power-absorption-based scaling factor K
 and the $T_0(x,y,z)$ and $\Delta T(x,y,z)$ which have previously
 25 been calculated in $\text{MODE}=1$ and are present in the main
 memory result in the sought temperature distribution
 $T(x,y,z)$ when equation (15) is applied, said
 temperature distribution then being output to the GUI.
 Since the BHTE does not need to be solved in the case
 30 of the fast H controller, the method described above is
 executed by means of a standard processor in a matter
 of seconds.

It is pointed out that the power-absorption-based
 35 scaling performed in the case of the fast H controller
 ($\text{MODE}=3$) (power-absorption-based scaling factor K as
 per equation 21) is based on the specific power
 absorption rate (SAR) and is therefore fundamentally
 different than the scaling which is performed in the T

selection (MODE=1) on a (limit) temperature basis (temperature-based scaling factor K as per equation 19). In addition, it is noted that the power-absorption-based scaling factor K cannot be formed simply by forming a ratio of H values in the case of the fast H controller (equation 21), which is explained by the nonlinearity that is generally present in the characteristic curve $SAR_{fe}=f(H)$.

The second exemplary embodiment which is described here involves calculation of the basal temperature distribution and the relative temperature increment distribution in MODE=1 (T selection) and provision of said distributions in the main memory as a basis for the fast H controller which is sometimes subsequently called (MODE=3). Other exemplary embodiments are likewise conceivable. By way of example, the two temperature distributions could be calculated and provided in the main memory (only) when the fast H controller is first called. In this case, the simulator would react to the first call to the first H controller more slowly, while the subsequent calls to the fast H controller would then be reacted to very quickly, i.e. virtually without waiting times, with the output of the temperature distribution that results from the input H field strength.

The second exemplary embodiment described here has two program components for calculating a specific temperature distribution on the basis of a prescribed or a user-defined H field strength value, namely once on the H selection (MODE=2) and furthermore on the (fast) H controller. In another exemplary embodiment, it would also be possible for just the (fast) H controller to be provided. However, it is noted that the H selection calculates a specific temperature distribution independently of a basal temperature distribution and a relative temperature increment distribution. The presence of two independent

calculation paths in one program package may be advantageous for test purposes, for example, and for maintenance and further development.

- 5 One of the two paths of calculation may also be better suited in a specific environment, e.g. a hardware environment, or according to specific requirements. Thus, in one particular exemplary embodiment, the simulator may be of configurable design, for example.
- 10 An experienced user would set the simulator such that, by way of example, basal temperature distribution and relative temperature increment distribution are not written out in MODE=1 (T selection), so as to save main memory. From his experience and the output from the T
- 15 selection (MODE=1), the user already favors a particular H value anyway, which means that the resultant, final temperature distribution can be calculated by calling the H selection once. Since the main memory requirement is limited in this case, such a
- 20 configuration is sometimes suitable for a hardware configuration with accordingly limited resources too.

- In yet another variant, the automatic start of the T selection (MODE=1) is dispensed with. Instead, the
- 25 simulator awaits a user input. If this comprises an appropriate command, the calculation of the T selection can begin, e.g. on the basis of the prescribed temperature limit values. If the user input comprises an H field strength value, the H selection can be
- 30 started, or the fast H controller (this may in turn be dependent on the available hardware resources). If the latter basal temperature distribution and relative temperature increment distribution are not yet available, they ought to be produced upon the first
- 35 call.

Interfaces between temperature simulator and main program core

In the first exemplary embodiment, the input values for the simulator were transferred to the simulator via an external text directory interface from main program core. To this end, a text file SimInput.txt was formed
5 which had a particular firmly defined line-based structure. The input values were read from SimInput.txt when the exe programs were called. In the simulator described here (in the second exemplary embodiment), SimInput.txt is no longer in existence and the data are
10 transferred via an internal interface between the main program core and the simulator program library via main memory, i.e. the data are transferred via an internal program interface.

15 At the simulator end, this interface is implemented by means of argument lists. The simulator input is generated from main program core (for example in C++) and transferred to the FORTRAN simulation library by means of argument lists. By way of example, the input
20 arrays and input parameters comprise:

- 1-D array with CT data, i.e. HU values;
- 1-D array with LV data, i.e. the segmented labels;
- input parameters in argument lists, comparable with those from the former text file SimInput.txt

25 from the first exemplary embodiment.

The simulator output is generated in the FORTRAN library and transferred to the main program core or the GUI by means of argument lists. By way of example, the
30 output arrays or parameters comprise:

- 1-D array with the temperature values $T(x,y,z)$; and
- output parameters in argument lists which may be required in the GUI and for producing a therapy

35 plan (some of these parameters are written to an output file SimOutput.txt in the first exemplary embodiment).

The 3D CT data can be represented in the form of dynamic 1D FORTRAN arrays which can be read into the main program core in the "patient data" step and in the "segmentation" step.

5

An array can represent the 3D CT data for a regular 3D grid, the elements (pixels) of which have associated CT density values ("Hounsfield units" values, i.e. "HU values"). The geometric reference to the position
 10 (x,y,z) of an element in the CT grid is obtained by means of the x,y,z index and the statements relating to the bounding box which are transferred to the simulator in the main memory from the main program core. The CT data record has to correspond to the postoperative
 15 planning CT and contain image information about the nanoparticles (following instillation of the magnetic fluid). For the simulator, particularly the HU values in the nanoparticle pixels are of interest. From these values, the simulator derives information about the
 20 iron concentration which is present in the body following the instillation. The information is relevant to the calculation of the SAR and then the temperature.

A further array can represent coded "labeled volume"
 25 (LV) data (labels) that are generated as a result of the segmentation on the basis of the planning CT. In the geometric service, this array maps a regular 3D grid, the elements of which have associated coded labels (numbers). The geometric reference to the 3D
 30 position (x,y,z) of an element in the LV grid is obtained by means of the index and the statements relating to the bounding box. The bounding box of such an LV data record or grid is identical to that of the CT data record. The LV data (labels) are used to
 35 describe the following three categories of regions:

- geometric-anatomical regions (exterior, "head", "tumor"): This information is required for calculating the temperature distribution. In

particular, the thermal interface between the body and the exterior is modeled in the simulator, and therefore its geometry must be known. The tumor should also be represented, although the simulator
 5 can compute even without a segmented tumor. In a precise sense, the "head" region means "head minus tumor".

- Nanoparticle areas (source volumes): geometric
 10 positions (marked as labels) of the nanoparticles ("nanodeposits") latched in the tissue. These nanoparticle positions need to be communicated to the simulator as an input for determining the SAR. The SAR is produced only at the positions of the
 15 nanoparticles. The nanoparticle areas can overlap the geometric-anatomical regions and the regions with, for example, thermal limit conditions. If segmented nanoparticle regions are not present, the program is terminated.

20
 - Thermal limit condition regions: Regions (e.g. organs) in which particular temperatures $T_{\text{limit}}(x,y,z)$ are not meant to be exceeded. In a second exemplary embodiment, a distinction is
 25 drawn just between the treatment area (PTV) and the rest of the head (non-PTV region), i.e. the region outside the treatment area, hence the healthy tissue. The limit condition regions can overlap the geometric-anatomical regions and the
 30 nanoparticle areas. As a standard option, the PTV region can be produced in a segmentation editor as a tumor plus a tumor border of a desired width. If the segmented PTV region is not present, the program is terminated.

35
 The coding of the LV data can be implemented in the main step "segmentation" by using, for each element of an 8-bit label, 6 bits for coding the geometric-anatomical information and 1 bit for coding the

nanoparticles (YES/NO) and the PTV (YES/NO), respectively.

Re the differences between the first and second
5 exemplary embodiments

The first exemplary embodiment, described with reference to figures 2-5, differs from the second exemplary embodiment, described with reference to figures 6-9, in the following aspects, inter alia:

- 10 - linking of the temperature simulator as a program library ("SOUP integration");
- other programming/implementation of the H controller or fast H controller.

15 In the first exemplary embodiment, the temperature simulator is implemented in the form of separate/autarkic execution programs. In the second exemplary embodiment, the temperature simulator is implemented as a program library. In this case, the
20 temperature simulator programs are not called as separate exe files via an external directory interface, but rather they need to be managed as methods of a program library that is linked to the main program core by using an internal interface that can be actuated
25 directly from the main program core. One of the advantages of this solution is that it is not necessary for large volumes of data to be written to or read in from the hard disk via external directories (as in the case of the first exemplary embodiment). Hence, the
30 comparatively slow hard disk write and read operations are dispensed with, which can raise the execution speed of the simulator. A possible source of error is also eliminated in this manner.

35 In relation to the operation of the "H controller" in the first exemplary embodiment in contrast to the "fast H controller" of the second exemplary embodiment, it is noted that the simple H controller involves the numerical calculation of two temperature distributions,

namely the basal temperature distribution and the relative temperature increment distribution, in a manner similar to that in MODE=1, by solving the BHTE twice. A loop is then called with i=10 passes, for example. For each pass, a predefined H field strength value H(i) serves as an input, so that calculations for a total of 10 H field strength values, e.g. from 5 kA/m to 14 kA/m, are performed in 1 kA/m steps. Each loop pass i=1...10 involves the determination of a power-absorption-based scaling factor K(i) by which the temperature increment distribution is multiplied. i=10 resultant temperature distributions are obtained, formed on the basis of the scaling scheme described further up. These i=1...10 temperature distributions are then written in succession to an external hard disk directory. From there, it can be loaded as required by the user.

Behind this approach to a solution, there is the assumption that the ten distributions (i=1...10) can be calculated in the background (in a manner similar to a batch job), while the user is looking at the temperature distribution ascertained in the first automatic pass (Mode=1) on the screen. This means that the user loses no time and, when he is finished looking at the temperature distribution, has 10 further temperature distributions available which cover the entire H field strength range that can be set. He can therefore change over between these temperature distributions. If he is interested in a specific value which lies between the firmly prescribed H(i) values, he could calculate a pass with Mode=2 (H selection) again for this value.

In the practical application, this requires a comparatively large amount of memory space on the hard disk for large data records, however, in order to store all 10 distributions; a typical value in this case is in the order of magnitude of 2 GBytes. Writing the 10

temperature distributions to the hard disk and reading them from the hard disk takes a correspondingly long time. Sequentially loading the temperature data records from the hard disk is associated with a series of
5 operations, for example loading the contours, calculating a catheter spline, etc., these possibly being comparable with a pass of the BHTE from the point of view of resource consumption. Sometimes, the advantage of changing over between the different
10 previously calculated data records is thus inexhaustible.

The "simple" H controller based on the first exemplary embodiment provides only temperature distributions for
15 firmly predefined H field strengths. If a value between the predefined values is of interest, it is necessary to start a temperature simulator pass, e.g. using the H selection (Mode=2). This means at least one numerical solution to the BHTE, that is to say a time-intensive
20 calculation.

The second exemplary embodiment realizes a different approach for the H controller, which in this case is called a "fast H controller". This is distinguished
25 from the simple H controller by speed, since it does not require a numerical solution to the BHTE, but rather scales the provided (previously calculated in the T selection step) relative temperature increment distribution. In other words, fast H controller
30 ascertains the power-absorption-based scaling factor K for a single H field strength value, and the respective temperature distribution is then formed on the basis of the scaling approach described further up.

35 The fast H controller therefore performs no time-consuming and memory space intensive advance calculation of multiple (for example 10) distributions, and is therefore particularly suitable for large data records, for example. Any desired H field strength

value can be set and can be calculated in a resource saving manner. However, the fast H controller requires a prior pass in Mode=1. The two temperature distributions calculated there need to be available to
5 the fast H controller as an input. Appropriate main memory space needs to be available.

The first exemplary embodiment of a simulator for a simulation tool therefore tends to require longer for
10 execution, and also requires more hard disk memory (this is usually not a problem for systems that are customary today), but requires less main memory. Hence, this simulator is sometimes particularly suitable for execution on a PC, for example a standalone PC, or else
15 a mobile computer such as a notebook or the like. By contrast, the second exemplary embodiment tends to work more quickly, particularly for processing H field strength values that are input by the user, and requires less hard disk memory space, but a larger main
20 memory. Hence, the second exemplary embodiment of a simulator for a simulation tool tends to be suitable for use on powerful computers such as workstations or in mainframe systems.

25 Further modifications of the exemplary embodiments are conceivable which result in hybrid forms between the functionalities described for the first and second exemplary embodiments. It is thus conceivable for an executable file such as sim_t.exe from the first
30 exemplary embodiment to write the basal temperature distribution and the relative temperature increment distribution to the hard disk, from where it can then be read in again by another executable file, such as sim_hr.exe, as described in the first exemplary
35 embodiment. In this way, it is possible to provide a "fast H controller" without numerically solving the BHTE again, but the writing and reading of the data to and from the hard disk might slow down the cycle. Nevertheless, this modification may be advantageous for

particular software configurations, hardware configurations and/or applications overall.

5 The invention is not limited to the exemplary embodiments described here and the aspects highlighted therein; on the contrary, a large number of modifications that are within the scope of action of a person skilled in the art are possible within the area indicated by the appended claims.

10

For the sake of completeness, the subject matter of the patent application establishing priority is repeated in briefly summarized form below:

15 1. A computer-aided simulation method for providing assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body, wherein the hyperthermia treatment comprises the application of
20 a magnetic field in a treatment volume by means of a magnetic field applicator, wherein thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic
25 nanoparticles deposited in the body, and wherein the method comprises the following steps:

- in a first calculation step ("T selection"), calculation of a field strength value that needs to be set on the applicator on the basis of a
30 geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment;
- in an optional second calculation step ("H controller"), calculation, for each field strength
35 value from a plurality of prescribed field strength values, of a temperature distribution that is to be expected for at least part of the body volume; and

- provision of the calculated field strength value and optionally the calculated temperature distribution in order to provide assistance for the user in planning the thermotherapy.

5

2. The method according to subject 1, wherein the temperature limit value or one of a plurality of temperature limit values relates to a maximum temperature only within the treatment volume that is to be heated.

10

3. The method according to subject 2, wherein the temperature limit value relates to a prescribed temperature maximum in a range from 60°C to 100°C, preferably 70°C to 90°C, particularly 80°C, in the treatment volume.

15

4. The method according to one of the preceding subjects, wherein the temperature limit value or one of a plurality of temperature limit values relates to a maximum temperature outside the treatment volume that is to be heated.

20

5. The method according to subject 4, wherein the temperature limit value relates to a prescribed temperature maximum in a range from 40°C to 45°C, particularly 43°C, outside the treatment volume.

25

6. The method according to one of the preceding subjects, wherein two temperature limit values which each relate to different volumes are used in the first calculation step ("T selection").

30

7. The method according to one of the preceding subjects, wherein the calculation result from the first calculation step ("T selection") is taken as a basis for automatically performing a third calculation step ("H selection") when the field strength value calculated in the first calculation step ("T

35

selection") is greater than a prescribed maximum field strength value, particularly a maximum settable field strength value on the applicator, wherein a temperature distribution that is to be expected is calculated in the third calculation step ("H selection") for the prescribed maximum field strength value.

8. The method according to one of the preceding subjects, wherein no temperature limit value is used in the calculations in the second calculation step ("H controller") and/or in the third calculation step ("H selection").

9. The method according to one of the preceding subjects, wherein the calculations in the second calculation step ("H controller") are performed for a plurality of prescribed field strength values that can be set on the applicator, preferably between 3 and 20 field strength values, particularly preferably between 5 and 10 field strength values.

10. The method according to one of the preceding subjects, wherein the second calculation step ("H controller") is initiated after the first ("T selection") and possibly third ("H selection") calculation steps by a user input.

11. The method according to one of the preceding subjects, wherein output of the calculation results is followed by the performance of a fourth calculation step ("H selection"), in which a user input of field strength is accepted and, on the basis of the accepted field strength, a temperature distribution that is to be expected is calculated.

12. The method according to one of the preceding subjects, wherein the calculation of the field strength value that is to be set in the first calculation step ("T selection") does not comprise an iteration in which

temperature distributions are calculated from chosen field strength values so as to iteratively arrive at the sought field strength value.

5 13. The method according to one of the preceding subjects, wherein the first calculation step ("T selection") has the following steps:

- calculation of an average power absorption density ("SAR_aver") in the applicator magnetic field in
 10 the deposit volume, wherein a relative power absorption density is calculated on the basis of a measured geometric distribution of the nanoparticles, a prescribed bioheat transfer equation is solved precisely once in order to
 15 obtain a basal temperature distribution without power absorption, and the bioheat transfer equation is solved precisely once in order to obtain a relative temperature increment distribution on the basis of the relative power
 20 absorption density; and wherein the relative power absorption density is scaled by a scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative
 25 temperature increment distribution;
- calculation, on the basis of the calculated average power absorption density and the calculated mass of the nanoparticles, of a
 30 reference power absorption rate ("SAR_Fe") which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example; and
- calculation of a field strength value on the basis
 35 of the calculated reference power absorption rate and a prescribed characteristic curve which relates to a relationship between reference power absorption rate and applied field strength.

14. The method according to one of the preceding subjects, wherein the calculation of the temperature distributions in the second calculation step ("H controller") comprises precisely two calculations of
 5 temperature distributions regardless of the number of prescribed field strength values.

15. The method according to one of the preceding subjects, wherein the second calculation step ("H controller") has the following steps:

- calculation of a relative power absorption density distribution (" $\Delta\text{SAR}(x,y,z)$ ") and a relative average power absorption density (" $\Delta\text{SAR}_{\text{aver}}$ ") on the basis of a measured geometric distribution of
 15 the nanoparticles;
- provision of a basal temperature distribution (" $T_0(x,y,z)$ ") on the basis of a solution to a prescribed bioheat transfer equation without power absorption, and provision of a relative
 20 temperature increment distribution (" $\Delta T(x,y,z)$ ") on the basis of a solution to the bioheat transfer equation with the calculated relative power absorption density distribution (" $\Delta\text{SAR}(x,y,z)$ ");
- performance of the following steps for each field
 25 strength value from the plurality of prescribed field strength values:
 - o calculation of a reference power absorption rate (" $\text{SAR}_{\text{Fe}(i)}$ ") which indicates the specific power absorption rate of an undiluted
 30 magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective field strength value and a prescribed characteristic curve which relates to a relationship between reference power
 35 absorption rate and applied field strength ;
 - o calculation, on the basis of the reference power absorption rate (" $\text{SAR}_{\text{Fe}(i)}$ ") and the calculated mass of the nanoparticles in the

deposit volume, of an average power absorption density ("SAR_aver(i)");

o calculation of a scaling factor ("K(i)") on the basis of the respective average power absorption density ("SAR_aver(i)") and the relative average power absorption density ("ΔSAR_aver");

o calculation of a respective temperature distribution ("T(x,y,z,i)") on the basis of the basal temperature distribution ("T0(x,y,z)"), the relative temperature increment distribution ("ΔT(x,y,z)") and the scaling factor ("K(i)").

16. A computer-aided simulation method ("T selection") for providing assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body, wherein the hyperthermia treatment comprises the application of a magnetic field in a treatment volume by means of a magnetic field applicator, wherein thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and/or superparamagnetic nanoparticles deposited in the body, wherein the method relates to the calculation of a field strength that needs to be set on the applicator on the basis of a geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment ("T selection"); wherein the method has the following steps:

- calculation of an average power absorption density ("SAR_aver") in the applicator magnetic field in the deposit volume, wherein a relative power absorption density is calculated on the basis of a measured geometric distribution of the nanoparticles, a prescribed bioheat transfer equation is solved precisely once in order to

obtain a basal temperature distribution without
 power absorption, and the bioheat transfer
 equation is solved precisely once in order to
 obtain a relative temperature increment
 5 distribution on the basis of the relative power
 absorption density; and wherein the relative power
 absorption density is scaled by a scaling factor
 which is obtained on the basis of the at least one
 10 prescribed temperature limit value, the basal
 temperature distribution and the relative
 temperature increment distribution;
 - calculation, on the basis of the calculated
 average power absorption density and the
 calculated mass of the nanoparticles, of a
 15 reference power absorption rate ("SAR_Fe") which
 indicates the specific power absorption rate of an
 undiluted magnetic fluid containing the nano-
 particles, for example;
 - calculation of a field strength value on the basis
 20 of the calculated reference power absorption rate
 and a prescribed characteristic curve which
 relates to a relationship between reference power
 absorption rate and applied field strength ; and
 - provision of the calculated field strength value
 25 for providing assistance for the user in planning
 the thermotherapy.

17. A computer-aided simulation method ("H controller")
 for providing assistance in thermotherapy planning,
 30 wherein the thermotherapy comprises hyperthermia
 treatment of a tumor volume in a body volume of a human
 body, wherein the hyperthermia treatment comprises the
 application of a magnetic field in a treatment volume
 by means of a magnetic field applicator, wherein
 35 thermal energy can be introduced into at least one
 deposit volume by power absorption in the applied
 magnetic field by means of magnetic, paramagnetic
 and/or superparamagnetic nanoparticles deposited in the
 body, wherein the method relates to the calculation,

for each field strength value from a plurality of prescribed field strength values, of a temperature distribution that is to be expected for at least some of the body volume ("H controller"); and wherein the

5 method has the following steps:

- calculation of a relative power absorption density distribution (" $\Delta\text{SAR}(x,y,z)$ ") and a relative average power absorption density (" $\Delta\text{SAR}_{\text{aver}}$ ") on the basis of a measured geometric distribution of the nanoparticles;
10
- provision of a basal temperature distribution (" $T_0(x,y,z)$ ") on the basis of a solution to a prescribed bioheat transfer equation without power absorption, and provision of a relative temperature increment distribution (" $\Delta T(x,y,z)$ ") on the basis of a solution to the bioheat transfer equation with the calculated relative power absorption density (" $\Delta\text{SAR}(x,y,z)$ ");
15
- performance of the following steps for each field strength value from the plurality of prescribed field strength values:
20
 - o calculation of a reference power absorption rate (" $\text{SAR}_{\text{Fe}(i)}$ ") which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective field strength value and a prescribed characteristic curve which relates to a relationship between reference power absorption rate and applied field strength ;
25
 - o calculation, on the basis of the reference power absorption rate (" $\text{SAR}_{\text{Fe}(i)}$ ") and the calculated mass of the nanoparticles in the deposit volume, of an average power absorption density (" $\text{SAR}_{\text{aver}(i)}$ ");
30
 - o calculation of a scaling factor (" $K(i)$ ") on the basis of the respective average power absorption density (" $\text{SAR}_{\text{aver}(i)}$ ") and the
35

relative power absorption density
 ("ASAR_aver");

o calculation of a respective temperature
 distribution ("T(x,y,z,i)") on the basis of
 5 the basal temperature distribution
 ("T0(x,y,z)"), the relative temperature
 increment distribution ("ΔT(x,y,z)") and the
 scaling factor ("K(i)");

- provision of the calculated temperature
 10 distributions in order to provide assistance for
 the user in planning the thermotherapy.

18. A computer program for carrying out the method
 according to one of the preceding subjects when the
 15 computer program is executed on a programmable computer
 device.

19. A data storage medium on which the computer program
 according to subject 18 is recorded.

20

20. A computer device designed for providing assistance
 in thermotherapy planning,
 wherein the thermotherapy comprises hyperthermia
 treatment of a tumor volume in a body volume of a human
 25 body,
 wherein the hyperthermia treatment comprises the
 application of a magnetic field in the treatment volume
 by means of a magnetic field applicator,
 wherein thermal energy can be introduced into at least
 30 one deposit volume by power absorption in the applied
 magnetic field by means of magnetic, paramagnetic
 and/or superparamagnetic nanoparticles deposited in the
 body,
 and wherein the computer device comprises the following
 35 components:

- a first calculation component ("sim_t.exe")
 designed to calculate a field strength value that
 needs to be set on the applicator on the basis of
 a geometric distribution of the nanoparticles and

at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment;

- a second calculation component ("sim_hr.exe"),
5 designed to optionally calculate, for each field strength value from a plurality of prescribed field strength values, a temperature distribution that is to be expected for at least some of the body volume; and
- 10 - a component for providing the calculated field strength value and optionally the calculated temperature distributions in order to provide assistance for the user in planning the
thermotherapy.

15

21. A computer device designed for providing assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body, wherein the hyperthermia
20 treatment comprises the application of a magnetic field in the treatment volume by means of a magnetic field applicator, wherein thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic,
25 paramagnetic and/or superparamagnetic nanoparticles deposited in the body, wherein the computer device has a component ("sim_t.exe") which is designed to calculate a field strength that needs to be set on the applicator on the basis of a geometric distribution of
30 the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment; and wherein the component ("sim_t.exe") has the following modules:

- a module for calculating an average power
35 absorption density in the applicator magnetic field in the deposit volume, wherein a relative power absorption density is calculated on the basis of a measured geometric distribution of the nanoparticles, a prescribed bioheat transfer

- equation is solved precisely once in order to obtain a basal temperature distribution without power absorption, and the bioheat transfer equation is solved precisely once in order to obtain a relative temperature increment distribution on the basis of the relative power absorption density; and wherein the relative power absorption density is scaled by a scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution;
- a module for calculating, on the basis of the calculated average power absorption density and the calculated mass of the nanoparticles, a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example;
 - a module for calculating a field strength value on the basis of the calculated reference power absorption rate and a prescribed characteristic curve which relates to a relationship between reference power absorption rate and applied field strength; and
 - a module for providing the calculated field strength value in order to provide assistance for the user in planning the thermotherapy.
22. A computer device designed for providing assistance in thermotherapy planning, wherein the thermotherapy comprises hyperthermia treatment of a tumor volume in a body volume of a human body, wherein the hyperthermia treatment comprises the application of a magnetic field in the treatment volume by means of a magnetic field applicator, wherein thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic

and/or superparamagnetic nanoparticles deposited in the body, wherein the computer device has a component ("sim_hr.exe") which is designed to calculate, for each field strength value from a plurality of prescribed
 5 field strength values, a temperature distribution that is to be expected for at least some of the body volume; and wherein the component ("sim_hr.exe") has the following modules:

- a module for calculating a relative power
 10 absorption density distribution and a relative average power absorption density on the basis of a measured geometric distribution of the nanoparticles;
- a module for providing a basal temperature
 15 distribution on the basis of a solution to a prescribed bioheat transfer equation without power absorption, and providing a relative temperature increment distribution on the basis of a solution to the bioheat transfer equation with the
 20 calculated relative power absorption density distribution;
- a module for performing the following steps for each field strength value from the plurality of prescribed field strength values:
 - 25 o calculation of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the
 30 respective field strength value and a prescribed characteristic curve which relates to a relationship between reference power absorption rate and applied field strength;
 - 35 o calculation, on the basis of the reference power absorption rate and the calculated mass of the nanoparticles in the deposit volume, of an average power absorption density;
 - o calculation of a scaling factor on the basis of the respective average power absorption

- density and the relative power absorption density;
- o calculation of a respective temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the scaling factor;
- a module for providing the calculated temperature distributions in order to provide assistance for the user in planning the thermotherapy.

23. A system, comprising a computer device according to one of subjects 20 to 22 and a magnetic field applicator.

24. A system, comprising a computer program according to subject 18, a data storage medium according to subject 19, a computer device according to one of subjects 20 to 22 or a system according to subject 23, and also comprising a magnetic fluid containing magnetic nanoparticles.

25. A method for controlled heating of an organ or tissue, containing the steps of
- A) introduction of magnetic, paramagnetic and/or superparamagnetic particles into an organ volume or tissue volume,
 - B) ascertainment of the particle quantity and/or distribution in the organ volume or tissue volume,
 - C) calculation of a field strength that is able to be set on the basis of the method according to subject 1 or 16 or of a temperature distribution on the basis of the method according to subject 17,
 - D) deposition of thermal energy by means of application of a magnetic field, wherein the applied field strength corresponds to the calculated field strength or to the field strength derived from a calculated temperature

distribution, in each case with a deviation of +/- 10%, preferably +/- 5%, particularly +/- 1%.

26. A method for treating a tumor in a patient,
5 containing the steps of
- A) introduction of magnetic, paramagnetic and/or superparamagnetic particles into a tumor volume,
 - B) ascertainment of the particle quantity and/or distribution in the tumor volume,
 - 10 C) calculation of a field strength that is able to be set on the basis of the method according to subject 1 or 16 or of a temperature distribution on the basis of the method according to subject 17,
 - 15 D) deposition of thermal energy by means of application of a magnetic field, wherein the applied field strength corresponds to the calculated field strength or to the field strength derived from a calculated temperature
20 distribution, in each case with a deviation of +/- 10%, preferably +/- 5%, particularly +/- 1%.

2,828,139

CLAIMS

1. A computer-aided simulation method for providing assistance to a user in
thermotherapy planning,

5 wherein the thermotherapy comprises hyperthermia treatment of a tumor
volume in a body volume of a human body,

wherein the hyperthermia treatment comprises an application of a magnetic
field in a treatment volume by means of a magnetic field applicator,

10 wherein thermal energy can be introduced into at least one deposit volume by
power absorption in the applied magnetic field by means of magnetic,
paramagnetic and superparamagnetic nanoparticles deposited in the body,

and wherein the method comprises the following steps:

15 in a first calculation step ("T selection"), calculation of a field strength value that
needs to be set on the applicator on the basis of a geometric distribution of the
nanoparticles and at least one prescribed temperature limit value which is not
meant to be exceeded by the hyperthermia treatment;

20 wherein the field strength value is calculated in the first calculation step ("T
selection") on the basis of a prescribed characteristic curve which indicates a
relationship between a reference power absorption rate ("SAR_Fe") and the
field strength value.

2. The method of claim 1, wherein the field strength value is also calculated in the
first calculation step ("T selection") on the basis of at least one calculated
temperature distribution for supporting the user in planning the thermotherapy.

3. The method of claim 1, wherein the method comprises the following further step after the first calculation step: in a second calculation step ("H controller", "fast H controller") calculation of a temperature distribution that is to be expected for at least part of the body volume for:

5 each field strength value from a plurality of prescribed field strength values,
 and
 a user-defined field strength value.

4. The method of any one of claims 1 to 3, wherein a temperature limit value or one of a plurality of temperature limit values relates to a maximum temperature only within the treatment volume that is to be heated wherein the temperature limit value relates to a prescribed temperature maximum in a range from 60°C to 100°C, in the treatment volume, and/or the temperature limit value or one of a plurality of temperature limit values relates to a maximum temperature outside the treatment volume that is to be heated, wherein the temperature limit value relates to a prescribed temperature maximum in a range from 40°C to 45°C outside the treatment volume.

5. The method of claim 3 or 4, wherein a) no temperature limit value is used in the calculations in the second calculation step ("H controller", "fast H controller"), or b) the calculations in the second calculation step ("H controller") are performed for a plurality of prescribed field strength values that can be set on the applicator, between 3 kA/m and 20 kA/m, or c) the second calculation step ("H controller", "fast H controller") is initiated after the first calculation step ("T selection") and possibly a third ("H selection") calculation step by a user input.

6. The method of any one of claims 1 to 4, wherein a) a calculation result from the first calculation step ("T selection") is taken as a basis for automatically performing a third calculation step ("H selection") when the field strength value calculated in the first calculation step ("T selection") is greater than a prescribed maximum field strength value, particularly a maximum settable field strength value on the applicator, wherein a temperature distribution that is to be expected is calculated in the third calculation step ("H selection") for the prescribed maximum field strength value, or b) no temperature limit value is used in the calculations in the third calculation step ("H selection"), or c) the calculation of the field strength value that is to be set in the first calculation step ("T selection") does not comprise an iteration in which the temperature distributions are calculated from chosen field strength values so as to iteratively arrive at a sought field strength value.

7. The method of any one of claims 1 to 3, wherein the first calculation step ("T selection") has the following steps:

calculation of an average power absorption density ("SAR_aver") in the applicator magnetic field in the at least one deposit volume, wherein a relative power absorption density (" $\Delta\text{SAR}(x,y,z)$ ") is calculated on the basis of a measured geometric distribution of the nanoparticles, a bioheat transfer equation describing a model is numerically solved precisely once in order to obtain a basal temperature distribution (" $T_0(x,y,z)$ ") without power absorption, and the bioheat transfer equation is numerically solved precisely once in order to obtain a relative temperature increment distribution (" $\Delta T(x,y,z)$ ") on the basis of the relative power absorption density; and wherein the relative power absorption density (" $\Delta\text{SAR}(x,y,z)$ ") is scaled by a temperature-based scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution;

calculation, on the basis of the calculated average power absorption density and a calculated mass of the nanoparticles, of a reference power absorption rate ("SAR_Fe") which indicates a specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example;

5 calculation of the field strength value ("H") on the basis of the calculated reference power absorption rate ("SAR_Fe") and the prescribed characteristic curve which relates to a relationship between reference power absorption rate ("SAR_Fe") and applied field strength value ("H"); and

10 optional calculation of a respective temperature distribution (" $T(x,y,z)$ ") on the basis of the basal temperature distribution (" $T_0(x,y,z)$ "), the relative temperature increment distribution (" $\Delta T(x,y,z)$ ") and the temperature-based scaling factor;

15 wherein the basal temperature distribution (" $T_0(x,y,z)$ ") and/or the relative temperature increment distribution (" $\Delta T(x,y,z)$ ") are provided for at least one further use ("fast H controller") beyond the first calculation step.

8. The method of claim 7, wherein a) in the second calculation step ("fast H controller"), regardless of prescribed or user-defined field strength values, the provided basal temperature distribution (" $T_0(x,y,z)$ "), previously calculated in the first calculation step, and the provided relative temperature increment distribution (" $\Delta T(x,y,z)$ "), previously calculated in the first calculation step, are used, or b) in the second calculation step ("H controller"), regardless of a number of prescribed and/or user-defined field strength values, no more than two temperature distributions are calculated, namely the basal temperature distribution (" $T_0(x,y,z)$ ") and/or the relative temperature increment distribution (" $\Delta T(x,y,z)$ ").

9. The method of any one of claims 7 to 8, wherein in the second calculation step (H controller", "fast H controller"), the temperature distribution that is to be expected is calculated by means of power-absorption-based scaling of the calculated or provided relative temperature increment distribution ($\Delta T(x,y,z)$).

5

10. The method of any one of claims 8 to 9, wherein the second calculation step ("H controller", "fast H controller") has the following steps:

i) calculation of the relative power absorption density (" $\Delta SAR(x,y,z)$ ") and a relative average power absorption density (" ΔSAR_{aver} ") on the basis of the measured geometric distribution of nanoparticles;

10

ii) provision of the basal temperature distribution (" $T_0(x,y,z)$ ") on the basis of a numerical solution to the bioheat transfer equation describing a model without power absorption, and provision of the relative temperature increment distribution (" $\Delta T(x,y,z)$ ") on the basis of the numerical solution to the bioheat transfer equation with the calculated relative power absorption density (" $\Delta SAR(x,y,z)$ ");

15

iii) performance of the following steps for each field strength value from the plurality of prescribed field strength values and the user-defined field strength value:

a) calculation of the reference power absorption rate (" SAR_{Fe} ") which indicates the specific power absorption rate of the undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective field strength value (" H ") and the prescribed characteristic curve which relates to the relationship between the reference power absorption rate (" SAR_{Fe} ") and applied field strength value (" H ");

20

b) calculation, on the basis of the reference power absorption rate ("SAR_Fe") and the calculated mass of the nanoparticles in the deposit volume, of the average power absorption density ("SAR_aver");

c) calculation of a power-absorption-based scaling factor on the basis of the respective average power absorption density ("SAR_aver") and the relative average power absorption density ("ΔSAR_aver"); and

d) calculation of the respective temperature distribution ("T(x,y,z)") on the basis of the basal temperature distribution ("T0(x,y,z)"), the relative temperature increment distribution ("ΔT(x,y,z)") and the power-absorption-based scaling factor.

11. The method of claim 1, wherein the method has the following steps:

calculation of an average power absorption density ("SAR_aver") in the applicator magnetic field in the deposit volume, wherein a relative power absorption density ("ΔSAR(x,y,z)") is calculated on the basis of a measured geometric distribution of the nanoparticles, a bioheat transfer equation describing a model is numerically solved precisely once in order to obtain a basal temperature distribution ("T0(x,y,z)") without power absorption, and the bioheat transfer equation is numerically solved precisely once in order to obtain a relative temperature increment distribution ("ΔT(x,y,z)") on the basis of the relative power absorption density; and wherein the relative power absorption density ("ΔSAR(x,y,z)") is scaled by a temperature-based scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution;

calculation, on the basis of the calculated average power absorption density and a calculated mass of the nanoparticles, of the reference power absorption rate

("SAR_Fe") which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example;

calculation of the field strength value ("H") on the basis of the calculated the reference power absorption rate ("SAR_Fe") and the prescribed characteristic curve which relates to the relationship between the reference power absorption rate ("SAR_Fe") and applied field strength value ("H");

optional calculation of a respective temperature distribution ("T(x,y,z)") on the basis of the basal temperature distribution ("T0(x,y,z)"), the relative temperature increment distribution ("ΔT(x,y,z)") and the temperature-based scaling factor;

provision of the calculated field strength value ("H") in order to provide assistance for the user in planning the thermotherapy; and

optional provision of the calculated temperature distribution ("T(x,y,z)") in order to provide assistance for the user in planning the thermotherapy.

12. A computer device designed for a computer-aided simulation method as claimed in any one of claims 1 to 10, wherein the computer device comprises:

a first calculation component ("sim t.exe", "mainsubroutine_sim_t_voxel win") designed to calculate the field strength value that needs to be set on the applicator on the basis of the geometric distribution of the nanoparticles and at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment;

a second calculation component ("sim_hr.exe", "mainsubroutine_sim_hr_voxel win"), designed to calculate "the temperature distribution that is to be expected for at least some of the body volume for each field strength value from the plurality of prescribed field strength values, and/or the user-defined field strength value; and

a third component for providing the calculated field strength value in order to provide assistance for the user in planning the thermotherapy.

5 **13.** The computer device of claim 12, wherein the third component for providing the calculated field strength value also provides at least one calculated temperature distribution in order to provide assistance for the user in planning the thermotherapy.

10 **14.** A computer device designed for a computer-aided simulation method as claimed in claim 11, wherein the computer device has a component ("sim_t.exe", "mainsubroutine_sim_t_voxel_win") which is designed to calculate the field strength value that needs to be set on the applicator on the basis of the geometric distribution of the nanoparticles and, the at least one prescribed temperature limit value which is not meant to be exceeded by the hyperthermia treatment; and
15 wherein the component ("sim_t.exe", "mainsubroutine_sim_t_voxel_win") has a module for calculating the field strength value on the basis of the prescribed characteristic curve, wherein the characteristic curve indicates the relationship between power absorption rate and field strength value, wherein the computer device has the following module:

20 a module for calculating the average power absorption density in the applicator magnetic field in the deposit volume, wherein the relative power absorption density is calculated on the basis of a measured geometric distribution of the nanoparticles, a bioheat transfer equation describing a model is numerically solved precisely once in order to obtain the basal temperature distribution
25 without power absorption, and the bioheat transfer equation is numerically solved precisely once in order to obtain the relative temperature increment distribution on the basis of the relative power absorption density; and wherein

the relative power absorption density is scaled by the scaling factor which is obtained on the basis of the at least one prescribed temperature limit value, the basal temperature distribution and the relative temperature increment distribution ("temperature-based scaling factor");

5 a module for calculating, on the basis of the calculated average power absorption density and a calculated mass of the nanoparticles, the reference power absorption rate which indicates the specific power absorption rate of the undiluted magnetic fluid containing the nanoparticles, for example;

10 a module for calculating the field strength value on the basis of the calculated reference power absorption rate and the prescribed characteristic curve which relates to the relationship between the reference power absorption rate and applied field strength value; and

a module for providing the calculated field strength value in order to provide assistance for the user in planning the thermotherapy.

15
15. The computer device of claim 14, wherein the computer device further has the following module:

20 a module for calculating the respective temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the temperature-based scaling factor.

16. The computer device of claim 14 or 15, wherein the computer device further has the following module:

25 a module for providing the calculated temperature distributions in order to provide assistance for the user in planning the thermotherapy.

17. A computer device designed for executing a computer-aided simulation method for providing assistance in thermotherapy planning, the thermotherapy comprising hyperthermia treatment of a tumor volume in a body volume of a human body, the hyperthermia treatment comprising an application of a magnetic field in a treatment volume by means of a magnetic field applicator, wherein thermal energy can be introduced into at least one deposit volume by power absorption in the applied magnetic field by means of magnetic, paramagnetic and superparamagnetic nanoparticles deposited in the body, wherein the method comprises calculation, for each field strength value from a plurality of prescribed field strength values and a user-defined field strength value, of a temperature distribution that is to be expected for at least some of the body volume; wherein the temperature distribution that is to be expected is calculated by means of power-absorption-based scaling of a calculated or provided relative temperature increment distribution (" $\Delta T(x,y,z)$ "); wherein either:
- a) a provided basal temperature distribution (" $T_0(x,y,z)$ ") and/or the provided relative temperature increment distribution (" $\Delta T(x,y,z)$ ") is used;
 - or
 - b) no more than two temperature distributions are calculated, namely the basal temperature distribution (" $T_0(x,y,z)$ ") and/or the relative temperature increment distribution (" $\Delta T(x,y,z)$ ");
- wherein the computer device has a component (" sim_hr.exe ", " $\text{mainsubroutine_sim_hr_voxel_win}$ ") which is designed to calculate, for each field strength value from the plurality of prescribed field strength values and the

user-defined field strength value, the temperature distribution that is to be expected for at least some of the body volume;

and wherein the component ("sim_hr.exe",
"mainsubroutine_sim_hr_voxel_win") has a module for calculating the
5 temperature distribution that is to be expected by means of power-absorption-
based scaling of the calculated or provided temperature increment distribution
("ΔT(x,y,z)"), wherein:

a) the component ("mainsubroutine_sim_hr_voxel_win") is designed to
calculate the temperature distribution that is to be expected in order to
10 use, regardless of prescribed and/or user-defined field strength values,
the provided basal temperature distribution ("T0(x,y,z)"), previously
calculated in the component "mainsubroutine_sim_t_voxel_win", and/or
the provided relative temperature increment distribution ("ΔT(x,y,z)")
("fast H controller"), previously calculated in the component
15 "mainsubroutine_sim_t_voxel_win", or

b) the component ("sim_hr.exe") for calculating the temperature
distribution that is to be expected is designed to calculate, regardless of
the number of prescribed and/or user-defined field strength values, no
more than two temperature distributions ("H controller"), namely the basal
20 temperature distribution ("T0(x,y,z)") and/or the relative temperature
increment distribution ("ΔT(x,y,z)").

18. The computer device of claim 17, wherein the computer device has the following
modules ("H controller", "fast H controller"):

25 a module for calculating a relative power absorption density distribution and a
relative average power absorption density on the basis of a measured geometric
distribution of the nanoparticles;

a module for providing the basal temperature distribution on the basis of a numerical solution to a bioheat transfer equation describing a model without power absorption, and providing the relative temperature increment distribution on the basis of the numerical solution to the bioheat transfer equation with the calculated relative power absorption density distribution;

a module for performing the following steps for each field strength value from the plurality of prescribed field strength values and the user-defined field strength value:

calculation of a reference power absorption rate which indicates the specific power absorption rate of an undiluted magnetic fluid containing the nanoparticles, for example, wherein the calculation is based on the respective field strength value and a prescribed characteristic curve which relates to a relationship between reference power absorption rate and applied field strength value;

calculation, on the basis of the reference power absorption rate and a calculated mass of the nanoparticles in the deposit volume, of an average power absorption density;

calculation of the power-absorption-based scaling factor on the basis of the respective average power absorption density and the relative power absorption density;

calculation of a respective temperature distribution on the basis of the basal temperature distribution, the relative temperature increment distribution and the power-absorption-based scaling factor;

a module for providing the calculated temperature distributions in order to provide assistance for the user in planning the thermotherapy.

19. A system, comprising a computer device of any one of claims **17** to **18** and a magnetic field applicator.

20. A system, comprising a magnetic fluid containing magnetic nanoparticles and a)
5 the computer readable memory as claimed in claim **10**, or b) the computer
program product as claimed in claim **11**, or c) the computer device as claimed in
one of claims **12** to **18** and the magnetic field applicator.

Figures

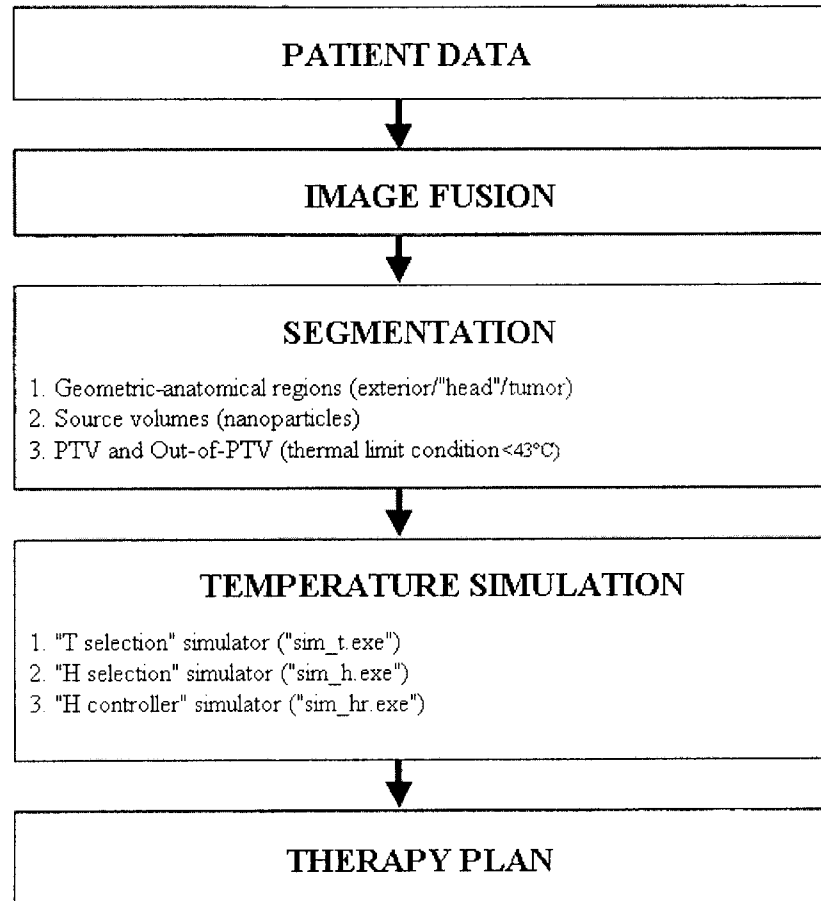
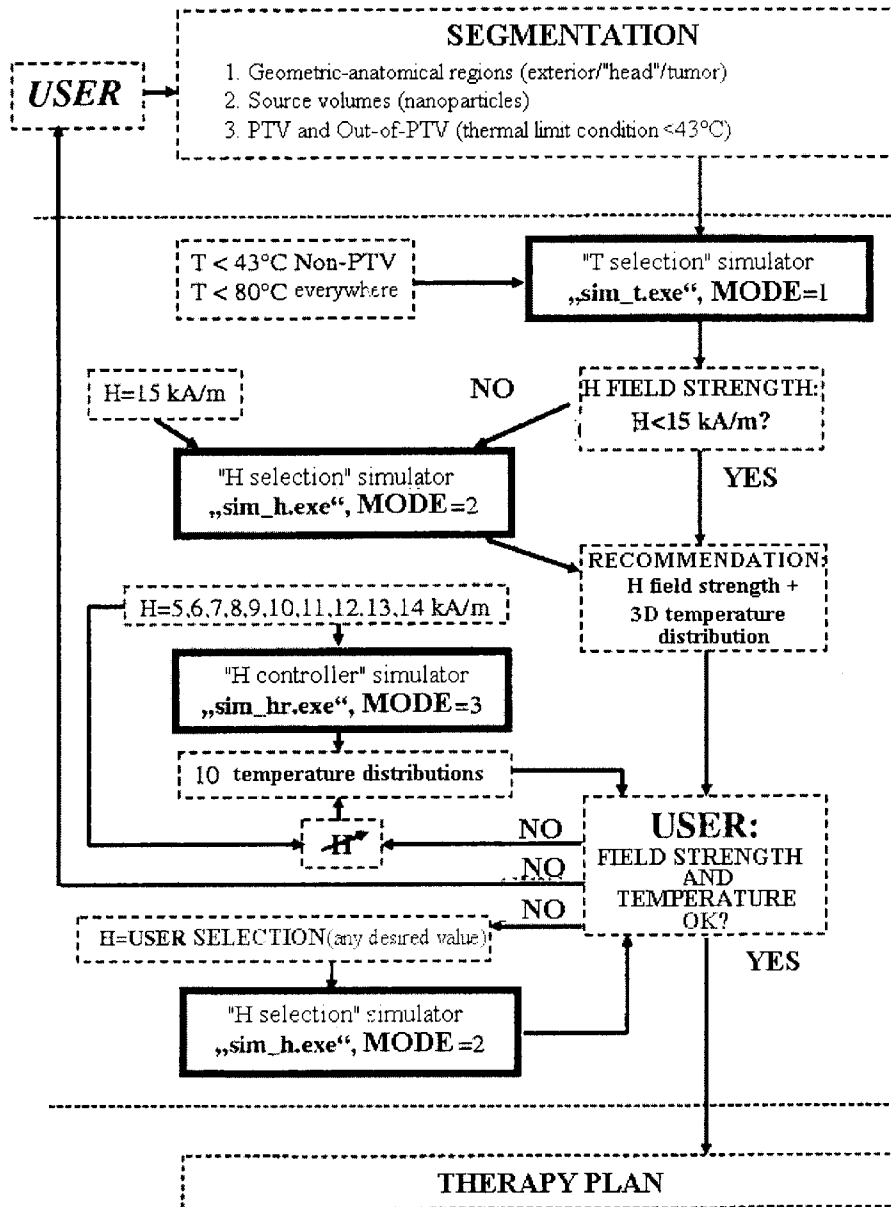
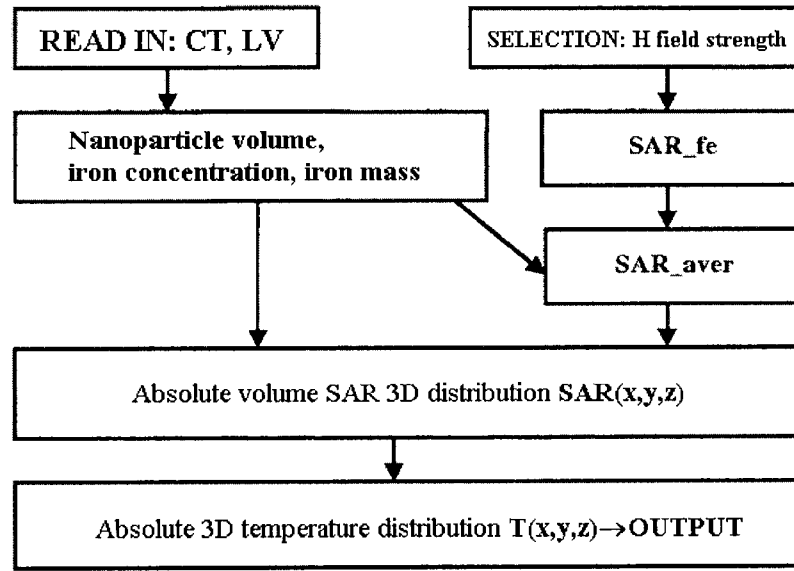
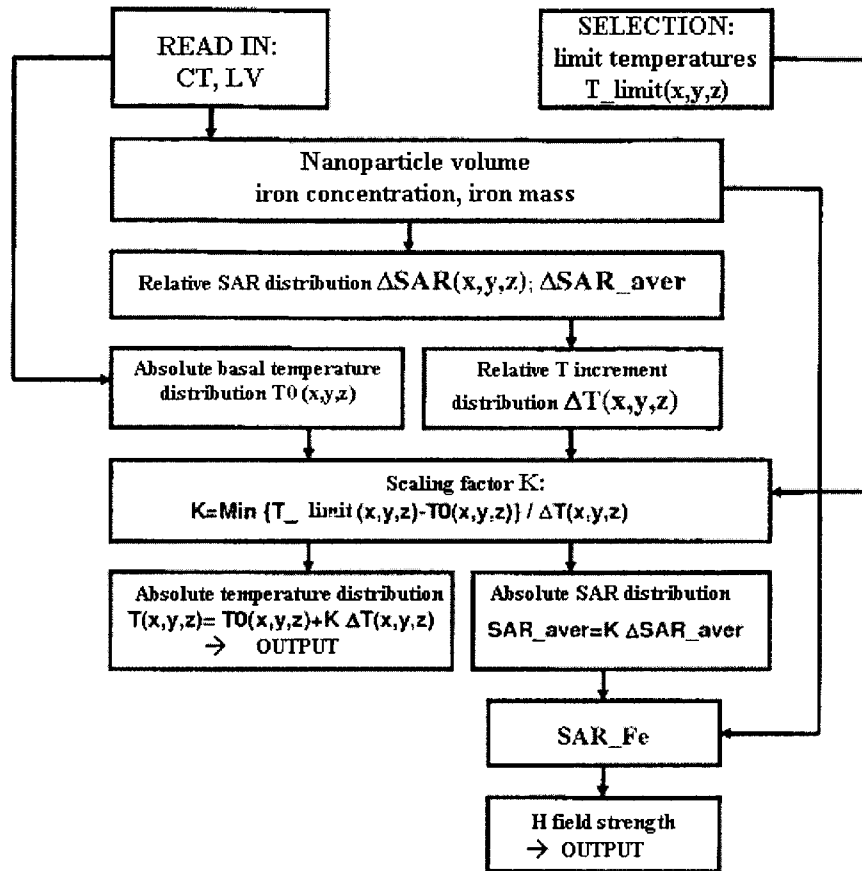


Fig. 1

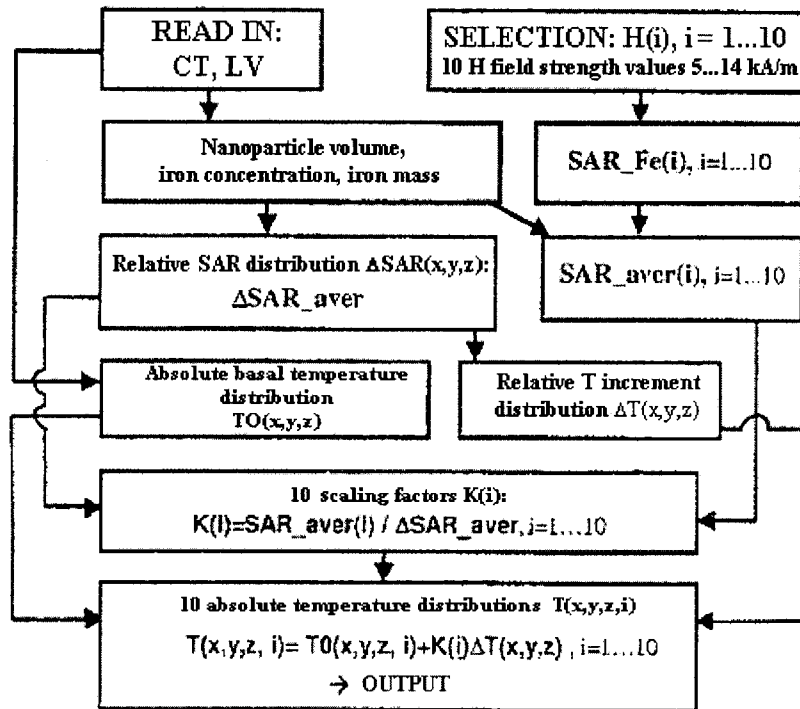
**Fig. 2**

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**Fig. 3**

**Fig. 4**

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**Fig. 5**

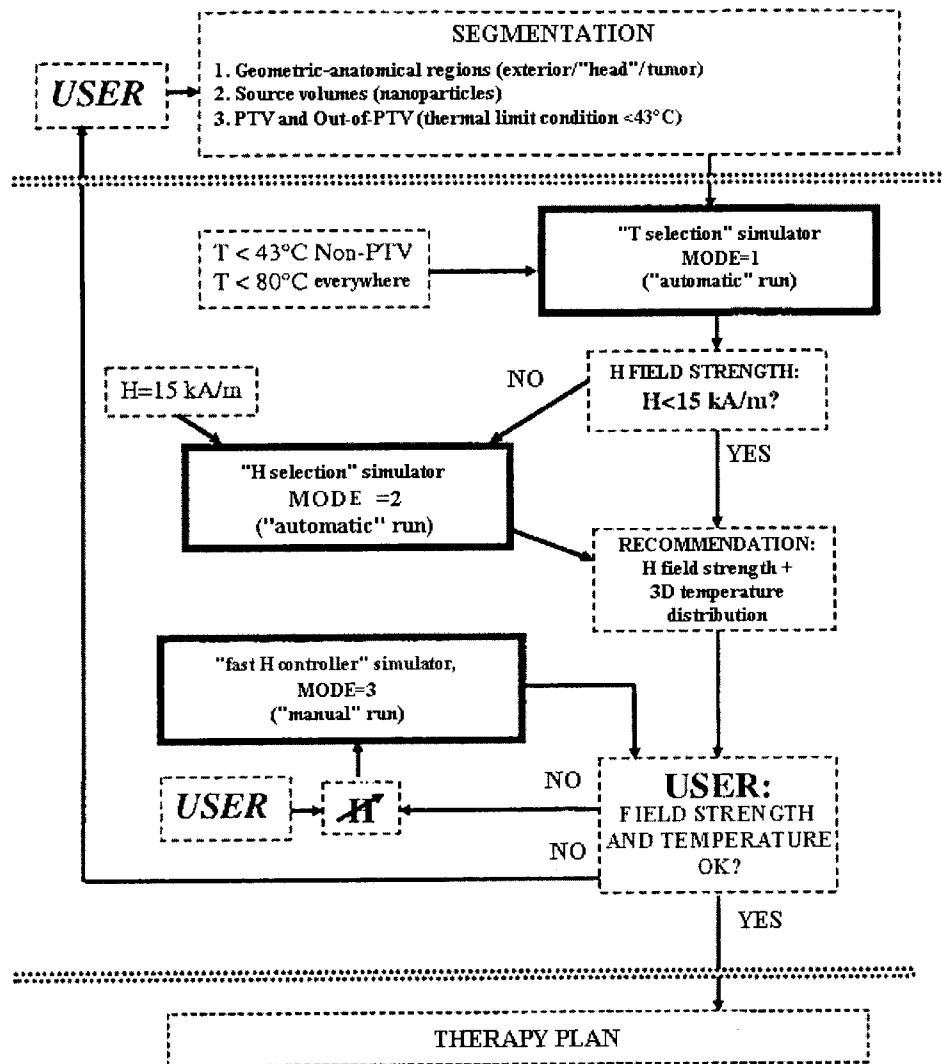
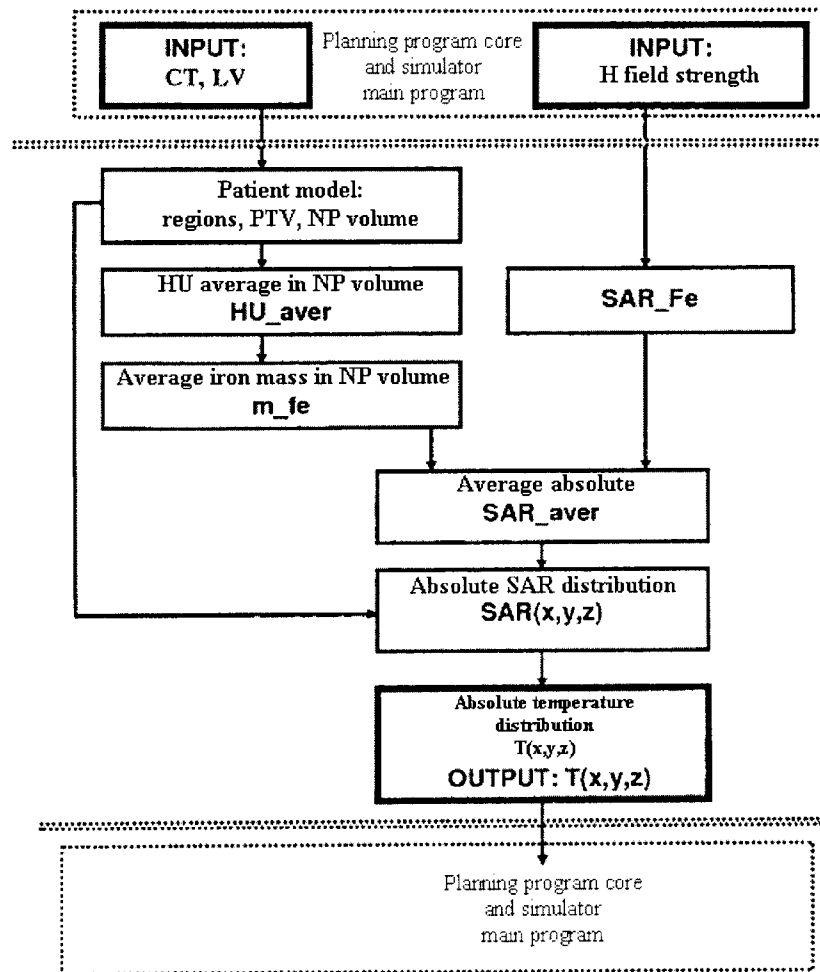
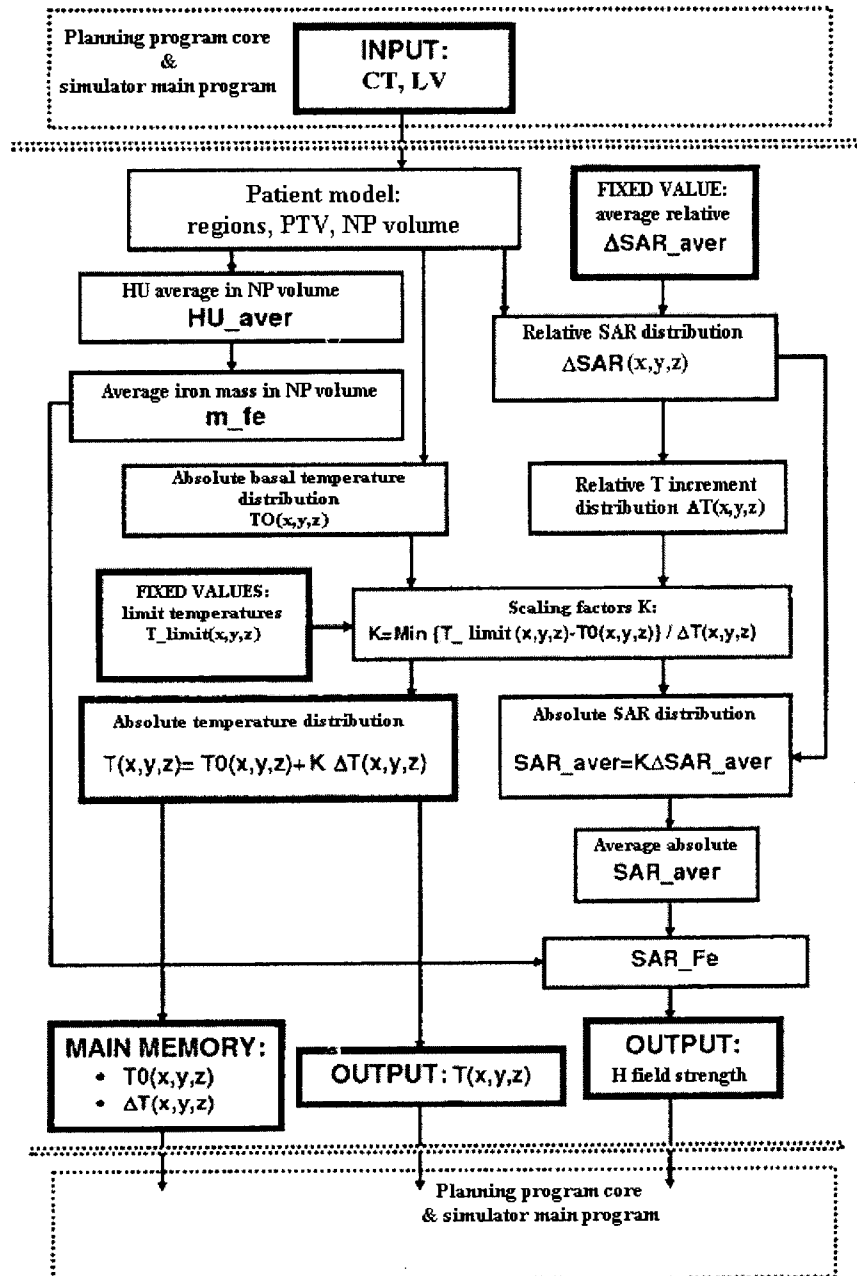


Fig. 6

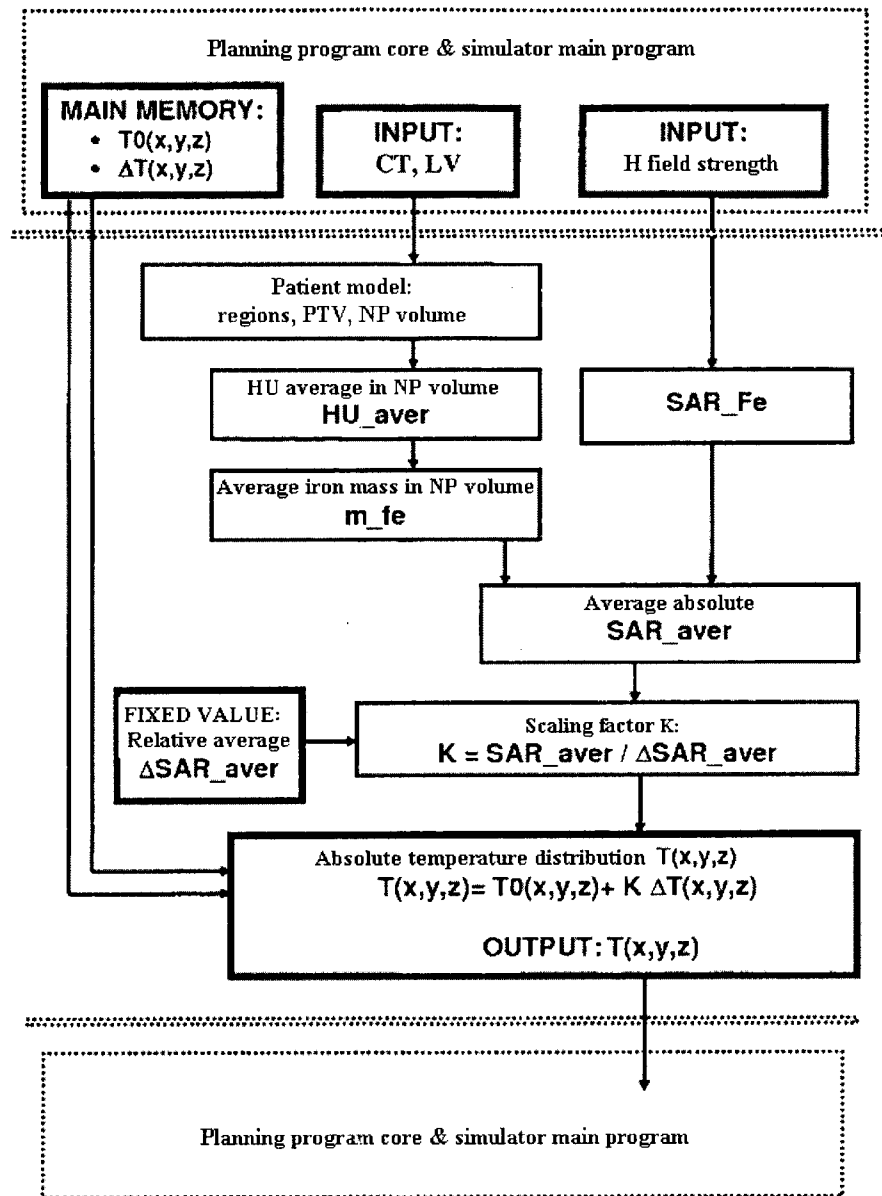
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**Fig. 7**

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**Fig. 8**

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**Fig. 9**

Planning program core & simulator main program

MAIN MEMORY:

- $T_0(x,y,z)$
- $\Delta T(x,y,z)$

INPUT:
CT, LV

INPUT:
H field strength

Patient model:
regions, PTV, NP volume

HU average in NP volume
 HU_{aver}

Average iron mass in NP volume
 m_{fe}

SAR_{Fe}

Average absolute
 SAR_{aver}

FIXED VALUE:
Relative average
 ΔSAR_{aver}

Scaling factor K:
 $K = SAR_{aver} / \Delta SAR_{aver}$

Absolute temperature distribution $T(x,y,z)$
 $T(x,y,z) = T_0(x,y,z) + K \Delta T(x,y,z)$

OUTPUT: $T(x,y,z)$

Planning program core & simulator main program