

University of Groningen

Positioning system for radiotherapy

Both, Stefan; Guterres Marmitt, Gabriel

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Both, S., & Guterres Marmitt, G. (2023). Positioning system for radiotherapy. (Patent No. WO2023163589).

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



(51) International Patent Classification:
A61N 5/10 (2006.01)

(21) International Application Number:
PCT/NL2023/050085

(22) International Filing Date:
21 February 2023 (21.02.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
22158005.3 22 February 2022 (22.02.2022) EP

(71) Applicants: **RIJKSUNIVERSITEIT GRONINGEN** [NL/NL]; Broerstraat 5, 9712 CP Groningen (NL). **ACADEMISCH ZIEKENHUIS GRONINGEN** [NL/NL]; Hanzeplein 1, 9713 GZ Groningen (NL).

(72) Inventors: **BOTH, Stefan**; Radiotherapy Department, Universitair Medisch Centrum Groningen, Hanzeplein 1, 9713 GZ Groningen (NL). **MARMITT, Gabriel Guterres**; Radiotherapy Department, Universitair Medisch Centrum Groningen, Hanzeplein 1, 9713 GZ Groningen (NL).

(74) Agent: **WITMANS, H.A.**; V.O., P.O. Box 87930, 2508 DH Den Haag (NL).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,

(54) Title: POSITIONING SYSTEM FOR RADIOTHERAPY

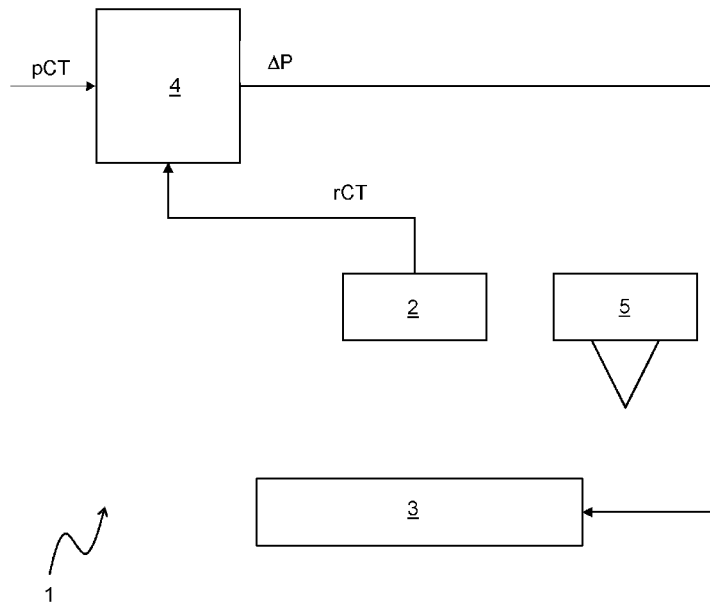


FIG 1

(57) Abstract: A system (1) for positioning a patient for radiotherapy in accordance with patient specific data including a first volumetric image (e.g. a pCT image) of the patient comprising tissue label data and dose specification data is provided that comprises an imaging device (2), a positioning device (3) and an optimization controller (4). The imaging device (2) is configured to provide a second volumetric image (e.g. an rCT image) of the patient including a designated part of the patient to be treated. The positioning device (3) is provided to hold the patient in a variable position and/or orientation in the beam of radiation for an accurate intervention to a designated part of the patient. The optimization controller (4) comprises a dose based control module configured to provide registration control data (ΔP) to guide the positioning device (3) so that the actually applied treatment dose optimally matches the planned treatment dose.



TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*

Title: Positioning system for radiotherapy

Field

The present invention pertains to a positioning system for radiotherapy.

5 The present invention further pertains to a training system.

The present invention still further pertains to a training method.

Background

10 Radiotherapy (also called radiation therapy) is a cancer treatment that uses high doses of ionizing radiation to kill cancer cells and shrink tumors. As a preparation for the treatment, a radiation oncologist in collaboration with a medical physicist and a radiation therapist designs a treatment plan that aims to result in an effective irradiation of malignant area(s), while minimizing exposure to healthy tissue.

15 The radiation oncologist bases the treatment plan on the location of the malignant area(s) from a 3D/4D CT image of the patient obtained prior to the treatment. In this connection it is noted that throughout the description the wording "image" is used to denote a volumetric image data set or scan obtained from a volumetric imaging method. Non-limiting examples of volumetric imaging
20 methods are CT, CBCT, PET, MRI, and synCT. During the course of treatment, which usually comprises multiple treatment sessions the actual situation may differ from the situation as observed in the 3D/4D-image. This may be due to various causes, such as the position of the patient, a change in shape of the tumor, a loss or gain of weight of the patient and internal movements resulting
25 from breathing and the patient's heart beat.

Haehnle et al, 2017 Phys. Med. Biol. **62** 165, describe a method for interactive multi-objective dose-guided patient positioning. The method proposed therein aims to reposition the patient such that an optimal dose distribution is achieved, i.e. a dose distribution that best matches the objectives of effective
30 irradiation of malignant areas, while sparing healthy areas, in particular sparing organs at risk (OAR). The method proposed therein comprises a first step wherein a 3D cone-beam computed tomography (CBCT) scan is obtained with the

patient in the treatment position. In the first step a rigid alignment is computed for which the anatomical structures of the patient of the original image best coincide the anatomical structures in the CBCT scan. In a second step, dose distributions are computed that would be achieved when applying the original
5 treatment plan to the patient with this rigid realignment and for multiple alignments different from this alignment within a space C of accessible shifts. Furthermore dose distributions for intermediate alignments are computed by interpolation. It is a disadvantage of the known method that the dose computation for the various alignments imposes a substantial computational
10 burden and involves a substantial computation time.

SUMMARY

It is an object of the present invention to provide an improved positioning system requiring less computational resources.

15 In accordance therewith an improved positioning system is provided as defined in claim 1.

The improved system claimed therein positions the patient for treatment in a beam of radiation in accordance with patient specific data including a first image of the patient. The first image is typically a 3D/4D- image, obtained with a
20 volumetric imaging method as mentioned above, for example obtained with a CT or and less frequently an MRI or PET/CT scanner. The patient specific data is provided by a medical specialist, for example an oncologist, for example using a planning tool. During the treatment planning process the target and organs at risk are segmented, the adequate number of beam orientations or arc lengths are
25 established relative to the isocenter, and based on the physician prescribed dose to tumor and objectives for organs at risk, the plan is optimized and calculated to determine the best dose distribution for a particular patient. The treatment plan is typically delivered over several weeks of treatment, 5 days a week.

The improved system further comprises an imaging device that is
30 configured to provide a second image(scan) of the patient including the part of the body to be treated Also the imaging device for providing the second image is typically a 3D-imaging device like a CT-scanner or an MRI scanner. The second

image provides more recent information about the location and sizes of tissues and structures in the body of the patient, preferably immediately prior to a treatment session.

The improved system further comprises a positioning device such as a
5 treatment couch for holding the patient in a variable position and/or orientation in the beam of radiation for an accurate intervention to a designated part of the patient. The positioning device is controlled by an optimization controller comprised in the improved system. The optimization controller is configured to provide registration control data, i.e. control data that controls the position
10 and/or orientation of the positioning device to guide the positioning device based on the first image and the second image. The optimization controller comprises a dose based control module that is configured to compute an optimized repositioning of the patient by performing a dose-guided optimization. To that end the dose based control module is configured to perform at least the following
15 operations.

It performs neuromorphic data processing operations to first image data obtained from the first image to render first feature map data. It also performs the same neuromorphic data processing operations to second image data obtained from the second image to render second feature map data. Subsequently it
20 concatenates the first feature map data and the second feature map data to provide concatenated feature map data. It then performs further neuromorphic data processing operations to the concatenated feature map data to provide a correction vector indicative for a required registration of the patient for dose based optimization. The concatenated feature map data is for example a feature
25 map comprising both the first feature map data and the second feature map data. Due to the fact that the steps of the method are performed in this order, i.e. first respective feature map data is extracted from each image and the feature map data so obtained is then concatenated it is rendered possible that the same neural network architecture can be trained and used with different types of
30 images, such as CBCT/MRI. For this reason, registration between different image types (CT+CBCT or CT+MRI) could be performed by the same neural network.

As specified in more detail below, a dose based control module as specified for the improved system can be easily trained to perform the registration in an efficient manner.

In an embodiment, the improved system further comprises a geometry
5 based control module and a transformation module. The geometry based control module is configured to perform a geometrical rigid registration to provide a first estimate for a required registration of the patient based on the first image and the second image. This geometrical rigid registration is based on a registration of rigid structures in the body of the patient, such as bones, or markers that are
10 deliberately introduced at the time of planning the treatment. This geometrical rigid registration would be sufficient in the hypothetical case that no morphological changes occur in the body of the patient. In practice however, such morphological changes do occur, for example due to change of weight and changes in the size of the tumor to be treated. Accordingly, the geometry based control
15 module is provided in addition to the dose-based control module, but not as a replacement. The registration provided by the geometry based control module is however a first approximation that serves as a starting point for the dose-based control module. To compensate for a correction that is already provided by the first estimate, the transformation module is provided to transform either of the
20 first image or the second image to compensate for a difference in registration as indicated by the first estimate. The dose based control module in this embodiment of the improved system is configured to determine an estimate for a required additional registration of the patient based on the first image and the second image of which one is transformed. For example, the transformation
25 module transforms the second image in accordance with the first approximation as if the registration of the patient were already corrected in accordance with the first approximation, and the dose based control module determines the estimate for the required additional registration correction on the basis of the first image and the transformed second image. Alternatively, the transformation module
30 transforms the first image in accordance with the inverse of the transformation specified by the first approximation, and the dose based control module determines the estimate for the required additional registration correction on the

basis of the inversely transformed first image and the second image. It is an advantage of the embodiment of the improved system that further comprises a geometry based control module and a transformation module as described above that the dose based control module can be trained more easily. The geometry based control module and transformation module can be implemented in a straightforward manner requiring only modest computation effort.

In embodiments of the improved system the dose based control module comprises a first and a second, mutually identical convolutional neuromorphic processing branch, a neuromorphic concatenation stage and a fully connected neuromorphic stage.

In these embodiments, the first convolutional neuromorphic processing branch is configured to receive the first image data obtained from the first image and to provide the first feature map data based on the received first image data.

The second convolutional neuromorphic processing branch is configured to receive the second image data obtained from the second image and to provide the second feature map data based on the received second image data. It is noted that instead a single convolutional neuromorphic processing unit can be used in a time shared manner for computation of the first feature map data and the second feature map data from the first and the second image data respectively.

The neuromorphic concatenation stage is configured to receive the first feature map data and the second feature map data and to provide the concatenated feature map data based on the first feature map data and the second feature map data.

The fully connected neuromorphic stage is configured to receive the concatenated feature map data and to provide the correction vector indicative for the correction in the registration.

In exemplary embodiments the mutually identical convolutional neuromorphic processing branches each comprise a plurality of stages with a convolutional neuromorphic layer. Typically the mutually identical convolutional neuromorphic processing branches or the single convolutional neuromorphic processing branch applied in a time-shared manner comprises up to ten stages, e.g. 5 stages.

In addition to a convolutional neuromorphic layer the stages may comprise one or more of a batch normalization layer, an activation layer, e.g. a ReLU layer, for example a leaky ReLU activation layer, a pooling layer, e.g. a max pooling layer etc.

5 An embodiment of the improved system further comprises a third control module that is configured to compute a correction vector for dose-guided optimization by applying a gradient descent algorithm. Also in this embodiment the dose based control module is optionally combined with the geometry based control module.

10 In an example of this embodiment, the third control module comprises the following components.

- a) A transformation vector modifier configured to generate a set of modified transformation vectors for each transformation vector at its input.
- 15 b) An image transformation module that is configured to provide a set of modified second images by transforming the second image in accordance with respective modified transformation vectors of the set of modified transformation vectors.
- c) A dose simulation module configured to provide for each modified
20 second image an estimated spatial dose distribution.
- d) A dose volume histogram computation module to compute an expected dose volume histogram resulting for each estimated spatial dose distribution.
- e) An evaluation module to compute a quality measure that indicates the
25 expected quality of the treatment based on the computed expected dose volume histogram for each estimated spatial dose distribution.
- f) A gradient descent module to compute a single next iterated
30 transformation vector based on the respective values for the expected quality determined for the modified transformation vectors of the set of modified transformation vectors.

In operation the third control module iteratively computes a transformation vector until further iterations do not result in a substantial

increase of the quality measure. Alternatively a predetermined maximum number of iterations may be specified. As a still further alternative the iteration stops as soon as one of these two conditions is met.

5 The simulation module in this example may estimate the spatial dose distribution with a Monte Carlo simulation.

10 The quality measure may additionally be based on an estimation of the normal tissue complication probability (NTCP), indicative for a probability that normal tissue is affected by the treatment. In an embodiment the third module further comprises a treatment effect computation module that provides an indication for this probability associated with the spatial dose distribution estimated by the dose simulation module. In this computation the treatment effect computation module may take into account one or more of RT-structure information and information about prognostic factors. In this embodiment the evaluation module is configured to compute the quality measure based on the
15 computed expected dose volume histogram and based on the estimation of the normal tissue complication probability.

According to a second aspect of the present disclosure a training system for training a dose based control module is provided that comprises.

- 20 a) a first input for receiving a first image of a patient, the first image comprising tissue label data and dose specification data.
- b) a second input for receiving a second image of the patient, the second image including a designated part of the patient to be treated and being taken at a point in time later than the first image.
- 25 c) a third input to receive a Golden Truth (GT) indication of a transformation vector specifying a correction of the position and/or orientation of the patient with which a dose delivered to the patient optimally approximates the dose as originally intended in accordance with the first image.
- d) a transformation vector generator unit to generate a plurality of transformation vectors.
- 30 e) an image transformation unit to obtain respective transformed second images by applying the transformation vectors to the second image.

- f) an addition unit which for each transformed second image computes the corresponding GT-correction vector from the GT-indication of the second image and the transformation vector with which the transformed second image was obtained.
- 5 g) a loss computation module to determine for each transformed second image a loss based on the difference between the GT-correction vector and a correction vector estimated by the dose based control module when the first image and the transformed second image are provided as input.
- h) an update module for updating parameters of the dose based control
10 module based on the computed loss.

The update module is for example configured to update the parameters of the dose based control module by a back propagation procedure.

In accordance with a third aspect of the present disclosure a method for training a neuromorphic dose based control module is provided that comprises
15 the following operations.

- a) Providing a first image of a patient comprising tissue label data and dose specification data.
- b) Providing a second image of the patient including a designated part of the patient to be treated, therewith also providing a Golden Truth (GT)
20 indication of a transformation vector specifying a correction (x_c , y_c , z_c) of the position and/or orientation of the patient with which a dose delivered to the patient optimally approximates the dose as originally intended in accordance with the first image.
- c) Generating an augmented set of second images by applying mutually
25 different geometrical transformations, e.g. translations and/or rotations in three dimensional space to the second image and for each species of the augmented set of second images computing the Golden Truth for the required correction from the GT-indication of the second image and the transformation with which that species was obtained from the second
30 image.
- d) With the dose based control module computing a respective output vector indicative for a correction of the position and/or orientation of the patient

for each pair of the first image and a species of the augmented set of second images.

e) For each species of the augmented set of second images computing a loss from the difference between the correction specified by the respective output vector and the respective GT.

f) Updating parameters of the dose based control module to reduce the loss.

The training system according to the second aspect and training method according to the third aspect enable an efficient training of the dose based control module in that for each manually labeled second image a plurality of transformed second images are automatically generated that are used for training.

It is noted that an exemplary embodiment of the improved position correction system comprising the third control module is configured to update parameters of the dose based control module based on a loss defined by a difference between the correction vector determined by the third control module and the correction vector determined by the dose based control module. The loss defined by the difference is for example a distance measure, e.g. a block based distance measure (L1), an Euclidian distance measure (L2) or an L_∞ distance measure. This renders it possible to perform a further training of the dose based control module even when it is already in use.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other aspects are shown in more detail with reference to the drawings. Therein:

FIG. 1 schematically shows an embodiment of a system for positioning a patient for treatment in a beam of radiation from a radiation source;

FIG. 2 shows a further embodiment;

FIG. 3 shows a component of that embodiment;

FIG. 4 shows an exemplary part of said component in further detail;

FIG. 5 schematically illustrates an embodiment of a method for training a neuromorphic dose based control module;

FIG. 6 schematically shows an embodiment of a training system for training the dose based control module;

FIG. 7 shows a further embodiment of the positioning system;

FIG. 8 shows an exemplary component of said embodiment in more detail;

FIG. 9 schematically shows a further embodiment of the system;

FIG. 10A, 10B, 11A-11D and 12A – 12D show experimental data obtained
5 in the process of training the neural network of FIG. 4;

FIG. 13 shows further experimental data.

DETAILED DESCRIPTION OF EMBODIMENTS

10 FIG. 1 schematically shows a system 1 for positioning a patient for treatment in a beam of radiation from a radiation source 5, for example a photon radiation source or a proton radiation source in accordance with patient specific data. The patient specific data includes a first image pCT of the patient that comprises tissue label data and dose specification data. As shown in FIG. 1, the
15 system comprises an imaging device 2, a positioning device 3, and an optimization controller 4.

The positioning device 3, such as a robotic couch, is provided for holding the patient in a variable position in the beam of radiation from the radiation source 5 for an accurate intervention to a designated part of the patient.

20 The patient specific data is provided by an oncologist before the treatment of the patient and typically specifies a series of treatment sessions over a period of time. In accordance therewith the radiation source 5 is configured to issue a controlled beam of radiation with a predetermined distribution for a predetermined time.

25 Therewith it is necessary to properly register the patient. That is, the patient must be properly positioned in the beam of radiation. For that purpose the imaging device 2 is configured to provide a second image rCT of the patient that includes a designated part of the patient to be treated.

30 The optimization controller 4 is configured to provide positioning control data ΔP to guide the positioning device 3 based on the first image pCT and the second image rCT.

One approach is to register the patient such that positions of rigid structures in the body, such as bone tissue or markers identified in the second image match those of the positions in the first image pCT.

It is however not necessarily sufficient to simply position the patient in exactly the orientation as foreseen by the oncologist while preparing the treatment. This is due to the fact that the distribution of tissues of the body of the patient may have changed in the time interval between the date of the preparation of the treatment and the date of a treatment session. It may for example be the case that the patient has lost or gained weight or that the tumor which is treated has shrunk or instead increased in size.

As shown in more detail in FIG. 2, to take into account such morphologic changes in time, the optimization controller 4 comprises a dose based control module 41 that is configured to compute a registration of the patient so that the applied dose optimally matches the dose as specified by oncologist in the treatment plan.

As shown in FIG. 3, in operation the dose based control module 41 performs neuromorphic data processing operations to first image data obtained from the first image pCT to render first feature map data F1. The dose based control module 41 in operation also performs the same neuromorphic data processing operations to second image data obtained from a second image rCTq to render second feature map data F2. The first image pCT and second image rCTq comprise voxelized volumetric x-ray data in DICOM files of CT modality.

Subsequent to these operations it concatenates the first feature map data F1 and the second feature map data F2 to provide concatenated feature map data Fc. Then it performs further neuromorphic data processing operations to the concatenated feature map data Fc to provide a correction vector ΔPd indicative for a required repositioning of the patient for dose based optimization.

In an embodiment the dose based control module 41 is configured to perform the specified operations with a suitably programmed general purpose processor. In the embodiment of FIG. 3, the dose based control module 41 comprises a first convolutional neuromorphic processing branch 411,

a second convolutional neuromorphic processing branch 412 identical to the first convolutional neuromorphic processing branch 411, a neuromorphic concatenation stage 413 and a fully connected neuromorphic stage 414.

The first convolutional neuromorphic processing branch 411 is configured
5 to receive the first image data obtained from the first image pCT and to provide the first feature map data F1 based on the received first image data. The second convolutional neuromorphic processing branch 412 is identical to the first convolutional neuromorphic processing branch 411 and is configured to receive the second image data obtained from the second image rCT and to provide the
10 second feature map data F2 based on the received second image data. The neuromorphic concatenation stage 413 is configured to receive the first feature map data F1 and the second feature map data F2 and to provide concatenated feature map data Fc based on the first feature map data and the second feature map data. The fully connected neuromorphic stage 414 is configured to receive
15 the concatenated feature map data Fc and to provide the output vector ΔP_d indicative for the correction in the registration.

Referring again to FIG. 2, it is shown therein that the system 1 for positioning further comprises a geometry based control module 42 and a transformation module 43.

20 In operation, the geometry based control module 42 performs a geometrical rigid registration to provide a first estimate ΔP_g for a required repositioning of the patient based on the first image pCT and the second image rCT. In the embodiment shown, the transformation module 43 in operation transforms the the second image to compensate for a difference in registration as indicated by
25 the first estimate ΔP_g . The dose based control module 41 in operation then determines an estimate ΔP_d for a required additional repositioning of the patient based on the first image pCT and the transformed second image rCTg. In the example shown the dose based control module 41 adds (adder 45) the first
30 estimate ΔP_g from the geometry based control module 42 and the estimate ΔP_d from the dose based control module 41 to compute the positioning control data ΔP for guiding the positioning device.

In an alternative embodiment the dose based control module 41 directly computes the positioning control data ΔP from the first image pCT and the second image rCT. This has the advantage that the transformation module 43 and the adder 45 are not required, which simplifies the system 1. The
5 embodiment of the system as it is shown in FIG. 2 however has the advantage that training of the dose based control module 41 is simplified.

An exemplary structure of a convolutional neuromorphic processing unit 6 which may be used both for the convolutional neuromorphic processing branch 411 and the convolutional neuromorphic processing branch 412 is shown in FIG.
10 4. In the embodiment shown, the convolutional neuromorphic processing unit 6 comprises a plurality n of convolutional neuromorphic processing layers $6_1, \dots, 6_n$, for example a few to a few tens of layers. In the example shown, the selected value for n is equal to 5. Furthermore, in the example shown, a convolutional neuromorphic processing layer comprises a 3D-convolutional layer
15 611, a batch normalization layer 612, an activation layer 613, for example a ReLU activation layer, such as a leaky ReLU activation layer and a 3D-Pooling layer 614, for example a Max Pooling layer. By way of example, the 3D-convolution window of the 3D-convolutional layers 611 has a size of $3 \times 3 \times 3$ voxels, and the window used by the 3D-Pooling layers 614 has a size of $2 \times 2 \times 2$ voxels. In
20 this example, the window sizes are the same for all convolutional neuromorphic processing layers, but this is not necessary. In the example shown the 3D-convolutional layer 611 of the first convolutional neuromorphic processing layer 6_1 has 8 filters, and the 3D-convolutional layer 611 of each subsequent convolutional neuromorphic processing layer has twice the number of filters of
25 the preceding one. Therewith the convolutional neuromorphic processing unit 6 provides at its output a 128-dimensional feature vector.

FIG. 5 schematically illustrates a method for training the neuromorphic dose based control module 41. As shown therein, the method comprises the following operations.

30 First volumetric image data, e.g. planning CT image data pCT of a predetermined planning CT image is provided in step S1 to the first convolutional neuromorphic processing branch 411.

Second volumetric image data, for example from a predetermined repeated CT image data is provided in step S2 and an augmented set of predetermined second image data $\{rCT_1, \dots, rCT_n\}$ is obtained in step S3 by applying mutually different transformations $\{\Delta P_1, \dots, \Delta P_n\}$ in three dimensional space to the
5 predetermined repeated CT image rCT . In addition the Golden Truth $\{\Delta P_{g1}, \dots, \Delta P_{gn}\}$ for the required correction for each species of the augmented set of second images is computed from the GT indication of the second image and the transformation applied to that species.

In other examples the volumetric image data is synthetic CT (sCT) image
10 data, e.g. based on CBCT or MRI.

Each of the second image data $\{rCT_1, \dots, rCT_n\}$ is then provided in step S4 to the convolutional neuromorphic processing branch 412.

As a result, the dose based control module 41 computes for each pair of first image data pCT and a species rCT_i of the augmented set of second image
15 data an output vector $\{\Delta P_{o1}, \dots, \Delta P_{on}\}$ that is indicative for a correction in the registration.

In step S5 for each pair i a loss L_i is computed from the difference between the correction specified by the output vector ΔP_{oi} computed by the dose based control module 41 and the respective GT ΔP_{gi} for that pair.

20 The weights of the first and the second, mutually identical convolutional neuromorphic processing branch 411, 412, the neuromorphic concatenation stage 413 and the fully connected neuromorphic stage 414 are then updated in step S6 to minimize the loss L_i , for example using backpropagation.

FIG. 6 schematically shows a training system for training the dose based
25 control module 41. As shown in FIG. 6, the training system comprises a first input IP for receiving a first image of the patient, in this case a planning CT image pCT comprising tissue label data and dose specification data. The training system also comprises a second input IR for receiving a second image rCT of the patient. The second image rCT includes a designated part of the patient to be
30 treated and is taken at a subsequent point in time. An oncologist H determines which correction, e.g. a position correction (x_c, y_c, z_c) of the patient is necessary to optimally deliver the dose as originally intended by the treatment plan. A

transformation vector generating unit 10 generates a plurality of transformations, e.g. translations (x_i, y_i, z_i) to be applied to the second image rCT by an image transformation unit 12 to obtain transformed second images rCT_i . The correction (x_c, y_c, z_c) is taken as the Ground Truth (GT) value of the correction that is optimal for the second image rCT . Based on this GT value and the known transformation applied to the second image rCT to obtain the translated second images rCT_i , the addition unit 14 computes the corresponding GT-value $(x_{c_j}, y_{c_j}, z_{c_j})$ for each transformed second image rCT_i . The dose based control module 41 that is to be trained compares each translated second image rCT_j with the first image pCT and estimates the required correction vector $(x_{o_j}, y_{o_j}, z_{o_j})$. The loss computation module 16 determines the difference between the estimated correction vector $(x_{o_j}, y_{o_j}, z_{o_j})$ and the corresponding GT-value $(x_{c_j}, y_{c_j}, z_{c_j})$ and outputs a Loss value L_j , for example a value indicative for a distance between the estimated correction vector $(x_{o_j}, y_{o_j}, z_{o_j})$ and the corresponding GT-value $(x_{c_j}, y_{c_j}, z_{c_j})$ in the space defining the translation vector. The distance measure is for example a Manhattan distance, an Euclidian distance or an L_∞ measure. The current network parameters of the dose based control module 41 are then updated so as to minimize the loss, for example using back propagation.

FIG. 7 shows a further embodiment of the positioning system that further comprises a third control module 44 configured to compute a complete dose-guided optimization by applying a gradient descent GD algorithm. The third control module 44 receives a output vector ΔP_0 indicative for a correction in the registration as computed by the dose based control module 41. In an alternative embodiment the input of the third control module 44 is the output ΔP as computed in the embodiment shown in FIG. 2.

FIG. 8 shows an embodiment of the third control module 44 in more detail. As shown in that embodiment, a transformation vector modifier 440 is provided that generates a set of modified transformation vectors $\{\Delta P_{j1}, \dots, \Delta P_{jn}\}$ for each transformation vector ΔP_j at its input. Accordingly, for the transformation vector ΔP_0 received from the dose based control module 41 it generates the set of modified transformation vectors $\{\Delta P_{01}, \dots, \Delta P_{0n}\}$. The image transformation module 441 provides a set of transformed second image data $\{rCT_{j1}, \dots, rCT_{jn}\}$.

Each species of modified second image data rCT_{jk} is obtained by transforming the second image data (rCT) in accordance with a respective modified transformation vector ΔP_{jk} .

Based on the predetermined radiation therapy plan (RT-plan), a dose simulation module 442 then provides for each modified repeated CT image data rCT_{jk} an estimated spatial dose distribution D_{jk} . The simulation module 442 for example uses a Monte Carlo simulation to estimate the spatial dose distribution D_{jk} .

For each of the estimated spatial dose distributions D_{jk} a treatment effect computation module 443 computes an indication $NTCP_{jk}$ of the effect of the estimated spatial dose distribution on the patient. This computation takes into account RT-structure information and information about prognostic factors.

In addition a dose volume histogram (444) computation module computes for each estimated spatial dose distributions D_{jk} an expected dose volume histogram DVH_{jk} taking into account RT-structure information.

An evaluation module 445 computes an overall quality measure Q_{jk} that indicates the expected quality Q_{jk} of the treatment based on the computed indications $NTCP_{jk}$ and DVH_{jk} for the estimated spatial dose distributions D_{jk} .

The gradient descent module 446 computes a single next iterated transformation vector ΔP_{j+1} . To that end the gradient descent module 446 determines which direction in the space wherein the transformation vector is defined results in the highest improvement of the expected quality.

By way of example, in case the transformation vector ΔP_j comprises the components $(\Delta x_j, \Delta y_j, \Delta z_j)$, the transformation vector modifier 440 may generate a set of modified transformation vectors $\{\Delta P_{j1}, \dots, \Delta P_{jn}\}$, wherein the modified transformation vector has components $(\Delta x_j + dx_k, \Delta y_j + dy_k, \Delta z_j + dz_k)$, wherein the displacements dx_k, dy_k, dz_k are uniformly distributed in a volume centered around the origin in the space of the transformation vector. The gradient descent module 446 may then select as the next iterated transformation vector ΔP_{j+1} the one of the modified transformation vectors ΔP_{jk} corresponding to the highest value for Q_{jk} .

In the embodiments described above, it is presumed that the transformation vector space is a three-dimensional space. The transformation vector in that case is a three-dimensional vector in the mutually orthogonal spatial directions x,y,z. In these embodiments the dose based control module (41) is configured to provide positioning control data ΔP a three-dimensional control vector that causes the positioning device to assume a corrected position in the three-dimensional space. In practice already substantial improvements are achieved therewith. In other embodiments the transformation vector is a higher dimensional vector that not only comprises components for the spatial directions x,y,z, but also comprises one or more components related to the orientation in space. In these other embodiments the dose based control module 41 is not only configured to provide positioning control data to cause the positioning device to assume a corrected position in the three-dimensional space, but the dose based control module 41 is also configured to provide orientation control data to cause the positioning device to assume a corrected orientation in the three-dimensional space. Therewith a further improvement of dose control is possible.

FIG. 9 schematically shows a further embodiment of the system. As in the embodiment of FIG. 2, a geometry based control module 42 is included. In this embodiment the geometry based control module 42 provides its computed correction vector ΔP_g to the input of the dose based control module 42 as well as to the input of the further control module 44. Based on the correction vector ΔP_g provided at their respective inputs the dose based control module 42 and the further control module 44 each compute a correction vector ΔP_0 , ΔP_g respectively for dose based positioning. A quality assessment module 46 additionally comprised in this embodiment of the system compares the correction vector ΔP_g computed by the further control module 44 with the correction vector ΔP_0 computed by the dose based control module 42. Based on the comparison the quality assessment module 46 determines a final correction vector ΔP_f , and the system positions the patient according to the final correction vector ΔP_f so obtained.

EXPERIMENTAL RESULTS

In a first experiment the neural network as shown in and described with reference to FIG. 3 was trained for the purpose of providing a geometry based correction vector.

5

A first test was performed with one patient image pair (pCT + rCT). The rCT-image was augmented 1000x by applying synthetic shifts between -10 and 10cm over the x, y and z directions.

10 Results of the training process are shown in FIG. 10A and 10B.

FIG. 10A and 10B respectively show the training loss expressed as the mean square error (MSE) and the mean absolute error (MAE) as a function of the number of training epochs. Upon completion of the training the neural network estimated the geometrically based correction vector with a Mean Absolute Error

15 of less than 1 mm for all axis.

In a second experiment a second training/validation set was used where data from 45 patients was used. Each patient had one pCT and 5 repeated CTs, for a total of 225 image pairs. These images were then augmented x5 with synthetic

20

shifts of -5 to +5 cm in x, y and z axis. The total number of images used was 1125 images.

Results of the training process are shown in FIG. 11A – 11D. FIG. 11A and 11B respectively show the training loss expressed as the mean square error (MSE) and the mean absolute error (MAE) as a function of the

25

number of training epochs during a short training period (100 epochs). FIG. 11C and 11D respectively show the training loss expressed as the mean square error (MSE) and the mean absolute error (MAE) as a function of the number of training epochs during a long training period (600 epochs). Upon completion of the long training period the neural network estimated the

30

geometrically based correction vector with a Mean Absolute Error of less than 3 mm for all axis.

In a third experiment the neural network as shown in and described with reference to FIG. 3 was trained for the purpose of providing a dose based correction vector. In this case, a daily dose is first evaluated at the current patient position in the rCT images. Then, the network is trained with the
5 planning dose and daily dose in order to optimize a translational shift previously obtained by gradient descent.

Results of the training process are shown in FIG. 12A – 12D.

FIG. 12A and 12B respectively show the training loss expressed as the mean square error (MSE) and the mean absolute error (MAE) as a function of the
10 number of training epochs during a short training period (30 epochs).

FIG. 12C and 12D respectively show the training loss expressed as the mean square error (MSE) and the mean absolute error (MAE) as a function of the number of training epochs during a long training period (80 epochs). Upon
15 completion of the long training period the neural network estimated the dose

based correction vector with a Mean Absolute Error of less than 1.2 mm for all axis. In any case a relatively modest number of training examples is sufficient for the network which is already trained to compute a geometry based correction as training does not need to start from scratch.

20 FIG. 13 shows a comparison of the computation speed involved in three approaches to achieve a dose-based optimization. The comparison was performed for 10 head and neck cancer patients previously treated with proton radiotherapy at the GPTC. For each patient, these computations require imaging data (planning CT and repeated CTs, segmentation files) and treatment data
25 (radiotherapy plan) in DICOM format.

The three approaches comprise:

- 1) The RS-MC dose engine from RaySearch's Treatment Planning System (TPS) software called RayStation.
- 2) The gradient descent method when using the fast Monte Carlo code called
30 gPMC, which has been developed at the Massachusetts General Hospital (MGH). This is a GPU based dose engine for proton therapy which focuses on dose and LET calculations only.

3) The computation by the CNN as specified with reference to FIG. 4. For each patient the left column shows the computation time involved. The computation according to approaches 1 and 2 were performed with the GPU-based clinical RayStation client configuration comprising:

- 5 o 12 physical cores dual socket Intel 2.6GHz CPUs
 - o NVIDIA RTX8000 GPU
 - o 48 GB DDR3 ECC RAM
 - o 2x 150 SSDs in RAID 1
- 10 The CNN based optimization was performed with the CNN of FIG. 4 implemented on the clinical QA platform server at the GPTC, comprising:
- o 24 physical cores dual socket Intel 3.0GHz CPUs
 - o 2x NVIDIA GTX 1080 GPUs
 - o 64 GB DDR4 RAM
 - 15 o 4x 250 GB SSDs

FIG. 13 shows for each patient the computation times involved with the approaches 1), 2) and 3) respectively.

20 The results are summarized in the following table

Approach	Tmin (min)	Tmax (min)	Tav (min)
RS-MC	32	65	45
gMC	4	8	6
CNN	1	1	1

In summary it can be seen that a very fast dose based optimization is achieved with the CNN-based method (3). Even if the CNN-based computation were performed with the GPU-based clinical RayStation client configuration it would still be significantly faster than the RS-MC based method. The optimization result obtained by this method (3) can be independently verified with the gMC based approach (2), which also is substantially faster than the RS-MC based

approach. Therewith also the verified optimization result can be achieved substantially faster than is possible with the RS-MC based approach.

CLAIMS

1. A system (1) for positioning a patient for treatment in a beam of radiation in accordance with patient specific data including a first image (pCT) of the patient comprising tissue label data and dose specification data, the system
5 comprising:

an imaging device (2) configured to provide a second image (rCT) of the patient including a designated part of the patient to be treated;

10 a positioning device (3) for holding the patient in a variable position and/or orientation in the beam of radiation for an accurate intervention to a designated part of the patient; and

an optimization controller (4) configured to provide registration control data (ΔP) to guide the positioning device (3) based on the first image (pCT) and the second image (rCT); wherein the optimization controller (4) comprises a dose
15 based control module (41) configured to compute an optimized registration of the patient by performing a dose-guided optimization,

the dose based control module being configured to:

perform neuromorphic data processing operations to first image data obtained from said first image (pCT) to render first feature map data (F1);

20 perform said neuromorphic data processing operations to second image data obtained from said second image (rCT) to render second feature map data (F2);

concatenate the first feature map data (F1) and the second feature map data (F2) to provide concatenated feature map data (Fc);

25 perform a further neuromorphic data processing operations to the concatenated feature map data (Fc) to provide a correction vector indicative for a required registration of the patient for dose based optimization,

characterized in that the system comprises a further control module (44) configured to compute a correction vector for dose-guided optimization by

30 applying a gradient descent (GD) algorithm,

the further control module (44) comprising:

a transformation vector modifier (440) to generate a set of modified transformation vectors ($\{\Delta P_{j1}, \dots, \Delta P_{jn}\}$) for each transformation vector (ΔP_j) at its input;

5 an image transformation module (441) to provide a set of modified second images ($\{rCT_{j1}, \dots, rCT_{jn}\}$) by transforming the second image (rCT) in accordance with respective modified transformation vectors (ΔP_{jk}) of the set of modified transformation vectors ($\{\Delta P_{j1}, \dots, \Delta P_{jn}\}$);

a dose simulation module (442) to provide for each modified second image (rCT_{jk}) an estimated spatial dose distribution (D_{jk});

10 a dose volume histogram (444) computation module to compute an expected dose volume histogram (DVH_{jk}) resulting for each estimated spatial dose distribution (D_{jk});

15 an evaluation module (445) to compute a quality measure (Q_{jk}) that indicates the expected quality (Q_{jk}) of the treatment based on the computed expected dose volume histogram (DVH_{jk}) for each estimated spatial dose distribution (D_{jk});

20 a gradient descent module (446) to compute a single next iterated transformation vector (ΔP_{j+1}) based on the respective values for the expected quality (Q_{jk}) determined for the modified transformation vectors (ΔP_{jk}) of the set of modified transformation vectors ($\{\Delta P_{j1}, \dots, \Delta P_{jn}\}$).

2. The system (1) according to claim 1, further comprising:

25 a geometry based control module (42) to perform a geometrical rigid registration to provide a first estimate (ΔP_g) for a required registration correction of the patient based on the first image (pCT) and the second image (rCT),

a transformation module (43) to transform either of the first image or the second image to compensate for a difference in registration as indicated by the first estimate (ΔP_g),

30 wherein the dose based control module (41) is configured to determine an estimate (ΔP_d) for a required additional registration correction of the patient based on the first image (pCT) and the second image (rCT) of which one is transformed.

3. The system according to claim 1 or 2, wherein the dose based control module (41) comprises:

a first convolutional neuromorphic processing branch (411) being
5 configured to receive the first image data obtained from the first image (pCT) and to provide the first feature map data (F1) based on said received first image data,

a second convolutional neuromorphic processing branch (412) identical to the first convolutional neuromorphic processing branch (411) and being
configured to receive the second image data obtained from the second image

10 (rCT) and to provide the second feature map data (F2) based on said received second image data,

- a neuromorphic concatenation stage (413) being configured to receive the first feature map data (F1) and the second feature map data (F2) and to provide the concatenated feature map data (Fc) based on the first feature map data and
15 the second feature map data;

- a fully connected neuromorphic stage (414) being configured to receive the concatenated feature map data (Fc) and to provide the correction vector (ΔPd) indicative for the correction in the registration.

20 4. The system according to claim 3, wherein the mutually identical convolutional neuromorphic processing branches (411, 412) each comprise a plurality of stages (6_1,...,6_n) with a convolutional neuromorphic layer (611).

5. The system according to claim 4, wherein each stage (6_1,...,6_n) of the
25 convolutional neuromorphic processing branches comprises a batch normalization layer (612).

6. The system according to claim 4 or 5, wherein each stage (6_1,...,6_n) of the convolutional neuromorphic processing branches comprises a leaky ReLU
30 activation layer (613).

7. The system according to claim 4, 5 or 6, wherein each stage (6_1,...,6_n) of the convolutional neuromorphic processing branches comprises a pooling layer (614).
- 5 8. The system according to claim 5, wherein the pooling layer (614) is a max pooling layer.
9. The system according to one of the preceding claims, wherein the
10 simulation module (442) estimates the spatial dose distribution (Djk) with a Monte Carlo simulation.
10. The system according to any of the preceding claims, further comprising a
15 normal tissue complication probability (NTCPjk) associated with each estimated spatial dose distribution (Djk) on the human body, taking into account one or more of RT-structure information and information about prognostic factors wherein the evaluation module (445) is configured to compute the quality
measure (Qjk) based on the computed expected dose volume histogram (DVHjk)
20 and based on the estimation of said probability.
11. The system according to any of the preceding claims, being configured to update parameters of the dose based control module (41) based on a loss defined by a difference between the correction vector determined by the third control
25 module (44) and the correction vector determined by the dose based control module (41).
12. The system according to any of the preceding claims, wherein the further control module (44) is configured to receive the correction vector (ΔP_0) provided
30 by the dose based control module (41) at its input and wherein the system is configured to position the patient according to the correction vector computed by the further control module.

13. The system according to claim 2, wherein the further control module (44) is configured to receive the correction vector (ΔP_g) provided by the geometry based control module (42) at its input, the system further comprising a quality
5 assessment module (46) to compare the correction vector computed by the further control module (44) with the correction vector computed by the dose based control module (42), wherein the system is configured to position the patient according to a correction vector (ΔP_f) determined by the quality assessment module (46) based on the comparison.

10

14. A training system for training a dose based control module (41) comprising:

a first input (IP) for receiving a first image (pCT) of a patient, the first image comprising tissue label data and dose specification data;

15

a second input (IR) for receiving a second image (rCT) of the patient, the second image (rCT) including a designated part of the patient to be treated and being taken at a point in time later than the first image;

20

a third input (H) to receive a Ground Truth (GT) indication of a transformation vector specifying a correction (x_c, y_c, z_c) of the position and/or orientation of the patient with which a dose delivered to the patient optimally approximates the dose as originally intended in accordance with the first image;

a transformation vector generator unit (10) to generate a plurality of transformation vectors (x_i, y_i, z_i);

25

an image transformation unit (12) to obtain respective transformed second images (rCT_i) by applying the transformation vectors (x_i, y_i, z_i) to the second image (rCT);

30

an addition unit (14) which for each transformed second image (rCT_i) computes the corresponding GT-correction vector ($x_{c_j}, y_{c_j}, z_{c_j}$) from the GT-indication of the second image (rCT) and the transformation vector (x_i, y_i, z_i) with which the transformed second image (rCT_i) was obtained;

a loss computation module (16) to determine for each transformed second image a loss based on a difference between the corresponding GT-correction

vector and the correction vector (x_{oj} , y_{oj} , z_{oj}) estimated by the dose based control module when the first image and the transformed second image are provided as input;

an update module (18) for updating parameters of the dose based control
5 module (41) based on the computed loss.

15. A method for training a neuromorphic dose based control module (41), comprising:

Providing (S1) a first image (pCT) of a patient comprising tissue label data
10 and dose specification data;

Providing (S2) a second image (rCT) of the patient including a designated part of the patient to be treated, therewith also providing a Ground Truth (GT) indication of a transformation vector specifying a correction (x_c , y_c , z_c) of the position and/or orientation of the patient with which a dose delivered to the
15 patient optimally approximates the dose as originally intended in accordance with the first image;

Generating (S3) an augmented set of second images ($\{rCT_1, \dots, rCT_n\}$) by applying mutually different geometrical transformation $\{\Delta P_1, \dots, \Delta P_n\}$ in three dimensional space to the second image (rCT) and for each species of the
20 augmented set of second images computing the Ground Truth for the required correction from the GT indication of the second image and the transformation applied to that species;

With the dose based control module (41) computing (S4) a respective output vector $\{\Delta P_{o1}, \dots, \Delta P_{on}\}$ indicative for a correction (x_c , y_c , z_c) of the position
25 and/or orientation of the patient for each pair of the first image (pCT) and a species (rCT_i) of the augmented set of second images ($\{rCT_1, \dots, rCT_n\}$);

For each species (rCT_i) of the augmented set of second images ($\{rCT_1, \dots, rCT_n\}$) computing (S5) a loss (L_i) from the difference between the correction specified by the respective output vector and the respective GT;
30 Updating (S6) parameters of the dose based control module (41) to reduce the loss (L_i).

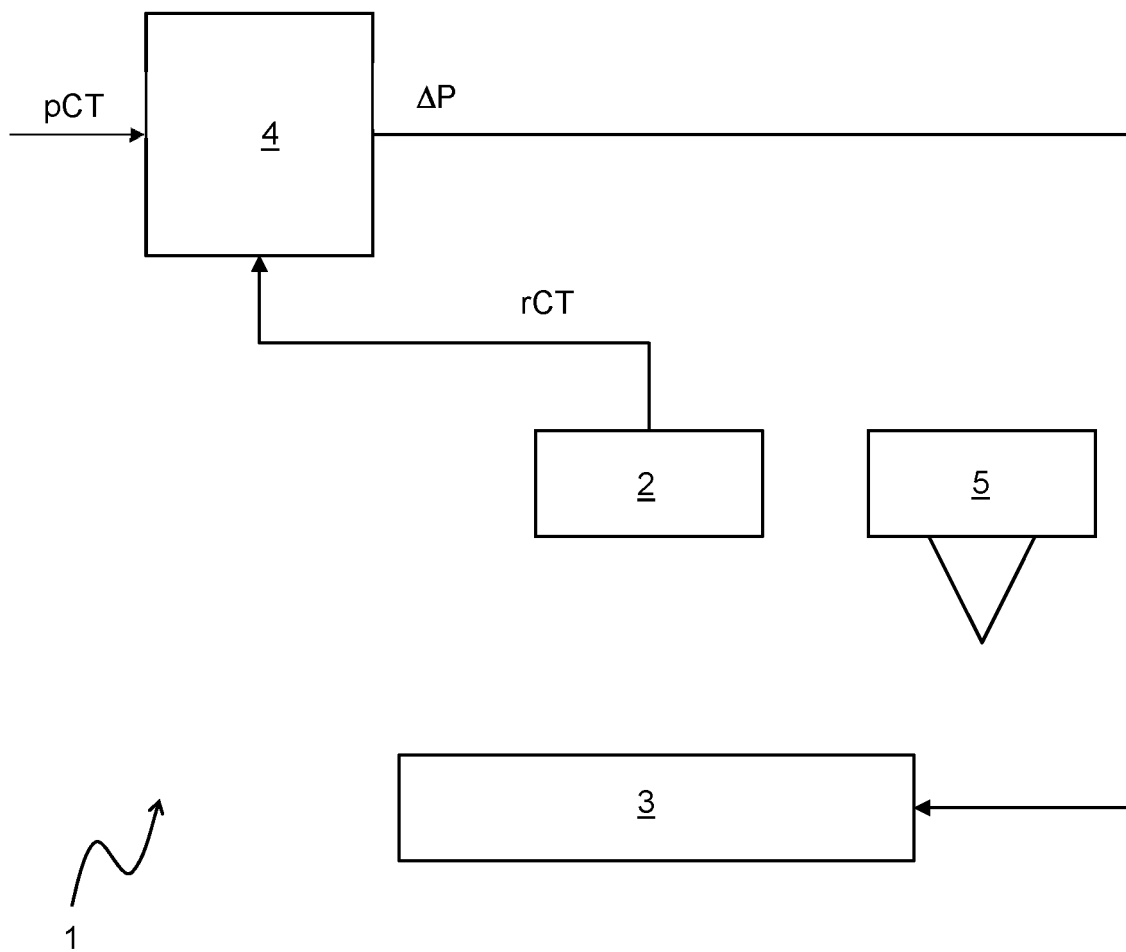


FIG 1

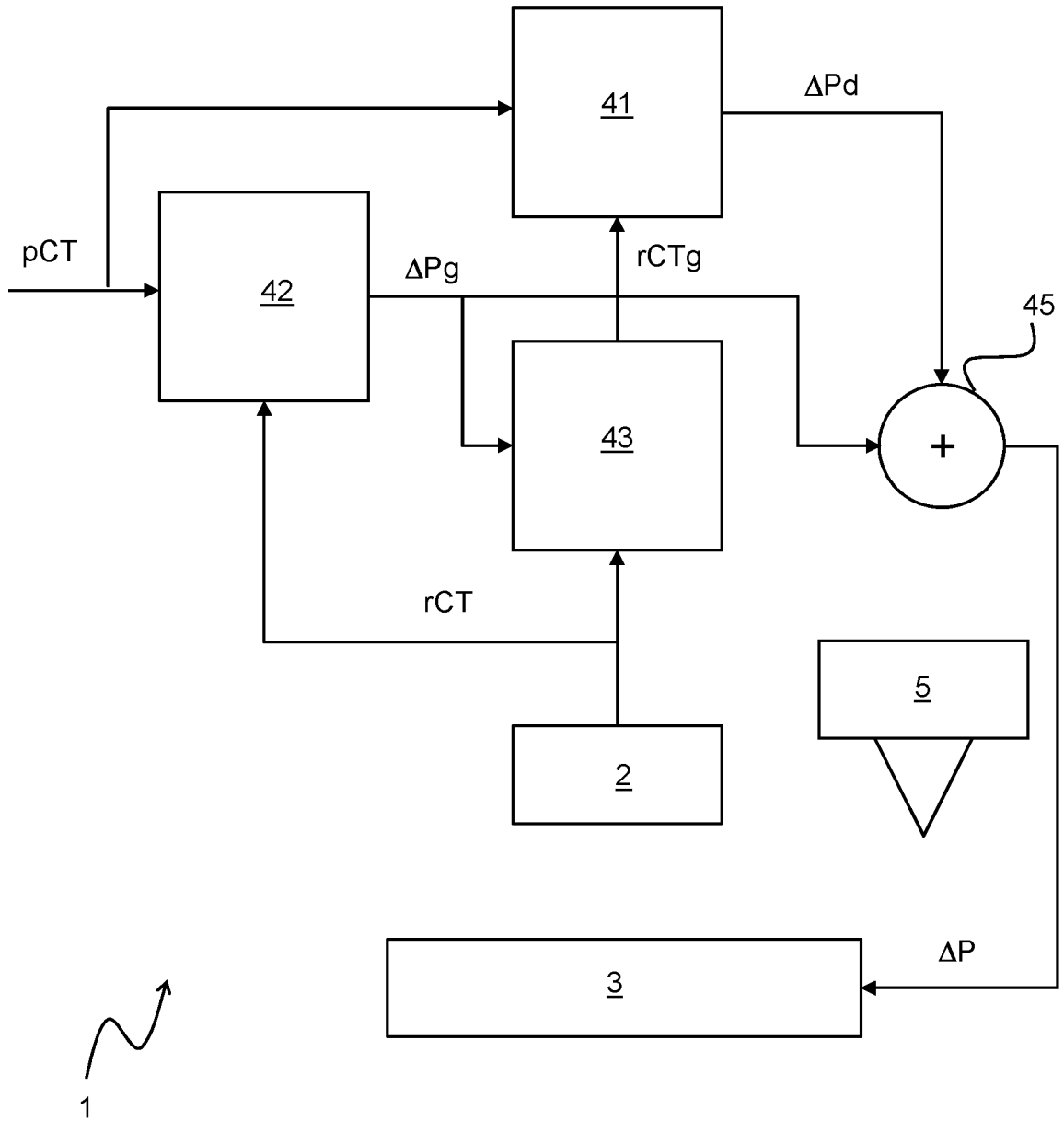


FIG 2

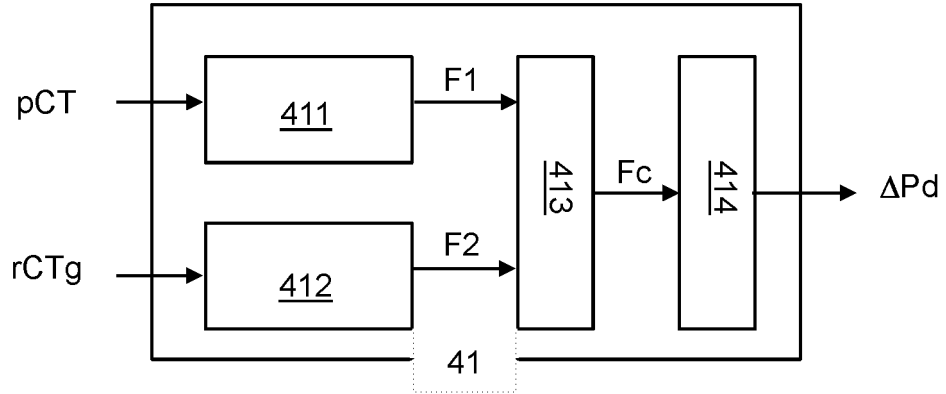


FIG 3

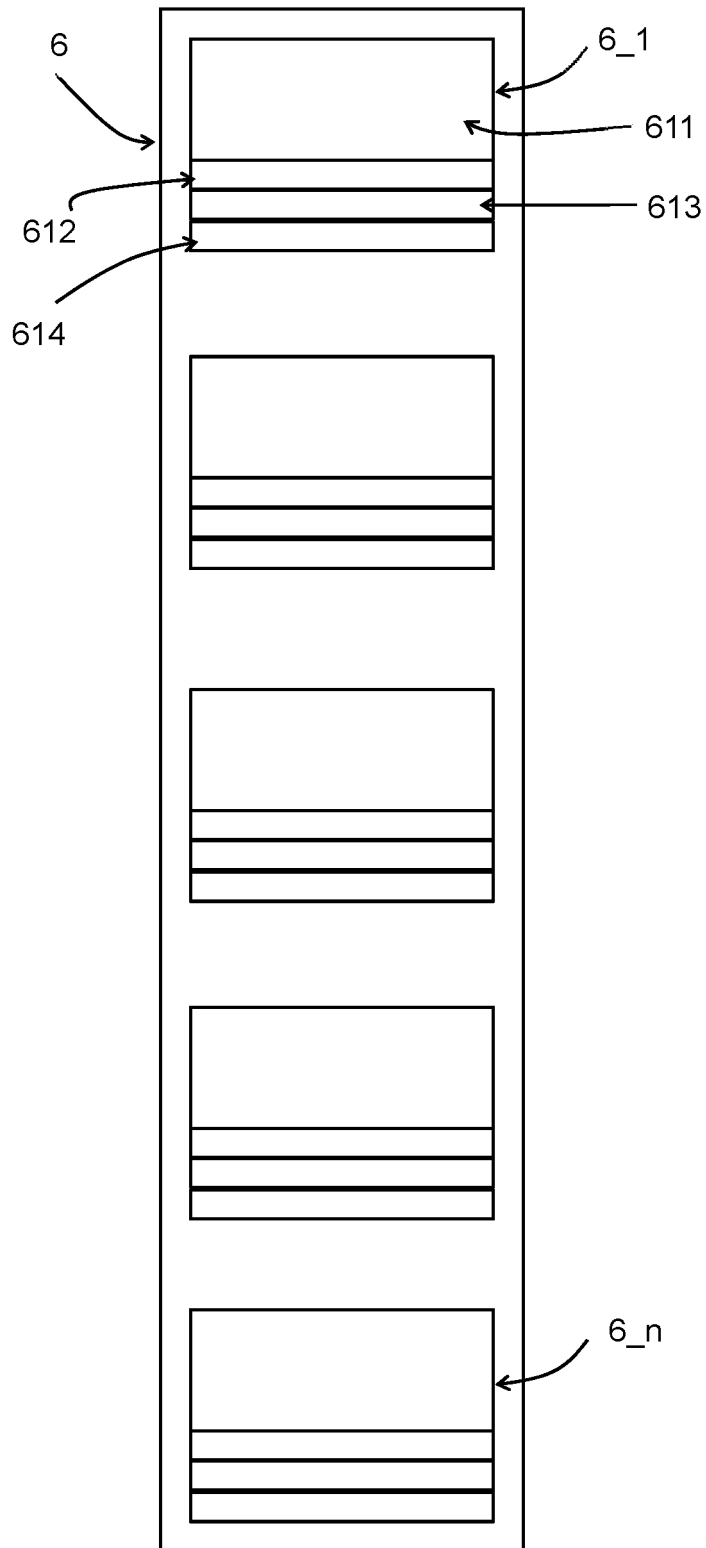


FIG 4

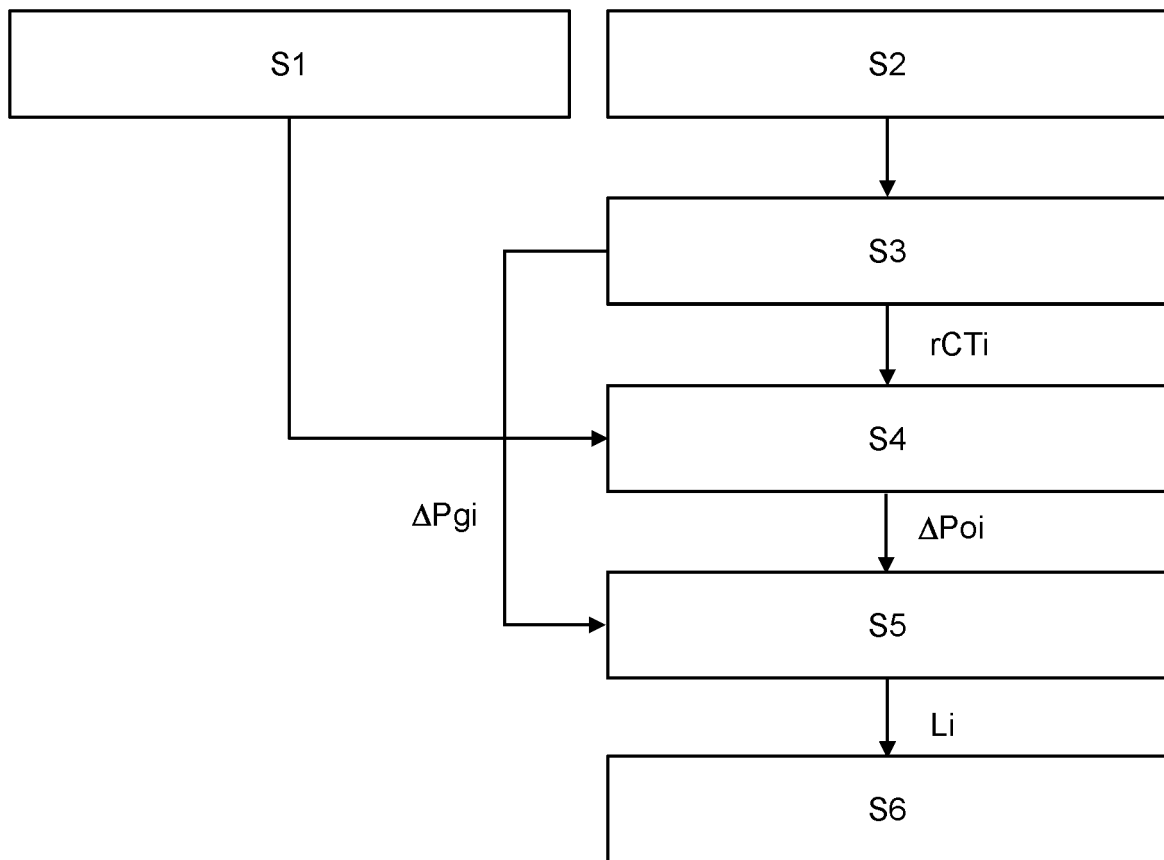


FIG 5

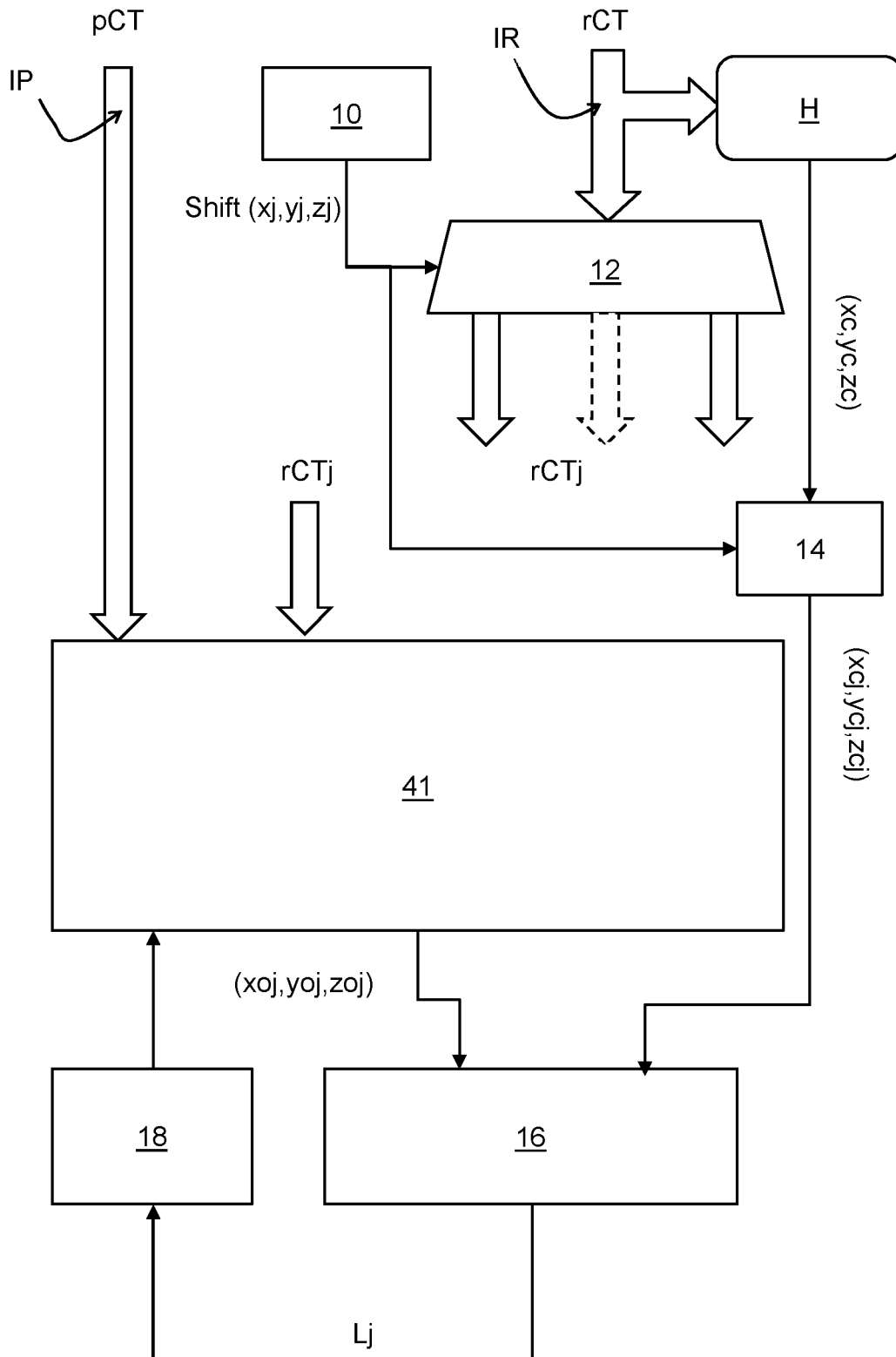


FIG 6

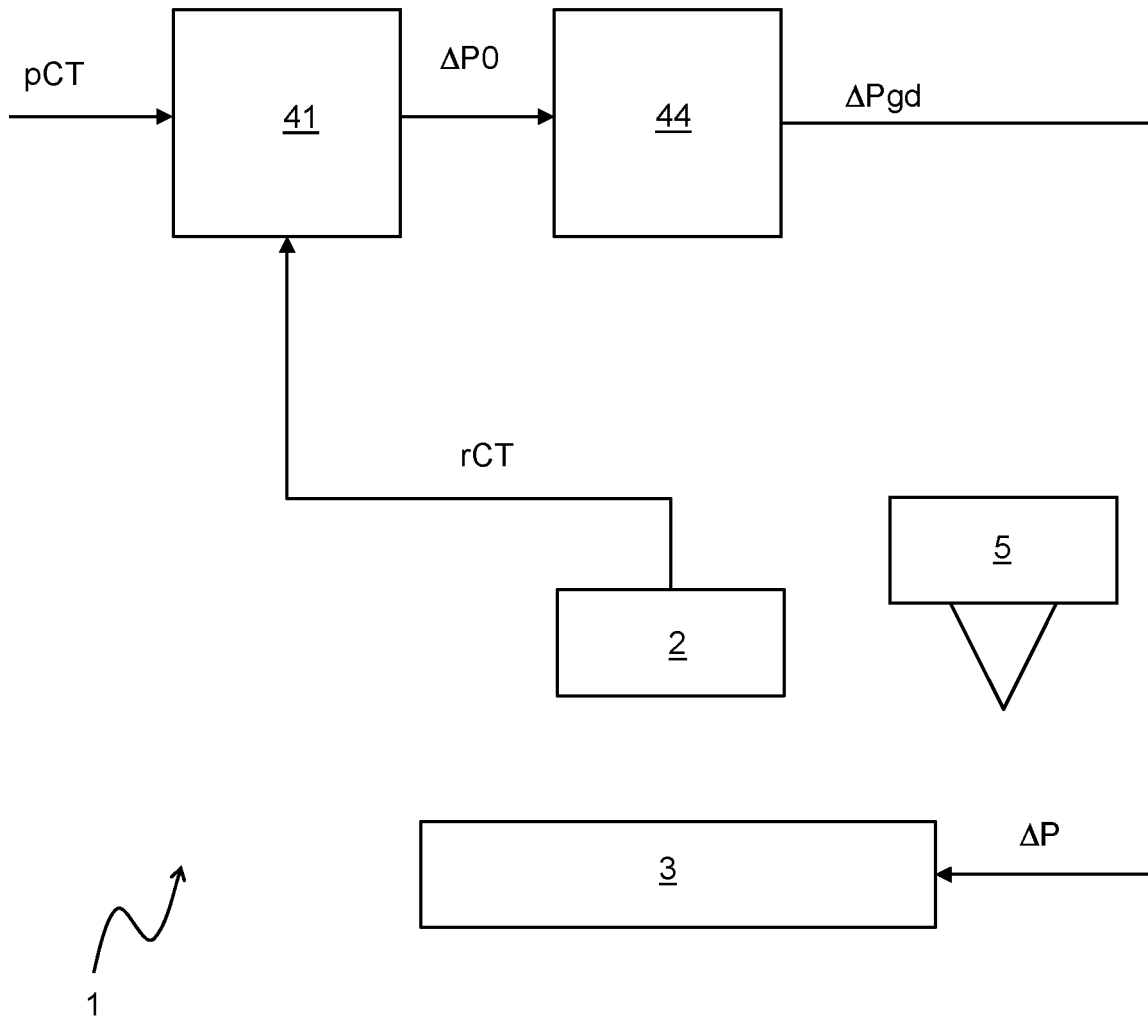
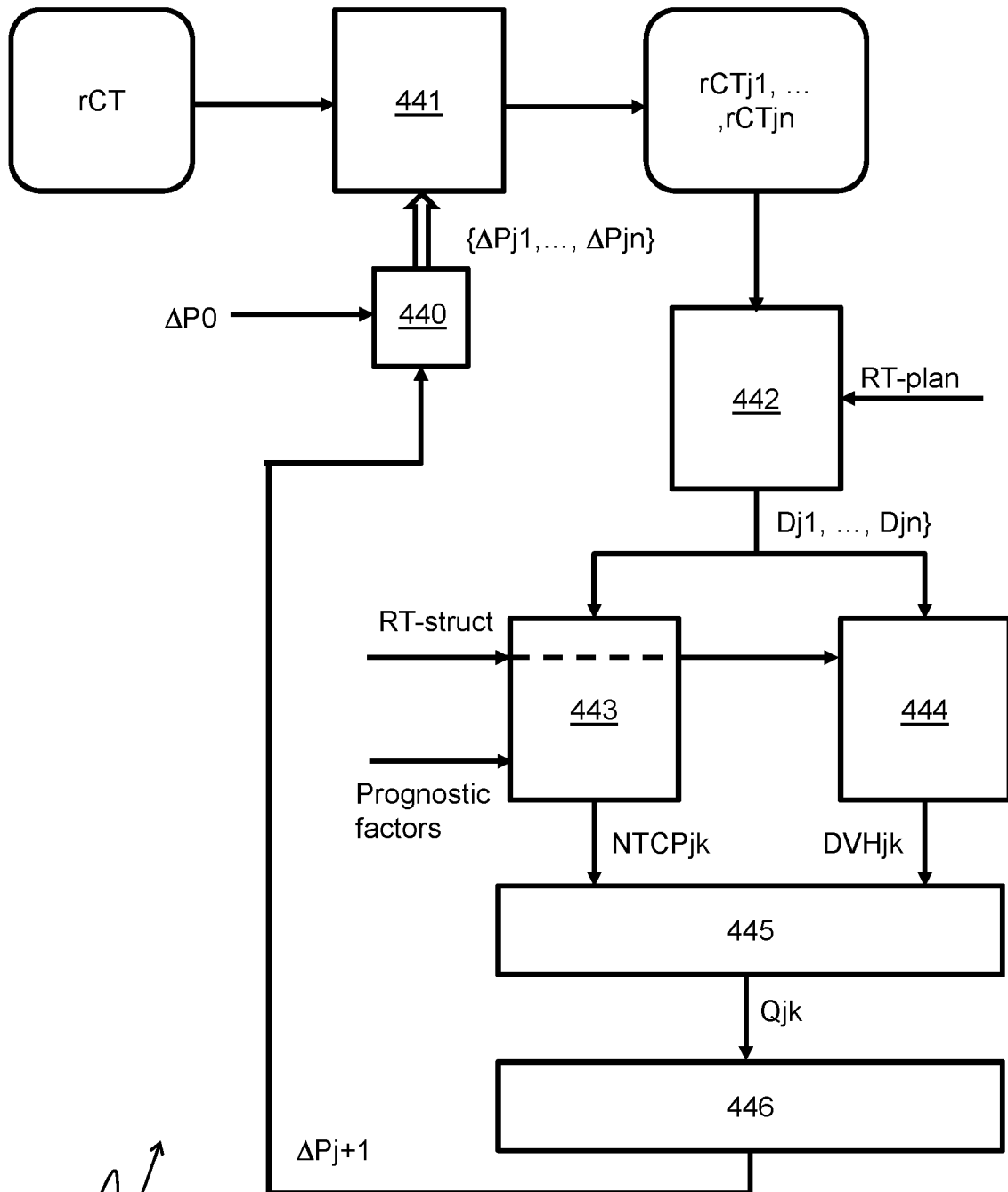


FIG 7



44 ↗

FIG 8

9/12

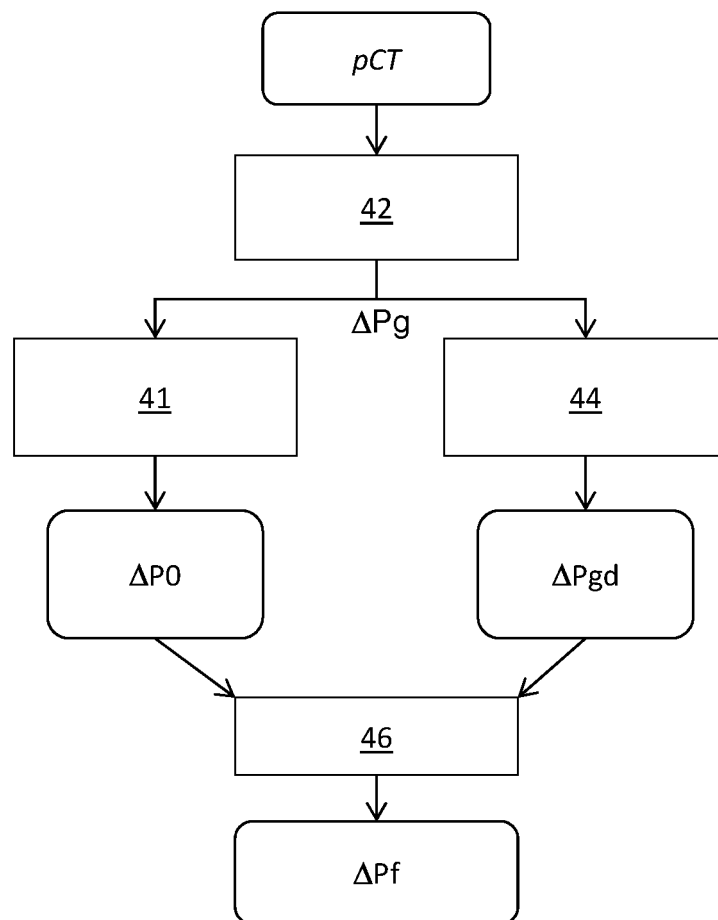


FIG 9

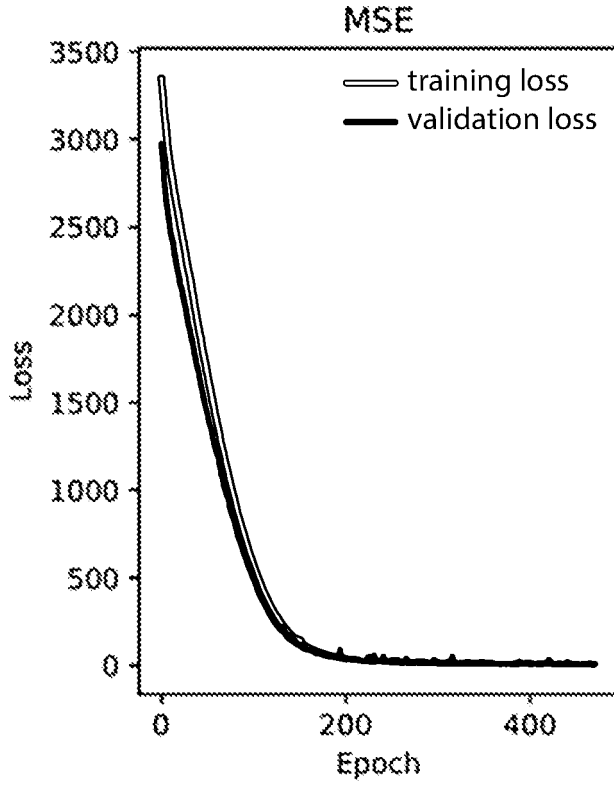


FIG 10A

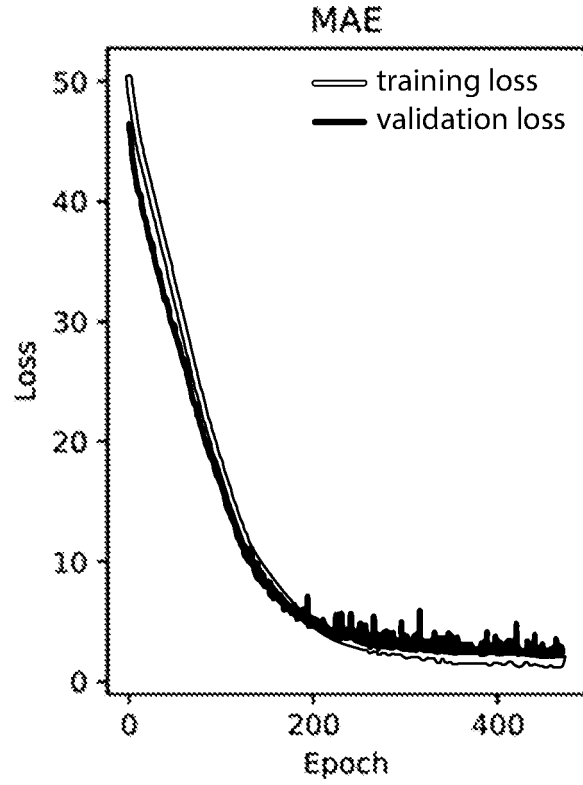


FIG 10B

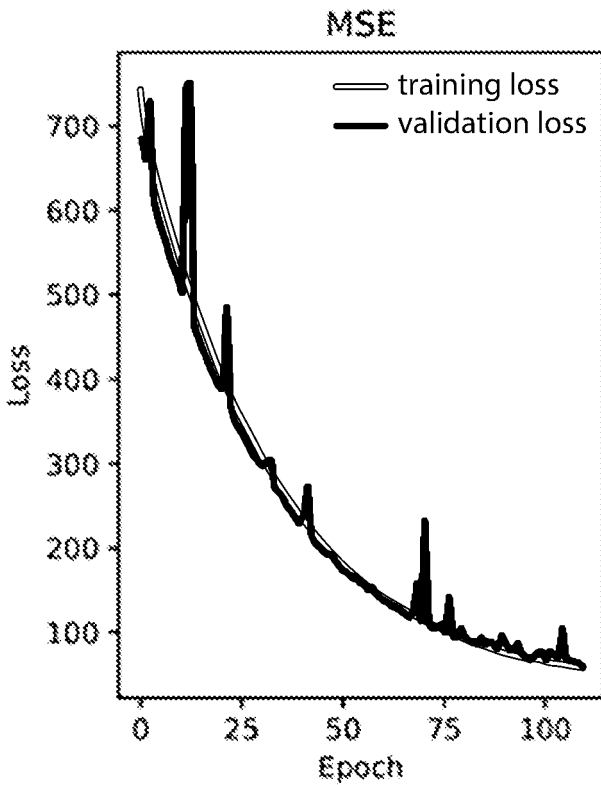


FIG 11A

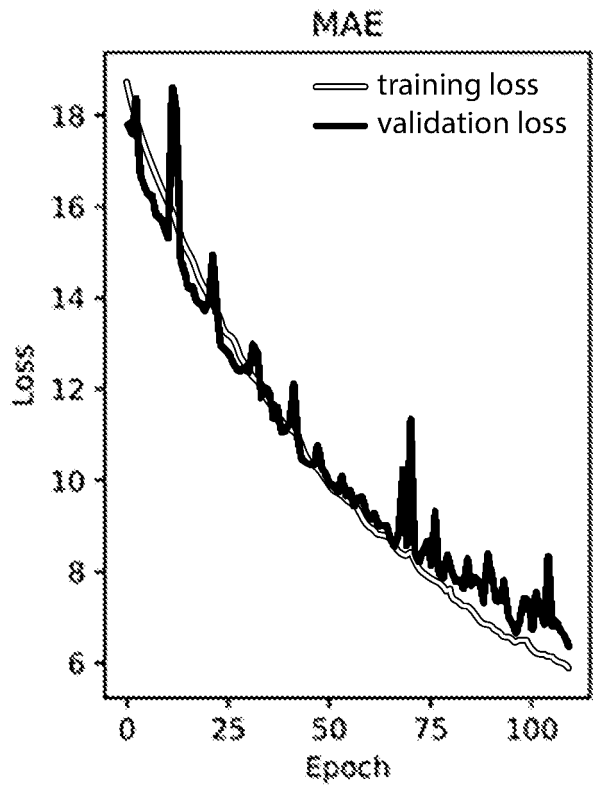


FIG 11B

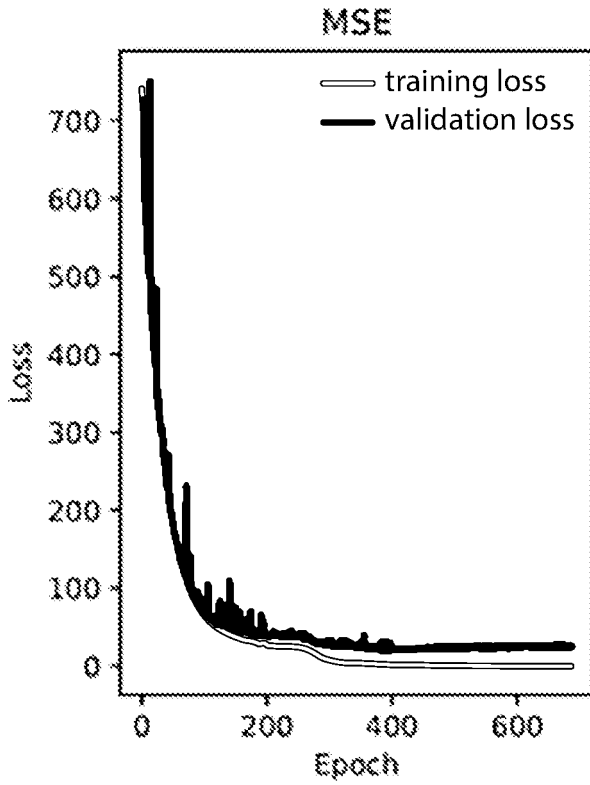


FIG 11C

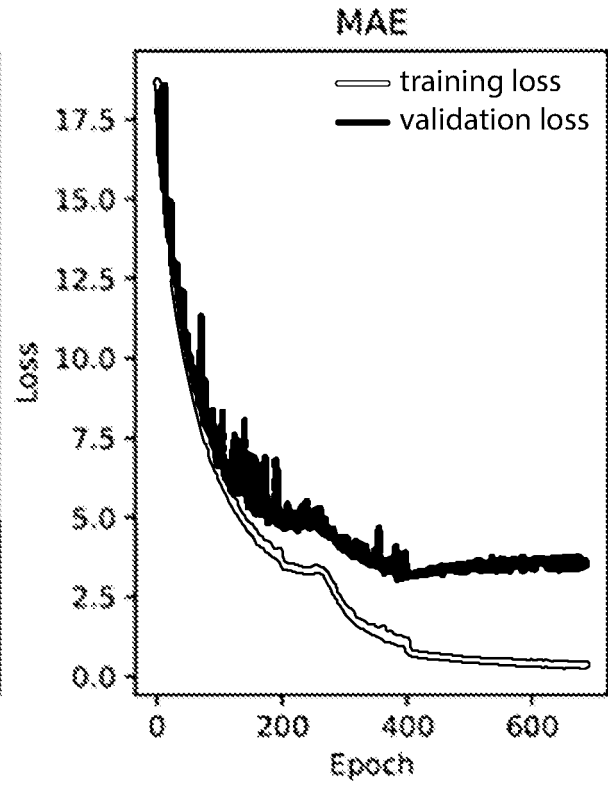


FIG 11D

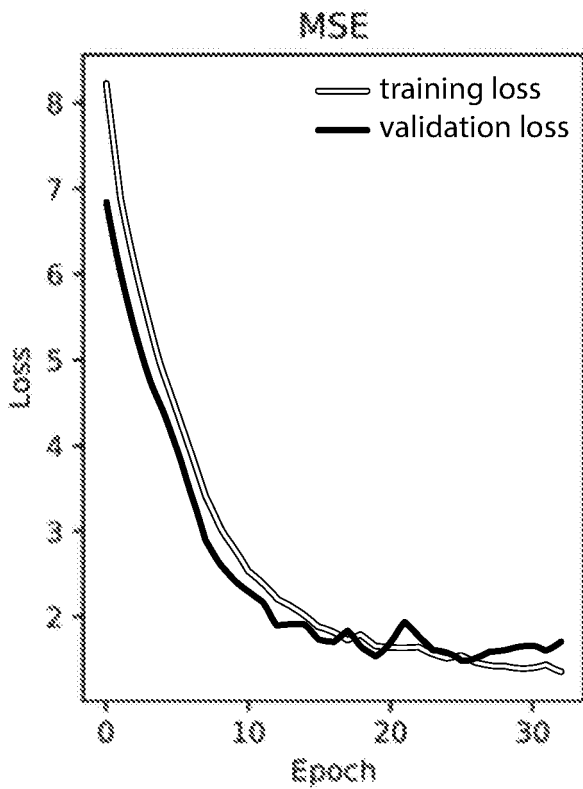


FIG 12A

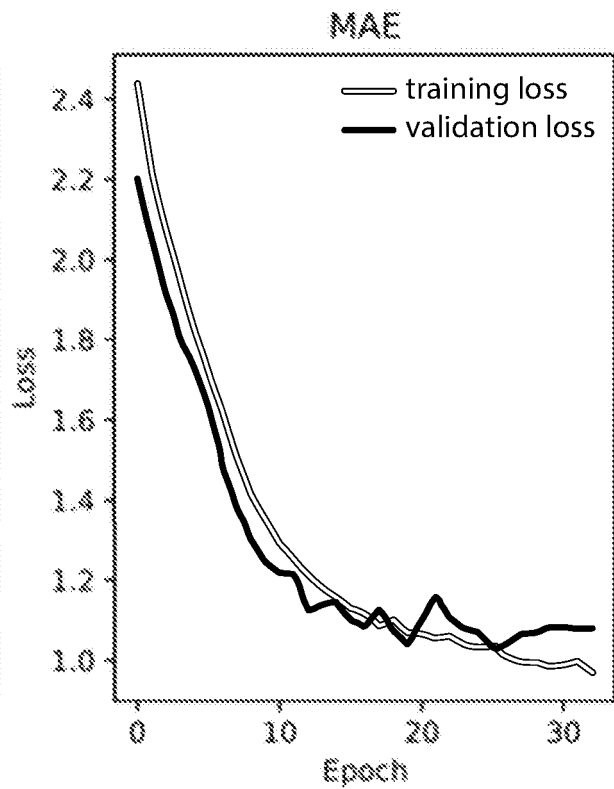


FIG 12B

12/12

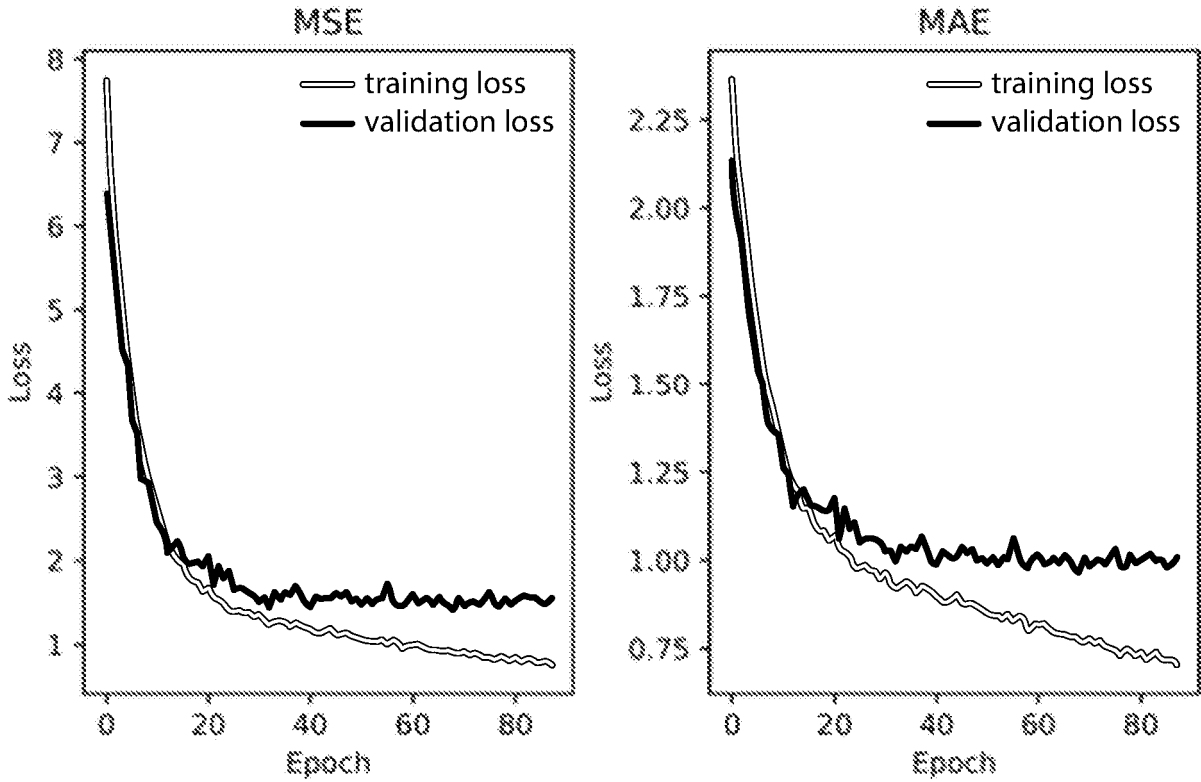


FIG 12C

FIG 12D

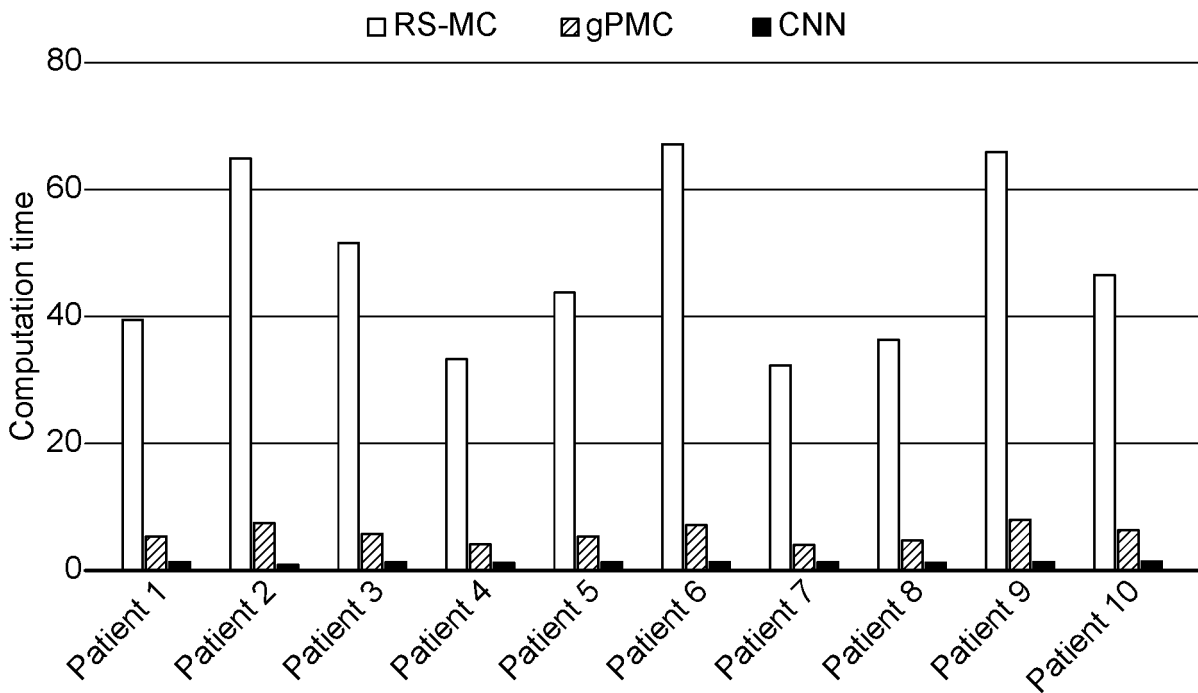


FIG 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2023/050085

A. CLASSIFICATION OF SUBJECT MATTER INV. A61N5/10 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/184107 A1 (ELEKTA LTD [CA]) 23 September 2021 (2021-09-23) the whole document -----	1-15
A	WO 2019/169455 A1 (NGUYEN DOAN TRANG [AU]; KEALL PAUL [AU]; MYLONAS ADAM [AU]) 12 September 2019 (2019-09-12) page 13, paragraph 1 - paragraph 3 ----- -/--	1-15
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search	Date of mailing of the international search report	
27 April 2023	11/05/2023	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Beck, Ewa	

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2023/050085

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>XIN ZHEN ET AL: "Deep convolutional neural network with transfer learning for rectum toxicity prediction in cervical cancer radiotherapy: a feasibility study", PHYSICS IN MEDICINE AND BIOLOGY, INSTITUTE OF PHYSICS PUBLISHING, BRISTOL GB, vol. 62, no. 21, 11 October 2017 (2017-10-11), pages 8246-8263, XP020321197, ISSN: 0031-9155, DOI: 10.1088/1361-6560/AA8D09 [retrieved on 2017-10-11] abstract</p> <p>-----</p>	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2023/050085

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021184107 A1	23-09-2021	EP 4121976 A1	25-01-2023
		WO 2021184107 A1	23-09-2021

WO 2019169455 A1	12-09-2019	US 2021038921 A1	11-02-2021
		WO 2019169455 A1	12-09-2019
