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# (54) METHOD FOR MEDICAL IMAGING IN TOF-PET TOMOGRAPHY

VERFAHREN ZUR MEDIZINISCHEN BILDHERSTELLUNG IN TOF-PET TOMOGRAPHIE PROCÉDÉ D'IMAGERIE MÉDICALE EN TOMOGRAPHIE TOF-PET

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- (73) Proprietors:
  - Uniwersytet Jagiellonski 31-007 Kraków (PL)
  - Uniwersytet Marii Curie Sklodowskiej 20-031 Lublin (PL)
- (72) Inventors:
  - MOSKAL, Pawel 32-061 Czulowek (PL)
  - JASINSKA, Bozena
    - 20-807 Lublin (PL)
- (74) Representative: Kancelaria Eupatent.pl Sp. z.o.o
   UI. Kilinskiego 185
   90-348 Lodz (PL)

- (56) References cited: WO-A1-2015/028604
  - KRZYSZTOF KACPERSKI ET AL: "Performance of three-photon PET imaging: Monte Carlo simulations", ARXIV.ORG, CORNELL UNIVERSITY LIBRARY, 201 OLIN LIBRARY CORNELL UNIVERSITY ITHACA, NY 14853, 12 July 2005 (2005-07-12), XP080202627, DOI: 10.1088/0031-9155/50/23/019
  - ALKHORAYEF M ET AL: "Measurement of three gamma annihilation by lanthanum-based crystals compared with Nal(TI) and HPGe", JOURNAL OF RADIOANALYTICAL AND NUCLEAR CHEMISTRY, KLUWER ACADEMIC PUBLISHERS, DO, vol. 291, no. 2, 10 July 2011 (2011-07-10), pages 493-496, XP019998192, ISSN: 1588-2780, DOI: 10.1007/S10967-011-1316-3
  - KAMINSKA D ET AL: "A feasibility study of ortho-positronium decays measurement with the J-PET scanner based on plastic scintillators", THE EUROPEAN PHYSICAL JOURNAL C, SPRINGER BERLIN HEIDELBERG, BERLIN/HEIDELBERG, vol. 76, no. 8, 9 August 2016 (2016-08-09), pages 1-14, XP036058147, ISSN: 1434-6044, DOI: 10.1140/EPJC/S10052-016-4294-3 [retrieved on 2016-08-09]

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## Description

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[0001] The invention relates to a method for medical imaging in TOF-PET tomography, based on the ratio of  $3\gamma/2\gamma$ quanta which are formed during the electron-positron annihilation. The method described in the present invention may be applied in PET medical diagnosis using pharmaceuticals labelled with any positron-emitting radioisotope.

- [0002] Positron Emission Tomography (PET) is a commonly known diagnostic method which allows for imaging of metabolism of selected substances in a living organism. Its possible applications include imaging of a patient's body enabling determination of the size and localisation of a neoplasm as well as search for metastases. The PET technique allows for detecting the metastases even at a stage which cannot be detected by other methods, normally used for 10 detection of anatomical or morphological changes.
  - [0003] Prior to PET examination, a patient receives a radiopharmaceutical containing a radioisotope, e.g. <sup>18</sup>F or <sup>11</sup>C, having nuclei which undergo a beta plus decay, emitting a positron. The PET technique used currently is based on annihilation of a positron emitted by a radiopharmaceutical and an electron originating from the patient's body, yielding two guanta, which have an energy of 511 keV each. PET tomographs enable recording of the annihilation guanta (511
- 15 keV). For every recorded event, spots of interaction of the guanta in the tomograph and time differences between the interaction events of the recorded quanta (called time of flight, TOF) are determined. Then, knowing the spots and times for a large number of recorded events, a distribution of density of the annihilation spots is reconstructed, corresponding to the image of intensities of the radiopharmaceutical's metabolisation in the patient's organism.
- [0004] As is described in the Patent Application No. PCT/PL2015/050038, radiopharmaceuticals may be divided in 20 general into two classes depending on the type of radioisotopes used. The first, most frequently used class, comprises isotopes, which after the emission of a positron transform into a daughter nucleus in the ground state. This group includes e.g. <sup>18</sup>F, which as a result of a nuclear reaction emits a positron and is transformed into a stable nucleus of <sup>18</sup>O. The second class of isotopes, including e.g. <sup>44</sup>Sc or <sup>14</sup>O, during a beta plus decay are transformed into a daughter nucleus in the excited state, which emits subsequently the excitation energy in the form of a gamma quantum. Deexcitation of
- 25 the daughter nucleus occurs almost immediately with an average interval of the order of several picoseconds (e.g. 2.6 ps for <sup>44</sup>Sc).

[0005] Although the deexcitation quantum is not used in PET imaging currently, and in fact its interaction in the tomograph may lead to an additional background, Patent Applications Nos. PCT/PL2015/050038 and WO2012/135725 have described recently a possibility to utilise it for simultaneous imaging with several radiopharmaceuticals, and Patent

- 30 Application No. WO2015/028604 discloses a method for morphometric imaging, utilising a deexcitation quantum for determination of lifetimes of ortho-positronium (o-Ps) atoms formed inside body cells during PET imaging. Application No. WO2015/028604, and then also Application No. PCT/PL2015/050038 describes that in order to define the image of ortho-positronium lifetimes, a deexcitation quantum should be recorded in every event, determining the time of creation of an o-Ps atom, as well as quanta from two- or three-quantum annihilation should be recorded, which allow for defining
- the moment of decay of the positronium atom. The average ortho-positronium lifetime ( $T_{o-Ps}$ ) and the probability of its 35 formation (P<sub>n-Ps</sub>) determined in every voxel of the image serve as a morphological indicator, additional and independent of the Standardised Uptake Value (SUV). In the paper by R. Pietrzak et al. "Influence of neoplastic therapy on the investigated blood using positron annihilation lifetime spectroscopy", NUKLEONIKA 2013, 58 (1): pp. 199-202, it was proved that the lifetimes of orto-positronium atoms in the blood of patients suffering from leukaemia change after radi-40

## otherapy.

[0006] However, the solution pertaining to morphometric imaging described in the Patent Application No. WO2015/028604 is limited to radiopharmaceuticals containing isotopes which emit a deexcitation quantum, and excludes use of isotopes most common in the PET, such as e.g. <sup>18</sup>F and <sup>11</sup>C, which, while decaying to the ground state of the final nucleus, emit only a positron, not emitting any deexcitation quantum. Moreover, there are no known methods in

- 45 prior art at present, which could utilise all types of radio-markers used in the PET diagnostics for morphometric imaging. [0007] Therefore, it would be highly desirable to develop a method for measuring a parameter which would replace the direct ortho-positronium lifetime measurements in living organisms, and to apply this method in a tomograph which allows for reconstructing images of this parameter, enabling use of radiopharmaceuticals that contain both isotopes emitting deexcitation quanta, and those which do not emit these quanta.
- 50 [0008] The solution described in the Patent Application No. WO2015/028604 was based on the observation that there is a correlation between the o-Ps lifetime ( $T_{o-Ps}$ ) and the size of the void in which the positronium atom is trapped (Eldrup, D. Lightbody, J.N. Sherwood, "The temperature dependence of positron lifetimes in solid pivalic acid", Chem. Phys., 63, (1981) 51). If the sizes of the voids are of the order of angstroms, T<sub>o-Ps</sub> is very sensitive to even relatively small changes in the size or shape (B. Jasinska, A.E. Koziot and T. Goworek "Void shapes and o-Ps lifetime in molecular crystals", 55 Acta Phys. Polon. A95 (1999) 557).

[0009] The solution according to the present invention is based on other observations, namely:

(i) the size of the void space between molecules is determined by the  $f_{o-Ps^{-}3\gamma}$  fraction of the o-Ps atoms annihilating

with  $3\gamma$  emission. It is a consequence of the correlation between  $f_{0-Ps}-_{3\gamma}$  and  $T_{o-Ps}$ , which may be expressed using the following equation:

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 $f_{o-Ps-3v} = \tau_{o-Ps}/\tau_{o-Ps-vacuum}$ (1)

where  $T_{o-Ps-vacuum}$  is the value of the o-Ps lifetime in vacuum, equal to 142 ns;

(ii) a change in the  $f_{0-Ps^-3\gamma}$  fraction accompanying a change in the size of the void volume between molecules manifests itself as a change in the  $f_{3\gamma2\gamma} = N_{3\gamma}/N_{2\gamma}$  ratio in the positron-electron annihilation into  $3\gamma$  and into  $2\gamma$ .

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**[0010]** To determine the dependence of  $f_{0-Ps^-3\gamma}$  on the  $f_{3\gamma^2\gamma}$  ratio measured experimentally by the method according to the present invention, it is necessary to discuss both processes leading to two-quantum annihilation, and three-quantum annihilation.

- **[0011]** A positron penetrating a human body (originated for the  $\beta^+$  decay of a radioisotope) may annihilate directly with one of electrons of the studied object or it may form a bound state with an electron - a positronium (Ps) atom. Then, positronium may be trapped inside a void volume between molecules of the studied body. Ps may be formed in two states: para-Ps (in which the positron and the electron have a total spin equal to zero) or ortho-Ps (spins of both particles add up to a spin value equal to 1). According to the laws of conservation of quantum numbers, para-Ps decays with emission of an even number of quanta, mainly  $2\gamma$ , both in vacuum and in a medium. On the other hand, an o-Ps atom
- 20 in vacuum annihilates mainly with 3γ emission, while in matter, o-Ps may annihilate additionally into two quanta in a so-called pick-off process with one of electrons of the surrounding medium. Thus, in the studied medium, o-Ps may annihilate by one of the two processes: some fractions by a spontaneous decay to 3γ, and the remaining fraction by a pick-off process to 2γ. The ratio of these two fractions depends on the size of the void space. The larger the void space, the longer the o-Ps lifetime is, and the larger the f<sub>o-Ps<sup>-3y</sup></sub> fraction of annihilation with emission of 3γ quanta.
- [0012] Free annihilation and the pick-off process occur mainly with 2γ emission, only the 1/372 fraction of these annihilations of a positron with an electron occurs with 3γ emission.
   [0013] Including both described above pathways for 3γ quanta generation in annihilation processes, the f<sub>3γ2γ</sub> ratio may be expressed as:

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$$f_{3y2y} = \frac{f_{3y}}{1 - f_{3y}}$$
(2)

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where  $f_{3\gamma}$  is the fraction of annihilation to 3y, having the following form:

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$$f_{3\gamma} = \frac{\left(1 - \frac{4}{3}P_{o-Ps}\right)}{372} + \frac{\tau_{o-Ps}}{\tau_{o-Ps-vacuum}}P_{o-Ps}$$
(3)

where  $P_{o-Ps}$  is the probability of ortho-positronium, depending on properties of the molecular structure of the studied object. While deriving the above dependence, annihilations to four or more gamma quanta were omitted, as their share is of the order of 10<sup>-6</sup> at most; the fact that the pick-off process may occur also by an annihilation to  $3\gamma$  (1/372 ×  $P_{o-Ps}$ ×(1- $f_{o-Ps}$ - $_{3\gamma}$ )) was omitted too, as the share from these processes is insignificant, and moreover, the main goal of deriving the above formula consists in proving that the  $f_{3\gamma2\gamma}$ = $N_{3\gamma}/N_{2\gamma}$  fraction (being a function of the lifetime ( $T_{o-Ps}$ ) and o-Ps formation probability ( $P_{o-Ps}$ )) is correlated with sizes and concentration of the voids volumes, thus it may be used as a measure (a morphometric indicator) of porosity of the studied organism's tissues.

[0014] The f<sub>3γ2γ</sub>=N<sub>3γ</sub>/N<sub>2γ</sub> fraction may be determined experimentally as a ratio of numbers of events recorded during the object imaging with 3γ and 2γ emissions or from energy spectra, by one of the two methods: "peak to peak" or "peak to valley". However, the latter method is burdened with numerous additional requirements discussed e.g. in the paper "Three-Quantum Annihilation in Porous Vycor Glass" by B. Jasinska, J. Wawryszczuk and R. Zaleski, Acta Phys. Polon.

55 A 107 (2005) 821.

**[0015]** In the human body, positronium atoms may be formed and trapped both in high-density tissues and in biofluids. In tissues, the voids volumes between molecules have sizes of the order of 1 nm so the expected fraction of o-Ps atoms annihilating with  $3\gamma$  emission is of the order of 1%. To emphasize morphometric differences between the tissues, a

morphometric indicator is defined in the present invention, having a form of a relative difference of the  $f_{3\gamma 2\gamma}$  ratio in the studied medium  $(f_{3\gamma 2\gamma})_t$  and the  $(f_{3\gamma 2\gamma})_r$  value in a reference material, expressed as per mille:

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$$\delta_{3\gamma} = \frac{(f_{3\gamma 2\gamma})_t - (f_{3\gamma 2\gamma})_r}{(f_{3\gamma 2\gamma})_r} \times 1000\% .$$
 (4)

- **[0016]** In living organisms, water constitutes a good reference material. The values of the lifetime and the o-Ps formation probability measured in purified water amount to:  $T_{o-Ps}$ =1.8 ns,  $P_{o-Ps}$  = 30% ("Incorporation of the Magnetic Quenching Effect into the Blob Model of Ps Formation. Finite Sized Ps in a Potential Well", Stepanov et al., Mater. Sci. Forum, Vol. 666, 109-114 (2010)). In aqueous solutions, the lifetime increases to approx.  $T_{o-Ps}$  = 2.0 ns. Based on the published results of investigations pertaining to organic materials (molecular crystals, polymers, long-chain alkanes) and small known number of papers on studies of neoplasms, the expected values of lifetimes ranges from about 1 to about 5 ns,
- and the o-Ps formation probabilities in a human organism from about 10 to about 40%. For exemplary values ( $T_{o-Ps} = 4$  ns and  $P_{o-Ps} = 40\%$ ), the morphometric indicator reaches  $\delta_{3\gamma} = 50\%$ , and for the lowest discussed values ( $T_{o-Ps} = 1$  ns and  $P_{o-Ps} = 10\%$ )  $\delta_{3\gamma} = -50\%$ o.

**[0017]** The present invention relates to a method for medical imaging in TOF-PET tomography according to the appended claims.

<sup>20</sup> **[0018]** An example embodiment of the imaging method is illustrated in Fig. 1 showing a flow chart of a process for reconstruction of the  $3\gamma/2\gamma$  fractions of annihilating positrons in an exemplary TOF-PET detector.

Example

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<sup>25</sup> **[0019]** For recording of gamma quanta, PET tomographs known in prior art may be used, consisting of both organic and inorganic scintillators, after using the method described in the present invention, which allows for recording both two-quantum and three-quantum annihilations.

**[0020]** In Fig. 1, a flow chart of a procedure for obtaining a 3D image of the  $3\gamma/2\gamma$  ratio originating from positron-electron annihilation vs. the location of the studied object is illustrated. Tomograph 110 comprises detectors which allow for

- 30 determining the position and time of the reaction in the tomograph of gamma quanta emitted from the studied object. Electric signals from the detectors 110 are read and processed into digital form by a data acquisition system (DAQ) 111, and then they are transmitted in step 112 to a recording device, which processes them in step 113 or stores on a disc. Data acquisition may be performed using method known in prior art. A processor 113 identifies detectors which have recorded the quanta from 3γ and 2γ annihilations, using conventional methods known to persons skilled in the art.
- <sup>35</sup> **[0021]** The event is identified as recording of two or more quanta in the defined time interval (e.g. of several nanoseconds).

**[0022]** The events classified as  $2\gamma$  annihilation are used for reconstruction of a metabolic image 124 by TOF-PET methods 121, 122, 123 known in prior art.

[0023] The events classified as 3γ annihilation are used for reconstruction of (x,y,z) coordinates of the point, in which the annihilation has occurred, and the plane of response (POR) 132. The identification is carried out using a processor 131, by methods known in prior art (e.g. those described in Patent Application No. WO2015/028604). The plane of response is defined as a plane containing point, in which 3γ interacted with the detectors. In the next step 133, based on the data of 132, a 3γ annihilation density image, 133, is reconstructed.

- **[0024]** The conventional  $2\gamma$  image obtained in the TOF-PET 124 and the  $3\gamma$  image 134 are used by a processor 141 for reconstruction of a  $3\gamma/2\gamma$  morphometric image 142. The reconstructed images 124, 134, and 142 are visualised in step 143. The morphometric image is defined by calculating the value of the  $\delta_{3\gamma}$  parameter for every voxel, according to the dependence (4), where the  $f_{3\gamma2\gamma}$  ratio is determined based on the corresponding normalised  $2\gamma$  and  $3\gamma$  images. The image is normalised so as to the integral of the values over all voxels of the normalised  $2\gamma$  image is equal to the total number of  $2\gamma$  annihilations which have occurred in the imaged part of the studied object. Analogically, the integral
- <sup>50</sup> of the events in the whole normalised  $3\gamma$  image is equal to the total number of  $3\gamma$  annihilations in the imaged part of the studied object.

**[0025]** To enhance the diagnostic options, prior to the morphometric reconstruction 141, the  $2\gamma$  image 124 and  $3\gamma$  image 134 may be improved (i.e. corrected for attenuation of gamma quanta in the studied object) using anatomical or morphological images. The latter may be obtained simultaneously or sequentially by the KT or MR tomographic imaging techniques known in prior art. To improve the diagnostic quality, the obtained  $3\gamma/2\gamma$  morphometric images may be overlaid

onto anatomical or morphological images. **[0026]** The described method may be used also in imaging using several isotopes. In such a case, the processor 113 identifies also the signals originating from deexcitation guanta (if recorded) emitted by a certain class of isotopic markers

discussed earlier. Energy of these quanta has a value characteristic for each isotope. Thus, in the case of multiisotopic imaging, the two-quantum and three-quantum annihilations events may be classified correspondingly for every isotope, enabling simultaneous imaging using radiopharmaceuticals labelled with radioisotopes from various isotope classes discussed in the present description. It is particularly important e.g. of the case of monitoring of production of various  $\beta^+$ -radioactive isotopes during hadron therapy.

- **[0027]** The presented method of  $3\gamma/2\gamma$  imaging and the morphometric indicator  $\delta_{3\gamma}$  have the following advantages:
  - the δ<sub>3γ</sub> indicator is a measure of porosity of tissues of the studied organism and serves as a measure of advancement
    of structural changes in cell on the molecular level;
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 δ<sub>3γ</sub> is an additional indicator for SUV - standardised indicator of cell metabolism being defined in PET, and it provides additional information useful in diagnosing;

the 3γ/2γ image does not depend on the time of examination, so it does not need to be corrected for the decrease
 of the radioisotope activity in the studied object in time, which is of high significance in examinations requiring moving the patient along the scanner to record images of various body parts;

- also the  $\delta_{3\gamma}$  indicator value does not depend on time elapsed from the administration of the radiopharmaceutical to the patient. Thus, the knowledge of the physical or biological half-life of the radiopharmaceutical, or its initial activity is not necessary to determine the  $\delta_{3\gamma}$  value;
- the morphometric indicator  $\delta_{3\gamma}$  and the SUV indicator may be determined simultaneously during the same examination;
- <sup>25</sup> the  $\delta_{3\gamma}$  morphometric image may be determined using all radiopharmaceuticals utilised in the PET techniques, thus, as opposite to other morphometric indicator known in prior art, it is not limited only to the class of radioisotopes emitting a deexcitation quantum;
- determining the  $\delta_{3\gamma}$  value does not require recording of a deexcitation quantum, which leads to an increase in the imaging efficiency while compared to other currently known indicators for morphometric imaging;
  - the presented system allows for dividing images originating from various radioisotopes in the case of multiisotopic imaging, provided that these isotopes emit deexcitation quanta with various energies.
- <sup>35</sup> **[0028]** The technical solutions presented herein are outlined, described and defined in relation to specific preferred applications. However, the discussed various versions of imaging are only examples and they do not exhaust the full scope of the technical solution presented herein. The scope of protection is not limited to the described examples, but only to the following claims.

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## Claims

- 1. A method for medical imaging in TOF-PET tomography, comprising the following steps:
  - introducing an object containing a positron-emitting radioisotope into a diagnostic chamber of a tomograph,
    - recording gamma quanta emitted from an imaged part of the object by means of the tomograph,
    - attributing recorded events to  $2\gamma$  and  $3\gamma$  annihilation subgroups,-reconstructing a  $2\gamma$  image of the imaged part of the object,
    - reconstructing a 3γ image of the imaged part of the object,

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characterized in that, the method further comprises the steps of:

- normalising the  $2\gamma$  image to obtain a normalised  $2\gamma$  image so that the integral of the values over all voxels of the normalized  $2\gamma$  image is equal to the total number of  $2\gamma$  annihilations which have occurred in the imaged volume, - normalising the  $3\gamma$  image to obtain a normalised  $3\gamma$  image so that the integral of the values over all voxels of the normalised  $3\gamma$  image is equal to the total number of  $3\gamma$  annihilations which have occurred in the imaged volume, - determining a value of a morphometric indicator  $\delta_{3\gamma}$  for every voxel of the imaged part of the object based on the following dependence:

$$\delta_{3\gamma} = \frac{\left(f_{3\gamma 2\gamma}\right)_{t} - \left(f_{3\gamma 2\gamma}\right)_{r}}{\left(f_{3\gamma 2\gamma}\right)_{r}} \times 1000\%$$

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where:

 $(f_{3\gamma2\gamma})_t$  is a ratio of count number of annihilations with  $3\gamma$  emission to a count number of annihilations with  $2\gamma$  emission, calculated for every voxel of the imaged part of the object based on the normalized  $2\gamma$  image and the normalized  $3\gamma$  image, and  $(f_{3\gamma2\gamma})_r$  is a ratio of count number of annihilations with  $3\gamma$  emission to a count number of annihilations with  $2\gamma$  emission in a reference material,

- visualising the morphometric image of the imaged part of the object, having voxels based on the determined values of the morphometric indicators  $\delta_{3\gamma}$ 

The method according to claim 1, further characterised in that in a defined time interval, two gamma quanta are recorded originating from the two-quantum positron-electron annihilation (2γ) and one or no quantum from the deexcitation.

**3.** The method according to claim 1, further **characterised in that** in a defined time interval, three gamma quanta are recorded originating from the three-quantum positron-electron annihilation (3γ) and one or no quantum from the deexcitation.

4. The method according to claim 1, further **characterised in that** anatomical and/or morphological images of the object are created simultaneously or sequentially, and the obtained morphometric image  $\delta_{3\gamma}$  is overlaid onto the mentioned anatomical and/or morphological images of the object.

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5. The method according to claim 1, further **characterised in that** the object comprises more than one positron-emitting radioisotope, and the gamma quanta are recorded for every radioisotope respectively.

## 30 Patentansprüche

1. Verfahren zur medizinischen Bildgebung in der TOF-PET-Tomografie, umfassend die folgenden Schritte:

- Einführen eines Objekts, das ein Positronen emittierendes Radioisotop enthält, in eine Diagnosekammer eines Tomografen,

- Aufzeichnen von Gammaquanten, die von einem abgebildeten Teil des Objekts emittiert werden, mittels des Tomografen,

- Zuordnen aufgezeichneter Ereignisse zu  $2\gamma$  und  $3\gamma$ -Vernichtungsuntergruppen,
- Rekonstruieren eines 2γ-Bildes des abgebildeten Teils des Objekts,
- Rekonstruieren eines 3y-Bildes des abgebildeten Teils des Objekts,

## dadurch gekennzeichnet, dass das Verfahren ferner die folgenden Schritte umfasst:

 Normalisieren des 2γ-Bildes, um ein normalisiertes 2γ-Bild zu erhalten, sodass das Integral der Werte über alle Voxel des normalisierten 2γ-Bildes gleich der Gesamtzahl von 2γ-Vernichtungen ist, die in dem abgebildeten Volumen aufgetreten sind,

- Normalisieren des 3y-Bildes, um ein normalisiertes 3γ-Bild zu erhalten, sodass das Integral der Werte über alle Voxel des normalisierten 3y-Bildes gleich der Gesamtzahl von 3γ-Vernichtungen ist, die in dem abgebildeten Volumen aufgetreten sind,

50 - Bestimmen eines Werts eines morphometrischen Indikators  $\delta_{3\gamma}$  für jedes Voxel des abgebildeten Teils des Objekts auf Grundlage der folgenden Abhängigkeit:

$$\delta_{3\gamma} = \frac{(f_{3\gamma 2\gamma})_{t} - (f_{3\gamma 2\gamma})_{r}}{(f_{3\gamma 2\gamma})_{r}} \times 1000\%$$

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## wobei:

- $(f_{3\gamma 2\gamma})_t \text{ ein Verhältnis der Zählzahl von Vernichtungen bei 3y-Emission zu einer Zählzahl von Vernichtungen bei 2\gamma-Emission ist, die für jedes Voxel des abgebildeten Teils des Objekts auf Grundlage des normalisierten 2\gamma-Bildes und des normalisierten 3y-Bildes berechnet wird, und <math display="block"> (f_{3\gamma 2\gamma})_r \text{ ein Verhältnis der Zählzahl von Vernichtungen bei 3y-Emission zu einer Zählzahl von Vernichtungen bei 2\gamma-Emission in einem Referenzmaterial ist,$ 
  - Visualisieren des morphometrischen Bildes des abgebildeten Teils des Objekts mit Voxeln auf Grundlage der bestimmten Werte der morphometrischen Indikatoren  $\delta_{3r}$
  - Verfahren nach Anspruch 1, ferner dadurch gekennzeichnet, dass in einem definierten Zeitintervall zwei Gammaquanten, die aus der Zwei-Quanten-Positron-Elektron-Vernichtung (2γ) stammen, und ein oder kein Quant aus der Aberregung aufgezeichnet werden.
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- Verfahren nach Anspruch 1, ferner dadurch gekennzeichnet, dass in einem definierten Zeitintervall drei Gammaquanten, die aus der Drei-Quanten-Positron-Elektron-Vernichtung (3γ) stammen, und ein oder kein Quant aus der Aberregung aufgezeichnet werden.
- **4.** Verfahren nach Anspruch 1, ferner **dadurch gekennzeichnet**, **dass** anatomische und/oder morphologische Bilder des Objekts gleichzeitig oder nacheinander erzeugt werden und die erwähnten anatomischen und/oder morphologischen Bilder des Objekts mit dem erhaltenen morphometrischen Bild  $\delta_{3\gamma}$  überlagert werden.
  - Verfahren nach Anspruch 1, ferner dadurch gekennzeichnet, dass das Objekt mehr als ein Positronen emittierendes Radioisotop umfasst und die Gammaguanten jeweils f
    ür jedes Radioisotop aufgezeichnet werden.

## Revendications

30 1. Procédé d'imagerie médicale en tomographie TOF-PET, comprenant les étapes suivantes :

- introduction d'un objet contenant un radio-isotope émetteur de positrons dans une chambre de diagnostic d'un tomographe,

- enregistrement des quanta gamma émis par une partie imagée de l'objet au moyen du tomographe,
- attribution des événements enregistrés aux sous-groupes d'annihilations à 2γ et à 3γ,
- reconstruction d'une image 2γ de la partie imagée de l'objet,
- reconstruction d'une image 3γ de la partie imagée de l'objet,

caractérisé en ce que, le procédé comprend en outre les étapes de :

- normalisation de l'image  $2\gamma$  pour obtenir une image  $2\gamma$  normalisée de sorte que l'intégrale des valeurs sur tous les voxels de l'image  $2\gamma$  normalisée soit égale au nombre total d'annihilations à  $2\gamma$  qui se sont produites dans le volume imagé,

- normalisation de l'image 3γ pour obtenir une image 3γ normalisée de sorte que l'intégrale des valeurs sur tous les voxels de l'image 3γ normalisée soit égale au nombre total d'annihilations à 3γ qui se sont produites dans le volume imagé,

- détermination d'une valeur d'un indicateur morphométrique  $\delta_{3\gamma}$  pour chaque voxel de la partie imagée de l'objet sur la base de la fonction suivante :

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$$\delta_{3\gamma} = \frac{\left(f_{3\gamma 2\gamma}\right)_t - \left(f_{3\gamma 2\gamma}\right)_r}{\left(f_{3\gamma 2\gamma}\right)_r} \times 1000\%$$

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où :

 $(f_{3\gamma 2\gamma})_t$  représente un rapport du nombre de comptage d'annihilations avec émission  $3\gamma$  sur un nombre de comptage d'annihilations avec émission 2y, calculé pour chaque voxel de la partie imagée de l'objet sur la base

de l'image  $2\gamma$  normalisée et de l'image  $3\gamma$  normalisée, et  $(f_{3\gamma 2\gamma})_r$  représente un rapport du nombre de comptage d'annihilations avec émission  $2\gamma$  dans un matériau de référence,

- visualisation de l'image morphométrique de la partie imagée de l'objet, qui comporte des voxels basés sur les valeurs déterminées des indicateurs morphométriques  $\delta_{3\gamma}$ 

2. Procédé selon la revendication 1, caractérisé en outre en ce que dans un intervalle de temps défini, deux quanta gamma sont enregistrés qui proviennent de l'annihilation positonélectron à deux quantums (2γ) et un ou aucun quantum de la désexcitation.

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- 3. Procédé selon la revendication 1, caractérisé en outre en ce que dans un intervalle de temps défini, trois quanta gamma sont enregistrés qui proviennent de l'annihilation positronélectron à trois quantum (3γ) et un ou aucun quantum de la désexcitation.
- **4.** Procédé selon la revendication 1, **caractérisé en outre en ce que** des images anatomiques et/ou morphologiques de l'objet sont créées simultanément ou séquentiellement, et l'image morphométrique  $\delta_{3\gamma}$  obtenue est superposée sur les images anatomiques et/ou morphologiques mentionnées de l'objet.
  - 5. Procédé selon la revendication 1, caractérisé en outre en ce que l'objet comprend plus d'un radio-isotope émetteur de positrons, et les quanta gamma sont enregistrés pour chaque radio-isotope, respectivement.

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Fig. 1

## **REFERENCES CITED IN THE DESCRIPTION**

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## Patent documents cited in the description

- PL 2015050038 W [0004] [0005]
- WO 2012135725 A [0005]

#### Non-patent literature cited in the description

- R. PIETRZAK et al. Influence of neoplastic therapy on the investigated blood using positron annihilation lifetime spectroscopy. NUKLEONIKA, 2013, vol. 58 (1), 199-202 [0005]
- ELDRUP, D. LIGHTBODY; J.N. SHERWOOD. The temperature dependence of positron lifetimes in solid pivalic acid. Chem. Phys., 1981, vol. 63, 51 [0008]
- B. JASINSKA ; A.E. KOZIOT ; T. GOWOREK. Void shapes and o-Ps lifetime in molecular crystals. *Acta Phys. Polon. A,* 1999, vol. 95, 557 [0008]

- WO 2015028604 A [0005] [0006] [0008] [0023]
- B. JASINSKA ; J. WAWRYSZCZUK ; R. ZALESKI. Three-Quantum Annihilation in Porous Vycor Glass. *Acta Phys. Polon. A,* 2005, vol. 107, 821 [0014]
- STEPANOV et al. Incorporation of the Magnetic Quenching Effect into the Blob Model of Ps Formation. Finite Sized Ps in a Potential Well. *Mater. Sci. Forum*, 2010, vol. 666, 109-114 [0016]