Positronium imaging in J-PET with an iterative activity reconstruction and a multistage fitting algorithm

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ABSTRACT

Positronium imaging is a new technique complementary to positron emission tomography (PET) based on the histogramming of time delay between the emission of a de-excitation photon, and a consequent electron-positron annihilation, to estimate the mean lifetime of orthopositronium (o-Ps), which depends on the local size of the voids, concentration of oxygen and bioactive molecules. We improve the resolution and reduce noise in positronium imaging by building time-delay spectra from the PET activity reconstructed by a 3-photon time-of-flight maximum likelihood expectation maximisation. The method was tested on the data measured for four human-tissue samples injected by $^{22}$Na and put in the Jagiellonian PET “Big barrel” scanner. Due to an ill-posed problem of fitting time-delay histograms, a multistage optimisation procedure was explored along with inferential analysis of the solution space. Run in parallel for multiple sets of initial guesses, we compared the second-order Levenberg-Marquardt algorithm (LMA) and the direct search Nelder-Mead simplex (NMS) method. The LMA proved to be faster and more precise, but the NMS was more stable with a higher convergence rate. The estimated mean o-Ps lifetimes in the 1.9 ns – 2.6 ns range were consistent with the reference results, while other fitting parameters allowed differentiation between the two patients who provided the tissue samples.

KEYWORDS

Jagiellonian PET, positronium imaging, MLEM, ill-posed problem, nonlinear optimisation
INTRODUCTION

Positronium imaging is a new multiphoton diagnostic method, complementary to positron emission tomography (PET), that focuses on the properties of positronium (Ps) in a living organism [1–3]. As a hydrogen-like bound of an electron (e⁻) and a positron (e⁺), Ps can exist in two states, depending on spin – para-positronium (p-Ps) or ortho-positronium (o-Ps) – with the corresponding mean lifetimes in vacuum 125 ps and 142 ns, respectively [4]. In a typical PET scan, up to 40% of all recorded coincidences happen due to Ps decay, of which 75% comes from o-Ps. The majority of them originate from the e⁺e⁻ annihilations, which produce pairs of 511-keV photons, since the natural o-Ps self-decay into three γ-photons is obscured by the surrounding matter due to picking up an electron with an opposite spin or via conversion o-Ps → p-Ps, following its self-decay [2, 4–6].

Positronium imaging requires time-of-flight (TOF) information and specific β⁺ decay sources (²²Na, ⁴⁴Sc, ⁶⁸Ga) that emit an additional de-excitation (prompt) photon out of the intermediary nucleus – at about the same time when a Ps is created [2, 7–9]. That facilitates the measurement of time delays between prompt emissions and e⁺e⁻ annihilations, arranged into histograms (spectra) for each voxel. The histograms are later used to estimate the local perturbations of a mean o-Ps lifetime that reflects structural anomalies in matter, such as oxygen concentration, porosity or size of intra-molecular voids in hypoxic tumours [10–13]. Recent works about positron annihilation lifetime spectroscopy (PALS) report that o-Ps lifetimes correlate well with the results acquired via histopathological or cardiac myoxma imaging [14–16]. The up-to-date advancements in PET technology – sensitivity gain [17–21] and TOF resolution [22–24] – can further expand the application of positronium imaging in biology and nuclear medicine.

The first ex-vivo experiments with an ²²Na isotope have been recently conducted in the “Big barrel” Jagiellonian PET (J-PET) prototype built of plastic scintillators [3], which detect γ-photons using the Compton scattering and also collect TOF information [25]. Despite relatively high time resolution (~ 450 ps), there are issues with lower sensitivity (partially resolved by multilayer geometry and large axial field-of-view (FOV) [26]) and an additional axial smearing. Recently, a hybrid iterative reconstruction method was proposed for positronium imaging and tested on the simulated data with a generic o-Ps decay model [27].

Time-delay spectra can be described as a sum of multiple exponential decay contributions, additionally smeared by a Gaussian due to a TOF uncertainty [28, 29]. Their modelling is often affected by overfitting and can be simplified given some features are either known (e.g. decay constant for p-Ps) or measured beforehand [30]. Nevertheless, a nonlinear optimisation remains an ill-posed problem sensitive to the initial guess and prone to converge at local minima. Diverse solutions were proposed to address such a challenge: direct deconvolution [31], refined fitting [32, 33], multistage constrained minimisation [34] and the inverse Laplace transform with regularisation [5]. More advanced statistically based methods included a Markov Chain Bayesian inference [35] and an iterative, maximum log-likelihood lifetime estimation [36]. Those approaches expect to produce reliable results, but exhibit slower performance and could be unpractical for positronium imaging with thousands of voxels.

In this work, we propose an inferential approach for exploring the solution space of fitting parameters and multithread optimisation launched for random sets of initial guesses, gradually optimised through a multistage minimisation procedure. On processing the experimental data for human tissue samples, we firstly employ an iterative reconstruction method and then compare from the practical viewpoint the application of a second-order Levenberg-Marquardt algorithm (LMA) [37, 38] and a derivative-free direct search Nelder-Mead simplex method (NMS) [39] to time-delay spectra.

OBJECTS OF STUDY AND METHODS

Experimental setup and data collection

The “Big Barrel” J-PET scanner, utilised for the measurements, comprises 192 detector modules cylindrically arranged into three sparse layers of the radii 425 mm, 467.5 mm and 575 mm [25]. One module includes an EJ-230 plastic scintillator of the size 7 mm × 19 mm × 500 mm and two Hamamatsu R9800 vacuum photomultipliers (PM) mounted at the opposite ends.

The experimental datasets have been acquired during the experiment with four objects – cardiac myxoma and adipose-tissue samples taken from two different patients [3]. The samples were provided by John Paul II Hospital in Kraków (bioethical consent no. 1072.6120.123.2017). To withstand the 8-day-long measurement they were put in a 10% formalin solution. As a source of β⁺ decay with prompt, a ²²Na isotope that undergoes the reaction: ²²Na → ²²Ne⁺e⁻ + v → ²²Ne⁺γ₁₂₇₄ + e⁻ + v (γ₁₂₇₄ denotes the 1274 keV de-excitation photon) was chosen. Fig. 1. gives the basic information about the experimental setup. A 2-mm ²²Na source encapsulated by a 7-μm thin Kapton foil was put between each of the samples, split in two parts and covered by a holder, as shown. Wrapped into a parafilm, the arrangement constituted one 20 mm × 20 mm cylindrical chamber. The four objects were fixed equidistantly from the FOV centre at the vertices of a square, with the side 162 mm located at a central XY plane of the Big Barrel (z = 0 mm). The injected activities were higher for the first patient: 0.345 MBq for cardiac myxoma, 0.393 MBq – for adipose tissue, compared to 0.238 MBq and 0.230 MBq, respectively, for the second one.

The data were collected, filtered and postprocessed using a cutting-edge DAQ system and a dedicated IPET Framework [40, 41]. First, an electric signal at a PM must cross one or more thresholds within a 23-ns time window, then a scattering hit in a strip is generated if two signals from the opposite PMs fall within a narrower 5-ns gap and, finally, coincidence candidates are collected for multiple hits.
within a window of 200 ns. The following filtering procedure is based on the analysis of time-over-threshold distribution for the prompt and 511-keV gammas, concluded by two geometrical conditions imposed on hit locations. More details can be found in [3, 40].

The dataset used in this work comprised $2.9 \times 10^6$ three-gamma coincidences, represented by three hits:

$$(t, p_h),$$
where $t$ is a time and $p_h \equiv (x_h, y_h, z_h)$ is a scattering point for a photon $h$.

### Three-photon TOF MLEM

The activity concentration in the studied tissue samples was estimated by a maximum likelihood expectation maximisation (MLEM) algorithm [42, 43], adapted in list mode for three-photon events with TOF and introduced in our prior work [27]. An unknown activity concentration $\lambda_i$ in the $i$-th voxel was iteratively updated at the $n$-th iteration as follows:

$$\lambda^{(n+1)}_j = \lambda^{(n)}_j \frac{\sum_{\nu} m_{\nu,j} \sum_{\nu \in \nu_j} m_{\nu,j} K_{\text{TOF}}(\Delta l) K_{\text{Z}}(\Delta z)}{\sum_{\nu} m_{\nu,j} \sum_{\nu \in \nu_j} m_{\nu,j} K_{\text{TOF}}(\Delta l) K_{\text{Z}}(\Delta z) + b_{\nu}}$$

(1)

Here, denotes one coincident event, $\nu$ represents a three-hit constellation “bin” in a PET scanner, $b_\nu$ is its additive factor (scattered and random events) and $m_{\nu,j}$ is an element of a joint system matrix that reflects the detection probability for $\nu$, given the photons are emitted from voxel $j$ [43]. Considering the emissions of a prompt and two annihilation photons are uncorrelated, the system matrix can be decoupled in two corresponding parts – $m_{\text{prompt},j}$ and $m_{\text{ann},j}$, so that $\nu = i + l$ for a triplet of detectors (a pair $i$ and a single one $l$. In addition, we account for TOF and axial smearing, specific for the J-PET, as Gaussian kernels $K_{\text{TOF}}(\Delta l)$ and $K_{\text{Z}}(\Delta z)$. The variables $\Delta l$ and $\Delta z$ describe the geometric offset of a voxel $j$ from the emission point in the event $e$.

We shall neglect the attenuation, the additive factors $b_\nu$ and the sensitivity correction denominator $\sum_{\nu} m_{\nu,j}$ in (1), since the chambers with the samples are small and placed symmetrically. That would simplify the update formula:

$$\lambda^{(n+1)}_j = \lambda^{(n)}_j \frac{\sum_{\nu} m_{\nu,j} K_{\text{TOF}}(\Delta l) K_{\text{Z}}(\Delta z)}{\sum_{\nu} m_{\nu,j} K_{\text{TOF}}(\Delta l) K_{\text{Z}} + b_{\nu}}$$

(2)

The voxel space $J$ here ignores most of the FOV and covers only a small volume of significance (VOS), limited geometrically by the cross-sections of the scintillator strip pair $i$ and the shapes of $K_{\text{TOF}}(\cdot)$ and $K_{\text{Z}}(\cdot)$, typically at three standard deviations (SDs) – $\pm 3_{\text{SD}}$ and $\pm 3_{\text{SD}}$, respectively. An example is shown in Fig. 2. The VOS shape resembles an ellipsoid outside of which the detection probability is effectively zero (more details can be found in [27]).

We estimate and on-the-fly, using an original method with multiple projectors introduced in [27]. That accounts for the detector resolution even better than using a point-spread function [44].

### Building time-delay spectra

Once TOF MLEM achieves the acceptable PET activities $\lambda_i$, in terms of spatial resolution, we aggregate the weighted probabilities of a time delay $\Delta t = t_{\text{ann}} - t_{\text{prompt}}$ – registered in a voxel $j$ during an event – into a histogram, or time-delay spectrum. Those probabilities are calculated for the $(n + 1)$-th iteration as:

Fig. 1. Experimental setup: chamber assembly (left) and schematic depiction of the source locations on the transverse plane $(z = 0 \, \text{mm})$ inside the Big Barrel J-PET (right).
where is the adjusted LOR length and \( c_0 \) is the speed of light. The corresponding detection probabilities (3) are consequently added to the histogram bin at \( \Delta t_j \), producing a time-delay spectrum (see the inset in Fig. 2.). As in the previous works [3, 27], we built the spectra only for the voxels whose reconstructed activity exceeds 5% of its maximum, rejecting the rest as noise.

### Multistage fitting procedure

A time-delay histogram is modelled as a sum of exponential decay functions convoluted with a Gaussian profile representing the measurement uncertainty and added to some stable background [28, 29]:

\[
f(\Delta t) = \sum_k I_k \exp \left( -\frac{\Delta t}{T_k} \right) \ast K_{EMG}(\Delta t, \mu_{EMG}, \sigma_{EMG}) + Bgr
g(\Delta z) = \sum_k I_k \exp \left( -\frac{\Delta z}{L_k} \right)
\]

where \( I_k \) are the intensities of the \( k \)-th contributor, \( T_k \) is the lifetime of the \( k \)-th component, and \( K_{EMG}(\Delta t, \mu_{EMG}, \sigma_{EMG}) \) is the Gaussian kernel with the mean \( \mu_{EMG} \) and the SD \( \sigma_{EMG} \) (EMG stands for the “exponentially modified Gaussian”) and Bgr is the background.

According to the notation in Fig. 2. (ignoring indices), the eventual time delays are recalculated as follows:

\[
\Delta t_j = t_{j,ann} - t_{j, prompt} = t_0 + \frac{t_{j, prompt} - \frac{L_{j, LOR}}{c_0}}{2}
\]

Fig. 2. Schematic depiction of a VOS for a three-photon coincidence with the geometric correction of the variables \( t_{j, prompt} \) and obliqueness \( \vartheta^* \) – to adjust the times \( t_{j, ann} \) and \( t_{j, prompt} \) for an exemplary voxel. An example of a time-delay spectrum built of weighted detection probabilities (3) and fitted by a realistic decay model (red curve) is shown on the inset. For convenience, all indices are omitted, i.e. \( t_{i, ann} \equiv t_{j, ann}, t_0 \equiv 0 \) etc.
(τ_p-Ps = 125 ps), but we merged the direct e^+e^- annihilations and (word missing) in the source material into a single component (I_{dir}, τ_{dir}). As mentioned, the nonlinear fitting of (5) with many unknown parameters is an ill-posed problem that requires a thorough analysis of the solution space. To design a fast solution able to process multiple voxels we considered two numerical methods:

- LMA (Levenberg-Marquardt algorithm), a second-order gradient-based method that interpolates between the Gauss-Newton algorithm and the gradient descent, depending on a damping factor that adjusts the step size [37, 38]. While fast and accurate, an LMA may require more computations, and it assumes that the cost function is smooth and well-behaved and that the initial guess is close to the true solution.

- NMS (Nelder-Mead (simplex) method), a derivative-free approach that uses a polytope (simplex) with n + 1 vertices in n dimensions to search for a minimum [39]. It does not require any information about the gradient, is more robust and can handle noisy and unpredictable cost functions (no Hessian is needed). However, the NMS is slower and less precise than second-order methods and prone to converge to a nonstationary point or oscillate indefinitely.

For convenience, all the histograms of Δt were normalised by their sums. To address the concern of a bad initial guess, we first analysed the solution space of all free parameters:

- I_{dir}, I_{p-Ps}, I_{o-Ps}, τ_{dir}, τ_{o-Ps}, Bgr, µ_{EMG} and σ_{EMG} – by fitting time-delay spectra for a few selected voxels near the centres of the tissue samples. The explored ranges of these variables, where the LMA and NMS most likely converge, were used to prepare 50–100 sets of uniformly distributed initial guesses. For each such guess we launched a multistage curve fitting for all of the spectra. At first only intensities I_{dir}, I_{p-Ps} and I_{o-Ps} were set free, with the other parameters fixed. Next we released µ_{EMG} and σ_{EMG} and, finally, the rest of the variables. The procedure resembles the one from the PALS Avalanche [34].

For comparison, we additionally executed a single-run fitting for each voxel, when all parameters were set free at an instant. Out of the resulting outcomes that did converge, we took the one with the lowest root mean squared error (RMSE) with respect to the histogram as the solution.

The multistage and single-run minimisation algorithms with multiple initialisations of fitting variables were implemented using parallel computing and R libraries minpack.lm and nloptr [45, 46].

RESULTS

Reconstructed activity and positronium image

The cross-sections in Fig. 3., top show MLEM progress in activity reconstruction for the 3-photon coincidences in the four tissue samples. Slightly higher levels are observed for the first patient. The resolution recovery, most crucial along the axial
Fig. 5. Histograms of the convergence rate, built for all nonzero voxels in a positronium image after 6-th MLEM iteration, depending on the constraints for the initial guess (see in the text) and the optimisation algorithm. Left histograms represent a single-run, those right – a multistage minimisation.

Tab. I. The relative intensities and the lifetimes of the decay contributions, estimated at the 6-th MLEM iteration and averaged for each sample.

<table>
<thead>
<tr>
<th>METHOD</th>
<th>PARAMETER</th>
<th>CARDIAC MYXOMA</th>
<th>ADIPOSE MISSUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PATIENT 1</td>
<td>PATIENT 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idir,%</td>
<td>60.44 (44)</td>
<td>66.50 (51)</td>
</tr>
<tr>
<td></td>
<td>fdir, ns</td>
<td>0.412 (3)</td>
<td>0.417 (2)</td>
</tr>
<tr>
<td></td>
<td>Ip-Ps,%</td>
<td>23.07 (45)</td>
<td>15.02 (53)</td>
</tr>
<tr>
<td>LMA (multistage)</td>
<td>lo-Ps,%</td>
<td>16.64 (15)</td>
<td>18.95 (11)</td>
</tr>
<tr>
<td>LMA (single-run)</td>
<td>lo-Ps, ns</td>
<td>1.949 (11)</td>
<td>1.994 (08)</td>
</tr>
<tr>
<td></td>
<td>Idir,%</td>
<td>60.44 (44)</td>
<td>66.50 (51)</td>
</tr>
<tr>
<td></td>
<td>fdir, ns</td>
<td>0.412 (3)</td>
<td>0.417 (2)</td>
</tr>
<tr>
<td></td>
<td>Ip-Ps,%</td>
<td>23.07 (45)</td>
<td>15.01 (54)</td>
</tr>
<tr>
<td>LMA (multistage, 2 components)</td>
<td>lo-Ps,%</td>
<td>16.64 (15)</td>
<td>18.95 (11)</td>
</tr>
<tr>
<td>LMA (single-run, 2 components)</td>
<td>lo-Ps, ns</td>
<td>1.949 (11)</td>
<td>1.995 (08)</td>
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<tr>
<td></td>
<td>Idir,%</td>
<td>51.8 (11)</td>
<td>59.3 (13)</td>
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<td></td>
<td>fdir, ns</td>
<td>0.406 (31)</td>
<td>0.413 (31)</td>
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<tr>
<td></td>
<td>Ip-Ps,%</td>
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<td>13.58 (76)</td>
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<td>18.79 (16)</td>
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<td></td>
<td>Idir,%</td>
<td>54.00 (50)</td>
<td>60.22 (60)</td>
</tr>
<tr>
<td></td>
<td>fdir, ns</td>
<td>0.413 (2)</td>
<td>0.409 (2)</td>
</tr>
<tr>
<td></td>
<td>Ip-Ps,%</td>
<td>28.95 (47)</td>
<td>20.33 (58)</td>
</tr>
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<td>NMS (multistage)</td>
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<td>19.80 (07)</td>
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<tr>
<td></td>
<td>fdir, ns</td>
<td>1.915 (03)</td>
<td>1.948 (04)</td>
</tr>
</tbody>
</table>

*Denotes the o-Ps component with larger contribution.
J-PET direction, slows significantly after about 10 iterations (for a 2.5 mm × 2.5 mm × 2.5 mm voxel).

The results of the positronium imaging acquired using the LMA are presented in Fig. 3., bottom for the sixth and tenth iterations, along with the adjusted chi-squared statistic $X^2_{adj}$ and the coefficient of determination $R^2_{adj}$. With the background set to 1 for the latter, we can see its slight deterioration at the edges of the sources, which indicates that the 5%-threshold chosen for activity cutoff was fairly reasonable. Voxel dimensions were the same as for the activity concentration.

Solution space and convergence rate

To explore the possible ranges for the fitting parameters, we prepared 300 random sets of initial guesses and launched 300 optimisation runs for several voxels with the least noisy time-delay spectra. The runs that successfully converged constituted an (incomplete) multidimensional solution space. Its shape strongly depended on the overall statistics, the initial guess and the optimisation method.

Fig. 4. demonstrates some two-dimensional projections of the solution space in the form of bivariate kernel density estimators (KDEs), composed for an exemplary time-delay spectrum (one voxel) and fitted by the LME and NMS. It is important to note that, although the distributions vary noticeably for the two nonlinear solvers (launched for the same set of initial guesses), the most probable solutions are more or less the same. The minimal RMSE with respect to the time-delay histogram, which we use as a criterion in a search of the optimal solution, almost perfectly matches the KDE peaks.

After having explored the expected ranges for fitting parameters, we considered the convergence rate, in which sense the gradient-based LMA is exceptionally sensitive. Fig. 5., left shows two histograms for the percentage of the successfully converged fitting runs in the single mode, composed for the voxels with $\tau_{o-Ps} > 0$. The “more constrained” means initial guesses were more densely seeded around the KDE peaks of the solution space, while the “less constrained” implies $\times 10$ higher upper bounds for the intensities and the lifetimes. The convergence rate is even lower for the multistage optimisation using the LMA and inferior for the NMS method (Fig. 5., right).

In order to acquire a complete positronium image for all voxels using the prior analysis of the solution space, the expected convergence rate and the performance of the algorithms (the NMS is slower), we prepared the 75 sets of initial guesses for the LMA and 42 – for the NMS.

Decay contributions depending on the optimisation method

Tab. I. compares the selected fitting parameters averaged over voxels covering each tissue sample, obtained for various minimisation algorithms. In addition to the multistage optimisation, the LMA results are revealed for a single-run mode and $f(\Delta t)$ in (5) comprising two o-Ps decay components. The lifetimes $\tau_{o-Ps}$ are consistent with each other regardless of the nonlinear solvers applied. On the other hand, we observe a slight difference between $\tau_{dir}$ for the
tissue types and can also distinguish between the two patients from the relative intensities (I). The model with two o-Ps components looks redundant for the measured data: it results in very similar lifetimes yet produces more error and is more prone to overfit.

The comparison between the optimisation methods can be further explored using histograms of the fitting parameters (Fig. 6, top). The distributions may differ quite noticeably (as for $a_{\text{Bgr}}$ and $Bgr$) and/or exhibit diverse shapes for the LMA and NMS. At the same time, the histograms for RMSE (not shown) were very similar, with the averages $\text{IRMSE}_{\text{LMA}} = 3.8 \text{ ps}$ and $\text{IRMSE}_{\text{NMS}} = 4.9 \text{ ps}$, respectively.

More information can be extracted from the cross-sections, in particular difference images (Fig. 6, bottom). For instance, unlike the averages in Tab. I, only the LMA results in $I_{\text{dir}}$ being visually distinguishable for the two patients (bottom left).

**DISCUSSION**

The average o-Ps lifetimes in Tab. I. are generally consistent with the results revealed in the previous work for a generic back-projection positronium image reconstruction [3]. Other parameters exhibit more variance, possibly as a consequence of a less constrained fitting model. It is important to note that the systematically different $\bar{I}_{\text{dir}}$ (Fig. 6, bottom left), $I_{\text{p-Ps}}$ and $I_{\text{o-Ps}}$ for the two patients had not been observed in the earlier study. That feature might be related to the higher injected activities for the samples taken from the first patient, which require further investigation.

While a function $f(x)$ with one o-Ps decay component appears to be acceptable for the current experiment, we anticipate the need for two or more in case of porous materials or similar objects [48, 49]. Furthermore, an inferential study of the solution space and a multistage optimisation would be more crucial for more variables added to the decay model. One can also investigate the advanced implementations with statistical mechanisms [35, 36], but they affect performance and may also require prior knowledge about the objects of study.

PALS Avalanche software may be merged with the 3-photon TOF MLEM, as well. Although not elaborated here, we intend to explore such a possibility in the future, in particular for the studies of larger objects, where sensitivity, attenuation and additive factors will have to be taken into account. It is yet to be explored whether a minimal RMSE used for the selection of an optimal solution applies to volumetric phantoms too.

The LMA is generally better and faster than the NMS, but the latter, being more predictable and gradient-free, could be more applicable to noisy or sparse PET data. This may become an important asset for positronium imaging, considering the lower sensitivity of the current generation of J-PET prototypes.

**CONCLUSION**

We have successfully utilised the 3-photon TOF MLEM, accompanied by a nonlinear fitting of time-delay spectra using two diverse optimisation methods to obtain the positronium image of the four chambers with human tissues in the Big Barrel J-PET. An exploration of the multidimensional solution space in multistage mode is demonstrated as a tool to resolve an ill-posed problem of modelling PL histograms. Consequent minimisation runs launched in parallel for randomly set initial guesses could serve as an alternative to slower probabilistic methods. The acquired results were consistent with the prior o-Ps lifetime studies and showed the difference between both the tissue types and the patients whom they were taken from.

**FUNDING**

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**INFORMED CONSENT**

Informed consent was obtained from all individuals included in this study.

**ETHICAL APPROVAL**

The local Institutional Review Board deemed the study exempt from review.

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