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Experimental uses of positronium and potential for biological applications

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Abstract—Positrons are widely used in molecular imaging through the Positron Emission Tomography (PET) imaging technique. However PET only reconstruct the distribution of the positron emitting radioisotopes, and because the β^+ isotopes are linked to a vector molecule, the distribution of β^+ isotopes is correlated to the distribution of a given biological function.

Positron-electron annihilation can transit through a meta-stable called positronium, which can exist in two spin states : the single state - parapositronium - and the triplet state - orthopositronium. The orthopositronium lifetime (τ_{oPs}), formation probabilities and decay modes are sensitive to the physical and chemical state of the neighboring medium and could therefore provide information on the tissues themselves during a PET acquisition. However, traditional PET only relies on the detection of the two annihilation photons, therefore the lifetime and annihilation higher multiplicity annihilations are not accessible to such PET paradigm.

This review will present some of the use cases of positronium as a specific signature for event selection in astrophysics and particle physics, and as a probe for the microscopic state of materials and tissues. These usages of positronium highlight the interest for positronium for diagnostic in medical science, the projects for using positronium in upcoming PET tomographs are then presented.

Index Terms—Orthopositronium, molecular imaging, positronium

I. INTRODUCTION

Positrons (anti-matter partners of electrons) are widely used in medical imaging, mainly in Positron Emission Tomography (PET). PET is a powerful imaging technique that is used to map biological functions in the subject's body. It relies on the detection of the annihilation of positron from β^+ isotopes such as ^{18}F , associated to a vector molecule. The positrons travel and thermalize across a short distance before annihilating with electrons, resulting, in the majority of cases, in the production of two 511 keV annihilation photons emitted in opposite directions and detected by an array of scintillating detectors surrounding the subject.

The spatial distribution of the annihilations is used to reconstruct a three-dimensional image of the radioactive tracer distribution in the body, highlighting the desired biological functions. PET is particularly useful in oncology [1], [2], as it is used to detect cancerous lesions and monitor response to therapy. It can also be used in pharmacology to study the distribution of new molecules [3], [4], and a recent increase of interest in botanical sciences is observed.

In general, thanks to the nearly endless radiotracer diversity, allowing to study a large array of biological processes, PET is an important quantitative research tool in the clinical and preclinical fields, and more widely, in all areas of life science [5].

Most recent developments in PET are focused on improving detection efficiency and time resolution, both in an effort to improve the overall final image quality. The imaging principle however remains based on reconstructing the topological density of the radiotracer, and the temporal evolution of that distribution. More information can in principle be extracted from the annihilation process itself, that can inform on the chemical and physical state of the biological tissues, although this is not yet taken advantage of in commercial PET systems.

Positron annihilation can transit through a meta-stable bound state called positronium. The positronium state forms singlet (total spin $S = 0$) and triplet ($S = 1$) spin states respectively called para- and ortho- positronium. The parapositronium (p -Ps) decays primarily to two back-to-back 511 keV photons with a lifetime of 0.125 ns in vacuum, and the orthopositronium (o -Ps) decays mainly to three photons adding up to two electron masses (m_e), with a lifetime of 142 ns in vacuum [6]. However, o -Ps formation probability, lifetime and decay modes are highly sensitive to the physical and chemical environment, mostly due to pick-off interactions with nearby electrons [7], and conversion and oxydation with surrounding free radicals [8], [9].

In materials science and engineering, the study of positronium formation and annihilation is used as a probe for nano-scale physical and chemical properties of solids and liquids. It is used in wide ranges of applications such as evaluating the micro-porosity of bulk materials [11], the oxygen partial pressure in porous compounds [12], or even the surface tension of molecular liquids [13].

In biology, positronium has been used on small tissue samples to study hypoxia [14]–[16], and the size of free volumes in tumors [17], [18] and blood clots [19]. While these measurements are ways to quantify the physical and chemical state of the tissues, no correlation is yet established to specific biological processes, nor can it yet be used in predictive diagnostics. The promises of using positronium in biological and medical sciences has been highlighted recently [20] and using positronium as an imaging technique is a relatively novel field, proposed by P. Moskal [21]–[23], and gaining a lot of attention over the last few years.

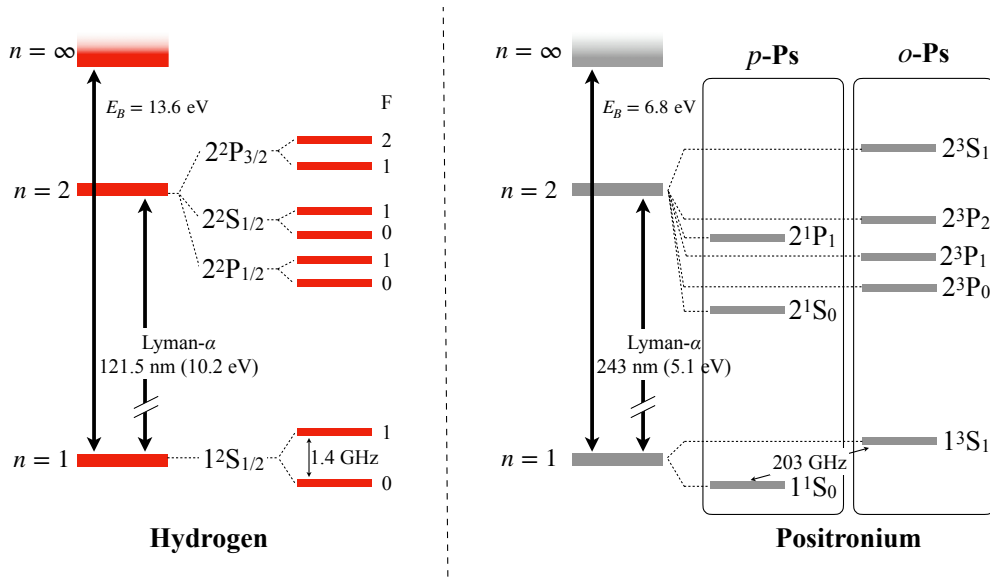


Fig. 1. Hydrogen and positronium energy levels, modified from [10]. The energy levels of positronium are similar to the ones of hydrogen with a factor of two, because of the change in reduced mass of the system, which is m_e for hydrogen, and $m_e/2$ for positronium, due to the change of a proton in hydrogen into an positron in positronium.

While positrons used in PET undergo such positronium state, traditional two-photon PET only observes the products of the annihilation of the positron or positronium, and not its formation. It is therefore impossible to evaluate the o -Ps lifetime (τ_{oPs}). This imaging requires a change in isotope, using (β^+, γ) isotopes, including but not limited to ^{44g}Sc , ^{72}As , ^{88g}Rb , or ^{94m}Tc [24]–[26], which emit a prompt γ as a marker of the emission of the positron, and therefore would allow to measure τ_{oPs} . To this date demonstration of the possibility of performing *in-vivo* imaging with positronium candidate events has been presented by the Jagiellonian PET (J-PET) research group [27], [28], in this case, the average lifetime over the regions of interest delineated by standard PET is used to overcome the low (β^+, γ) branching ratio of ^{68}Ga and the large spatial resolution of the J-PET prototype in this acquisition mode.

In the following sections, we will first present the physical properties of positronium in the quantum electrodynamics frameworks and describe the formation and interaction processes. We will then describe the main experimental techniques available to perform positronium studies before focusing on examples of the uses of positronium in various physics fields. Finally, we will present the existing studies of positronium behaviour in biological samples, and the newly proposed field of positronium imaging, introduced in 2018 [21], [23].

II. FORMATION, INTERACTION AND ANNIHILATION OF POSITRONIUM

The first theoretical discussions of positronium were performed by Pirenne [29], [30] and Wheeler [31]. Positronium was later experimentally evidenced by Deutsch in 1951 by observing the apparition of positronium lifetime in the annihilation time distribution of positrons in gases [32], by observing

a three quanta positron annihilation [33], and by measuring the fine structure resonance between p -Ps and o -Ps [34].

A. Positronium in Quantum Electrodynamics

As the simplest purely leptonic electromagnetically bound state, being composed of two low-mass leptons, positronium is, for all practical purposes, fully described by Quantum Electrodynamics (QED). The absence of hadronic components suggests that positronium energy levels and decay rates can be calculated to very high precision, limited only by the order of the corresponding perturbative expansion, which opens up the possibility to test QED bound-state theory with unprecedented precision.

QED is the most precisely tested theory in physics, and agrees with all observations performed so far, having been tested at the part per trillion level (i.e. parts in 10^{12}) [10]. Because the theory is so well established it is possible to use precision measurements of Ps to search for effects that may be caused by elements not included in the theory.

Observables of interest for testing QED are energy intervals, measured using laser and microwave spectroscopy, decay rates, measured using positron annihilation lifetime spectroscopy, and decay modes, measured using polarization and momentum measurements to look for forbidden symmetries.

The general selection rule for the annihilation of positronium from a state of orbital angular momentum l and total spin s into n photons is given by $(-1)^{l+s} = (-1)^n$ [7]. Therefore p -Ps in a ground state ($l = 0, s = 0$) will decay into an even number of photons while o -Ps in the ground state ($l = 0, s = 1$) decays in an odd number of photons, greater than one since a single photon decay is forbidden because of momentum conservation.

For positronium formation in an un-polarized medium, the four electron/positron spin states $|\uparrow\uparrow\rangle$, $|\uparrow\downarrow\rangle$, $|\downarrow\uparrow\rangle$, and $|\downarrow\downarrow\rangle$ are

equally probable. Thus the formation of o -Ps and p -Ps :

$$o\text{-Ps} = \left\{ |\uparrow\uparrow\rangle; \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle + |\downarrow\uparrow\rangle); |\downarrow\downarrow\rangle \right\} \quad (1)$$

$$p\text{-Ps} = \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle - |\downarrow\uparrow\rangle) \quad (2)$$

should follow a 3:1 ratio. This ratio has been observed in low density gas, the $3\gamma:2\gamma$ events ratio (respectively from o -Ps and p -Ps annihilation) approaches 3:1 with decreasing gas density, reflecting the statistical ratio of the triplet and singlet states [7].

Positronium energy levels, illustrated in figure 1, are similar to the hydrogen levels scaled by the ratio of reduced masses between hydrogen and positronium. Due to the large difference between the proton and electron masses, the reduced mass of hydrogen is $\sim m_e$, where it is $m_e/2$ for positronium. The energy level of the ground state o -Ps is higher than that of the ground state p -Ps due to the spin-spin interaction between the electron and the positron. This difference is called the hyperfine structure of the ground state positronium, which is about 203 GHz [35].

Photons from the annihilation are intricated, with a correlation of their polarization states. This correlation can be found in the angular distribution of their Compton scatters, which can provide an accurate test of Bell's theorem to the possibility of constructing a physical theory that describes the "real factual situation" in the Einstein–Podolsky–Rosen paradox [36]. The polarization of the o -Ps annihilation photons has been used to perform tests of the P, T and CP invariances in the J-PET tomograph with precision at the order of 10^{-4} [37].

An in depth review of the theoretical fundamental aspects of positronium physics can be found in [38], [39] that covers extensively the QED aspects of the positronium.

The first experimental measurements of $\tau_{p\text{-Ps}}$ found an annihilation rate of $\Gamma_{2\gamma}(1^1S_0, \text{exp}) = 7.99(11) \times 10^9 \text{ s}^{-1}$ (i.e. a lifetime of 125 ± 2 ps) from studying the radio-frequency resonance linewidth as a function of power in a Zeeman experiment and extrapolating to zero power by [40]. First measurements of $\tau_{o\text{-Ps}}$ are performed by measuring o -Ps annihilation in a moderating gas and extrapolating at zero density, [41] found a rate of $\Gamma_{3\gamma}(1^1S_1, \text{exp}) = 7.275(15) \times 10^6 \text{ s}^{-1}$ (i.e. a lifetime of 137.4 ± 0.3 ns), and [42] found a rate of $\Gamma_{3\gamma}(1^1S_1, \text{exp}) = 7.262(15) \times 10^6 \text{ s}^{-1}$ (i.e. 137.7 ± 0.3 ns). The evolution of $\tau_{o\text{-Ps}}$ measurements is shown in figure 2. It is notable that early measurements of o -Ps annihilation rates (e.g. from [6] and [42]) deviate from the expected theoretical values, a problem known as the o -Ps paradox. This was solved in 1995 by using slow positron beams and including higher order corrections to the extrapolations to zero-density media [43]–[45]. The latest measurements for p -Ps and o -Ps lifetimes are summarized in table I.

TABLE I
BEST ANNIHILATION LIFETIME MEASUREMENTS TO DATE FOR PARA- AND ORTHO- POSITRONIUM, COMPARED TO THE THEORETICAL VALUES EXTRACTED FROM [10].

	Theoretical value	Measurement	Rel. precision	Year
p -Ps	125.1624(3) ps	125.14(3) ps [46]	213 ppm	1994
o -Ps	142.0459(4) ns	142.04(2) ns [47]	156 ppm	2009

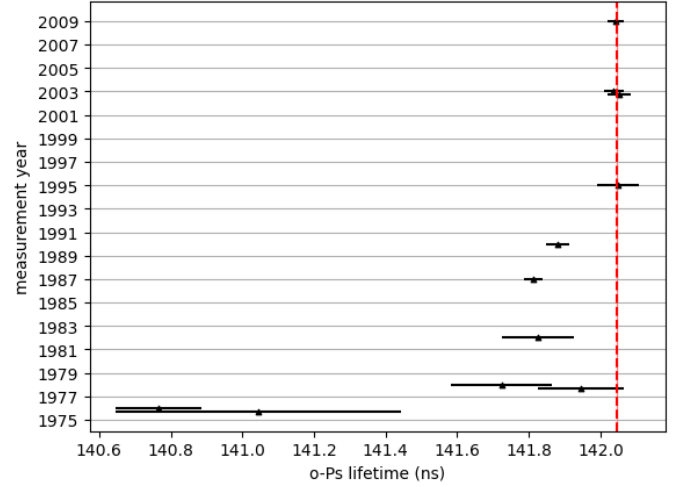


Fig. 2. Evolution of the experimental determination of the vacuum value of $\tau_{o\text{-Ps}}$ compared to the theoretical value. The values are extracted from, in chronological order : [48], [49], [50], [51], [52], [53], [54], [43], [45], [55], [47]

B. Positronium formation process

In gases, positronium can be formed if the positron kinetic energy T is in the range $E_i - E_{ps} \leq T \leq E_i$, where E_i is the gas first ionization energy, and E_{ps} is the positronium binding energy in the ground state (6.8 eV), known as the Ore gap mechanism [7], [56].

In bulk metal, positron annihilate directly with conduction electrons from delocalized Bloch states without forming positronium. Positronium formation is only possible in pores or atomic vacancies [7].

In insulators, when the energy requirements for the Ore gap mechanism are not met, the 'Spur process' can happen, mostly in insulating solids and liquids, positronium can be formed by the capture of an electron in the ionization trail of the positron [57].

Experiments in solids indicate that the positronium work function is negative in most materials, i.e. a strong positronium affinity to low density regions of the materials : free volumes in organic materials, color centers in ionic crystals, and atomic vacancies in metals. In solids, Ps can be found in delocalized quantum states that are repelled by the atomic cores of the host material, which are also the locus of higher electron density, thus where collision probability would be higher. Because they propagate in lower density regions of the material, the thermalization process of positrons is slower than that of the electrons [58], [59].

C. Positronium interaction with its surrounding

While *o*-Ps has a long lifetime (compared to *p*-Ps) in vacuum of ~ 142 ns, in practice in materials that lifetime is drastically reduced. This is due to the interactions of *o*-Ps with its surrounding medium. The main process of interaction is the “pick-off process” a process in which a positron in *o*-Ps state annihilates during a collision with an atomic electron of the right spin resulting in the vast majority of cases in a 2γ decay [7], effectively undergoing direct annihilation with that new electron. The pick-off process may also lead to a 3γ decay, but with a much lower probability [20] The probability of undergoing pick-off process in liquids is described by the Ferrell bubble model, depending on the surface tension and the presence of dissolved gas [60]. Other interaction processes include conversion and oxydation, i.e. the interaction with radiolytic products created by the positron during thermalization (e^- , H_3O^+ , HO^- radicals, free radicals) [8], and oxydation O_2 can oxydize positronium through the process : $Ps + O_2 \rightarrow e^+ + O_2^-$ Spin exchange by interaction with O_2 (and other paramagnetic molecules) magnetic moment causes an exchange from the *o*-Ps to the *p*-Ps states [9].

Because these interactions involve either direct annihilation of the positron partner in the *o*-Ps or conversion of the *o*-Ps to the *p*-Ps states, which have a virtually null lifetime compared to the orthopositronium lifetime, the overall *o*-Ps lifetime is therefore drastically reduced by the presence of surrounding electrons or radiolytic products. Moreover, since the final annihilation process involves a state that is no longer *o*-Ps, the annihilation to three photons is drastically suppressed in favor to a two-photon annihilation.

In solids, Ps can be found in delocalized quantum states that are repelled by the atomic cores of the host material. In metals, positronium are mostly found in atomic vacancies, and in crystals, they are mostly found in color centers, with lower atomic density. In organic materials, positronium are found in the free volumes, the empty space created by the steric hindrance of large molecules. In each of these cases, the measurement of τ_{oPs} and the formation fraction of *o*-Ps can inform on the size of these lower electronic density sites, and their proportion in the bulk of the material. In liquids, the deposited energy during positron thermalization creates nanoscopic cavitation bubbles in which *o*-Ps can be formed, the size of these bubbles depends directly on the surface tension of the liquid and impacts τ_{oPs} . As such, *o*-Ps formation and annihilation can be considered a probe of the free volumes and vacancies in a material at the nanometer level. The relationship between the average size of the vacancy and the *o*-Ps lifetime is modeled by the Tao Eldrup model [61], [62] :

$$\tau_{oPs}^{-1} = 2 \left[1 - \frac{R}{R + \Delta R} + \frac{1}{2\pi} \sin \left(\frac{2\pi R}{R + \Delta R} \right) \right] (\text{ns}^{-1}) \quad (3)$$

where R is the characteristic radius of the inter-molecular voids in a material, assuming a spherical void shape, and $\Delta R = 1.66 \text{ \AA}$ is obtained by fitting the observed lifetimes for molecular liquids of various surface tensions [63].

III. EXPERIMENTAL TECHNIQUES FOR STUDYING POSITRONIUM ANNIHILATION

A. Positron annihilation lifetime spectroscopy (PALS)

The lifetime of the positron in a medium can be accessed by the time delay between the emission of the positron and the detection of the annihilation photons. The positron emission can be detected by several means, either by the detection of a prompt gamma from the nuclear relaxation of the daughter nucleus in the β^+ decay, or by the detection of the scintillation signal of the positron in a scintillating medium, or by the detection of the Cherenkov light for medium with high enough optical index that the positron is emitted above the Cherenkov threshold. The number of annihilation photons can vary depending on the annihilation process and the formation of *o*-Ps or *p*-Ps. The total energy sum of the photons in coincidence should be $2 \times m_e c^2$, however some experimental setup rely only on the detection of 511 keV photons, in which case the collection of only one of the photons with the correct energy is enough to detect the positron annihilation.

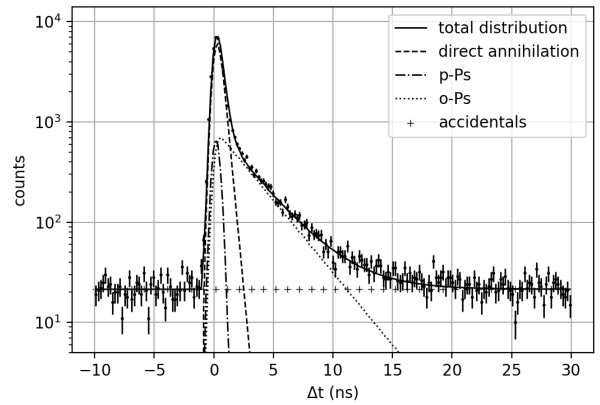


Fig. 3. Example of simulated time distribution of the delay between prompt gammas and annihilation photons (Δt) used to study positronium formation and lifetime. If positronium is formed, at least three exponential contributions are found : direct annihilation (dashed line), *p*-Ps (dash-dotted line) and *o*-Ps (dotted line). Since τ_{oPs} is sensitive to the surrounding medium, multiple τ_{oPs} can in principle be measured if enough material variabilities are present. The full distribution (solid line) is also composed of a constant background from random coincidences (cross-signed line), and is convoluted with the time resolution function of the experimental apparatus used to perform the measurement, here modelled by a 500 ps full width half maximum Gaussian.

Figure 3 shows the distribution of time delays between the prompt gamma from ^{22}Na decays and the detection of positron annihilation photons. The distribution can be described by the sum of three or more exponential contributions, corresponding to the direct positron annihilation, and the formation of *p*-Ps and *o*-Ps :

$$f(t) = \begin{cases} \tau_{\text{Acc}} + \sum_i I_i \frac{1}{\tau_i} e^{-t/\tau_i}, & \text{if } t > 0 \\ \tau_{\text{Acc}}, & \text{otherwise} \end{cases} \quad (4)$$

where τ_{Acc} is the accidental coincidence rate, I_i and τ_i are the relative intensities and lifetimes of the various annihilation processes. Because of the time resolution of the experimental apparatus this distribution is convoluted to the resolution

function $P(t)$ of the system. The count rate can therefore be expressed as :

$$N(t) = \int_0^{\text{inf}} P(t-x)f(x)dx \quad (5)$$

Typical values to report during a PALS study are the lifetimes and intensities for each annihilation process. The lifetimes can be linked to the size of free volumes through the Tao-Eldrup model from Eq. 3.

B. Coincidence Doppler Broadening Spectroscopy (CDBS)

CDBS is the measurement of a broadening of the energy spectrum of the true coincidence of two 511 keV annihilation photons beyond the energy resolution of the spectrometer, which provides information on the positron or positronium momentum at the moment of annihilation, as well as information on the momentum of the electron it annihilated with [12], [64]. Since the momentum distribution depends on the site of annihilation, the chemical environment of positron annihilation sites can be appropriately identified by CDBS technique. Two momentum regions are identified in a $(E_1 - E_2)$ plot, where E_1 and E_2 are the energies of each annihilation photons in the coincidence, as illustrated in figure 4 :

- S region : a region at low momentum around the annihilation peak, which reflects the contribution of positron annihilation by free and valence electrons. This parameter depends on factors such as direct (free positrons) or indirect (Ps formation) annihilation, probability of positron trapping, and density of the sample and its morphology.
- W region : a higher momentum region, on each side of the annihilation peak, typically, which relates to the positron annihilation by core electrons.

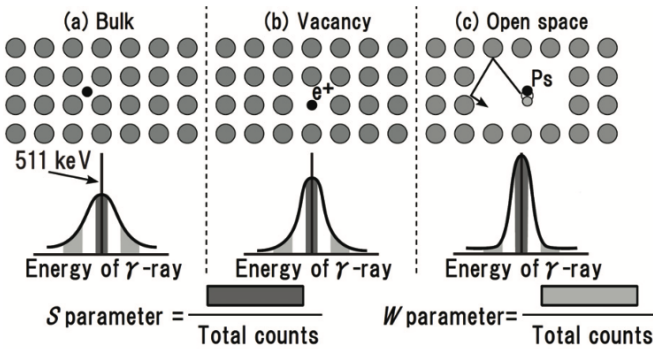


Fig. 4. Schematic summarizing the impact on medium vacancies on the energy difference spectrum between the two annihilation photons, and materializing the regions that enter in the computation of the S and W parameters. figure extracted from [64] with the agreement of the publisher.

For example, in [65] sets requirements for the S parameter of a difference of less than $3 \times 10^{-3} m_e c^2$ between the two photon energies and for the W parameter, the energy difference between the two photons needs to lie in the two bands within a 10 to $25 \times 10^{-3} m_e c^2$ on each side of the central energy peak at $E_1 - E_2 = 0$. It is to be noted that these numerical values are examples and depend on the studied materials and detector resolution, they are not fixed a priori by physics. While PALS

is most sensitive to the size of elementary free volume, CDBS allows to evaluate the positronium chemical interaction with its environment, by providing a ratio of annihilations with valence or core electrons.

C. Angular correlation of annihilation radiation (ACAR)

ACAR investigates the electronic band structure of materials such as metals, alloys and semiconductors [66], [67]. In two quanta annihilations, the two annihilation photons are emitted in exactly opposite directions in the frame of the positron-electron pair. In the laboratory frame, a small angular deviation from π of $\theta = p_t/m_e c$ is observed, originating from residual transverse momentum p_t of the electron-positron pair or of the positronium at the moment of annihilation, where the momentum \vec{p} can be written as the sum of longitudinal momentum \vec{p}_l , along the emission direction of the photons, and \vec{p}_t the transverse momentum. The width of the peak around $\theta = \pi$ provides information on the typical energy of electrons and positrons, and additional peaks at higher values of θ provide information on the lattice reciprocal vector, in the case of well-defined crystalline structures.

Because ACAR relies on the assumption that two photons are emitted, only direct annihilation and p -Ps annihilation are detectable, the three quanta annihilation from o -Ps is not usable, however the two-photon annihilation resulting from o -Ps interactions with its surrounding is. The momentum distribution of the center of mass in direct annihilation is shifted towards higher values than that of the p -Ps, leading to a broader ACAR distribution for direct annihilation than for p -Ps formation.

When PALS provides a measurement of the size of free volumes, and CDBS provides information on the energy of the interacting electrons, the ACAR technique provides complementary information about the shape and periodicity the free volumes in materials [68]. This provides valuable information on crystals, but also on metals or materials with periodic electronic band structures.

IV. POSITRONIUM IN MATERIALS SCIENCE

One of the major use of positronium is the study of material structure through PALS. The orthopositronium lifetime and production probability is used to probe the size of free volumes at the molecular level on the surface layer of materials. Then the size of free volumes is linked to various material properties (porosity, structural defects, ...), or environmental variables such as humidity or temperature. While listing all studies using this measurement is beyond the scope of this review, we present below a few examples of its use cases.

Studies have shown a reduction of τ_{oPs} in solids and liquids with temperature and pressure as the free volume size is reduced [69]. Positronium formation in metals and crystals from slow positron beams has been used to study defects in the structure [11], [70], [71], although [71] pointed out the limitation of this technique for metals since positrons do not propagate in metals, due to the high probability of undergoing direct annihilation with one of the free conduction electrons, only the few tens of nanometers of the surface can be probed.

The porosity of materials can be evaluated by PALS through the correlation of τ_{oPs} with pore size: although pores are not empty volumes, they are filled with gas, much less dense than the surrounding material, i.e. with a lower electronic density for positronium to interact with. This is used to study the density of aerogels [12], [72], [73], the pore sizes in silica film [74] and the free volume changes of nanopores in nanostructured $MgAl_2O_4$ ceramic materials [75].

A study over various organic liquids (benzene, n-hexane, TMS, methanol, ethanol, n-butanol, n-hexanol, n-octanol, and water as a reference) found a correlation between the electronic polarizability of the molecules and the lifetime of free positrons (from direct annihilation), and a correlation between the square root of the surface tension and the lifetime τ_{oPs} of orthopositronium from pick-off process [76]. Organic solids, such as polystyrenes, offer a few well defined free volumes repeated throughout the material, it is therefore possible to fit multiple values of τ_{oPs} from a given volume [77] corresponding to these well defined sizes.

For studies in material sciences, where no biological information is sought, positrons are usually emitted from a ^{22}Na source directly adjacent to the material sample to be studied, or a beam of cold positrons is employed, to better constrain the depth of penetration of the positrons in the materials and study the structure of samples at given depths. In that latter case, positrons emitted from a source are reflected by a metallic surface at thermal temperatures, and accelerated by an electrostatic accelerator to desired energies [7]. Conversely to PET imaging where a vector molecule is required to bring the radioisotope to a given part of the body expressing a desired biological function, in the case of materials science no topological information is required, therefore no vector is needed.

Finally, in more complex bio-mimetic materials such as phospholipids, the increased packing achieved through self assembly modifies the amount of free volumes and PALS can be used to measure phase transitions in the molecular chain assembly [78].

V. POSITRONIUM IN EXPERIMENTAL ASTRO- AND PARTICLE-PHYSICS

In astrophysics, positronium formation in galactic gases is studied by comparing the red-shifted 511 keV γ line, evidence of direct positron annihilation and p -Ps formation, to the lower energy γ continuum, indicating of o -Ps 3γ decay [79].

A more confidential use of orthopositronium is its use in neutrino physics. Detection of electron anti-neutrinos from nuclear reactors and β decays in geologic layers (geo-neutrinos) is achieved through the inverse beta decay reaction $\bar{\nu}_e + p \rightarrow n + e^+$. Events are selected based on the double coincidence of a prompt signal (positron scintillation and annihilation) and the delayed neutron capture. Separation between neutrino events and (β, n) decays from cosmogenic-generated radio-nuclides such as 9Li or 8He in organic liquid scintillator-based detectors is not possible in an event by event basis unless a distinction between electrons and positrons can be achieved. While the positronium lifetime is typically too

short for neutrino detectors to separate the photons from the positron scintillation from those from the 511 keV annihilation photons, a modification of the scintillation pulse shape can be observed when o -Ps is formed compared to the scintillation of an electron, or when p -Ps is formed [80], [81].

The event-by-event o -Ps selection have been used in the Double Chooz reactor neutrino experiment [82] and is proposed for the upcoming JUNO [83] experiment, to obtain a lower-statistic but cleaner sample of neutrinos, in order to better evaluate backgrounds in their full statistic neutrino selection. The Borexino experiment also used o -Ps to statistically evaluate their backgrounds [84].

Solar neutrino experiments rely on the measurement of electron recoil during neutrino elastic scattering on an electron. An important background in these neutrino search comes from β^+ decays in the detector, mostly from ^{11}C . In these cases orthopositronium tagging can be used to reduce the background [84].

VI. STUDIES OF POSITRONIUM IN BIOLOGICAL SAMPLES

Positrons used in biology and medicine are confined to their use in PET as far as imaging techniques go, but PALS has been applied to a few biological samples, highlighting correlations between lifetime modifications and various characteristics of the studied sample.

Free volume voids play a key role in dynamic processes in biological systems, including permeability of small molecules, and diffusion of drugs through cell membranes [85]. The PALS technique, by allowing a direct estimation of free void sizes, is critical to understand physical and mechanical properties of complex systems such as collagen [86], porcine eye lens [87], rat brain sections [88], and human skin [89]–[92]

Tracking the changes of the relative weights of o -Ps interactions with its surrounding, through modification of τ_{oPs} or through the $3\gamma/2\gamma$ ratio, has been used to evaluate the change in void size in treated and un-treated tumors such as in colonic adenocarcinoma [17] and as a marker for cellular hypoxia [14], [16]. However, inside biological materials, the picture is more complicated than in materials science. Defects and free volumes are not homogeneously spread throughout the material. Moreover, the coupling of positronium states to the surrounding material can occur with a wide variety of molecules, and the local chemistry also plays a role, along with the size of free volumes. In that setting, positronium lifetime and formation probability depend on the healthiness of the material, its nanostructure and concentration of bio-active molecules. These factors are indicative of the stage of development of metabolic disorders of tissues. It is therefore believed that positronium decay can provide new input in medical diagnosis.

o -Ps have been used on vegetal tissues, for example to study the microstructure in seeds [93], [94] or the decomposition of starch [95]. Correlations between free volume size and lead concentration in the tissues have been studied by [96].

Positronium has also been used to investigate animal tissue. Slow positron beams have been used to study in-situ the impact

of humidity of mouse skin [92]. A decrease of positronium lifetime and an increase of production intensity is observed with the incident positronium energy of slow positron beams. This effects reaches asymptotic behaviour at positron energies above 5 keV [97]. This dependency has a negligible impact for studies using radioactive positron sources such as ^{22}Na or ^{44}Sc , which produce positrons up to ~ 1.2 MeV.

Studies on rat brain sections with and without tumor [88] pointed out the problem of subject-to-subject and organ-to-organ variability preventing from establishing a clear universal $\tau_{o\text{-Ps}}$ measurement. For a given subject however, a systematic decrease of $\tau_{o\text{-Ps}}$ between healthy and pathologic tissues is found, indicating that a relative $o\text{-Ps}$ measurement could be used in future diagnostics.

Positronium lifetime in porcine eye lens [87], [98] shows a correlation with temperature of the tissue sample. Pathologies often imply an elevation of temperatures that can modify the physical structure of the tissues.

PALS was used on human muscles to demonstrate that water in the cells is in liquid form rather than in micro-crystals [99]. The first PALS study on live human cancer cells was performed on 3D carcinoma cell cultures, showing the difference of free voids in the cultures treated or not with a transforming growth factor β (TGF- β), showing the impact on cellular growth medium on the development of the culture and demonstrating the ability of PALS to detect such changes [17]. Cellular culture models such as 3D spheroids are a useful tool to study $o\text{-Ps}$ [100], and to better understand the information that a PALS study can yield and its importance in medical diagnostics. Cancer cells are known to over-express cellular markers such as HER2 [101], [102] on their membrane, which creates free volumes near the cell through steric hindrance. A measure of $\tau_{o\text{-Ps}}$ modification could allow to measure this excess and help in the diagnostic. A ^{44}Sc -labelled tracer for studying HER2 expression of cancer cells has already been studied [103], making this a realistic use of PALS for cancer diagnostic [20]. Similarly, the decrease of free volume size for the TNF- β cellular receptor compared to the TNF- α has been linked to its increased cytotoxicity for forming necrosis in tumors [104]. PALS can also be used to distinguish between different types of soft tissues, such as leiomyomas and normal myometrium tissues on *ex-vivo* samples [105], or cardiac myxoma and adipose tissues [18], [106].

PALS studies on human skin cancerous samples with squamous cell carcinoma and basal cell carcinoma show a decrease of $\tau_{o\text{-Ps}}$ of similar magnitude, but the most significant difference with healthy skin sample is the decrease of $o\text{-Ps}$ formation probability, which allows to distinguish between samples of healthy skin, squamous and basal cell carcinomas [91]. However, melanoma samples present no significant differences with healthy samples for positron beam energies above 2 keV [90], which could be attributed to the lower concentration of melanoma cells in the sample than in the case of squamous and basal cell carcinoma samples, or to the

fact that melanoma cells do not present a significant physical or chemical change compared to healthy skin cells.

PALS measurement on human hair have demonstrated the ability of PALS to provide information on UV-induced hair damage at molecular level for virgin and bleached [107], an important input for cosmetic industry. The bleached hair undergoes photodamage faster in comparison with the virgin hair. PALS can also be used to study the diffusion time of commercial dyes in the porous network of free volumes in the hair [108]. The lifetime decreases up until complete absorption of dye in the hair, then reaches a plateau as all available free volume is occupied.

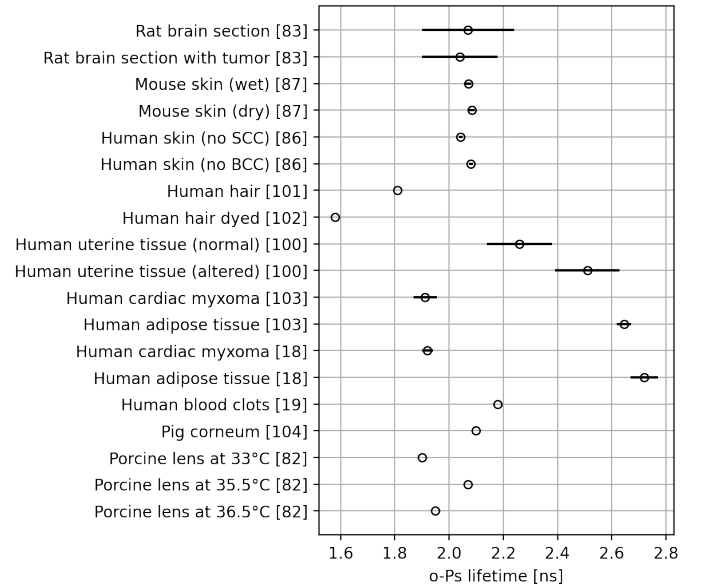


Fig. 5. $o\text{-Ps}$ lifetime in various biological tissues, ranging from ~ 1.6 to ~ 2.8 ns, values compiled from [18], [19], [87], [88], [91], [92], [105]–[109]

VII. POTENTIAL APPLICATIONS OF ORTHOPOSITRONIUM IN MEDICAL IMAGING

Positronium formation can be used in PET as a way to select a lower-statistic but purer sample of events, with spatial information from the three-quanta decay of $o\text{-Ps}$, allowing to perform PET imaging with enhanced spatial information, or as a way to probe the physical and chemical properties of the tissues in which the annihilation occurs from positronium lifetime imaging.

A. $o\text{-Ps}$ decay : 3γ annihilation

The three annihilation photons from $o\text{-Ps}$ annihilation originate from the same point in space and time. It is therefore possible to extract the position of the emission on an event-by-event basis where traditional 2γ PET can only procure a line

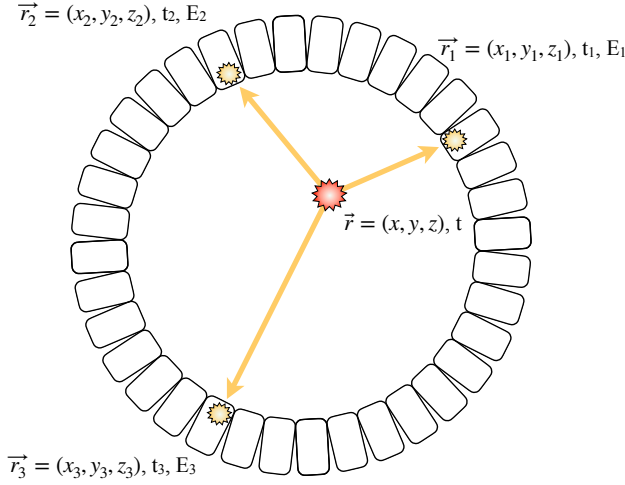


Fig. 6. Schematic representation of the annihilation localization in $3\gamma o\text{-Ps}$ annihilation imaging, defining the variables necessary for event reconstruction.

of response. In order to satisfy the momentum conservation, the photons must satisfy the following conditions [110], [111]:

$$\begin{aligned}
 p_x &= \sum_{i=1}^3 \frac{E_i}{c} \frac{x - x_i}{|\vec{r} - \vec{r}_i|} = 0, \\
 p_y &= \sum_{i=1}^3 \frac{E_i}{c} \frac{y - y_i}{|\vec{r} - \vec{r}_i|} = 0, \\
 p_z &= \sum_{i=1}^3 \frac{E_i}{c} \frac{z - z_i}{|\vec{r} - \vec{r}_i|} = 0, \\
 E_1 + E_2 + E_3 &= 2 \times m_e c^2 \simeq 1022 \text{keV} \quad (6)
 \end{aligned}$$

where \vec{r} represents the annihilation location, $\vec{r}_{i=1,2,3}$ the position at which each of the three photons is detected with an energy E_i . Here we assume that the positronium annihilation occurs at rest, or with a negligible residual momentum. A residual momentum would yield a non-planarity of the three emitted photon directions. Solving this set of equations with the \vec{r}_i known to the intrinsic resolution of the detectors allows to reconstruct the $\vec{r} = (x, y, z)$ position of the annihilation. Here the limiting factor on the spatial resolution of the reconstructed point is the finite energy resolution of the detectors. An energy resolution of a few percents is required to produce usable images, which is rarely the case of scintillator based tomographs. This approach, however, can be envisioned with semi-conductor based PETs such as cadmium zinc telluride (CZT) detectors which can reach 1 – 7% energy resolution at 511 keV [112]–[114], but with worse time resolution than scintillator-based detectors.

Another approach, for worse energy resolution, but better time resolution, detectors, is to perform tri-lateration [115] :

the three photons are emitted at the same time t . A time of flight analysis allows to locate decays on an event-by-event basis.

The positions and time of detection of each photons need to satisfy :

$$(x - x_i)^2 + (y - y_i)^2 + (z - z_i)^2 = c^2(t - t_i)^2 \quad (7)$$

Moreover, the three annihilation photons are emitted in a plane, which allows to constrain the position of the searched annihilation to the plane containing the three photodetections, reducing the problem to an effectively 2D reconstruction. This is one of the proposed approaches for positronium-based reconstruction in the J-PET tomograph.

While this technique has the advantage of event-by-event annihilation localization, and the use of triple coincidence reduces greatly the noise linked to random coincidences, the 3γ annihilation mode is a rare occurrence, since it only occurs in $o\text{-Ps}$ decay, if no pick-off, nor oxydation, nor conversion happened, and to some fraction of direct annihilation. Even in the case where $o\text{-Ps}$ is formed, any interaction of $o\text{-Ps}$ with the surrounding material will result in a 2γ annihilation. The count rate for such an imaging mode is expected to be low and require either a very high activity injected to the patient, or a very long acquisition time. Simulations performed assuming the final configuration and performance of the J-PET prototype yield a resolution (RMS) of 2.1 cm for the X and Y coordinates (transaxially with respect to the tomograph) and 2.3 cm for the Z coordinate (axially), with the main limiting factor for the resolutions being the time resolution of the system [115]. Using this method, J-PET has performed the first experimental 3γ images of the walls of a cylindrical vacuum chamber at the center of which a point-like ^{22}Na source is placed [116]. The spatial resolution in that case depends on the temporal resolution of the PET, typically of the order of 250 ps at the time this review is written, but in constant improvement, partly driven by the 10 ps challenge [117].

Another advantage of being able to exploit the 3γ decays to perform an image is to then perform the same image with the standard 2γ PET, then the voxel-to-voxel ratio of $3\gamma/2\gamma$ annihilations informs on the annihilation medium.

B. 3D in-vivo PALS imaging with (β^+, γ) isotopes

Positron emission tomographs rely on the detection of annihilation photons in order to reconstruct the biodistribution of the radiotracer in a subject. Because no information is provided on the decay time, PETs are unable to perform PALS-like studies under the current paradigm. A considerable amount of information, encoded in the annihilation process, is therefore lost, such as free volume size or chemical composition of the tissues. In order to perform PALS-like studies, a prompt γ , correlated to the positron emission is required. Changing the isotope from β^+ to (β^+, γ) where the relaxation of the daughter nucleus produces a prompt γ within a few picoseconds of positron emission from the β^+ decay, allows to solve this issue.

There are several potential (β^+, γ) isotopes that would be suited for positronium imaging [24]–[26], however the best

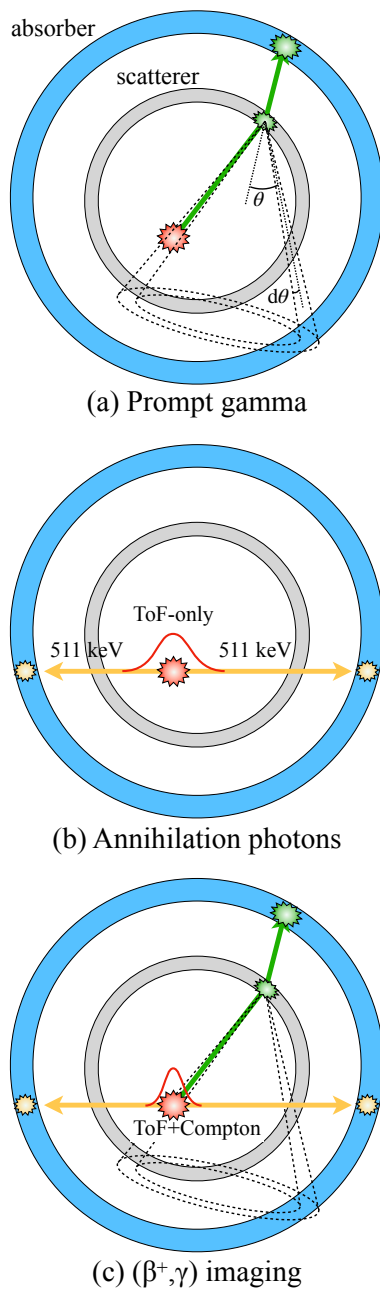


Fig. 7. Annihilation localization in (β^+ , γ) imaging. (a) The incident direction of the prompt γ can be estimated thanks to the Compton scatter information between the scattering and the absorber layers to a probability Compton cone. (b) The detection of the two annihilation photons define a line of response as is usual in 2γ PET. The localization of the annihilation can be improved from being completely delocalized on the line from using time of flight (ToF) information. (c) The intersection of the line of response and the Compton cone enhances the resolution on the annihilation localization that would be provided with only ToF on the line of response.

candidate seems to be ^{44g}Sc which has a lifetime realistically suited to perform molecular imaging [24], [118]. Furthermore, ^{44g}Sc -radiolabelled tracers are already developed [119] and many biodistribution studies with ^{44g}Sc labelled DOTA-peptides have been performed [120]–[128]. Other isotopes are considered, such as ^{124}I and ^{66}Ga which have vector

molecules allowing to study genome instability, the expression of specific surface agents or to induce angiogenesis and could be of interest for positronium lifetime imaging of the tissues surrounding the regions expressing these biological functions [129].

A particular issue with relying on triple coincidence events from (β^+ , γ) isotopes is that while the two annihilation photons are collinear, the prompt γ is emitted in a completely un-correlated direction. So while detecting the second annihilation photon provided that one is detected is only a matter of cross section, not solid angle, the detection of the prompt γ add the inefficiency linked to the solid angle a second time. The coincidence count rate for a 2γ detection is proportional to $\epsilon_{\Omega}\epsilon_{\sigma_1}\epsilon_{\sigma_2}$, where ϵ_{Ω} is the detection solid angle, and ϵ_{σ_1} and ϵ_{σ_2} are the probabilities that the photons 1 and 2 will interact in the crystals they cross, and the count rate for a prompt γ and 2 annihilation photons is proportional to $\epsilon_{\Omega}^2\epsilon_{\sigma_1}\epsilon_{\sigma_2}\epsilon_{\sigma_p}$, where the new term ϵ_{σ_p} corresponds to the interaction probability of the prompt γ . An increase of detection solid angle of the tomograph is crucial to keep an event rate high enough to reconstruct an image. While the overall efficiency to detect 3γ events is approximately 10 times lower than that of 2γ events, a the gain in solid angle from a full body scanner can overcome that effect and actually provide a better efficiency than a standard 2γ acquisition on a 20 cm axial field of view PET scanner [129]. This issue is addressed by the development of total-body PET [130] such as the uExplorer [131], the PennPET explorer [132], Siemen's Biograph Vision Quadra [133], and the J-PET [134], [135] tomographs.

Even with the advent of full body scanners, the (β^+ , γ) imaging technique is orders of magnitude more efficient than the detection of 3γ annihilation for several reasons [20]: first, in the tissues, due to interactions with the surrounding medium, $o\text{-Ps} \rightarrow 2\gamma$ is about 70 times more probable than $o\text{-Ps} \rightarrow 3\gamma$, second, the attenuation, or partial attenuation of 3γ events in the body is much larger than the 2γ annihilation, because of the higher number of photons and because of their lower energies increasing the interaction probabilities. Finally, the detection efficiency of 3γ is lower than the for 2γ . This efficiency gap between the two imaging techniques is a major criterion to explain the preference of the (β^+ , γ) PALS technique for positronium imaging in [106].

The full body coverage of the uExplorer PET/CT is achieved by assembling eight conventional PET rings composed of modules of LYSO (Lutetium Yttrium Orthosilicate) crystal matrices. This provides all the advantages of LYSO:Ce crystals for the detection of 511 keV annihilation photons, especially a high detection efficiency, while offering the many advantages of full body coverage in terms of possible clinical studies [136], [137].

The J-PET tomograph [134], [138], [139] on the other hand is designed as a succession of plastic scintillator strips axially distributed around the patient and read out at both

ends by PMTs. The advantage is that an increase of coverage to a full body PET does not imply an increase of the number of read out channels which only depends on the section of the tomograph, while in the case of the uExplorer, the number of read out channels grows as the surface of the tomograph. However, the low interaction cross section of plastic scintillator imposes the need for a thick detection material, which means many strips on the radial direction. It is also to be noted that in organic scintillators, the primary mode of interaction for photons in the 100 keV to MeV energy range is Compton interaction, which not only allows for detection of the 511 keV photons, but in principle brings new information on the incident direction of the photons, useful to reduce noise when pairing two detections in a coincident event.

The XEMIS and XEMIS2 prototypes [140]–[142] are liquid xenon time projection chambers, they rely on the detection of the triple coincidence of the prompt γ and the reconstruction of the two annihilation photons. The ability to reconstruct the succession of Compton and photoelectric interactions allows these detectors to predict a cone of incident direction for the prompt γ . This detection mode relies on the use of ^{44g}Sc , but no imaging was performed with the reconstruction of positronium lifetime. As illustrated in figure 7, the directionality of the prompt γ reconstruction allows to improve the localization of the decay along the line of response by the intersection of the line of response with the Compton incident direction cone [143], [144].

Other prototypes plan on using the prompt gamma from the (β^+, γ) annihilation to improve on the decay localization [145], which could in time have the capabilities to study $\tau_{o\text{Ps}}$ in vivo. This prototype uses a first pixellated scattering inner layer surrounded by a pixellated absorber layer. A coincident hit in the scattering layer and in the absorber layer with time, space and energy compatibility allows to reconstruct the incident direction of the prompt γ , within a probability cone. The lower energy annihilation photons are detected in the absorber layer and define the line of response. The annihilation is located at the point(s) where the Compton cone intersects the line of response. While some detectors rely on separate scattering and absorber layers such as in [106] or [145], others rely on their ability to reconstruct multiple Compton interactions within the same layer and do not require a scattering and absorbing layer such as [143].

The prompt gamma is used to provide the β^+ decay time and serve as a marker of positron emission. The detection of the annihilation photons then marks the annihilation of the positron, either through a direct annihilation or after transiting through a positronium state. This measurement would permit to measure the lifetime of positrons in the body. However, in most iterative PET image reconstruction algorithms, the final reconstructed radiotracer distribution is an ersatz distribution that would produce a collection of line of responses compatible with the observed collection of line of response actually observed. Information on an event-by-event basis is lost. This makes it impossible to propagate the time

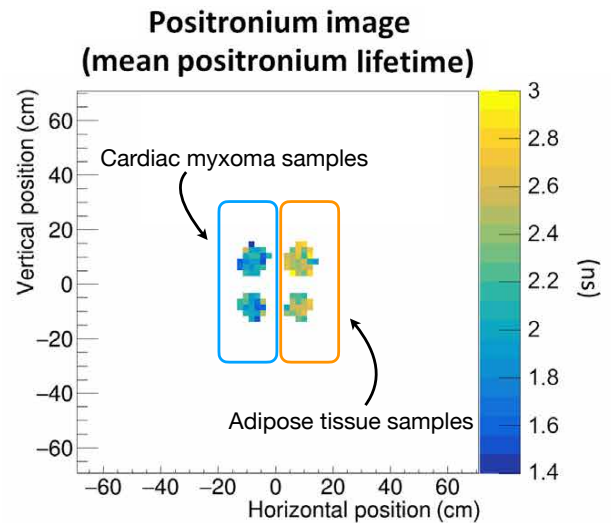


Fig. 8. First positronium lifetime image from the J-PET research group, modified and annotated from [106], under Creative Commons Attribution License 4.0 (CC BY).

delays of individual coincidences to a given voxel in the final image volume. Simple reconstructions such as filtered back projection can be modified to distribute the time delay of each events along their line of response but are sub-optimal in terms of spatial resolution of the reconstructed image. This reconstruction technique was employed for the proof of concept of positronium imaging performed by the J-PET research group [106] which produced the first positronium lifetime image, in figure 8, of four samples in the field of view of the J-PET tomograph : two cardiac myxoma and two adipose tissue samples. To produce this image, each sample was placed in a holder along with a ^{22}Na source ranging from ~ 0.2 to ~ 0.4 MBq, which produced the prompt γ at the moment of annihilation and irradiated the samples with positrons. For each voxel in the image, the mean value of the distribution of the time delays is reported. As the lifetime for direct annihilation and $p\text{-Ps}$ are not dependent of the medium, and are much smaller than the time resolution of the tomograph, the mean lifetime is strongly correlated to the lifetime of $o\text{-Ps}$, and provides information on the annihilation medium.

Positrons in figure 8 were produced by a ^{22}Na source directly in contact with the samples, however, in order to perform *in vivo* positronium imaging, (β^+, γ) isotopes must reach the regions of interest in the body. Therefore this imaging requires a radiotracer similar to what is traditionally used in PET. Among the several (β^+, γ) radioisotopes considered, ^{44g}Sc seems the best candidate with a lifetime realistically suited to perform molecular imaging [118], [129], and already studied associated pharmaceuticals and biodistributions [119]–[128]. However, none of these pharmaceuticals are used in clinical practice yet.

The positronium information will be an additional layer from the uneven tracer distribution, often expressed as the standard uptake value (SUV), i.e. the relative local concentration of

tracer compared to the averaged tracer concentration in the full body. A region with higher SUV means a higher concentration of the expression of the biological function targeted by the tracer, hence a higher probability of anomalous cells in that region. This region will also provide a higher statistical measurement for positronium lifetime. A comparison of τ_{OPs} between healthy and pathological regions of a same organ will therefore suffer from this large difference of statistics when evaluating the various τ_{OPs} values. However, positronium imaging in PET will add a layer of information to the simple SUV, enabling medical diagnostic to hopefully detect physical and chemical changes in tissues before their impact on the biological functions manifest into a radiotracer uptake change [22].

In the wake of developing PET prototypes able to perform positronium imaging, and the growing interest of this imaging modality in the field, reconstruction algorithms are being developed to recover higher spatial resolution in the final image than filtered back projection algorithms, while propagating the time delay distributions to each individual voxel. Likelihood maximization algorithms associated to multiple lifetime fitting are being developed [146], [147]. [148] reaches a 4 mm spatial resolution on 2D simulated phantoms. [149] studied the impact of the coincidence time resolution (CTR) of tomographs on the ability to reach high spatial and temporal resolution. The CTR has two impacts on the final positronium lifetime image : it introduces spatial blurring in the image, making it harder to distinguish neighbouring regions of separated positronium lifetimes, and it introduces an error on the measured lifetime, preventing separation of regions with lifetime differences small compared to the CTR (i.e. a CTR of 500 ps and a lifetime difference of 0.2 ns).

The SPLIT algorithm [150] proposes a statistical lifetime reconstruction by reconstructing consecutive activity images with a progressively increasing coincidence window between the prompt γ and the annihilation photons. This algorithm was shown to perform similarly to a likelihood maximization algorithm such as [151] and [152], while keeping a better stability in lifetime measurement when positronium sources are close to each other. In addition to Monte-Carlo simulations, the SPLIT algorithm has been successfully applied to actual J-PET ex-vivo data.

At the time of this review, while the first *in-vivo* positronium image of the brain has been presented using ^{68}Ga -PSMA as radiotracer [27], [28], no definitive use of positronium imaging to medical diagnosis has been proposed, since a change in positronium lifetime means a change in free volumes in tissue, which can have many underlying causes. However the development of tools to study the behaviour of τ_{OPs} in vivo may procure a way to better understand this parameter and find use cases not yet foreseen. The important variability from subject to subject of τ_{OPs} for similar healthy tissue, preventing to establish a reference atlas, is an additional limitation, but can be mitigated by the comparison, when possible, for a same patient of τ_{OPs} from a healthy part of a tissue to its pathological region.

VIII. CONCLUSION

Positron annihilation lifetime spectroscopy is widely used in materials science to study the structure of materials at the atomic level. The application of PALS in life sciences is still in its early stage. Natural tissues and organs are highly complex systems with the chemical compositions and physical structures that can vary significantly from sample to sample, variables to which PALS is highly sensitive. Moreover, the interpretation of PALS results require very well characterized, controlled, and systematic samples. Studies have been performed to correlate the positron lifetime in *ex vivo* biological samples to various parameters, including oxygen saturation in tissues, temperature, or presence of lead. Knowing the parameter being varied, PALS is a good tool to follow its evolution, but linking a change in positronium lifetime to a single parameter is not yet understood. The best approach in this application is to pursue interdisciplinary investigations in a joint effort among physical, chemical, biological, and medical scientists.

Thanks to the development of high sensitivity full body PET with improving time resolution, the possibility to use *in vivo* positronium events as a way to extract information on the surrounding tissue from the positron annihilation itself has been proposed. A proof of concept has been performed by the J-PET research group who produced the first voxelized image of the positronium mean lifetime in four biological samples.

Limits to spatial and temporal resolutions of the images are mostly linked to the temporal resolution of the apparatus and the activity per voxel. Moreover, the uncertain correlation of a change in τ_{OPs} to a given pathology, and the important variability, for a given tissue, from one subject to another are obstacles that will need to be overcome before positronium lifetime imaging can be used in a medical setting.

The future high sensitivity full body 3γ -capable PET will provide a powerful mean of measuring τ_{OPs} *in-vivo*, overcoming these first two limitations. This will allow biologists to perform high resolution studies on larger sample sizes, hopefully highlighting correlations to pathologies, and making τ_{OPs} imaging a promising tool for future clinical diagnostics.

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