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NOTE

The three-photon yield from e+ annihilation in various fluids

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Abstract
Positronium in the triplet state decays by the emission of three photons and it has been proposed that their simultaneous detection can be used for medical imaging. The three-photon yield has been observed to be enhanced in low O2 levels in some fluids but has never been measured in biologically relevant liquids. In this study, the delayed three-photon decay yield, at both high and low O2 levels, has been extracted by fitting the time dependence of the two-photon yield to a set of coupled differential equations. The differential equations, in a simple yet seemingly satisfactory fashion, account for the e+ capture to form positronium, its decay and the interconversion of the two spin configurations. Our results indicate that the delayed three-photon fraction is 0.25% in water (or blood-like) samples and exhibits no (or exceedingly small) dependence on the dissolved oxygen content. If one assumes that the direct component contributes a fraction expected by annihilation on free electrons (1/372), then the total three-photon fraction is 0.52% in the samples of biological relevance.

1. Introduction

Recent papers by Kacperski and Spyrou (Kacperski and Spyrou 2005, Kacperski et al 2004) have raised the possibility of using the three-photon decay of triplet (ortho) positronium for medical imaging. The detection of the three correlated photons allows for event-wise source localization when both energy and detection position of the three photons are achieved. In addition to this very attractive feature, Kacperski et al also remind us that the interconversion of triplet to singlet is conceivably sensitive to biology. Specifically, as unpaired spins (like those on the O2 molecule) enhance the conversion of the triplet state to the singlet state, material depleted in O2 might exhibit enhanced three-photon emission. It is this possibility that attracted our interest. Forty-year-old work (Lee and Celitans 1966, Gray et al 1967, 1968)
suggests that this is unlikely for aqueous samples. The present work (unfortunately) confirms these results.

The absolute three-photon fraction is estimated in the present work by adding the experimentally determined delayed three-photon decay fraction to a direct fraction predicted by Ore and Powell (1949) for annihilation on free electrons. The latter was verified by Bertolaccini et al (1965) by the direct coincidence detection of three photons, at equilateral angles, and assuming that the Ore–Powell energy distribution and correlation was valid.

It has been established that some cancerous lesions are hypoxic with O2 concentrations in some tumours as low as 5–10% of the normal saturation values. This difference leads to tumour cells’ sensitivity to chemical or radiation therapy. Having the ability to determine in advance the hypoxic status of cancerous lesions can be highly beneficial in patient treatment, allowing for adaptation of the regime of radiation or chemical therapy depending on a particular patient’s hypoxic status. Several PET and SPECT imaging agents aim at measuring hypoxia (Rajendran and Krohn 2005, Ballinger 2001, Nunn et al 1995, Lewis and Welch 2001, Koh et al 1992, Rasey et al 1996, Fujibayashi et al 1997). While these agents have had various degrees of success at imaging hypoxia, they all require the injection of a second tracer in addition to the [18F]-FDG injection (which the patients are already subjected to in the course of their cancer diagnostics). As discussed in Kacperski and Spyrou (2005), imaging hypoxia using the three-gamma events from the [18F]-FDG injection would be beneficial as a second injection will not be necessary, thus saving time, money and stress to the patients. The question of whether low O2 level in samples of biologically relevant liquids yields a larger number of three-photon events is addressed in this work.

2. Experiment

2.1. Sample preparation

High and low O2 concentration 10 ml samples were prepared by bubbling compressed air (80% N2, 20% O2) or N2 gas (99% purity), respectively, and following the O2 concentration with an oxygen probe (O2 meter, Chemical MicroSensor model #1201, Diamond General Dev. Corporation) until a stationary value was reached. The probe was calibrated using the manufacturer recommended technique. Specifically, the high-O2 calibration sample was made by bubbling compressed air in water for 20 min, at which time the O2 level had saturated at approximately 20%. 50 mg of Na2SO3 was added to the low-O2 samples to chemically scavenge any remaining dissolved O2 through conversion to sulfate. The addition of sulfite and the N2 bubbling led to samples with dissolved O2 levels below the sensitivity of the probe (less than 0.1%).

All solutions were prepared in 10 ml vials and sealed from ambient air with a rubber septa. After adding 2.5 μCi of 22Na, a second seal with wax foil was added to further reduce contact with room air. Our technique for preparing the low-O2 samples was compared to the freeze–pump–thaw (FPT) technique for water samples. Both techniques led to O2 levels below the sensitivity of the probe. The N2 bubbling technique was used in the results reported below as it could be used on all samples, as opposed to the FPT technique which is not suitable for biological samples.

The liquid samples were iso-octane, water, saline, 3% human serum albumin (HSA) and animal blood. Iso-octane is not a biological molecule but was used in this study as an example of a liquid with a known O2 effect on the three-photon yield. Saline (0.9% NaCl in water) was studied because it is a major component of living tissue. Serum albumin is the most prevalent protein (584 amino acids) circulating in blood. Its primary function is to carry fatty acids,
thyroid hormones and some steroid hormones through the bloodstream and is also of prime importance in maintaining proper osmotic balance. It is however highly charged and thus this solution should also be viewed as strongly ionic. A low-O₂ blood sample was also tested by taking venous blood from a live dog. This sample was placed in a Vacutainer™ containing sodium heparin to prevent coagulation.

2.2. Data collection

The time dependence of the two-photon yield was determined using standard pulse-counting techniques. Three-parameter events consisting of the two pulse heights and the time difference between the two photons were recorded in list mode and sorted off-line. Data runs (each lasting 2–3 days) were taken for each sample.

The two-photon counters were small caesium fluoride (CsF) scintillators (2.54 cm diameter and 4 cm long) set at right angles 5 cm from the vial surface with a lead brick placed between the photon detectors to reduce detector-to-detector scattering. These scintillators were chosen for their very fast light output (rise times of less than 1 ns and decay time of ~3 ns.) The start of the coincidence circuit was the triggering by one of the CsFs, with its constant-fraction discriminator (CFD) set above the 511 keV region so that the photopeak of the 1275 keV photon (prompt decay of excited state in the β-daughter ²²Ne) and some of its Compton distribution were used. The CFD for the other detector was set to trigger for pulses above ~400 keV (thus including the 511 keV annihilation photon). Off-line gating selected only the photopeak regions (1275 keV region for the start detector and 511 keV for the stop detector).

The time calibration was done by inserting precalibrated delay cables and the time resolution of the system, \( \sigma = 0.25 \text{ ns} \), determined by a Gaussian fit of the time distribution of the prompt back-to-back 511 keV photons.

Sample time spectra for iso-octane and water are shown in figure 1. The well-known characteristic shape, a prominent direct and singlet decay peak followed by a triplet delay pick-off component, is seen in all data sets. The relative magnitude and decay characteristics of the delayed two-photon component encode the delayed three-photon yield. The method of extraction of the three-photon yields is explained in the next section.

3. Analysis and results

The thermalization, capture and decay of positrons in condensed media are complicated processes, which have been the subject of intense investigation. Our objective is not to describe the physical process in detail, as is done by Seeger (2000) and is needed for positron age–momentum correlation (AMOC) measurements (Castellaz et al 2002), but rather only to extract the delayed three-photon yield and to see if there is sensitivity to the O₂ concentration. In this sense, the present work parallels the very early work by Lee and Celitans (1966) and Gray et al (1967) as well as the more recent work by Kino et al (2000). However, these works only employed a simple multi-exponential fitting procedure to fit the delayed (tail) region, and thus neither a direct-delayed decomposition nor an absolute delayed three-photon yield could be determined. On the other hand, this early work did look for O₂ sensitivity (in the relevant tail of the time distribution), and thus we can compare our O₂ sensitivity results to these previous works.

Our overall logic is to fit a small set of rate constants by comparing the solutions of coupled differential equations to the experimental data. The differential equations do not detail the various reactions (spin conversion, oxidation and complex formation) and therefore cannot
Figure 1. Time dependence of two-photon annihilation in saturated (triangles) and deoxygenated (squares) samples of (a) iso-octane and (b) water. The solid curves represent fit to the solutions of the differential equations. The data and fits for the O₂ saturated fluids are multiplied by 10.

shed light on these processes, but they capture enough of the physical process to yield, via integration, the delayed three-photon decay fraction. With \( p, Ps, T, S \) being the instantaneous positron, positronium, triplet and singlet fractions, \( \lambda_{di}, K_{cap}, K_p \) being the direct decay, \( e^+ \) capture (by \( e^- \) to create \( Ps \)) and pick-off rate constants, and \( \lambda_T \) and \( \lambda_S \) the intrinsic decay rates (7.04 × 10⁻³ ns⁻¹ and 7.99 ns⁻¹), our simple model for the fraction time derivatives is

\[
\begin{align*}
\dot{p} &= -p(K_{cap} + \lambda_{di}), \\
\dot{Ps} &= pK_{cap} - (\lambda_SS + \lambda_T T), \\
\dot{T} &= pK_{cap}f_T + f_T K_p S - (\lambda_T + f_S K_p)T, \\
\dot{S} &= pK_{cap}f_S + f_S K_p T - (\lambda_S + f_T K_p)S,
\end{align*}
\] (1a, 1b, 1c, 1d)

with initial conditions

\[
p(t = 0) = 1, \quad Ps(0) = 0, \quad T(0) = 0 \quad \text{and} \quad S(0) = 0. \] (1e)

The factors \( f_T \) and \( f_S \) (3/4 and 1/4) are included to account for the spin degeneracies. The two- and three-photon (direct and delayed) yields are extracted from the time integrations

\[
F_2 = F_{2d} + F_{2de} = \int_0^\infty dt(\lambda_{di} f_{di2} p + \lambda_S S), \] (2a)

\[
F_3 = F_{3d} + F_{3de} = \int_0^\infty dt(\lambda_{di} f_{di3} p + \lambda_T T). \] (2b)
Three-photon beta decay

Table 1. The delayed ($F_{de}^3$) and total ($F_3$) three-photon yields as well as the fit parameters ($K_p$ and $K_{cap}/\lambda_d$) for the various liquid samples (HSA is for human serum albumin).

<table>
<thead>
<tr>
<th>Material</th>
<th>Oxygen</th>
<th>$F_{de}^3$ (%)</th>
<th>$F_3$ (%)</th>
<th>$K_p$ (ns$^{-1}$)</th>
<th>$R = K_{cap}/\lambda_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iso-octane Low</td>
<td>0.58</td>
<td>0.85</td>
<td>1.34</td>
<td>2.15</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.39</td>
<td>0.65</td>
<td>2.27</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>Water    Low</td>
<td>0.26</td>
<td>0.52</td>
<td>2.77</td>
<td>3.05</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.25</td>
<td>0.51</td>
<td>2.84</td>
<td>3.07</td>
<td></td>
</tr>
<tr>
<td>Saline   Low</td>
<td>0.24</td>
<td>0.51</td>
<td>2.86</td>
<td>3.14</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.24</td>
<td>0.51</td>
<td>2.98</td>
<td>3.07</td>
<td></td>
</tr>
<tr>
<td>HSA      Low</td>
<td>0.25</td>
<td>0.51</td>
<td>2.64</td>
<td>3.30</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.25</td>
<td>0.51</td>
<td>2.95</td>
<td>2.96</td>
<td></td>
</tr>
<tr>
<td>Blood    Venous</td>
<td>0.25</td>
<td>0.52</td>
<td>2.86</td>
<td>3.02</td>
<td></td>
</tr>
</tbody>
</table>

The decay of the prominent direct component is taken from the Ore–Powell value ($f_{d3} = 1/372$ with $f_{d2} = 1 - f_{d3}$). This value has been confirmed in metals for which the theory of free electrons is plausible. On the other hand, the fraction decaying by three photons not forming Ps in the materials of biological relevance is not known and is the largest source of uncertainty in the total three-photon fraction. Direct three-photon detection experiments can obtain the absolute three-photon yield (by comparison to Al in which there is no Ps formation and thus the total yield is the direct component) (Seweryniak 2006). The agreement of such a work with the $F_3$ fractions of the present work would confirm that the Ore–Powell value is also correct for the direct component in samples of biological relevance.

To compare with experimental data, we convolute the instantaneous two-photon yield with a normalized Gaussian ($G$) with the correct width ($\sigma = 0.25$ ns) and add an experimentally determined background rate (BkGd):

$$Y_2(t) = \int_{t-3\sigma}^{t+3\sigma} \left[ \lambda_d S(t') + \lambda_d f_{d2} p(t') \right] G(t-t') \, dt' + \text{BkGd}. \quad (3)$$

The parameters $\lambda_d$, $K_{cap}$ and $K_p$ were determined for each data set by a $\chi^2$ minimization procedure. (That is, the differential equations were iteratively solved, adjusting the rate constants so as to produce a minimum $\chi^2$.) It turns out that $Y_2(t)$ (and $F_3$) are only sensitive to the pick-off time constant $K_p$ and the ratio $\lambda_d/K_{cap}$. The solid curves in figure 1 show representative fits while table 1 shows the numerical results for the three-photon yield as well as the fit parameters. Model-dependent rational errors based on variation of the results with different weighting schemes in the definition of $\chi^2$ are about 5% of the reported $F_{de}^3$ values. Only for iso-octane is there a change in the three-photon fraction with dissolved O$_2$. This result is consistent with previous findings and indicates that one should not expect a three-photon enhancement in O$_2$-deprived matter of biological relevance.

4. Discussion

As mentioned in the introduction, research in the 1960s studied the pick-off rate in many fluids and had determined the triplet fraction in the delayed component. Lee and Celitans found a 60% increase in the decay time of a degassed iso-octane sample as compared to one that is air saturated. This increase is in approximate agreement with the relative change in our pick-off rates, which determine (inversely) the decay time in the tail region. The constancy of the delayed three-photon fractions $F_{de}^3$ in all of the aqueous samples provides convincing evidence
that one should not expect a biological O$_2$ effect (one that depends on solute concentrations) in the delayed component.

Beyond the lack of an O$_2$ effect for biologically relevant materials, we estimate that the total fraction of three-photon decays is $\sim 0.52\%$. This value is almost equally composed of a direct component, for which we have simply assumed the Ore–Powell value, and a delayed component, which we have measured. This value is very close to the value used in the recent simulations by Kacperski and Spyrou (2005).

5. Conclusions

Three-gamma imaging is potentially more powerful than standard PET because each event bears the complete position information enabling the localization of the activity distribution without use of back-projection tomographic techniques. However, only a subfraction of the three-photon events are usable as each photon energy must be above the detection threshold and only total energy deposition events can be used, as a tight total energy window and time window (<$5$ ns) must be applied (for typical source strengths used in imaging) to reduce the strong background from two-photon decay pile-up events. However, these conditions can be met with high-resolution semiconductor detectors as pointed out in Kacperski and Spyrou (2005), and construction of a detection system with the required attributes for such studies is not beyond the reach of current technology.

The present work answers one question raised by Kacperski and Spyrou (2005) concerning the potential biological sensitivity of the three-photon imaging. Unfortunately, one should not expect any sensitivity to the level of dissolved O$_2$. Our results indicate that the overall three-photon yield is about $0.5\%$ in all samples. These conclusions assume that the direct three-photon yield is identical to that for free e$^-$s. Only direct measurement of the three-photon yield can determine if this assumption is correct (Seweryniak 2006).

Whether the information gained from the three-gamma decays is sufficient to merit construction of a special purpose camera is unclear and requires more investigations. On the other hand, a PET camera offering high energy resolution and fine spatial sampling, such as one built with solid-state detectors (such as CdZnTe), should permit the analysis of the three-photon events along with the more prevalent two-photon events and allow us to determine the added benefit of the three-gamma decay.

Acknowledgments

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