Imaging ortho-positronium lifetimes for molecular imaging

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Positron Emission Tomography (PET) is a medical imaging technique widely used for the diagnostic and evolution monitoring of numerous pathologies including cancers and Alzheimer's disease. This technique relies on the detection of the two 511 keV photons from the annihilation of positrons in a body to reconstruct the bio-distribution of positron emitter radio-isotopes (β^+ isotopes).
These isotopes are associated to vector molecules, the purpose of which is to highlight a specific cellular process (e.g., metabolic activity, osteoclastic activity, copper consumption,…). The varying density of β^+ emitters informs on the presence or absence of vector molecules, and therefore of given biological functions. As a functional imaging technique, PET scans differ from and complement anatomical imaging techniques, such as X-ray CT scans, that image anatomical structures instead of biological functions.
Most recent developments in PET focused on 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 density of radiotracer.
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 from in commercial PET systems**. Positron annihilation can transit through a meta-stable bound state called **positronium**. The positronium state forms singlet and triplet spin states respectively called para- and ortho-positronium.
The para-positronium (P-Ps) decays primarily to two 511 keV photons with a lifetime of 0.125 ns and the ortho-positronium (O-Ps) decays mainly to three photons adding up to 1022 keV, with a lifetime of 142 ns in vacuum. **However, O-Ps formation probability, lifetime and decay modes are highly sensitive to the physical and chemical environment**, mostly due to quenching collisions with the surrounding medium.
In materials science and engineering, the study of positron annihilation lifetime spectroscopy (PALS) is used as a probe for nano-scale physical and chemical properties of materials. It is used in wide ranges of applications such as evaluating the micro-porosity of bulk materials [1], the fraction of oxygen in porous materials [2], or even the surface tension of molecular liquids [3].
In biology, PALS has been used on small tissue samples to study hypoxia [4], and the size of free volumes in tumors [5]. While these measurements are ways to quantify the physical and chemical state of the tissues, no correlation is yet established to a pathology, nor can it yet be used in predictive diagnostics.

While positrons emitted from the isotopes 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 (τO-Ps). This imaging would require a change in isotope, using (γ, β^+) isotopes, such as ^{44}Sc, ^{72}As, ^{82g}Rb or ^{94m}Tc [6], which emit a prompt γ as a marker of the emission of the positron, and therefore would allow to measure τO-Ps. To this date no in-vivo study of τO-Ps was performed using a PET scanner. This can be linked to several limitations:

- **The PET scanner performances**. The best commercial PET scanners have only recently reached a coincidence time resolution (CTR) around 250 ps [7], which would start allowing to map τO-Ps, but limit the resolution of small fluctuations.
  Another limitation on the PET performance is that the detection efficiency of most scanners is too low to detect triple coincidence events with enough statistics to perform a diagnostic-worthy image. The new generation of whole-body scanners such as the Explorer PET [8] might

yield enough detection efficiency to perform such image, but their data acquisition system (DAQ) is not designed to look for triple coincidence events.

- **The lack of known medical interest** for such a diagnostic tool, stemming from the relative sparse use of this method to study biological samples, and therefore the **lack of understanding of** the underlying biological causes to a O-Ps lifetime modification.
- **The absence of widespread radiotracer** using (γ, β_+) isotopes. Given the difficulty to bring a new tracer molecule to the market, and have it approved for medical use, it is realistic to believe that no significant push to develop such a tracer will be made until the medical benefits of using τO-Ps imaging can be fully demonstrated.

As stated previously, the improvement of performances in the new generation of PET scanners should soon allow to measure τO-Ps in situ, and hopefully bring a new diagnostic tool for following the evolution of cancers and other pathologies, and for predicting the impact of treatments. While current PETs are not designed for 3-γ imaging, some prototypes, including Xemis-2 [9] and J-PET [10], have already stated their intention to use such events. J-PET has performed a proof of concept of τO-Ps measurement with ex-vivo samples and a ^{22}Na source, however their detection efficiency and spatial resolution limit their ability to move to in-vivo measurements. However, the medical interest for such a parametric imaging remains to be definitively established, and for this, tools to image τO-Ps need to be developed so a better understanding of its behaviour can be gained.

The goal for this PhD will be to take part in designing an innovative imaging device to image τO-Ps in a biological sample, and developing reconstruction algorithms that can go beyond bio distribution reconstruction and actually image τO-Ps. These objectives will allow to establish the list of requirements for future PET scanners to be able to measure τO-Ps in-vivo with optimal performances.

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