Positronium in medicine and biology

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In positron emission tomography, as much as 40% of positron annihilation occurs through the production of positronium atoms inside the patient's body. The decay of these positronium atoms is sensitive to metabolism and could provide information about disease progression. New research is needed to take full advantage of what positronium decays reveal.

Positronium Physics

Positronium atoms are bound states of an electron and its antiparticle, the positron. Positronium has two ground states, which are distinguished by their decay processes and their lifetimes, which differ by a factor of more than 1,000. Spin-zero para-positronium is even under charge conjugation symmetry — that is, exchanging all particles with their anti-particles results in the same atom — and in vacuum has a lifetime of 125 ps, decaying to two photons. Spin-one ortho-positronium is odd under charge conjugation and in vacuum has a lifetime of 142 ns, decaying to three photons. More details of the fundamental physics of positronium are given in BOX 1.

Positronium decays in biological material

However, inside biological materials, the picture is more complicated. In that setting, positronium mean 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 human tissues. Thus, positronium decay studies can provide new input in medical diagnosis[1].

In general, the mean lifetime of positronium depends on the size of free volume between atoms, whereas its formation probability depends on the concentration of voids. In addition, both these characteristics depend on the availability of biofluids and bioactive molecules, which can interact with the emitted positrons as well as with the formed positronium. Key bio-active molecules include free radicals, reactive oxygen species and anti-oxidants. In the free space between atoms, positronium decays as it does in vacuum. However, within molecules there are additional annihilation possibilities and the mean lifetime of ortho-positronium decreases considerably compared with the lifetime in vacuum, from 142 ns to a few nanoseconds[2]. The key processes (FIG. 1) are interaction with surrounding electrons (pick-off process that proceeds mostly via two photon annihilation) and ortho-positronium into para-positronium conversion catalysed by interactions with bio-active molecules such as oxygen or other functional groups that are present in the intermolecular spaces. All these processes are typically of similar strength, with the details dependent on the size of intermolecular voids and the concentration of bio-active molecules. Key observables are the positronium lifetime in the medium, the ratio of two-photon to three-photon decay rates and the probability of positronium production in the biomaterial.

Measuring positronium lifetimes

The fate of the positronium atom is investigated by positron annihilation lifetime spectroscopy (PALS). The advantage of using PALS to investigate the structural transformations and micro-environmental changes of a biological sample is that PALS is nondestructive and preserves the structural characteristics of the sample. In particular, PALS can test for structural changes in biological polymeric systems such as chitosan, bilayer interphases (emulsions, liposomes and micellar systems) or self-assembled biomimetic systems as bio-membranes. In terms of specific membrane diffusion and permeability properties, PALS is sensitive to the nanostructural changes caused by the formation of bioactive nanoparticles used in drug delivery systems. The structural stability of complex biological structures and molecules inside a living organism during metabolic processes is maintained by the formation of intracellular hydrogen

Box 1 | **Positronium in fundamental physics**

Precision measurements of positronium spectroscopy and decays offer clean probes of QED (quantum electrodynamics) and tests of fundamental symmetries (charge conjugation, charge-parity reversal and time reversal) with electrons and positrons. The information from positronium decays is complementary to that from precision measurements of the fine structure constant and electron electric dipole moment. Possible invisible decays of positronium are sensitive to dark matter scenarios involving 'mirror matter' models. Laser-excited Rydberg states of positronium will provide the positron component in new precision tests of gravity acting on anti-hydrogen planned at CERN. Bose–Einstein condensates of positronium have been suggested as the gain medium for a gamma-ray laser. For reviews of positronium physics, see REFS[6,7].

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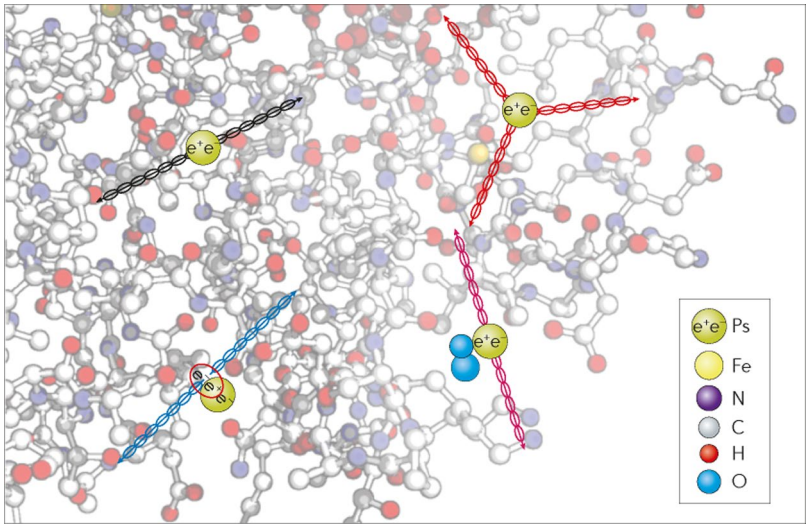

Fig. 1 | **Possible decays of positronium atoms trapped in the intramolecular voids in haemoglobin.** In the free space between atoms, para-positronium decays to two photons (black arrows) and ortho-positronium decays to three photons (red arrows). Positronium (Ps) can annihilate through the interaction with an electron from the surrounding molecule (blue arrows indicate the resulting photons). Ortho-positronium can interact with an oxygen molecule and convert into para-positronium, which subsequently decays into two photons (magenta arrows). Image courtesy of A. Kamińska and E. Kubicz, Jagiellonian University, Poland.

bonding interactions. For example, de-hydration and re-hydratation processes are maintained by the formation of an intracellular carbohydrate glass, which preserve the integrity of biomolecules. PALS techniques allow assessment of intermolecular hole size both in amorphous and crystalline bio-substances (so far studied in trehalose, a polysaccharide), to show the correlation between the intermolecular hole size and activated water diffusion[3]. For such biological systems, PALS can give a unique opportunity to have a deeper insight towards understanding nanostructure, the concentration of bio-active molecules and dimensional void spaces at nanometre and sub-nanometre scale. It is the only technique enabling effective and nondestructive studies of the structure of matter at the nanoscale and it allows one to follow in detail processes of positron–electron interaction with the medium, which until now have not been included during positron emission tomography (PET) investigation.

Medical applications

One of the biggest challenges of diagnostic medicine is early recognition of disease and precise localization of its cause. PET addresses this challenge by enabling detection of cancer at the early stage of its development, when it is not yet visible as a morphological change. In PET diagnosis, the patient is administered pharmaceuticals marked with a radioactive isotope that emits positrons. Thermalized positrons either annihilate directly with electrons in the patient or they first form a metastable positronium state that can become trapped inside free volumes between molecules (FIG. 1). Indeed, in routine PET imaging up to about 40% of the positron annihilations form metastable positronium as an intermediate state[1].

However, positronium production is currently neither recorded nor used for PET imaging. Presently, the parameter used to determine the degree of metabolic changes is the standardized uptake value (SUV) index, which expresses the uptake of the radiopharmaceutical in a volume unit relative to the average uptake throughout the whole body. The higher the SUV index, the higher the probability of occurrence of cells with a disturbed metabolism in a given region of tissue. New developments in PET technology include the advent of high-efficiency total-body PET scanners[4] and new methods enabling the in vivo imaging of positronium properties by combining PALS and PET techniques in one tomography system[1].

Positronium imaging will allow PET diagnosis to go beyond the present SUV standard. PALS has recently been applied to probe differences in free volume voids at the sub-nanometre scale for cancer detection at different stages. At present, this technique has successfully distinguished cancer from healthy tissue by in vitro probing of human tissues[2] or in the in vitro organoid (3D cell culture) systems[5]. A technique that combines PALS and PET in clinical use must enable determination of positronium parameters in a position-sensitive manner, and it needs to be scaled to work for living organisms. Recently, a first possible solution designed for the size of a human body was proposed[1].

In vitro studies comparing the positronium properties in cancerous and healthy tissues suggest that the ortho-positronium mean lifetime is correlated with the grade of development of metabolic disorders in cancer cells. Investigations with large patient sample and cancer types to more accurately quantify this correlation are ongoing[2]. One key hypothesis for this correlation is a link to the concentration of oxygen, which differs for most cancers from its concentration in normal tissues (hypoxia).

Challenges

Future studies will require research with cell cultures grown in a laboratory in which the degree of malignancy can be selected in a controlled manner. To arrive at clinically useful conclusions a concerted effort of the broader community is needed to verify whether positronium properties differ in healthy and cancerous tissues; whether positronium properties vary with the type of the cancer; whether positronium properties depend on the malignancy grade for a given cancer type; and whether and to what extent positronium properties in a given cancer type are patient dependent.

Owing to the dependence of the ortho-positronium lifetime on bio-active molecules, decisive experiments will need to be performed in vivo, requiring the development of PET with capability of positronium imaging[1]. In parallel, to understand the mechanism that correlates the grade of cancer and the positronium properties it is necessary to perform investigations with laboratory-grown 3D cell colonies (spheroids). Here, one of the biggest challenges lies in growing spheroids with dimensions of about one millimetre, corresponding to the typical range of positrons emitted from beta-plus isotopes commonly available in laboratories, such as ^{22}Na. This Comment acts as an invitation to the broader community to join this emerging science.

1. Moskal, P. et al. Feasibility study of the positronium imaging with the J-PET tomograph. *Phys. Med. Biol.* **64**, 055017 (2019).
2. Jasinska, B. et al. Human tissues investigation using PALS technique. *Acta Phys. Pol. B* **48**, 1737 (2017).
3. Kilburn, D. et al. Organization and mobility of water in amorphous and crystalline trehalose. *Nat. Mater.* **5**, 632–635 (2006).
4. Badawi, R. D. et al. First human imaging studies with the EXPLORER total-body PET scanner. *J. Nucl. Med.* **60**, 299–303 (2019).
5. Axpe, E. et al. Detection of atomic scale changes in the free volume void size of three-dimensional colorectal cancer cell culture using positron annihilation lifetime spectroscopy. *PLOS ONE* **9**, e83838 (2014).
6. Cassidy, D. B. Experimental progress in positronium laser physics. *Eur. Phys. D* **72**, 53 (2018).
7. Bass, S. D. QED and fundamental symmetries in positronium decays. Preprint in *arXiv* https://arxiv.org/abs/1902.01355 (2019).

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Competing interests
The authors declare no competing interests.