2021 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC) | 978-1-6654-2113-3/21/$31.00 ©2021 IEEE | DOI: 10.1109/NSS/MIC44867.2021.9875702

Quantum Sensing for Biomedical Applications

K. Shimazoe, H. Tomita, *Member, IEEE*, D. Watts, P. Moskal, A. Kagawa, P.G. Thirolf, D. Budker, C.S. Levin, *Member, IEEE*

***Abstract*–Quantum technology, such as the quantum computers, has attracted significant attention in recent years. In nuclear medicine, powerful and highly sensitive molecular imaging modalities such as PET (Positron Emission Tomography), SPECT (Single Photon Emission CT) and MRI (Magnetic Resonance Imaging) provide accurate morphological and functional information. Exploiting certain aspects of quantum mechanics may bring further improvements in sensitivity, spatial resolution and enable novel capabilities in the field of biomedical imaging and sensing. In this workshop, the possibilities of biomedical applications inspired by quantum technology were discussed. The following exciting topics were covered: quantum entanglement in PET, dynamic nuclear polarization toward more sensitive MRI, quantum sensors based on the ^{229m}Th nuclear clock, plans of an advanced high-energy gamma-ray source at CERN, laser-assisted radiation detection, solid-state quantum sensors such as those based on nitrogen vacancy centers in diamond, quantum sensing using cascade multi photons, and a laser-based radioactive isotope analysis.**

I. Introduction to Quantum Sensing

Quantum technology has attracted increasing attention because of the recent developments of and investment in quantum computers, which will be useful for calculations in numerous fields, such as quantum chemistry. In the plenary session at the 2021 IEEE Nuclear Science Symposium, the development of optical quantum computers in Japan was introduced and explained [1]. In addition to quantum computers, quantum devices, software, life science, materials and sensors are regarded as important fields of quantum technology. In workshop WS3, the possibility of quantum sensors for biomedical applications was discussed. Technically, an increasing utilization or precise control of electron spin, nuclear spin, photon entanglement, laser, polarization and energy state will provide new opportunities to enhance conventional imaging capabilities and generate new imaging concepts. Aside from concepts presented in the invited talks, there are several candidates in quantum sensors for possible biomedical applications. The NV center, which is one of the most popular quantum sensors, utilizes the electron spin state controlled by a magnetic field and emission by fluorescence [2]. Recently the NV centers are applied for the detection of various biological phenomena as well as for measurements, such as those of pH, temperature, magnetic field in micro-environment in cell-level experiments [3]. For example, although it is not a nuclear medical technique, the utilization of spin states inspires further development of ultrasensitive sensors. Utilization of multi-photon emitting cascade nuclides is also attractive in nuclear medicine. The gamma-ray cascade photon correlation depends on the nuclear spin state of the intermediate state. The detection capability of pH is reported through cascade gamma-rays (^{111}In) using the spatio-temporal correlation of two gamma-rays [4]. Recent progress in laser technologies allows highly sensitive detection of long-lived radiocarbon ^{14}C based on laser absorption spectroscopy [5]. A mid-infrared laser based ^{14}C detection system is under development for biomedical applications as an alternative to conventional methods such as liquid scintillation counting and accelerator mass spectrometry [6].

The workshop featured six invited speakers who discussed various aspects of future biomedical applications of quantum sensing and related technologies.

Manuscript received December 15, 2021.

K. Shimazoe is with the University of Tokyo, Tokyo, 113-8656 Japan (e-mail: shimazoe@bioeng.t.u-tokyo.ac.jp).

H. Tomita is with Nagoya University, Nagoya, 464-8603 Japan (e-mail: tomita@nagoya-u.jp).

D. Watts is with University of York, York, YO10 5DD United Kingdom (e-mail: daniel.watts@york.ac.uk).

P. Moskal is with Jagiellonian University, Institute of Physics, Krakow, Poland (e-mail: p.moskal@uj.edu.pl).

A. Kagawa is with Osaka University, Osaka, Japan (e-mail: kagawa@ee.es.osaka-u.ac.jp).

P. Thirolf is with Ludwig-Maximilians-Universität München, Garching, D-85748 Germany (e-mail: peter.thirolf@physik.uni-muenchen.de).

D. Budker is with Helmholtz Institute, Johannes Gutenberg University, Mainz, Germany and University of California, Berkeley, USA (e-mail: budker@uni-mainz.de).

C.S. Levin is with Stanford University, CA 94305 USA (e-mail: cslevin@stanford.edu).

II. Workshop Summary

In the workshop, the first two talks (D. Watts and P. Moskal [7,8]) were related to the "quantum PET" concepts using quantum entanglement features of annihilation photons. Recently it was confirmed that annihilation 511 keV photons show correlations consistent with the hypothesis that they are entangled via a Compton scattering method with potential to improve the image quality of PET images by identifying the entanglement. They discussed the loss of entanglement in the scattering process. The configuration to detect Compton scattering is under evaluation. Systems using CZT and plastic scintillators [14] were introduced. Another aspect of quantum PET is the utilization of the positronium states (para-positronium and ortho-positronium) to detect the microenvironment in the cells [15]. The measurement of the time difference between gamma-ray and annihilation photon provides the ratio of states by using the difference in the lifetime of the positronium states. This may provide additional biological information for conventional PET imaging. The utilization of three-photon decays will also be expected in future developments. First positronium and multi-photon PET images were demonstrated [16,17].

A. Kagawa [9] discussed dynamic nuclear polarization to increase the sensitivity of MRI. Electron spin plays an important role in certain biological phenomena, such as magnetic detection. His research of nuclear spin related biological chemical reactions was introduced. Nuclear polarization technology can be applied to both MRI and nuclear medicine imaging.

P. Thirolf [10] introduced a unique and interesting quantum sensor based on a ^{229m}Th nuclear clock. The nuclear clock is expected to be a future precise nuclear frequency standard exceeding the present accuracy of atomic clocks. The current status and future prospects of the technology were introduced. This technology can also be used as a highly sensitive quantum sensor in the future.

D. Budker [11] presented the plan of "Gamma Factory" at CERN that will expand many nuclear physics horizons by generating high-energy gamma rays. The factory will also be useful to generate radioisotopes for medical applications.

In the last talk, C.S. Levin [12,13] reported the investigation of a new detection method for ionizing radiation interactions. Conventional radiation detectors rely on charge collection in direct conversion detectors or scintillation photon collection in indirect detectors. This newly proposed method based on ionization-induced optical property modulations seems promising to enhance timing resolution for TOF-PET.

Appendix: Abstracts of the Speakers

1. D. Watts, *MeV scale photon quantum entanglement and its application in PET imaging*

Abstract: Positron Emission Tomography is a technique widely used for medical research and clinical diagnosis. It utilises the back-to-back emission of annihilation photons to image metabolic processes inside of the body. PET images are obtained with significant in-patient scattering and random backgrounds, which reduce image resolution and contrast. Here we demonstrate the benefits of exploiting the quantum entanglement between the two annihilation photons, underpinned by our development of the first GEANT4 simulation to include such quantum entanglement effects. The simulation results were verified by comparison with experimental data from a cadmium zinc telluride PET demonstrator. As an indication of the potential benefits for PET, we present a simple method to quantify and remove in-patient scatter and random backgrounds using only the entanglement information in the PET events. Current results and an outline of the ongoing programme will be presented.

2. P. Moskal, *Positronium and quantum entanglement imaging, a new trend in positron emission tomography*

Abstract: We report on the progress in the development of positronium imaging and quantum entanglement imaging achieved thus far by the J-PET collaboration. The main objectives of the presented research are to develop a positronium imaging method, and to assess the diagnostic potential of positronium applications as a biomarker of tissue pathology [15]. Positronium is a bound state of positron and electron. It is abundantly produced in the inter- and intra-molecular spaces in the organism subjected to Positron Emission Tomography. Properties of positronium such as e.g. mean lifetime and production probability depend on the size of intra-molecular voids and on the concentration in them of free radicals and paramagnetic molecules playing a role in cellular metabolism. Therefore, positronium may be used as a hallmark of the molecular environment in which it is formed [15]. To translate positronium imaging into clinical diagnostics, two independent research challenges need to be addressed. Firstly, a method for the spatially resolved in-vivo reconstruction of positronium properties need to be developed (referred to as positronium imaging) [16,17], and secondly, a correlations between these properties and the type and degree of tissue pathology need to be established. The emerging methods of positronium imaging, and research towards application of quantum entanglement in PET [14,18], require high sensitivity and high time resolution of PET systems. These are now becoming achievable with the advent of the total-body PET systems and constantly improving time resolution. We will present the status of development of positronium and quantum entanglement imaging and will discuss its applicability in context of the newly introduced total-body PET systems.

3. A. Kagawa, *Highly polarized nuclear spins for biological applications*

Abstract: Nuclear magnetic resonance (NMR) spectroscopy provides a variety of information for non-invasive materials. However, due to the low thermal polarization of nuclear spins at room temperature even in a high magnetic field, the inherent low sensitivity limits the range of applications. Dynamic nuclear polarization (DNP) can significantly enhance the low nuclear spin polarization using unpaired electron spins, which have higher polarizations than nuclear spins in the same experimental conditions. Recently, dissolution-DNP (d-DNP) attracts much attention because it can monitor real-time chemical reactions and metabolic processes in liquids. D-DNP experiments have been implemented at extremely low temperatures (~ 1 K) and high magnetic fields (> 3 T) to obtain near unity electron polarization,. After the DNP experiments, the samples are rapidly dissolved by host solvents and a secondary NMR or MRI superconducting magnet. We introduce our developed d-DNP instrument to experimentally verify a conjecture "quantum dynamical selection" recently proposed nuclear spin-dependent biological reactions. While the conventional DNP, which is implemented at low temperature in a high magnetic field using free radicals, is the most versatile method, several techniques such as para hydrogen, nitrogen-vacancy center in diamonds, and optically pumped gases are studied as promising candidates to obtain extremely high nuclear polarization. The sources of high polarization in these methods are not thermally equilibrated electron spins, and these techniques do not require high magnetic fields and/or cryogenic temperatures. DNP using photo-excited triplet electron spins (triplet-DNP) has also been carried out under low magnetic fields and relatively high temperatures. While triplet-DNP has advantages for the experimental conditions, it has to overcome several problems to become a versatile method such as d-DNP.

4. P. Thirolf, *Development of a ^{229m}Th Nuclear Clock: Status and Perspectives for a Unique Quantum Sensor*

Abstract: Today's most precise time and frequency measurements are performed with optical atomic clocks. However, it has been proposed that they could potentially be outperformed by a nuclear clock, which employs a nuclear transition instead of an atomic shell transition. There is only one known nuclear state that could serve as a nuclear clock using currently available technology, namely the isomeric first excited state of ^{229}Th. Evidence for its existence until recently could only be inferred from indirect measurements, suggesting since 2009 an excitation energy of 7.8(5) eV, representing the lowest nuclear excitation so far reported in the whole landscape of known isotopes. In 2016, the first direct detection of this nuclear state could be realized via its internal conversion decay branch, laying the foundation for precise studies of its decay parameters. Subsequently, a measurement of the half-life of the neutral isomer was achieved, confirming the expected reduction of 9 orders of magnitude compared to the one of charged ^{229m}Th. Collinear laser spectroscopy was applied to resolve the hyperfine structure of the thorium isomer, providing information on nuclear moments and the nuclear charge radius. Most recently, also the cornerstone on the road towards the nuclear clock, which is a precise and direct determination of the excitation energy of the isomer, could be achieved by locating the isomeric excitation energy as 8.19(12) eV. Hence major progress on the properties of this elusive nuclear state could be achieved in the last four years, opening the door towards an all-optical control and thus the development of an ultra-precise nuclear frequency standard. Such a nuclear clock promises intriguing applications in applied as well as fundamental physics, ranging from geodesy and seismology to the investigation of possible time variations of fundamental constants and the search for Dark Matter.

5. D. Budker, *Expanding physics horizons with the Gamma Factory at CERN*

Abstract: The Gamma Factory (GF) is an ambitious CERN proposal for a source of photons with energies up to about 400 MeV and photon fluxes up to 10^{17} photons per second, exceeding those of the currently available gamma sources by orders of magnitude. The high-energy (secondary) photons are produced via resonant scattering of the primary laser photons by highly relativistic partially-stripped ions circulating in the accelerator. The secondary photons are emitted in a narrow cone and the energy of the beam can be monochromatized, eventually down to the ppm level, via collimation, at the expense of the photon flux. In this talk, we will highlight the opportunities offered by the GF in fundamental physics across many subfields.

6. C.S. Levin, *Investigations of a new approach to detect ionizing radiation interactions using modulation of optical properties*

Abstract: Recently there has been considerable effort in the field of positron emission tomography (PET) to enhance annihilation photon pair coincidence time resolution (CTR) in order to advance time-of-flight (TOF)-PET performance, which boosts reconstructed image signal-to-noise ratio (SNR), resulting in better visualization and quantification of molecular pathways of disease using PET. Currently the CTR in PET is limited by the scintillation mechanism employed for detection of 511 keV photon interactions, with the best CTR being on the order of 150-250 picoseconds for 4×4×20 mm^3 length crystal elements used in clinical TOF-PET systems. However, we have experimentally shown that ionizing photon interactions in principle contain much more precise photon arrival information, in the realm of less than one picosecond using the modulation of optical properties (for example, refractive index, absorption, polarization, etc.) that results from the fast transient production of ionization-induced charge carriers. In this talk we describe a range of optics experiments and simulations that study this optical property modulation-based ionizing radiation detection method. Extropolation from x-ray laser experiments combined with simulations of single 511 keV photon interactions predict that a CTR on the order of 1 picosecond is possible using this approach [13], although thus far this level of performance has eluded us experimentally.

ACKNOWLEDGMENT

This workshop is supported by PRESTO (Quantum Bioscience FY2017-2022), Japan Science and Technology Agency (JST). We also thank director Prof. M. Setou for help.

REFERENCES

[1] A. Furusawa, "Large-scale quantum computing with quantum teleportation", *IEEE NSS 2021* Plenary talk NP-01-04, (2021).

[2] A. Gruber, *et al.,* "Scanning confocal optical microscopy and magnetic resonance on single defect centers." *Science* 276.5321 (1997): 2012-2014.

[3] A. Kuwahata *et al*, "Magnetometer with nitrogen-vacancy center in a bulk diamond for detecting magnetic nanoparticles in biomedical applications", *Scientific Reports* **10**, 2483 (2020).

[4] F. Sensui, *et al.*, "Quantum sensing of pH around local environment via cascade photon angular correlation in nuclear medicine imaging", *IEEE MIC 2021* M-13-03, (2021).

[5] I. Galli *et al.*, "Molecular gas sensing below parts per trillion: Radiocarbon-dioxide optical detection," *Phys. Rev. Lett.* **107**, 270802 (2011).

[6] V. Sonnenschein *et al.*, "A cavity ring-down spectrometer for study of biomedical radiocarbon-labeled samples", *Journal of Applied Physics* **124**, 033101, (2018).

[7] D. Watts, "MeV scale photon quantum entanglement and its application in PET imaging", *IEEE NSS/MIC/RTSD 2021* WS03-02, (2021).

[8] P. Moskal, "Positronium and quantum entanglement imaging, a new trend in positron emission tomography", *IEEE NSS/MIC/RTSD 2021* WS03-03, (2021).

[9] A. Kagawa, "Highly polarized nuclear spins for biological applications", *IEEE NSS/MIC/RTSD 2021* WS03-04, (2021).

[10] P. Thirolf, "Development of a ^{229m}Th Nuclear Clock: Status and Perspectives for a Unique Quantum Sensor", *IEEE NSS/MIC/RTSD 2021* WS03-06, (2021).

[11] D. Budker, "Expanding physics horizons with the Gamma Factory at CERN", *IEEE NSS/MIC/RTSD 2021* WS03-07, (2021).

[12] C.S. Levin, “Investigations of a new approach to detect ionizing radiation interactions using modulation of optical properties”, *IEEE NSS/MIC/RTSD 2021* WS03-08, (2021).
[13] L. Tao *et al*, “Ionizing photon interactions modulate the optical properties of crystals with femtosecond scale temporal resolution” *Physics in Medicine and Biology* **66**, 045032, (2021).
[14] P. Moskal *et al.*, ”Feasibility studies of the polarization of photons beyond the optical wavelength regime with the J-PET detector,” *Eur. Phys. J. C* **78**, 970, (2018).
[15] P. Moskal, B. Jasinska, E. Ł. Stepien, S. Bass, ”Positronium in medicine and biology,” *Nature Reviews Physics* **1**, 527, (2019).
[16] P. Moskal *et al.*, ”Positronium imaging with the novel multi-photon PET scanner,” *Science Advances* **7**, eabh4394, (2021).
[17] P. Moskal *et al*., ”Testing CPT symmetry in ortho-positronium decays with positronium annihilation tomography,” *Nature Communications* **12**, 5658, (2021).
[18] B. Hiesmayr, P. Moskal, “Witnessing Entanglement In Compton Scattering Processes Via Mutually Unbiased Bases”, *Scientific Reports* **9**, 8166 (2019).