Positron Emission Tomography: Can crystals used in particle detectors save lives?

Did you ever wonder if antimatter really exists and where apart from CERN can you find it? Actually, it is routinely used in nuclear medicine, in a device known as PET scanner. When you try to google the word "PET", you will be overwhelmed by images of dogs and cats… But PET also stands for Positron Emission Tomography, which is a medical imaging technique being used daily in the hospitals to look in the bodies of thousands of patients without operation and produce detailed 3D images of the inside of the body, for example to detect tumors. It is based on principles of particle physics ("electron-positron annihilation") and uses detectors, electronics and image reconstruction technologies developed at research laboratories, such as CERN and others [1, 2, 3].

Development of such instrumentation in the second half of the twentieth century resulted in significant contributions in other areas, including various medical applications, PET being only one good example of spin-off from the fields of nuclear and particle physics.

How does PET work?

The PET imaging technique allows to visualize physiological activities in biological systems and measure changes in metabolic processes, like blood flow, regional chemical composition and absorption; showing both normal but also any abnormal areas and functions of the body. The drug composed of molecules involved in the body's metabolism (e.g. glucose) and radioactive substances (radioisotopes / radiopharmaceuticals) attached to it, is intravenously injected into the body as a tracer. Different tracers are used for various imaging purposes, depending on the target process within the body (for example, 18F-FDG is used to detect cancer, NaF18 F for the bones and oxygen-15 for blood flow). In the case of tumors, for example, the glucose, once injected, is taken up in different proportions by healthy and cancerous cells (commonly used glucose will be taken mostly by energy consuming cancerous cells). The radioisotopes are unstable atoms emitting positrons (antiparticles of the electron with positive charge). Most commonly used are radioisotopes with short half-life, to keep low the dose absorbed by the body (e.g. 109 minutes for 18F, 20 minutes for 11C and 1 hour for 68Ga). When the positron emitted from the radioisotope meets an ordinary electron present in the surrounding atoms of the body tissue, they are both transformed into a pair of photons (particles of light) in a process called annihilation. So one can say that the PET technique "illuminates" biological systems from the inside. Emerging photons are captured by a detector composed of several cameras placed around the body and converted into a readable signal by a computer providing a 3D image construction of the injected body (this method is called tomography). The photon detectors used in PET have been developed as an instrument for particle and nuclear physicists, who use them to study for example the foundations of the early universe or Higgs boson.

PET evolution

While PET was not invented at CERN, some early and very essential nuclear and particle physics experimental instrumentation developments at CERN boosted significantly the PET techniques evolution and resulted in innovative applications in medicine among other sectors [4]. The evolution of PET imaging as used today in hospitals started in 1950s in Massachusetts General Hospital in Boston, where the "first positron-imaging device" to record 3D data of the brain was used [5].

Detectors used in early PET scanners are called scintillators (from phosphorescent materials, which re-emit the absorbed energy in the form of light) and are coupled with photomultipliers (to increase the signal). They have good energy resolution for low-energy photons and high efficiency what makes them particularly suitable for medical imaging. In the course of the years different other detectors developed for particle physics experiments were used[1].

Nowadays the development of other type, the TOF (Time-Of-Flight) PET[2], based technology of Silicon Photomultipliers [6], is of particular interest, since thanks to different measuring technique it provides accuracy in localizing the tumor with less dose for the patient [7]. CERN made pioneering contribution to PET when in 1970s new and completely different technology, which would provide considerably higher spatial resolution then scintillator-based scanners, was explored there [8]. The PET forerunner called HIDAC (high-density avalanche chamber) based on CERN Physics Nobel Prize for invention of high energy particles detector from 1968 [9], produced the first mouse's skeleton image in 1977 (Fig.1 left). After, the HIDAC-PET was developed and later installed and evaluated clinically in Cantonal Hospital of Geneva (HUG), where the first images of patients were recorded in 1982 (Fig. 1 right). After these pioneering studies several different PET scanners designs and data reconstruction tools were explored worldwide [], including the full human body PET images in 2018 [10,].

Not everybody is aware that at CERN there is a Crystal Clear Collaboration (CCC) [11, 12] with mission to identify the most suitable scintillating crystals to pave the way for the discovery of the Higgs boson (these are used for example in CMS and ALICE detectors). Since 1995 CCC branched out into development of several new PET prototypes for different types of cancer (e.g. breast cancer [13]) and small animals, based on CERN scintillating crystals.

PET scanners are only one example of how research, in particular in particle physics shaped the evolution of medical technologies. Enjoy details of the PET story told by former CERN scientist David Townsend [14] and discover more about CERN medical applications [15, 16].

1 NaI (Tl) with PMTs silicon photomultipliers were used in the early PET scanners; new scintillators introduced in the course of the years (already developed for particle physics experiments) were BGO (Bi4Ge3012), CsI(Tl), LSO (Lu2SiO5 Cerium-doped lutetium oxyorthosilicate) etc. Photomultiplier tubes evolved to multichannel photomultipliers, Avalanche Photodiodes (AVDs) and Silicon PhotoMultipliers.

2 In conventional PET the point where electron-positron annihilation occurred is recognized along a line of response (LOR). The intersection of many lines of response gives the point where annihilation happened. The two photons have to be synchronous, therefore a coincidence within a time window of less than 15 ns is required. The Time Of Flight technique is based on the fact that, if the detection system has time resolutions in the 100 ps range, by measuring the time difference between the coincident photons we can localise their point of origin along the Line Of Response.

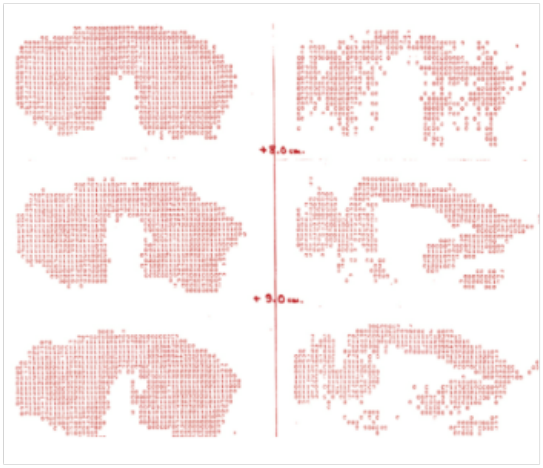
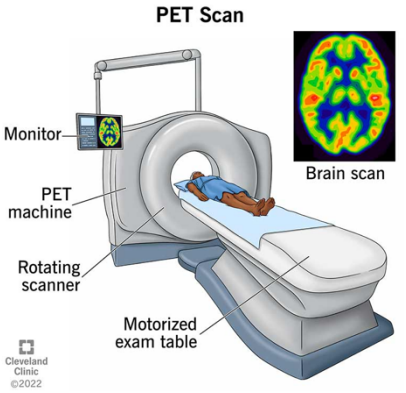


Figure 1 left: *First CERN PET mouse image: detectors' raw data record (left); skull's and tail's reconstruction (right)*

Figure 1 right: *Dual HIDAC-PET camera used the first time for image of patients, Geneva Cantonal Hospital*

Addendum 1: Hybrid techniques

The concerted efforts of many groups world-wide [] for over more than 40 years have resulted in the today's commercially available combined scanners, PET/CT[3] [17,], SPECT/CT, PET/MRI[4] [18], offering better functionality and benefits of different techniques, and reducing cost and number of medical exams for patients. These modern techniques of "hybrid imaging" offer the combination of information on body functions (from PET) with anatomical details (from CT or MRI). The benefits could be clearly seen in Fig.3. Today, most whole-body anatomical imaging for oncology is performed with X-ray based computed tomography (CT). It was a former CERN scientist, David Townsend, working at the University Hospital in Geneva (HUG), who first thought of incorporating the CT scanner into the PET camera based on its forerunner ART/PRT-1[5] developed at CERN. The first such instrument was in operation in Geneva by the end of the 1990s and now all PET cameras that are commercially available from the major international companies are combined PET/CT scanners.



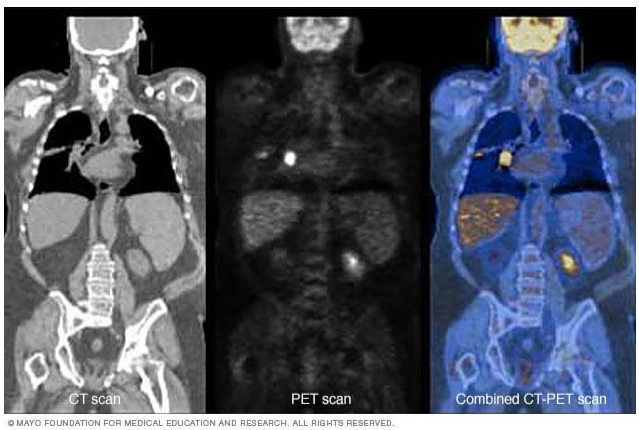


Figure 2 left: *PET scanner used in hospitals, it is a large machine with a round, donut-shaped hole in the middle.*
Figure 2 right: *Images from CT (body anatomy), PET (function anomalies) and combined PET-CT scanner (right).*

3 Computer tomography (CT) scan is an imaging technique using computer-processed combinations of multiple X-ray (high energy photons) measurements taken from different angles of biological systems in order to produce cross-sectional inside images of a body.

4 The single photon emission computed tomography (SPECT) is a form of non-invasive nuclear imaging used to understand how organs inside the body work.

5 ART is advanced rotating tomograph and PRT-1 is Partial Ring Tomograph.

Parameter	Ultrasound	Optical imaging	CT scanner	MRI scanner	PET camera
Anatomical detail	OK	Good	Good	Excellent	Poor
Spatial resolution	OK	Good	Good	Excellent	OK
Clinical penetration	OK	Poor	Excellent	Excellent	Poor
Sensitivity	Poor	Poor	Poor	Poor	Excellent
Molecular imaging	Poor	Poor	Poor	OK	Excellent

Figure 3: *Comparison of benefits of different medical imaging techniques. Credit [].*

Unlike CT, the magnetic resonance imaging (MRI) using superconducting magnets, another important instrument used by particle physicists, provides good contrast in soft tissue and therefore is used in brain and spinal malignancies, and anatomical imaging is performed with magnetic resonance. In 2008, both the Philips and Siemens medical companies developed their first PET/MRI prototypes for humans, while Philips has commercialized the whole-body TOF-PET/MRI system. First combined scanner in Europe was installed in HUG in 2011. Since 2015, a new PET/MRI project aiming for further improvements of brain imaging started in Geneva [19].

Addendum 2: People, places and technologies

The late 1970s and early 1980s was a period of considerable innovation in PET instrumentation with a number of different scanner designs under development, while the majority were scintillator-based. CERN physicists Alan Jeavons and David Townsend explored different technology, called the high density avalanche chamber (HIDAC) offering higher spatial resolution. HIDAC is a multi-wire proportional chamber (MWPC) based on the 1992 CERN Physics Nobel Prize George Charpak's invention (1968), which incorporates an additional novel high-density converter to improve the 511 keV photons' detection sensitivity from the annihilation process to be used for medical imaging. HIDAC was the first to explore an innovative technology with physicist Jeavons' brainchild. In 1977, CERN radiobiologist Marilena Streit-Bianchi injected a mouse with sodium fluoride labelled with fluorine-18 positron emitter (FDG18), which, releasing its positrons, annihilated immediately into a pairs of photons traveling in opposite directions along a straight line. It was so that a new camera developed at CERN showed the first mouse's skeleton image (Fig. 1 Left). To record the positron pairs, Jeavons and Townsend placed a HIDAC detector to the left and right of the mouse. Thanks to a computer program stored on punch cards, it was possible to reconstruct the annihilation locations' data, thus revealing the sodium fluoride distribution in the mouse bones.

The dual HIDAC-PET camera from CERN was then developed further, installed, and evaluated clinically in the Nuclear Medicine department of the HUG, under the direction of Alfred Donath, and in 1982 for the first time recorded images of patients (Fig.1 Right).

After these pioneering studies a number of different PET scanners' designs were explored worldwide. In 1985, a breakthrough was made in PET Imaging by the Ron Nutt and Mike Casey block detector invention, based on Bismuth germanium oxide (BGO) crystals at the Computer Technology and Imaging Inc (CTI), Knoxville Tennessee, US (Fig. 4). By coupling a scintillator block, an 8x4 small crystals cut array, into four photomultiplier tubes, Nutt and Casey simplified the complexity and cost of the imaging detector, thus resulting in the development of multiring PET scanners for research usages. Through these scintillators, a much higher sensitivity and a better count rate performance could be achieved than with the HIDAC cameras, although with poorer spatial resolution.

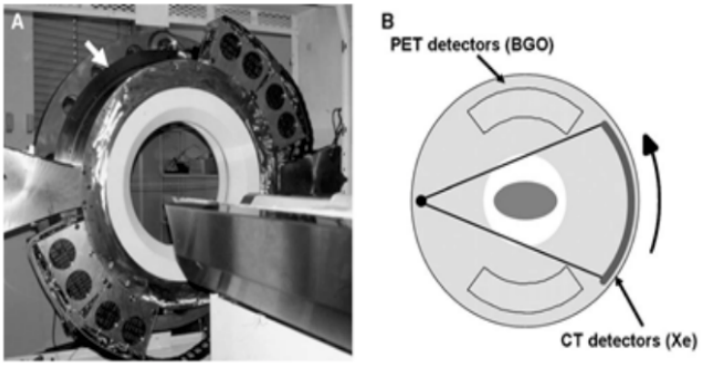


Figure 4: *PET detector invention based on Bismuth germanium oxide (BGO) crystals*

HIDAC-PET scanners were able to give 3D acquisition modes against the 2D mode by PET scanners. Together with Benno Schorr, a CERN mathematician, Rolf Clackdoyle and David Townsend developed a very efficient 3D reconstruction algorithm that, implemented and evaluated at the HUG, demonstrated the PET data acquisition and fully 3D reconstruction feasibility. A step that could lead in the 90's to multiring PET scanners 3D images and to new faster scintillators' improvements.

In 1989, another development took place with profound consequences on the PET imaging field. The Geneva group together with Terry Jones' at the Hammersmith Hospital in UK, started developing a new PET scanner, the Partial Ring Tomograph (PRT-1) with the objective to realise a cost-effective PET scanner design by rotating two opposite banks of block detectors having better sensitivity and being able to acquire 3D data format. Thus, reducing substantially the cost, being a scanner with fewer detectors. This new design was assembled at CERN using a modified gantry from the University of California, Los Angeles (UCLA). It was a PET scanner consisting of two 48 transaxial per 2 axial 8x8 crystal blocks arrays. The PRT-1 prototype blocks were identical to the BGO crystals full ring scanner but needed only one third of detectors.

In 1991, the PRT-1 recorded its first patient brain's FDG18 image at the HUG. Two years later, a second PRT-2 prototype with better performance was clinically evaluated at the University of Pittsburgh Medical Centre (UPMC) in the US and at the Swiss Paul Scherrer Institute (PSI).

The Geneva group took a step forward combining the CT anatomical with the PET functional data through the PET/CT scanner prototype, installed at the UPMC in 1998. The idea for developing this dual modality imaging prototype originated from the University of California San Francisco (USCF), thanks to the work of physicist Bruce Hasegawa and others who in 1995 designed and evaluated a system combining the single photon emission computed tomography (SPECT) with CT. The PET/CT scanner design was based on PET detector blocks, originating from an advanced rotating tomograph (ART) scanner mounted on the rotating support rear of CT components.

From 1989 to 1990, an ART/PRT-1 scanner was developed at CERN by David Townsend, Martin Wensveen, and Henri Tochon-Danguy and evaluated clinically at the HUG. Wensveen later was invited to CTI Inc to evolve the device into a commercial version. A low-cost PET scanner with good clinical performance was realized, successfully evaluated thanks to its affordability and accessibility. Today, the ART/PRT-1, a PET forerunner combined with a PET/CT scanner, has a major impact on medical imaging.

Personal stories

To add a small anecdote to the story of the evolution of PET, Martin Wensveen agreed to share with IPPOG some of his personal experiences pointing out how much some things can move on just from fortunate coincidences that bring the right people together, at the right time, at the right place.

He happened to join the group of Townsend and Jeavons following some "cross-road" decisions in his personal life. While working in Munich for the European Southern Observatory (ESO), he saw a job announcement on the board of the canteen where he was going for lunch while looking for an apartment in Munich. He found it interesting, reacted promptly and next week had a job at CERN as an engineer for the NA24 experiment. While this was a good step for his professional career, it was not so good for his family life. Couple of years later, he was forced to look for a complementary job to afford his divorce expenses, which brought him to the Cantonal Hospital of Geneva to work in the evenings with the group of Jeavons and Townsend on the PET-CT scanner. With his careful design, Wensveen was able to create extra space that made possible the implementation of CT inside of the PET scanner, which led to a more functional combined device.

While Wensveen after working on PET projects continued to work on CERN experiments, both Jeavons and Townsend have devoted their careers to improving medical imaging. Jeavons started the Oxford Positron Systems Company to produce high-resolution PET systems for small animals. Townsend became chief physicist at the University of Pittsburgh PET Facility, Professor of Medicine and Radiology as well as Director of the Cancer Imaging and Tracer Development Program at the University of Tennessee, head of PET and SPECT development for the Singapore Bio-imaging Consortium under the Agency for Science, Technology and Research (A*STAR) and Professor of Radiology at the National University of Singapore. In 2004, he won the Clinical Scientist of the Year Award from the Academy of Molecular Imaging for his co-invention, together with Ron Nutt for the combined PET/CT scanner.

CERN radiologist Marilena Streit-Bianchi after 41 years of career reminisced about her role in the first PET image taken at CERN: "I am very proud. The inventiveness of these two physicists and their desire to develop a special PET camera resulted in the further development of a perfectly safe method to inquire what is happening in the body" [20].

Conclusions

Medical imaging techniques, such as PET scanners, provide a clear demonstration of the beneficial impacts on daily life from fundamental research in physics via innovative technological applications.

References

[1] The Physics of PET/CT scanners, Ruth E. Schmitz, Adam M. Alessio, and Paul E. Kinahan, Imaging Research Laboratory Department of Radiology University of Washington,

https://depts.washington.edu/imreslab/education/Physics%20of%20PET.pdf

[2] Positron emission tomography : basic sciences, Dale L Bailey, David W Townsend, Peter E Valk and Michael N Maisey (Eds), Springer, 2005, ISBN 1852337982, https://media.hugendubel.de/shop/coverscans/162PDF/16210674_lprob_1.pdf

[3] Recent developments in PET Detector Technology, Lewellen TK., Phys Med Biology, 2008 Sep 7 ;53(17): R287-317. doi: 10.1088/0031-9155/53/17/R01,

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891023/

[4] PennPET Explorer acquires first human images, Cynthia E Keen, Physics World, Nuclear Medicine, 20 Nov 2019, https://physicsworld.com/a/pennpet-explorer-acquires-first-human-images/

[5] Positron Emission Tomography and CERN (30 years review of PET history), Martin Wensveen, presentation, CERN, 2014,

https://drive.google.com/file/d/1YbwygQPNc_6Qd0Z4ninEGqNfcQTN_vRI/view

[6] The new opportunities for high time resolution clinical TOF PET, Conti, M., Bendriem, B., *Clin Transl Imaging* **7**, 139–147 (2019). https://doi.org/10.1007/s40336-019-00316-5;

https://link.springer.com/article/10.1007/s40336-019-00316-5

[7] Time-of-Flight PET, Joel S. Karp, Society of Nuclear Medicine, PET center of excellence newsletter, Volume 4, Issue 4, Fall 2006, https://s3.amazonaws.com/rdcms-snmmi/files/production/public/docs/PETCENews_Fall06.pdf

[8] Detailed and credited in the monograph of Townsend in the book "From Physics to Daily Life[B. Bressan, From Physics to Daily Life. Applications in Biology, Medicine, and Healthcare, p. 85., Wiley Blackwell, 2014.

[9] 1992 CERN Physics Nobel Prize for George Charpak's multiwire proportional chamber (MWPC) invented in 1968, https://www.nobelprize.org/prizes/physics/1992/summary/

[10] Human Images From World's 1st Total-Body Scanner Unveiled, 2018,

https://explorer.ucdavis.edu/news; https://explorer.ucdavis.edu/media/video

https://www.youtube.com/watch?v=Op0eTSYXx8g

[11] Crystal Clear Collaboration, CERN, https://crystalclearcollaboration.web.cern.ch

[12] Crystal Clear, 30 years on, CERN Courier, https://home.cern/news/news/experiments/crystal-clear-30-years

[13] ClearPEM for breast cancer, CERN Courier, https://cerncourier.com/a/clearpem-clarifies-breast-cancer-diagnosis/

[14] From the Third Collisions CERN Alumni event (only accessible from CERN accounts) https://weblecture-player.web.cern.ch/?year=2024&id=1304845c10

[15] CERN 70th anniversary event on "From particle physics to medicine", duration 2 hours: https://www.youtube.com/watch?v=WhgDZKr9GQQ; https://cern70.cern/from-particle-physics-to-medicine/

[16] CERN short 5 minutes video "From particle physics to medicine" https://www.youtube.com/watch?v=aK7u7Yvpc5Q

[17] PET and CT: a perfect fit, CERN Courier; https://cerncourier.com/a/pet-and-ct-a-perfect-fit/

[18] PET and MRI: providing the full picture, CERN Courier; https://cerncourier.com/a/pet-and-mri-providing-the-full-picture

[19] La technologie développée pour les expériences LHC du CERN appliquée à l'observation du fonctionnement du cerveau, Communiqués de presse, UNIGE, https://www.unige.ch/communication/communiques/2015/cdp150729

[20] Forty years since the first PET image at CERN, CERN Courier, https://home.cern/news/news/knowledge-sharing/forty-years-first-pet-image-cern