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Achieving 10 ps coincidence time resolution in TOF-PET is an impossible dream

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OVERVIEW

A number of hardware and software developments in positron emission tomograph (PET) instrumentation during the last two decades have enabled improved localization of the position of annihilation along the line of response through precise measurement of the difference between the arrival times of the two annihilation photons. This concept is referred to as time-of-flight (TOF) PET and is implemented virtually on almost all commercial PET scanners. One limitation of this technology is the limited precision in the localization of the annihilation point owing to inherent uncertainty in the detector blocks and readout electronics which introduces some ambiguity in the photon arrival times. A large number of clinical studies have unequivocally demonstrated that incorporation of TOF information in PET image reconstruction improves signal-to-noise ratio and lesion detectability as well as increases patient throughput through reduction of scanning time. However, the magnitude of this improvement is correlated with patient size and coincidence time resolution (CTR). The latter was in the range of 550–600 ps on commercially available PET scanners but was recently reduced down to 350 ps on the first digital PET scanner commercialized by Philips Healthcare and more recently to ~214 ps by Siemens Healthineers. Further improvement of the CTR might be possible but exact determination of the lower bound on CTR that is likely to be achieved in the near future seems difficult. In this regard, while some think that 10 ps CTR is possible and could be achieved within the next few years, others think that such a target is not viable and will unlikely to be reached with the technology available today. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is Dennis R. Schaart, Ph.D. Dr. Schaart heads the section Medical Physics & Technology at the Radiation Science & Technology department of Delft University of Technology (TU Delft). He started his career as an R&D physicist at Nucletron (now Elekta), where he developed new devices for brachytherapy. He obtained his doctoral degree (with highest honors) at TU Delft in 2002. He subsequently joined the university to start a research line on radiation detectors for PET. His present research activities focus on novel methods and technology for diagnostic imaging and image guidance in proton radiotherapy. Dennis leads the Technology for Oncology programme of the TU Delft Health Initiative and is a member of the R&D Program Board of the

Holland Proton Therapy Centre (HollandPTC), a joint initiative of Erasmus Medical Centre (Erasmus MC), Leiden University Medical Centre (LUMC), and TU Delft. He has (co-)authored over 150 papers in refereed journals and is a frequently invited speaker in international meetings.

Arguing against the proposition is Sibylle Ziegler, Ph.D. Dr. Ziegler has a long-standing experience in PET detector development, system characterization, and pre-clinical data analysis of nuclear medicine images. She studied Physics at the Johannes Gutenberg-University Mainz where she completed her Ph.D in Physics in 1989. She then habilitated at the Technical University Munich (TUM) in 2003. Between her dissertation and habilitation, Dr Ziegler worked at the MRC Cyclotron Unit at the Hammersmith Hospital in London and the German Cancer Research Center in Heidelberg. From 2008 to 2017, Dr Ziegler was Adjunct Professor at the School of Medicine at the TUM. Since 2016, she is the Head of pre-clinical research at the Department of Nuclear Medicine at Ludwig-Maximilians-University Munich (LMU) and since 2017, she is Adjunct Professor at the School of Medicine at LMU.

FOR THE PROPOSITION: DENNIS R. SCHAART, PH.D.

Opening Statement

The first TOF-PET scanners were developed in the 1980's already, but the low density scintillators used at the time provided poor spatial resolution and detection efficiency. TOF PET scanners based on dense scintillators became available in the second half of the 2000's, offering CTR of ~600 ps in combination with good spatial resolution and sensitivity. The introduction of the silicon photomultiplier (SiPM) constituted the next technological breakthrough. High-resolution systems with CTRs near 200 ps are currently available. In laboratory experiments, SiPMs enabled CTR values of ~100 ps around 2009 already.[1] More recently, a CTR of ~60 ps was reported.[2]

Unfortunately, this chronology of past achievements does not justify the tempting expectation that 10 ps PET systems will come within reach at some point. To understand this, it is crucial to note that the stochastic nature of the emission, transfer, and detection of scintillation photons in a PET detector makes that the CRT is ultimately limited by photon counting statistics. For the combination of bright scintillators and efficient photosensors typically employed in PET scanners, the lower bound on the CTR can be predicted using Cramér-Rao theory.[3] This allows us to identify three major physical obstacles on the route to 10 ps PET. [Correction added on 29 April 2020, after first online publication: The third sentence in the above paragraph which starts with "To understand this" has been updated.]

First, the randomness in the scintillation photon emission times makes the lower bound on the CTR proportional to $\sqrt{N/\tau}$, with N being the number of detected photons and τ the scintillator decay time (the rise time plays a less prominent role). Unfortunately, τ tends to increase with increasing light yield in lanthanide-activated scintillators.[4] In practice, a material like $LaBr_3$:Ce probably has a near-optimum value of $\sqrt{N/\tau}$.

Second, the spread in photon transfer times further increases the variance of the timing signal, unless the crystal has infinitesimal dimensions.[1,2] Moreover, the spread as well as the mean of the optical transfer times vary with the position of interaction.[5] Thus, 10 ps PET requires detector designs in which these effects can be mitigated, for example, through clever signal processing (time resolution recovery).[6]

Third, the finite single-photon time resolution (SPTR) and, especially, photodetection efficiency (PDE) of the photosensor affects the CTR. SiPMs currently outperform PMTs in this respect. Unfortunately, the associated improvement of CTR values is about to saturate, as some SiPMs have PDE's exceeding 60% already.

In conclusion, it appears unlikely that ongoing improvement of current detector technology will bring 10 ps within reach.[7] Hope must therefore be drawn from research into novel timing methods.[8] Some of the physics being investigated in this new field is very exciting. To be viable, though, a novel PET detector concept must provide spatial resolution, energy resolution, and — last but not least — high detection efficiency; the benefits of TOF only apply to actually registered coincidences. Thus, 10 ps PET remains an impossible dream until we find a new detector concept that fulfills all requirements.

AGAINST THE PROPOSITION: SIBYLLE ZIEGLER, PH.D.

Opening Statement

We are limited by adhering to the classical concept of long scintillation crystals for full energy deposition of annihilation quanta, combined with fast light sensors. There are novel developments in materials, photodetectors with integrated electronics, and signal processing that should be exploited to overcome the technical hurdles in reaching 10 ps coincidence time resolution, since there seem to be no physical limits.[8]

With small, fast scintillators ($3 \times 3 \times 5$ mm^3), fast photosensors and matching electronics coincidence time resolution of 100 ps could be achieved already 10 yr ago.[1] When using longer crystals for improved sensitivity, timing resolution degrades drastically owing to light collection inside the scintillator. Hence, is the 10 ps dream still impossible or this has changed in the last 10 yR?

By using a “side-wise” readout Cates et al. measured less than 100 ps coincidence timing resolution with 20 mm long crystals, the length we typically find in clinical PET scanners and which yield 137 ps coincidence time resolution when read out on the narrow ends.[9] The authors of this study conclude that with further optimization, the 10 ps resolution may be within reach based on this unconventional idea.

Plastic scintillators offer excellent coincidence timing performance, but have never been a realistic choice for PET owing to their low sensitivity with no full energy deposition via photoelectric effect. They could, on the other hand, make 10 ps coincidence time resolution possible based on the first scatter interaction of 511 keV photons in a highly segmented scintillation volume and parallel electronic readout. Of course, there will only be limited information on the energy of the incoming photon. Turtos et al.[10] reported on their idea of using a metamaterial, combining slabs of a fast plastic and an inorganic scintillator to overcome the low detection efficiency of plastic scintillators. Coincidence timing resolution of shared events was 55 ps, and 35 ps for the plastic scintillator alone. The authors are further focusing their research on implementing nanocomposite scintillating layers with high-Z inorganic materials towards the goal of 10 ps coincidence time resolution.

The use of a Cherenkov radiator for detecting the 511 photons is still a relatively new approach for fast coincidence timing. By integrating a Cherenkov-radiator and a micro-channel plate photomultiplier tube, a coincidence timing resolution of 30 ps was recently achieved by Ota et al.[11]

Another major limiting factor in timing resolution is the combination of photodetector and readout electronics. Prototypes of new 3D digital silicon photomultipliers including embedded signal processing have recently been characterized[12] and show reduced timing jitter of 8 ps. This is still a factor of 2 higher than the one needed for 10 ps coincidence time resolution, but the authors identify potential solutions in the next generation of chips.

Dreams are important for overcoming limits. If we step out of our well-known paths, achieving 10 ps coincidence time resolution in TOF-PET is a possible, though challenging, dream.

REBUTTAL: DENNIS R. SCHAART, PH.D.

I can only agree with my opponent that dreams are crucial for pushing boundaries. As scientists, though, we are obliged to calibrate our dreams against the current knowledge of the underlying physics. This is why I outlined the main factors that make it hard to reach a CTR of 10 ps with conventional scintillators, even in what could be called the "infinitesimal-crystal approximation."

We appear to agree that novel timing approaches must be explored and Dr. Ziegler cites several interesting attempts in this direction. The experiment by Ota et al.,[11] for example, is important in that it demonstrates that the physics of positron annihilation do not exclude a CTR of 30 ps.

Let us recall, however, that the effect of TOF can be expressed as an increase in effective sensitivity. Given a subject diameter $D > 0$:

$$S_{\mathrm{eff},D} \propto \eta_{\mathrm{det}}^2 \, \eta_{\mathrm{geom}} \, \frac{D}{\Delta t} \tag{1}$$

with η_{det} the singles detection efficiency, η_{geom} the angular coverage, and Δt the CTR. Although this model may be somewhat oversimplified, it suffices to point out a pitfall in the search for 10-ps PET. In many studies that focus on improving Δt using prompt photons, for example, only the events with the highest number of prompt photons are accepted. If accepting a fraction $f < 1$ of the singles improves Δt by a factor $g > 1$, the net sensitivity gain equals $f^2 g$, which may be smaller than one!

It follows that we must improve Δt while maintaining a high η_{det} (as well as good spatial and energy resolution). Moreover, we should compare the benefit of better TOF with the option to increase η_{geom}. Two-meter-long PET systems with extremely high sensitivity have recently become available, offering new possibilities, such as total-body dynamic imaging.[13] The exciting results obtained with these, still very expensive, systems warrant research into detectors with improved cost-effectiveness.[14,15]

In conclusion, rather than pushing time resolution *per se*, my “impossible dream” is a detector technology that enables us to increase $S_{\mathrm{eff},D}$ by a few orders of magnitude *and* at the same time reduce the cost of PET scans.

REBUTTAL: SIBYLLE ZIEGLER, PH.D.

The proponent’s arguments are all valid and both of us acknowledge the impressive advances in timing resolution for PET detectors.

Our views mainly differ when it comes to defining the requirements for a viable PET detector system. The proponent points out that even if there was a detector that can achieve 10 ps system time resolution, this detector will probably not fulfill essential requirements for a realistic PET scanner. I argue that 10 ps coincidence time resolution may allow us to re-consider our view on system requirements. In the case of 10 ps coincidence time resolution, image generation will be very different from what we are currently used to, with no reprojection step needed in a very defined, local assignment of the annihilation event. Thus, some familiar concepts may not be applicable anymore.

System sensitivity is a major issue. We even reduce the effective detector sensitivity by eliminating Compton-only events in the detector to reduce the contribution of scatter events. It has been shown that the signal-to-noise characteristics of a breast PET scanner could be maintained with only 2/3 of a complete ring, if timing resolution was 300 ps.[16] Thus, we can expect a huge gain in signal-to-noise in case of 10 ps time resolution.

All available materials that may allow time resolution values of 10 ps come with a low interaction probability and very low photopeak fraction. Consequently, the 10 ps TOF-PET system will need to consist of a large sensitive volume, segmented into smaller detection elements to maintain time and spatial resolution. We need to think about giving up on the idea of photopeak detection and weigh the gain offered by 10 ps TOF imaging versus energy information. Maybe the scatter contribution in reconstruction-less image generation is less of an issue? Joint estimation of emission and attenuation distribution in TOF-PET has been studied before.[17,18] This may also offer new directions in estimating scatter contribution.

CONFLICTS OF INTEREST

Dr. Schaart and Dr. Ziegler have no relevant conflicts of interest.

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