

## RETHINKING POSITRON EMISSION TECHNOLOGY FOR EARLY CANCER DETECTION

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Current PET technology, which detects cancer indirectly by measuring the size of tumors, is contrasted with a new technology that emphasizes measuring directly the abnormal metabolic activity characteristic of the very first cancerous cells by improving the efficiency of the medical imaging device hundreds of times. Rather than maximizing spatial resolution, this approach minimizes the abnormal metabolic threshold needed for early cancer diagnosis. A redesigned detector assembly takes full advantage of innovations in electronics to implement real-time algorithms that allow the use of economical crystal detectors. The tradeoffs inherent in choosing components, such as crystals, sensors, and electronics, for achieving the largest reduction in cancer deaths is discussed and justified. Theoretical calculations and prototype data are provided in references that demonstrate that all this can be achieved at a significantly lower radiation dosage and per exam cost to the patient.

### 1. Introduction

Positron Emission Technology is a non-invasive imaging method to obtain *quantitative* biochemical and molecular information of abnormal physiological processes in the body. In order to make the best use of this technology, it is important

- to accurately measure and count, within a given time, the maximum number of signals (pair of photons) related to the physiological functions of interest (HEMODYNAMICS: blood flow, blood volume, perfusion; METABOLISM: glucose, oxygen, amino acid, etc.; RECEPTOR FUNCTION: transporter/receptor of benzodiazepine, receptor of opioid, estrogen, etc.; MOLECULAR MECHANISM: DNA synthesis, etc.);
- to display the information in a meaningful way to the physician.

Current PET and PET/CT devices, however, capture only 1 out of 10,000 signals emitted from the tracer, and do not accurately measure their characteristics. They focus on measuring the dimensions of already formed tumors, instead of accurately measuring abnormal metabolism. This misuse of

the principle of operation of positron emission technology does not provide the information on metabolism needed by the physician. Even if current PET is modified to provide photon counts within a given time, the information is meaningless because the efficiency is too low.

## 2. Rethinking Positron Emission Technology for early cancer detection

In order to use Positron Emission Technology effectively for early cancer detection, a paradigm shift is necessary. To illustrate this, I am going to compare objectives, specifications and implementations of current PET, “Type A,” and the new technology, “Type B.” Type B makes use of innovations [1], [2] and has been implemented in a device called 3D-CBS [3].

The starting point for this paradigmatic shift must be the “Social Objective.” For Type B, it is to reduce cancer deaths through screening, early diagnosis and removal of the very first cancer cells. For Type A, it is to measure the shrinkage of tumors in order to justify the use of drugs, but in most cases does not save lives (as confirmed by the unchanged death rate). In some cases, it prolongs life for a few months at a high cost in suffering.

The specifications for the PET Type A and Type B (3D-CBS) follow from the social objectives. These specifications are compared in Table I.

Table I. Specifications for PET of Type A and Type B

| <b>Type A prioritized for profit</b>  | <b>Type B prioritized for the patient</b>  |
|---|--|
| <ul style="list-style-type: none"> <li>• Low cost of manufacturing the machine is important for maximizing profit</li> <li>• Optimized for measuring spatial resolution (to measure the shrinkage of a tumor for drug usage purposes)</li> <li>• Low efficiency (for the same reason as above, only measuring tumor shrinkage)</li> <li>• High radiation dose deemed acceptable as it is only for seriously ill patients</li> <li>• Long examination times (more than one hour to acquire data from 140 cm)</li> <li>• High cost of the examination (due to long exams times and high radiation dose) deemed acceptable as seriously ill patients or their insurance will pay. Competition could be sustained by playing on the following parameters: higher radiation dosage to the patient, scanning a smaller section of the body, recording fewer data which allow detection of tumors at an advanced stage only</li> <li>• Short detector is less expensive but results in long exam times and low efficiency</li> </ul> | <ul style="list-style-type: none"> <li>• Low cost of the examination (achieved by lowering radiation dose, and examination time) necessary for repetitive exams on ill patients and annual exams on asymptomatic patients, and they or their insurance will pay</li> <li>• Low radiation dose and short examination times (about 4 minutes) necessary to allow screening and repetitive exams on ill patients</li> <li>• Very high efficiency (able to count more photons, detect the very first cancerous cells and preempt metastasis)</li> <li>• Optimized for measuring sensitivity (same reason as above, preempting metastasis)</li> <li>• Long detector is more expensive but results in short exam times and higher efficiency because it acquires many data points simultaneously from the entire body</li> <li>• Higher cost of the machine is acceptable if it is sufficiently more efficient</li> <li>• Short time to recoup investment (because more patients can be examined per day)</li> </ul> |

Although a Type B machine has a higher initial cost, calculations show it will be advantageous in operating costs and it will take a shorter time to recoup the investment because it has the capability to examine more patients per day (see more details on page 160-165 of reference [4]).

Next, considering the constraints set by the objectives and the specifications, the details of the implementation can be defined. Table II describes these for Type A and B machines in terms of design implementation.

Table II. Implementation of the specification for PET of Type A and Type B

| <b>Implementation of Type A PET</b>  | <b>Implementation of Type B PET</b>  |
|--|--|
| <ol style="list-style-type: none"> <li>1. Reuse as much of existing technology as possible to maximize profit.</li> <li>2. Satisfy the expectations of the current market.</li> <li>3. Use nearly ideal, although costly crystals, especially if your company has a patent on that crystal.</li> <li>4. Continue to use the current “block detector” assembly to keep development costs low (although limitations in efficiency of such assembly have been determined experimentally by Andreaco [5], twelve years ago).</li> <li>5. Continue to use electronics with limited performance, with no communication between neighboring electronic channels, to keep production costs low.</li> <li>6. Use a short detector since, for the current detector design, sensitivity increases linearly with detector length.</li> <li>7. Do not try to reduce radiation for the safety of the patient (to less than 100 mrem required for annual screening) because the current design using a short detector cannot capture oblique photons at large angle making it impractical for screening anyway.</li> <li>8. Display pretty pictures (as close as possible to fine-grained photos) for marketing purposes and for showing tumor shrinkage, but not able to show minimum abnormal metabolism.</li> <li>9. Increase sensitivity only to acquire the data more quickly for making pictures so more patients can be examined.</li> </ol> | <ol style="list-style-type: none"> <li>1. The implementation must be completely different from the current PET.</li> <li>2. A new, different market is envisioned.</li> <li>3. Find the most cost effective combination of low cost crystals, sophisticated electronics, and detector length that meets the safety and exam cost requirements for annual screening and for a safe, repetitive exam on ill patient.</li> <li>4. Eliminate the “block detector” [6], assembly to allow hundreds of times greater efficiency improvements necessary to meet the objectives.</li> <li>5. Build sophisticated electronics that enable more efficient use of low cost crystals to detect and accurately measure all characteristics of as many photons as possible.</li> <li>6. Increase detector length since sensitivity increases exponentially with detector length for the 3D-CBS design.</li> <li>7. Do what is necessary (longer detector, capturing oblique photons at greater angle and more accurately) to lower the radiation dose to that permitted for annual screening.</li> <li>8. Display the information to the physician in a way that clearly shows abnormal metabolism. It must be easy to interpret, using color codes or symbols, but also provide precise numbers.</li> <li>9. Increase sensitivity to provide metabolic (nutrient flow rate) information necessary for early cancer detection.</li> <li>10. Capture accurately 1 out of 25 photons instead of 1 out of 10,000 captured by current PET. Use a detector assembly with no boundary limitation, a 3x3 algorithm for better spatial and energy resolution and a high computing power on each channel for best DOI measurement.</li> </ol> |

The innovative technology described in more detail in references [1], [2], [3], [4], has been developed to build a cost-effective Type B PET that finds its realization in the 3D-CBS. The key innovations are in four main areas:

1. Increasing the length of the detector (Field of View)
2. Improvement and simplification of the detector assembly
3. Innovations in the electronics which enable other innovations in:
  - a) executing precise algorithms for photon identification
  - b) accurately measuring the impact point and energy of oblique photons
  - c) reducing the initial number of the electronic channels, and
  - d) simplifying the method for identifying events in time coincidence
4. Innovation in the visualization of the information obtained

The synergy of coupling several innovations, such as the detector, sensors and the electronic system, enables execution of real-time algorithms for more accurate photon identification and allows a staggering increase in efficiency.

Figure 1 shows the clustering (see right in figure) that can be obtained when a simplified/improved detector assembly is coupled to the programmable electronics called 3D-Flow [1]. This allows the extraction of all characteristics (energy, “x”, “y”, “z” location, etc.) of the incident photon with the detector, and enables using economical crystals and capturing more photons [2].

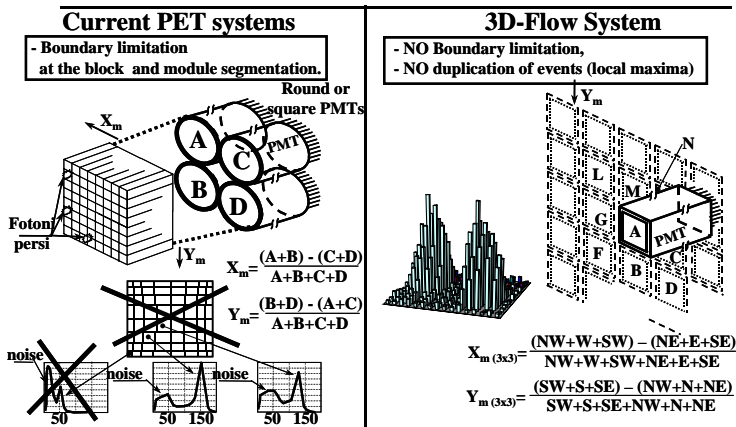


Figure 1 - Comparison between the signals obtained by the 2x2 PMT assembly (left) in current PET and clustering made possible with the 3D-Flow architecture (right) which allows centering a “cluster” (or trigger channel) on any electronic channel of the detector.

### 3. Current prospects for future Type A PET development cannot significantly reduce cancer death with early cancer detection

Why continue to build Type A PET when it misuses the principle of operation of positron emission technology and does not serve the need of the patient as its first priority? The specifications of current PET show sensitivity is

not considered important. Articles in scientific journals also confirm this trend for the future. Table III reports parameters extracted from the IEEE, 2003 article “NEMA NU2-2001 Guided Performance Evaluation of Four Siemens ECAT PET-Scanner” 0-7803-7, 2003, IEEE.

Table III The trend in development of Type A PET shows sensitivity has gotten worse over time.

|                                       | <b>Siemens/CTI PET and PET/CT Models</b> |              |              |              |
|---------------------------------------|--|--------------|--------------|--------------|
| YEAR                                  | 1992                                     | 1996         | 2000         | 2003         |
| Model                                 | EXACT                                    | HR+          | ACCEL        | EMERGE       |
| Detector Material: Crystal            | BGO                                      | BGO          | LSO          | LSO          |
| Crystal Dimensions (mm <sup>3</sup> ) | 6.75X6.75X20                             | 4.05X4.39X30 | 6.45X6.45X25 | 6.45X6.45X25 |
| Number of Crystals                    | 9216                                     | 18432        | 9216         | <5000        |
| Detector Ring Diameter (cm)           | 82.4                                     | 82.4         | 82.4         | 82.4         |
| Detector Length FOV (cm)              | 16.2                                     | 15.5         | 16.2         | 16.2         |
| Tangential Resolution (mm)            | 6.06                                     | 4.81         | 6.63         | 6.25         |
| Radial Resolution (mm)                | 6.38                                     | 4.97         | 6.14         | 6.63         |
| Axial Resolution (mm)                 | 6.25                                     | 5.22         | 6.49         | 6.52         |
| <b>Sensitivity (cps/MBq)</b>          | 5982                                     | <b>6650</b>  | <b>6362</b>  | <b>2259</b>  |

The patient is definitely not the priority if sensitivity is reduced from 6650 cps/MBq referred to 1996, to 6362 in the year 2000, to be even further reduced to 2259 cps/MBq in 2003. Over the past 10 years of submitting funding proposals for Type B PET, I have constantly been asked to modify my proposal towards building a Type A PET. Instead, my innovations enable the implementation of a PET of Type B, (or 3D-CBS) with increased sensitivity and emphasize directly measuring the abnormal metabolic activity characteristic of the very first cancerous cells by improving the efficiency of the medical imaging device hundreds of times, but it has been blocked for a decade. The book in reference [4] and the slides presented at the Conference, provide more details about my innovative technology, its proof of concept in hardware and the engineering of the concept into hardware for an industrial device.

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