Report of the Open Review of the Three-Dimensional Complete Body Screening Device (3D-CBS)

Held: July 1st, 2003

This is the report of the Local Committee, webcast participants, and experts in the field who have studied this project during the past years, who were charged to review Dario Crosetto's innovation, the 3D-CBS device.

This review was convened to validate, or refute, Crosetto's claims that his approach will capture over 400 times the number of photons in time coincidence than the current PET captures, with more accurate time and energy resolution, in a cost-effective manner, thus greatly improving PET accuracy and its benefits to the population. Therefore committee members were asked to find and point out any errors in his approach, provide constructive criticism and advice where appropriate, and recommend or oppose implementation.

Historically, too long a time has often elapsed before an innovative idea is recognized and its development is supported to usefulness. People are understandably cautious about radical new ideas, especially ones that claim improvements of two or three orders of magnitude. That is why this review was necessary; if no significant errors are found in Crosetto's calculations, and he can show that the 3D-CBS can be implemented with current technology, then skeptics should be open to progress even if it seems revolutionary.

This report comprises a list of committee members, the purpose of the review (Page 2), summary and conclusions (Page 2), the proof of concept and full simulation presented at the review (Page 4), a collection of comments and questions from reviewers and webcast participants during the review (Page 12), and comments from reviewers received after the review (Page 16).

Attachment A (Page 18) reports committee charges and procedures, the agenda for the review (Page 19) and the agenda of Crosetto's presentation "Why the 3D-CBS?" (Page 20). Attachment B (Page 21) reports comments and questions from people who have studied the 3D-CBS in the past and opinions from Siemens, GE, and others. There are also references to several papers containing details of the 3D-CBS and its proposed advantages (Page 27). (Page numbering cannot be seen in HTML, only pdf)

Local Committee:

Paul Bartholdi, Senior Physicist, Observatory of Geneva, Switzerland
Robert Burns, Oncologist, Doctors Hospital, Dallas, Texas
Frank Guy, Senior Physicist (Chair)
Paul Jerabek, PET Division; Chief, Research Imaging Center,
University of Texas Health Science Center, San Antonio
Jerry Merryman, 30 years of experience at Texas Instruments, co-inventor of the hand held calculator
Vernon Porter, 25 years of experience at Texas Instruments, Research Associate at U. of Texas, Dallas
Ruben Sonnino, Senior Executive at ST Microelectronics, one of the world's largest
semiconductor manufacturing companies
Kalpathy V. Venkatesan, Oncologist performing PET clinical studies at Patients Comprehensive
Cancer Center in Dallas, Texas

Purpose of Review

Because vague, unspecific and unsupported comments or criticisms (such as have been received in the past) are generally useless for improving either the 3D-CBS or its presentation, a questionnaire was submitted to the reviewers. The questionnaire was designed to elicit useful specific questions, comments and criticisms so that the information gained could be used to improve the system, develop a better presentation, answer questions that might be raised by investors or users, and correct any errors that might be found. The questions were divided into five groups:

- Efficiency for current PET
- Efficiency for the 3D-CBS
- Advantages of the 3D-CBS
- Cost Effectiveness
- The Impact of the 3D-CBS on Health Care

Each of these groups had specific statements or questions that the reviewers were asked to answer, usually with a "yes" or "no" signifying whether or not they agreed with the calculation or data. If reviewers did not agree with the presented statement or datum, they were asked to state why. This unusual approach was taken not to lead or pressure the reviewers, but so that any disagreement could be explored in detail to gain the maximum amount of useful information from the review and to settle any questions in the reviewers' minds.

Summary and Conclusions

The consensus of the reviewers is that the 3D-CBS can become an extremely valuable addition to health-care imaging technology and can lead to great improvements in early detection of cancer and other ailments, as well as becoming an important research tool. Crosetto has done an excellent job of implementing his ideas and in designing the electronics, given his limited economic resources. No error or fault could be found with his claims for the expected performance of the 3D-CBS. However, while substantial price reductions may eventually occur, both the reviewers and Crosetto agreed that they would likely be driven by competition. The technology improvement will at the beginning either give a greater profit to the manufacturers owning the rights and the users operating the 3D-CBS, or will allow them to sustain a greater examination price reduction. More study is needed here.
During the review, a demonstration was presented showing the hardware that has been developed and constructed. A full simulation of the electronics was shown. Plans for construction of the final parts of the prototype 3D-CBS were discussed. Together, these constituted a Proof of Concept to show that the 3D-CBS could be built in a cost-effective way and would function as predicted. Details of this proof are given in the following section, comprising:

1. Innovations: This explains the three key innovations that allow PET efficiency to be improved over 400 times. They are a) the electronics, b) the detector assembly, and c) the synergistic combination of these two.
2. Full simulation: The entire simulation of a 3D-Flow™ system was presented to the reviewers.
3. Implementation: This explains what has been built to implement the concept in FPGA on two prototype boards. These boards, that would cost hundreds of thousands of dollars each to develop according to normal industry design methods, were developed and constructed for $20,000 each by Crosetto using an extremely cost-efficient design method.
4. Plans for completion of construction: The main parts of the 3D-CBS have been designed and/or built to prove the feasibility and cost-effectiveness of the machine. Crosetto intends to purchase most of the remaining components off-the-shelf and to subcontract the construction of the electronics and the other parts that he designed and built for a few units. Thus the

hundreds of times PET efficiency improvements are a fingertip away and mainly depend on availability of funding.

One of the reviewers, with many inventions to his credit, summed up his impressions: **"I have seen many technological advances during my career and it was always impossible at the beginning to anticipate every possible benefit and use of the advance. The same must be true in this case – There will be far larger value to this than has so far been listed."**

The reviewers agreed that every effort should be made to bring this technology to fruition so that the medical profession, investors, and above all, the people, can benefit. Skeptics and investors must be shown the progress that has already been made; convincing arguments are shown in above sections 2 and 3 and in the following Proof of Concept. Resources must be found, and the reviewers thought that it was a good idea to place 3D-CBS machines in hospitals for evaluation. No technical or ethical reasons for further delay were raised. Of course if there are additional concerns, Crosetto is available to answer questions.

One reviewer, an expert in costs for implementation of the development of new electronics, stated:

"I am impressed by the level of quality of the work performed by Dario Crosetto in the various areas of the 3D-CBS, despite his limited economical and manpower resources. If I take for example the "photon detection board" that he built, I was impressed that Crosetto designed and build it with only $20,000 per board in 20 full programmable very large FPGA. In my experience in the industry the design, development, construction and debug of electronic boards of this magnitude and complexity is normally the work of a team of engineers costing hundreds of thousand of dollars, Crosetto did it all by himself achieving the objectives. Building the prototype board in FPGA was the right approach enabling, in the future, to an easy coast effective migration to a considerable lower cost board using "Hard Copy" or ASIC technology.

"After following Crosetto's work for quite sometime, I came to realize that what he claims, although sometime it is a very unknown and a risky novel approach, such as the challenge of routing the connection of 20,000 pins in only 8 PCB layers of an IBM PC board, turn to be feasible. He delivers what promise, and the quality of his work follows the most stringent requirements, and satisfies the highest quality in terms of using the most advanced technology, reliable tools, manufacturers and assembly techniques during its implementation.

"I am convinced that Crosetto can complete the job and get a lot of valuable products from any funding from investors or donors and use the funds effectively without too much overhead cost."

Proof of Concept and Full Simulation Presented to the Review
And Construction of the Final Parts of the 3D-CBS

Besides the material supporting his claims provided to the reviewers (see reference [1], [6], [2]and Attachment A), Crosetto described the conceptual sections of his inventions in a single figure (Figure 1, that was included among the materials provided to the reviewers, see reference [3]), and one reviewer summarized those concepts in the following paragraph:

"This novel technique provides better images in a shorter time with less radiation to the patient. A primary means of accomplishing this is the use of more detectors to cover a larger solid angle, but this requires a new electronic technique capable of handling the increased data rate and allowing a more efficient use of economical crystals in the detector. A novel electronic technique, combined with an improved/simplified detector assembly are the principal features of Crosetto's invention."

Furthermore, simulation and hardware were demonstrated to prove the concepts and the construction of the final electronics. These show that the 3D-CBS is feasible and cost-effective.

1. Innovations allowing improving of PET efficiency by a factor greater than 400

1.1. Key innovation of the electronics

Concept:
The concept of the 3D-Flow™ parallel-processing architecture that enables execution of a complex real-time algorithm, calculating different types of depth of interaction with zero dead time, and with data exchange with neighboring processors for a time longer than the time interval between two consecutive input data, is explained in several documents [4], [5], [6] (see also U.S. patent No. 5,937,202). This provides better energy measurement, which helps to reject scatter events more efficiently, and provides a way to improve spatial resolution by measuring more accurately the location where the incident photon hits the detector. It also increases sensitivity in accepting oblique photons by eliminating the parallax error in accurately measuring the depth of interaction. One of the key algorithms that can be changed for different detector types having crystals with different decay times is described in figure 34 at page 53 of reference [6].

This report shows how this concept was simulated and its hardware implementation was shown working flawlessly in hardware in FPGA. The concept of digital processing versus analog processing is shown in Figure 33 of [6]. Another aspect of the invention is the way these concepts are implemented in hardware; the way the North, East, West, and South (NEWS) connections are implemented on IBM PC boards or designed to be implemented in VME boards. This practical implementation is not only a concept, but now the IBM PC implementation with the NEWS information exchanged via flexible printed circuits is a reality that shows feasibility and cost-effectiveness (see description below).

Advantages compared to current technology:
The limitations of current technology are shown in the performance of the features and measurements reported by third parties at http://www.itnonline.net/, by the PET manufacturers, and in articles [7], [8]. The key measurements made by the PET manufacturer CTI, that show the limitation of current electronics in detecting photons at the edges and corners of a 2x2 PMT, are shown in [9].

Reference in the documentation, presentation, and discussion of this review:
See slides 26, 65, 66, 67, 68, 69, and section 4 of [6], Figure 34 of [6]. Time 01 hours, 11 minutes, 10 seconds and the 2x2 PMT algorithm at time 02 hours, 11 minutes and 00 seconds of the video of the review available on the web [10].

1.2. Key innovation of the detector assembly

The key innovation of the detector assembly is the construction of one or a few large cameras versus hundreds (or thousands) of small cameras, such as are used in current PET.

Advantages compared to current technology:
More details of the assembly of the detector, such as making equal length cuts (or no cuts) with reflecting material between crystals versus cuts of different lengths as implemented in current PET, are (described in [4], [6]). Those simplify assembly, lower the cost and increase the efficiency of the detector when used with the new 3D-Flow™ electronic architecture.

Reference in the documentation, presentation, and discussion of this review:
See slides 69, 70, and Appendix C.4 of [6], Figure 31 of [1], presentation and discussion in the video at 01 hours, 17 minutes, 00 seconds.

1.3. Key innovation of the synergistic combination of the two above

1. The 3D-Flow™ parallel-processing architecture allows the execution of complex algorithms with neighboring signals correlation in real time and provides the capability to extract more accurate information from the signals generated by the interaction between the incident photon and any type of crystal detector, allowing the use of more efficient economical crystals.
2. The coupling of the detector with the electronics is made in such way that there are no boundaries or fixed detector segmentations; rather, each sensor of the detector (PMT, APD, etc.) is an element of a large array with the capability to act as the center of a cluster of elements, all providing information.

Advantages compared to current technology:

1. A more sophisticated, powerful, digitally programmable electronics, implemented in a way made simple by an optimized placement of the components (such as over 20,000 pins routed in only eight layers of signals), and by the assignment of the signal to the pins of the components, permits more efficient use of economical crystals.
2. The one-to-one mapping of the detector array with a single array of electronic processing channels allows elimination of the inefficiency of current PET in capturing fewer photons, less accurately at the edge and corner of each of the hundreds (or thousands) of small cameras or at the edge of detectors with fixed segmentation.
3. The simplified architecture of the electronics and detector assembly allows expansion of the length of the PET detector without an exponential increase in the complexity of the electronics, as the architecture of current PET would require. This new architecture also allows the capture of more oblique photons with a simple, cost-effective electronics and results in greater uniformity of the image across the FOV.

Reference in the documentation, presentation, discussion of this review:
See slides 25, 26, 27 (at video time 00 h, 39 m, 00 s) 56 (at video time 01 h 06 m, 26 s), 69, 70 at 01 h, 17 m, 00 s) and Section 8 of [6], presentation and discussion in the video.

2. Full simulation of the concept

The entire simulation of a 3D-Flow™ system with an array of 12 x 12 electronic channels was shown to the review panel.

1. A file with typical patterns of data received from a detector array was sent to the input of the electronic array.
2. The simulator executed and showed the status of the calculation at each step at each processor node of the system. See slide 57 and video at time 01 hours, 08 minutes, 49 seconds.
3. The windows of the simulator could visualize any section of the 3D-Flow™ system, from the single three-dimensional array of processors in one window, to any portion of the array in different windows, to any details of any circuit in the system. See slide 57 and video at time 01 hours, 08 minutes, 49 seconds.
4. The flow of the data could be followed from the entry point of the system to the exit point.
5. Calculations of each step could be verified manually. The exit point provided information on the screen and on a file of the spatial ID, time-stamp, and energy of the cluster found that passed the criteria of the photon detection real-time algorithm as described in Figure 34 of [6].
6. Values of the internal units of each 3D-Flow™ processor could be displayed. The binary value of each pin of each component could be displayed and saved on a file. This binary value could be compared with the more detailed simulation from the Model Sim simulator in VHDL.
7. The results of the photons found not only proved the feasibility of the photon detection algorithm, but also the second section of the 3D-Flow™ system which routes the information consistently through different paths to fewer exit points, thus performing the channel reduction, was shown. The results of the photons found were then available at fewer exit points (compared to the number of input channels) with the complete information of spatial ID, time-stamp, and energy of the photon found. See slide 57 and video at time 01 hours, 08 minutes, 49 seconds.

3. Implementation of the concept in FPGA on two prototype boards

The proof that the 3D-Flow™ architecture is feasible and has the capability to execute a complex real-time algorithm with zero dead time, and with data exchange with neighboring processors for a time longer than the time interval between two consecutive input data, has been shown to the reviewers to be working in Altera® FPGA hardware with the following experimental setup.

1. Two boards, each with an Altera® FPGA (see www.altera.com) with over 1.7 million gates accommodating the circuits of four 3D-Flow™ processors are connected in cascade mode to implement two layers of the 3D-Flow™ system. The four processors on each board have the connection of the North ports with the South ports, and the West ports with the East ports.
2. One input board, which is connected to the input of the first board with the FPGA, has two sets of four 8-bit switches that allow the user to set two sets of values simulating the data received from the sensors (PMT or APD) of the detector at time zero and at time zero + 1.
3. One output board, which is connected to the output of the second board with FPGA, has two sets of four 8-bit LEDs that allow the user to visualize the result of the execution of the real-time photon detection algorithm (see Figure 34 of [6]). One set of four LEDs shows the results obtained from the execution of the algorithm on the first FPGA chip for the input data pattern at time zero and the second group of LEDs shows the result of the execution of the algorithm executed on the second FPGA chip for the input data pattern at time zero + 1.
4. Data are flowing through the 3D-Flow™ parallel processing system with point-to-point connections as described in the concept of the 3D-Flow™ architecture, which is set forth in U.S. patent 5,937,202 and in several documents [4], [6], and [1]. There is only one connection from the sensors to the first layer of the 3D-Flow™ system, a point-to-point connection between the two FPGA (representing 3D-Flow™ processors in different layers); and there is only one connection from the last layer of the 3D-Flow™ system to the output ports (the LED display in this case for

diagnostic purposes). All the arbitration of the flow of the input data and output results from processor to processor in different layers is achieved by the synchronous switching of the bypass switches internal to each 3D-Flow^{TM} processor.

5. The verification of the 3D-Flow^{TM} architecture concept is performed for a) the result of the calculation of the real-time photon detection algorithm by looking at the result values displayed on the two sets of four 8-bit LEDs, and b) the dynamic flow of the data through the system is verified by looking at the timing of the signals visualized on the oscilloscope.
6. The concept of the possibility to execute the real-time photon algorithm in a 3D-Flow^{TM} processor array is proven by verifying its execution in hardware and the result obtained on the LEDs of the experimental setup described above for each different input data pattern. For example, referring to Figure 34 of [6], if we set the values on the group of four switches (corresponding to four sensors at time T0) to the left thus: 20 on the top-left (C in section "n" of slide 26), 4 on the top-right (E in section "n" of slide 26), 6 on the bottom left (S in section "n" of slide 26), and 2 on the bottom right (SE in section "n" of slide 26), the expected result will be determined by the following calculation. Because of our connections North to South ports and West to East ports, after exchanging information with its eight neighbors, the processors at location C will have received the following information (see section "n" of slide 26): NW = 2, N = 6, NE = 2, W = 4, C = 20, E = 4, SW = 4, S = 6, and SE = 2. Because C is greater than its 8 neighbors, processor C will be determined to have found a photon candidate and the sum of its energy will be 48, which is the value displayed on the top-left LED of the left group of four 8-bit LEDs of the output board. The other three 8-bit LEDs of the same group will display zero because their inputs, having had lesser values than C, they are determined not to have found a photon candidate satisfying the real-time algorithm. At the same time a different pattern of values was set on the four 8-bit switches to the right of the input board (simulating the data from the same four sensors at time T0+1), and respectively: 20 on the top-left (C in section "n" of slide 26), 4 on the top-right (E in section "n" of slide 26), 38 on the bottom left (S in section "n" of slide 26), and 2 on the bottom right (SE in section "n" of slide 26). The expected result for this pattern will be determined by the following calculation. Because of our connections North to South ports and West to East ports, the processors at location C after exchanging information with its eight neighbors will have received the following information (see section "n" of slide 26): NW = 4, N = 20, NE = 4, W = 2, C = 38, E = 2, SW = 4, S = 20, and SE = 4. Because C is greater than its 8 neighbors, processor C will have found a photon candidate and the sum of its energy will be 98, which is the value displayed on the bottom-left LED of the right group of four 8-bit LEDs of the output board. The other three 8-bit LEDs of the same group will display zero because they did not find a photon candidate satisfying the real-time algorithm. This time the processor with value 20 will have received the following information from neighbors after exchanging information (see section "n" of slide 26). NW = 2, N = 38, NE = 2, W = 4, C = 20, E = 4, SW = 4, S = 38, and SE = 2. Because these values will not satisfy the photon detection algorithm of C being grater than all neighbors, this processor will abort the calculation (by executing a double branch which is shown on the lower signal of the oscilloscope). The other two processors will not find a photon candidate for the same reason.
7. The proof of the 3D-Flow^{TM} architecture concept is done by comparing the schematic of Figure 7 of U.S. Patent 5,937,202 (or a simpler description at Section 4 of [6], or table III, and figures 9 and 10 of [6]) with the timing relation of the signals on the oscilloscope or the video at hour 01, minute 55, and second 32. The top signal of the oscilloscope shows the arrival time of the data at the input of the first layer of the 3D-Flow^{TM} processors. The time interval between two input data is shorter than the execution time of the 3D-Flow^{TM} algorithm. Because of the data exchange with neighboring processors, the task cannot be split and executed into different units, as is done in classical pipelined architectures implemented in the instruction decoding/execution of a computer (or in an assembly line of a manufacturing company). This necessitates a parallel processing

system. However, when an application requires communication between neighboring processors, the physical implementation of a parallel processing system between different arrays of processors becomes difficult and impractical if a multiplexer is used to fan out from one input point to several parallel processing units as is typically done. This practical implementation problem has been solved as shown in the concept description of U.S. patent 5,937,202 and in the experimental set up shown in Slide 66 and in the video at 01 hours, 14 minutes, 03 seconds. In this implementation there are only point-to-point connections between different parallel processing units. The number of parallel processing units can increase almost indefinitely without incurring a problem of high fan out power dissipation, skewed because a fan out to a large number of components would have short and long connections, etc. The input data shown at the top signal of the oscilloscope are received only from the first layer of the 3D-Flow™ system. At the input of each 3D-Flow™ processor there is a FIFO that synchronizes the data flow and this, together with the data driven operation of each processor, allows good synchronization, enabling the execution of programs of different lengths or different execution times on each processor. Input data and output results are passed from layer to layer by means of the arbitration of a bypass switch on each processor. The second and third signal on the oscilloscope (see video at 01 hours, 55 minutes, 32 seconds) show the activity of one processor at the first layer and a processor at the second layer respectively executing the photon detection algorithm of Figure 34 of [6]. The "high state" shows the processor on "hold state" while during the "low state" the processor is executing the algorithm. The signal at the second line shows a longer execution time with a single branch operation indicating that the processor found a photon candidate, while the signal at the third line shows the execution of the algorithm on a processor at the second layer of the 3D-Flow™ system. The algorithm at this processor did not find a photon candidate, thus it aborts processing sooner and with a double branch gets ready to process the next data. Note that before the processor at the first layer ends the algorithm another datum arrives that is processed by the processor at the second layer. The number of layers is determined by the input data rate and the complexity of the algorithm. Because both parameters are known for each application, one can design a 3D-Flow™ system with the correct number of layers and processor speed that will cope with both of them, guaranteeing zero dead time.

4. Construction of the final components for the 3D-CBS

4.1 Overall design of the 3D-CBS:

As you can see from the following supporting material, the main parts of the 3D-CBS have been designed and/or built to prove the feasibility and cost-effectiveness of the machine. Crosetto's intention is to purchase most of the components off-the-shelf such as high voltage power supplies, photomultipliers, crystal detectors, etc. and to subcontract the construction of the electronics and the other parts that he designed and built for a few units. Thus the PET efficiency improvements by orders of magnitude are a fingertip away and mainly depend on availability of funding. No one was able to detect flaws in Crosetto's 3D-CBS system (see also references [11] [12]). The simulation, and the operation of the parts already built indicate that the system should work.

4.1.1. Physical layout

The physical layout of the entire 3D-CBS system is shown on slide 55.

4.1.2. Logical Layout

The logical layout of the entire 3D-CBS system is shown on slide 56.

4.1.3 Software for the development of new applications

The software suite called "Design Real-Time" includes 3D-Computing proprietary software of the 3D-Flow™ project to create a project, simulate, monitor and debug the hardware. It also includes third party software such as Model Sim from Model Technology and Quartus® from Altera® that is used to create and fully simulate an application (see slides 57 and 58) and then target it to a particular hardware for "System Monitoring" in real time during initialization and operation of the hardware system (see bottom box of slide 57 that includes the 3DF-SM and 3DF-HW).

Two of the important advantages of this approach are its scalability and adaptability to the latest technology or to the technology most cost effective for the production volume desired. This can be achieved because the entire design is in VHDL and C++, for a technology-independent implementation. Current design has been targeted to a fully programmable Altera® FPGA that can accommodate four 3D-Flow™ processors per chip. The same design can easily migrate to a future larger FPGA that will accommodate sixteen processors per chip (when sales volume will show a price advantage). It can migrate to a future more advanced FPGA, to "Hardcopy™" Altera® FPGA, or to ASIC as shown on slide 77. A typical application (see slide 57) consists of using the 3D-Flow™ processor IP (see center of slide) to design the real-time algorithm for a specific application with specific crystal detectors (see center of slide), to design the entire 3D-Flow™ system, to simulate the entire system and the details (see left of slide 77), and to compare the results of the detailed simulation of any chip of the system with the results obtained from the third party tools that have targeted the implementation to a specific hardware or component (FPGA, Hardcopy™, or ASIC) as shown on the right of slide 77. The Design Real-Time also can be used to create a Virtual Processing System (bottom left on slide) that can be tested by the "System Monitor" (center on the slide) through RS232 serial I/O ports before construction as was done and reported in [4].

4.2. Implementation of the 3D-CBS:

The experience gained from the experimental setup with the prototype boards described in Section 3, besides proving the concept in hardware, has provided essential information for proceeding with the construction of the IBM PC board to be used in series in the construction of the 3D-CBS. One of the most important results obtained is that the power consumption of an Altera® FPGA with four 3D-Flow™ processors is about 1.5 watts; thus a board with 17 chips and some ancillary logic will consume about 30 watts. This is the worst-case scenario, because the Hardcopy™ version of the Altera® FPGA is expected to consume 50% less. However, the information obtained will give confidence that designing an IBM chassis with a power supply distribution and capability to supply 50 watts per board with an adequate cooling system (as has been implemented) will certainly satisfy the requirements.

4.2.1. Photon detection board

Crosetto has shown (on the video at 01 hours, 11 minutes, 10 seconds) the details of the 3D-Flow™ DAQ-DSP photon detection board that he designed with Concept HDL (Cadence). He built the board for less than $20,000. A commercial autorouter could not route the layout, with connections of 2,211 components with over 20,000 pins, automatically in less than 16 layers, which is the limit for standard IBM PC board thickness. Crosetto solved the problem by placing the components in a particular location on the board and by a special assignment of the signals to the pins that would facilitate the routing, avoiding many vias and crossing connections. The board could then be successfully routed in part manually and in part with the autorouter in only eight layers of signals. Particular attention was paid to the power distribution, using six ground and power planes. He also had particular consideration for the clock distribution that was implemented so that two clocks correlated in phase are distributed from a single source to all components in different boards with a maximum skew of only 40 picoseconds between any two clock signals to the 3D-Flow™ processors in any place of the system. Crosetto has shown to the reviewers the layout of the board at different layers, in particular the power distribution and the clock distribution with traces of equal length to minimize the skew (see video at 01 hours, 04 minutes, 30 seconds, and slide top-left on slide 55, center of slide 56, and slides 65, 67, 68, and 69). The printed circuit (PCB) of the photon detection board was manufactured by one of the best companies manufacturing PCB for high-end technological applications. Crosetto purchased the components and/or received free samples and had the board assembled by one of the best companies using the most reliable processes (e.g. automatic pick and place of the components and temperature controlled soldering flow). Both companies are familiar with regulations needed to comply with electronics for medical equipment and have among their customers companies that manufacture medical equipment.

4.2.2. Coincidence detection board

The coincidence detection board is designed and ready for construction, it is only awaiting funding. The function of this board is to take the photon candidates that have been found by the 16-photon detection boards of Section 4.2.1. and identify those in time coincidence (within a user-selectable time interval as short as a few nanoseconds). See the description of the concept in Section 13.4.14 of [1]. The physical diagram of the board is shown at the center of slide 55; the logical function is shown on the right of slide 56.

4.2.3. ANIN board

An Analog Input board (ANIN) with four channels has been built. Now a sixteen-channel version with connectors that plug in as a daughter board to the 3D-Flow™ DAQ-DSP photon detection boards needs to be built. This 16-channel board has analog-to-digital converters and sixteen Constant Fraction Discriminator circuits that detect the arrival time, independent from the signal amplitude, of the photons at each electronic channel.

4.2.4. Flexible printed circuit for North, East, West, South communication

A flexible printed circuit carrying the Low Voltage Differential Signals (LVDS) between North, East, West and South ports of the processors on different boards, that can extend the 3D-Flow™ array to an infinite size, was designed and built as shown on the video. The connections are with 100-ohm matched impedance required for LVDS.

4.2.5 IBM PC chassis accommodating the electronics

The IBM PC chassis shown in the video at 01 hours, 14 minutes, 03 seconds and on slide 66 is of rugged and reliable construction with four redundant power supplies for the PCI connectors and an additional power supply for the external power connectors on each 3D-Flow™ DAQ-DSP photon detection board. It has three hot-swap fans 4.5" in diameter, four fans 1.5" in diameter, and one fan 3" in diameter. The backplane has 20 slots of which 18 will be used when the chassis is fully populated with boards. The power supplies and cooling have been dimensioned to satisfy with a large margin the requirements of boards using fully programmable Altera® FPGA. When the Hardcopy™ is used, the power consumption will drop considerably.

4.2.6. Detector

The components for a prototype detector arrived just before the webcast event on July 1st. Immediately afterward, Crosetto assembled the 16 photomultipliers (kindly provided by Photonis, France) with the crystal (kindly provided by Saint Gobain -Bicron - USA) enclosed in a container, as shown on slides 83. The High Voltage power supply (kindly provided by CAEN - Italy) and the detector worked immediately after assembly. The signals obtained from a Cs-137 source were shown on the oscilloscope and witnessed by the Chairman of the review after July 1st. See slides 01, 35, and 44 of the assembly of the detector.

4.2.7. Gantry

The gantry is shown in the video at 01 hours, 17 minutes, 54 seconds and on slide 71. Crosetto designed and built the gantry for the 3D-CBS in one month, working part time and spending only $5,000 in material. It is of rugged, reliable and safe construction. It is flexible, to accommodate a detector of circular geometry 16 cm in length, such as current PET, and allows an increase in length up to 1.8 meters. Besides the circular shape, it has the flexibility to accommodate detectors of different shapes such as cylindrical with smaller diameter for the head and elliptical for the torso. The upper section of the gantry has been tested to lift over 7000 lb pounds, almost five times the estimated weight of the portion of the detector to be lifted, which is about 1500 pounds).

4.2.8 Software for monitoring and troubleshooting during operation of the 3D-CBS

The software to monitor the 3D-Flow^{TM} electronics system is completed, including software repair routines that isolate problems such as a broken cable, processor, or component by loading into the processors that are neighboring to the malfunctioning cable or processor, a modified program that will not send data, or request data from that component. This will allow the system to operate even when some channels are out of service, postponing the hardware repair to when the hardware maintenance will be available. A broken channel in the 3D-CBS system with a long FOV, which normally captures more than 10% of the photons emitted by the patient's body, will still allow much better performance than a system with a short FOV, which detects only about 0.02% of the pairs of photons emitted through the patient's body.

Review Committee Comments

The following is a compilation of detailed committee comments and concerns that were written on the questionnaire. These comments can be used as background material and basis for guiding future work. All comments are not necessarily self consistent as some differing views were expressed. However, the chairman of the review panel asked for a last comment/explanation to Crosetto according to the rules spelled out in the procedure and then the entire comment was included in this report, unless the reviewer asked to omit it.

- **Efficiency for current PET**

Efficiency is defined here as the ratio between the pairs of photons in time coincidence detected by the instrument and the radiation activity in the patient during the scanning time. Efficiency was calculated for several factors, each of which contributed to the total efficiency. No reviewer disagreed with Crosetto's calculation of 0.01% to 0.02% total efficiency. For current PET technology, total efficiency was calculated from actual coincidence data and actual radioisotope doses. One reviewer calculated the efficiency to be 0.017%. Another made the comment:

"To the best of my knowledge, and after hearing the arguments on the subject in various discussions, I agree that the approach is right."

- **Efficiency for the 3D-CBS**

Reviewers agreed that the 3D-CBS efficiency would be about 10%.
Comments were as follows:

"The electronics have potential for providing a more efficient and more accurate means of detecting photons for PET applications."

"The format and the approach is correct. I can not speak for the exact % but the order of magnitude is correct."

The field-of-view contribution to the total calculated efficiency for the 3D-CBS was 95%, which was the ratio of the length of the detector to the patient's length, head to knees (normally, blood flow to the lower legs would be restricted during short examinations with O-15, water). Concerned that a fair comparison be made between machines, one reviewer commented, "95% only applies in comparing machines for full body scan." Of course the comment is correct. The 3D-CBS would normally be used in full-body examination mode, and would give the advantages of such examination, so the comparison is fair.

- **Advantages of the 3D-CBS**

Reviewers were asked if they agreed that the 3D-CBS approach provided advantages in sensitivity, spatial resolution, scatter rejection and algorithm complexity over current PET. Reviewers agreed with the claimed advantages, within the limits of their expertise. In this section, reviewers were also asked to grade the quality of the electronics. Some reviewers declined to comment on this portion of the questionnaire because it was outside of their area of expertise, but those who felt qualified to judge gave high marks to Crosetto's designs and construction. This comment was made:

"The working demo prove that the photon detection and FPGA are working fine (single board); his PC chassis looks of very good quality; the FPGA board looks simpler than expected for so many components and interconnections. Simplicity is the key to success!"

- **Cost Effectiveness**

This section generated considerable comment. Reviewers generally agreed that competition would drive patient examination price down as the 3D-CBS comes into widespread usage but noted that it was unclear just how much or how soon this price reduction would occur. Those reviewers who are familiar with the breakdown of PET pricing thought that Crosetto's estimate of $400 per exam was probably too optimistic; certain costs such as patient preparation, reading and evaluating results were unlikely to decrease much. Other costs such as facility, power, maintenance, radioisotope dose, and some personnel costs will certainly decrease as patient throughput increases. Some reviewers also questioned Crosetto's estimate of 30 patients per day; they thought 20 was a more realistic figure.
Comments:

Crosetto's comment: I agree that the examination price will be determined by the offer/demand and it may be much higher than the examination cost. The examination price will be lower as the competition increases. Please see how I calculated the operating costs of 14 cm FOV PET, 25 cm FOV PET and 147 cm FOV PET following criteria similar to the costs determined after more than 10 years of operation by the hospital in Zurich (Switzerland) and reported in the book [13] by Von Schulthess. Different regions in the world may have different costs for the same items. Please modify the costs that are more appropriate for your region and that you can support with evidence and recalculate the operating costs with those figures (I will appreciate if you could forward me your calculation and the supporting criteria you have used for your costs). I can be sure that the number you obtain will be lower than the examination price. The difference is the profit that hospitals, physicians, investors, etc., are making. It is expected to be higher when there are few 3D-CBS in the market and lower when the competition grows and will level them. So, this will be a big advantage for investors who will first support the 3D-CBS project and take the longer leap compared to the competition in being able to afford a much greater decrease in the examination price without losing money (or to make more profit during the initial period when the competition cannot have a device at as high a throughput and as good image quality as the 3D-CBS can provide)
Calculation of the operating costs: Please, see table I at page 1 of [6] and notes 10, 11, 12, 13, and 14 at page 7; and table X at page 28, notes 41, 42, 43, 44, 46, and 47 at page 28 of [6] and tables XII, and XIII at page 29. (If you think that I left out some costs that should be there, please write me an email and I will be glad to add those).
The following are the criteria/assumption used to calculate the operating costs. Please provide your input for any figure/assumption/criteria that you wish to correct in order to better reflect the costs at your facility (or region).

1. Capital amortization (over a period of 8 years). Assumed: $1M, for < 14 cm FOV; $2.2M for 25 cm FOV; and $6M for 150 cm FOV
2. Capital cost (5%). Assumed per year: $50K, for < 14 cm FOV; $110K for 25 cm FOV; and $300K for 150 cm FOV.
3. Service contract. Assumed per year: $60K, for < 14 cm FOV; $100K for 25 cm FOV; and $200K for 150 cm FOV

4. Upgrading. Assumed per year: $60K, for < 14 cm FOV; $100K for 25 cm FOV; and $150K for 150 cm FOV
5. Building. Assumed to cost $720,000
6. Personnel. Assumed to require ½ MD, 2 technologists/administrators for the < 14 cm FOV for 5 days/week for the < 14 cm FOV; ½ MD, 3 technologists/administrators for the 25 cm FOV for 5 days/week for the 25 cm FOV; 1 MD, 3 technologists/administrators for the 150 cm FOV for 5 days/week (Assuming MD salary = $200K/year and technologists/administrators = $50K per year)
7. Radioisotope FDG. The cost of the radioisotope is assumed to be the same of about $3,400/day for the three types of PET. (Although the 150 cm FOV PET requires less radiation per exam, the patient throughput is much greater so the total quantity of radioisotope per day can be the same using a conservative estimate).

(End of Crosetto's comment)

"3rd party payers don't want to pay for preventive health care; don't use the words 'preventive screening'."

Crosetto's comment: This statement is certainly true for many 3rd party payers but it is related to marketing and does not have a bearing in validating or invalidating technology that provides benefits in lower radiation, better image quality and lower examination cost. I may leave the decision to the marketing people what would be the best strategy, whether to open a new market for preventive screening or not. A good machine that provides the above benefits will sell itself.

"Lowered cost? Only cost that will be lowered initially will be the cost of the pharmaceutical radioisotope. Big advantage is increased number of tests per hour."

Crosetto's comment: This may well be the case initially, but please see at page 13 the calculation of the operating cost.

"Cost effectiveness will be driven by the success of the machine development, approval, marketing and long-term benefit."

Crosetto's comment: I agree that cost-effectiveness is related to volume. The more units are built, the cheaper manufacturing cost will be. However, there is a cost-effectiveness before that, which is related to how the machine is designed and which is much more important than the saving in volume production. For example, trying to build a PET with LSO with 1.5 meters in length will have an astronomical cost and there will be no capability to satisfy the demand of LSO crystals because there are not enough production facilities in the world. On the other hand, a PET with BGO or NaI(TI) 1.5 meters long with a simpler detector assembly, electronics that can extract more efficiently the information from the economical detector, and having approximately the same number of PMTs as a current PET 25 cm in length, can be called a cost-effective implementation.

"Higher throughput not necessarily will translate into lower cost of personnel. It will increase the throughput of the examination, but you will need more personnel in preparing the patient for the examination and the final reading and interpretation of the results. Some detailed analysis by the expert in this field is appropriate."

Crosetto's comment: please see the calculation of the operating costs. It is true that the cost of personnel in absolute figures per day (or month, or year) will increase (as is shown in my calculations in [6]). My statement was made in terms of personnel cost per examination.

- **<u>The Impact of the 3D-CBS on Health Care</u>**

To a statement that the 3D-CBS makes it possible to view images of biological processes as a streaming video, one reviewer commented: "Whether it makes it possible to view images as a streaming video instead of a still picture will depend on the reconstruction software – which was not addressed."

Crosetto's comment: Current PET cannot provide such functionality because the data are not captured simultaneously from the entire body. Even for an organ it is difficult to have a streaming video from current PET because their efficiency in capturing oblique photons is low and it will require giving too high a radiation dose to have enough statistics to run a video instead of accumulating photons for a static image. Computers are doubling their performance about every two years and there are rendering/animation/display programs that perform even more complex operations; note, for example, the reconstruction of an event in high-energy physics, or the animations made by the company Pixar.

Reviewers were asked to write down possible benefits of 3D-CBS technology that are not possible with current PET technology. The following comments were received:

"Lower dosage; better imaging; faster completion; simultaneity and correlation; possibly – lower cost. Overall comment: I have seen many technological advances during my career and it was always impossible at the beginning to anticipate every possible benefit and use of the advance. The same must be true in this case – There will be far larger value to this than has so far been listed."

"I believe that the front end electronics has potential for providing a more efficient and accurate means of detecting photons for PET applications."

"The zero dead time provided by the 3D architecture is very important. It permits powerful (new) algorithms to be applied without losing photons. The very good time resolution is also important, especially for research. Any <u>new</u> system as the 3D-CBS will certainly open new doors for health and research that we can not think of in advance. This has been proved on all occasions in the past when new instruments were developed. Just think about the first telescope of Galileo!"

Questions from the webcast participants during the review

Dr. Michele Barone from Demokritos Scientific Research Center in Athens, Greece, and member of the CMS collaboration at CERN asked a question on how much power consumption the 3D-Flow™ DSP photon detection board requires.
Crosetto's answer was that the current version shown at the review accommodates 17 large FPGA with 1.7 million gates fully programmable (PLD). It consumes about 30 watts. However, in the 3D-CBS unit, the "Hardcopy™" version of those Altera® FPGA will be used which will consume about 50% as much power as the PLD version. The board consumption will not drop to 50% because there are other FPGA that will remain in the PLD version. As a precaution, however, the chassis power supply and cooling system has been designed to provide and sustain twice the estimated required power consumption.

Responses received after the review

Reviewers were asked to send in any additional comments or questions by email after the review was over. These are the relevant comments that were received:

"…..the only reason I answered that question "No" as to why I felt that 3D-CBS would not lower the overall healthcare cost was because what happens most often when a technology is introduced, the new technology does not become a replacement test for the old test for some time because people are still getting familiar with the new test and during that time the radiologist is also recommending doing the old test first. To give you an example, when the CT scan was originally introduced it took some time for it to completely replace the nuclear liver spleen scan. So for some time, what actually happened was people were doing the nuclear spleen scan and then also doing the CT scan so instead of one test they were doing two tests for some time until the radiologist and the doctors became familiar with the technology. When familiarity was accomplished in say three or four years time, then the CT scan completely replaced the nuclear medicine scan to evaluate the liver and no one ordered the nuclear scans. Similarly, I suspect that when the 3-D PET scan is introduced, for a certain period of time people might not just do the 3-D PET scans immediately but might actually do a regular PET scan and then also do a 3-D PET scan. This is the reason why I answered that question in the manner that I answered saying that it would not lower the health care costs immediately but over a period of years when all the doctors and radiologist become familiar with the technology and much clinical research becomes available saying that it is a replacement test. Then, people will stop doing the old test and simply do the new test."

Crosetto's comment: This statement that sometimes oncologists and radiologists will request both examinations points out an important factor to keep in mind when planning the introduction of the 3D-CBS to the medical community. However, it does not have a bearing in validating or invalidating technology that provides benefits in lower radiation, better image quality and lower examination cost. For example when the Euro was introduced in Europe, billions of dollars were spent during the first months (years) by private industries and by the governments because of the learning curve and because of double accounting (old currency and the new currency), however, it was not a good reason to stop the change. Most of the time when there is a change, this creates a higher cost during the first phase. However, it is a poor reason for not having the change because otherwise there will never be progress.

"I really enjoyed the meeting and learned a lot about the 3-D PET scan and the various possibilities that it can offer. I am truly excited about the 3-D complete body scanner and I certainly feel that it would make a tremendous impact in the field of oncology once it has been introduced and people become very familiar with the use of this technique and clinical research has been done which bears out this data. Again, you had asked the question about the new possibilities for an oncologist from having the 3-D complete body scan and this would most certainly be a great help towards early diagnosis of malignancies which most often translates into cure for malignancies and that is why I feel that this technology ultimately will have a tremendous impact in my field."

"I believe that the front end electronics for the proposed 3D-CBS system represents a new and interesting technology to improve the sensitivity and resolution of PET relative to that which is currently available with existing systems. As Mr. Crosetto is well aware of, the improvement in PET scanner technology that has occurred over the past 20+ years has resulted in relatively small incremental improvements in these parameters using for the most part, derivatives of already existing technology. Indeed, probably the biggest technological improvement may be merely the increase in computing power available to handle the acquisition and processing streams associated with PET scanning. Hence, the 3D-CBS system has the potential to offer new technology that in the long run will benefit the PET industry. My only recommendation is to move forward."

"I am impressed by the level of quality of the work performed by Dario Crosetto in the various areas of the 3D-CBS, despite his limited economical and manpower resources. If I take for example the "photon detection board" that he built, I was impressed that Crosetto designed and build it with only $20,000 per board in 20 full programmable very large FPGA. In my experience in the industry the design, development, construction and debug of electronic boards of this magnitude and complexity is normally the work of a team of engineers costing hundreds of thousand of dollars, Crosetto did it all by himself achieving the objectives. Building the prototype board in FPGA was the right approach enabling, in the future, to an easy coast effective migration to a considerable lower cost board using "Hard Copy" or ASIC technology.

"After following Crosetto's work for quite sometime, I came to realize that what he claims, although sometime it is a very unknown and a risky novel approach, such as the challenge of routing the connection of 20,000 pins in only 8 PCB layers of an IBM PC board, turn to be feasible. He delivers what promise, and the quality of his work follows the most stringent requirements, and satisfies the highest quality in terms of using the most advanced technology, reliable tools, manufacturers and assembly techniques during its implementation.

"I am convinced that Crosetto can complete the job and get a lot of valuable products from any funding from investors or donors and use the funds effectively without too much overhead cost."

"I believe that D. Crosetto has done a remarkable job of synthesizing both novel and mundane advances in the quest for a high performance PET imaging device. He has analysed the problem areas in extreme detail and found a solution for each and every deficiency in the classic approach to PET design. As a consequence, I believe that the multiple improvements he has implemented will not just simply multiply but will form a synergism which will give even more benefit than calculated."

****

This concludes (except for Attachments A and B) the Report of the Open Review of the Three-Dimensional Complete Body Screening Device (3D-CBS), held July 1st, 2003. It has been a pleasure and a challenge to serve as Chairman of this Review Committee. I sincerely thank all the reviewers who gave their time and effort to this important task. We all hope and trust that this effort will result in a significant advance in medical imaging and will be of benefit to the medical community and, most significantly, to the many individuals – and their loved ones – who will benefit from early detection of cancer.

Signed

Frank W. Guy

Frank W. Guy

Attachment A:

Review of the 3-D Complete Body Screening (3D-CBS) project
July 1st, 2003. DeSoto, TX 75115

Charges to the Reviewers

Greetings and Introduction

Purpose of the Review

- Historically, too long a time has been elapsed between the formation of an innovative idea and its development to usefulness. People are understandably cautious about radical new ideas, and the greater the claim for improvement, the greater the skepticism. However, we all know that progress is not always evolutionary; sometimes it is revolutionary.
- Our job today is to reduce delay and hasten the acceptance of a groundbreaking new concept for a medical imaging machine, the 3-D Complete Body Screening. This idea is too important and too potentially beneficial to too many people, for unnecessary delay. Hospitals need it, doctors need it, investors need it, and above all the general public needs it. We consider this review a necessary step toward gaining timely recognition and implementation of the 3D-CBS.

Agenda of review:

- Overview: Motivation to develop the 3D-CBS; Concept: Benefits; Commercialization.
- Initial questions that you may have after the overview.
- Description of the equipment.
- Technical discussion and specific questions concerning each part or facet of the system.
- General questions and concerns, feasibility of the concept, and any specific questions that did not occur to you during the other sessions.
- Conclusions and assessments. Complete questionnaire.

Questionnaire

- We have compiled a list of questions and concerns that may be raised during the course of this review. These are presented in the questionnaire, and we would appreciate your careful consideration and comments on each of item.
- On the questionnaire items: If you have any comments, questions, disagreements, or concerns, that you feel have not been adequately addressed today, or feel that further explanation would be helpful, then please either bring this up during the conclusion session or write them down for a written response. Also, please bring up anything that you feel should be in the questionnaire, but has not been addressed.

Follow-up Timeline for the completion of the review

- July 1: Hand out questionnaire.
- July 6: If you need further time to formulate a question, read some references, or do some calculations or research, please do so and submit your comments and questions to Dario Crosetto by email (at Crosetto@att.net and copy to the Chairman of the review, Frank Guy, at: fglinac@azmail.net) on or before this date. Please do not raise any new issues after July 6; we should not stretch the dialog out indefinitely.

- July 7: Dario Crosetto will email answers to questions written on the questionnaires. (He will also send a copy to the Chairman of the review panel Frank Guy)
- July 11: Crosetto will email answers to questions submitted by email on or before July 6. (He will also send a copy to the Chairman of the review panel)
- July 15: Reviewers please email your recommendation to Crosetto by this date (please also send a copy to the Chairman). Please comment as to whether or not his answers to your questions were satisfactory. If unsatisfactory, please say why.
- July 21: First draft of panel recommendations compiled by Chairman of the review panel will be emailed to reviewers for your approval and comments, summarizing everyone's opinion and concerns. If you are unsatisfied with Crosetto's answers to your questions, your comments will be included, and Crosetto will explain further.
- July 28: Reviewers please send approval and/or comments on the draft to Frank Guy (at fglinac@azmail.net).
- August 4: Final draft emailed to reviewers.
- August 11: Release of reviewers' report

============ End of Charges to the reviewers and procedure =================

3D-CBS OPEN Review, Day Agenda (O = Open to; C = Closed)

- 9:00 Charges to the reviewers (C)
- 9:30 Introduction (O)
- 9:40 Why the 3D-CBS (O)
- 10:40 Q&A (O)
- 11:10 Equipment and Tools developed for the 3D-CBS (O)
- 12:30 Lunch
- 13:00 Specific questions on PET efficiency (where is the theoretical limit, how far are current PET from it, how close can we get to the theoretical limit) (O)
- 13:20 Specific questions on cost-effectiveness (FOV vs. machine cost, vs. examination cost, etc.) (O)
- 13:40 Specific questions on detector (O)
- 14:00 Specific questions on electronics (O)
- 14:20 Specific questions on testability (simulation, hardware) (O)
- 14:30 Coffee break
- 14:35 Specific questions on detector geometry mechanics (gantry) (O)
- 15:15 Specific questions on medical impact, benefits, and safety to the patient (O)
- 15:35 What has Crosetto built, what is needed to complete the 3D-CBS. Q&A. Any other issue/question (O)
- 16:00 Conclusions and assessments. Complete questionnaire (C)

Agenda of Crosetto's presentation: Why the 3D-CBS?

- NEEDS and MISSION: Defeat Cancer with early detection
- Need a medical imaging device at very high sensitivity, low radiation, good image quality, low examination cost. Solution: the 3D-CBS (Advantages)
- Visualize yourself in the future (Not too far, because the technology is here)
- Lost photons in current PET and PET/CT
- Limiting factors of current PET and distinctive innovative features of the 3D-CBS
- Who will want the 3D-CBS (the market)
- FDA Approval Procedure
- What is the best way to bring this invention to the public (in the shortest possible time and to the largest possible number)
- How Barriers to enter the market/roadblocks are overcome
- How to measure progress toward the mission from contributions by foundations/donors
- How to protect investors to get to a rapid and large commercialization of the 3D-CBS
- Advantages to all parties (Patients, Investors, Manufacturers, Insurance and Pharmaceutical companies, Government, Hospitals, and Doctors)
- Operating costs of the commercial version of the 3D-CBS. Amortization costs. Lowering health care costs.
- The product: Physical & Logical layout and the software for the 3D-CBS
- Cost of the 3D-CBS and when the donation of a unit can be made to a hospital
- Details of the 3D-CBS and its advantages
- A word of thanks to the following companies/foundations

Attachment B:

The following is a collection of documents (testimonials, facts, meetings, opinions, etc) from different experts who in the past have evaluated Crosetto's innovative technology that enables efficiency improvements of hundreds of times over current PET by building a new device that he terms the 3D-CBS.

Many people have had questions and concerns about Crosetto's inventions, which is understandable; Dr. James Ralph (BNL) has said that happens every time someone claims improvements of two to three orders of magnitude. However, no one in this case could point out flaws sustained by scientific arguments in Crosetto's design and implementation that would invalidate his claim.

A common statement that Crosetto received when he first set forth his new idea of improving electronics that would allow the use of economical crystals, simplify detector assembly and capture more photons more accurately, was: "…it is not necessary to extend the FOV because the largest organ is only 15 cm," or that it was not cost-effective because a few attempts made in the past showed that it was not advantageous economically and technically.

These negative reactions are shown to be mistaken by the fact that Crosetto's approach and design is being copied and a few people and companies are reversing their trends and going in the same direction. GE even announced on February 2002 a PET Discovery VI with 6 x NaI(TI) crystals in a hexagonal ring coupled to 570 PM-Tubes with 1 ADC per tube and an Axial FOV of 50 cm. The new product was announced on the web for some time at the beginning of 2002 and then was withdrawn. Now Hamamatsu has announced a new PET with 60 cm axial FOV. An executive scientist from General Electric wrote a message to a scientist at one of the largest international research center commenting: "…on excellent contribution which D. Crosetto is making to the field."

The answer to the problems encountered in the past by the people/companies who attempted to design and build a PET with a long axial FOV is here now. It is spelled out clearly in Crosetto's patent pending, and in his documentation available on publications and on the web. It has been explained during the OPEN review on July 1st, 2003. The proof that he has solved the problem of building a cost-effective PET with long FOV comes from the fact that previously, no one attempted to build it; while now, after his patents, books and published documents, it is possible to build it. One more thing; it shows that it would be worthwhile to provide funding to further advance his research, that is:

- His being tenaciously focused in pursuit of the goal of improving medicine for the benefit of the people, while recent history shows that during the past years many industries have lost sight of this goal and have been more driven by the bottom line than the good of society in general.
- His focus in building a machine that improves the image quality, lowers the radiation and lowers the examination cost by making use of more economical crystals and more sophisticated (but not necessarily more expensive) electronics and a simpler detector assembly, versus the traditional trend during the past decades (and still today) of improving only the crystal efficiency, without focusing on lowering the examination cost.

Above all, the fact that after two decades the industry followed one trend and now is changing to follow Crosetto's trend is a significant indicator of the worth of his ideas, and a good reason to provide a minimum funding to allow him to proceed with his PET advances for the betterment of health care. He has already achieved a great deal; he has finished or proven most of the technical advances, and there is very little doubt that the remainder will be just as successful. Now the concept must be fleshed out with an actual machine that will prove the major advantages of the 3D-CBS. The next step depends upon smart, compassionate investors or contributors that realize how much this machine will mean to the people and how great the benefits will be to those who help now. Government agencies such as SBIR, with the mission to fund people with ideas but with no capital, would have encouraged other inventors in the same situation if they could have recognized Crosetto's innovation before he had to continue to translate his concept in hardware with his own hard work and funding from friends and other sources.

List of statement/documents accumulated during the past years:

1. Meeting/review at 900 Hideaway Pl. DeSoto Texas on November 6, 2002 with Siemens President of Nuclear medicine Michael Reitermann and Director of the PET group Vilim Simcic

I (Frank Guy) was present during this meeting together with six other people. Crosetto presented his claims very clearly and supported them with scientific arguments, calculations, simulation and hardware demonstrations. As agreed by all the people present at the meeting, it was recorded on tape and it was also agreed in writing that Siemens would not provide to Crosetto any proprietary or confidential information.

The president of Siemens Nuclear Medicine, the director of PET, and subsequently the head of the Siemens advanced research Dr. John Engdahl and their expert on electronics, Dr. Fred Macciocchi in a following conference call on November 25, 2002, at which I was also present, could not refute Crosetto's claims and his comparisons with Siemens technology, calculations and findings.

Following are more excerpts from letters, emails and testimonials from other scientists during the past years:

2. General Electric:

- 1999: Dr. James Colsher and David McDaniel looked at Crosetto's novel approach of the electronics that he presented at the IEEE conference in Seattle (WA). Their opinion (followed with additional phone conversation with McDaniel) was that Crosetto's novel approach was good for the future but their plan would not allow them to consider it in the short term.

- 2000: Dr. Charles Stearns met Crosetto at the 3D-Computing booth at the IEEE industrial exhibition conference in Lyon (France). Crosetto gave him and Dr. William Moses, from Lawrence Berkeley Laboratory, who was also present at the booth, a copy of his book [1]. Stearns commented that the figure at page 150-151 in Crosetto's book, related to the GE patent, well described the GE implementation of the electronics in GE's PET.

- 2003: Email from GE executive scientist to a scientist in one of the largest international research laboratories states the following about Crosetto's work: "…Just to let you know, the GE team has very thoroughly reviewed the material published by Dr. Crosetto, not just now, but even earlier. The reviewers were technical folks who design PET systems, and PhD level scientists who have been working in PET imaging for over 15-20 years." He goes on to say that GE is not interested in pursuing Crosetto's approach for the near term but "This by no means is a judgment on excellent contribution which Dr. Crosetto is making to the field."

3. Dr. Dale Bailey was in the team who designed the whole body PET that became known as the CTI ECAT EXACT3D, the one with the longest FOV (25 cm) ever built.

- 2000, November, Dr. Bailey comments on Crosetto's book were:
"…I am pleased to see your proposal with its focus on improving solid angle for detection of photons, and thus the sensitivity. There are two obstacles that must be tackled to significantly advance PET technology – increasing sensitivity and reducing motion artefacts. Higher resolution PET will not result if these two issues are not addressed. Motion can often be suppressed, but not eliminated, by using a shorter scanning duration, and therefore increasing sensitivity will go some way to solving this issue as well. In short, I believe that improving sensitivity is the way to improve the value of PET. Improving sensitivity will impact on: resolution, motion, artifacts, patient throughput, data quality, detection ability." He also makes the following statement regarding spatial resolution: "…I believe that the brain images from this camera have not been bettered to this day, even though newer cameras boast higher resolution. My view is that the higher resolution is not achieved in practice because the devices have sacrificed sensitivity."

4. Dr. Stefano Buono, a physicist working between CERN (the European Laboratory for Particle Physics) and CRS4 (The Center for Advanced Studies, Research and Development in Sardinia) on Nobel Prize winner Carlo Rubbia's project of the 'Energy Amplifier', an Accelerator Driven System (ADS) capable of eliminating nuclear waste and producing clean energy. Dr. Buono's review of Crosetto's book [1] is also available at Amazon.com.

- 2000, August. Dr. Buono writes the following comments after reviewing Crosetto's book [1]: "…It is amazing how revolutionary inventions come from the capacity of putting together technological progress in different fields and a few simple but smart ideas. The final result looks "simple", "evident", but only "after". This is the case of Crosetto's invention which is in my view a real revolution: the possibility of transforming a PET scanner into a one year check-up tool is a real breakthrough in the battle again cancer and I wish it will be a reality as soon as possible. …. I really hope that this device could be developed as soon as possible regardless of the current economical practice in the industry of delaying the introduction of innovative tools to absorb investment costs. Our health is much more important!"

5. Prof. Alberto Del Guerra, Director and Head of the Speciality School in Medical Physics - University of Pisa, Italy, Chairman of the 1999 IEEE Nuclear Science Symposium and Medical Imaging, Seattle (WA).

- 2000, September. Dr. Del Guerra reviewed Crosetto's book [1] and wrote the following comments: "…In this book this new electronics architecture proposed is very interesting and can in fact solve some of the problems of limited DAQ rate in clinical PET systems. In particular, I would fully encourage the implementation of Application as described in chapter 16…"

6. Dr. Pier Giorgio Innocenti, former Division leader of Electronics and Computing in Physics (ECP) at CERN, Geneva, Switzerland. Dr. Innocenti has known Crosetto for the past 25 years. He was one of the CERN group leaders who invited and offered to Crosetto a position of "Scientific Associate" which he accepted from 1988-1990.

- 2000, November, Dr. Innocenti writes the following about Crosetto's book [1]:
  "… I have spent most of my professional life in the design, construction and use of detectors of ionizing radiation, primarily in particle physics experiments, both in the US and in Europe. …. Before commenting on Crosetto's proposal I wish to stress one of the essential features of a particle physics experiment. Modern accelerators produce dense beams of particles which interact with matter, generating a high rate of events: as each event consists of many particles, one has to treat up to hundred billion particles per second. In order to detect rare interesting events (one event in a thousand billions) one must be able to measure particles properties and to perform pattern recognition operations on groups of particles very quickly. This requires fast and advanced electronics and algorithms. Developments originating from particle physics can therefore be transferred advantageously to other fields, like medical imaging, to improve efficiency and quality, because they are capable of treating a vast amount of data in a short time.

  “Crosetto's proposal improves on previous PET techniques in three areas:

  i - It increases the input rate on each detector channel and stores subsequent events (pipelining) while the previous event is being processed: hence exposure time is reduced and no emerging photon pairs are discarded, thus reducing the radiation dose to the patient.

  ii - It correlates the signals from detectors within a large cluster: this provides a much more precise measurement of each photon, thus reducing event losses and improving efficiency.

  iii - It extracts the coincidence of the back-to-back photons with a far simpler algorithm: this permits the use of a large number of individual detectors to extend the field of view (FOV) over the patient.

  “In short, the proposed system will drastically reduce the radiation dose to the patient, shorten the scanning time and produce an image of improved resolution.

  “The design principles of the proposed 3D-Flow^{TM} system are sound and rest on Crosetto's long experience in electronics design and digital signal processing.

  “My perception of the proposal is very positive and I hope that the ideas will materialize in an instrument which is badly needed."

7. Prof. Stephen DeRenzo, Lawrence Berkeley Laboratory

- 2000, December, Dr. DeRenzo reviewed Crosetto's book. In his review, Dr. DeRenzo is mainly addressing the detector aspects of a PET device. Dr. DeRenzo agrees with Crosetto on the limited capability of current PET to capture only one pair of photons out of 10,000 emitted by the patient’s body. He stated: "… The main loss of events at high event rates is due to deadtime in the detector, not the electronics. That is why we are working on new scintillators with good stopping power, high light output, and sub-ns decay time. We do not view the electronics as a problem, either in terms of performance or cost." Dr. DeRenzo’s expertise in detector crystals is well known but he has apparently overlooked the contribution that Crosetto's innovative electronics approach can make. A different assembly of the detector, combined with Crosetto's electronics, can extract more accurate information from the interaction of the photon with the crystal; in particular it allows a better utilization of economical crystals. Current PET efficiency has already improved thanks to the improvement of the electronics and it will further improve when the best match between electronics and a different assembly of the detector is pursued.

8. **Dr. Habib Zaidi** is a senior physicist and head of PET physics and instrumentation group at Geneva University Hospital, Switzerland. Dr. Zaidi's review of Crosetto's book is also available at Amazon.com.

- 2001, January. Dr. Zaidi writes the following as a review of Crosetto's book [1]:
  "This book presents a proposal for a novel scanner design based on knowledge gained from the author's experience in the field of high energy physics that should allow faster data acquisition with less cost to health care organisations and radiation dose to the patient for cancer screening purposes. The use of the 3D-Flow™ electronics system which proved to be very useful in other areas and constitutes one of the major contributions of the author might be a sensitive solution for hardware design of medical imaging systems. The book is generally well written, unique ... amply illustrated with relevant and helpful diagrams as well as extensive bibliographies ... should be on the bookshelves of both researchers and students of nuclear medical imaging."

9. **Dr. Catharinus Verkerk** was appointed in 1980 by Nobel Prize winner Abdus Salam to be director of the Colleges on Microprocessors. Dr. Verkerk is still carrying on those Colleges and is a former, retired group leader of the Data Handling Division at CERN, Geneva, Switzerland. He has known Crosetto for the past 24 years and has included him in his team of lecturers and instructors at the College on Microprocessors. He invited Crosetto to give a lecture at the1990 CERN School of Computing in Ysermonde, Belgium.

- 2001, October, Dr. Verkerk writes in a letter commenting Crosetto's work:
  "… Your experience in instrumentation for these experiments, combined with your inventiveness, led you to a solution which can be called revolutionary. Your ideas as described in your paper looked perfectly sane, but as a retired physicist who also spent several years in instrumentation, I would like to be able to touch things with my hands. Therefore I was happy to see a few hardware boards under test. That you now can test to a reasonable extent your algorithms for reconstructing the point where the photons was emitted is an enormous step in the right direction."

10. **Dr. Joseph Dent** is Assistant Professor, Department of Biology, McGill University (Canada). He runs a lab of 6 full-time grad-students and research assistants.

- Dr. Dent writes the following comments on Crosetto's innovation and book [1]:
  "…Are claims of a quantum leap in efficiency sound? It is clear that much of the information available from PET measurements is lost using current detection technology and it is easy to see why this is the case. Thousands of photon pairs flying in opposite directions must be caught, measured and computationally reunited, all in real time, to generate the PET image. The current system simplifies this difficult task by only considering the photons that make what amount to direct hits on the detector crystal. But those photons that are not direct hits also carry useful information that is normally lost. The conundrum is that extracting the information from these other photons is computationally demanding and attempts to do so using traditional sequential information processing methods would slow the whole process so much that it would result in the loss of the very information one seeks to acquire.

  "3D-CBS is an ingenious solution to this conundrum. The 3D-Flow™ architecture of the 3D-CBS combines pipelining and parallel processing methods to extract essentially all of the information in real time. The ability of parallel processing methods to speed information processing has a proven track record in areas such as weather prediction and molecular modeling. The efficiency of its architecture allows the 3D-CBS to capture this information even at low processor speeds using relatively inexpensive components. The combination of parallel processing and pipelining technologies is an advance that has the potential to impact many commercial applications. Indeed, the 3D-CBS system is similar in many ways to the most powerful parallel-processing machine in existence, the human brain.

  "Although one cannot predict the course of a technology this revolutionary, the outlines of what 3D-CBS makes possible have been nicely sketched by Dr. Crosetto. Primarily, the ability to economically screen people for cancer early and often will help reduce cancer mortality. The efficacy of early screening has been demonstrated conclusively by the screens that are currently in use: Pap smears, mammograms and prostate exams. The problem is that these simple cheap tests are the exception; most tests are too expensive, too invasive and/or too specific for rare cancers to justify their use in mass-screening programs. However, the reduced cost and radiation dose of PET using the 3D-CBS technology changes this equation. 3D-CBS PET has the potential catch many types of cancer with a single cost-effective, non-invasive exam.

  "It is clear that the sort of combined pipelining and parallel-processing architecture that 3D-CBS represents will become the standard for medical PET imaging. It is only a question of when."

11. **Dr. Joel Karp**, Department of Radiology, University of Pennsylvania Medical Center.

- 2002, August, Dr. Karp in one email to Crosetto writes:
  "Thank you very much for sending me your book, which I received on Friday. I did briefly look through it to get a better appreciation about your proposals for improved PET…." Then he expresses some difficulties that he and his group encountered on the approach of extending the FOV of a PET, that at first was stated in one of his articles as believed to be advantageous as stated in Section IV, of [14], page 1580 "We believe that we can extend this design even further in the axial dimension. An advantage of the PENN-PET system, with continuous detectors, is that the increase in performance as a function of axial FOV is greater than the corresponding increase in cost and complexity." Crosetto followed up with a specific argument that provides a solution to their difficulties.

References:

[1] Crosetto, D. "400+ times improved PET efficiency for lower-dose radiation, lower-cost cancer screening." ISBN 0-9702897-0-7. Available at Amazon.com

[2] Crosetto, D.: Figure summarizing where photons are lost in current PET and how those are captured in the 3D-CBS. See www.3d-computing.com/pb/ lostphotons.pdf

[3] Crosetto, D.: Figure summarizing the key elements of the inventions which is available at www.3d-computing.com/pb/3D-CBS_fig_old.pdf, which has been recently updated and sent on September 17, 2003 to the reviewers. See at www.3d-computing.com/pb/3D-CBS_fig.pdf

[4] Crosetto, D.: "LHCb base-line level-0 trigger 3D-Flow implementation." Nuclear Instruments and Methods in Physics Research, Section A, vol. 436 (Nov. 1999) pp. 341-385.

[5] Crosetto, D., "System Design and Verification Process for LHC Programmable Trigger Electronics" IEEE NSS-MIC Seattle (WA) Oct. 24-30, 1999.

[6] Crosetto, D., "Saving lives through early cancer detection: Breaking the current PET efficiency barrier with the 3D-CBS." Presented on May 16, 2001 at the University of Geneva, Switzerland, on May 18 at the University of Turin, Italy and on May 21, 2001 at the University hospital of Geneva. Available at www.3d-computing.com/pb/3d-cbs.pdf.

[7] DeGrado, T.R. et al.: "Performance Characteristics of the Whole-Body PET Scanner." Journal of Nuclear Medicine, vol. 35(8):1398-1406, August 1994

[8] Wienhard, K. et al.: "The ECAT EXACT HR: Performance of a New High Resolution Positron Scanner." IEEE TNS., 1997, pp. 1186-1190.

[9] Cherry, S.R., et al..: "A comparison of PET detector modules employing rectangular and round photomultiplier tubes." IEEE Trans. Nucl. Sci, vol. 42(4):1064-1068 (August 1995).

[10] www.3d-computing.com

[11] Crosetto, D.: "A modular VME or IBM PC based data acquisition system for multi-modality PET/CT scanners of different sizes and detector types." Presented at the IEEE Nuclear Science Symposium and Medical Imaging Conference, Lyon, France, 2000, IEEE-2000-563, http://www.3d-computing.com/pb/ieee2000-563.pdf.

[12] Crosetto, D.: "Real-time, programmable, digital signal-processing electronics for extracting the information from a detector module for multi-modality PET/SPECT/CT scanners." Presented at the IEEE Nuclear Science Symposium and Medical Imaging Conference, Lyon, France, 2000, IEEE-2000-567, submitted to IEEE, Trans. Nucl. Science. http://3d-computing.com/pb/ieee2000-567.pdf

[13] Von Schulthess, Gustav K.: "Clinical Positron Emission Tomography (PET) Correlation with Morphological Cross-Sectional Imaging." University hospital, Zurich, Switzerland. Published by Lippincott Williams & Wilkins. 2000

[14] Karp, J. et al.: "Effect of Increased Axial Field of View on the Performance of a Volume PET Scanner." IEEE NSS-MIC, Conf. rec. 1991 pp. 1574-1578, vol. 3