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- (54) **Title:** DETECTOR ARRAY WITH TIME-TO-DIGITAL CONVERSION HAVING IMPROVED TEMPORAL ACCURACY

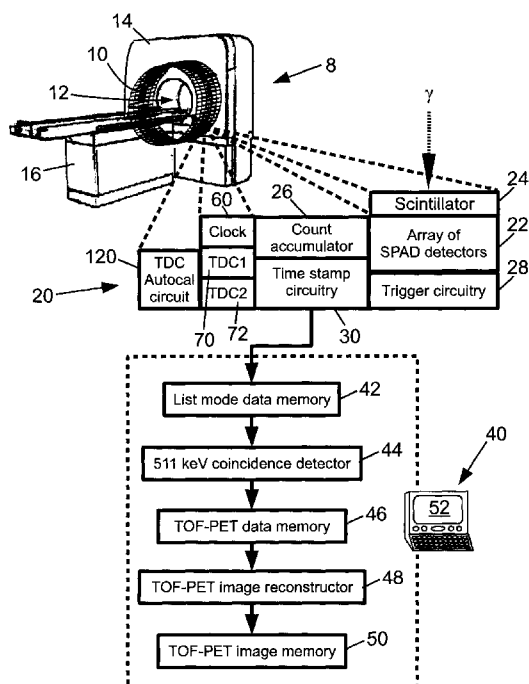


Fig. 1

(57) **Abstract:** A detector (22) detects an event. First and second time-to-digital converters (TDCs) (70, 72) generate first and second time stamps (TS1, TS2) for the detection of the event. The first TDC and the second TDC are both synchronized with a common clock signal (62) that defines a fixed time offset between the second TDC and the first TDC. An autocalibration circuit (120) adjusts the first TDC and the second TDC to keep the time difference between the second time stamp and the first time stamp equal to the fixed time offset between the second TDC and the first TDC. The detector may be a detector array, and trigger circuitry (28) propagates a trigger signal from a triggering detector of the array of detectors to the first and second TDC's. Skew correction circuitry (132, 134, 136, 142, 60, 162) adjusts a timestamp (TS) based on which detector is the triggering detector.



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DETECTOR ARRAY WITH TIME-TO-DIGITAL CONVERSION HAVING IMPROVED TEMPORAL ACCURACY

DESCRIPTION

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The following relates to the radiation detection arts. It particularly relates to high-speed radiation detectors for positron emission tomography (PET), especially time-of-flight (TOF) PET, and will be described with particular reference thereto. However, the following relates more generally to high speed radiation detectors for other types of radiological imaging, as well as to high-speed radiation detectors for other applications such as astronomy.

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In PET imaging, a radiopharmaceutical administered to a human patient or other imaging subject emits positrons, each of which in turn annihilates with an electron of the surrounding imaging subject in an electron-positron annihilation event to produce two oppositely directed 511 keV gamma rays. In conventional PET imaging these two oppositely directed gamma rays are detected by radiation detectors surrounding the imaging subject as two substantially simultaneous radiation detection events that define a line of response (LOR) therebetween. In time-of-flight (TOF) PET, the small time difference (or lack thereof) between the two substantially simultaneous detection events is used to further localize the positron along the LOR.

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To provide useful TOF localization, the 511 keV gamma rays should be detected with sub-nanosecond temporal resolution. Radiation detectors capable of achieving these speeds include photomultiplier tube (PMT) detectors and silicon-based single-photon avalanche diode (SPAD) detectors (also sometimes referred to as an avalanche photodiode or APD operating in Geiger mode). Such detectors typically perform detection of the 511 keV gamma rays in conjunction with a scintillator. SPAD detectors advantageously leverage mature silicon microelectronics fabrication technology to enable monolithic integration of a two-dimensional detector array on a silicon substrate. Time stamping circuitry may be integrated monolithically on the same silicon substrate as the SPAD array, or may be formed on a separate silicon substrate that is operatively connected with the SPAD array as a hybrid circuit. This is advantageous since the time stamp electronics

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should be located with the SPAD array, for example on the PET detector gantry, and preferably either on the same chip as the SPAD array or close to it (e.g., as a 3D stack of chips). Some illustrative examples of SPAD detector arrays for TOF-PET or other high-speed applications are disclosed in: Frach et al., U.S. Pat. No. 7,723,694 issued May 25, 2010 which is incorporated herein by reference in its entirety; Fiedler et al, U.S. Pat. No. 7,626,389 issued Dec. 1, 2009 which is incorporated herein by reference in its entirety; and Prescher et al., U.S. Pub. No. 2010/0182011 A1 published July 22, 2010 which is incorporated herein by reference in its entirety.

Although radiation detectors such as PMT or SPAD detectors are capable of sub-nanosecond temporal resolution, actually achieving this is contingent upon providing suitable electronics including time-stamping circuitry. In one approach, triggering circuitry generates a signal pulse or other trigger signal at the time of detection. In the case of a scintillator/detector array configuration, a single 511 keV gamma ray produces a scintillation comprising many photons in the optical or other wavelength range, and a single “pixel” of the detector array comprises a sub-array of SPAD detectors that accumulate a photon count corresponding to the 511 keV gamma ray. In such cases, the trigger circuitry is designed to trigger on the first detected photon or on some other trigger criterion such as the tenth detected photon or so forth.

However the trigger is configured, the time stamp circuitry relates the time of the trigger signal to a system clock to provide the time stamp. However, the time resolution of the system clock may be too coarse for TOF PET. For example, a system clock operating at 200 MHz produces a clock pulse every 5 ns, which is insufficient for sub-nanosecond timestamp resolution. In such cases, the system clock is treated as a coarse counter and a fine counter is provided to assess temporal offset of the trigger signal from a reference point of the clock (e.g., rising edge of the clock pulse, or falling edge of the clock pulse).

The approaches are found to provide sufficient (e.g., sub-nanosecond) temporal resolution for a given radiation detector pixel at a given time. However, spatial variation across the detector array, also called “skew”, can produce substantial errors. Also, voltage and/or temperature variation can cause drift in the output of the fine counter over time. The combination of skew and temporal drift can substantially degrade the effective temporal resolution of the PET detector array.

The following contemplates improved apparatuses and methods that overcome the aforementioned limitations and others.

According to one aspect, a method comprises: detecting an event; generating a trigger signal associated with the detection of the event; generating a first time stamp for the trigger signal using a first time to digital converter (TDC); generating a second time stamp for the trigger signal using a second TDC having a fixed time offset relative to the first TDC; and associating a time stamp with the event based on the first time stamp, the second time stamp, and a comparison of (1) the time difference between the second time stamp and the first time stamp and (2) the fixed time offset. In some such methods the first TDC is synchronized with a common clock signal, the second TDC is synchronized with the common clock signal, and the synchronizing operations determine the fixed time offset of the second TDC relative to the first TDC as the period of the common clock signal or as a fixed fraction or multiple of the period of the common clock signal. In some such embodiments the detecting comprises detecting a radiation particle using an array of positron emission tomography (PET) detectors, and the method further comprises: repeating the detecting, generating of the trigger signal, generating of first and second time stamps, and associating to acquire a data set of time stamped radiation detection events; generating a time of flight (TOF) PET data set from the data set of time stamped radiation detection events; and reconstructing the TOF PET data set to generate a PET image.

According to another aspect, an apparatus comprises: a detector configured to detect an event; a first time to digital converter (TDC) configured to generate a first time stamp for the detection of the event; a second TDC configured to generate a second time stamp for the detection of the event, there being a fixed time offset between the second TDC and the first TDC; and an autocalibration circuit configured to adjust the first TDC and the second TDC to keep the time difference between the second time stamp and the first time stamp equal to the fixed time offset between the second TDC and the first TDC. In some such apparatus the first TDC and the second TDC are both synchronized with a common clock signal that defines the fixed time offset between the second TDC and the first TDC. In some such apparatus the first TDC measures a first time interval and transforms the first time interval into the first time stamp using a first transform operation,

the second TDC measures a second time interval and transforms the second time interval into the second time stamp using a second transform operation, and the autocalibration circuit adjusts the first and second transform operations to keep the time difference between the second time stamp and the first time stamp equal to the fixed time offset
5 between the second TDC and the first TDC. In some such apparatus the first transform operation includes applying a first look-up table and the second transform operation includes applying a second look-up table.

According to another aspect, a positron emission tomography (PET) system includes radiation detectors comprising the apparatus set forth in the immediately
10 preceding paragraph and a processor configured to generate time of flight (TOF) PET data from the output of the radiation detectors and to reconstruct the TOF PET data to generate an image.

According to another aspect, an apparatus comprises: an array of detectors configured to detect an event; trigger circuitry configured to propagate a trigger signal
15 associated with the detection of the event from a triggering detector of the array of detectors to time stamp circuitry configured to generate a time stamp for the detection of the event; and skew correction circuitry configured to adjust the time stamp based on which detector is the triggering detector. In some such apparatus the skew correction circuitry comprises delay elements incorporated into the trigger circuitry to delay the
20 propagation of the trigger signal to the time stamp circuitry based on which detector is the triggering detector. In some such apparatus the skew correction circuitry is configured to adjust the generated time stamp based on a skew correction look-up table tabulating the skew correction for each detector of the array of detectors.

According to another aspect, in an apparatus as set forth in the immediately
25 preceding paragraph the time stamp circuitry comprises: a first time to digital converter (TDC) configured to generate a first time stamp for the detection of the event based on the trigger signal; a second TDC configured to generate a second time stamp for the detection of the event based on the trigger signal; and an autocalibration circuit configured to adjust the first TDC and the second TDC to keep the time difference between the second time
30 stamp and the first time stamp equal to a predetermined fixed time offset between the second TDC and the first TDC.

One advantage resides in providing improved temporal resolution for radiation detection events.

Another advantage resides in providing more accurate time-of-flight PET imaging.

Another advantage resides in providing automatic self-calibration of time-to-digital
5 converter (TDC) devices.

Another advantage resides in providing improved spatial/temporal resolution for a radiation detector array.

Numerous additional advantages and benefits will become apparent to those of ordinary skill in the art upon reading the following detailed description.

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The invention may take form in various components and arrangements of components, and in various process operations and arrangements of process operations. The drawings are only for the purpose of illustrating preferred embodiments and are not to be construed as limiting the invention.

15 FIGURE 1 diagrammatically shows a time-of-flight positron emission tomography (TOF-PET) system.

FIGURE 2 diagrammatically shows time stamp sub-circuitry the radiation detectors of the TOF-PET system of FIGURE 1.

FIGURE 3 diagrammatically shows timing pulses of the system clock and first and
20 second time-to-digital converter (TDC) devices.

FIGURE 4 diagrammatically shows typical look-up table (LUT) values for first and second TDC's.

FIGURE 5 diagrammatically shows time stamp processing using the TDC's of FIGURE 1.

25 FIGURE 6 diagrammatically shows an illustrative embodiment of the TDC autocalibration circuit of FIGURE 1.

FIGURES 7 and 8 diagrammatically show first and second illustrative skew correction embodiments, respectively.

FIGURE 9 diagrammatically shows an embodiment incorporating tunable delay
30 elements into the trigger circuitry to provide skew correction.

With reference to FIGURE 1, a time-of-flight positron emission tomography (TOF-PET) scanner **8** includes a plurality of radiation detectors **10** arranged to view an imaging region **12**. In FIGURE 1, the plurality of radiation detectors **10** are arranged in several rings of detectors along an axial direction; however, other arrangements of radiation detectors can be used. Moreover, it is to be appreciated that the plurality of radiation detectors **10** is diagrammatically illustrated; typically the radiation detectors are housed within a housing **14** of the scanner **8** and thus are not visible from the outside, and typically each ring of radiation detectors includes hundreds or thousands of radiation detectors. In some PET scanners, only a single ring of radiation detectors is provided, in others, two, three, four, five, or more rings of radiation detectors are provided. It should be appreciated that detector heads can be used in place of the detector ring structure shown in the Figures. The TOF-PET scanner **8** includes a couch **16** or other support for positioning a human patient or other imaging subject in the imaging region **12**. Optionally, the couch **16** is linearly movable in the axial direction generally transverse to the rings of radiation detectors **10** to facilitate acquisition of three-dimensional imaging data. Additionally or alternatively, the imaging subject can be held stationary, and the plurality of rings of radiation detectors used to acquire three-dimensional TOF-PET imaging data. In yet other embodiments, only a single ring of detectors is provided, the imaging subject remains stationary, and the resulting image is two-dimensional.

A suitable radiopharmaceutical is administered to the patient or other imaging subject prior to initiation of TOF-PET imaging. The radiopharmaceutical includes a radioactive substance that undergoes radioactive decay events that emit positrons. The positrons rapidly annihilate with nearby electrons of the imaging subject. The resulting positron-electron annihilation event produces two oppositely directed gamma rays having energies of 511 keV. The gamma rays travel at the speed of light, i.e. $\sim 3 \times 10^8$ meters/sec. Since the imaging region **12** typically has a diameter or other characteristic dimension of about one meter or less (and more typically about 30-40 cm for a human imaging subject), the time-of-flight for a gamma particle from the position of the positron-electron annihilation event to one of the detectors of the plurality of radiation detectors **10** is about a few nanoseconds or less. Thus, the two oppositely directed gamma rays strike two of the radiation detectors substantially simultaneously.

With continuing reference to FIGURE 1, a single detector pixel **20** of the annular ring of radiation detectors **10** is shown in diagrammatic representation including associated on-board electronics. The detector pixel **20** comprises an array of silicon-based single-photon avalanche diode (SPAD) detectors **22** viewing a scintillator **24** that produces a scintillation or burst of light when a (diagrammatically indicated) 511 keV gamma ray γ strikes the scintillator **24**. The scintillator **24** is selected to provide high stopping power for 511 keV gamma rays with rapid temporal decay of the scintillation burst. Some suitable scintillator materials are LSO, LYSO, MLS, LGSO, LaBr and mixtures thereof, although other scintillator materials can also be used. The scintillation or burst of light is received by the array of detectors **22** which may, by way of illustrative example, be fabricated monolithically on a silicon substrate. An optional planar light pipe (not shown) can be interposed between the scintillator **24** and the array of detectors **22** to improve optical coupling between the scintillator **24** and the array of detectors **22**. The scintillator **24** and optional light pipe are optionally encased in a reflective coating which directs scintillation light toward the array of detectors **22**.

The use of the array of detectors **22**, rather than a single detector, for the detector pixel **20** is due to the generation of a scintillation or burst of light responsive to the scintillator **24** absorbing the single 511 keV gamma ray γ . Each SPAD of the array of detectors **22** can in general detect a single photon – thereafter it must recover including rebuilding the electric field over the *p/n* junction of the avalanche diode. By using the array of detectors **22** a count accumulator **26** accumulates a count of single-photon detections, and this count correlates with the total energy of the absorbed particle (that is, the 511 keV gamma ray γ in the illustrative example). A higher energy particle would be expected to produce a higher count while a lower energy particle would be expected to produce a lower count. Thus, the total count of photon detections over the time interval of the scintillation event can be used in “energy windowing” to filter out detection events that are not likely (on the basis of total particle energy) to be 511 keV gamma rays associated with positron-electron annihilation events.

The array of detectors **22** has associated trigger circuitry **28** whose purpose is to generate a trigger signal associated with the detection event. In a typical approach, the trigger circuitry comprises a trigger network connected with all SPAD devices of the array of detectors **22**, and the trigger network is configured to switch from a quiescent (or “off”)

state to a triggered (or “on”) state responsive to a single SPAD detecting a photon. Alternatively, the switch can occur after a selected number of photon detections, and/or validation circuitry can be included, so as to reduce likelihood of generating a “false” trigger signal. The trigger signal is used by time stamp circuitry **30** to generate a digital time stamp for the detection event.

In an illustrative approach, the array of detectors **22** comprising SPAD devices may be fabricated monolithically on a silicon substrate. The trigger circuitry **28** may also be monolithically integrated on the same silicon substrate, in the same circuit layer as the SPAD devices (i.e., interleaved between SPAD rows/columns) or disposed in a separate circuit layer, e.g. below the array of SPAD devices. The associated count accumulation and time stamp electronics **26**, **30** may also be monolithically integrated on the same silicon substrate as the array of detectors **22**, or may be disposed on a separate silicon substrate connected with the detector array substrate. In either case, the electronics **26**, **30** (or various portions thereof) may be variously embodied, for example as a field programmable gate array (FPGA), application-specific integrated circuitry (ASIC), suitably programmed microprocessor or microcontroller, various combinations of the foregoing, or so forth. While the single diagrammatically represented detector pixel **20** is described by way of illustrative example, it is to be understood that the PET detector ring **10** includes many thousands, tens of thousands, or more such detector pixels. Various numbers of detector pixels may be integrated on a single silicon substrate to form a detector module of (without loss of generality) $N \times M$ detector pixels (where each detector pixel includes an instance of the SPAD array **22**). Some suitable detector pixels are set forth, by way of illustrative example, in: Frach et al., U.S. Pat. No. 7,723,694 issued May 25, 2010 which is incorporated herein by reference in its entirety; Fiedler et al, U.S. Pat. No. 7,626,389 issued Dec. 1, 2009 which is incorporated herein by reference in its entirety; and Prescher et al., U.S. Pub. No. 2010/0182011 A1 published July 22, 2010 which is incorporated herein by reference in its entirety.

It is further to be appreciated that the disclosed detector pixel is merely an illustrative example, and other detector pixel configurations are also contemplated. For example, in a direct conversion detector pixel, a single detector is configured to directly absorb and detect the 511 keV gamma ray without the use of an intervening scintillator. In such an embodiment, the scintillator **24** is omitted, the array of detectors **22** is replaced by

a single direct-conversion detector, and the trigger circuitry **28** is simplified to a single binary switch that activates when the single-particle detector is activated.

With continuing reference to FIGURE 1, the circuitry **26, 30** generates, for each radiation particle detection event, a “list mode” set of data including the time stamp generated by the time stamp circuitry **30**, the particle energy as represented by the photon count accumulated by the count accumulator **26**, and spatial coordinates of the detector pixel **20**. The list mode data for these events are suitably communicated off the PET scanner **8** to a suitable data processing device such as an illustrative computer **40**, and are stored in a list mode data memory **42**. The data processing device **40** implements suitable data processing. For PET data, the data processing device **40** suitably implements a 511 keV coincidence detector **44** that searches the list mode data to identify substantially simultaneous 511 keV particle detection events. The searching suitably employs an energy window to filter out particle detection events corresponding to particles having energies well above or well below 511 keV, and then employs a time window to identify remaining (at least approximately) 511 keV detection events that occurred as “substantially simultaneous” pairs, that is, two 511 keV detection events that occurred within a sufficiently small time window so that both detected 511 keV gamma rays could have originated from a single positron-electron annihilation event. Such a detected pair defines a “line of response” or LOR connecting the two detecting pixels. In the case of TOF PET, the small time difference between the two “substantially simultaneous” detection events is used to further localize the positron-electron annihilation event along the LOR.

The resulting energy- and coincidence-filtered 511 keV detection event pairs constitute a TOF PET data set that is suitably stored in a TOF PET data memory **46**. This TOF PET data set is optionally reconstructed by a TOF PET data reconstructor **48** also suitably implemented by the computer or other data processing device **40** in order to reconstruct a PET image that is suitably stored in a TOF PET image memory **50**, or displayed on a display device **52** integral with or in operative communication with the data processing device **40**, or otherwise utilized. The TOF PET data reconstructor **48** may use substantially any suitable reconstruction algorithm, such as iterative forward/backward projection (including TOF localization of the projections), a filtered backprojection reconstruction algorithm, or so forth.

With continuing reference to FIGURE 1 and with further reference to FIGURES 2 and 3, an illustrative embodiment of the time stamp circuitry and associated timing components is described. The time stamp processing is referenced to a coarse clock **60**. To provide some quantitative examples herein, the clock **60** is assumed herein to produce a clock signal **62** cycling at 200 MHz (corresponding to a clock cycle period of 5 ns); however, it is to be understood that a faster or slower clock cycle can be employed. The illustrative clock signal **62** is a square wave having a 50% duty cycle; however, other waveforms can be employed for the clock signal. For illustrative simplicity, in Fig. 1 the clock **60** is shown as a component of the detector pixel **20**; more typically, however, the clock is located elsewhere and the clock signal **62** is input to the detector pixel **20**.

The clock signal **62** has a period of 5 ns, which is too coarse to provide the sub-nanosecond resolution desired for time stamping of 511 keV gamma ray detection events. To provide finer resolution, two time-to-digital converter (TDC) devices **70**, **72** are provided. The first TDC **70** is also denoted herein as “TDC1” or as “fine counter 1” or “FC1”, while the second TDC **72** is also denoted herein as “TDC2” or as “fine counter 2” or “FC2”. While in principle a single TDC would be sufficient, as disclosed herein there are substantial advantages to employing the illustrated two TDC **70**, **72**. These advantages include elimination of “dead zones” in which one of the TDC **70**, **72** provides unreliable results, and providing for automatic calibration of both TDC **70**, **72** to compensate for drift in the output of the fine counter over time due to voltage and/or temperature variation.

With particular reference to FIGURE 2, each TDC **70**, **72** receives the same input from the trigger circuitry **28**. Each TDC **70**, **72** is synchronized with the common clock signal **62**, which is used to synchronize respective fine counters **74**, **76** that are used to measure the time difference between the detected event (as represented by the trigger signal generated by the trigger circuitry **28**) and a reference feature of the first fine counter **74** (for TDC1 **70**) or the second fine counter **76** (for TDC2 **72**). The reference feature may be a rising edge, or a falling edge, or other suitable feature of the fine counters **74**, **76**. In the illustrative examples the latching will be to the rising edge E_R of the fine counter **74**, **76**. The time difference measurement performed by each TDC **70**, **72** is suitably based on a time-to-distance measurement according to one of tap line, a Vernier, a pulse-shrinking, and a constant current capacitor discharge, or the like. By way of illustrative example, some suitable TDC configurations are disclosed in Frach et al., U.S. Pub. No.

2009/0236532 A1 published Sept. 24, 2009 which is incorporated herein by reference in its entirety.

At the input of each TDC **70**, **72**, a respective storage element **80**, **82**, such as a flip-flop, latch, or the like, is latched when the trigger signal is present. If the input is stable the switch will latch at the subsequent rising edge E_R of the respective fine counter **74**, **76**. However, if the trigger signal is received at the input during a meta-stable region, i.e. during the setup or hold times, the switch may become meta-stable and the trigger signal will not be latched until the next rising edge E_R of the fine counter **74**, **76** leading to a significant increase in the timestamp error.

If only a single TDC was provided, then there would be no way to accommodate this timestamp error. In the illustrative approach, however, two TDC **70**, **72** are provided. To reduce timing errors stemming from meta-stability at the input, each TDC **70**, **72** is synchronized to a different fine counter **74**, **76** in a manner that ensures that at least one storage element **80**, **82** will latch properly at any time.

With particular reference to FIGURE 3, in the illustrative example the fine counter **76** of TDC2 **72** is “out of phase” by 180° respective to the fine counter **74** of TDC1 **70**. This means that the rising edges E_R of the fine counter **74** are “in between” the rising edges E_R of the fine counter **76**, and vice versa. Because of this, unstable or meta-stable regions **90** of TDC1 **70** lie within the stable regions **92** of TDC2 **72**, and conversely unstable or meta-stable regions **94** of TDC2 **72** lie within the stable regions **96** of TDC1 **70**. The two 180° out-of-phase fine counters **74**, **76** are readily generated from the clock signal **62** as 100 MHz counters by frequency divide-by-2 circuits (not shown).

The approach of FIGURE 3 is an illustrative example, and other approaches can be used to provide twin TDC with a fixed time offset. For example, a phase shift of other than 180° between the two fine counters can be used, or the two TDC can latch off different reference features. (As an example of the latter approach, the two TDC can use the same (in-phase) fine counter but have one TDC latch off the rising edge and the other TDC latch off the falling edge).

With returning reference to FIGURE 2, the first TDC **70** computes a time difference **100** between the detected event (as represented by the trigger signal generated by the trigger circuitry **28**) and a reference feature (e.g., rising edge) of the first fine counter **74**. Similarly, the second TDC **72** computes a time difference **102** between the

detected event and a reference feature of the second fine counter **76**. These time differences **100**, **102** typically do not directly equal the desired time stamp. Rather, a first transform operation is performed to convert the time difference **100** into a first time stamp **TS1**, and a second transform operation is performed to convert the time difference **102** into a second time stamp **TS2**. The transform operation determines the offset in time units and adds that offset to the reference time provided by the clock signal **62**. In the illustrative embodiment, the first TDC **70** applies a first look-up table **LUT1** in performing the transform that generates the first time stamp **TS1**, while the second TDC **72** applies a second look-up table **LUT2** in performing the transform that generates the second time stamp **TS2**. The look-up tables **LUT1**, **LUT2** optionally also identify respective select bits **104**, **106** that indicate whether the detected event lies in one of the unstable or metastable regions **90**, **94**. Instead of look-up tables, a suitably calibrated empirical transform function may be employed. Further data processing circuitry **108** generates a final time stamp **TS** for the detection event based on the first and second timestamps **TS1**, **TS2** generated by the twin TDC **70**, **72**. In one suitable approach, the circuitry **108** discards the output of a TDC if its select bits indicate the detected event lies in an unstable or metastable region for that TDC – necessarily, the detected event will lie in a stable region for the other TDC and so that TDC reading is used. If both TDC **70**, **72** are stable, then the circuitry **108** may average or otherwise aggregate the first and second timestamps **TS1**, **TS2** to generate the final timestamp **TS**.

With reference to FIGURES 4 and 5, a quantitative illustrative example of operation of the TDC **70**, **72** and timestamp circuitry **30** is described. This example uses the clock signal **62** with frequency 200 MHz, and uses the two fine counters **74**, **76** with frequency 100 MHz and 180° phase offset, as shown in FIGURE 3. The fine counters **74**, **76** thus have periods of 10 ns (that is, twice the 5 ns period of the clock signal **62**). The bin width of each TDC varies. The look-up tables **LUT1**, **LUT2** are therefore used to translate the fine counter values in relative time units to the absolute time reference of the 200 Mhz system clock signal **62**. FIGURE 4 diagrammatically illustrates possible look-up table values for TDC1, TDC2 **70**, **72** respectively. In this example the accuracy of the TDC is 9 bits over a period of 10ns, so that each “bin” has a width $10 \text{ ns} / 512 \sim 19.5 \text{ ps}$. The look-up tables **LUT1**, **LUT2** can be generated in various ways, such as using a delay line measurements, or random hits measurements, or so forth.

FIGURE 5 illustrates use of the TDC **70**, **72** with look-up tables **LUT1**, **LUT2** for time stamp measurements. The CC1 and CC2 indicates clock cycles of the fine counters **74**, **76** of the TDC **70**, **72** each operating at 100 Mhz. Each increment of the clock cycle CC indicates an increment of 512 which is 10 ns. The first time stamp **TS1** generated by the first TDC **70** is given by $CC1 + LUT(FC1)$, where $LUT(FC1)$ indicates the output of the look-up table **LUT1** for the fine counter input designated “FC1”. Analogously, the second time stamp **TS2** generated by the second TDC **72** is given by $CC2 + LUT(FC2) + 256$, where the offset 256 corresponds to 5 ns. Whether the circuitry **108** selects the first time stamp **TS1** output by TDC1 **70** or the second time stamp **TS2** output by TDC2 **72**, or an average of these two, depends upon the location in the time axis. For example, at times when TDC1 **70** has no valid timestamp generation (regions **90** indicated in FIGURE 3, around 0 ns in the example of FIGURE 5), the second time stamp **TS2** output by TDC2 **72** is selected as the output time stamp **TS**. Averaging of the two time stamps **TS1**, **TS2** when both TDC **70**, **72** are stable is advantageous to reduce jitter.

With returning reference to FIGURE 1, another advantage recognized herein of using two TDC **70**, **72** is that this enables providing an automatic TDC calibration circuit **120** for calibrating both TDC **70**, **72** to compensate for drift in the output of the fine counters **74**, **76** over time due to voltage and/or temperature variation. TDC autocalibration approaches disclosed herein take advantage of two observations. First, the drift of the two TDC **70**, **72** can be expected to be identical or nearly so. This is a consequence of the two TDC **70**, **72** being in the same environment (and hence at the same temperature, experiencing the same ambient humidity, and so forth) and being driven by a common voltage source (so that any voltage variation should be the same for both TDC **70**, **72**).

The second observation made herein is that the second TDC **72** should always have the same fixed time offset respective to the first TDC **70**. (Or, turned around, the first TDC **70** should always have the same fixed time offset respective to the second TDC **72**). This is a consequence of the two TDC **70**, **72** being synchronized with the common clock signal **62**. As best seen in FIGURE 3, in the illustrative embodiment the fixed time offset between the two TDC **70**, **72** should be precisely 5 ns corresponding to one period of the clock signal **62**; however, depending upon the phase offset of the two fine counters, or the (optionally different) choice of reference features for use in the two TDC, the fixed time offset may be different.

The second TDC **72** should always have the same fixed time offset respective to the first TDC **70**. It therefore follows that if the time difference between the second time stamp **TS2** and the first time stamp **TS1** is different from this fixed time offset, then this difference is due to drift over time of the two TDC. Moreover, the direction of the drift is readily ascertained. If the time difference between the second time stamp **TS2** and the first time stamp **TS1** is less than the fixed time offset, then the fine counters **74**, **76** have periods that are too short – this can be corrected by a multiplication factor incorporated into the transform that is greater than one. On the other hand, if the time difference between the second time stamp **TS2** and the first time stamp **TS1** is greater than the fixed time offset, then the fine counters **74**, **76** have periods that are too long – this can be corrected by a multiplication factor incorporated into the transform that is less than one.

In view of the foregoing, the TDC autocalibration circuit **120** employs the following algorithm: upon detecting an event, a trigger signal associated with the detection of the event is generated, the first time stamp **TS1** for the trigger signal is generated using the first TDC **70**, and the second time stamp **TS2** for the trigger signal is generated using the second TDC **72**. A time calibration of the two TDC **70**, **72** is then calculated responsive to the time difference between the second time stamp **TS2** and the first time stamp **TS1** being different from the *a priori*-known fixed time offset.

In a suitable approach, the first time stamp **TS1** is generated by the first TDC **70** by measuring the first time interval **100** (using the fine counter **74**) and transforming the first time interval **100** into the first time stamp **TS1** using a first transform operation (including applying the look-up table **LUT1** in the illustrative embodiment). Similarly, the second time stamp **TS2** is generated by the second TDC **72** by measuring the second time interval **102** (using the fine counter **76**) and transforming the second time interval **102** into the second time stamp **TS2** using a second transform operation (including applying the look-up table **LUT2** in the illustrative embodiment). The adjusting then comprises adjusting the first and second transform operations responsive to the time difference between the second time stamp **TS2** and the first time stamp **TS1** being different from the fixed time offset. In one suitable approach, this is done by including into the first transform operation a multiplication factor, and including into the second transform operation the (same) multiplication factor. The adjusting then comprises increasing the multiplication factor if the time difference between the second time stamp **TS2** and the first time stamp

TS1 is smaller than the fixed time offset, and decreasing the multiplication factor if the time difference between the second time stamp **TS2** and the first time stamp **TS1** is larger than the fixed time offset.

With reference to FIGURE 6, an illustrative embodiment of the TDC autocalibration circuit **120** is described. The circuit of FIGURE 6 is configured for the quantitative example disclosed herein in which the clock signal **62** has a frequency of 200 MHz, each fine counter **74**, **76** has a frequency of 100 MHz and the two fine counters **74**, **76** are offset in phase by 180°, and the accuracy of each TDC **70**, **72** is 9 bits over a period of 10ns, so that each “bin” has a width $10\text{ ns} / 512 \sim 19.5\text{ ps}$. The difference between the time stamp **TS1** output by the look-up table **LUT1** of TDC1 **70** and the time stamp **TS2** output by the look-up table **LUT2** of TDC2 **72** should be always 256 (which corresponds with 5 ns). This is the fixed time offset in this quantitative example. However, the actual time difference between the second time stamp **TS2** and the first time stamp **TS1** will change if the slopes of the fine counters **74**, **76** drift, for example due to voltage and/or temperature variation. A multiplicative correction factor **M** for correcting the slopes can be generated based on the time difference between the first and second time stamps **TS1**, **TS2** and the *a priori*-known fixed time offset (e.g., 256 or 5 ns).

The TDC calibration circuit **120** of FIGURE 6 is activated each time an event is processed to be assigned a time stamp. The TDC **70**, **72** generate respective outputs **100**, **102** which are multiplied by the multiplication factor **M** (also denoted “mul_factor” herein) which will initially be set to 1.0 (corresponding to no correction). The results **100**, **102** are input to the respective look-up tables **LUT1**, **LUT2**. The resulting time stamps **TS1**, **TS2** are compared at a comparator **122**, and a decision block **124** generates a feedback signal **126** that is used to adjust the multiplication factor **M** (if an adjustment is needed). If the distance determined by the comparator **122** is above 256 (meaning the slope is too steep) then the feedback signal **126** is suitably a “do_decr” signal that causes the multiplication factor **M** to be decremented by a selected amount (for example, if the multiplication factor **M** or “mul_factor” has an accuracy of 12 bits and is represented in a hexadecimal notation, then the decrement may be from 0x800 to 0x7FF).

Conversely, if the slope is too shallow, then the feedback signal **126** is a “do_incr” signal that causes the multiplication factor **M** to be incremented by the selected amount so as to compensate for the too shallow slope. Still further, if the slope is correct such that the

TS1, **TS2** difference equals 256 then the feedback signal **126** is “hold” which causes no change in the multiplication factor **M**.

When the next event is detected and its trigger signal propagated to the time stamp circuitry **30** for time stamping, the TDC calibration circuit **120** is again invoked, this time with the multiplication factor **M** slightly less than 1.0. The outputs **100**, **102** are now multiplied with a `mul_factor` which is somewhat below 1.0 so as to provide correction for the “too steep” slopes. This will be continued for every event detection/timestamping so that the multiplication factor **M** (`mul_factor`) is adjusted to compensate for any drift to maintain the fixed time offset of (in this quantitative example) 256 (or 5 ns).

If one of the TDC **70**, **72** is in an unstable or meta-stable condition (e.g., state **90** for TDC **70** or state **94** for TDC **72** as indicated in FIGURE 3, which condition is indicated by suitable values of the select bits **104**, **106** shown in FIGURE 2) the corresponding iteration of operation of the TDC calibration circuit **120** is optionally skipped.

The approach of the TDC autocalibration circuit **120** of FIGURE 6 employs the increment “`do_incr`” or decrement “`do_decr`” of fixed magnitude, and the feedback signal **126** identifies only the “direction” of adjustment of the multiplication factor **M**. This approach is suitable assuming that the TDC drift is relatively slow, as is expected for drift caused by temperature and/or voltage variation, so that iterative incrementing or decrementing of the multiplication factor **M** can keep up with the slow drift. In another contemplated approach, both the direction and the magnitude of the feedback signal **126** is computed based on the magnitude of the timestamp **TS1**, **TS2** difference so as to provide a single adjustment of the multiplication factor **M** that should correct the drift in a single adjustment (that is, not incrementally). This approach entails modifying the decision block **124** to compute the magnitude of the feedback signal **126** based on the magnitude of the difference between the timestamps **TS1**, **TS2**.

The TDC autocalibration circuit **120** described with particular reference to FIGURES 1 and 6 provides compensation for temporal drift of the TDCs. In embodiments in which the detector pixel comprises a two-dimensional array of detectors (e.g., a two-dimensional array of SPAD), the pixel also optionally includes correction for skew. The source of skew error is that the trigger signal corresponding to an event detection (e.g., a 511 keV particle detection in the case of PET imaging) is generated by a single triggering detector of the array of detectors. If the temporal characteristics of this triggering varies

amongst the detectors of the array of detectors, then the trigger signal timing depends upon which detector acted as the triggering detector. Such variation can be reduced by configuring the trigger circuitry **28** in a “balanced” fashion such that the propagation path length from any detector of the array of detectors to the time stamp circuitry **30** is always the same. See, for example, Prescher et al., WO 2009/019660 A2 published Feb. 12, 2009 and incorporated herein by reference in its entirety for some illustrative trigger circuits designed to reduce skew. Nonetheless, even with balancing of the trigger circuitry **28** during detector array design, it is expected that process variations may result in substantial skew being observed in the detector array.

The approaches for skew correction disclosed herein are based upon assessing the skew by measuring propagation time of a trigger signal from each detector to the time stamp circuitry **30**, and correcting the skew based on these measurements. The measurement step can employ various manual, automated, or semi-automated measurement procedures. In an optical approach, a laser generating picosecond light pulses is applied to individual SPAD cells of the detector array, and a map of the delay between the laser pulse and the time stamp across the detector array provides data for assessing skew of the detector array. Instead of optically activating individual SPAD cells, dedicated current injection circuitry may be provided in the detector array. In some embodiments the detector array includes inhibit logic that can “turn off” the triggering capability of selected SPAD cells, so that the triggering characteristics of individual SPAD cells can be characterized in isolation. See, e.g., Frach et al., U.S. Pat. No. 7,723,694 issued May 25, 2010 which is incorporated herein by reference in its entirety.

With reference to FIGURE 7, once the skew characteristics of each SPAD **130** of the array of detectors **22** is characterized, this information is used to create a skew correction look-up table **132**. The position of the triggering SPAD cell that detected the first photon is stored. In the embodiment of FIGURE 7, this is accomplished by a set of row flip-flops **134** and a set of column flip-flops **136** that together store the (row,column) index if the triggering SPAD cell at the periphery of the pixel detector array **22**. The (row,column) coordinates are input to the skew correction look-up table **132** which outputs the skew correction for the triggering SPAD cell to the time stamp circuitry **30** (see FIGURE 1) for use in correcting the time stamp. In a typical approach, the skew correction look-up table **132** stores time offsets, and the time offset for the triggering SPAD cell is

added to (or, in some embodiments and for some triggering SPAD cells, possibly subtracted from) the time stamp **TS** to generate the skew-corrected time stamp.

With reference to FIGURE 8, in an alternative embodiment the position of the triggering SPAD cell is stored at the individual SPAD cell. The master trigger signal **140** (used to start the TDC) is fed back to each SPAD cell, with minimum delay to minimize the number of multiple detections, and this signal **140** is then used to latch the status of the cell via a flip-flop **142**. This information is input to the skew correction look-up table **132** as in FIGURE 7 (aspect not shown in FIGURE 8) for generating the skew correction.

With reference to FIGURE 9, in another approach the trigger circuitry **28** is modified by the addition of tunable delay elements in order to correct the skew. As shown in FIGURE 9, the trigger circuitry **28** suitably comprises a network of signal combining nodes, of which FIGURE 9 shows signal combining nodes **150**, **152**, **154** by way of illustrative example. The trigger signal originates at a triggering SPAD cell of the set of SPAD cells comprising the detector array **22**, and the trigger signal propagates through the nodes **150**, **152**, **154** of the trigger circuitry **28** to reach the time stamp circuitry **30**. The network of nodes is optionally balanced so that the trigger signal traverses the same number of nodes to reach the time stamp circuitry **30** regardless of which SPAD cell **130** serves as the triggering SPAD cell. Nonetheless, some differences in the total trigger signal propagation may occur depending upon which SPAD cell is the triggering SPAD cell.

Toward this end, selected nodes, such as the illustrative nodes **150**, **152**, include respective delay elements **160**, **162** that are tunable to correct any skew. The delay elements **160**, **162** may, for example, comprise digitally controlled delay elements such as are described in Maymandi-Nejad et al., "A Digitally Programmable Delay Element: Design and Analysis", IEEE Trans. on Very Large Scale Integration (VLSI) Systems vol. 11 no. 5 pages 871-878 (2003) which is incorporated herein by reference in its entirety. Other types of delay elements may be used, such as a designed buffer circuit or buffers with variable loads.

The delay elements **160**, **162** are tunable in that the delay introduced by each delay element **160**, **162** is individually configurable. Based on the skew measurements the delays imposed by the delay elements **160**, **162** are set to correct for skew. A delay element can be placed at each node or, alternatively, at a subset of nodes (as in FIGURE 9, where nodes **150**, **152** include respective delay elements **160**, **162** but the node **154** does not include a

delay element). The range and the minimum adjustable delay step of each delay element **160, 162** can be chosen based on its position in the trigger network.

The approach of FIGURE 9 in which delay elements **160, 162** are included in the trigger circuitry **28** has certain advantages. The skew is corrected independent of the number of detected photons. Additionally, the design condition of balance of the trigger network can be relaxed since any imbalance in the trigger network can be compensated by adjustment of the delay elements **160, 162**.

The disclosed detectors with time stamping having increased robustness against temporal drift and spatial skew are described with illustrative reference to TOF PET, as illustrated diagrammatically in FIGURE 1. However, the disclosed detectors will find more general application, for example in single photon detector arrays used in various instruments and areas of astronomy, physics, and so forth.

The invention has been described with reference to the preferred embodiments. Obviously, modifications and alterations will occur to others upon reading and understanding the preceding detailed description. It is intended that the invention be construed as including all such modifications and alterations insofar as they come within the scope of the appended claims or the equivalents thereof.

CLAIMS

Having described the preferred embodiments, the invention is now claimed to be:

1. A method comprising:
detecting an event;
generating a trigger signal associated with the detection of the event;
generating a first time stamp **(TS1)** for the trigger signal using a first time-to-digital converter (TDC) **(70)**;
generating a second time stamp **(TS2)** for the trigger signal using a second TDC **(72)** having a fixed time offset respective to the first TDC; and
associating a time stamp with the event based on the first time stamp, the second time stamp, and a comparison of (1) the time difference between the second time stamp and the first time stamp and (2) the fixed time offset.
2. The method of claim 1, wherein the associating comprises:
adjusting a time calibration of the first TDC and a time calibration of the second TDC responsive to the time difference between the second time stamp and the first time stamp being different from the fixed time offset.
3. The method of any one of claims 1-2, further comprising:
(i) synchronizing the first TDC **(70)** with a common clock signal **(62)**; and
(ii) synchronizing the second TDC **(72)** with the common clock signal **(62)**;
wherein the synchronizing operations (i) and (ii) determine the fixed time offset of the second TDC responsive to the first TDC as the period of the common clock signal or as a fixed fraction or multiple of the period of the common clock signal.
4. The method of any one of claims 1-3, wherein:
the generating of the first time stamp **(TS1)** using the first TDC **(70)** comprises measuring a first time interval **(100)** and transforming the first time interval into the first time stamp using a first transform operation;

the generating of the second time stamp **(TS2)** using the second TDC **(72)** comprises measuring a second time interval **(102)** and transforming the second time interval into the second time stamp using a second transform operation; and

the associating comprises adjusting the first and second transform operations responsive to the time difference between the second time stamp and the first time stamp being different from the fixed time offset.

5. The method of claim 4, wherein:

the first transform operation includes multiplying by a multiplication factor **(M)**;

the second transform operation includes multiplying by the multiplication factor **(M)**; and

the associating comprises increasing the multiplication factor **(M)** if the time difference between the second time stamp and the first time stamp is smaller than the fixed time offset and decreasing the multiplication factor **(M)** if the time difference between the second time stamp and the first time stamp is larger than the fixed time offset.

6. The method of any one of claims 1-3, wherein:

the generating of the first time stamp **(TS1)** using the first TDC **(70)** comprises measuring a first time interval **(100)** and transforming the first time interval into the first time stamp using a first transform operation including multiplying by a multiplication factor **(M)**;

the generating of the second time stamp **(TS2)** using the second TDC **(72)** comprises measuring a second time interval **(102)** and transforming the second time interval into the second time stamp using a second transform operation including multiplying by the multiplication factor **(M)**; and

the associating comprises increasing or decreasing the multiplication factor **(M)** to reduce any difference between (1) the time difference between the second time stamp and the first time stamp and (2) the fixed time offset.

7. The method of any one of claims 4-6, wherein the first transform operation includes applying a first look-up table **(LUT1)** and the second transform operation includes applying a second look-up table **(LUT2)**.

8. The method of any one of claims 1-7, wherein the detecting is performed using an array of detectors **(22)**, the trigger signal is generated by a triggering detector of the array of detectors, and the method further comprises:

delaying the trigger signal by a delay time selected based on the triggering detector.

9. The method of claim 8, wherein the delaying comprises:

providing tunable delay elements **(160, 162)** in a trigger signal network **(28)** associated with the array of detectors **(22)**; and

setting delay times for the tunable delay elements to compensate skew of the array of array of detectors.

10. The method of any one of claims 1-7, wherein the detecting is performed using an array of detectors **(22)**, the trigger signal is generated by a triggering detector of the array of detectors, and the method further comprises:

adjusting the first time stamp **(TS1)** and the second time stamp **(TS2)** based on the triggering detector.

11. The method of any one of claims 1-10, wherein the associating comprises:

associating the event with one of (i) the first time stamp **(TS1)**, (ii) the second time stamp **(TS2)**, and (iii) an aggregation of the first time stamp and the second time stamp;

wherein the associating selects between (i), (ii), and (iii) based on an assessment of reliability of the first time stamp and of the second time stamp.

12. The method of any one of claims 1-11, wherein the detecting comprises detecting a radiation particle using an array of positron emission tomography (PET) detectors **(10)**, and the method further comprises:

repeating the detecting, generating of the trigger signal, generating of first and second time stamps **(TS1, TS2)**, and associating to acquire a data set of time stamped radiation detection events;

generating a time-of-flight (TOF) PET data set from the data set of time stamped radiation detection events; and

reconstructing the TOF PET data set to generate a PET image.

13. An apparatus comprising:
a detector **(22)** configured to detect an event;
a first time-to-digital converter (TDC) **(70)** configured to generate a first time stamp **(TS1)** for the detection of the event;
a second TDC **(72)** configured to generate a second time stamp **(TS2)** for the detection of the event, there being a fixed time offset between the second TDC and the first TDC; and
an autocalibration circuit **(120)** configured to adjust the first TDC and the second TDC to keep the time difference between the second time stamp and the first time stamp equal to the fixed time offset between the second TDC and the first TDC.

14. The apparatus of claim 13, wherein the first TDC **(70)** and the second TDC **(72)** are both synchronized with a common clock signal **(62)** that defines the fixed time offset between the second TDC and the first TDC.

15. The apparatus of any one of claims 13-14, wherein:
the first TDC **(70)** measures a first time interval **(100)** and transforms the first time interval into the first time stamp **(TS1)** using a first transform operation;
the second TDC **(72)** measures a second time interval **(102)** and transforms the second time interval into the second time stamp **(TS2)** using a second transform operation;
and
the autocalibration circuit **(120)** adjusts the first and second transform operations to keep the time difference between the second time stamp and the first time stamp equal to the fixed time offset between the second TDC and the first TDC.

16. The apparatus of claim 15, wherein:
the first transform operation includes multiplying by a multiplication factor **(M)**;
the second transform operation includes multiplying by the multiplication factor **(M)**; and
the autocalibration circuit **(120)** is configured to adjust the multiplication factor **(M)** to keep the time difference between the second time stamp **(TS2)** and the first time stamp **(TS1)** equal to the fixed time offset between the second TDC and the first TDC.

17. The apparatus of claim 16, wherein the autocalibration unit **(120)** is configured to increase the multiplication factor **(M)** if the time difference between the second time stamp **(TS2)** and the first time stamp **(TS1)** is smaller than the fixed time offset and to decrease the multiplication factor if the time difference between the second time stamp and the first time stamp is larger than the fixed time offset.

18. The apparatus of any one of claims 15-17, wherein the first transform operation includes applying a first look-up table **(LUT1)** and the second transform operation includes applying a second look-up table **(LUT2)**.

19. The apparatus of any one of claims 13-18, wherein the detector comprises an array of detectors **(22)** and the apparatus further comprises:

trigger circuitry **(28)** configured to propagate a trigger signal associated with the detection of the event from a triggering detector of the array of detectors to the first and second TDC's **(70, 72)**, the trigger circuitry including delay elements **(160, 162)** configured to delay propagation of the trigger signal based on which detector is the triggering detector.

20. The apparatus of any one of claims 13-18, wherein the detector comprises an array of detectors **(22)** and the apparatus further comprises:

trigger circuitry **(28)** configured to propagate a trigger signal associated with the detection of the event from a triggering detector of the array of detectors to the first and second TDC's **(70, 72)**; and

skew correction circuitry **(132, 134, 136, 142, 160, 162)** configured to adjust a timestamp **(TS)** generated from the first timestamp **(TS1)** and the second timestamp **(TS2)** based on which detector is the triggering detector.

21. The apparatus of any one of claims 13-20, wherein the detector **(22)** comprises an array of silicon-based single photon avalanche detector (SPAD) cells **(130)**.

22. A positron emission tomography (PET) system including:

radiation detectors **(10)** comprising the apparatus of any one of claims 13-21; and

a processing device **(40)** configured to generate time-of-flight (TOF) PET data from the output of the radiation detectors and to reconstruct the TOF PET data to generate an image.

23. An apparatus comprising:

an array of detectors **(22)** configured to detect an event;

trigger circuitry **(28)** configured to propagate a trigger signal associated with the detection of the event from a triggering detector of the array of detectors to time stamp circuitry **(30)** configured to generate a time stamp **(TS)** for the detection of the event; and

skew correction circuitry **(132, 134, 136, 142, 160, 162)** configured to adjust the time stamp based on which detector is the triggering detector.

24. The apparatus of claim 23, wherein the skew correction circuitry comprises delay elements **(160, 162)** incorporated into the trigger circuitry **(28)** to delay the propagation of the trigger signal to the time stamp circuitry **(30)** based on which detector is the triggering detector.

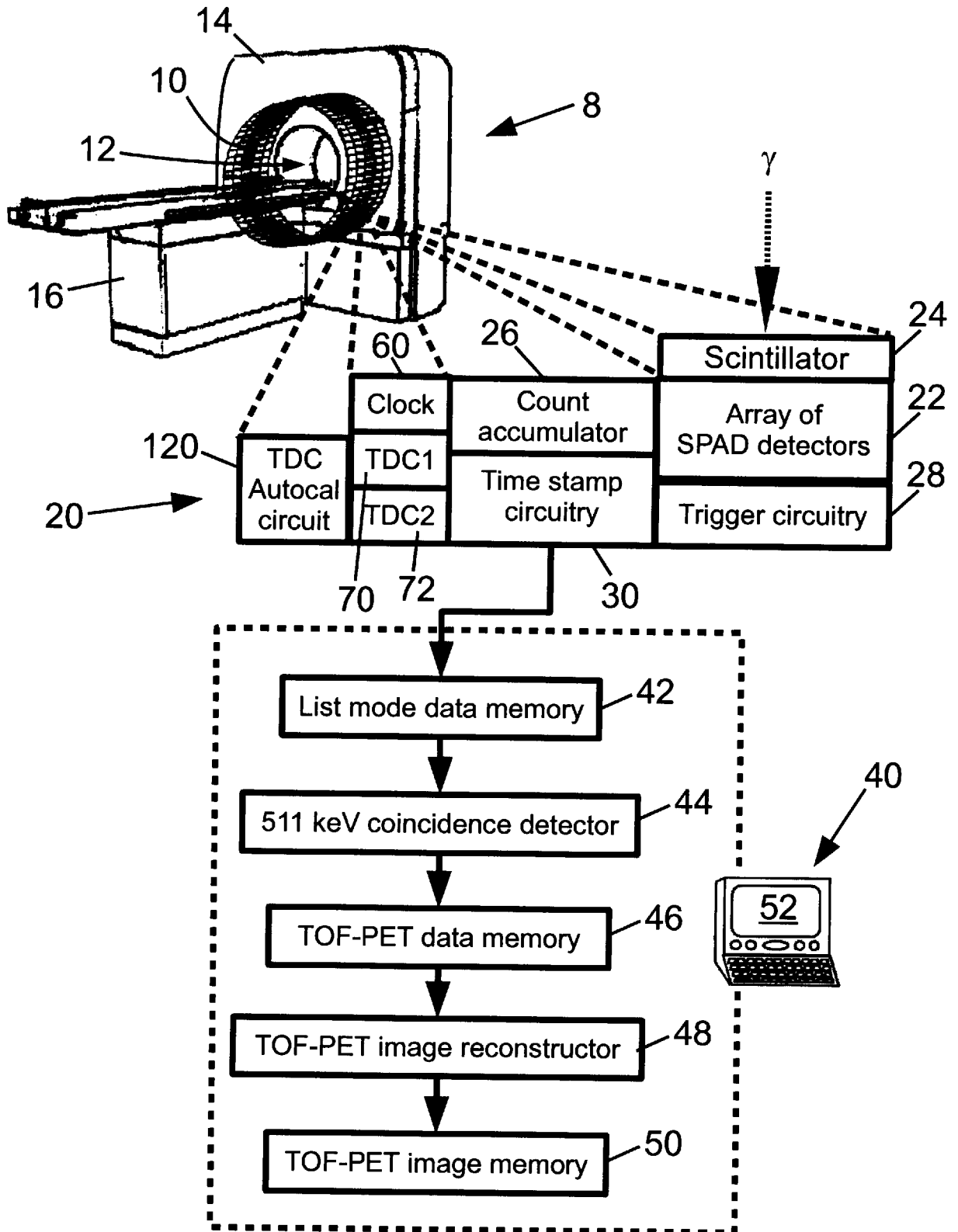
25. The apparatus of claim 23, wherein the skew correction circuitry **(132, 134, 136, 142)** is configured to adjust the generated time stamp **(TS)** based on a skew correction look-up table **(132)** tabulating the skew correction for each detector of the array of detectors **(22)**.

26. The apparatus of any one of claims 23-25, wherein the time stamp circuitry **(30)** comprises:

a first time-to-digital converter (TDC) **(70)** configured to generate a first time stamp **(TS1)** for the detection of the event based on the trigger signal;

a second TDC **(72)** configured to generate a second time stamp **(TS2)** for the detection of the event based on the trigger signal; and

an autocalibration circuit **(120)** configured to adjust the first TDC and the second TDC to keep the time difference between the second time stamp and the first time stamp equal to a predetermined fixed time offset between the second TDC and the first TDC.

**Fig. 1**

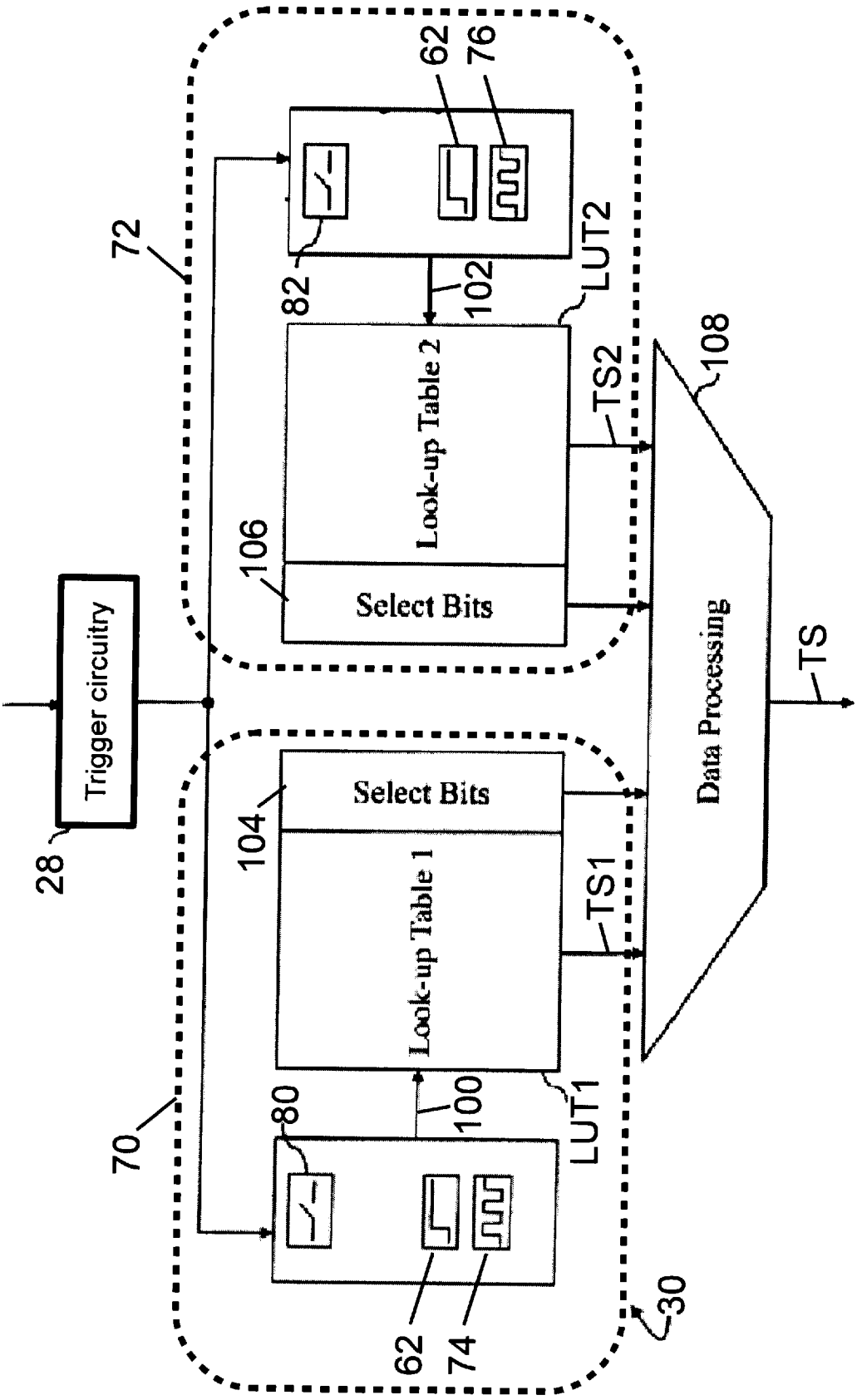


Fig. 2

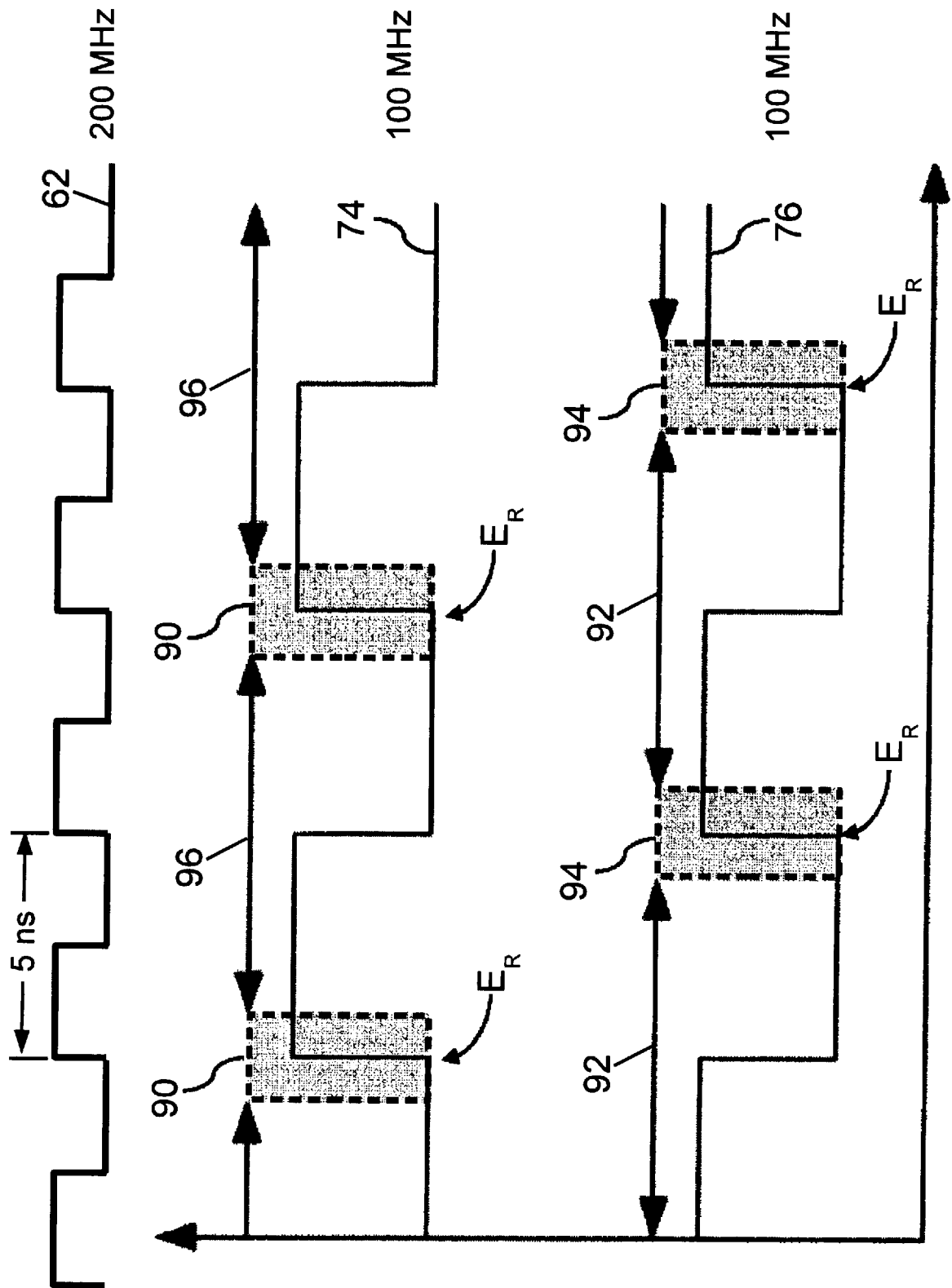
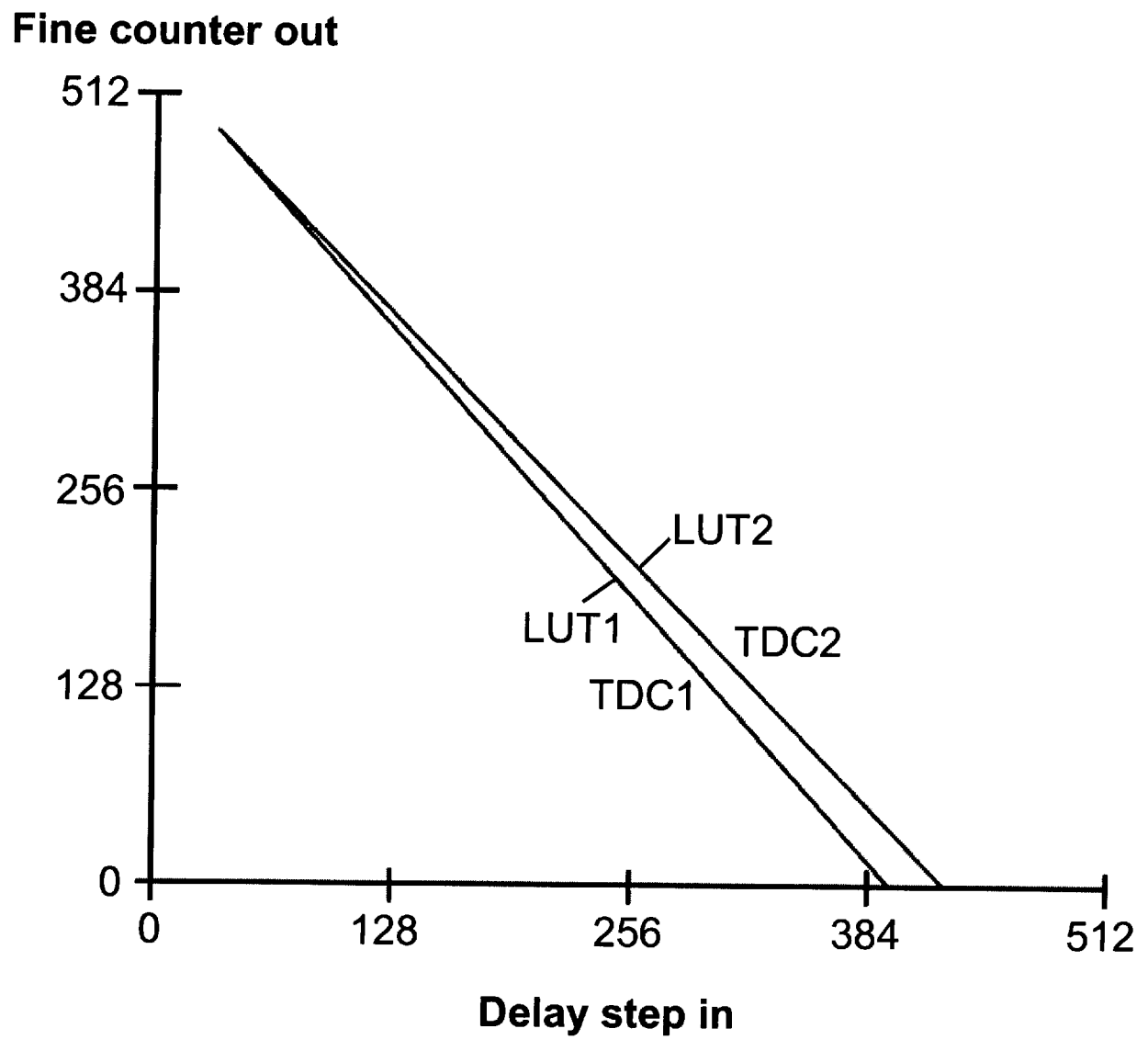
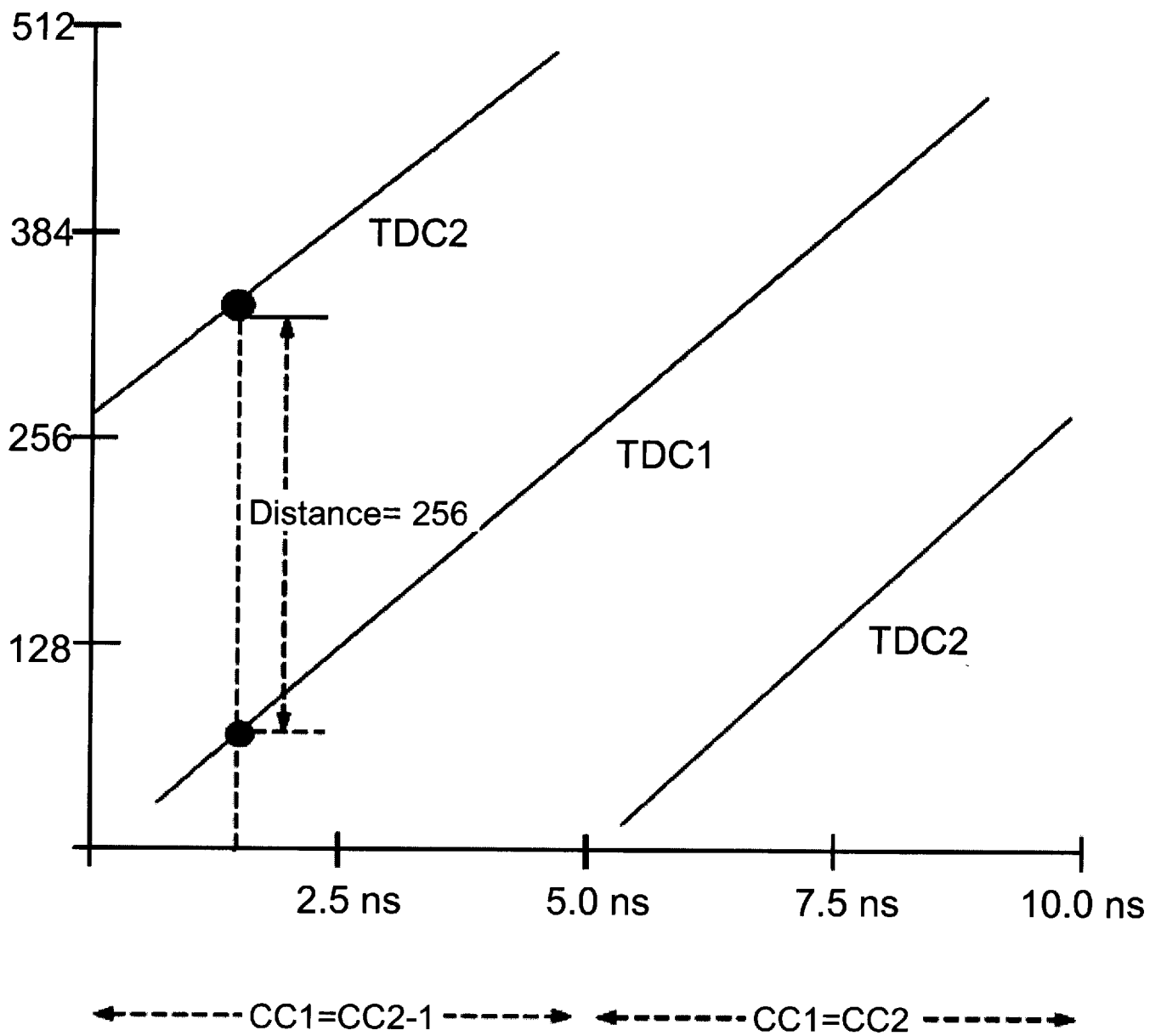


Fig. 3

**Fig. 4**

**Fig. 5**

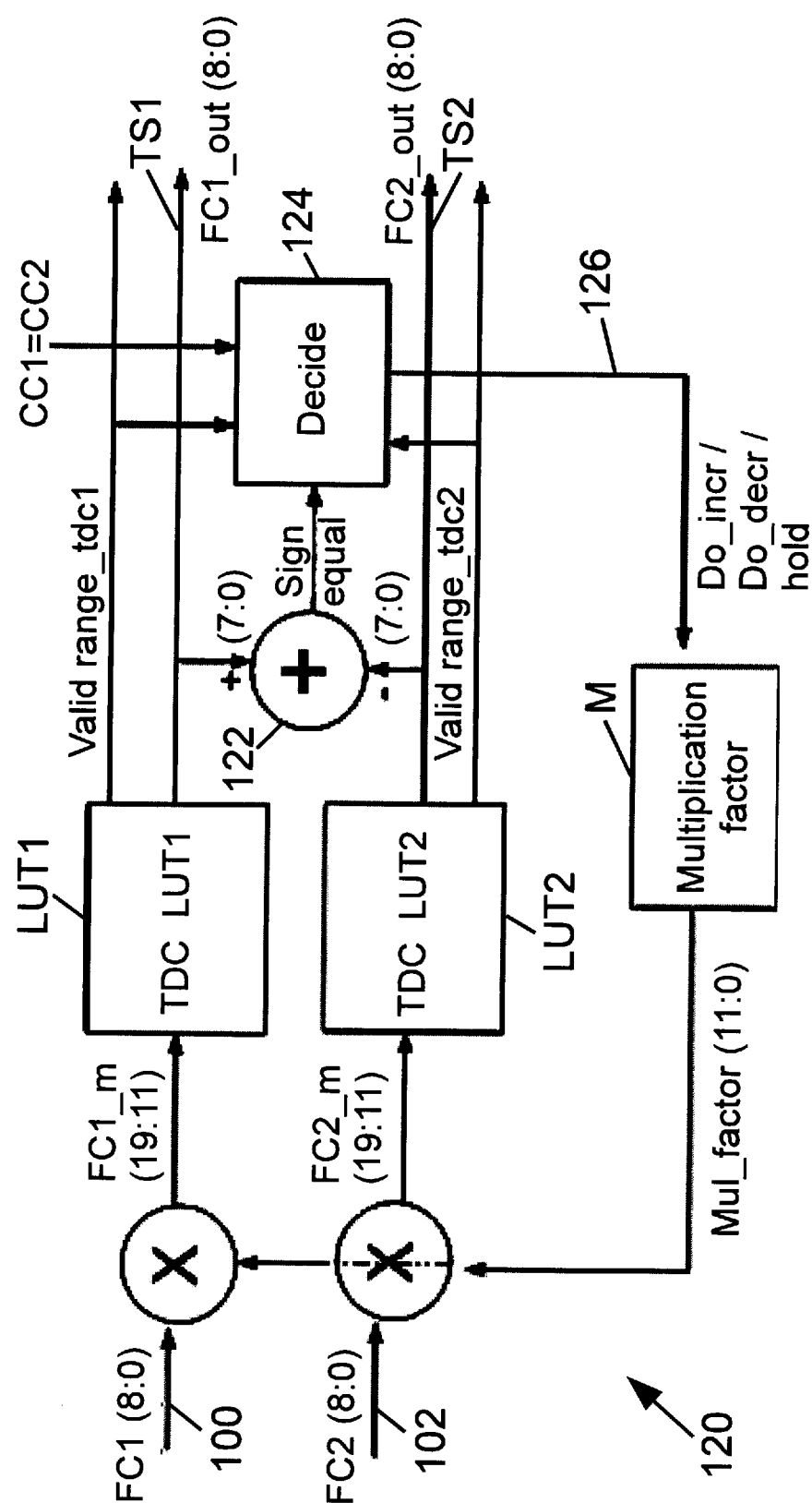
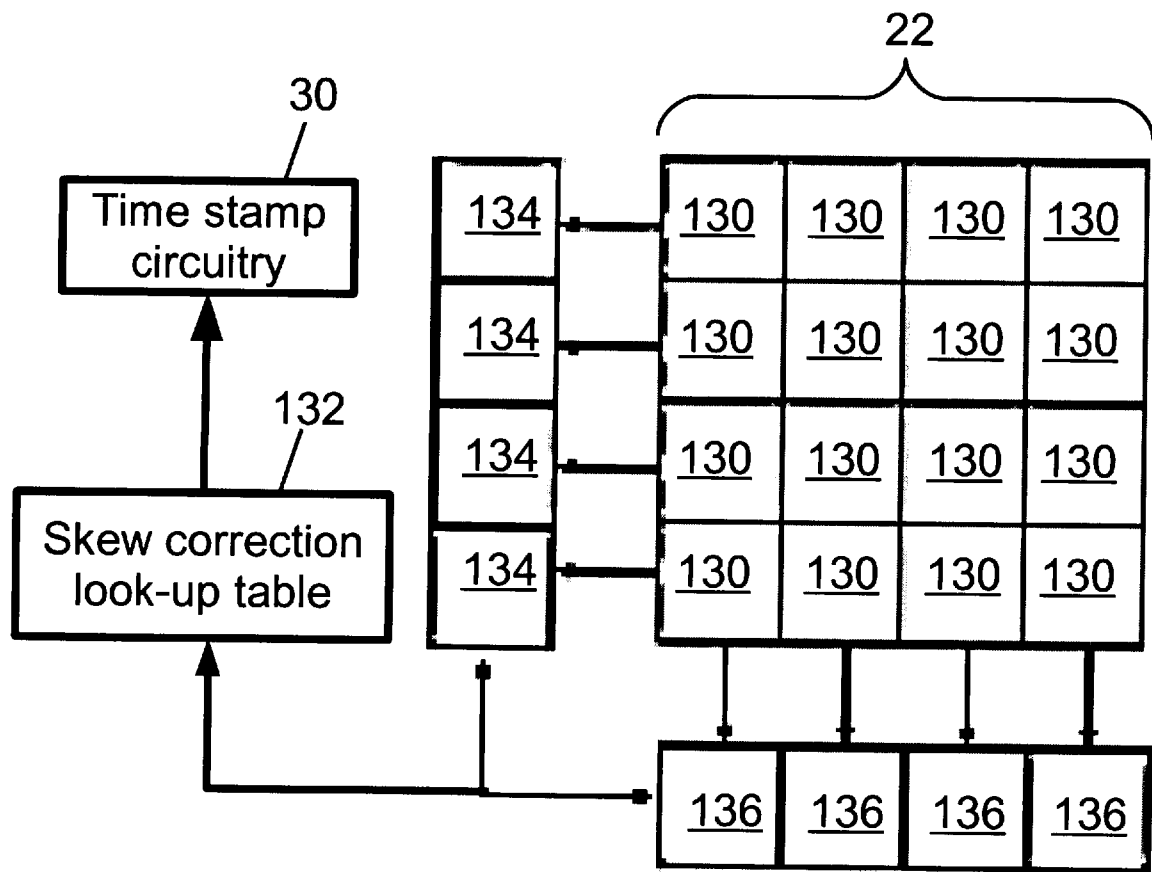
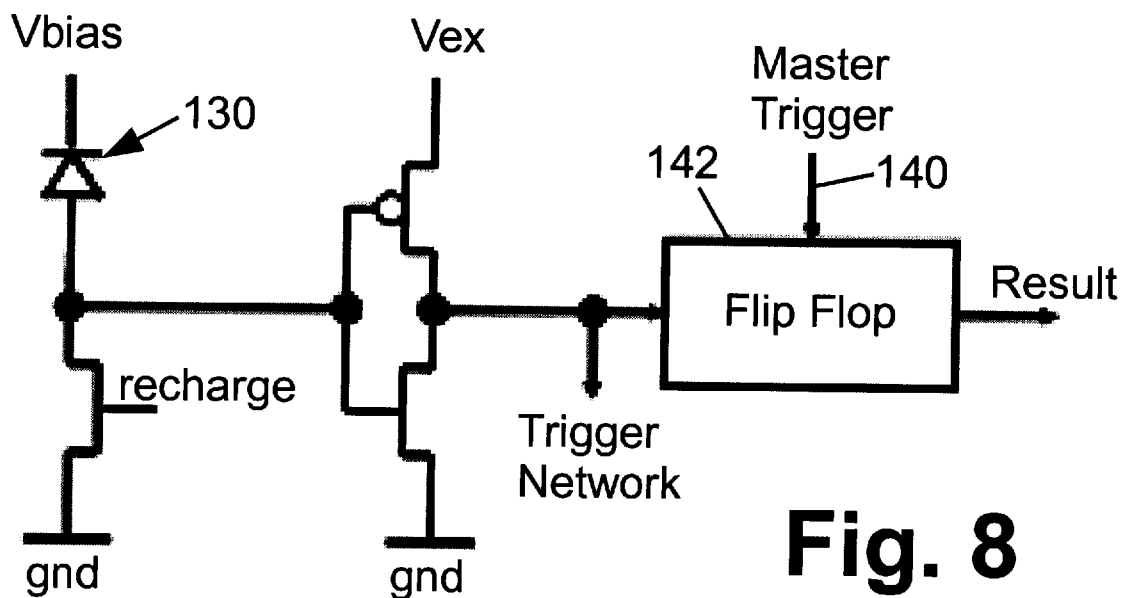
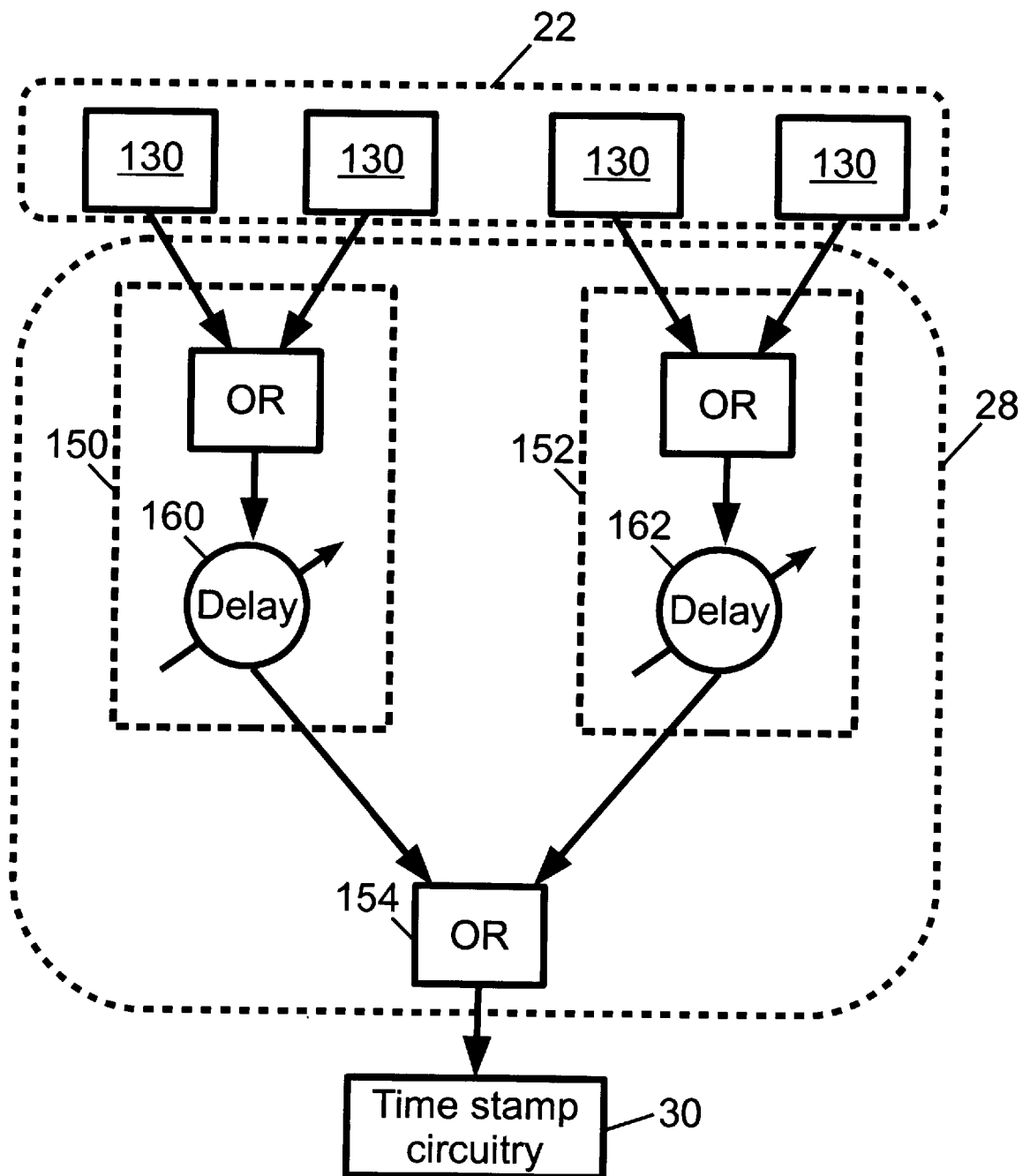


Fig. 6

**Fig. 7****Fig. 8**

**Fig. 9**