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(71) Applicant: APPLERA CORPORATION [US/US]; 850 Lincoln Centre Drive, Foster City, CA 94404 (US).

(72) Inventors: SAGATELYAN, Dmitry, M.; 120 Weymouth Ct., Alameda, CA 94502 (US). SLETTNES, Tor; 22336 Princeton Place, Castro Valley, CA 94552 (US).

(74) Agent: MALLON, Joseph, J.; KNOBBE, MARTENS, OLSON & BEAR, LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

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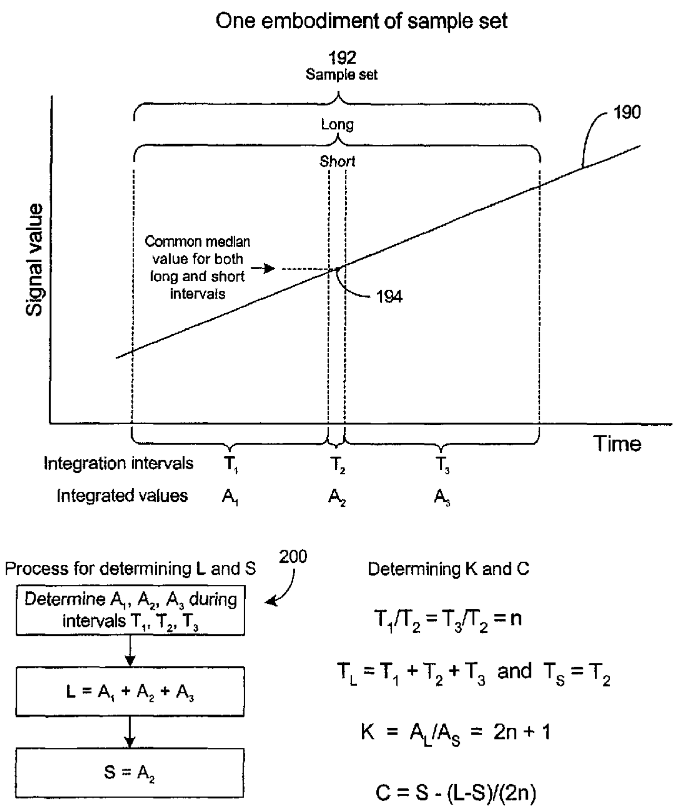
(54) Title: SYSTEM AND METHODS FOR DYNAMIC RANGE EXTENSION USING VARIABLE LENGTH INTEGRATION TIME SAMPLING



(57) Abstract: A photo-detector 122 generated signal 125 is measured as a sample set 192 comprising a long signal and a short signal. The short signal is scaled to the value of the long signal if the long signal exceeds a dynamic range 131 associated with the photo detector 122. In one embodiment, the short signal is obtained during a short time interval that is at the approximate middle of a long time interval such that the short and long intervals share a common median time value 194. Given such symmetry, an approximately linear signal 190 yields a proportionality parameter between the long and short signals thereby allowing the short signal to be scaled. The proportionality parameter facilitates determination of an integration independent component of the photo detector signal that should be removed from the measured long and short signals before scaling. A plurality of sample sets 260 can also be processed such that each sample set overlaps with its neighboring sample set, thereby increasing the effective number of sample sets.

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SYSTEM AND METHODS FOR DYNAMIC RANGE EXTENSION USING VARIABLE LENGTH INTEGRATION TIME SAMPLING

Background

Field

[0001] The present teachings generally relate to methods, software and apparatus useful for signal processing and, in various embodiments, to a system and method for resolving signals generated by a charge coupled device.

Description of the Related Art

[0002] Many photo-detectors such as charge coupled devices (CCD) are designed to detect light emissions and produce signals that can be resolved to quantify observed light intensity. Generally, conventional CCD's comprise one or more light-detecting elements that may be sensitive enough to detect as little as a few photo electrons. It is often desirable for a CCD device to possess a dynamic range of detection that extends several orders of magnitude with respect to the number of detectable photo electrons. Conventional solutions to increasing the dynamic range may include increasing the number of bits of analog-to-digital converters (ADC) associated with the CCD. This increase in the number of bits, however, also increases the cost of manufacture and processing time of the CCD. Another method for extending the dynamic range may involve splitting of the signal from a selected element into multiple signals that are hardware resolved. Each signal may further be provided with a different gain to thereby allow the split signals to collectively cover a wider dynamic range than that of a single signal. Such a hardware adaptation for dynamic range enhancement often requires costly retrofitting of the instrument and may not be practical to implement with existing devices. From the foregoing, it will be appreciated that there is a need for an alternative method by which the dynamic range of a CCD or other photo-detector device may be improved. Furthermore, there is a need for a dynamic range extension methodology that may be adapted for use with existing systems without necessitating significant hardware modifications.

Summary

[0003] In various embodiments, the present teachings disclose a system and methods for improving the dynamic range of detection for a CCD-generated signal using a variable length integration time sampling approach. In one aspect, an existing signal, having a predefined sampling pattern, is restructured into a wider dynamic range signal without the need for additional dedicated hardware. One or more constructs may be utilized, each of which may offer performance benefits for particular sampling implementations. Each construct may further be adapted for use with either shuttered or shutterless CCD devices, such as those used with some of the nucleic acid sequence analysis systems.

[0004] In various embodiments, the constructs for improving the dynamic range of detection assess a signal component using a per-frame analysis approach. Each frame may comprise long and/or short samplings determined, in part, by the duration of time for which a signal is generated from incoming light. Based on the scaling characteristics, an integration-independent component (offset) of the signal may be removed to facilitate scaling of the signal.

[0005] In one aspect, the invention comprises a method for dynamic range extension during the processing of a photo-detector acquired signal, the method comprising: Acquiring a first signal component

and a second signal component from a photo-detector wherein the first signal component comprises an integration of the photo-detector signal during a first time interval and wherein the second signal component comprises integration of the photo-detector signal during a second time interval wherein the second time interval is temporally proximal to and shorter than the first time interval such that the second signal component and the first signal component represent the acquired values of the photo-detector signal during a selected time period delineated by the first and second time intervals; Determining a scaling factor between the second signal component and the first signal component; Determining if the first signal component exceeds a selected dynamic range such that if the first signal component exceeds the dynamic range, scaling the second signal component by the scaling factor to approximate the first signal component; and thereafter using the scaled second signal component to represent the value of the signal during the selected time period.

[0006] In another aspect, the invention comprises a method for scaling of a signal generated by a photo-detector signal processor, the method comprising: Determining a first signal value L and a second signal value S for a sample set wherein the first signal value corresponds to a signal acquired during a first interval and wherein the second signal value corresponds to a signal acquired during a second interval, wherein the second signal value is less than the first signal value and wherein the first signal exceeds a specified range; Determining a proportionality parameter K between the first signal value and the second signal value; and Scaling the second signal value to approximate what the first signal value would be beyond the specified range.

[0007] In still another aspect, the invention comprises a method of sampling a photo-detector signal, the method comprising: Performing a series of integrations of the photo-detector signal wherein the series comprises alternating long and short integration intervals; and forming a plurality of overlapping sample sets wherein each sample set comprises integrations performed during at least one long interval to yield a first signal value and at least one short interval to yield a second signal value and wherein each sample set overlaps with its neighboring sample set by at least one of the long or short intervals.

[0008] In a still further aspect, the invention comprises a system for processing a photo-detector signal associated with a sequencing apparatus, comprising: A photo-detector that detects a labeled sample signal that is transformed into an electronic signal; An electronic signal processor that acquires one or more sample sets associated with the electronic signal wherein each sample set comprises a first signal value L and a second signal value S wherein the first signal value corresponds to an integrated photo-detector signal acquired during a first interval and wherein the second signal value corresponds to an integrated photo-detector signal acquired during a second interval that is less than the first interval; and wherein the signal processor is configured to determine a proportionality parameter K between the first signal value and the second signal value such that the second signal value can be scaled to the first signal value and wherein the processor outputs a processed signal representative of the sample set based on the first and second signal values.

Brief Description of the Drawings

[0009] Figure 1 illustrates an exemplary sequence analysis system incorporating a CCD label-detection component;

[0010] Figure 2 illustrates an exemplary method for software sampling of a signal comprising a series of long and short intervals;

[0011] Figure 3 illustrates a generalized signal scaling process that utilizes the long and short intervals from a sample set;

[0012] Figure 4 illustrates one embodiment of the analysis of a sample set comprising adjacent long and short intervals;

[0013] Figure 5 illustrates another embodiment of the sample set comprising a short interval interposed between long intervals such that a short signal is obtained from the short interval and a long signal is obtained from the long-short-long intervals;

[0014] Figure 6 illustrates another embodiment of the sample set including idle intervals interposed between integration intervals; and

[0015] Figure 7 illustrates an overlapping sampling method wherein portions of neighboring sample sets overlap to increase the number of sample sets.

Detailed Description of Certain Embodiments

[0016] These and other aspects, advantages, and novel features of the present teachings will become apparent upon reading the following detailed description and upon reference to the accompanying drawings. In the drawings, similar elements have similar reference numerals.

[0017] Figure 1A illustrates an exemplary schematic diagram for an analyzer 90 capable of sequence determination or fragment analysis for nucleic acid samples. In various embodiments, the analyzer 90 may comprise one or more components or devices that are used for labeling and identification of the samples by performing automated sequence analysis. The various components of the analyzer 90, described in greater detail hereinbelow, may comprise separate components or a singular integrated system. The present teachings may further be applied to both automatic and semi-automatic sequence analysis systems as well as to methodologies wherein some of the sequence analysis operations are manually performed.

[0018] It will further be appreciated that the dynamic range enhancement methods may be applied to numerous different types of photo and signal detection methodologies and are not necessarily limited to CCD signal detection and resolution. Additionally, although the present teachings are described in various embodiments in the context of sequence analysis, these methods may be readily adapted to other devices/instrumentation and used for purposes other than sequence analysis. For example, the present teachings may be applied to electronic telescopes and microscopes that utilize photo-detecting devices such as CCDs to improve the dynamic range and signal-to-noise ratio (SNR) of these instruments.

[0019] It will also be appreciated that the dynamic range enhancement methods may be applied to photo-detectors in general for a variety of applications, some of which are listed as examples above. Photo-detectors in general convert incident photons to electrical signals, and may include, by way example, CCDs, photomultipliers, or semiconductor based devices such as photo-diodes.

[0020] In the context of sequence analysis, the exemplary sequence analyzer 90 may comprise a reaction component 92 wherein PCR amplification or cycle sequencing of the sample is performed. Using these amplification techniques, a label such as a fluorescent or radioactive dideoxy-nucleotide may be introduced into the sample resulting in the production of a number of fragments of varying sequence lengths.

As is known in the art, one or more labels or dyes may be used during the amplification step to generate distinguishable fragment populations for each base to be subsequently identified. Following amplification, the fragments may then be subjected to a separation operation using a separation component 94. In one aspect the separation component 94 comprises a gel-based or capillary electrophoresis apparatus which separates the fragments into distinguishable populations. Using this approach, electrical current may be passed through the amplified sample fragments which have been loaded into a separation matrix (e.g. polyacrylamide or agarose gel). The application of electrical current results in the migration of the sample through the matrix. As the sample migration progresses, the labeled fragments are separated and passed through a detector 96 wherein resolution of the labeled fragments is performed.

[0021] In one aspect, the detector 96 may identify various sizes or differential compositions for the fragments based on the presence of the incorporated label. In one exemplary embodiment, fragment detection may be performed by generation of a detectable signal produced by a fluorescent label that is excited by a laser tuned to the label's absorption wavelength. Energy absorbed by the label results in a fluorescence emission that corresponds to a signal measured for each fragment. By keeping track of the order of fluorescent signal appearance along with the type of label incorporated into the fragment, the sequence of the sample can be discerned. A more detailed explanation of the sequencing process is provided in commonly assigned U.S. Patent No. 6,040,586, entitled "Method and System for Velocity-Normalized Position-Based Scanning."

[0022] Figure 1B, further illustrates exemplary components for the detector 96 which may be used to acquire the signal associated with a plurality of labeled fragments 100. As previously indicated, the labeled fragments 100 may be resolved by measuring the quantity of fluorescence or emitted energy generated when the fragments 100 are subjected to an excitation source 114 of the appropriate wavelength and energy (e.g. a tuned laser). The energy emissions 120 produced by a label 116 associated with the fragments 100 may be detected using a charge-coupled device (CCD) 122 as the fragments 100 pass through a detection window 123 where a plurality of energy detecting elements 124 capture at least some of the emitted energy from the label 116. In one aspect, an electronic signal 125 is generated by the CCD 122 that is approximately proportional to the relative abundance of the fragments 100 passing through the detection window 123 at the time of energy capture and the order which the fragments 100 appear in the detection window 123 may be indicative of their relative length with respect to one another.

[0023] A signal processor 126 is further configured to perform signal sampling operations to acquire the electronic signal generated by the CCD 122 in response to the fragments 100. In various embodiments, the signal processor 126 is configured to perform these sampling operations in a predetermined manner by signal acquisition over selected intervals. In many conventional signal processors, the pattern or timing of signal acquisition is limited by software and/or hardware imposed restrictions which limit the flexibility in analysis of the signal. This may further result in a limited dynamic range of signal acquisition. As will be described in greater detail hereinbelow, the present teachings may aid in overcoming some sampling limitations and provide increased flexibility in signal analysis and resolution. One desirable feature provided by various embodiments of the present teachings is the ability to utilize existing signal information in such a manner so as to improve the dynamic range of the system thereby potentially increasing its functionality.

[0024] In various embodiments, the signal 125 outputted by the CCD 122 may vary significantly between sample fragments 100. This presents a potential problem in conventional systems as the signal 125 may exceed the dynamic range of the signal processor 126 associated with the CCD 122 unless compensatory measures are taken. As illustrated in the simplified electropherogram 129 shown in Figure 1C, signals 125 may be acquired forming a signal distribution comprised of one or more signal intensity "peaks". Each peak may further be indicative of a detected fragment 100. The electropherogram 127 may further comprise a theoretical or experimental dynamic range limit 131 wherein peak intensities which exceed this limit 131 are subject to diminished accuracy in quantitation. This concept is exemplified by an exemplary peak 133 shown to exceed the dynamic range limit 131. In one aspect, if such an occurrence is left unmitigated, the quantitation and sequence resolution information arising from the peak 133 may be compromised. In various embodiments, the present teachings facilitate resolution of peak intensities which may exceed the normal signal processor tolerances and may establish a new dynamic range allowing for more accurate calculations to be performed with the available signal information.

[0025] In various embodiments, some of the information that may be determined through signal resolution and peak identification may include determination of the relative abundance or quantity of each fragment population. Evaluation of the signals may further be used to determine the sequence or composition of the sample using various known base sequence resolution techniques. It will further be appreciated by one of skill in the art that the exemplified signal distribution may represent one or more nucleic acid fragments for which the relative abundance of each fragment may be determined based, in part, upon the determination of the relative area associated with each peak. The present teachings may therefore be integrated into existing analysis approaches to facilitate peak evaluation and subsequent integration operations typically associated with sequence analysis.

[0026] In various embodiments, the analysis of the electropherogram 127 may be advantageously performed by the signal processor 126. The signal processor 126 may further be configured to execute on one or more processors. The signal processor's components may include, but are not limited to, software or hardware components, modules such as software modules, object-oriented software components, class components and task components, processes methods, functions, attributes, procedures, subroutines, segments of program code, drivers, firmware, microcode, circuitry, data, databases, data structures, tables, arrays, and variables. Furthermore, the signal processor 126 may output a processed signal or analysis results to other devices or instrumentation where further processing may take place.

[0027] Figure 2 illustrates one aspect of signal processing that may be implemented by the signal processor 126 described above in reference to Figure 1A-C. In various embodiments, a software controlled sampling method comprises an alternating series of having a long sample 134 and a short sample 136. These samples 134 reflect a time period where information is actively acquired from the CCD 122. Typically, an idle time interval (also referred to as "dead time") exists between adjacent sampling intervals. In the sampling scheme illustrated in Figure 2, an idle interval may be is interposed temporally between the long and short samples. In various embodiments, the idle interval may be substantially negligible when compared to the short or long sampling intervals. In other embodiments, the idle interval may be significant and account for an appreciable amount of the sampling time. As will be described in greater detail hereinbelow, when performing signal processing operations it may be desirable to account for idle time between signal samplings. In one aspect, identification of the idle time may be useful in improving the dynamic range of signal detection.

[0028] In various embodiments, the long sample 134 may represent an integration of the signal 125 during a time interval of T_L. Such an integration of the signal 125 from the CCD 122 may result in a measured signal L that includes an actual signal A_L and an integration independent component C (offset). The integration independent component C includes, but is not limited to, an on-chip amplifier bias and spurious charge associated with the CCD 122. Similarly, the short sample 136 may represent an integration of the signal 125 during a time interval of T_S. Such an integration of the signal 125 from the CCD 122 results in a measured signal S that may include an actual signal A_S and the offset C. Thus, the measured signals L and S may be expressed as

$$L = A_L + C \tag{1}$$

$$S = A_S + C. \tag{2}$$

Furthermore, a relationship between the actual signals A_L and A_S may be expressed as

$$\frac{A_L}{A_S} = K \tag{3}$$

where K is a proportionality parameter that depends on the nature of the actual signals A_L and A_S during their respective integration intervals T_L and T_S.

[0029] In one aspect, it is desirable to determine the actual signals A_L and A_S by subtracting the offset C from the measured signals L and S, respectively. The offset C may be determined by combining Equations 1-3 to yield

$$C = S - \frac{L-S}{K-1}. \tag{4}$$

Thus, for given values of L and S, by determining the signal dependent proportionality parameter K, the offset C may be determined with Equation 4. Then the resulting offset C may be subtracted from the measured signals L and S to yield the actual signals A_L and A_S, respectively. Once the actual signals A_L and A_S are determined, they may be either analyzed directly, or scaled in a manner described below.

[0030] In one aspect, a sample set comprises at least one long sample 134 and one short sample 136 that is temporally adjacent to the at least one long sample 134. As described below in greater detail, various combinations of the long and short samples may be formed to obtain such a sample set.

[0031] In one embodiment, the measured signals L and S may be obtained by directing the CCD signal 125 into a charge integrating analog to digital converter (ADC) and integrating for T_L and T_S respectively. In one aspect, the integrated signal may depend on the number of photo-electrons (N) generated by the CCD 122 where N obeys Poisson statistics. As is understood, relative intrinsic error associated with Poisson statistics may be expressed as $1/\sqrt{N}$. This relationship indicates that it is generally preferable for the integrated signal to be as large as possible within the dynamic range of the ADC. Thus in one aspect, long and short measurements that make up the sample set may be selectively scaled. It is generally preferable, for a given sample set where the CCD signal 125 is not relatively intense, that the long measurement is used for signal analysis if the long signal L is within the dynamic range of the ADC, since long measurements generally yield a signal with a higher signal-to-noise ratio. If the long signal L for a given sample set exceeds the dynamic range, then the short signal S may be scaled in a manner described below in order to extrapolate or approximate what the long signal L value might be. In this instance, the scaled value of the short signal S is then used for subsequent signal analysis.

[0032] Figure 3 illustrates a signal scaling process 140 that may be used to implement the aforementioned selective scaling approach. The process commences in a start state 142 and enters a loop 148 described below. In one aspect, the loop 148 cycles through an array or data structure that has been loaded with values for L and S acquired during CCD analysis of the sample. Alternatively, the loop 148 may progress in real time as analysis takes place. In state 144 of the loop 148, measured integral values of L and S of a sample set are determined. A decision state 146 that follows may be used to determine whether the value of L is off scale or exceeds the dynamic range of the instrumentation. In the instance where the dynamic range is not exceeded, L may be used for subsequent analysis as previously described. Thus in state 150, value of the offset C may be determined (according to Equation 4) from the measured values of L and S, along with the signal-specific value of the proportionality parameter K. In state 152 that follows, the offset C may be subtracted from the measured value of L to yield the actual signal A_L. In state 154 that follows, the scaled signal value that is to be used for subsequent analysis may be assigned the unscaled value of the actual signal A_L. The process 140 then determines in a decision state 156 whether the loop 148 should continue. If the loop 148 continues, then the process proceeds back to state 144 to initiate another cycle. If the loop 148 is complete, then the process terminates at a stop state 160.

[0033] In state 146, when the determination is made that the measured signal L exceeds the scaling limit, then it may be observed that the usefulness of the measured signal L is potentially limited, and thus the measured signal S may be processed and scaled so as to extrapolate as to where the actual long signal A_L might be. When initiating this extrapolation process, another decision state 162 may be entered that determines if the measured signal S itself exceeds the dynamic range. In one aspect, if the measured signal is within the dynamic range, then it may be processed and scaled in the manner described below.

[0034] In state 164, a value for the offset C is determined. In one aspect, the measured signal L may not be used for the current sample set since the value of C determined by using Equation 4 may produce an off scale result. Hence in one implementation of the process, the value of C may be obtained from the previous or a recent sample set. Offset determination in this manner is desirable as in many CCD systems, the offset C does not fluctuate substantially. This is typically true if the operating conditions, such as temperature, are controlled. Thus, the approximation method in state 164 is one manner for determining the value of C. In state 166 that follows, the offset C may be subtracted from the measured signal S to generate the actual signal A_S. In state 170 that follows, the actual signal A_S is scaled by a factor of K and may be assigned as the scaled signal value that is to be used for subsequent analysis. One method for determining the parameter K is described below. The process 140 then proceeds to the previously described decision state 156 to determine if the loop 148 should continue.

[0035] If the signal S is determined to be off scale in state 162, then both measured signals L and S may be considered off scale with regard to the dynamic range. In this instance, the process may identify each signal as having limited usefulness for the current sample set. In one implementation of the process, such off-scale measured signals may be "capped" or flagged in state 172 by a selected value so as to be easily recognizable during subsequent analysis. In one exemplary embodiment, the "actual" short signal A_S may be assigned a value of M, where M is the upper limit value of the dynamic range (for example, a 13-bit ADC has a dynamic range of 0-8191, and M=8192). In this manner, the capped signal value may be greater than scaled signals that were derived from the within-scale measured signals. Such easy identification of off-scale signals may then be dealt with in an appropriate manner during the subsequent analysis.

[0036] In one aspect, the sample set may comprise different combinations of the alternating short and long samples. Figures 4-6 illustrate various embodiments of the sample set and signal distribution characteristics. In each of the sample sets described hereinbelow, the measured signals L and S may be obtained in a sample set specific manner depending upon the characteristics of sampling. Furthermore, each sample set may be suited for a particular signal type resolution as described below. Thus the proportionality parameter K may be associated with a selected sample set to yield an operationally useful value in processing the signal information. In one aspect, determination of the sample set specific L, S, and K allows for determination of the scaled signal value described above in a generalized process in reference to Figure 3.

[0037] As illustrated in Figure 4, one embodiment of a sample set 182 comprises a combination of a long sample and an adjacent short sample. Alternatively, a sample set 186 may comprise a short sample followed by a long sample. Sample sets 182, 186 may be used when signals 180, 184, respectively, are either generally flat or change relatively slowly during the time interval associated with the sample sets. For such a signal, the integrated values of the actual signals A_L and A_S are directly proportional to their respective integration times T_L and T_S. Thus, $T_L/T_S = A_L/A_S$, where the ratio A_L/A_S is the definition of the proportionality parameter K (Equation 3). The integration time intervals may be selected such that T_L is greater than T_S by a factor of n, yielding

$$K = n \qquad (5a)$$

$$C = S - \frac{L-S}{n-1}. \qquad (5b)$$

Hence, the offset C can be determined according to Equation 5b, thereby allowing the scaled signal value to be determined in a manner described above.

[0038] As illustrated in Figure 5, another embodiment of a sample set 192 comprises a sequence of long-short-long sampling time intervals T_1, T_2, and T_3, with corresponding measured signals A_1, A_2, and A_3. The short sample comprises the measurement made during time interval $T_S = T_2$, and the long sample comprises the measurement made during time interval $T_L = T_1 + T_2 + T_3$. Thus, as illustrated in Figure 5, a process 200 for determining the measured signals L and S comprises determining A_1, A_2, and A_3 during time intervals T_1, T_2, and T_3, the measured signal $L = A_1 + A_2 + A_3$, and the measured signal $S = A_2$.

[0039] In various embodiments, the sample set 192 may be configured such that $T_1 = T_3$, and $T_1/T_2 = T_3/T_2 = n$, where n is a constant value. Given such a configuration, when a portion of a signal 190 encompassed by the sample set 192 is linear such as that shown in Figure 5, a common median value 194 is shared by both the short and long samples temporally and in terms of the signal value. From such a symmetry, it can be demonstrated that

$$K = \frac{A_L}{A_S} = 2n + 1 \quad (6a)$$

$$C = S - \frac{L - S}{2n}. \quad (6b)$$

Hence, the offset C can be determined according to Equation 6b, thereby allowing the scaled signal value to be determined in a manner described above. It will be appreciated that the sample set 192 illustrated in Figure 5 may be used when the CCD signal is approximately linear, at least during the interval encompassed by the sample set. In the instance where the CCD signal is not substantially linear, a systematic variance may be generated, however, this variance may be within the acceptable range for a given measurement and analysis.

[0040] In various embodiments, each of the long intervals T_1 and T_3 is selected to be approximately half of a "standard" non-segmented integration time. The short interval T_2 is typically substantially smaller than T_1 or T_3, and is selected to achieve, by methods disclosed herein, a desired dynamic range. It will be appreciated that the duration of the long and short intervals may be determined by the existing hardware used in the sequence analysis system. These durations may be modifiable or fixed depending on the type of instrument used. One advantage to the present teachings is that the disclosed methods may be applied to signal information generated by most conventional systems in its raw form without necessitating hardware modifications to improve the dynamic range.

[0041] Figure 6 illustrates another sample set 212 that accounts for the idle time intervals. In some respects, the sample set 212 is similar to the sample set 192 of Figure 5, with the exception that an idle time interval may be interposed between two adjacent sampling intervals. As such, the sample set 212 comprises a sequence of time intervals T_1 to T_5, wherein *T1* corresponds to a first long sample with measured signal A_1, T_2 corresponds to a first idle time interval, T_3 corresponds to a short sample with measured signal A_3, T_4 corresponds to a second idle time interval, and T_5 corresponds to a second long sample with measured signal A_5. In various embodiment, if a portion of a signal 210 encompassed by the sample set 212 is linear such as that shown in Figure 6, $T_1 = T_5$, and $T_2 = T_4$, therefore, a common median value 214 may be shared by both the short and long samples temporally and/or in terms of the signal value. Using such a symmetry, it may be shown that the ratio $A_L/A_S = (T_1 + T_3 + T_5)/T_3$.

[0042] In one implementation, the sample set 212 may be configured such that $T_1/T_3 = T_5/T_3 = n$, where n is a constant value. Thus,

$$K = \frac{A_L}{A_S} = 2n + 1 \quad (7a)$$

$$C = S - \frac{L - S}{2n}. \quad (7b)$$

Hence, the offset C can be determined according to Equation 7b, thereby allowing the scaled signal value to be determined in a manner similar to that described above. It will be appreciated that the sample set 212 illustrated in Figure 6 may be used when the CCD signal 125 is approximately linear, at least during the interval encompassed by the sample set. While the CCD signal 125 may not be substantially linear thereby generating a systematic variance, such variances may be within the acceptable range for a given measurement and analysis.

[0043] It will be appreciated that the first and second idle time intervals T_2 and T_4 are desirably similar in order to preserve the symmetry of the long and short samples, and thus facilitate establishing the common median value 214. In one embodiment, the idle interval may be a function of the CCD 122 and its associated signal processing devices, with a range of approximately 1 – 10 ms. In one aspect, the idle intervals T_2 and T_4 are selected to be as short as possible, usually limited by camera hardware and/or control firmware. The long intervals T_1, T_5, and the short interval T_3 therebetween may be selected in a similar manner as that described above in reference to Figure 5.

[0044] The various implementations of the CCD signal scaling process described above are typically repeated for a plurality of sample sets during measurement of the fragments 100 for a given sample. In one aspect, a sampling method may include overlapping of the sample sets in a manner described below. Figure 7 illustrates a series of alternating long and short integration intervals, with idle intervals interposed therebetween. It will be appreciated that while the sampling method of Figure 7 is described in context of having the idle intervals, the sampling method is equally applicable to situations where the idle interval is either relatively small or substantially negligible.

[0045] In various embodiments, an overlapping sampling method 240 comprises a plurality of sample sets with each sample set having the short interval interposed between the two long intervals. Such a sample set is described above in reference to Figure 6. An exemplary segment of CCD signal sampling comprises a sequence of long interval 242, short interval 244, long interval 246, short interval 250, long interval 252, and short interval 254.

[0046] A first exemplary sample set 260 comprises a short measured signal $S1$ obtained by integrating during the short interval 244 and a long measured signal $L1$ obtained by integrating during the intervals 242, 244, and 246. A second exemplary sample set 262 comprises a short measured signal $S2$ obtained by integrating during the short interval 250 and a long measured signal $L2$ obtained by integrating during the intervals 246, 250, and 252. Thus, the first and second sample sets 260 and 262 overlap in the long interval 246. Such an overlapping allows the number of samples sets (data points) to be increased for a given measurement pass. If the measurement pass comprises a total time interval having N non-overlapping sequential sample sets, the overlapping allows the number of sample sets to increase to approximately $2N$.

[0047] In one aspect, the various long-short-long integration methods described above in reference to Figures 5-7 can be adapted to reduce the effects of noise (thereby increasing the signal to noise ratio) associated with the CCD camera. In Figures 5-7, the short integration time interval is interposed between two long integration time intervals, and the measured long signal is the sum of the integrated values during the long-short-long intervals (*lsl* method). As described below in greater detail, if a long signal is instead comprised of the two long integration time intervals and excludes the short interval (*ll* method), the signal to noise ratio (SNR) of the measurement can be increased.

[0048] Such a scheme, in reference to Figure 5, yields in a similar manner described above, $L = A1 + A3$, $S = A2$, $K = 2n$, and $C = S - (L\text{-}S)/(2n - 1)$. When applied to the configuration illustrated in Figure 6, this scheme yields $L = A1 + A5$, $S = A3$, $K = 2n$, and $C = S - (L\text{-}S)/(2n - 1)$.

[0049] One advantage attained by reducing the number of samplings in the long signal L (two instead of three) relates to the noise σ associated with the CCD. As is generally understood, the noise σ

refers to an intrinsic uncertainty introduced during the process of quantifying the signal on the CCD and, in most cases, may be estimated as a square root of quadratures of it's main components – read noise σ_R and shot noise σ_S. For on-scale signal, including the weak signal where the increase in SNR is particularly useful, the SNR can be expressed as

$$SNR = \frac{A_L}{\sigma} = \frac{A_L}{\sqrt{\sigma_S^2 + \sigma_R^2}} = \frac{A_L}{\sqrt{A_L + \sigma_R^2}} \tag{8}$$

where A_L represents the actual signal and σ represents the overall noise during the measurement.. And since the shot noise σ_S follows Poisson statistics, $\sigma_S^2 = A_L$.

[0050] For the *lsl* and *ll* methods illustrated in Figures 5-7, each of the two long intervals is approximately *n* times as long as the short interval. Hence, $A_{lsl} = \frac{2 \cdot n + 1}{2 \cdot n} \cdot A_{ll}$, where A_{lsl} is the actual signal for the *lsl* method and A_{ll} is the actual signal for the *ll* method. Furthermore, the *lsl* method integrates during three separate time intervals such that the individual interval noises add in quadrature to yield $\sigma_{lsl}^2 = 3\sigma_R^2 + A_{lsl}$; similarly, the *ll* method integrates during two separate time intervals, yielding $\sigma_{ll}^2 = 2\sigma_R^2 + A_{ll}$. Thus, a ratio of SNR for the *ll* and *lsl* configurations can be expressed as

$$\frac{SNR_{ll}}{SNR_{lsl}} = \frac{2n}{2n+1} \sqrt{\frac{3\sigma_R^2 + A_{ll} \dfrac{2n+1}{2n}}{2\sigma_R^2 + A_{ll}}}. \tag{9}$$

For a typical operating configuration where n = 20, A_{ll} = 8000 electrons, and σ_R = 80 electrons rms, the ratio SNR_{ll}/SNR_{lsl} = 1.12, indicating an approximately 12% increase in the signal to noise ratio. As indicated in Equation 9, the ratio SNR_{ll}/SNR_{lsl} can be increased further by selecting a different values *n*, A_L, σ_R, or any combination thereof.

[0051] Although the above-disclosed embodiments of the present invention have shown, described, and pointed out the fundamental novel features of the invention as applied to the above-disclosed embodiments, it should be understood that various omissions, substitutions, and changes in the form of the detail of the devices, systems, and/or methods illustrated may be made by those skilled in the art without departing from the scope of the present invention. Consequently, the scope of the invention should not be limited to the foregoing description, but should be defined by the appended claims.

WHAT IS CLAIMED IS:

1. A method for dynamic range extension during the processing of a photo-detector acquired signal, the method comprising:

acquiring a first signal component and a second signal component from a photo-detector wherein the first signal component comprises an integration of the photo-detector signal during a first time interval and wherein the second signal component comprises integration of the photo-detector signal during a second time interval wherein the second time interval is temporally proximal to and shorter than the first time interval such that the second signal component and the first signal component represent the acquired values of the photo-detector signal during a selected time period delineated by the first and second time intervals;

determining a scaling factor between the second signal component and the first signal component;

determining if the first signal component exceeds a selected dynamic range;

if the first signal component exceeds the dynamic range, scaling the second signal component by the scaling factor to approximate the first signal component; and

using the scaled second signal component to represent the value of the signal during the selected time period.

2. The method of Claim 1, wherein scaling the second signal component further comprises subtracting an integration independent offset component from the second signal component prior to scaling by the scaling factor.

3. The method of Claim 2, wherein the selected time period comprises the second time interval residing substantially adjacent to the first time interval.

4. The method of Claim 2, wherein the period comprises a series of long-short-long integration times wherein a short integration time is interposed between two long integration times and wherein the first time interval comprises at least two long integration times, wherein the short and long time intervals share a common median value in time thereby allowing scaling of signals that vary approximately linearly in time.

5. The method of Claim 1, wherein the selected time period comprises the first time interval followed by the second time interval.

6. The method of Claim 5, wherein an intervening time interval resides between the first and the second time intervals.

7. The method of Claim 1, wherein the selected time period comprises substantially the first time interval.

8. The method of Claim 7, wherein the second time interval resides substantially within the first time interval.

9. The method of Claim 1, wherein the selected time interval comprises the first time interval and the second time interval, each residing substantially adjacent to one another.

10. The method of Claim 1, wherein the photo-detector comprises a CCD, a photomultiplier, or a semiconductor based device.

11. A method for scaling of a signal generated by a photo-detector signal processor, the method comprising:

determining a first signal value L and a second signal value S for a sample set wherein the first signal value corresponds to a signal acquired during a first interval and wherein the second signal value corresponds to a signal acquired during a second interval, wherein the second signal value is less than the first signal value and wherein the first signal exceeds a specified range;

determining a proportionality parameter K between the first signal value and the second signal value; and

scaling the second signal value to approximate what the first signal value would be beyond the specified range.

12. The method of Claim 11, wherein the specified range comprises a dynamic range of a component of the photo-detector signal processor.

13. The method of Claim 12, wherein the component of the photo-detector signal processor comprises an analog-to-digital converter.

14. The method of Claim 13, further comprising;

determining an offset component for the sample set; and

adjusting the first and second signal values to account for the offset component.

15. The method of Claim 14, further comprising assigning a scaled signal value for the sample set based upon the first and second signal values.

16. The method of Claim 15, wherein the offset component is subtracted from the first and second signal values.

17. The method of Claim 16, wherein the offset component comprises an integration independent signal C.

18. The method of Claim 17, wherein the offset C is determined according to the equation $C=S-(L-S)/(K-1)$.

19. The method of Claim 18, wherein assigning the scaled signal value for the sample set comprises:

selecting an offset adjusted first signal value to be the scaled signal value if the first signal value is within the specified range;

scaling the offset adjusted second signal value to the first signal value and assigning the scaled offset adjusted second signal value be the scaled signal value for the sample set if the first signal value exceeds the specified range and the unscaled second signal value is within the specified range; and

assigning a default value to the scaled signal value for the sample set if both the first and second signal values exceed the specified range.

20. The method of Claim 19, wherein the scaled second signal value is obtained by multiplying the offset C adjusted second signal value by the proportionality parameter K.

21. The method of Claim 18, wherein the first interval comprises a long interval and the second interval comprises a short interval substantially adjacent to the long interval.

22. The method of Claim 21, wherein the long interval is longer than the short interval by a factor of approximately *n* such that for a slow varying signal, the proportionality parameter *K* is approximately equal to *n* and offset C is determined according to the equation $C = S-(L-S)/(n-1)$.

23. The method of Claim 21, wherein the first interval comprises a long-short-long component sequence and the second interval comprises the short component of the long-short-long component sequence of the first interval such that the first and second intervals share a common median time value approximately centered about the short interval.

24. The method of Claim 23, wherein the long interval is longer than the short interval by a factor of approximately *n* such that for an approximately linear signal, the proportionality parameter *K* approximately equal to *2n+1* and offset C is determined according to the equation $C = S-(L-S)/(2n)$.

25. The method of Claim 21, wherein the first interval comprises a long-idle-short-idle-long component sequence and the second interval comprises the short interval of the long-idle-short-idle-long component sequence of the first interval wherein the idle component intervals correspond to dead times.

26. The method of Claim 25, wherein the first and second intervals share a common median time value approximately centered about the short interval.

27. The method of Claim 26, wherein the long interval is longer than the short interval by a factor of approximately *n* such that for an approximately linear signal, the proportionality parameter *K* is approximately equal to *2n+1* and offset is determined according to the equation $C = S-(L-S)/(2n)$.

28. The method of Claim 21, wherein the first interval comprises a long-long component sequence wherein the first signal excludes a short component interposed between the two long components, and wherein the second interval comprises said short component such that the first and second intervals share a common median time value approximately centered about the short interval.

29. The method of Claim 28, wherein the long interval is longer than the short interval by a factor of approximately *n* such that for an approximately linear signal, the proportionality parameter *K* approximately equal to *2n* and offset C is determined according to the equation $C = S-(L-S)/(2n-1)$.

30. The method of Claim 29, wherein the first signal's signal to noise ratio is improved by excluding a noise associated with the photo-detector during the short component wherein the noise includes a shot noise and a read noise.

31. The method of Claim 11, further comprising obtaining a plurality of sample sets wherein each sample set overlaps a neighboring sample set by at least one of the first or second intervals.

32. The method of Claim 11, wherein the photo-detector signal comprises a CCD, a photomultiplier, or a semiconductor based device.

33. A method of sampling a photo-detector signal, the method comprising:

performing a series of integrations of the photo-detector signal wherein the series comprises alternating long and short integration intervals; and

forming a plurality of overlapping sample sets wherein each sample set comprises integrations performed during at least one long interval to yield a first signal value and at least one short interval to yield a second signal value and wherein each sample set overlaps with its neighboring sample set by at least one of the long or short intervals.

34. The method of Claim 33, wherein the sample set comprises integrations performed during a sequence of long-short-long time intervals so as to overlap with its neighboring sample set by at least one of the long intervals thereby increasing the number of sample sets obtained from the series of integrations.

35. The method of Claim 34, wherein the sample set further comprises idle intervals so as to yield a sequence of long-idle-short-idle-long intervals.

36. The method of Claim 33, wherein the first signal value comprises a sum of integrations of the photo-detector signal performed during the long-short-long intervals, and wherein the second signal value comprises the integration of the photo-detector signal performed during the short interval such that the first and second signal values share a common median time value.

37. The method of Claim 33, wherein for an approximately linear photo-detector signal, the common median time value of the first and second signal values allow the second signal to be scaled to the first signal value when the first signal value exceeds a specified dynamic range.

38. The method of Claim 33, wherein the first signal value comprises a sum of integrations of the photo-detector signal performed during the two long intervals while excluding the short interval, and wherein the second signal value comprises the integration of the photo-detector signal performed during the short interval such that the first and second signal values share a common median time value.

39. The method of Claim 33, wherein the first signal's signal to noise ratio is improved by excluding a noise associated with the photo-detector during the short component wherein the noise includes a shot noise and a read noise.

40. The method of Claim 33, wherein the photo-detector signal comprises a CCD, a photomultiplier, or a semiconductor based device.

41. A system for processing a photo-detector signal associated with a sequencing apparatus, comprising:

a photo-detector that detects a labeled sample signal that is transformed into an electronic signal;

an electronic signal processor that acquires one or more sample sets associated with the electronic signal wherein each sample set comprises a first signal value L and a second signal value S wherein the first signal value corresponds to an integrated photo-detector signal acquired during a first interval and wherein the second signal value corresponds to an integrated photo-detector signal acquired during a second interval that is less than the first interval; and

wherein the signal processor is configured to determine a proportionality parameter K between the first signal value and the second signal value such that the second signal value can be scaled to the first signal value and wherein the processor outputs a processed signal representative of the sample set based on the first and second signal values.

42. The system of Claim 41, wherein the signal processor further adjusts the first and second signal values to account for identified offset.

43. The system of Claim 42, wherein identified offset is subtracted from the first and second signal values.

44. The system of Claim 43, wherein the offset comprises an integration independent signal component C determined by the equation $C = S - (L - S)/(K - 1)$.

45. The system of Claim 44, wherein the processed signal comprises:

the offset adjusted first signal value if the first signal value is within a dynamic range associated with the photo-detector;

a scaled second signal value if the first signal value exceeds the dynamic range and the second signal value is within the dynamic range; and

a specified value if both of the first and second signal values exceed the dynamic range.

46. The system of Claim 45, wherein the scaled second signal value comprises the offset adjusted second signal value multiplied by the proportionality parameter K.

47. The system of Claim 41, wherein the first interval comprises a long interval and the second interval comprises a short interval that is substantially adjacent to the long interval.

48. The system of Claim 47, wherein the long interval is longer than the short interval by a factor of approximately n such that for a slow varying photo-detector signal, the proportionality parameter K is approximately equal to n and offset is given by the equation $C = S - (L - S)/(n - 1)$.

49. The system of Claim 41, wherein the first interval comprises a long-short-long component sequence and the second interval comprises the short component interval of the long-short-long component sequence of the first interval such that the first and second intervals share a common median time value approximately centered about the short interval.

50. The system of Claim 46, wherein each of the long intervals is longer than the short interval by a factor of approximately n such that for an approximately linear photo-detector signal, the proportionality parameter K is approximated as $2n+1$ and the offset is determined according to the equation $C = S - (L - S)/(2n)$.

51. The system of Claim 41, wherein the first interval comprises a long-idle-short-idle-long component sequence and the second interval comprises the short component interval of the long-idle-short-idle-long component sequence of the first interval wherein the idle intervals correspond to dead times associated with the photo-detector and wherein the first and second intervals share a common median time value approximately centered about the short interval.

52. The system of Claim 51, wherein each of the long intervals is longer than the short interval by a factor of approximately n such that for an approximately linear photo-detector signal, the proportionality parameter K is approximated as $2n+1$ and the offset is determined according to the equation $C = S - (L - S)/(2n)$.

53. The system of Claim 41, wherein the first interval comprises a long-long component sequence wherein the first signal is not acquired during a short component interposed between the two long components, and wherein the second interval comprises said short component such that the first and second intervals share a common median time value approximately centered about the short interval.

54. The system of Claim 53, wherein the long interval is longer than the short interval by a factor of approximately n such that for an approximately linear signal, the proportionality parameter K approximately equal to $2n$ and offset C is determined according to the equation $C = S - (L - S)/(2n - 1)$.

55. The system of Claim 54, wherein the first signal's signal to noise ratio is improved by excluding a noise associated with the photo-detector during the short component wherein the noise includes a shot noise and a read noise.

56. The system of Claim 41, wherein the photo-detector comprises a CCD, a photomultiplier, or a semiconductor based device.

57. The system of Claim 41, wherein the signal processor obtains a plurality of sample sets wherein each sample set overlaps with its neighboring sample set by at least one of the first and second intervals.

FIGURE 1A

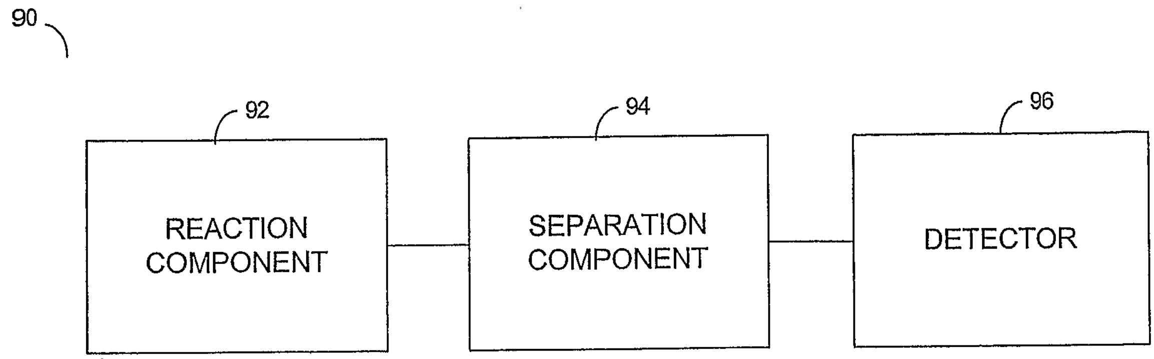


FIGURE 1B

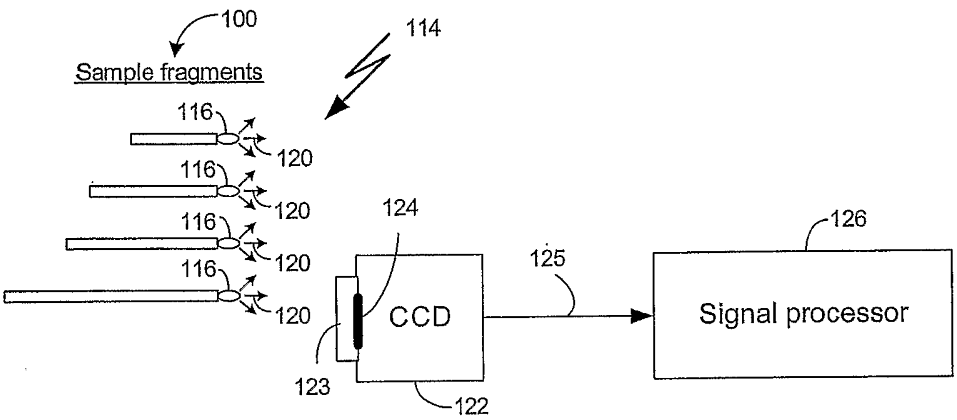
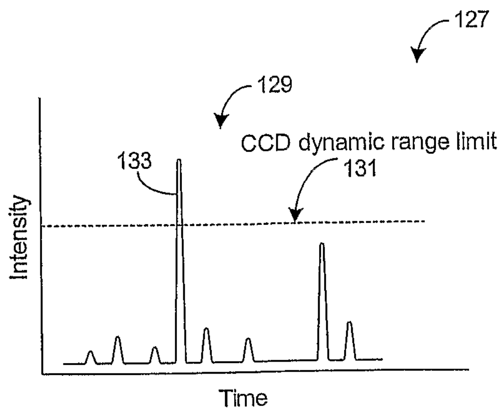


FIGURE 1C



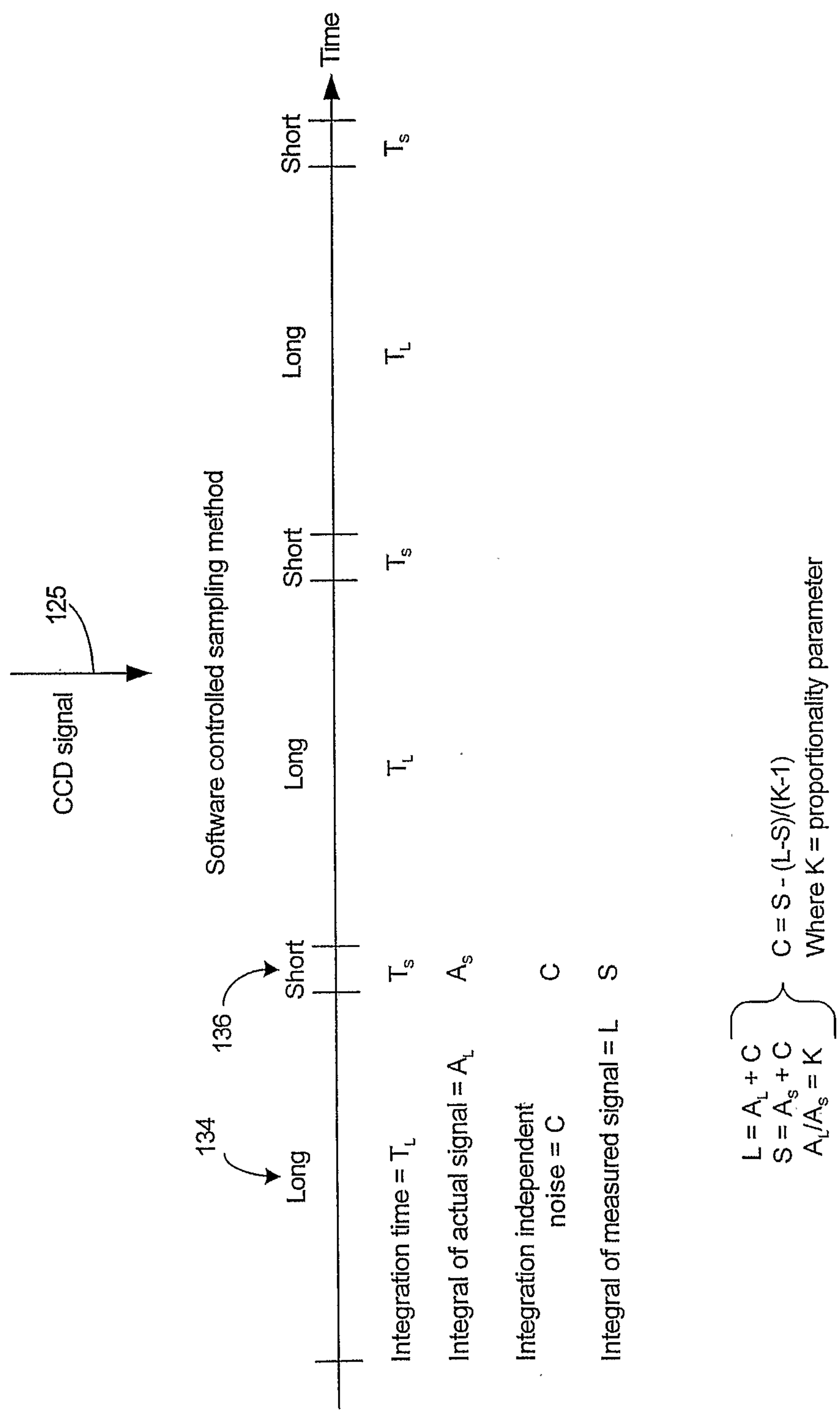

CCD signal
125
Software controlled sampling method
Time
134
136
Long
Short
Long
Short
Long
Short
Integration time = T_L
T_s
T_L
T_s
T_L
T_s
Integral of actual signal = A_L
A_s
Integration independent noise = C
C
Integral of measured signal = L
S
$L = A_L + C$
$S = A_s + C$
$A_L/A_s = K$
$C = S - (L-S)/(K-1)$
Where K = proportionality parameter

FIGURE 2

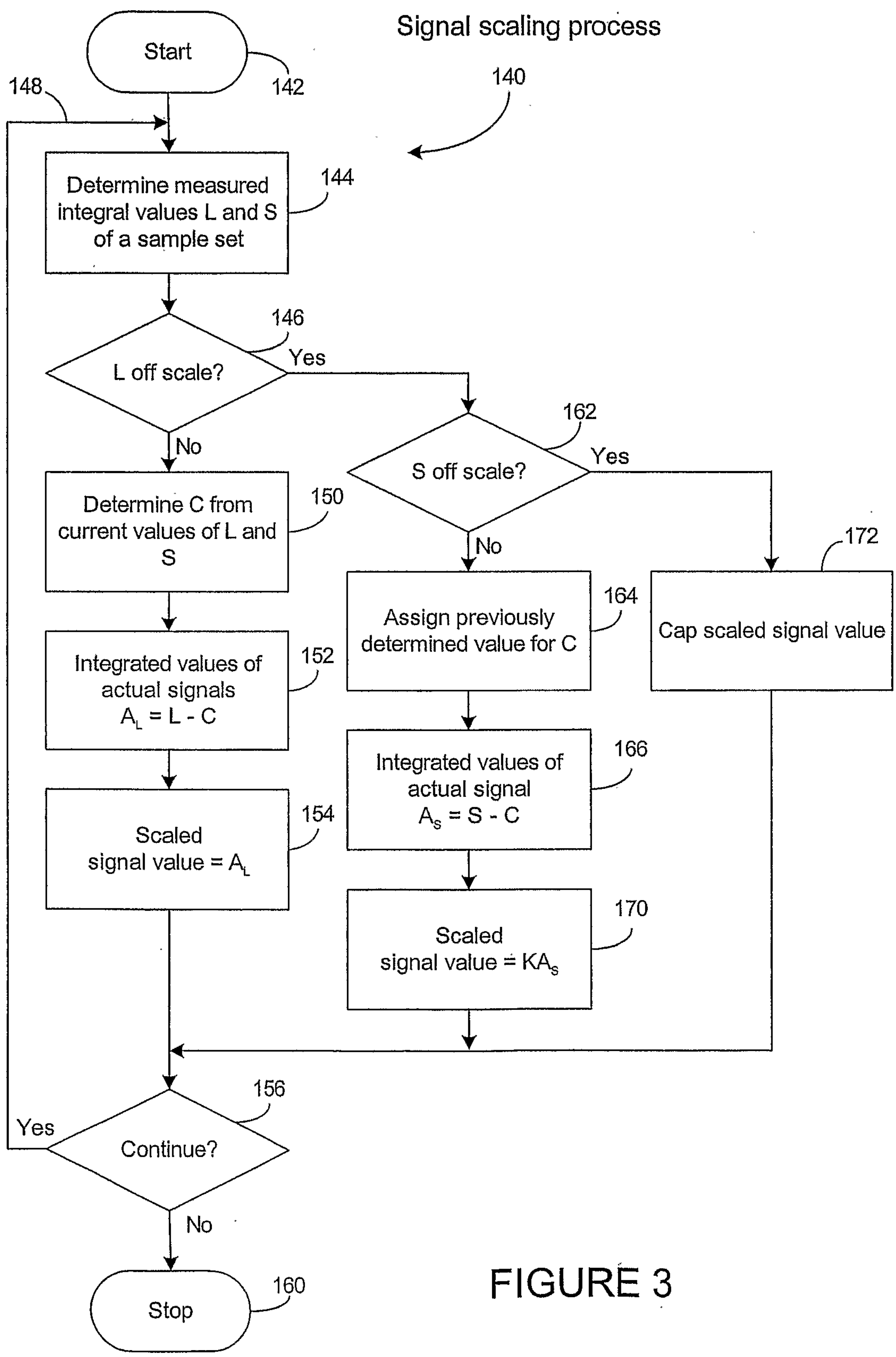
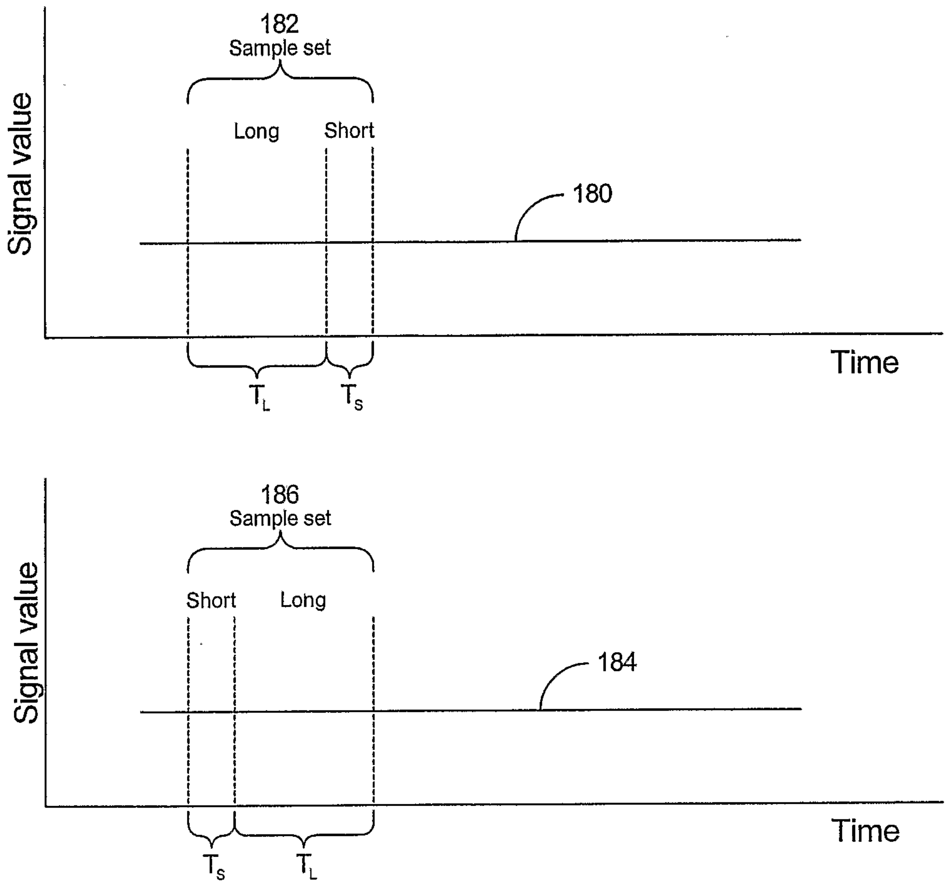

Signal scaling process
140
Start
142
148
Determine measured integral values L and S of a sample set
144
L off scale?
146
Yes
No
Determine C from current values of L and S
150
Integrated values of actual signals A_L = L - C
152
Scaled signal value = A_L
154
S off scale?
162
Yes
No
Assign previously determined value for C
164
Integrated values of actual signal A_S = S - C
166
Scaled signal value = KA_S
170
Cap scaled signal value
172
Continue?
156
Yes
No
Stop
160

FIGURE 3

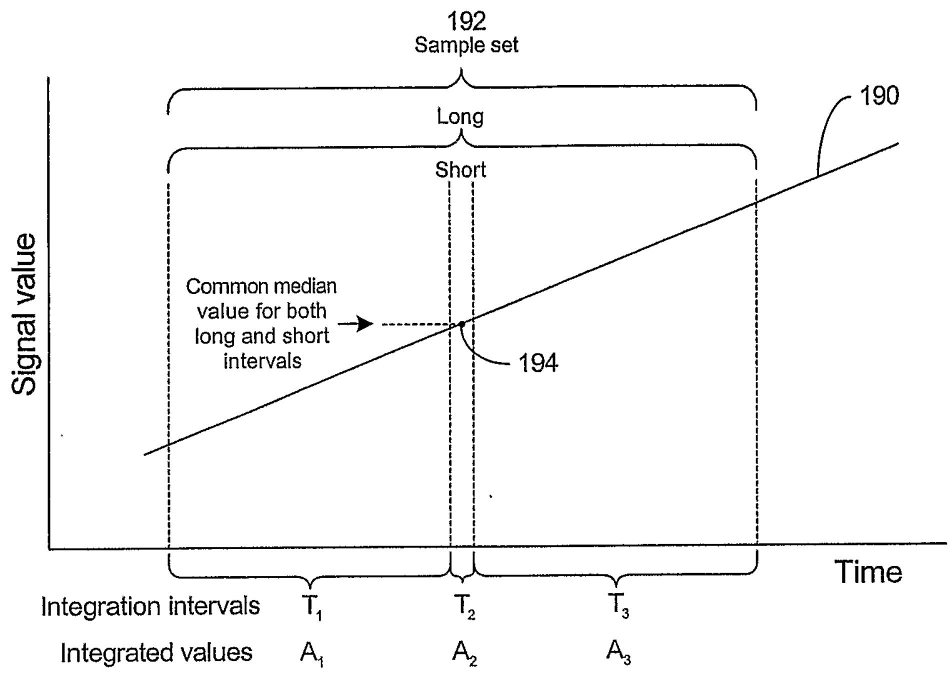
One embodiment of sample set

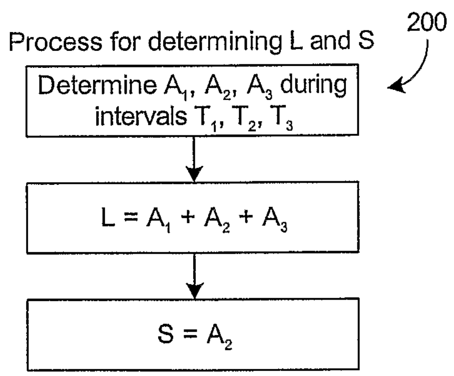


$T_L/T_S = A_L/A_S = n \Rightarrow K = n \Rightarrow C = S - (L-S)/(n-1)$

FIGURE 4

One embodiment of sample set





Determining K and C

$$T_1/T_2 = T_3/T_2 = n$$

$$T_L = T_1 + T_2 + T_3 \text{ and } T_S = T_2$$

$$K = A_L/A_S = 2n + 1$$

$$C = S - (L-S)/(2n)$$

FIGURE 5

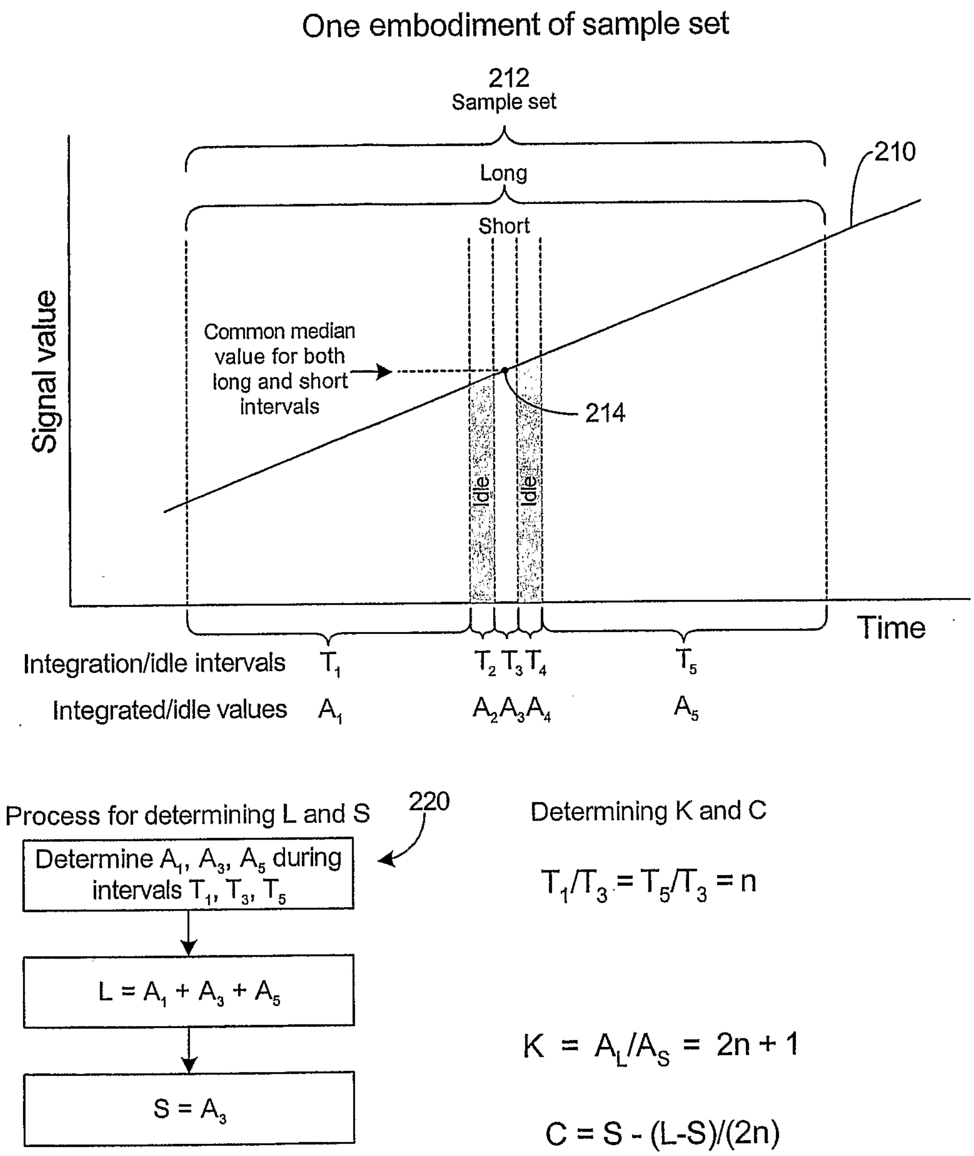

One embodiment of sample set
212
Sample set
210
Long
Short
Signal value
Common median value for both long and short intervals
214
Idle
Idle
Time
Integration/idle intervals
T_1
$T_2\ T_3\ T_4$
T_5
Integrated/idle values
A_1
$A_2 A_3 A_4$
A_5
Process for determining L and S
220
Determine A_1, A_3, A_5 during intervals T_1, T_3, T_5
$L = A_1 + A_3 + A_5$
$S = A_3$
Determining K and C
$T_1/T_3 = T_5/T_3 = n$
$K = A_L/A_S = 2n + 1$
$C = S - (L-S)/(2n)$

FIGURE 6

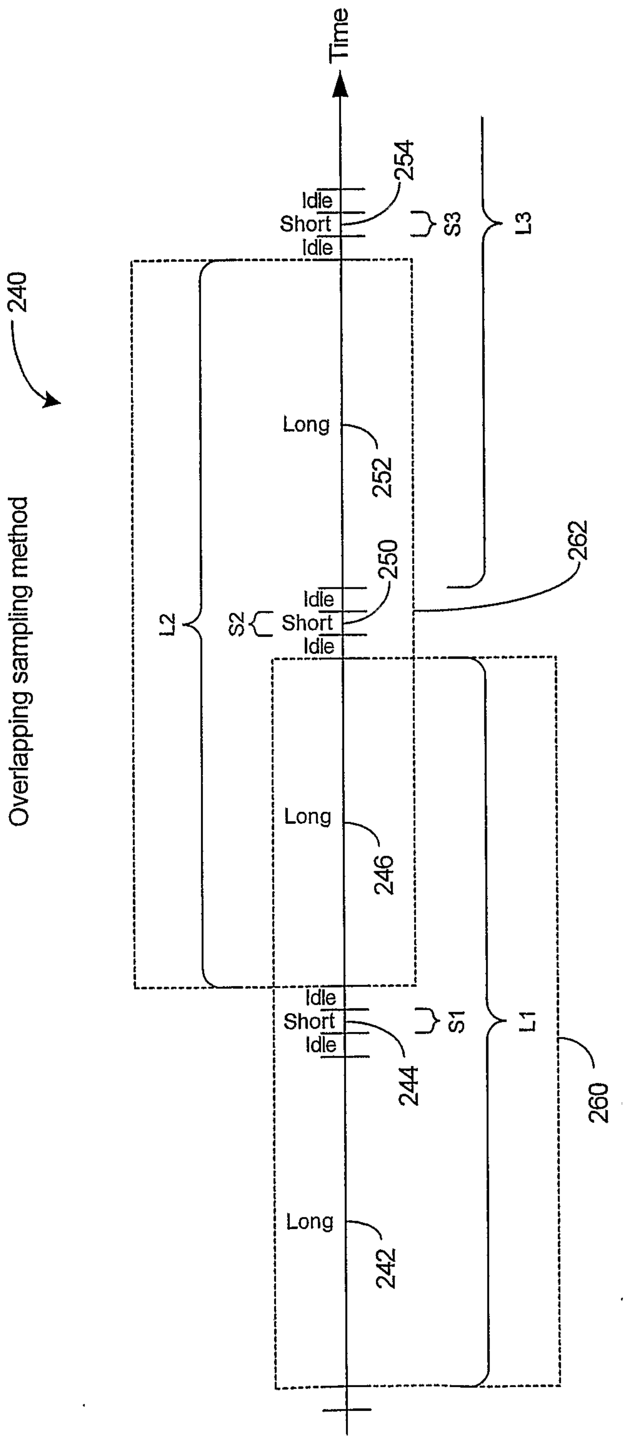

Overlapping sampling method
240
Time
Idle
Short
Idle
254
S3
L3
Long
252
262
Idle
Short
Idle
250
S2
L2
Long
246
Idle
Short
Idle
244
S1
L1
260
Long
242

FIGURE 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/32081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N21/64 G01J1/42 H04N3/15

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N G01J H04N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/122126 A1 (LENZ REIMAR) 5 September 2002 (2002-09-05)	1-22,32, 33, 40-48, 50,56
Y	page 1, paragraph 14 page 2, paragraph 17 - paragraph 19 page 2, paragraph 21 - paragraph 22 ---	23-31, 34-39, 49, 51-55,57
Y	WO 97 17800 A (FOSSUM ERIC C ;CALIFORNIA INST OF TECHN (US); YADID PECHT ORLY (US)) 15 May 1997 (1997-05-15) page 13, line 13 - line 23 page 14, line 8 - line 33 ---	23-31, 34-39, 49, 51-55,57
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2004	26/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Navas Montero, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/32081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 008 486 A (BECHTEL JON H ET AL) 28 December 1999 (1999-12-28) column 2, line 8 - line 11 column 2, line 39 - line 46 column 4, line 28 - line 34 column 6, line 1 - line 4 column 6, line 57 - line 64 column 7, line 7 - line 10 ---	1,11,41
A	ORLY YADID-PECHT: "WIDE-DYNAMIC-RANGE SENSORS" OPTICAL ENGINEERING, SOC. OF PHOTO-OPTICAL INSTRUMENTATION ENGINEERS. BELLINGHAM, US, vol. 38, no. 10, October 1999 (1999-10), pages 1650-1660, XP000859855 ISSN: 0091-3286 page 1657, left-hand column, line 27 -page 1658, left-hand column, line 4 -----	1,11,41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/32081

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		EP 0862829 A1	09-09-1998
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		CA 2315145 A1	08-07-1999
		DE 69816126 D1	07-08-2003
		EP 1044561 A1	18-10-2000
		JP 2002500476 T	08-01-2002
		WO 9934592 A1	08-07-1999