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Photon Spectroscopy
by picoseconds differential Geiger-mode Si Photomultiplier

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ABSTRACT

The pixel array silicon photomultiplier (SiPM) is known as an excellent photon sensor with picoseconds avalanche process with the capacity for millions amplification of photoelectrons. In addition, a higher quantum efficiency(QE), small size, low bias voltage, light durability are attractive features for biological applications. The primary disadvantage is the limited dynamic range due to the 50ns recharge process and a high dark count which is an additional hurdle. We have developed a wide dynamic Si photon detection system applying ultra-fast differentiation signal processing, temperature control by thermoelectric device and Giga photon counter with 9 decimal digits dynamic range.

The tested performance is six orders of magnitude with 600ps pulse width and sub-fW sensitivity. Combined with 405nm laser illumination and motored monochromator, Laser Induced Fluorescence Photon Spectrometry (LIPS) has been developed with a scan range from 200~900nm at maximum of 500nm/sec and 1nm FWHM. Based on the Planck equation $E=h\nu$, this photon counting spectrum provides a fundamental advance in spectral analysis by digital processing. Advantages include its ultimate sensitivity, theoretical linearity, as well as quantitative and logarithmic analysis without use of arbitrary units. Laser excitation is also useful for evaluation of photobleaching or oxidation in materials by higher energy illumination. Traditional typical photocurrent detection limit is about 1pW which includes millions of photons, however using our system it is possible to evaluate the photon spectrum and determine background noise and auto fluorescence(AFL) in optics in any cytometry or imaging system component. In addition, the photon-stream digital signal opens up a new approach for picosecond time-domain analysis. Photon spectroscopy is a powerful method for analysis of fluorescence and optical properties in biology.

Keywords: Single Photon, Silicon Photomultiplier, Differential Geiger-mode, Motored Monochromator, Laser Induced Photon Spectroscopy(LIPS), Auto-fluorescence, Raman, Photon Stream Digital (PSD)

1. INTRODUCTION

The photon is one of elementary particle "Boson" defined as quanta by Planck (1901)[1] and Einstein (1905)[2]. It is an energy packet which is proportional to Planck's constant and frequency. Single photon detection offers the ultimate sensitivity of single light energy packet and can be described by SI units. From a theoretical point of view, light intensity has no limitation of linearity and dynamic range. If it is possible to detect single photon with infinite rate, it must be the ideal photo sensor. This is the important target for photo sensing systems. On the other hand, available photo sensors have several limitations such as sensitivity, dynamic range, bandwidth and noise. Since the invention of the photomultiplier tube (PMT) in 1936 by RCA [3], the PMT has been widely used for low level light detection in particle physics, astronomy and biology. Excellent performance of PMTs is based on an avalanche effect which can amplify from a single electron hole pair impinging on the photocathode to millions of electrons via cascaded dynodes in a vacuum. Using the avalanche effect, it is possible to detect a single photon as an impulse signal. Thus, photon counting by a PMT is applied for extremely lower level photon detection. Regarding the counting rate, a typical photoelectron(PE) pulse has 10ns pulse width and limited count rate up to 10Mega counts per second (cps) due to traveling distance in vacuum, stray capacitance and limited amplification bandwidth. Considering photocathode quantum efficiency(QE) to be around 20%, 10Mcps is therefore equivalent to several 10s of pW in visible wavelength.

Within cellular analysis by flow cytometry which is our research area, it is necessary to detect wide dynamic range fluorescence in the range from pW up to μ W. In order to detect this wide dynamic range, flow cytometry has traditionally used PMTs in the photocurrent mode with variable gain by acceleration via high voltage adjustment. Ultra-high rate single photon detection to meet cellular analysis is quite challenging because 1nW fluorescence includes over one Giga photon per sec. This is the reason that it is difficult to recognize light as energy packets and thus usually detects it as photocurrent as the integral of total photons. In order to detect Giga rate pulses, it is mandatory to move from the Mega to the Giga Hertz domain in electronic design. Fortunately, Moor's law in semiconductor industry has been migrated to GHz clock CPU or GHz wireless communication. In addition, Silicon Photomultiplier (SiPM) with avalanche Geiger-mode amplification is now available commercially with rapidly changing options. Achieving ultra-high rate photon detection for the next generation cellular analysis is the motivation and target for our current development.

2. MATERIAL AND METHOD

The pioneering work on silicon avalanche effect was achieved by RCA[4], Shockley Laboratory [5] and later by many research institutes and companies in 1960's and early '70s. The first single photon avalanche diode (SPAD) was commercialized by Perkin-Elmer. Recently, the pixel array silicon photomultipliers designed to expand linearity have been developed and produced by many companies. The silicon photomultiplier is a solid-state device which produces electron hole pair at a PN junction by incident photons. Depending on the electric field, a photoelectron is accelerated and produces an avalanche effect in a micron-based distance which is called "Geiger" mode. The SiPM is potentially attractive for photon detection because of its compact size, lower bias voltage, high quantum efficiency, wide wavelength sensitivity, illumination durability, magnetic insensitivity and array capability. On the other hand, the limited dynamic range even by arrayed pixel structure and high dark count rates are considered drawbacks for a variety of applications. Due to its limited dynamic range, the SiPM has been used as a time-resolved binary sensor for particle physics [6] , Lidar [7] or medical TOF-PET [8]. How to break through the limited dynamic range has been the key question that has limited biological applications.

2.1 Differential Geiger-mode silicon multiplier for sub-ns photoelectron pulse

Conventional application by SiPM or PMT requires larger sensor area for high collection efficiency in free space optics. This direction has a trade-off with higher count rate and lower dark count. A basic concept in electronics to achieve higher speed is that shorter and smaller is better as demonstrated within the history of semiconductor development. In order to obtain high coupling efficiency even by small sensor size, the use of fiber optics is the best solution to resolve this trade-off relationship. In addition, biological application focuses heavily on the light intensity itself, and have less concern on photon pulse height as might be important in high energy physics. Biological applications have a slightly different approach and requirements compared to conventional SiPM applications. Figure 1 shows typical PMT and silicon photodiode structures. The induced electron at the PMT photo-cathode is amplified by over ten stage dynodes. Dynode structure in a vacuum requires a distance of several ten millimeters. During the amplification process, the electron velocity disperses, resulting in the photoelectron having a continuous pulse height. Recently, Hamamatsu developed a small size micro-PMT[1] which is manufactured by the Silicon Micro Electro Mechanical Systems (MEMS) process[9].

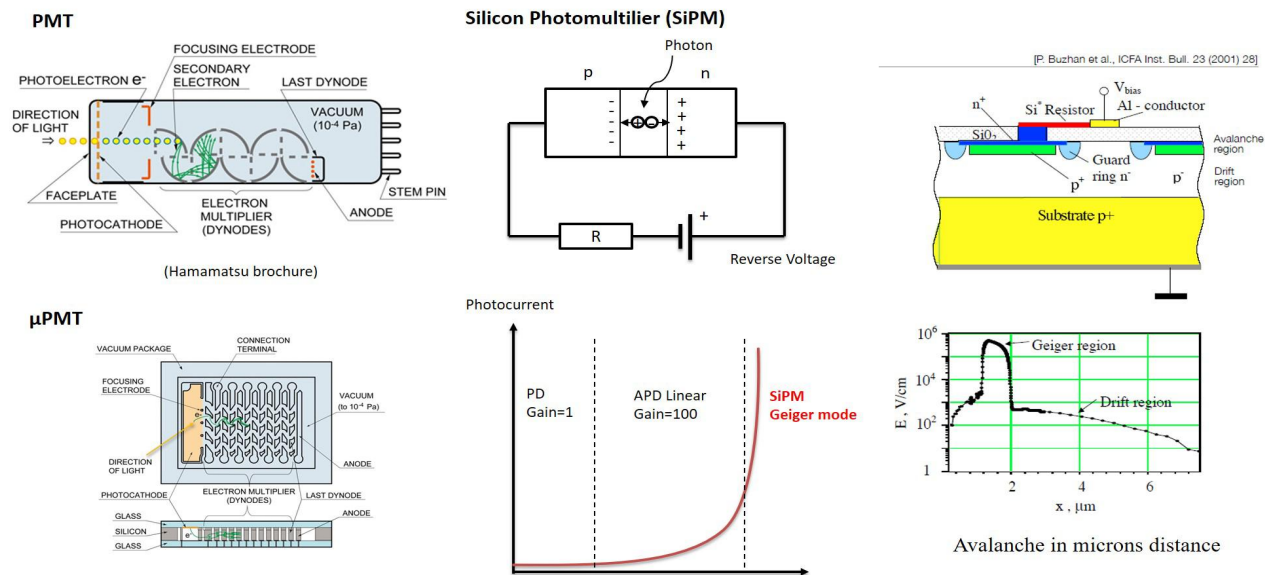[1] http://www.hamamatsu.com/jp/en/product/category/3100/3065/index.html

Fig. 1 PMT and Si Photomultiplier

The silicon photo sensor has a PN junction with applied reverse voltage. The induced electron hole pair by an incident photon is accelerated by the reverse electric field in a micron-based distance. At a low electric field, a silicon photo sensor works as a PIN photo diode with unity gain. Increasing the electric field, the linear avalanche mode amplifies the photoelectron number by 10~100 times. When the electric field is higher than 10^5 V/cm, amplification gain approaches a million and is called Geiger mode. An accelerated photoelectron within a micron distance exhibits a uniform velocity distribution and shows a step-wise PE height distribution. Geiger mode amplification is mentioned as "micro plasma" or "fire" which triggers cross-talk and after-pulse characteristics. The avalanche effect in such a short (microns) distance is extremely fast in the order of 100ps. Once fired, a recharge process is required in which is several of 10ns. Thus, the recharge process is considered the limitation of linearity and dynamic range because firing is a binary mode function with a significant dead-time. In order to improve the linearity, modern SiPM exhibits a pixel structure with 10 to 50 microns microcells. This pixel structure also improves cross-talk and after-pulse. However, instead of a linearity improvement, a smaller pixel size decreases Photo Detection Efficiency (PDE) defined by QE x fill factor x firing probability.

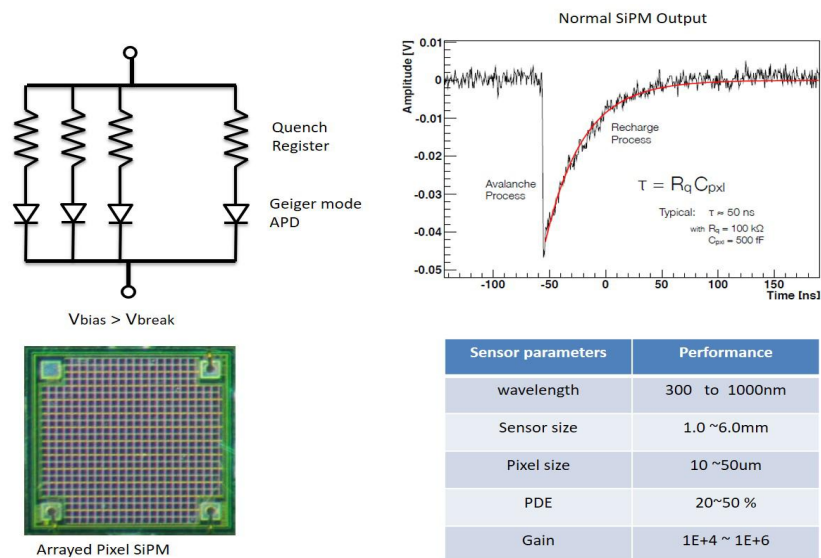| Sensor parameters	Performance
wavelength	300 to 1000nm
Sensor size	1.0 ~6.0mm
Pixel size	10 ~50um
PDE	20~50 %
Gain	1E+4 ~ 1E+6

Fig. 2 Pixel SiPM and typical signal waveform

Careful signal observation at different incident intensity levels suggests that the avalanche process itself exists even during the recharge process. From an electrical perspective, ps ultra-fast transition might be separately identified with several 10ns transitions by use of a differential circuit. This simple approach created a breakthrough on the linearity limitations as shown in Figure 3. Fig.3 (b) waveform demonstrates that multiple photoelectrons are detected even within the quenching process (normal dead time). We have termed this process as the "differential Geiger mode", and it is now possible to obtain multiple photoelectron outputs even during roll-up signal conditions[10]. Differential Geiger mode is basically signal processing, so it is possible to apply to any SiPM which has a rapid avalanche process in the picoseconds time domain. Fundamental challenges in this process were ultra-fast differentiation without parasitic capacitance and inductance. As the result, we designed an in-pixel capacitor and GHz amp combination with an integrated metal package which achieves a Gaussian photoelectron pulse with 600ps width.

Differential Geiger mode has an expanded photon detection dynamic range which is not determined by the pixel number but by the pulse-pair resolution as a Gaussian pulse. Current pulse-pair resolution is close to 1ns and expected up to 1Gcps photoelectron count rate. Normal output is amplified by a DC coupled transimpedance amplifier which is useful for photo current detection and pedestal control.
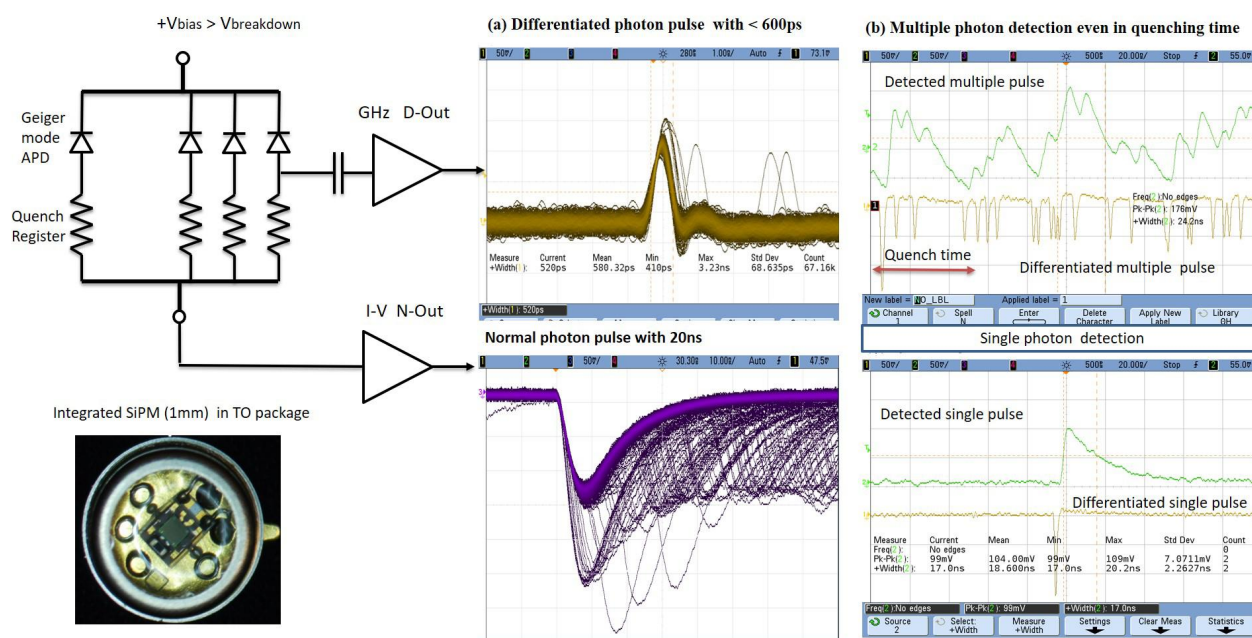

Fig. 3 Differential Geiger mode and detected waveform

After confirming multiple photon detection at less than 600ps, another critical issue to solve was the impulse counter. Commercial universal counters require several ns pulse width with a limited counting rate. Even a GHz bandwidth digital oscilloscope's counting capability is limited by its sampling rate. In order to meet our target, a Giga photon counter which has 300ps pulse resolution and max. 1.8Gcps count rate was developed by using the latest Emitter Coupled Logic (ECL) Integrated Circuit (IC) and control software. The 9 decimals digit counter is equivalent to binary 30 bits resolution if dark count is ideally zero.

In order to expand the detection dynamic range, dark count-rate (DCR) reduction is critically important. The dark count is highly dependent upon sensor size and temperature. By use of optical fibers and aberration free collection optics, it is possible to apply a smaller sensor size for fluorescence detection. Dark count rate is proportional to sensor area and the latest SiPM has been improved to DCR=30kcps/mm^2.   In addition, temperature dependence of measured data has to be eliminated for accurate counting.

We have developed an integrated metal package (TO5) which includes a small size sensor, thermistor and thermoelectric cooler (Peltier device) sealed in dry nitrogen. The temperature of the device is controlled by less than +/-0.05℃ by a PID (Proportional-Integral-Differential) controller. Lower temperature control has another advantage because signal amplitude increases proportional to the temperature coefficient characteristics of the sensor. This improves the signal-to-noise (S/N) ratio. The evaluated characteristic is shown in Fig.4. Fig.4 (a) shows DCR temperature dependence for various overvoltage levels. DCR is exponentially reduced dependent on temperature. It is possible to estimate DCR level at specific temperature from fitting the curve. Fig.4 (b) shows PE characteristics at -30℃ and overvoltage +1.5~+2.5V. Using this condition, DCR we have achieved less than 100cps/mm^2 as our current best value at this time. This figure also shows cross talk and after pulse about 1%.   The curve-fit suggests the feasibility of achieving 10 cps/ mm^2 via the latest thermoelectric control technology. Fig.4(c) shows linearity measurement from a power meter at 405nm. Counting rate shows up to 300Mcps at 1,000pW incident light. The current saturation count is approximately 500Mcps and counting sensitivity per pW is about 350kcps/pW. From DCR 100cps to saturation at 500Mcps shows over six orders of magnitude dynamic range. DCR standard deviation is about 10% at average rate of 100cps. This demonstrates the ability to distinguish 10aW intensity difference in signals. Unfortunately, available power meters have no capability of measuring less than 10pW. How to calibrate sensor sensitivity less than pW region is the next question. It might be necessary to estimate true light energy by Planck equation, appropriate standard light source and different type of single photon sensors.
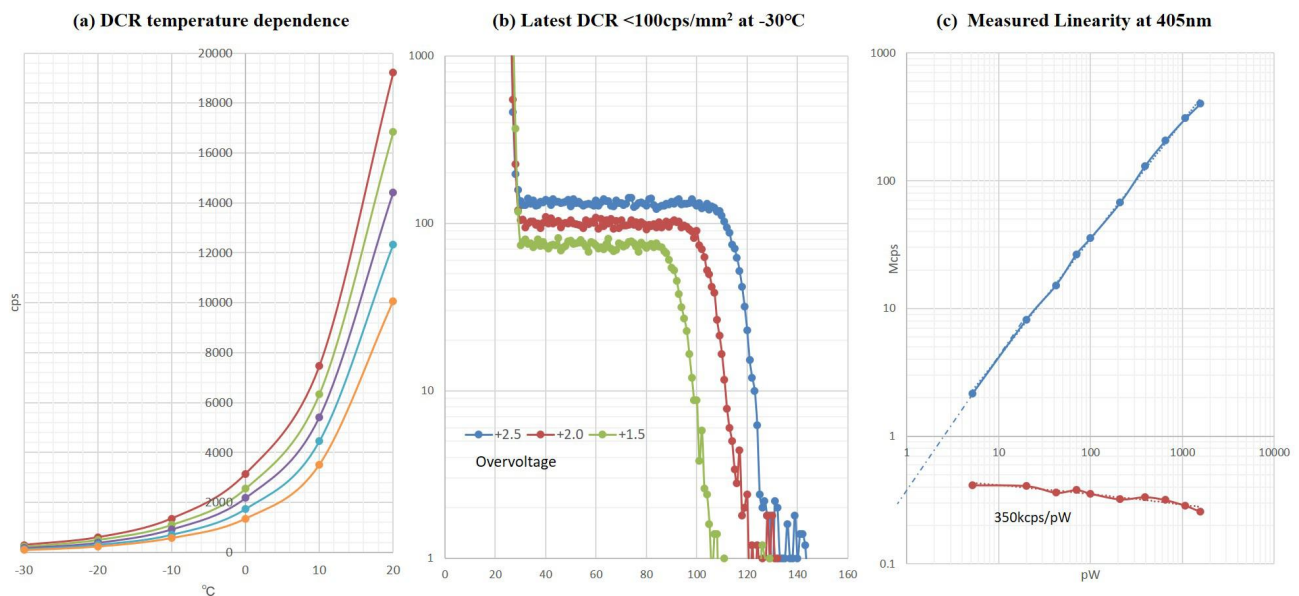

Fig. 4   Developed Si Photon Detector Characteristics

2.2 Wide dynamic range photon spectroscopy combined with motored monochromator

Wide dynamic range photon sensor and motored monochromator creates a fundamental difference in the capacity to obtain spectral intensity measurements. Previous spectral analysis assumes optics and instrument are essentially black boxes. The use of "Arbitrary units" in the ordinate or vertical axis is a common indication when producing spectrum figures. On the other hand, photon counting defines a quantitative detected intensity on the sensor and thus it is possible to estimate intensity by SI units. Using fiber optics makes it convenient to measure input and output intensity without ambient light. For any instrument, it is possible to estimate Input – Output ratio even if the instrument internal optical design is unknown. If the collection optics parameters are known, it is possible to estimate total emission intensity quantitatively. Quantitative analysis prefers simple configuration as spectrometer. Therefore, a motored monochromator with concave holographic grating was combined with our newly developed photon sensor system and the specification is shown in Fig.5.
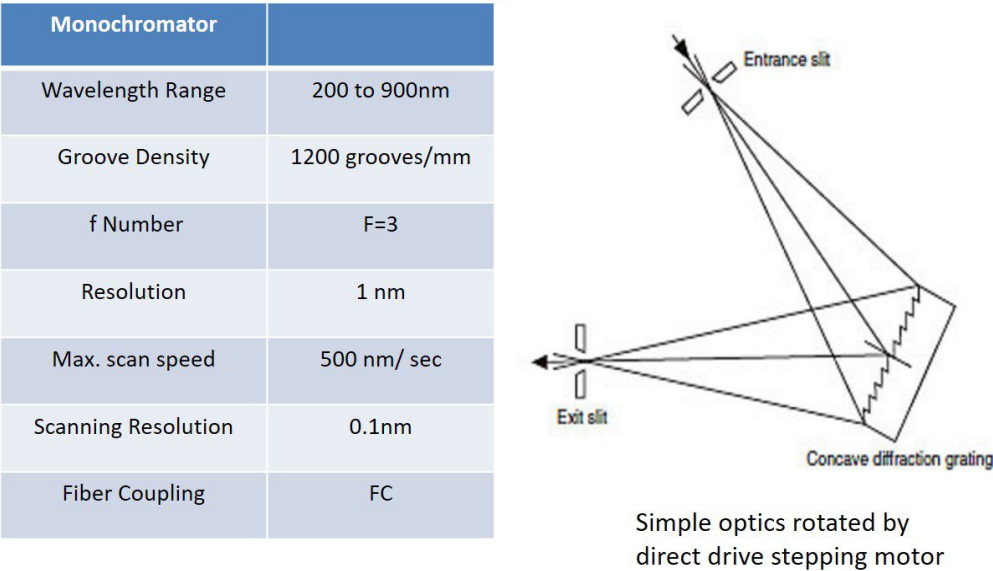
Monochromator	
Wavelength Range	200 to 900nm
Groove Density	1200 grooves/mm
f Number	F=3
Resolution	1 nm
Max. scan speed	500 nm/ sec
Scanning Resolution	0.1nm
Fiber Coupling	FC

Simple optics rotated by
direct drive stepping motor

Fig. 5   Motored Monochromator

The spectrometer design has both the entrance and exit directly coupled to FC fiber connectors making it easy to measure diffraction and coupling efficiency at any specific wavelength. It is also possible to apply a slit at the entrance and exit for higher spectral resolution if desired. A reflective concave grating is directly driven by a stepping motor covering from DUV (200nm) to IR (900nm) wavelength with high speed (500nm/s). Highly sensitive photon detection demands several innovations on instrument design to prevent internal reflection and stray light including auto fluorescence so that wider dynamic range spectral analysis can be achieved.

Over six orders of magnitude photon counting capability contributes quantitative and logarithmic spectral analysis. Fig.6 shows He-Ne laser spectrum which measures 633nm peak and gas discharge spectrum simultaneously. The use of the logarithmic scale can indicate low level discharge line spectrum of helium and neon gas at 1nW incident intensity. Laser peak is measured in pW and discharge in fW level from photon energy.
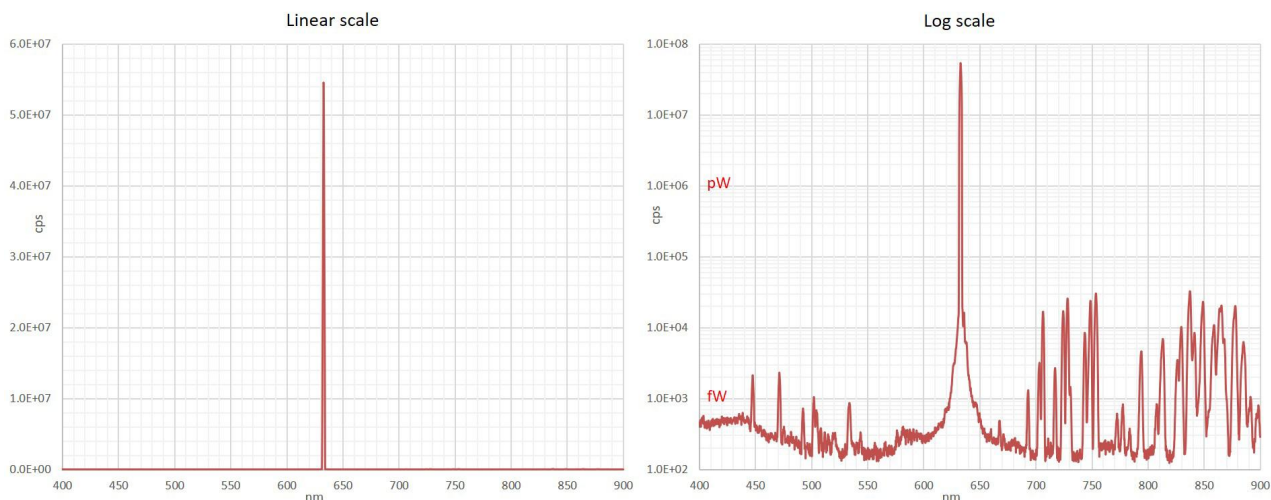
Fig. 6   He-Ne Laser Spectrum with discharge light

Logarithmic scale is possible to analyze small fluctuation under high level light intensity. While use of a wider logarithmic scale may not be common, it provides a considerable amount of quantitative information not available using a traditional linear scale.

2.3 Laser Induced Photon Spectroscopy (LIPS) for Raman and Fluorescence Analysis

Cellular analysis and advanced biomedical imaging technology commonly utilize laser excitation and emitted fluorescence detection. Laser exposure has been migrating toward shorter wavelengths and higher areal intensity in recent times. A variety of Stokes-shift fluorescence molecules are the essential components in flow cytometry technology. In order to evaluate basic biomedical and optical materials, the Laser Induced Photon Spectroscopy (LIPS) has been developed. A 405nm laser was selected as the initial excitation source because of higher excitation energy and the shortest visible wavelength and transmittance for typical polymers, liquids and glass materials.

Fig.7 is a block diagram of LIPS. The system is separated into Laser Induced Fluorescence (LIF) components and Single Photon Spectroscopy(SPS) components for ease of understanding. The LIF design depends upon laser wavelength and particular application. Linear polarized laser power is controlled by a halfwave plate and polarizer to fix the polarization direction. The laser is focused with focal length 100mm lens and passes through a laser bandpass filter. This bandpass filter is very important to eliminate spontaneous photons in the laser light. The best light source is a wavelength stabilized laser for accurate measurement. In addition, a Gaussian beam profile is important for measurement repeatability and theoretical analysis. In the case of laser diode unit, polarized single mode (PM) fiber output provides more precise lateral mode with better M^2 value. A sample at the focal point is excited and emits various wavelength of Rayleigh scatter, Raman scatter, photoluminescence and fluorescence. As is typical, this spectrophotometer uses orthogonal detection to reduce excitation light. However, because of the improvements of dielectric filters and laser beam collimation optics, LIPS can also detect at On-axis direction signals with appropriate long pass or notch filters. Due to collection lens NA, field size and focal depth, On-axis detection collects more emitted photon from excited volume or number of molecules.
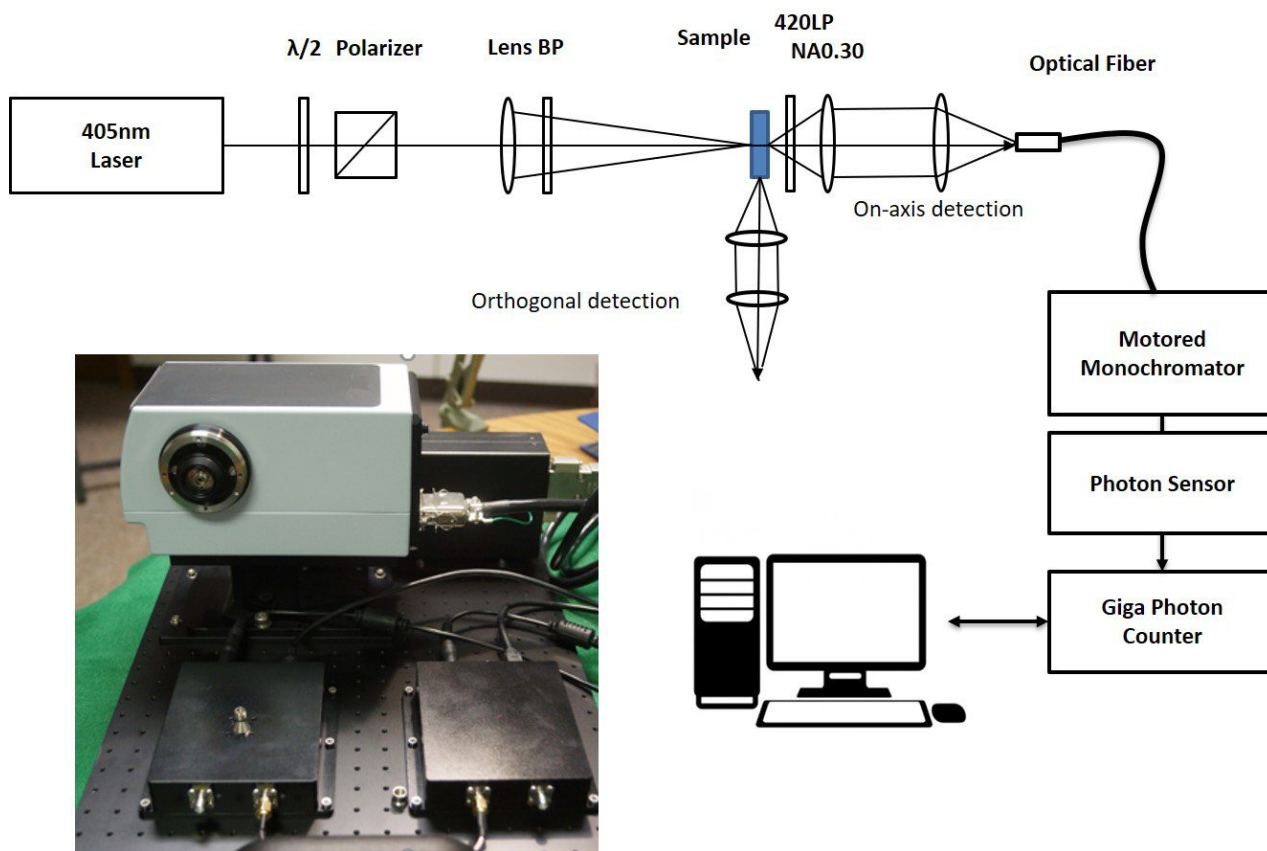
Figure 7 Laser Induced Photon Spectroscopy (LIPS) schematics

The collection lens is composed of a NA0.3 aspherical lens and fiber coupling lens to NA0.22 UV fiber. By inserting a rotational polarizer in the collimated portion, it is possible to observe polarization anisotropy, especially for liquid material. In order to cover a wide range of wavelengths, lens, filter substrate and optical fiber must be fused silica with the exception of the mold lens. The photon sensor cut-off wavelength is specified to be within 300nm to 800nm, but already a red enhanced sensor up to 1050nm is commercially available.

3.   RESULTS

  Molecular spectroscopy comprises a huge field including UV-Visible, Raman and NIR spectroscopy. The measurement of single photon spectroscopy has the potential to analyze each molecule transition state by time domain analysis.
  While our primary interests are not focused on the analysis of material properties, it is sometimes difficult to understand the experimental results based on traditional published knowledge. This might suggest photon spectral analysis opens up a new frontier. In this section, we will demonstrate several results from our current interest on cellular analysis and optical components.

3.1 Checking detection dynamic range and optical filter characteristics

 A standard lamp is useful to evaluate a wide range of wavelengths simultaneously. Fig. 8 (a) shows measured spectrum and dark count based on the Ocean Optics LS-1 halogen tungsten lamp. From sub-fW to nW range, we firstly confirmed targeting six order magnitude photon counting. Using this same standard lamp, it is also possible to evaluate optical filter

characteristics as shown on Fig.8(b). The 440LP, 500/20NF and 525/20BP filters are described with evaluation limit determined by background. It is easy to understand optical filter OD, spectral characteristics and recent progress of filter dielectric layer design. One remark is standard lamp light ray is not perfectly parallel to filter incident even though filter designed under parallel incident condition.
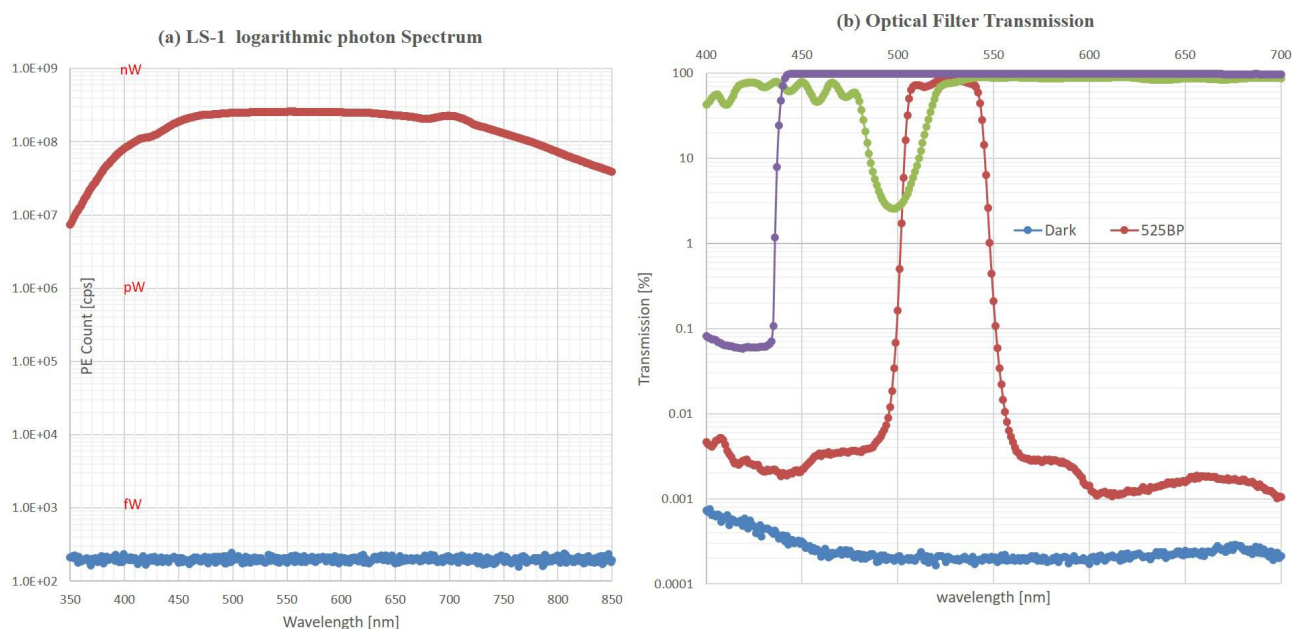

Figure 8 Measurement by standard lamp

We also identify that the PMT photocathode and SiPM wavelength sensitivity profile has a clear dependence on HV or overvoltage. In the case of SiPM, a higher overvoltage improves longer wavelength sensitivity but with an increased dark count.

3.2 Water and Fused Silica Raman and auto fluorescence(AFL)

Water (as a delivery fluid) and fused silica (for flow chamber) are basic materials found in virtually all flow cytometers. The water Raman peak is considered as a background noise measurement within a conventional system. Fig.9 (a) shows distilled water Raman spectrum by photon spectroscopy. The highest peak by O-H stretching at 468nm (3,200/cm), weak peak by O-H bending (1,600/cm) and very low isosbestic peak (7,000/cm) are found by 1.5nm FWHM spectral resolution and 5mW exposure. A typical flow cytometer utilizes 30~50mW of power at 405nm for cellular analysis. It is expected higher peak level proportional to exposure level in detected spectral bandwidth. In addition, when a wide background spectrum is found, the origin cannot easily be identified in traditional instruments. However, by applying photon detection to flow cytometry, a Raman peak needs to be recognized as one of the signal source. Photon counting spectral profile is possible to be calculated by adding or subtraction operation if the spectrum is stable. Indeed, the water Raman peak is highly reproducible and can be used as instrument reference. It might also be possible to compensate the Raman component as known background. This is the advantage of digital signal processing by photon counting that cannot be achieved by traditional current-based measurements.

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Further, the typical flow chamber that is usually made from fused silica is the heart of flow cytometry and is the key component for the laser spot to interrogate live cells as they flow through the chamber. Fused silica might generally be considered as an autofluorescence (AFL)-free material. However, our measured data shows fused silica is a more complicated and reversible on photobleaching. Fig.9 (b) shows two fused silica sample materials which includes Raman shift by Si ring structure D1 and D2, Si-O-Si or Si-H bonding. Another sample has a broad spectrum with a peak at 460nm. This spectrum shows photo-bleaching by continuous exposure followed by a recovery phenomenon after several

hours. The most probable causes of this phenomenon are surface contamination or internal structure not yet identified. Fused silica is a very important material especially where shorter wavelength optics are required. We are undergoing investigations with the highest quality manufacturers of these material to develop new analytical toolsets to ensure AFL-free fused silica or calcium fluoride optical components.
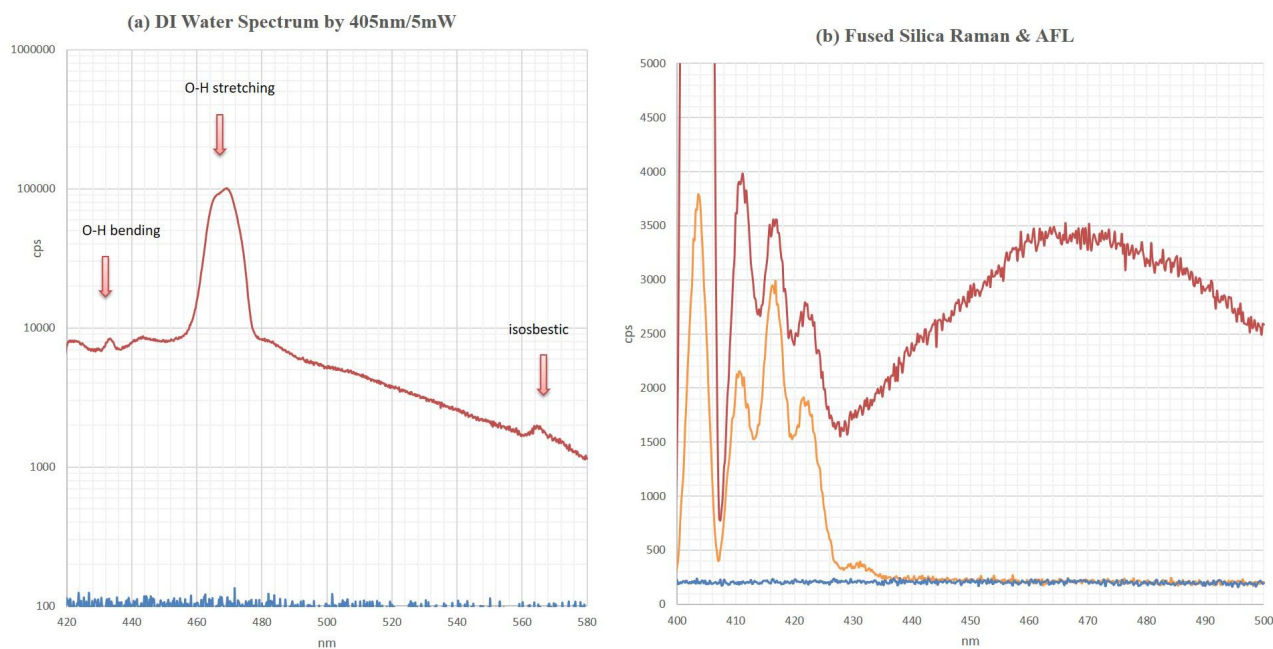

Figure 9   Water & Fused Silica Raman Spectrum

3.3 Objective Lens and Immersion Oil Auto fluorescence

The use of higher NA objective lens is a key functional device for fluorescence collection and imaging microscopy. More recent objective lens design is driven by higher NA and shorter wavelength in order to resolve fine structure by diffraction limited optics. Liquid immersion lens over NA1.0 can be also used for the highest resolution imaging in live cellular or tissue systems. A typical higher NA objective lens is assembled from many pieces with various refractive index optical glass. A fluorescence microscope objective lens produces fluorescence illuminated by shorter wavelength such as is commonly used in confocal or 2 photon microscopy. Fig.10 (a) shows the photon spectrum of various magnitude fluorescence objective lens illuminated by 405nm. Typical spectral pattern indicates special glass material like i-line glass. It appears that the photon spectrum can define a fingerprint for an objective lens design and the optical glass components. In addition, immersion oil can also contribute to high level fluorescence backgrounds. Some immersion oils are specified as AFL-free. Auto fluorescence is proportional to exposure intensity and thickness, in such case it is possible to estimate auto fluorescence level under practical use conditions.

Auto fluorescence may deteriorate visual imaging contrast ratio and photon imaging requires minimum background level. AFL-free objective lens design is quite challenging including the lens material and coating. As alternative approach, reflective objective lens is the candidate of AFL-free optics. Reflective lens was evaluated and found anti-reflective coating produces auto fluorescence. Pure metal coating may minimize AFL influence. Reflective lens has other issues on limited NA and deteriorated MTF characteristics compared with refractive optical design.
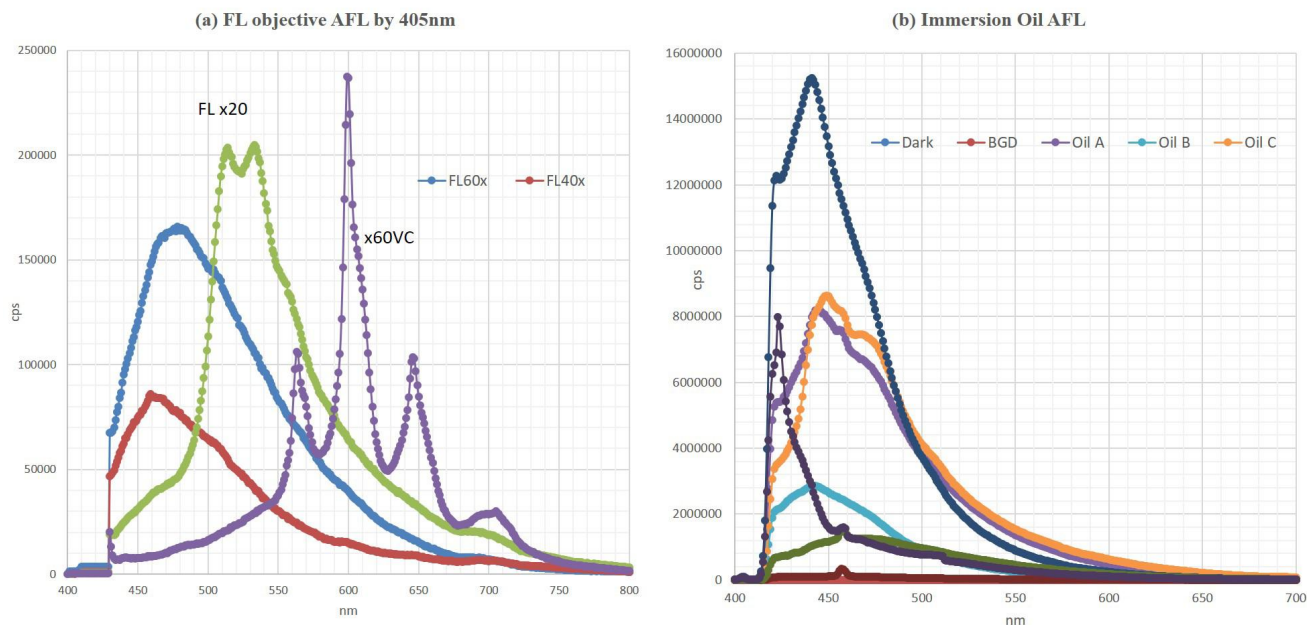
Figure 10 Objective Lens & Immersion Oils AFL excited by 405nm

4. DISCUSSION AND FIESIBILITY

Once the ability to make direct photon measurements, it is inevitable to evaluate based on the fundamental laws in physics. One is the Planck and Einstein law on radiation energy packets[1, 2] and another is law of the conservation of energy[11] which was also established by highly respected scientists since the 16th century such as R. Decartes and G.W. Leibniz and others. The simple question for photon spectroscopy is how to calibrate measured values based on absolute energy? The conventional power meter or calorimeter which has been used for light energy measurement for decades is no longer applicable for the single photon world. Is it possible to interpolate forwarding femto and atto watt levels based on Planck equation?   It might be "Yes", but an alternative method might be preferable and comfortable for common usage. Another question relating to energy conservation is that is there any possibility to create AFL-free material and optics? When 10mW at 405nm excites sample and detected 1kcps, 10 mW contains 2E+15 photon/s, detected 1kcps is equal to 1E-12 at PDE=50% - described as one "pico- ratio". Of course, this ratio depends on collection solid angle calculated as 2.5% at NA0.3 and spectrometer efficiency. How much is it possible to minimize the emitted/excited ratio from pico to femto would have a huge impact for the future photon base opto-electronics or digital photonics.

Additional question can be raised from On-axis and orthogonal detection geometry. In general, we consider that excited incoherent fluorescence is emitted uniformly to any solid direction. We sometimes observe different spectral profile between conventional orthogonal and On-axis detection, especially related to the broad background spectrum. There are many parameters to affect spectral profile such as excitation and collection volume, polarization and material characteristics. Spectral analysis is typically focused on spectral peak and wavelength, but quantitative photon spectroscopy might trigger new aspects on broad background spectrum.

What is the value and impact of expanding sensitivity and dynamic range over three orders of magnitude? This is the continued question from view point of technological value and variety of application.
Detected photoelectron pulses from samples exhibit one bit pulse stream with picoseconds time information termed as Photon Stream Digital(PSD). The 600ps pulse may have one tenth of time resolution for FWHM pulse width. Potentially, photon stream is valuable for fluorescence decay measurement in digital domain, time response

measurement at various biochemical reaction. This is new feature by photon spectroscopy. Combined with picosecond laser exposure or laser modulation, it might be possible to observe time domain phenomena such as Fluorescence Correlation Spectroscopy, Time-resolved Correlation Spectroscopy and other time analysis in digital.

5. CONCLUSION

Motivated by current cellular analysis requirements, a six orders magnitude dynamic range photon detection system and a Laser Induced Photon Spectroscopy (LIPS) technology have been developed. Based on the history in consumer electronics development suggests that once integrated solid state devices are introduced, it changes many aspects of our lives. Similarly, photon detection which was designed as a tool for specific scientific purposes may open basic opportunities in scientific research. The photon is the most familiar and inevitable elementary particle for scientists working in biomedical applications, and may be various photon base applications as digital photonics. Technological migration toward photon detection now provides a wider dynamic range and can compete with more traditional and less quantitative methods. Another interesting pathway of photon detection methods is to apply it to hyper spectral detection for cellular analysis and imaging. The ultimate SiPM style may be similar to current CCD or CMOS linear and 2D arrays. However, it will require photon counting functions and the processor must be integrated on a monolithic Silicon wafer. Technically it appears to be feasible using todays technological capabilities, but market demand to develop these tools may take many years. One major advantage of biomedical application research is that the discovery and detection tools can have a direct impact on human health. Photon detection will contribute to discover the truth that may be hidden within signal and sample noise and may open up a new Frontier.

REFERENCES

1.	Planck M (1901) Ueber das Gesetz der Energieverteilung im Normalspectrum. Annalen der Physik 309:553-563. doi: DOI: 10.1002/andp.19013090310.
2.	Einstein A (1905) Über einen die Erzeugung und Verwandlung des Lichtes betreffenden heuristischen Gesichtspunkt. Annalen der Physik 322:132-148. doi: DOI: 10.1002/andp.19053220607.
3.	Renker D (2006) Geiger-mode avalanche photodiodes, history, properties and problems. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 567:48-56. doi: DOI: http://dx.doi.org/10.1016/j.nima.2006.05.060.
4.	McIntyre RJ (1961) Theory of Microplasma Instability in Silicon. Journal of Applied Physics 32:983-995. doi: DOI: 10.1063/1.1736199.
5.	Shockley W (1961) Problems related to p-n junctions in silicon. Solid-State Electronics 2:35-67. doi: DOI: https://doi.org/10.1016/0038-1101(61)90054-5.
6.	Frach T (2012) Optimization of the digital Silicon Photomultiplier for Cherenkov light detection. Journal of Instrumentation 7:C01112. doi, http://stacks.iop.org/1748-0221/7/i=01/a=C01112.
7.	Agishev R, Comerón A, Bach J, Rodriguez A, Sicard M, Riu J, and Royo S (2013) Lidar with SiPM: Some capabilities and limitations in real environment. Optics & Laser Technology 49:86-90. doi: DOI: https://doi.org/10.1016/j.optlastec.2012.12.024.
8.	Ronzhin A, Albrow M, Los S, Martens M, Murat P, Ramberg E, Kim H, Chen CT, Kao CM, Niessen K, Zatserklyaniy A, Mazzillo M, Carbone B, Condorelli G, Fallica G, Piana A, Sanfilippo D, Valvo G, and Ritt S

(2013) A SiPM-based TOF-PET detector with high speed digital DRS4 readout. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment 703:109-113. doi: DOI: https://doi.org/10.1016/j.nima.2012.11.043.

9.   Jack WJ (2001) Microelectromechanical systems (MEMS): fabrication, design and applications. Smart Materials and Structures 10:1115. doi, http://stacks.iop.org/0964-1726/10/i=6/a=301.

10.   Yamamoto M, *Photon Detection: Current Status*, in *Single Cell Analysis: Contemporary Research and Clinical Applications*, J.P. Robinson and A. Cossarizza, Editors. 2017, Springer Nature: Singapore. p. 227-242.

11.   Mayer JR (1842) Bemerkungen über die Kräfte der unbelebten Natur. Justus Liebigs Annalen der Chemie 42:233-240. doi: DOI: 10.1002/jlac.18420420212.