Optical tomography can yield anatomical and molecular information about biological tissue. However, its spatial resolution is poor in thick samples owing to high scatter. Early photon approaches, where photon arrival times are measured with time-resolved detectors, provide one means of improving spatial resolution through selection of photons that travel a straighter path. Here, a novel approach to significantly enhance detection of early photons in time-correlated single photon counting with avalanche photodiodes has been discussed. Results suggest that the early photon detection rate can be increased by about 10 orders of magnitude by running the detector in a dead-time regime.

Enhanced detection of early photons in time-domain optical imaging by running laser power high enough to ensure that the count rate that causes dead time of the detectors, henceforth, this will be referred to as the “dead-time regime.”

Through tissues thicker than 1 mm, the vast majority of photons reaching the detector in transillumination (light source and detector on opposite sides of the sample) mode will be diffuse photons, having taken an indirect path through the tissue. All photons will have some interaction with the tissue at this level; however, photons that tend to scatter in a forward direction and are not absorbed (very early arriving or “forward scattering” photons), $I_{fs}$, can be estimated from the Beer–Lambert Law:

$$I_{fs}(l) = I_0 e^{-l(\mu_e + \mu_s)},$$

(1)

where $l$ is the diameter of the sample being imaged; $\mu_s$ and $\mu_e$ are the absorption and scattering coefficients of light in the tissue, respectively; and $I_0$ is the rate of photons emitted from the light source; typical values of $\mu_s$ and $\mu_e$ are 0.02 and 10 mm$^{-1}$, respectively, in the near-infrared regime (700–900 nm) [11].

A comparative approximation of the rate of all photons reaching the detector in diffuse media can be estimated by the diffusion approximation to the radiative transfer equation [12]:

$$I_{all}(l) = I_0 \frac{3\mu_s(1-g)NA}{4\pi l} e^{-l\sqrt{3\mu_s(\mu_e+(1-g)\mu_s)}},$$

(2)

where $g$ is the anisotropy of the scatter and is generally considered to be approximately 0.9 for biological tissue [11], and NA is the numerical aperture of the detector. Assuming NA = 0.05, $g = 0.9$, $\mu_s = 0.02$ mm$^{-1}$, and $\mu_e = 10$ mm$^{-1}$, the proportion of detected photons that are forward scattering as a function of sample thickness is

$$I_{fs}(l) \frac{4\pi l}{I_{all}(l)} = \frac{4\pi l}{3\mu_s(1-g)NA} e^{-l(\mu_e + \mu_s - \sqrt{3\mu_s(\mu_e+(1-g)\mu_s)})} = 27 \pi l e^{-9.8l}.$$  

(3)

Equation (3) estimates that through 1 mm tissue, as many as 1 in 200 near-infrared photons reaching the detector may be forward scattering. However, as tissue thickness increases, the exponential nature of Eq. (3) dominates and, by 4 mm, as few as 1 in $10^{14}$ photons reaching the detector are forward scattering. To identify rare forward scattering photons (the earliest arriving photons), one would require a detector with as fine a temporal resolution...
as possible. To date, the best temporal resolution is provided by time-correlated single photon counting (TCSPC) systems, typically using either photomultiplier tubes (PMTs) or SPADs to amplify the signal from a single photon event. However, conventional use of such systems has aimed to keep photon count rates low enough to limit dead-time/“pile-up” effects (i.e., limiting the occurrence of more than one photon arriving at the detector within the duration of the dead time of the system). By running these detectors in a sub-dead-time regime, the far more abundant diffuse photons will swamp forward scattering and other very early arriving photons. This keeps count rates of these rare photons below typical background levels [Fig. 1(a)] so that, even with increased exposure, signal cannot be recovered.

Using relatively robust SPAD detectors rather than PMTs for TCSPC, the latter of which is sensitive to overheating damage with high photon incidence rates, can allow for use of higher-powered light sources. In addition, while longer dead time of these detectors also limits the maximum photon count rate because of the dead time of the detector.

![Image](image_url)

**Fig. 1.** Effects of dead time on time-resolved pulsed light detection. (a) Rate of forward scattered photons reaching the detector is presented when running the laser at the ANSI safety limit (blue curve, 1019 photons/s laser output) and at a power just below the dead-time regime threshold (red curve, 107 photons/s laser output). The orange shaded region represents photon count rates below the background (populations that cannot be recovered by increased exposure time). (b) Relation between laser power, rate of photons hitting the detector, and rate of photons counted. (c) Simulated photon count rates as a function of arrival time just above the dead-time threshold (blue dashed curve, upper plot) and well above the dead-time threshold (black dashed curve, lower plot). The corresponding solid curves demonstrate how the dashed curve will be observed with dead-time saturation of later gates. The green curves demonstrate the probability of detecting a photon at the detector in a given time bin. (d) Simulated photon counts for various power levels as shown in (b). Note that all but the one corresponding to the 0.002 mW/mm² power (blue curve) are affected by dead time. (e) Schematic of the system.

In TCSPC, the occurrence of more than one photon arriving at the detector within the duration of the dead time of the system can provide a means to significantly enhance the number of detected early photons, while the later arriving photons will become increasingly masked by the detector’s dead time as photon rate at the detector increases.

The analytical solution of photon propagation through a 4 mm thick tissue was used to simulate a typical photon tissue transit-time point spread function with reduced scattering coefficient $\mu'_s = 1$ mm⁻¹ and absorption coefficient $\mu_a = 0.02$ mm⁻¹ [12]. This solution was then scaled to various photon count rates in 4 ps time bins (matching the characteristics of the TCSPC system described below) by normalizing to power levels achievable experimentally with an LDH-PC780 pulsed diode laser (PicoQuant, Berlin, Germany). The saturation and dead-time effect of the detector were implemented [14] with an assumption that the dead time was 80 ns (comparable to the detector in our system described below). The table in Fig. 1(b) demonstrates that with increasing laser power, the rate of photons reaching the detector increased linearly; however, because of the dead-time effect, the maximum rate of photon detection saturated at about $5 \times 10^5$ photons/s, assuming a laser pulse repetition rate of 5 MHz. The plots in Fig. 1(c) demonstrate that the rate of photons detected will underestimate the rate of photons incident on the detector at higher laser powers, with photon count rates in later gates decreasing as governed by dead-time effect principles [14]. Figure 1(d) demonstrates that with increasing power, the dead-time effect leads to an apparent shift in photon arrival time detection to earlier gates, thus boosting the probability of early photon detection at the expense of late arriving photon counting. This shift is not a true shift to earlier photons. In fact, the shape of the photon arrival time distribution incident on the detector does not change; only the scale increases [dashed curve in Fig. 1(c)]. It is rather the fact that the probability of detecting photons arriving in the early gates remains unchanged with laser power, while the probability of detecting the later arriving photons diminishes significantly with increased laser power because of the dead time of the detector.

**Table:**

<table>
<thead>
<tr>
<th>Laser power (mW/mm²)</th>
<th>Photon count rate at detector</th>
<th>Photon count rate detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.002</td>
<td>2.4x10⁶</td>
<td>2.3x10⁴</td>
</tr>
<tr>
<td>0.02</td>
<td>2.4x10⁹</td>
<td>1.9x10⁵</td>
</tr>
<tr>
<td>0.2</td>
<td>2.4x10¹³</td>
<td>4.9x10⁸</td>
</tr>
<tr>
<td>2</td>
<td>2.4x10¹⁰</td>
<td>5.0x10⁶</td>
</tr>
<tr>
<td>20</td>
<td>2.4x10⁹</td>
<td>5.0x10⁶</td>
</tr>
<tr>
<td>200</td>
<td>6.0x10⁶</td>
<td>5.0x10⁵</td>
</tr>
</tbody>
</table>

Therefore, by exposing TCSPC detection systems to pulsed light sources that will far exceed the detection dead-time limit of the detector, many orders of magnitude improvement can be achieved in the probability of detecting photons arriving in the earliest detectable gates. The remainder of this Letter explores these dead-time improvements in more detail through simulation and phantom experiments, demonstrating that the number of detected early photon remains linear at high laser power, and significant improvements in spatial resolution can be achieved by even marginally enhancing laser power.
The early photon system [Fig. 1(e)] consisted of a 785 ± 4 nm wavelength pulsed diode laser (LDH-PC780, PicoQuant) powered by a laser driver (PDL 800-B, PicoQuant) illumination source pulsed at 5 MHz and at full power. The pulse width of this laser is approximately 100 ps. (Note that shorter pulsed lasers are available that could further enhance this dead-time regime methodology; however, this laser is sufficient for demonstrating the effect, in principle.) A 0–4 OD attenuator (Thorlabs, Newton, NJ) was used to control the power of the laser source incident on the scattering medium without changing the shape of the laser pulse. Laser power exiting the variable attenuator was monitored with a power meter (S120C, Thorlabs). A 5 mm diameter cuvette filled with 1% Intralipid (Sigma-Aldrich, St. Louis, MI) and India ink (Winsor & Newton, London, UK) in water to match the optical properties of the simulations [11] was used as a phantom. Lenses (Thorlabs, Newton, New Jersey) were used for focusing the signal. The transmitted signal was then detected by a SPAD (PDM, PicoQuant) connected to a TCSPC module (PicoHarp 300, PicoQuant) to obtain temporal information at 4 ± 25 ps temporal resolution over the 200 ns pulse repetition period and with a dead time of approximately 80 ns. The effective detector area of the SPAD was 50 μm × 50 μm. The TCSPC system and laser driver were connected through a TTL port to reference the time of arrival of each photon to the nearest laser pulse. All control of the system was carried out with in-house software developed in MATLAB (Mathworks, Natick, Massachusetts).

Attenuation of the laser down to a power of 0.005 μW was needed to completely avoid dead-time effects at the detector. This occurs with this TCSPC approach when the inverse of the rate of photon detection is less than 5% of the duration of the dead time (~80 ns), capping the photon detection rate at approximately 2.5 × 10^5 photons/s. Increasing the laser power above this threshold triggered a warning on the built-in PicoHarp software, to notify the user that dead-time effects may be affecting photon count rates. Since the purpose of this Letter was to evaluate the effects of this dead time in aiding detection of rare early photons, the variable attenuator was decreased to increase power over a range of 0.05 to 0.5 mW, which was the maximum power of the laser under the defined settings. It should be noted that this was well below the ANSI safety limit for skin, which is ~2 W for this wavelength and type of light source. With ANSI safety limits being conservative limits for in vivo human studies, it is conceivable that the laser power could be increased by up to four or five orders of magnitude (to observe thicker tissue) compared to what was used as a maximum power in this Letter, further supporting the enormous potential of detecting early photons in a dead-time regime.

Figure 2(a) demonstrates the saturation characteristics observed with dead time in TCSPC match what was predicted by simulations of dead time [Fig. 1(d)]; specifically, that early-gate photon count rates increase with increased laser power, while later-gate photon count rates decrease commensurately maintaining the total count rate below the saturation limit for all laser powers yielding photon incidence rates at the detector that exceed 1/dead time. The saturation effect of the detector mainly affects the later gates of the temporal point spread function (TPSF), while the earliest gates are not affected. Moreover, as power increases from a range where all time bins are linear with power (detection rate <5% of pulse rate), the likelihood of one or more photons arriving at the detector within the dead time caused by detection of an earlier arriving photon increases. Since these photons will not be counted, earlier photons will always be detected preferentially to later arriving photons at high fluence rates, keeping their linearity in response to photon fluence at the expense of later-arriving photon detection efficiency [Fig. 2(b)]. Only at very high fluence rates, when close to one earliest gate photon arrives at the detector every pulse, will the linearity be affected in all gates.

To make the detector reach its saturation, the laser needs to be ramped up, and such a high signal can cause an effect called afterpulsing in the detector. In saturation mode after the dead time is over the trapped carrier can generate a late signal, which decreases exponentially but can spread over a few microseconds, also called afterpulsing. However, results of TPSFs presented in Fig. 2(c) in the dead-time regime and sub-dead time suggest that even though afterpulsing increases at higher intensities, it has no time correlation and can be considered an offset in the signal. To correct for this offset of temporally uniform background, the average rate of afterpulse detection per bin can be estimated from regions of the TPSF far from the measured light pulse, and then subtracted from all bins in the TPSF.

For further analysis, Monte Carlo simulation was used to test how much better resolution could be achieved if a certain time window was used for reconstruction [15]. Dead-time regime early-gate photons were compared to conventional early-gate photons, defined here as gates taken over a time span of 120 ps centered at 25% of the peak of the measured photon arrival distribution collected at a laser power below the detector dead-time regime [8,16]. The sensitivity function at a detector at location x_d for a light source at r, was obtained by convolving the time-resolved Monte Carlo (MC) simulation for a 4 x 4 x 4 mm sample with optical properties similar to tissue (μ_s = 0.02 mm^-1 and μ_a = 10 mm^-1, g = 0.9) with the instrument response function (IRF) [Fig. 2(d)].
where \( \mu_{\text{signal}} \) is the average of the signal intensity, while \( \sigma_{\text{noise}} \) is the standard deviation of the noise in the image. The SNR was computed to be 100.56 using our approach, while as low as 6.45 using the same bin in an unsaturated case, keeping in mind that a trade-off exists between the selection of the early photon and higher noise level in the images.

In this Letter, to the best of our knowledge, a first demonstration of a novel method to enhance detection of low-scattering, early arriving photons in time-resolved diffuse optical tomography is presented. We showed that by running a TCSPC detector in the dead-time regime detection of early arriving photons can be maintained while only later arriving photons will be affected by dead time. Our simulations suggest that up to 10 orders of magnitude improvements in early photon detection can be achieved through tissues thicker than a few millimeters. Furthermore, we demonstrate this phenomenon experimentally and through simulation, highlighting the fact that the earliest photons, once detected at rates higher than the background level, are detected in linear fashion for a wide range of laser powers (and despite the severe nonlinearity of later-arriving photon detection in this regime). Finally, a preliminary simulation of the levels of spatial resolution improvement achievable in the dead-time regime early photons compared to conventional early photons is presented with an SNR improvement of almost 20 times, with the caveat that lasers of much higher power and narrower pulse width can be used to further enhance spatial resolution to match the many orders of magnitude improvements predicted by the analytical models.

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**REFERENCES**


**Fig. 3.** Spatial resolution simulation and experimental results. Sensitivity profiles of (a) earliest gate photons and (b) conventional early photon gates from a Monte Carlo simulation, respectively. (c) Simulated 4 × 4 mm object with three high absorptive regions of 200 × 50 μm separated by 200 μm. Source-detector profiles through (d) simulation and (e) phantom.