

Measurement of tissue temporal point spread function (TPSF) by use of a gain-modulated avalanche photodiode detector

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Abstract. This paper describes an opto-electronic cross-correlator designed for measurement of the temporal point spread function (TPSF) of light at the bedside. Ultra-short (< 2 ps) pulses of light from a mode-locked laser were used to illuminate a tissue phantom. The light exiting from the tissue phantom was coupled by an optical fibre to a small-area ($200\ \mu\text{m}$ diameter, Hamamatsu S2381) avalanche photodiode (APD). The gain of the photodiode was modulated at the repetition rate of the pulsed laser (82 MHz). Usually the gain was approximately 100, but for a period of approximately 130 ps (FWHM) the gain was increased to approximately 105. A lock-in amplifier, which sampled the integrated APD current, gave an output proportional to the difference between the current in the low- and high-gain states. Hence a small section of the TPSF was selectively sampled. An overall temporal resolution of 275 ps FWHM was achieved. As the timing of the gain modulation was controlled by an all-electronic variable-time-delay system, the whole of the TPSF could be sampled without requiring any moving prism or mirror which is typical of many cross-correlators. Hence the system is mechanically very rugged, which enhances its durability in a portable instrument.

1. Introduction

When short pulses of light are incident on tissue, the photons collected some distance away will have undergone a distribution of transit times, due to the scattering in the tissue. This results in the collected light having slower rise and fall times than the incident light. This distribution, known as the temporal point spread function (TPSF), or impulse response of the tissue, can be measured with a streak camera. Such a technique has been used in a number of research laboratories throughout the world, including UCL, for measuring the TPSF (Delpy *et al* 1988, Das *et al* 1995). Chance *et al* (1988) used a micro-channel plate photomultiplier tube detector in a time-resolved spectrophotometer to obtain the TPSF of human muscle. These techniques are very powerful, as from the impulse response it is in principle possible (Patterson *et al* 1984) to calculate the optical properties of the tissue (the absorption coefficient μ_a and the transport scattering coefficient μ'_s).

A simple and inexpensive instrument capable of measuring the optical properties of the tissue at the bedside would find many clinical uses, but, unfortunately, both mode-locked lasers and streak cameras are large, expensive and require a stable operating position. Neither are suitable for moving frequently, although two different portable time-resolved instruments have recently been described by Benaron *et al* (1995) and Miwa *et al* (1995),

respectively, using alternative detection techniques. Hence a small portable instrument using inexpensive detection techniques is highly desirable.

Berndt (1987) and colleagues (Berndt *et al* 1988) have described a technique for the measurement of the lifetime of fluorescent materials using an opto-electronic cross-correlator. This used a mode-locked argon-ion laser as a source and a small-area avalanche photodiode (APD) (Sze 1981) as the detector. The APD was biased with a voltage added from two sources. The first was a stable fixed DC supply and the other a short-duration (130 ps FWHM) pulse of 2 V amplitude, derived from a second APD which sampled a fraction of the laser output, before it reached the fluorescent material. Since an APD has an internal gain mechanism (see figure 1) which is voltage dependent, the gain of the detecting APD was time dependent and would sample a small section of the decaying fluorescence signal. By varying the time delay τ between the fluorescence signal and the gain modulation pulse, it was possible to obtain the cross-correlation r_{xy} between the modulation pulses (x) and the fluorescence signal (y).

$$r_{xy}(\tau) = \lim_{T_0 \rightarrow \infty} \frac{1}{T_0} \int_{-T_0/2}^{T_0/2} f_x(t) f_y(t + \tau) dt \quad (1)$$

where T_0 is the period of the signals. In the Berndt system, the time delay τ was varied by changing the optical path length between the laser and the APD used for generation of the gain modulation pulses. This was achieved by moving a corner cube reflector in the optical path. The gain modulation pulse stream was itself modulated at a low frequency using a chopper wheel, enabling a lock-in detection system to be used. This resulted in a detection sensitivity of 0.001 photons/pulse.

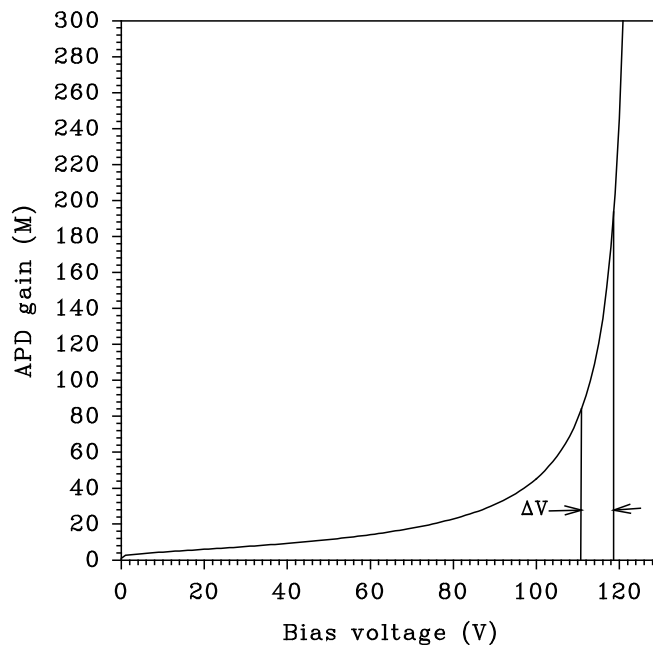


Figure 1. A graph showing a typical gain-bias voltage characteristic for an APD. Note that a small change in the bias voltage can be used to cause a change in the gain.

2. Method

Although in principle the Berndt system could be used to measure a tissue TPSF in the laboratory, there are a number of problems that prevent the technique being used in a portable instrument. These are the following.

(i) Some optical power would be required to fall on the second APD to generate the gain modulation pulses. In order to achieve large modulation pulses, which are necessary for an optimum S/N ratio, the optical power required would be quite large, resulting in non-linearity of the APD. As such the optical power necessary for a given output current would be much higher than is predicted by the usual equation for photocurrent in an APD:

$$i = M\eta Pe\lambda/hc \quad (2)$$

where M is the gain, η the quantum efficiency, P the optical power, λ the wavelength, e the charge on an electron, c the velocity of light in a vacuum and h Planck's constant. The optical power required to generate this current pulse would be unacceptably large if the source were a low-power pulsed semiconductor laser, such as would be necessary for a portable instrument.

(ii) The system requires a variable optical time delay of 3–5 ns for a tissue TPSF measurement—equivalent to a pathlength of 1.0–1.7 m in air. If implemented with a stepper motor and corner cube reflector, even if the optical path were folded several times, the system would be quite bulky and unsuitable for portable use, and it would be difficult to maintain precise optical alignment onto a photodiode which must have a small active area, since it must be a high-speed device.

(iii) The optical chopper required to generate a reference for the lock-in amplifier is another mechanical component, which would be better replaced by a more reliable electronic device for a portable instrument.

The system developed at UCL is shown in figure 2. A large Ti:sapphire laser, complete with its mode locker, was used to produce short (2 ps) optical pulses at a repetition rate of 82 MHz. This will be replaced by a small pulsed semiconductor laser diode (Vasilev 1995) in the final instrument. The light pulses were coupled via a 100/140 μm multi-mode optical fibre to the tissue phantom, then from the phantom to the detecting APD (Model S2381, Hamamatsu Photonics KK, Japan). An electrical signal from the mode locker, which was phase locked to the laser pulses, was passed through a narrow-band-pass filter (–3 dB points of 75.9 and 88.9 MHz) and amplified before reaching an electronic phase shifting network (R&K Co. Japan, model PS-3-82 MHz), which could shift the phase of the 82 MHz signal through a full 360° with a control voltage of 0–10.25 V DC. The phase was controlled by a computer fitted with a D/A card. After leaving the phase shifter, the 82 MHz sine wave was further amplified to a level of +27 dBm (500 mW), before reaching a step recovery diode (SRD) (Chang 1990). There was an automatic gain control (AGC) system (not shown in full) using a PIN diode as a control element, that maintained the drive to the SRD at a constant 500 mW, even though there were small variations in the insertion loss through the phase shifter as the phase shift was altered. A 1 kHz square wave from the reference output of a lock-in amplifier (SR830, Stanford Research Systems, CA, USA) was used to override the AGC system, so that the drive to the SRD would be either a 500 mW sine wave or zero.

The modulated sine wave was then used to drive a step recovery diode (model GC82RC with positive output, Herotek Inc, CA, USA) which produces short electrical pulses of 8 V peak and 130 ps FWHM at its drive frequency (82 MHz). Figure 3 shows an oscilloscope

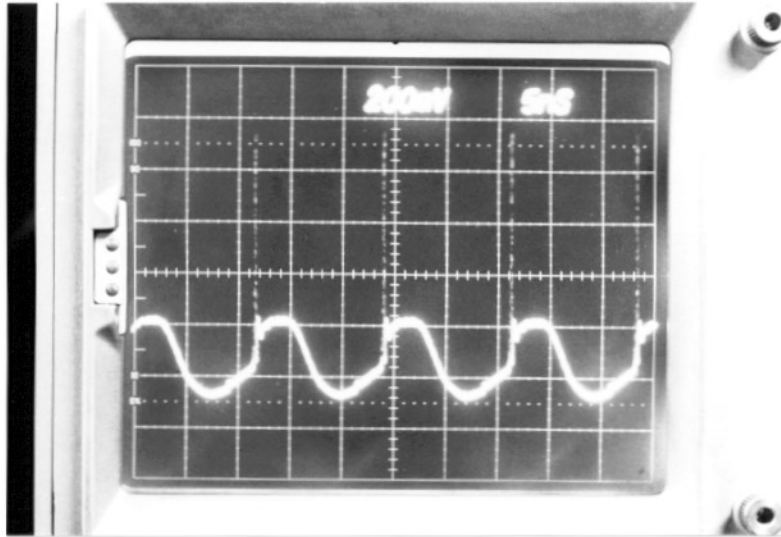


Figure 3. A sampling oscilloscope photograph showing the output of the SRD when driven with a continuous sine wave of 500 mW at 82 MHz. The vertical scale is 2 V/division, not 200 mV/division as shown, since a 20 dB attenuator is used on the SRD output. The time axis is 5 ns/division. Note the short-duration pulses, which are faint, due to the fast rise and fall times.

be as close to a delta function as possible. However, as can be seen from figure 3, the SRD output also contains an unwanted sinusoidal modulation component. Any gain modulation of the APD caused by signals other than the short pulse also results in an output from the lock-in amplifier which is not representative of the TPSF. There are two ways of correcting for the effects of this residual signal, both of which have been implemented as part of this study. These are the following.

(i) Use the SRD output together with its residual components to obtain the data, which would then be the cross-correlation of the complete SRD output and the desired signal. The distortion caused by the unwanted components of the SRD can then be removed in software. Since the unwanted signal is predominately a sine wave, the resulting distortion to the signal takes the form of a rectified sine wave, since the output of the lock-in amplifier gives the absolute magnitude of its input. Software subtraction of a rectified sine wave, of the correct amplitude and phase, then gives the true signal (Kirkby and Delpy 1995). However, the dynamic range of the system is compromised by this method.

(ii) Process the SRD output to remove the unwanted components before the signal is used to gain modulate the APD. To do this, a three-pole Butterworth high-pass filter with a cutoff frequency of 300 MHz was first tried, but the ringing of the filter caused an unacceptable performance loss. A three-pole Bessel filter gave a better, but still unacceptable performance. One further method which was tried was to add to the SRD's output a sine wave in anti-phase to the unwanted output. Although this significantly reduced the main 82 MHz component of the unwanted output, to the point where it was not visible on a spectrum analyser, some residual output remains, especially at 164 MHz and 246 MHz, so this was not 100% successful either. The most successful method was found to be to pass the SRD output through four series-connected HP 5082-2835 low-capacitance Schottky

diodes, with a turn-on voltage of approximately 500 mV each. Since the amplitude of the unwanted component is below the turn-on voltage of the four diodes in series, the output is predominately the desired short-duration pulses. Some resistive padding is used around the SRD and Schottky diodes, so that the return loss of the load on the SRD is greater than 20 dB. This does, however, reduce the APD output waveform by 10 dB.

To keep the temporal resolution of the system as short as possible, a number of steps have to be taken to reduce jitter and drift in the system. The exact location in the AC cycle at which the SRD produces the impulse needs to remain as stable as possible. This can be shown to depend on both the minority carrier lifetime of the semiconductor and the level of the RF drive power, which is why an AGC control system is used. The minority carrier lifetime of silicon is also very temperature dependent, so it is expected that the SRD, which is a small (30 mm long, with a 8 mm diameter) module, may eventually need to be temperature stabilized.

To prevent noise pick-up in the system, semi-rigid coaxial cable with a continuous copper screen was used throughout. Ordinary braided coaxial cable was found to have inadequate screening.

3. Results and discussion

The temporal response of the system was first measured by feeding the very short (< 2 ps) output pulses of the laser through a suitable neutral density filter directly onto the detecting APD, without any intervening scattering medium. The diode filtering circuit described above and shown in figure 2 was not installed at this time, so the SRD output shown in figure 3 was used to gain modulate the APD. It was necessary to fit a 20 dB attenuator between the SRD and bias-tee to ensure any reflections from the APD, which is not matched to 50Ω at its bias port, were not visible on the sampling oscilloscope. This measurement effectively gives the impulse response of the electronic system, since the laser pulses are much faster than the monitoring electronics. Figure 4 shows the output of the system without any attempt to remove the residual components from the SRD and figure 5(a) shows the same data after software processing to remove the residual output. An expanded view of figure 5(a) is shown in figure 5(b), where the temporal resolution can be seen to be approximately 275 ps FWHM.

Figure 6(a) shows the output of the system shown in figure 2, with the Schottky diodes included to remove the majority of the unwanted residual components from the SRD output. An expanded view of figure 6(a) is shown in figure 6(b), where the temporal resolution can be seen to be the same at 275 ps FWHM. The shift in the time axis is caused by changes in the lengths of the coaxial cables used in connecting the various RF components. The absolute levels of the signals are not directly comparable to those in figures 4 and 5, since the data in figure 6 were obtained with a focusing lens on the APD. However, it can be seen that the hardware method of residual removal has a higher S/N ratio, although there is a small ripple in the output at about 800–1000 ps, due to ringing on the falling edge of the SRD pulse, after it has passed through the diodes.

Figure 7 shows the system output when the TPSF of a tissue equivalent phantom (Firbank 1994, Firbank *et al* 1995) was measured. The output of the system is a convolution of the impulse response of the system and the TPSF. Since the convolution integral causes a reversal of the time axis, the output from the system is a time-reversed version of the TPSF, so the time axis has been reversed, to show the characteristic fast risetime/slow falltime of a tissue TPSF. The poor signal to noise level prevents the low light intensity at longer times in the TPSF being measured accurately. The dynamic range of the system is currently only

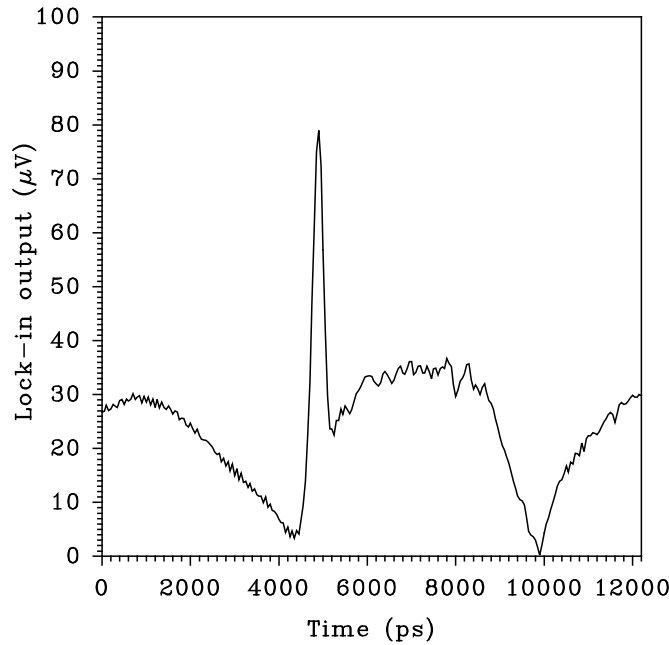
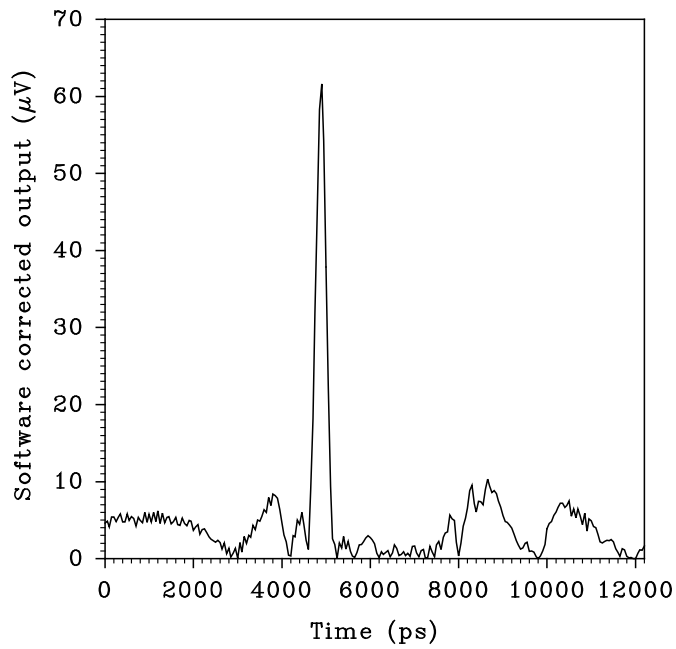


Figure 4. A graph showing the output of the system, with a short pulse of light (< 2 ps duration) incident on the APD. The wavelength of the light is 780 nm; the DC bias on the APD is 113 V.

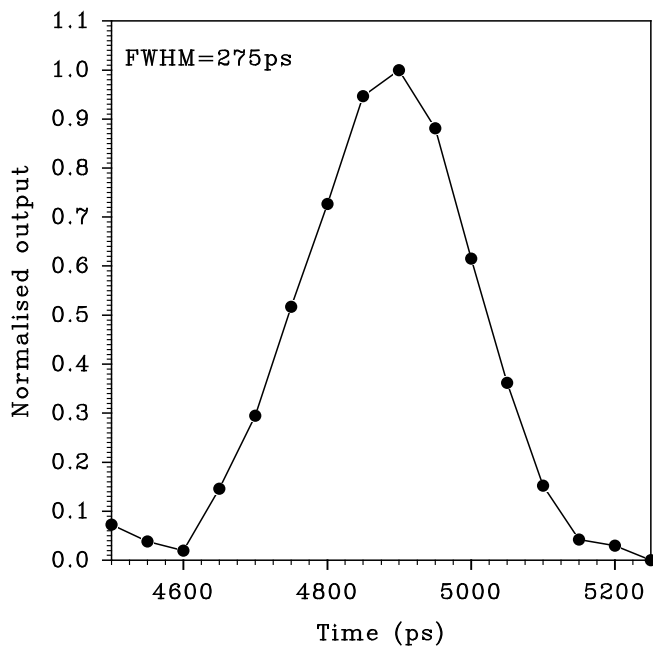
about 10 dB. To investigate the cause of this, the level of the residual noise in the signal was measured as the light intensity was altered by placing neutral density filters in front of the detecting APD. The level of the noise remained at approximately 10% of the peak signal, independent of the peak signal level. Hence an increase in signal also results in an increase in noise and no overall change in S/N ratio. This was found to be true with an average incident optical power ranging from 10 nW to 100 μ W. Below 10 nW, the S/N ratio increases due to the low signal amplitude. This finding would seem to indicate that the noise originates in the gain modulation circuitry and perhaps represents amplitude noise on the SRD pulse output. Further studies to confirm this are under way.

Also shown in figure 7 is the TPSF measured with a Hamamatsu synchroscan streak camera with a temporal resolution of less than 30 ps. The streak camera profile was scaled to have the same peak amplitude as the correlator data and the peak positions also matched. The two profiles are seen to be in good agreement, indicating the instrument is measuring the TPSF properly. Unlike the Hamamatsu streak camera, which can only measure over a 3.23 ns section of the whole TPSF at its slowest scan rate, the cross-correlator system allows measurement over the full 12.2 ns.

To examine the ultimate limits of the temporal response of the system, the 2 ps pulse from the laser was incident on the APD and the APD output was applied directly to the 50 Ω input of the sampling oscilloscope (Tektronix 7603 mainframe, with a 7S11 sampling unit and a 35 ps risetime S-4 sampling head). The resulting pulse had a risetime (10–90%) of approximately 200 ps, but a much longer falltime, giving an overall temporal resolution of 750 ps FWHM, which is the FWHM quoted on the manufacturers data sheet. Hence the temporal resolution of this complete system would appear to be significantly better (275 ps) than that of the APD alone (750 ps).

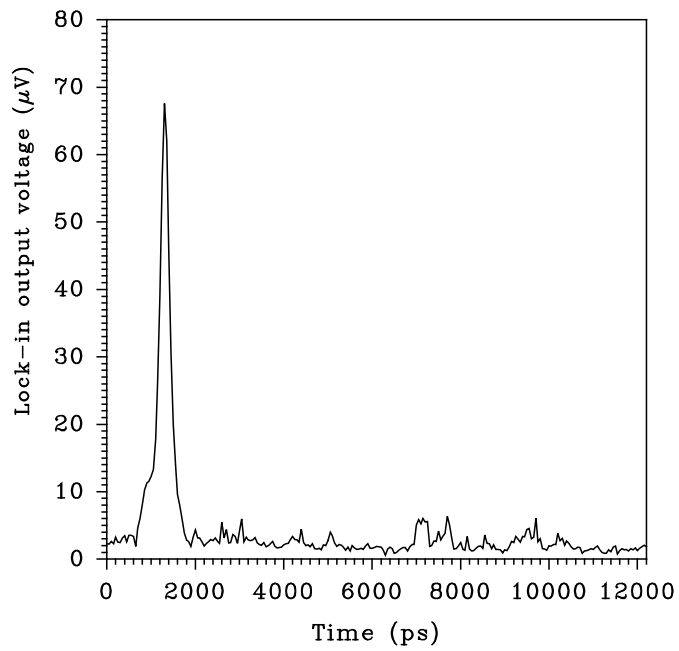


(a)

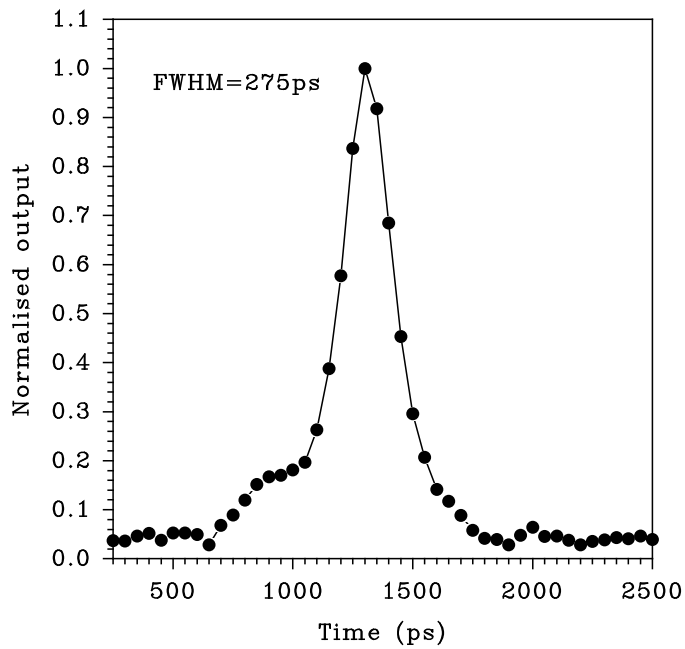


(b)

Figure 5. (a) Graph showing the same data as figure 4 after software removal of the residual 82 MHz rectified sine wave component. (b) An expanded view of the data in (a), showing an overall system temporal resolution of 275 ps FWHM.



(a)



(b)

Figure 6. (a) The impulse response of the system, after hardware remove of the residual SRD output. (b) An expanded view of the impulse response of the system shown in (a). The impulse response is seen to be 275 ps FWHM.

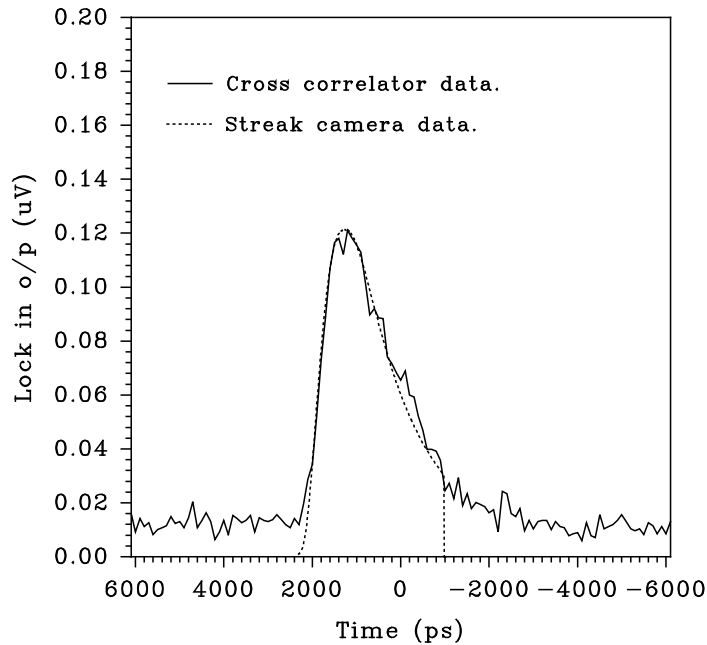


Figure 7. A measurement of the TPSF with both the cross-correlator (solid line) and a streak camera (dotted line) through a slab of tissue phantom, with $\mu_a = 0.001 \text{ mm}^{-1}$ and $\mu'_s = 2 \text{ mm}^{-1}$. The sharp cut-off of the falling edge of the streak camera data is due to the limited range of the streak camera. The residual noise on the system can be clearly seen. Note the direction of the time axis (see the main text for an explanation).

The temporal resolution of the cross-correlator system is limited by how fast the APDs gain can be changed, which is determined by a number of parameters, including

- (i) the SRD output impedance (50Ω),
- (ii) the SRD pulse width (130 ps),
- (iii) the APD load resistance (50Ω) and
- (iv) the APD junction capacitance (2 pF).

The RC time constant of the APD capacitance together with the source and load resistances is 200 ps, which, given the SRD pulse width, is not very different from the 275 ps FWHM measured for the complete cross-correlator.

However, when the APD is used to feed the 50Ω oscilloscope directly, the temporal resolution is dominated by the much longer time required for carriers to diffuse from the depletion region. We believe this is the reason the temporal response of the complete system is considerably faster than that of the APD alone.

4. Conclusions

A opto-electronic cross-correlator has been developed with a temporal response which is much faster than obtainable using just the APD alone. Since the system response is fast, the output should be close to the true tissue TPSF, although, for the intended application, it will probably be necessary to perform a deconvolution with the instrument response to enable the true TPSF to be determined. A comparison of a TPSF measured with the system

with that measured by a streak camera indicates good agreement. Since the system used only electronic components and was fibre coupled, it should be more mechanically rugged and portable than other techniques in use today, once the mode-locked laser is changed for a diode laser. It will also be significantly cheaper to build. The use of an SRD to generate the gain modulation impulses produced much shorter (130 ps) and larger-amplitude (~ 8 V) pulses than those that can be generated optically by using an APD (~ 2 V). The system also allows the variable time delay necessary to evaluate the cross-correlation to be implemented electronically, rather than by the usual mechanical/optical methods. Since no optical power is wasted in generating the reference pulses, all the optical power available from a pulsed optical source can be used for probing the tissue. The system temporal resolution is currently 275 ps FWHM, which is limited by the capacitance of the APD.

The dynamic range of the system is currently limited by a noise level which appears as a constant proportion of the measured signal level. We are currently investigating the best method to eliminate this problem, which we believe is caused by noise on the SRD output.

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