Differential amplitude scanning for retinal imaging: a theoretical study

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A differential amplitude scanning system for ophthalmoscopy is described theoretically. The Differential Scanning Ophthalmoscope (DSO) samples the retina with two laterally-displaced spots. The signal measured is the difference between the irradiance from these two locations. The theoretical analysis of the DSO shows it offers increased contrast at high spatial frequencies and only weak contributions from the low frequencies. This enables high-gain, low-noise detection that maximises contrast.

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The state-of-the-art in retinal imaging systems consists of scanning-based devices such as the Scanning Laser Ophthalmoscope (SLO) and Optical Coherence Tomography (OCT), but it is still not possible to clinically detect subtle changes in small retinal structures which would enable earlier disease detection.

In this Letter a novel retinal imaging technique is proposed: the Differential Scanning Ophthalmoscope (DSO). It is designed to detect small differences in reflectance across the retina, enabling accurate mapping of early disease-related change. Differential amplitude scanning has been studied and applied in microscopy [1, 2]. Ophthalmoscopy differs from microscopy in a number of key ways: the sample is non-stationary, light levels are restricted, and the optics of the objective lens (the eye's optics) suffer from considerable aberrations. The differential amplitude system proposed in this Letter is designed for robust imaging under these restrictions.

The DSO derives from the SLO but it is an inherently different device. In the SLO [3] a laser beam is focussed on the retina and light reflecting back is focussed through a pinhole and onto a photodetector. The pinhole makes the system confocal, enabling high axial resolution [3]. The beam is scanned so that the amplified signal from the detector yields a reflectance map of this region.

In the DSO, two beams are used such that the point-spread functions (PSFs) produced on the retina are laterally displaced with respect to each other. Light from both paths is

detected with a balanced photodetector pair, each with its own pinhole. The output is the difference between the signals from the two detectors, and therefore it is proportional to the difference in reflectance between the retinal regions illuminated by the PSFs.

Therefore the DSO is a differential amplitude imaging system. The intensity distribution of the image in an ideal confocal microscope is [2] $I_{SLO}(x,y) = |h_e \otimes r|^2$, where (x,y) are the coordinates of the image plane, h_e is the effective PSF of the confocal microscope, and for a reflective system such as the SLO $h_e = h^2$, where h is the amplitude PSF of the optics of the eye, r is the reflectance of the retina and $\otimes$ denotes convolution. We can write the intensity distribution of the differential amplitude system descibed above (i.e. the DSO) as

$$I_{DSO}(x,y) = |h_{e,1} \otimes r|^2 - |h_{e,2} \otimes r|^2 , \tag{1}$$

where the numerical subscripts distinguish between the PSFs produced by the two beams. As these PSFs are displaced laterally with respect to each other we can write

$$h_{e,1}(x',y') = h_{e,2}(x'-a,y') \tag{2}$$

for a shift of a along the $x'-$axis, where (x',y') are the coordinates of object space. If $\mathcal{H} = \mathcal{F}\{h\}$ and $\mathcal{R} = \mathcal{F}\{r\}$, where $\mathcal{F}$ denotes the Fourier transform operator, then

$$I_{DSO}(x,y) = \left|\mathcal{F}^{-1}\{\mathcal{H}_{e,1}\mathcal{R}\}\right|^2 - \left|\mathcal{F}^{-1}\{\mathcal{H}_{e,2}\mathcal{R}\}\right|^2 . \tag{3}$$

If (m,n) and (p,q) are both coordinate pairs in the Fourier domain corresponding to (x,y), then [4, 5]

$$\begin{aligned} I_{DSO}(x,y) = & \\ & \iiiint \mathcal{H}_{e,1}(m,n)\,\mathcal{H}^*_{e,1}(p,q)\,\mathcal{R}(m,n)\,\mathcal{R}^*(p,q)\ \times \\ & \qquad \exp\{-i2\pi[(m-p)x-(n-q)y]\}dm\,dn\,dp\,dq \\ & - \iiiint \mathcal{H}_{e,2}(m,n)\,\mathcal{H}^*_{e,2}(p,q)\,\mathcal{R}(m,n)\,\mathcal{R}^*(p,q)\ \times \\ & \qquad \exp\{-i2\pi[(m-p)x-(n-q)y]\}dm\,dn\,dp\,dq, \end{aligned} \tag{4}$$

where all integrals are over all space and * denotes complex conjugate. From the shift theorem for Fourier transforms [4] and from Eq. 2 we can write

$$\mathcal{H}_{e,2}(m,n) = \exp(-i2\pi am)\,\mathcal{H}_{e,1}(m,n), \tag{5}$$

$$\mathcal{H}^*_{e,2}(p,q) = \exp(i2\pi ap)\,\mathcal{H}^*_{e,1}(p,q). \tag{6}$$

Therefore, if we substitute Eqs. 5 and 6 into Eq. 4:

$$I_{DSO}(x,y) = \iiiint \{1-\exp[-i2\pi a(m-p)]\} \times \mathcal{H}_{e,1}(m,n)\,\mathcal{H}^*_{e,1}(p,q)\,\mathcal{R}(m,n)\,\mathcal{R}^*(p,q) \times \exp\{-i2\pi[(m-p)x-(n-q)y]\}dm\,dn\,dp\,dq. \tag{7}$$

Hence $(m-p, n-q)$ represent the spatial frequency components of the intensity image from the DSO, and the general transfer function (or transmission cross-coefficient) $C_{DSO}(m,n;p,q)$ [5] of the DSO is given by

$$C_{DSO}(m,n;p,q) = \{1-\exp[-i2\pi a(m-p)]\}\,\mathcal{H}_{e,1}(m,n)\,\mathcal{H}^*_{e,1}(p,q), \tag{8}$$

which to a first order approximation gives

$$C_{DSO}(m,n;p,q) = i2\pi a(m-p)\,\mathcal{H}_{e,1}(m,n)\,\mathcal{H}^*_{e,1}(p,q). \tag{9}$$

We can now compare this transfer function with the general transfer function for a confocal microscope [5]:

$$C_{SLO}(m,n;p,q) = \mathcal{H}_{e,1}(m,n)\,\mathcal{H}^*_{e,1}(p,q). \tag{10}$$

Unlike C_{SLO} which is separable into functions of (m,n) and (p,q) indicating a coherent imaging system [5], C_{DSO} indicates that the DSO is a partially coherent imaging system. The symmetry imposed by the term $i(m-p)$ for C_{DSO} (Fig. 2) confirms that the DSO is a differential amplitude imaging system [2]. Without any loss of generality, we can assume our object is a line object with variations along the $x'-$axis so that n and q are zero and we can reduce the general transfer functions to functions of two variables: $C(m,0;p,0) = C(m;p)$.

Figures 1 and 2 show plots of the general transfer functions for the SLO and DSO respectively. The $(m-p)$ axis represents spatial frequency components of the intensity image, with the DC term at the origin. As we would expect from a differential imaging system, the DSO has no DC term and very weak low frequency terms. When compared with the SLO, although the cut-off frequency is the same (as shown in Figs. 1 and 2, bottom), the DSO has higher contributions from the higher spatial frequencies giving better contrast imaging at these frequencies.

A detection system that is matched to the signal being measured can now be chosen. The retina is an object in which variations in amplitude reflectance over small areas are small, even though the range of values over larger retinal regions is considerably larger. Thus,

the dynamic range required for a detection system is much smaller in a differential imaging system than in a reflectance imaging one. This is illustrated in Fig. 3 in which the pixel values of a horizontal line across an SLO image are plotted together with their numerical derivative, which shows a markedly smaller range of values. Although in this example the derivative was obtained from the reflectance image, in the DSO the differential signal is inherent to the system. This enables the DSO to have a higher gain, leading to higher contrast.

The implications of noise must also be considered carefully, especially in view of the high gain. The differential image is inherent to the DSO; specifically, differentiation of the reflectance signals occurs after detection by the two photodetectors but before any signal amplification. The differentiation process is therefore unaffected by the noise introduced by the amplification electronics. The noise responses of the photodetectors are very closely matched in a balanced detection module, contributing to the low noise generation.

We now consider the light signals reflected from the retina. The dual beam is generated from a single laser beam that is split in two beams with orthogonal polarisation. These are adjusted subjectively by minimising the contrast of interference fringes formed by expanded beams on the retina so that the birefringence of ocular media is accounted for. As the lateral separation of the spots is small, the two beams propagate through near-identical paths in the optical media. Together with the common source, this ensures that any noise is common to both beams and will therefore not affect the differential signal. This is in stark contrast to techniques such as OCT where the reference beam does not propagate through the ocular media resulting in a noisy signal. This configuration thus allows for high amplification of the derivative signal without associated amplified noise.

We will finally determine the optimum centre-to-centre spot separation a for the DSO. If a is small, the signal will also be small as there is considerable overlap between the two PSFs. The signal will reach a maximum when there is no overlap between the two PSFs. This relationship is shown in Fig. 4 for the diffraction-limited case. Signal strength S is defined as the difference between the maximum and minimum values of

$$I_0(v) = \left|h_1^2(v)\right|^2 - \left|h_2^2(v)\right|^2, \tag{11}$$

where h_1 and h_2 are the amplitude PSFs of the two spots, v is the dimensionless optical coordinate linked to (x, y) (as defined by Wilson [2]) and hence $I_0(v)$ is the response of the DSO (Eq. 1) for an ideal point object. We are also interested in the separation of the two lobes of $I_0(v)$ and we define the lobe separation L as the separation of the maximum and minimum points of $I_0(v)$. L will vary linearly with a when there is no overlap between the two PSFs, but will increase at a slower rate for smaller a, as shown in Fig. 4. Although Eq. 9 shows that the spatial frequency content of the DSO image does not depend on a, the actual image obtained will; each pixel in a DSO image represents the difference between the retinal regions illuminated by the two PSFs, and therefore if a is small, it will represent edges of

recognisable retinal features. Reconstruction of a reflectance image from the differential image is also unambiguous when a is small enough. Hence, an optimum value for a is one that gives small L but large S; we therefore define a gradient signal $G = S/L$ whose maximum gives the ideal spot separation. For the diffraction-limited case (Fig. 4) the ideal spot separation is $a \approx 2$ (in units of v) which is approximately 1/4 the width of the PSF on the retina.

A differential amplitude scanning system for retinal imaging has been described and theoretically assessed showing its ability to image high frequency content with high contrast. Practical aspects of the DSO have been discussed. The platform can also be used to separate the spots axially, giving axial differentiation and high contrast detection of retinal layer interfaces. The application of appropriate filters to the return paths will transform the DSO into a phase-differentiation imaging device [2], ideally suited for *in-vivo* imaging of ganglion cells.

References

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List of Figures

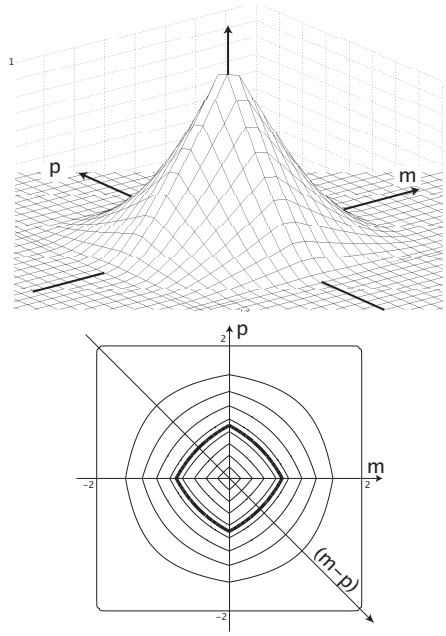

Fig. 1. Magnitude of the general transfer function $C_{SLO}(m;p)$ for the standard confocal microscope (SLO). Top: Amplitude plot (normalised), bottom: contour plot with the outermost square contour showing the frequency cut-off, and the thicker contour representing the 0.5 level. $m-$ and $p-$axes in units of v *(see text)*.

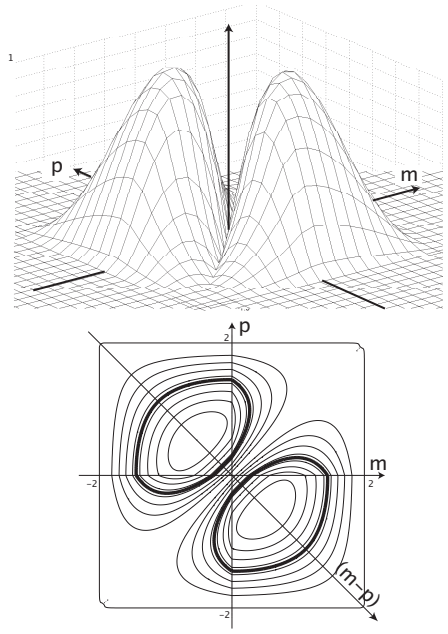

Fig. 2. Magnitude of the general transfer function $C_{DSO}(m;p)$ for the differential system (DSO). Plots and axes as in Fig. 1. The plots show that the DSO has no DC term and weak low-frequency contributions. Although the cut-off is the same as the SLO, higher frequencies contribute more in the DSO.

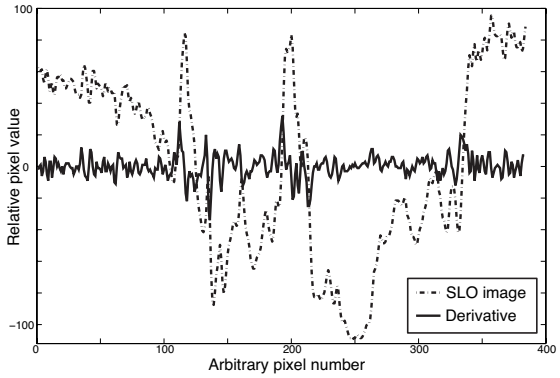

Fig. 3. Pixel values along a horizontal line of an SLO image and their numerical derivative.

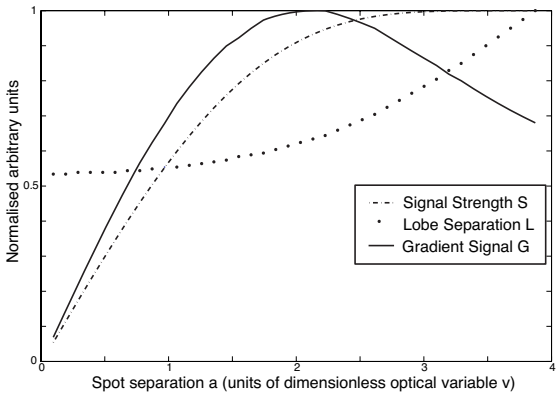

Fig. 4. Plots of parameters S, L and G against a.