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# Combination Biomaterial in Slowing down Cone Misalignment in Early Age-Related Macular Degeneration

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**Abstract**

When the ratio of intensities for both axial and peripheral entries for equal photometric effects is plotted against the pupil entry position a Stiles Crawford function (SCF) is obtained. As the SCF is modified in various retinal pathologies and especially a disturbance in the mechanism of photoreceptor alignment is observed in some forms of age-related macular degeneration (AMD), the waveguide approach of Stiles Crawford Effect is adopted to study AMD. In this approach, the spot-size ratio is evaluated for healthy and early AMD eyes to attempt an answer of the question: can the disturbed visual perceptions of patients with early stages of AMD be accounted for by improper alignment of macular cones? The results showed that, in fact, in early AMD the misalignment of cones led to complete elimination of retinal directionality as revealed from a fixed spot-size ratio for all pupil entry positions of light. It is also established that the directionality of retina is much more sensitive to misalignment of cones than to cone death. So, can we implant a biomaterial to slow down misalignment, a manifestation of ageing process? In the light of this, an implantable combination biomaterial of polymethylmethacrylate-titanium oxide (PMMA-$TiO_2$) is proposed to modulate the macular environment thereby slowing down the misalignment of cones.



***Keywords:***

Spot-size ratio;
Photoreceptor cone;
Age-relatedmacular degeneration;
Misalignment;
Combination biomaterial.

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## 1. Introduction

In 1933, Stiles and Crawford reported that light entering the human eye at the centre of the pupil was several times more effective in producing the sensation of vision than light entering near the pupil periphery. The physiological explanation of this phenomenon, later called the Stiles Crawford effect of the First Kind (SCE I), is that cone photoreceptors yield a directional sensitivity. Waveguide properties of cone photoreceptor inner segments, guiding the light to the outer segment photopigments, optimize absorption of axial incident light rather than off-axis light. The optical equivalent of this psychophysical effect is called the optical SCE [1,2]. A small fraction of the incident light is reflected back toward the pupil. In a healthy retina, more light is reflected toward the middle of the pupil, where most cone photoreceptors are aimed. In disease, the optical SCE is a sensitive indicator of cone photoreceptor disturbances [3].

Age related macular degeneration (AMD) is a degenerative disease primarily affecting the macula and an increasingly prevalent cause of irreversible blindness in the industrialized world. Early AMD is characterized by

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drusenandpigmentary abnormalities with relatively few visual symptoms. However, in its late stage, AMD often leads to a disabling central scotoma. It is known that drusen disturb the orderly alignment of overlying cone photoreceptors. The retinal epithelium (RPE) supplies the photoreceptors with nutrients and maintains the integrity of subretinal space. Thus, RPE changes may also affect the optical quality of the involved cone photoreceptors. Several electrophysiological and psychophysical studies aimed at examining the visual function in early AMD have found disturbances in light sensitivity and in adaptation throughout the retina regarding both cone and rod photoreceptors [4-8].

The pathological mechanism in at least some forms of AMD involves a disturbance in the mechanism of photoreceptor alignment. The uniquely high visual acuity that is normally achieved using the cone photoreceptors in the human fovea requires that these cones be able to achieve and maintain proper alignment towards the entrance pupil of the eye. Indeed, accurate alignment of foveal cones is necessary, but not sufficient, for high visual acuity. Thus, the question is: can the disturbed visual perceptions of patients with early stages of AMD be accounted for by improper alignment of macular cones? Disturbances in the central visual field are often detected as distorted perception of the lines on the Amsler grid [9]. However, Amsler grid reports are not very sensitive and have poor validity in the clinical assessment of early AMD [10,11].

Here, in this study we have adopted the approach of recreating the Stiles-Crawford function by interpreting perfect matching for axial entry of the beam and proportionate mismatching for corresponding degree of peripheral entries. That is, when the fraction of light power that is not able to be coupled to a fundamental mode of a foveal cone is computed, it is found that the mismatch is proportional to the degree of departure from the perfect matching for one hundred percent coupling. Thus, Stiles-Crawford effect of the first kind is shown to be the response of the retina to departure from perfect matching [12]. As the SCF is modified in various retinal pathologies [13] it has the potential of becoming an excellent bio-indicator in diseases that affect the photoreceptors. This technique of spotsize ratio departure is already successfully employed in case of retinitis pigmentosa [14]. As the SC function has been measured in patients with early stages of AMD and found to be reduced in one out of two cases examined [15], this has motivated us to employ this technique to show that, in fact, the visibility loss or reduction in SCF is due to disruption in cone alignment.

What are the processes, cellular or biochemical, associated with age related macular degeneration to be slowed down? One is oxidative stress and the other inflammation (shift in the balance between the synthesis and elimination of reactive oxygen species) [16]. Thus, the approach is to regulate the two phenomena by modulating the microenvironment of macular misalignment due to ageing and avoid the conventional use of drugs. Which biomaterial or combination biomaterial fits into the shoe? Polymethylmethacrylate (PMMA) has excellent optical properties, high degree of compatibility, and long term stability under physiological conditions [17]. Moreover, it can be processed as nanofibres by electrospinning method, as self-supporting membranes by slip-casting or as fine layers supported on various different substrates by spin-coating method. Titanium oxide ($TiO_2$) is a ceramic material with wide-spectrum semiconducting electrical properties (3.0- 3.3 eV). Out of many applications in a variety of technology fields its photocatalytic activity, which enables it to generate reactive oxygen and nitrogen species able to oxidize organic matter can be exploited to slow down the process of cone misalignment due to early age related macular degeneration [18] and thus, endows it with high degree of biocompatibility in the presence of physiological media [19]. The proposed approach of implanting a combination biomaterial of PMMA-$TiO_2$ aims to slow down the ageing of the extracellular environment of the eye tissue produced by these inflammatory species manifested as misalignment of cones.

## 2. Research Method

Here, we have presented the spot-size ratio departure technique [12,14]. Considering the propagation along the z-direction of a Gaussian beam whose amplitude distribution on the plane $z = 0$ is given by

$$E_{0,x}(x, y, z = 0) = Ae^{-\frac{x^2+y^2}{\omega_o^2}} \quad (1)$$

where$\omega_o$ is the radius of the spot at the retinal plane. This backscattered light allows imaging of the cones using optical coherence tomography [20]. And as the beam propagates toward the pupil, diffraction occurs and one obtains [21]

$$E_{0,x}(x, y, z) = \frac{iA\pi}{\lambda}\frac{2\omega_o^2}{2z + ik\omega_o^2}e^{-ik\left(z+\frac{x^2+y^2}{2R(z)}\right)}e^{\frac{-(x^2+y^2)}{\omega^2(z)}}$$

Where$R(z) = z\left\{1 + \frac{\pi^2\omega_o^4}{\lambda^2 z^2}\right\}$represents the radius of curvature of the wavefront assumed to be plane at the retinal plane and $\omega^2(z) = \omega_o^2\left(1 + \frac{\lambda^2 z^2}{\pi^2\omega_o^4}\right)$ representing the z-dependent spot size of the beam. For large values of z, $\omega(z) \cong \frac{\lambda z}{\pi\omega_o}$,representing the z-dependent spot size of the beam. For large values of z,

$$\omega(z) \cong \frac{\lambda z}{\pi\omega_o} \quad (2)$$

Implying$tan\,\theta \cong \frac{\omega(z)}{z} = \frac{\omega_1}{f_{eye}} = \frac{\lambda}{\pi\omega_o}$ or $\theta = \frac{r}{f_{eye}}$ where$r$ is the distance of the pupil entry point of the beam from the centre. The angle of incidence on the retina or the semiangle of the cone defining the diffraction divergence of the beam, $\theta$, for the schematic eye model is related to the pupil entrance point, $\theta = \frac{r}{f_{eye}} = \frac{3mm}{22.2mm} = 0.135$radian or equivalent to $(= \frac{180\times0.1351}{\pi})7.7^0$.

Thus, the radius of the spot at the beam waist,$\omega_o$, relates to the beam radius at the pupil $\omega(z)$= $\omega_1$ as $\omega_1 \cong \frac{\lambda f_{eye}}{n_{eye}\pi\omega_o} = \frac{0.55\times22.2}{1.33\pi} = 2.92\ mm$at the pupil or a pupil of nearly 3 mm radius.

(For, $\lambda = 0.55\,\mu m, \theta \cong 8^0, \omega_o =$ 1.00 µm, $f_{eye}$ =22.2 mm and $n_{eye}$ =1.33) [22]. The size of the cones is expected to increase from approximately 2.5 µm to 5 µm at $1^0$ to $10^0$ from the fovea, respectively [23]. This size of beam is used in high-resolution retinal imaging systems. Thus, writing $\omega_1\,\omega_o\ as\ \frac{\lambda f_{eye}}{n_{eye}\,\pi\omega_o}$, we get $\omega_1\,\omega_o = 5311\lambda(in\ \mu m)$.

In our model as the incident beam couples light only to the fundamental mode represented by a Gaussian function of width $2\omega_m$ (where $\omega_m$ is the waveguide mode spot size) the fraction of power that is not able to be transmitted to the photoreceptor if incident with its peak value at the photoreceptor axis can be found as [21]

$$1 - T(\theta) = 1 - \left[\frac{2\omega_o\omega_m}{\omega_o^2+\omega_m^2}\right]^2 exp\left[\frac{-2(\pi n_{eye}\,\omega_o\omega_m)^2\theta^2}{\lambda^2(\omega_o^2+\omega_m^2)}\right] \quad (3)$$

or

$$1 - T(r) = 1 - \left[\frac{2\omega_o\omega_m}{\omega_o^2+\omega_m^2}\right]^2 exp\left[\frac{-2(\pi n_{eye}\,\omega_o\omega_m)^2 r^2}{\lambda^2(\omega_o^2+\omega_m^2)f_{eye}^2}\right] = 1 - \left[\frac{2\times\frac{5311\lambda}{\omega_1}\omega_m}{\left(\frac{5311\lambda}{\omega_1}\right)^2+\omega_m^2}\right]^2 exp\left[-2\left(\frac{\pi n_{eye}}{\lambda f_{eye}}\right)^2\left(\frac{\omega_o^2\omega_m^2}{\omega_o^2+\omega_m^2}\right)r^2\right]$$

$$= 1 - \left[\frac{2\times\frac{5311\lambda}{\omega_1}\omega_m}{\left(\frac{5311\lambda}{\omega_1}\right)^2+\omega_m^2}\right]^2 exp\left[-2\left(\frac{\pi n_{eye}}{\lambda f_{eye}}\right)^2\left(\frac{\left(\frac{5311\lambda}{\omega_1}\right)^2\omega_m^2}{\left(\frac{5311\lambda}{\omega_1}\right)^2+\omega_m^2}\right)r^2\right]$$

$$= 1 - \left[\frac{2\times\frac{5311\lambda}{\omega_1\,\omega_m}}{1+\left(\frac{5311\lambda}{\omega_1\,\omega_m}\right)^2}\right]^2 exp\left[-2\left(\frac{\pi n_{eye}}{\lambda f_{eye}}\right)^2\left(\frac{\left(\frac{5311\lambda}{\omega_1}\right)^2\omega_m^2}{\left(\frac{5311\lambda}{\omega_1}\right)^2+\omega_m^2}\right)r^2\right]$$

$$= 1 - \left[\frac{2\times\frac{5311\lambda}{\omega_1\,\omega_m}}{1+\left(\frac{5311\lambda}{\omega_1\,\omega_m}\right)^2}\right]^2 exp\left[-2\left(\frac{\pi n_{eye}}{\lambda f_{eye}}\right)^2\left(\frac{\omega_m^2}{1+\frac{\omega_1^2\omega_m^2}{(5311\lambda)^2}}\right)r^2\right]$$

where $\theta = \frac{r}{f_{eye}}$, $\omega_1\,\omega_m$ is the product of the beam radius at the pupil and the waveguide mode spot size and r is the distance from the on-axis value. Thus, $1 - T(\omega_1\,\omega_m, \lambda) = 1 - \left[\frac{2\frac{5311\lambda}{\omega_1\,\omega_m}}{1+\left(\frac{5311\lambda}{\omega_1\,\omega_m}\right)^2}\right]^2 = 1 - \left[\frac{2\frac{K}{\omega_1\,\omega_m}}{1+\left(\frac{K}{\omega_1\,\omega_m}\right)^2}\right]^2 = \left(\frac{n^2-1}{n^2+1}\right)^2$ (4)

where $\frac{K}{\omega_1\,\omega_m} = n$ and $K = 5311\lambda$ assuming a constant wavelength for the beam passing axially through the pupil.

## 3. Results and Analysis

The Stiles-Crawford function (SCF) is written $\eta = \eta_o e^{-\rho r^2}$ where $\rho = 0.115 mm^{-2}$[24]. But, expressing it as visibility loss, $\chi = 1 - \frac{\eta}{\eta_o} = 1 - e^{-\rho r^2}$ where $\eta$ is the relative luminous efficiency as defined by Stiles and Crawford and then correlating it with Eq. 4, we get $\chi = 1 - e^{-\rho r^2} = \left(\frac{n^2-1}{n^2+1}\right)^2$. After working out the steps we finally get an equation for $n$ in terms of pupil entry point $r$ and vice versa for a normal eye as [12,14]

$$n = e^{\frac{\rho}{2}r^2} \pm \sqrt{e^{\rho r^2} - 1} \quad (5)$$

. The pupil profile of the healthy subject shows a Gaussian shaped reflection originating from the foveal cone photoreceptors (optical SCE), on a diffuse background. In the patient with early AMD, only a non directional diffuse background reflection was seen, that is, the visibility loss is almost 40 % for all pupil entry points of the incoming light [4]. Rewriting Eq (4) for an early AMD eye as $0.4 = \left(\frac{{n_{amd}}^2-1}{{n_{amd}}^2+1}\right)^2$ we get $n_{amd} \cong \pm 2$. Defining the discrepancy in departures ($\delta n$) between the spot-size ratio for a normal healthy eye ($n$) and the spot-size ratio for an early AMD eye ($n_{amd}$) as $\delta n = n - n_{amd}$, , we can express (using Eq 5)

$$\delta n = e^{\frac{\rho}{2}r^2} \pm \sqrt{e^{\rho r^2} - 1} - n_{amd} \quad (6)$$

$\delta n = e^{\frac{\rho}{2}r^2} + \sqrt{e^{\rho r^2} - 1} - n_{amd}$ (for n-fold departure)

$\delta n = e^{\frac{\rho}{2}r^2} - \sqrt{e^{\rho r^2} - 1} - n_{amd}$ (for 1/n-fold departure)

This discrepancy ($\delta n$) when plotted against the pupil entry point($r$) for n-fold, 1/n-fold departures (Figs. 1-3) we see that it increases with increase of pupil entry point as expected from a directional retina.

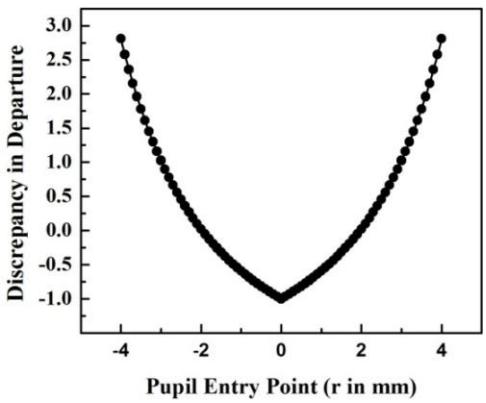


Figure 1.Response of discrepancy in departure to pupil entry points of the beam for n-fold departures

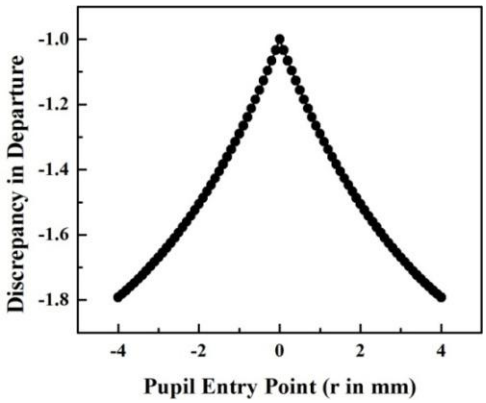


Figure 2. Response of discrepancy in departure to pupil entry points of the beam for 1/n-fold departures.

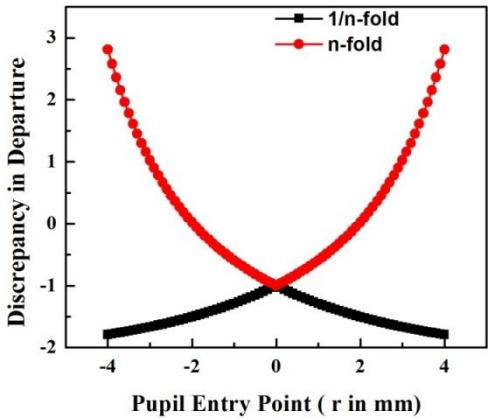


Figure 3. Response of discrepancy in departure to pupil entry points of the beam for both n-fold and 1/n -fold departures

As the spot-size ratio for an early AMD eye is independent of pupil entry point, the discrepancy in departure profile mimics the traditional SCE visibility diminution of a normal healthy eye. This result corroborates the experimental finding that in the patients with early AMD, only a non directional diffuse background reflection is seen [4]. It also assigns a value of $\rho = 0$ for an early AMD eye which is 0.115 [24] for a healthy eye and 0.067 for a retinitis pigmentosa eye [14].

In order to understand the non-directionality of an early AMD eye more deeply, we differentiated the spotsize ratio $(n)$ of a healthy eye and the spot-size ratio of an early AMD eye $(n_{amd})$ with respect to $(r)$ and study the response to $r$ as depicted below from Figs. 4-6.

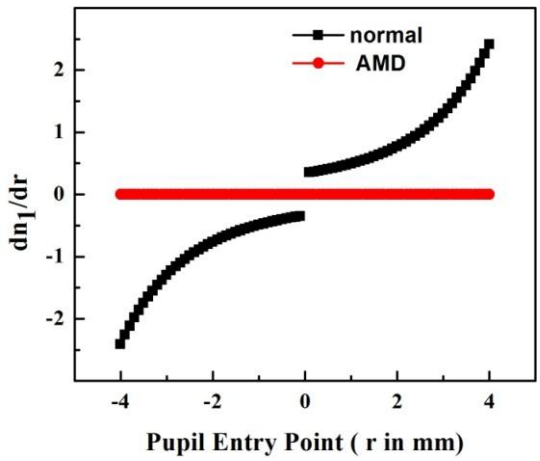


Figure 4.The comparison of slope for n-fold departure between normal and early AMD eyes

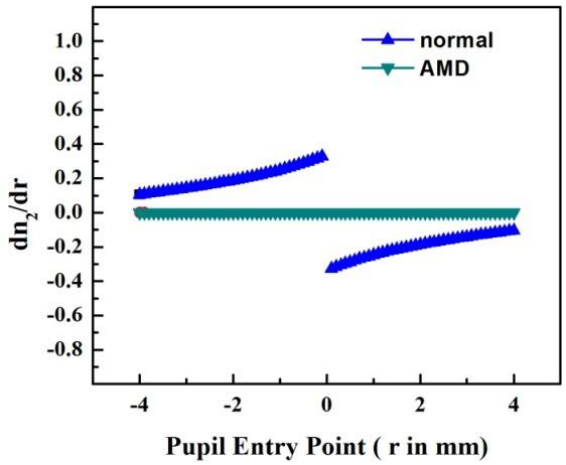


Figure 5.The comparison of slope for 1/n-fold departure between normal and early AMD eyes

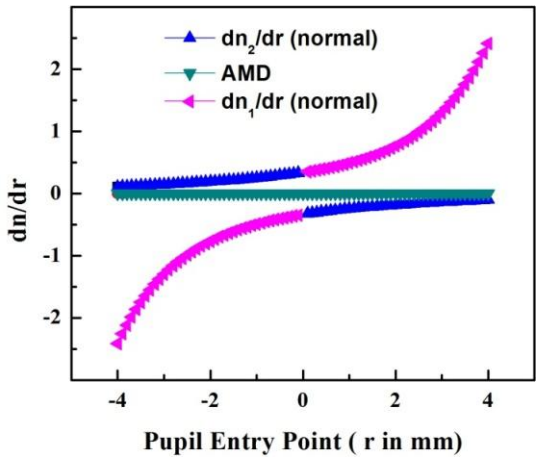


Figure 6. Comprehensive comparison of slopes of both
n-fold and 1/n-fold departures in case of normal and early AMD eyes

It is evident from figs 4-6 that, the slope of spot-size ratio for an early AMD eye is zero for all pupil entry points. This indicates that the early AMD has disrupted the alignment of the cones to such an extent that the cones fail to muster the required directional response to compensate for the loss of luminance efficiency due to oblique stimulation contrary to a healthy eye. And when we move toward the periphery from the central fovea, the discrepancy in slope between a healthy eye and an early AMD eye widens as expected because the discrepancy in slope is still governed by the directional SCE. Again, the visibility diminution is more probably, primarily due to misalignment of cones unlike cone loss in other photoreceptor diseases. And the other finding is that the disruption in cone alignment removes the directionality completely but cone loss only reduces the directionality as seen in retinitis pigmentosa [14]. Thus, the directionality of retina is much more sensitive to misalignment than to cone death.

## 4. Conclusion

We see that the spot-size ratio of an early AMD eye is a constant, independent of pupil entry positions of the incoming light. Thus, the discrepancy in spot-size ratio of an early AMD eye and that of a healthy eye is governed by the Stiles Crawford effect. Moreover, the slope of spot-size ratio of an early AMD eye is zero indicating the complete wash out of the directionality. The cones lack the perfect alignment so badly necessary in a healthy eye to provide a compensative response to loss of luminance efficiency due to oblique stimulation. Thus, our study from the perspective of spot-size ratio strongly points to the fact that in an early AMD eye the photoreceptor cones get misaligned as revealed from both the discrepancy in departure profile and zero slope of the spot-size ratio. It is also established that the directionality of retina is much more sensitive to misalignment than to cone death. In view of this finding, it is proposed to slow down the misalignment of cones primarily responsible for early AMD by implanting a combination biomaterial of PMMA-$TiO_2$ which also avoids the conventional use of drugs.

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