Open issues in the study of human retina

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This paper reports a concise survey on some characteristics of the human retina. The goal is to present some of the known parameters together with some open issues that still do not fit in the actual models of human vision. Colour and vision in general are still far from being well known mechanisms.

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Introduction

There are several papers and books that present the many characteristics of human retina. Its complex structure is composed by many biological elements and its behaviour is described by numerous parameters. In this article we present and discuss the main characteristics and functions of the human retina, evidencing the most interesting open issues in the way of the understanding how its physiological properties and topography affect our vision. Despite the fact that retina characteristics and structure are often presented as well-known, there are several points still to assess, like e.g. the total number of photoreceptors, the number of axons converging in the optical nerve and the size of the rod-free zone in the fovea. Among the difficulties in getting an agreeable evaluation there are errors in determining densities in histological tissue caused by post mortem shrinkage, difference in counting windows and misidentification of the foveal centre [1]. Another unresolved issue is the specificity of retinal neurons connectivity, since the responses of retinal elements can be related to the synaptic connections with other retinal cells, but how far this specificity goes is still a long way from being fully understood [2]. Retinal photoreceptor topography is also correlated to various perception phenomena, like the filling-in taking place in the retinotopic region corresponding to the optic disk, and the high differences in M to L cone ratio leading to no significant intersubjective differences in sensation, aspects that are still not fully explained.

Structure of the retina

The retina is a thin membrane in the inner part of the ocular bulb, and is regarded as an extension of the diencephalon since the optic nerve directly extends from it. The photoreceptors are particular neural cells of elongated shape capable of the process of phototransduction, converting a light stimulus into an electric signal [3]. Rods and cones are the photoreceptors located in the *stratum opticum* layer of the retina, the second closest layer to the *choroid*, after the retinal *pigment epithelium* directly faced by sensors, away from incidental light. Figure 1 illustrates the structure of the retina, with the light coming from the outside of the eye on the left side.

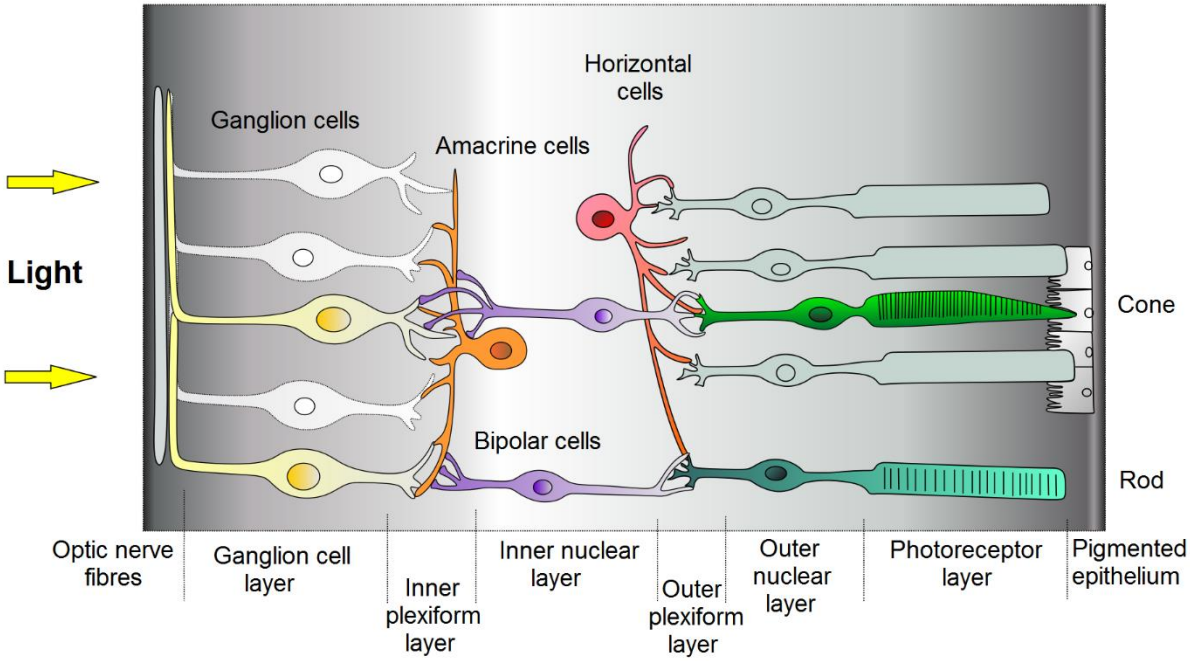


Figure 1: Photoreceptor and nerve layers in the retina[1].

The cones are less numerous and have a larger section than the rods, which are longer and thinner, and serve different purposes in the process of vision. The cones are responsible for the vision in conditions of daylight illumination, the *photopic* vision, and are also capable of the perception of chromatic signals. In contrast, rods can detect even the smallest amount of radiant energy, but they can only yield achromatic or grey levels of colour perception. Rods are only used in human *scotopic* vision, which happens in conditions of low illumination, making us unable to detect colours [4].

The bodies of the photoreceptor cells compose the *Outer Nuclear Layer*, followed by the *Outer Plexiform Layer*, containing a synaptic web constituted by the synaptic terminals of the photoreceptors and dendritic processes of horizontal and bipolar cells. The *Inner Nuclear Layer* contains the cell bodies of horizontal, bipolar, Müller and amacrine cells; next is the *Inner Plexiform Layer*, consisting of the axons terminals of the bipolar cells and a synaptic plexus of amacrine cells processes and ganglion cells dendrites. The *Ganglion Cell Layer* is composed of the cell bodies of the ganglion cells and of the displaced amacrine cells [5].

The retina divides visual information into parallel neural pathways, each with its own specialisation, this segregation of signals continues through different synaptic connections within the retina. The three

[1]Image taken from https://commons.wikimedia.org/wiki/File:Retina.svg.

best understood pathways in the human retina are the parasol, midget and small bistratified pathways [2]. *Parasol cells* receive input mostly from medium and long wavelength-sensitive cones via one or more diffuse bipolar cells, projecting into the *magnocellular* cells layer of the *lateral geniculate nucleus*, the area of the thalamus that connects the optic nerve to the occipital lobe, carrying the pathway signals into the brain. Another pathway begins in the *midget ganglion cells*, which receive input from a single cone in the fovea via a single midget bipolar cell, projecting into the *parvocellular* cells layers of the lateral geniculate nucleus. A third group of cells receives input from the short wavelength-sensitive cones, the *small bistratified cells*, identified in 1994 by Dacey and Lee [6], receiving on-excitation from the S cones and off-input from other cone types and are thought to project into the *koniocellular* cells layers of the lateral geniculate nucleus. While the magnocellular cells are responsible for the perception of movement and depth and the parvocellular detect colour and fine details, koniocellular cells are still not entirely characterised, since they are supposed to be composed of several subclasses and contribute to vision detecting aspects of spatial and temporal resolution [7]. The issue of how wiring in the retina produces functional specificity is still not entirely defined, since it needs a demonstration of a connectivity and an estimation of synaptic weighting. Also, the anatomical substrates of physiological properties like the wiring responsible for the surrounding mechanism of the receptive centre are still challenging to define.

From the centre of the retina, going 3 to 4mm towards the nasal retina, we can find the optic disk, the only retinal region devoid of photoreceptors, also called blind spot. This area acts as the exit point of the eye for the optic nerve, as all ganglion cells axons converge in this exact region, and entry point for the central retinal artery, which supplies blood to the retinal tissue. A graphical representation of cones and rods estimate distributions is shown in Figure 2, evidencing the absence of photoreceptors in the blind spot region.

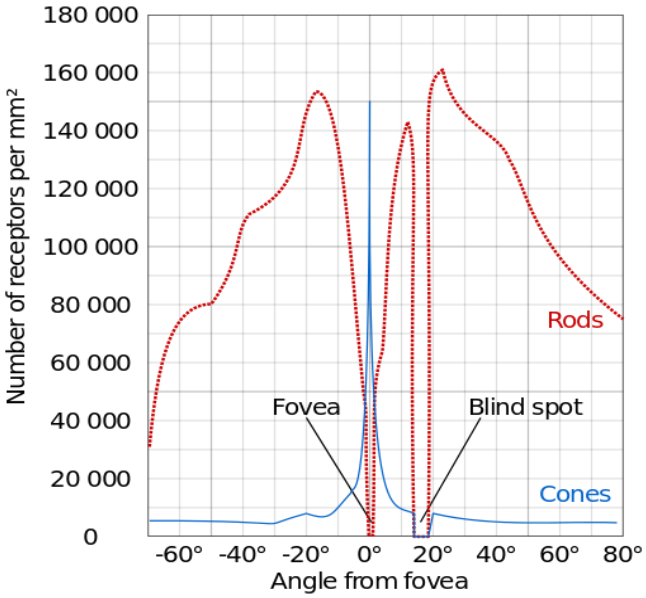


Figure 2: Horizontal section density of rods and cones in the retina, evidencing the areas of peak densities and the blind spot[2].

The area of the visual field corresponding to the physiological blind spot is perceptually filled-in and so we are normally unaware of its existence, as we can ascertain from the demonstration in Figure 3.

[2]Image taken from https://commons.wikimedia.org/wiki/File:Human_photoreceptor_distribution.svg.

Figure 3: Demonstration of the physiological blind spot. Closing the left eye and focusing on the left symbol with the right eye (or vice versa), at the appropriate distance between the observing eye and the focused symbol we can notice that the other symbol has disappeared.

It is still unclear how the blind spot is invisible in our normal vision and there are different hypothesis regarding the phenomena of filling-in. According to philosopher Daniel Dennett [8], rather than filling in, our brain finds out features present in our vision, like discrimination of motion or uniformity of colour in an area, and the task of interpretation is done, since the brain has no precedent of getting information from that gap of the retina. This theory was extensively contested by Vilayanur S Ramachandran [9], which in 1992 [10] experimented with the blind spot and scotomas (regions of blindness in the visual field caused by damage to a small portion of brain tissue), with the purpose of determining characteristics of the filling-in process and its relation to other types of visual processing, observing that filling-in occurs before some of the early stages of visual processing, such as motion detection or perceptual pop-out effect. He also suggested that a set of neurons should be generating a representation of the region being filled-in, hypothesis confirmed by Komatsu, Kinoshita and Murakami in 2000 [11] while studying the macaque brain, providing evidence that there are neurons in the retinotopic representation of the blind spot in the primary visual cortex that are activated when perceptual filling-in is seen at the blind spot by the animal.

Sensor characteristics

The outer segment of photoreceptors consists of a folded membrane structured in stacks of disks filled with *opsin*, an heptahelical protein that when exposed to light undergoes a physiochemical transformation generating an electric signal, transmitted to the neural cells in subsequent layers of the retina, starting a series of neural events that consists in the process of vision. In the human photoreceptors there are three types of opsins:

- A short-wavelength sensitive class (SWS1), found in cones
- A long-wavelength sensitive class (LWS), also found in cones
- A middle-wavelength sensitive class (Rh1), only found in rods, called *rhodopsin*

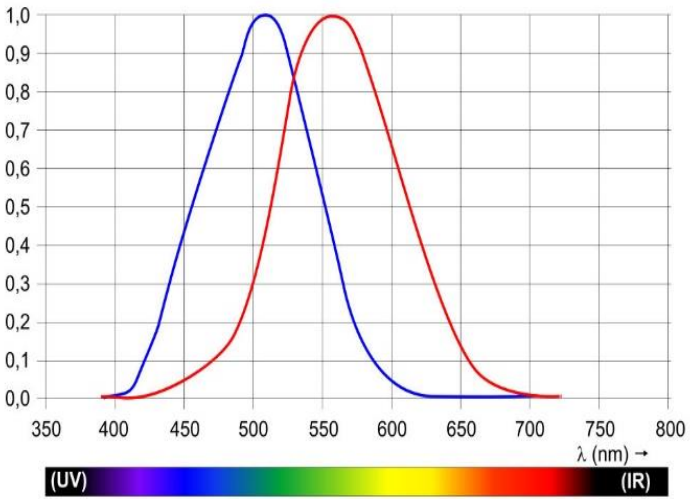
In 1997 [12] a fourth class of opsin was discovered, the melanopsin, found in humans in the intrinsically photosensitive retinal ganglion cells (ipRGCs), more similar morphologically to other retinal ganglion cell classes than to cones or rods and not involved in the process of image formation, but still mediating non-visual photoreceptive tasks, such as the regulation of circadian rhythms.

In conditions of intermediate illumination, both rods and cones are active in the process of vision (*mesopic* vision), but as the illumination decreases cones with a long-wavelength sensitivity tend to have a lower response than the short-wavelength cones, shifting our colour perception towards shorter wavelengths. In Figure 4 are visible the spectral sensitivities of human vision at the variation of

wavelength stimulus in both scotopic and photopic conditions, the photopic luminosity function is called V(λ) and the scotopic luminosity function is V'(λ).

The change in spectral vision from mesopic to scotopic is called the *Purkinje shift*, and it manifests with a variation of contrast under different levels of illumination, making red tonalities appear brighter in daylight and blue-green tonalities brighter at dusk. The dual mechanism of the visual system can be spotted in the dark adaptation curve, as seen in Figure 5.

This difference in sensitivity is caused by the different speeds of photopigment regeneration in cones, approximately 7 minutes, while for the rods it is approximately 30 minutes.



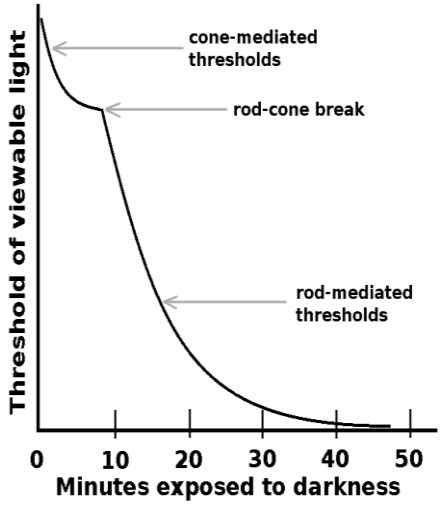


Figure 4 (left): Scotopic (blue) and photopic (red) luminosity functions. The horizontal axis is wavelength in nm, the vertical axis is relative sensitivity[3].
Figure 5 (right): Adaptation of the human eye in darkness[4].

Colour vision

Human colour vision has the characteristic of being trichromatic, as stated in 1801 by Thomas Young [13] and developed by Helmholtz in 1852 [14]: the number of independent variables in colour vision is three, as in the three primary colours of addictive synthesis (red, green, blue) or the three pigments of subtractive synthesis (cyan, yellow, magenta). This characteristic of trichromacy is attributed to a physiological characteristic of the eye: the three types of cones in the retina and their different spectral sensitivities, namely the short (S), middle (M) and long (L) wavelength sensitive cones. The cone sub-mosaic of the three sensitivities samples the retinal image performing a neural coding of spectral information. Spectral sensitivities have been observed and the peak of maximum absorption for the S, M and L cones lies in the 440nm, 545nm and 565nm wavelength frequencies of the visible spectrum [15], as shown in the normalised responsivity curves in Figure 6.

It has to be noted the strong overlap between M and L cones. Sampling colours directly with three optical filters of this sensitivity leads to a very poorly saturated set of colours as visible in Figure 7. In fact, such wide overlap results in a very low maximum M to L signal ratio [16].

[3]Image taken from https://commons.wikimedia.org/wiki/File:LuminosityCurve1.svg.
[4]Image taken from http://sciencequestionswithsurprisinganswers.org/2013/08/09/how-long-does-it-take-our-eyes-to-fully-adapt-to-darkness/.

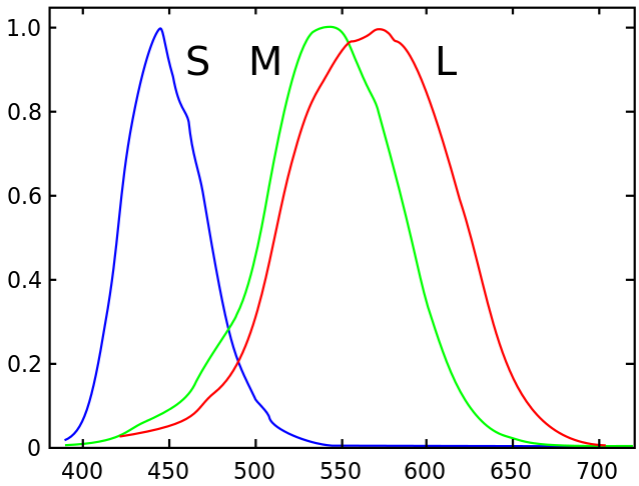


Figure 6: The relative spectral sensitivity functions for the (red) L, (green) M, and (blue) S retinal cone cells. The horizontal axis is wavelength in nm, the vertical axis is relative sensitivity[5].

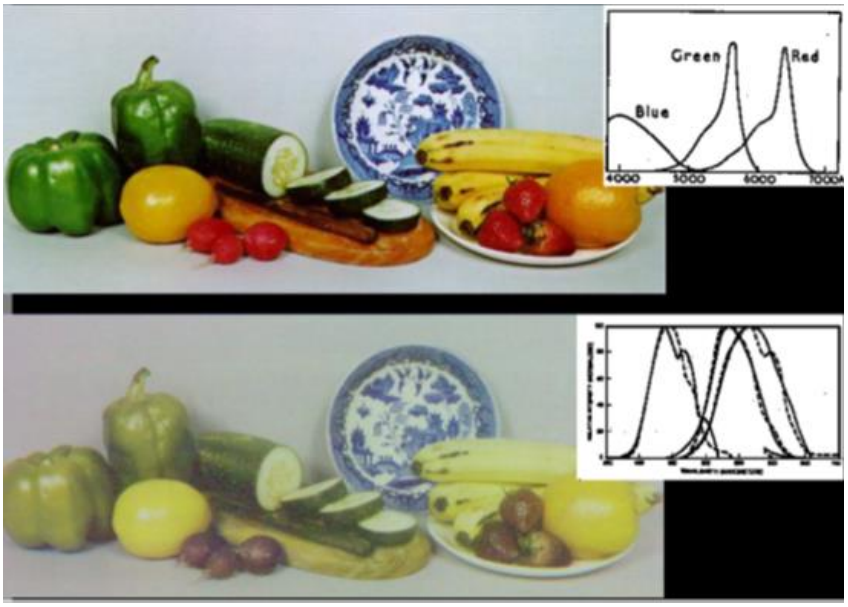


Figure 7: An image acquired with film (top) and sampled with the spectral sensitivity functions of the three cone cells (bottom). Image taken from Rizzi and McCann, 2007 [16].

This example evidences that colour sensation is not just a retinal process, latter cortical stages are supposed to be the responsible of filling this gap in sensation [17]. The fact that spatial comparison plays a role in the normalisation of colour sensation is shown also in the experiment from [18], where colour differences caused by different colour matching functions are strongly lowered by spatial comparison.

The cone opsins are independent from the wavelength captured, signalling only the rate of captured photons, so that lights of different spectral distribution will appear identical if they produce the same absorptions in the cone photopigments. Trichromatic colour vision requires the comparison of these absorptions in different photopigments, each cone class contributing to the hue of a visual stimulus through two opponent mechanisms, as first observed by Hewald Hering in 1892 [19] and expanded by Hurvich and Jameson in 1957 [20]. They observed that there are colour combinations that the human

[5]Image taken from https://commons.wikimedia.org/wiki/File:Cones_SMJ2_E.svg.

visual system is unable to perceive together, and formulated the colour-opponent process theory, stating that in colour vision there are three opponent channels, red and green, blue and yellow, black and white. This theory explains the phenomena, caused by cone bleaching, of complementary-colour afterimage, for example when we stare at a red patch of colour for a sufficiently long time and then we immediately look a white surface, we can often perceive an equally shaped green patch of colour on that surface. This opponent process happens in the bipolar and ganglion cells in the substrates of the retina, transforming the signal from cones by combining them, as depicted in the diagram in Figure 8.

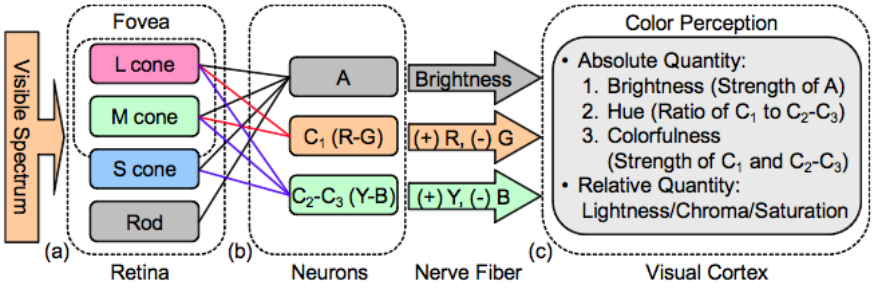


Figure 8: A model of the opponent process[6].

Sensors distribution

The total number of photoreceptors is usually reported as around 120 millions of rods and 6 millions of cones [21]. For other sources these numbers slightly vary becoming for example 5 millions of cones and 100 millions of rods [22], 91 millions of rods and 7 millions of cones [23], and 90 millions of rods and 4.5 millions of cones [24]. One of the first study on the retina is by Osterberg in 1935 [25] on a 16 years old male, reporting 6,300,000-6,800,000 cones and a number between 110,000,000 to 125,000,000 rods. Curcio *et al.* (1990) [1], studying 7 people between 27 and 44 years old found 4.08-5.29 millions cones with an average of 4.6 millions of cones, and 77.9-107.3 millions of rods (average 92 millions) with an average ratio of 1:20. Jonas, Schneider and Naumann [26] on 21 human cornea donors aged between 2 and 90 years found a mean count of rods that was 60,123,000 +/- 12,907,000 and a mean count of cones of 3,173,000 +/- 555,000.

For the following numerical data we will refer to the findings of Curcio *et al.* [1]. The peak of cone density (199,000 cones/mm^2 average) is located in the *fovea centralis*, a pit in the centre of the retina about 2mm wide, at the centre of which is a rod-free zone corresponding to approximately 1.5 to 2 degrees of human vision. Unlike the rest of the retina, in this region bipolar and gangliar cells connected to the foveal cones are not in front of them but are located in the borders of the fovea, so that the photoreceptors directly receive the radiations focalised from the eye's optical system. Furthermore, every foveal cone has its single reserved bipolar-gangliar pathway to the brain, thus making the fovea the region with the highest visual acuity in the retina. Cone density immediately decreases from the peak at the centre so that half-maximum density can be found at only 120 to 150μm from the foveal centre, declining unevenly across meridians, faster in the vertical than the horizontal meridian. This decline in cone density slows down in the peripheral retina, it is still worth noting that at the same eccentricities, densities of cones in nasal retina are 40-45% greater than in the temporal retina. Then, in the far periphery, cone density levels off or increases slightly, with values 13 to 17% higher than the

[6]image taken from https://commons.wikimedia.org/wiki/File:Diagram_of_the_opponent_process.png.

lowest densities along the same meridian. At the edge of the rod-free zone, rod density rapidly increase with eccentricity up to 100,000 rods/mm^2 in a horizontally oriented elliptical ring at approximately the same eccentricity of the optic disk called the rod ring. The retinal area with the highest rod density, called the hot spot, is found in the superior retina with an average density of 176,000 rods/mm^2. After the rod ring, rod density declines gradually towards the far periphery, to a minimum of 30.000 rods/mm2. Figure 9 shows a computer generated colour-coded map of mean photoreceptor density in human retina, with colour coding determining spatial density in cells per 1,000/mm^2.

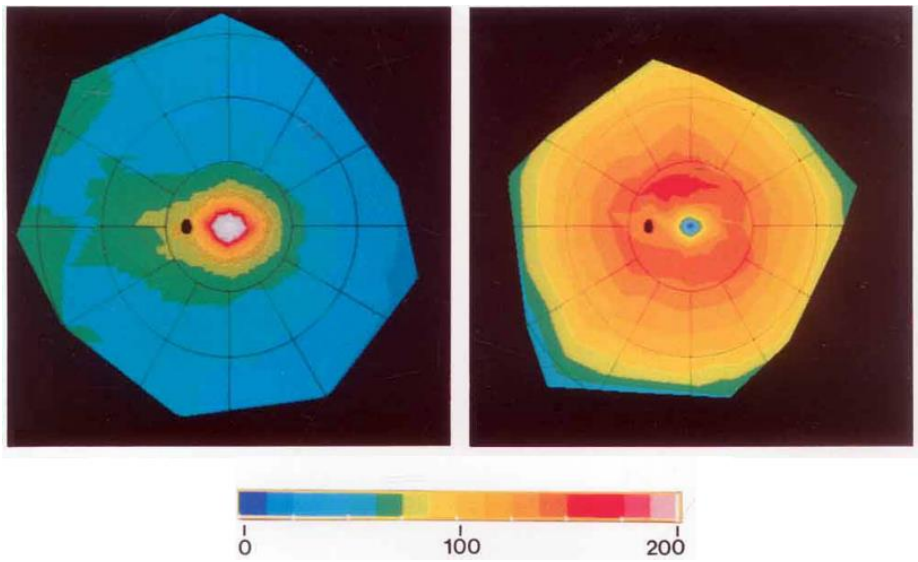


Figure 9: Colour-coded map of the density of (left) cones and (right) rods in an entire left eye retina, computer generated by Curcio et al.*, 1990 [1].*

Considering the average values, there are more than 120 millions of photoreceptors conveying on the optical nerve, composed by around one millions of fibres, with a ratio of 100:1.

There are also discrepancies regarding the number of axons in the optical nerve: Bruesch and Arey in 1942 [27] reported 564,776-1,140,030 axons, in the same period Polyak (1941) [28] increased the number to 800,000-1,000,000 axons, and more recently Quigley, Addicks and Green (1982) [29] with 1,200,000 axons. Also, in Oleari (1999) 1.3 millions are reported [23], while in their experiments Jonas *et al.* in 1992 [30] found a range between 770,000 and 1.7 million nerve fibres.

It has been observed that the S cones mosaic in the retina is independent from the M and L cones mosaic, and also seems to have a non-random distribution, appearing in a quasi-hexagonal array [2]. S cones population is observed to be around 7% of all cones in the retina, the highest density is found in a ring at 0.1-0.3mm eccentricity and they are absent from a zone in the site of cone peak density with a 100μm diameter according to Curcio *et al.* [31], a 300 μm diameter according to Purves *et al.* [24], a 400-600μm diameter according to Polyak [28] and a 750μm diameter according to Hendrickson and Youdelis [32]. The appearance of M and L cones is genetically regulated by the X chromosome, selecting the respective cone opsin gene. Thanks to the development of imaging techniques using adaptive optics, it has been possible to visualise and identify the cones, observing that L and M cones are not completely randomly distributed, it has been in fact observed that there are evident departures from the L and M cones average ratio in the human retina, the value of which is approximately 2:1 [33]. For extended stimuli of high spatial frequencies, the grain of the photoreceptors mosaic can interfere with visual experience, like in the case of high frequency black and white patterns which appear to contain coloured areas, because of the inability of the visual system to detect colour and brightness information from the

aliased or undersampled retinal image. On the other hand, for sufficiently large stimuli, in spite of the high spatial distribution variance of cones in different subjects, a difference in subjective perception has not been observed, suggesting that some perception mechanism may compensate for this variability [34], however the process behind this robust behaviour is still unclear.

In 2005, Hofer, Singer and Williams [35] used retinal densitometry to determine the locations of S, M and L cones in patches of retina in the same eccentricity of five subjects with normal colour vision (Figure 10) to test how small spatial scale stimuli are perceived after the cortical circuitry elaboration.

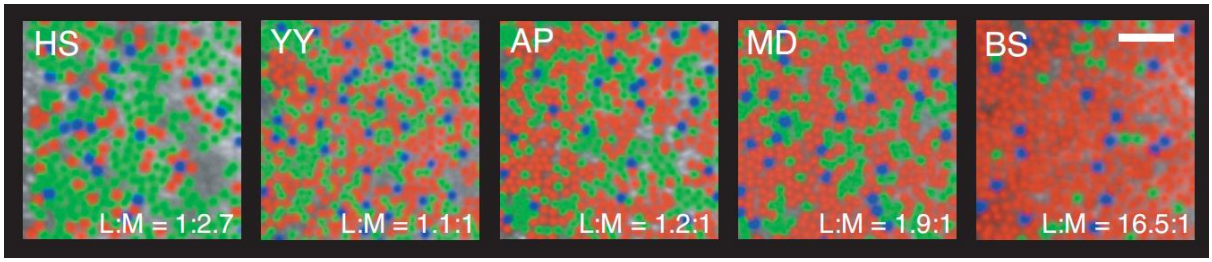


Figure 10: The retinal mosaics of the five subjects [35], each subfigure shows the location of L (red), M (green), and S (blue) cones in patches of retina at approximately 1-deg retinal eccentricity and the correspondent L:M cone ratio. Image taken from Hofer, Singer and Williams, 2005 [35].

Using adaptive optics, tiny flashes of 500nm, 550nm and 650nm light were used to stimulate an area corresponding to less than half the diameter of an individual cone across the characterised retinal area, and then the subject would describe the hue appearance of the flash. The experiment resulted in a large number of hue categories used to describe the perception of the same stimulus, as shown in Figure 11, reporting blue or purple sensation even when subjected to 550nm and 650nm flashes of light at a threshold for L and M cones, indicating that light absorption in S cones is not essential for the sensation of these hues, in contrast with the standard model of colour opponency, and also that it is possible to experience a white sensation with the excitation of a single cone.

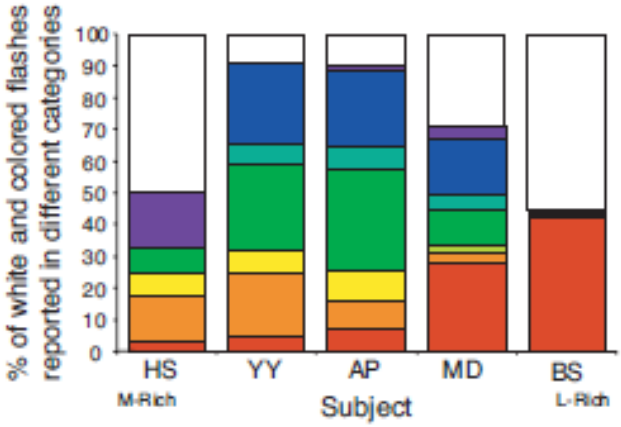


Figure 11: The colour sensations reported by subjects when viewing a small spot of 550nm light. Image taken from Hofer, Singer and Williams, 2005 [35].

This experiment evidences that stimulating two cones with the same photopigment can bring to different colour sensations, even in the absence of stimulation in other regions of the retina or different wavelength-sensitive cones. This interesting evidence suggests the need of overcoming the Helmoltz elemental theory of vision; spatial distribution of stimuli has probably a role in this shift of paradigm.

Conclusions

The progress of retinal research, in particular on spatial distribution of photoreceptor cells is often tied to the progress in retinal imaging systems. Adaptive optics has proven to be an invaluable aid for the study of the human photoreceptors in vivo and have greatly helped to have an insight of spatial characteristics of rods and cones. Regardless these progress, further research is required to better understand spatial characteristics of the retina, like e.g. an agreeable average quantity of cones, optic nerve fibres and the size of the rod-free zone in the fovea, since estimations of these parameters are often based on a limited sample of individuals. Moreover, many aspects are still not clearly explained by the research, like how spatial distribution and mean cone density [36] or synchronisation between ganglion cells affects the sampling of a retinal image [37]. There is also no definitive answer on how the filling-in phenomena of the blind spot works, in spite of the attempts to verify the current theories. Further investigative methods to explore these processes can be quantitative and modelling approaches, to statistically analyse how distribution affects visual perception.

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