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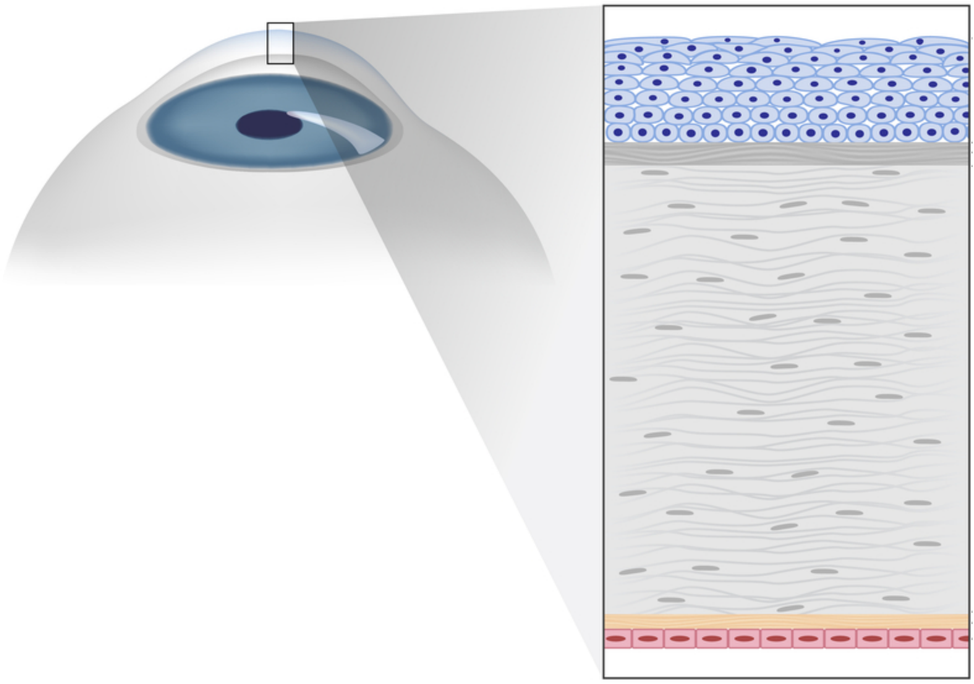

More Accurate Optical Measurements of the Cornea

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1. Introduction

Lein Applied Diagnostics' device measures the thickness of the central cornea, that is, the distance between the epithelium and endothelium surfaces

Background

Several techniques exist to measure the thickness of ocular structures, such as histology, ultrasound, optical coherence tomography, and confocal microscopy. Lein Applied Diagnostics have developed a low-cost system which has sufficient sensitivity to provide measurements of the thickness of the central cornea, that is, of the difference in distance between the epithelium (or anterior cornea) and endothelium (or posterior cornea) surfaces from a reference point located at the optical axis, as shown in Figure 1.

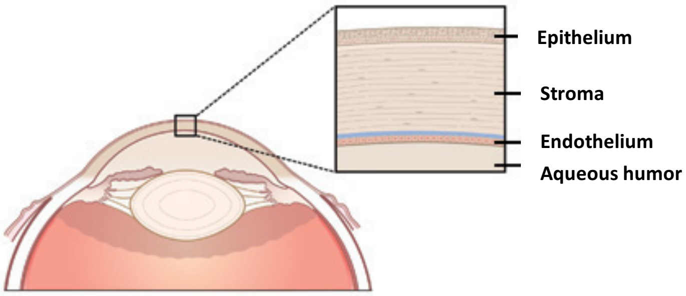

Figure 1: Schematic of the eye and main corneal layers.

An accurate measurement of the central corneal thickness is vital for the diagnosis of glaucoma, a leading cause of vision loss. Glaucoma is an eye disease that usually happens when fluid builds up in the front part of the eye, increasing the intraocular eye pressure (IOP) and damaging the optical nerve. Therefore, the risk of developing glaucoma can be determined by measuring the IOP. The thickness of the central cornea can mask an accurate reading of this pressure, causing doctors to treat patients for a condition that may not really exist or to leave patients at risk untreated.

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The non-contact system developed by Lein is based on a confocal focus-detection scheme. A beam of light produced by a single-mode optical fibre, which is used as a pinhole, illuminates a lens system composed of an achromatic lens (similar to a biconvex lens) and a plano-convex lens, as shown in Figure 2. The light is collimated (i.e. made parallel) by the first lens and focused on the tissue by the second lens. The reflected light from the cornea is collected and relayed back to the fibre, which also acts as a detector. The thickness measurement is performed by moving the plano-convex lens forward in order to scan its focal point through the thickness of the cornea, and logging the intensity signal of the light reflected back from the sample. When the focal plane passes the endothelium, the scan direction is reversed.

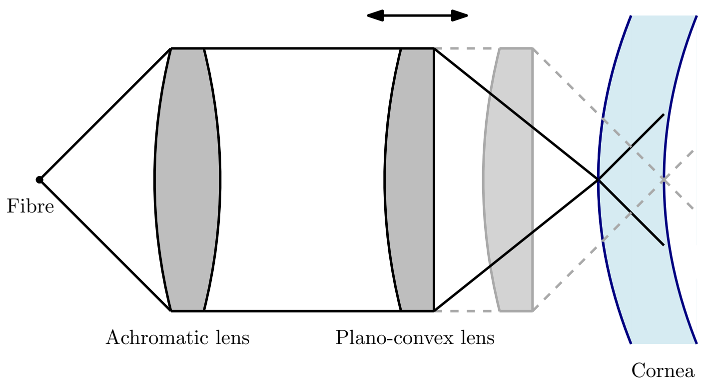

Figure 2: Schematic of the lens system.

The reflected light intensity is maximum when the focal point is at a surface or internal interface, that is, when there is an abrupt change in the refractive index. Therefore, we would expect at least two intensity peaks to appear every time the focal point scans across the corneal thickness: one for the anterior cornea (AC) and one for the posterior cornea (PC). The difference in position between these two maxima, Δz, is directly proportional to the thickness of the sample, t, by $t = n_c \Delta z$, where n_c is the refractive index of the cornea.

The signal reflected by the posterior cornea is very weak and is usually corrupted by random noise

Light emerging from the cornea passes through a watery fluid called the aqueous humor. Since the change in the refractive index between the cornea and aqueous humor is relatively small compared to the change at the air-cornea interface, a ray refracted from the air-cornea interface will only be slightly redirected at the cornea-aqueous humor interface. As a consequence, the signal reflected by the posterior cornea is very weak, and thus the posterior peak is much more difficult to detect. Moreover, the signal is usually corrupted by random noise that may be due to imperfections in the optical system, movement of the eye during the test, or presence of microstructures within the cornea. Our aim is to improve the accuracy and efficiency of the thickness measurements by enhancing the quality of the signal first, proposing a new peak detection algorithm and analysing the use of different statistics or estimates of the thickness.

2. Algorithms for optical measurements

Threshold-dependent peak detection algorithm

The current peak detection algorithm that Lein applies to the raw signals is based on user preselection of thresholds for each of the peaks. The algorithm involves applying a moving average filter to each single scan, detecting the peaks that are above the threshold, fitting a quadratic curve to both peaks, and selecting the position of the maximum of the parabola as the peak position. The refractive index is assumed to be known and thus the thickness of the sample is computed. Once a reasonable number of scans, usually 10, are valid (meaning that both an anterior and a posterior peak have been detected), all the thickness values obtained are averaged.

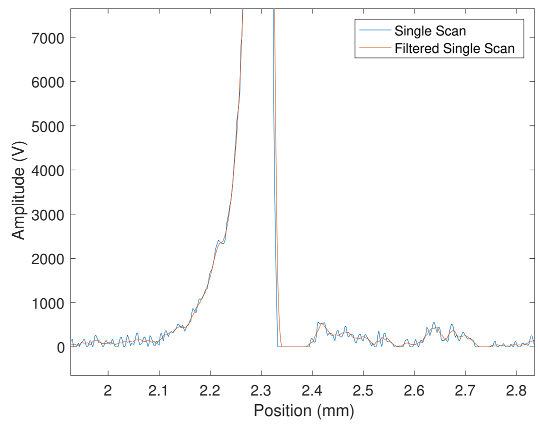

Figure 3: Single scan (blue) and moving average filtered scan (orange). The AC peak is located around 2.3 mm and the PC peak should be around 2.6-2.7 mm, although it is not that clear.

A very low threshold can lead to the selection of outlier peaks, and a very high threshold may not be able to find any peak

However, the output of the current algorithm depends strongly on the choice of threshold. While the selection of a threshold to detect the anterior peak (AC) is straightforward, since it presents the maximum intensity of the signal, the PC peak intensity is quite small and is usually of the same order of magnitude as the peaks due to noise (see Figure 3). A very low threshold for the PC peak can lead to the selection of unwanted secondary peaks or outliers, and a very high threshold may not be able to find any peak at all.

Signal processing techniques

We propose two signal processing techniques to improve the quality of the signal before applying a peak detection algorithm. These are:

Signal averaging reduces the appearance of the random multiple peaks due to noise, while maintaining the PC peak

- **Signal averaging:** By averaging a block of replicate measurements, we are able to reduce the multiple peaks found between the AC and PC peak, believed to be due to random noise, while maintaining the PC peak. After increasing the signal to noise ratio, the posterior peak is now easier to detect (see Figure 4 right), at least by eye, compared to looking at a single scan from Figure 4 (left). As a result, more accurate thickness measurements are obtained when applying a peak detection algorithm to the mean scan.

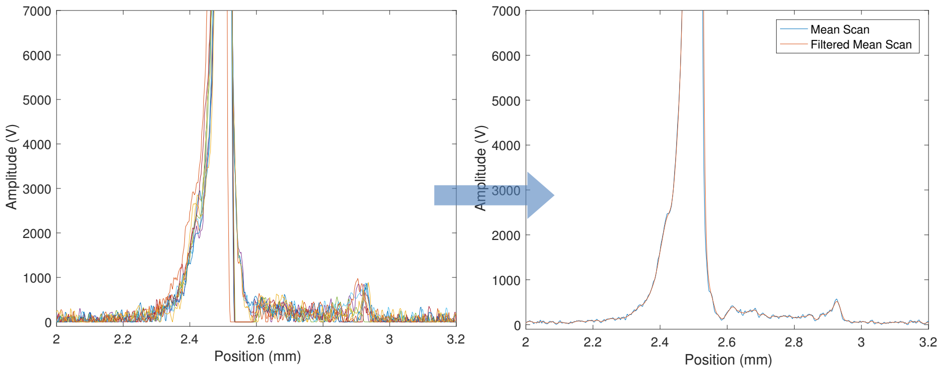

Figure 4: (left) 10 aligned scans, and (right) mean of the scans (blue) + moving average filter (orange).

The application of a matched filter to the mean scan results in a very smooth and well defined PC peak profile with the greatest prominence

- **Matched filter:** This technique is based on matching a known template with an unknown signal to detect the presence of the template in the signal. We take the AC peak profile of the scan to analyse as the template since it is easy to detect, and use this to detect the PC peak. This makes sense since we know that both peaks share the same profile. In Figure 5, we show the output of the filter when applied to a mean scan rather than a single scan since it provides the best results. We see a very smooth and well defined PC peak profile which has the greatest prominence. This method works well even on very noisy measurements, where signal averaging may not be enough.

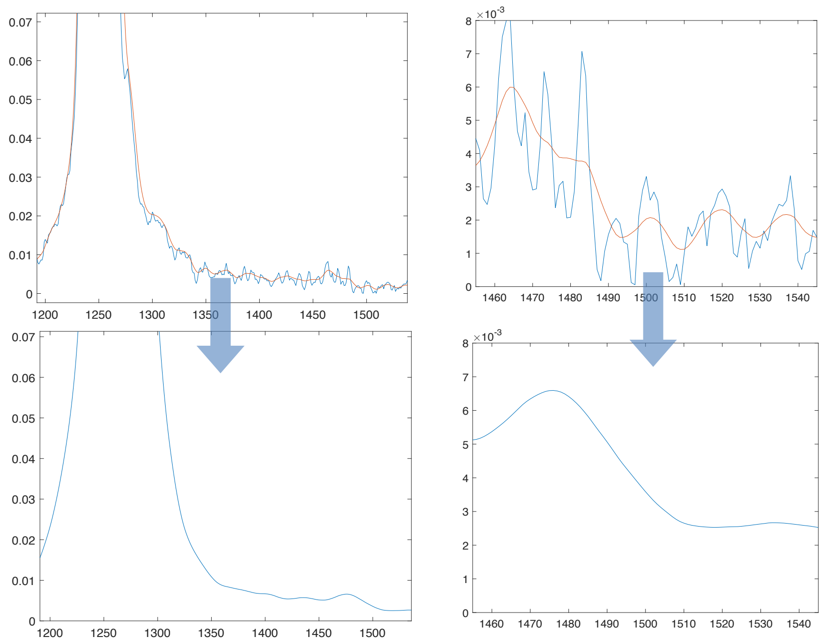

Figure 5: (top figures) Mean scan and filtered version, and (bottom figures) output of the matched filter on the mean scan for very noisy measurements. The figures on the right-hand side are a zoomed region of the pictures on the left around the PC peak.

Prominence-based PC peak detection algorithm

> We compare the height of the current peak with the height of the peak immediately to its right. The PC peak is the peak with the greatest prominence.

The techniques described in the previous section result in a significant improvement, in the sense that the posterior peak is clearer and easier to detect, at least by sight. However, after averaging or filtering the signal, the PC peak amplitude may decrease slightly, so the use of a fixed threshold value to detect the peak is still a problem. After improving the quality of the signal, we can develop a more robust and threshold-independent PC peak detection algorithm based on peak prominences. We compare the heights (h) of the peaks found within a distance from the AC peak (a human cornea thickness should be in the range 0.3-0.7 mm) with the height of the peak immediately to their right. Let h_0 be the median of the signal, which represents the background noise level. The peak prominences are defined by $p_i = h_i/h_{i-1}$, $i = 1, 2 \ldots$, where the peaks are ordered from right to left. We select as PC peak, the peak with the greatest prominence. Moreover, we associate a weight to each thickness calculation, representing the quality of the scan, and so the final corneal thickness is taken as the weighted mean or median of the thickness values that we obtain. We choose the weights to be the difference between the first and second highest peaks prominences. Thus, we give more relevance to scans with a PC peak with higher prominence, and at the same time, this relevance is reduced when similar peaks are close by.

3. Algorithms performance

In Figure 6, we compare the performance of the algorithms as we increase the number of scans used in the final calculation of the thickness. We test the threshold-dependent algorithm in single scans and in mean scans from blocks composed of 5 single scans, and the prominence-based algorithm in mean scans after applying the matched filter (believed to produce the best results). The dataset is from the same subject and contains very noisy measurements.

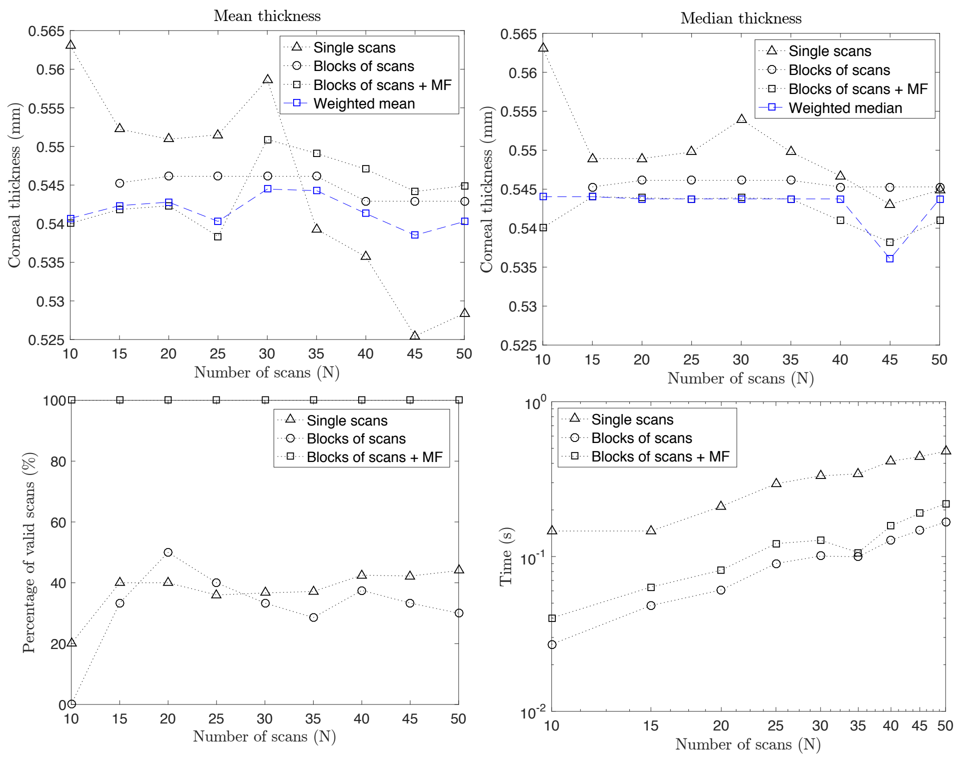

Figure 6: Mean and weighted mean (top left), median and weighted median (top right) corneal thickness, percentage of valid scans (bottom left), and computational times (bottom right) of all the algorithms. Notice that weighted mean/median is only computed for the prominence-based algorithm (Blocks of scans + MF).

In the presence of noisy scans, the single scans approach (currently used by Lein) normally uses a random peak as the PC peak. This is due to noise in the signal which is above the

The prominence-based peak detection algorithm is able to detect peaks that fall below the threshold and were not detected by the previous methods

fixed threshold and within a certain position from the AC peak, and therefore the mean produces very poor results. In the blocks approach, the random fluctuations disappear when averaging scans; thus it does not use false PC information so it is more reliable. However, averaging may reduce the amplitude of the peaks and sometimes this approach may not give any result even with the presence of a clear PC peak in the mean scan, due to the fixed threshold being too large. The prominence-based peak detection algorithm (Blocks of scans + MF) overcomes this problem and is able to detect the peaks that fall below the threshold, and does not discard any scan (see Figure 6 bottom left, where the squares can be seen at the top). The weighted mean shows the best results since it associates very low weights to bad quality blocks, so they do not contribute much towards the final thickness calculation. The median thickness (top right) seems to give reasonable values for all the algorithms except for the single scans approach. Finally, the computational time of all the algorithms increases with the number of scans considered, as expected. The single scans approach is the most computational expensive since the peak detection algorithm is applied to every single scan, while for the other approaches it is applied to the mean scan of each block. Notice that there are some parameter values that can be modified in the simulations, such as the number of scans per block or the threshold value, leading to slightly different results.

Robustness

The single scans approach, currently used by Lein, is the most computational expensive, and presents the greatest standard deviation for the mean

To test the robustness of the algorithms, we generate 100 new datasets from the one used before, by permuting the scans and selecting 25 random scans out of 50. We obtain all the mean and median values for the new datasets, and fit a Gaussian probability density function to the results obtained for each algorithm, as shown in Figure 7. As expected, the width of the Gaussian for the weighted mean is the smallest, meaning that it gives more consistent and precise results, while the thickest width is obtained for the mean of the single scans approach, having the greatest standard deviation. On the other hand, the median seems to give precise results in all algorithms since it is not affected by the presence of outliers. However, note that the single scans approach produces very different results for both statistics so it may not be too reliable.

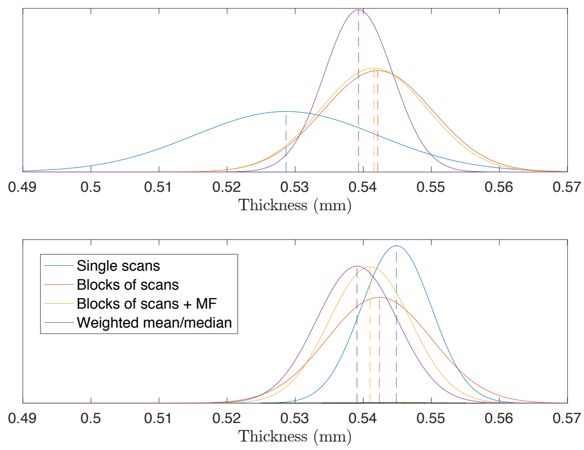

Figure 7: Probability density functions of the mean (top) and median (bottom) thickness.

Kalman filter

The Kalman filter enables a measurement over time of the estimate of the thickness and its error as we add more scans

The Kalman filter consists of a set of mathematical equations that implement a predictor-corrector type estimator that is optimal in the sense that minimizes the estimated error variance. We use this filter to estimate the thickness of the cornea given some thickness measurements found using previous algorithms. The thickness values estimated by the filter are similar to those obtained if we average all the measurements up to k, for iteration k of the filter. However, with the Kalman filter we are more certain about the estimate and it provides an accurate error estimation at every step. Moreover, at the final step, we expect the algorithm to converge to the true state. This is helpful for Lein since it enables a measurement over time of the estimate of the thickness and its error, as we collect and analyse more scans.

We show the thickness obtained using the prominence-based method in Figure 8 (right). This method not only uses information from all the scans (blocks), but also presents a variance, approximately from block 4 (20 scans), smaller than the variance of the final estimate for the single scans approach (left).

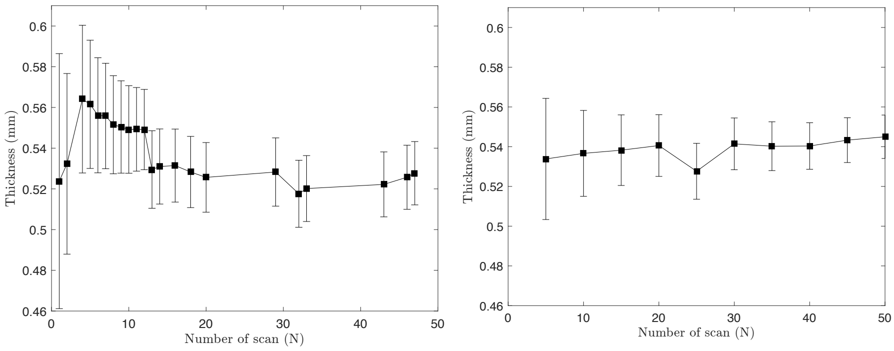

Figure 8: Thickness and standard deviation at each Kalman filter iteration, when using measurements from the single scans (left) and prominence-based algorithm (right) approaches.

4. Discussion, Conclusions & Recommendations

We have proposed two signal processing techniques: signal averaging and matched filter, that improve the quality of the signal before using a peak detection algorithm, by increasing the signal to noise ratio and enhancing the profiles of the peaks. Since the use of a prefixed threshold leads to errors in the measurements and to the discarding of valuable scans, we proposed a more robust and simpler threshold-independent peak detection algorithm for the PC, that is based on peaks prominences. For the best performance, the input scan should be a mean scan from a block, after applying the matched filter.

We compared the performance of all the techniques and algorithms discussed when using different statistics: mean and median, and their weighted versions (only for the prominence-based approach). The use of the weighted mean and prominence-based algorithm is recommended, if the mean of the thickness values obtained is the preferred estimate. This algorithm produces results even from very noisy scans, whereas the current single scans algorithm can take a long time in practice to get 10 valid scans. Finally, we briefly investigated the application of the Kalman filter, which provides an alternative way to generate thickness and error estimates at every iteration. This approach has the potential to indicate when to stop scanning based on a more refined measure.

5. Potential Impact

All the signal processing techniques and algorithms we have discussed in this report can be easily implemented in the software of the confocal scanning prototype developed by Lein. This would enable the company to obtain more accurate and precise measurements, and in less time than with the current method.

Dan Daly, CEO of Lein, said *"3% of the global population over 40 years of age, that's 60 million people, have glaucoma. It is estimated that without corneal thickness measurements 5% of those tested will be given a false negative result and about 9% a false positive. Clearly there is a demand for a compact, cost effective corneal thickness measurement system and this excellent mathematical analysis of our confocal results goes a long way towards making that achievable."*