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Tear film stability assessment by corneal reflex image degradation

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Tear film stability assessment is one of the main tests in dry eye diagnosis. However, to date, no test methodology has been adopted as the gold standard due to several reasons, such as the methods being invasive, subjective, or unfeasible for the clinical environment. In this paper, a method that overcomes the above-mentioned limitations for tear film stability measurements is presented, and is based on the degradation of corneal reflex images caused by breakups. The experimental setup, which is based on recording the corneal reflex image or the first Purkinje image, is described, as well as the method used to determine tear film stability by means of the associated breakup time (BUT) using corneal reflex image degradation. Images obtained through simulations of the experimental setup are also shown. Moreover, BUT measurements performed using both the conventional fluorescein method and the proposed method in nine healthy adults are presented. Both the experimental and simulation images show corneal reflex image degradation due to the appearance of breakups in the tear film, highlighting the potential of the method to assess tear film stability. We have shown that the corneal reflex image degrades when the tear film breaks up and, thus, the proposed method can be used to assess tear film stability.

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1. INTRODUCTION

There are several tests in clinical practice for dry eye diagnosis, such as questionnaires, measurements of tear film stability or breakup time (BUT), staining, and reflex tear flow. Among them, BUT measurements can be considered the most used. They consist of measuring the time until initial breakup of the tear film following a blink [1]. The traditional BUT measurement is invasive, as it includes fluorescein instillation, and therefore the measurement may not be an accurate reflection of tear film stability status [1]. However, in recent years, big efforts have been made to develop objective and non-invasive methods for dry eye diagnosis based on new technologies, such as corneal topography [2,3], various interferometric techniques [4–6], and double-pass techniques [7]. As explained in the DEWS report, to date, no gold standard exists for the diagnosis of dry eye [1], and some of the methods based on new technologies are unfeasible in clinical environments because they cannot be adapted for daily clinical practice, where inexpensive and easy-to-use tools are needed.

After blinking, the tear film is regenerated in a process that takes a few seconds, and, afterward, it degrades [2] and finally breaks up. Despite the discrepancy in how the tear rupture happens and the uncertainty about traditionally described "dry spots" occurrence, there is general consensus about the appearance of breakups in the tear film when blinking is prevented [8,9]. The breakups in the tear film cause abrupt height differences in its surface (the tear film is about 3 μm and becomes thinner when blinking is prevented [10]) and, moreover, its smoothness can be lost if the corneal epithelium is exposed (which does not always occur). When illuminated with coherent light, breakups in the tear film could produce diffraction patterns and speckle on the corneal reflex image, caused mostly by phase differences. Thus, after blinking, the corneal reflex image would remain without significant changes until the breakup, in which time the corneal reflex image would be altered or degraded due to the previously cited effects owing to phase differences induced by the breakup.

In this paper, we present a method for the assessment of tear film stability by means of breakup measurements based on corneal reflex image degradation caused by breakups. The proposed method is noninvasive, objective, simple to use, and has a low cost. Additionally, it is oriented toward daily clinical practice and could serve as a screening tool.

2. MATERIALS & METHODS

A. Setup

The proposed setup consists of a system to record the corneal reflex image or first Purkinje image, as shown in Fig. 1(a). The light source (LS) consists of an infrared laser diode ($\lambda = 780$ nm) coupled to an optical fiber and collimated, and it illuminates the eye with an incidence angle of 27 deg, relative to the optical axis of the eye. The light reflected on the tear film is recorded using a CCD camera (CCD 1, uEye UI-2220-M, pixel size 8.3 μm × 8.3 μm) after passing through a lens with a focal length of 50 mm and a diameter of 50 mm (L1). The images are defocused 1 diopter, because this facilitates the detection of changes in corneal reflex images. The system allows for measuring over a circular area with a diameter of 3.70 mm. An auxiliary camera (CCD 2, uEye UI-2220, pixel size 8.3 μm × 8.3 μm, focal length objective 25 mm) is used for pupil monitoring and centering.

B. Image Processing

After blinking, the corneal reflex remains without changes [Fig. 1(b), upper], but when the breakup happens, the corneal reflex image is degraded and the image breaks into several structures [Fig. 1(b), lower], which can be visually appreciated easily. To objectively determine the occurrence of such breakups, and due to its simplicity, the number of structures in which the image is broken as a result of the breakups is counted. For this purpose, the image is binarized (Fig. 2) and the structures are detected using the Matlab software and its image toolbox (MathWorks Inc., 2015). The number of counted structures is plotted against time and an exponential curve is fitted. While the tear film is stable, the corneal reflex image stays the same, and the number of counted structures is nearly constant. However, when the tear film breaks up, the corneal reflex image is degraded and the number of structures suddenly increases. Thus, the BUT corresponds to the moment when the number of structures increases, which is the end of the horizontal asymptote of the fitted curve, identified automatically by a Matlab routine designed for this purpose. A line linking the initial and final points of the exponential curve is created and the perpendicular distance from each point of this line to the exponential curve is calculated. The point in which the distance is the largest is identified as the BUT.

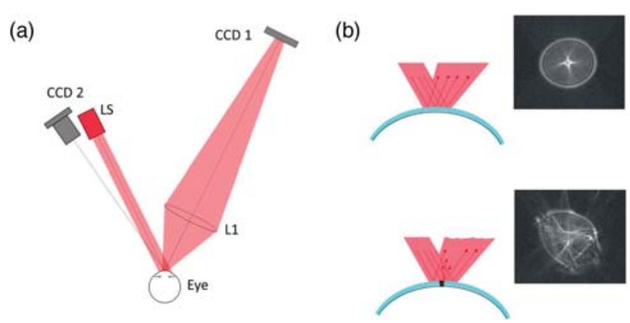

Fig. 1. (a) Schematic diagram of the proposed setup. LS, light source; L1, lens; CCD 1 and CCD 2, CCD cameras. (b) Representation of light reflections on tear films and images recorded from (upper) a smooth and regular tear film and (lower) a broken up tear film with a breakup.

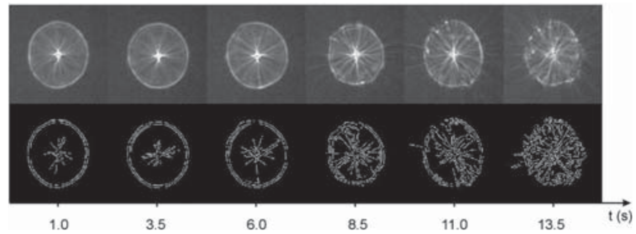

Fig. 2. Corneal reflex image sequence after blinking. Raw (upper) and binarized (lower) images are shown. t(s): time in seconds after blinking.

C. Simulation

The images obtained with the experimental setup were reproduced in simulations using Matlab. The cornea and the illumination conditions were approximated as a flat surface impinged by a collimated beam with a diameter of 4 mm with normal incidence. The length and the number of pixels of the surface were 8 mm and 256 × 256 pixels, respectively. In the presence of breakup, the light reflected by the surface was simulated as a beam with constant amplitude and local phase variations at the location of the breakups. The breakups were circular structures 0.2 mm in diameter and $2.50 \pm 0.15\lambda$ ($\lambda = 780$ nm) deep, distributed randomly along the pupil. The amplitude and phase of the electromagnetic field of the light reflected by the simulated surface was computed at the focus of a lens with a focal length $f' = 50$ mm. Considering a distance between the surface and the lens of 50 mm and defining the field after the surface as U_o, the amplitude and phase at the observation plane were computed by applying the following formula of diffraction in a Fraunhofer approximation [11]:

$$U_i = F^{-1}\left\{\frac{1}{j\lambda f} \exp\left[j\frac{k}{2f}(u^2 + v^2)\right] F\{U_o\}\right\}.$$

In this equation, F and F^{-1} denote the direct and inverse Fourier transforms, respectively, $k = 2\pi/\lambda$ denotes the wave number, and (u, v) are the spatial coordinates of the observation image plane. The intensity that reached the camera's sensor was then simulated by propagating light in the free space at an extra distance of $z = 30$ mm in order to have a separation between lens and camera of 80 mm. This defocused version of the field was computed by [11]

$$U_d = F^{-1}\{F\{U_i\} \exp[-j\pi\lambda z(f_x^2 + f_y^2)]\},$$

where (f_x, f_y) represent the coordinates of the field in the Fourier domain.

D. Participants and Examination Protocol

All participants gave their written informed consent after a written and verbal explanation of the nature and aims of the study. The research followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hospital Mutua de Terrassa (Terrassa, Spain). The criteria for inclusion were as follows: no history of ocular conditions, eye surgery, and/or pharmacological treatment. Measurements were carried out in only one eye; due to the configuration of the setup, the left eye was chosen in all cases. Nine healthy adults (six female and three male) participated in the study, with a mean age ± standard deviation of 29.9 ± 9.5 years (ranging from 22 to 53 years).

The tear film stability of each participant was assessed using two methods: the clinically widely used BUT using fluorescein and the noninvasive breakup time (NIBUT) based on the method proposed in this work.

3. RESULTS

In Fig. 2, the sequence of corneal reflex images after blinking for a particular case (participant #9) is shown from left to right, with a time interval of 2.5 s between each image. The first image on the left corresponds to a post-blink image. The upper images correspond to the raw images recorded, while the lower ones correspond to the binarized images used to count the number of structures. It can be seen in the figure that the raw images remained stable for some time (images 1 to 3) and degraded afterward, mainly after the fourth image (8.5 s). In the binarized images, the increase of the number of structures in which each image is divided can be clearly appreciated.

In Fig. 3, the corneal reflex image 1 s after blinking (upper) and in breakup conditions (lower) are shown for the rest of the participants. Participants #4 and #7 blinked before corneal reflex image degradation could be seen. In the other cases, the image degradation from the post-blink to the breakup condition is clear. The way the corneal reflex image is degraded can differ depending on the participant, as shown in Fig. 3. This means that the same pattern is not always shown in the broken up images, but the breakup of the tear film can be easily detected. As can be seen, the image size can differ inter- and intra-participant. This effect could be attributed to differences on the refraction of the cornea or to little displacements of the participants, but more experiments have to be performed to approach this effect.

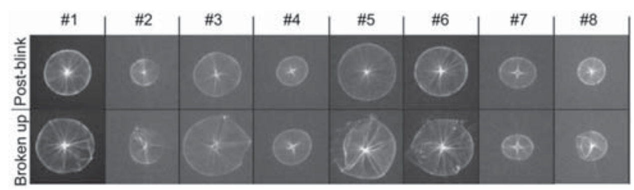

Fig. 3. Post-blink (upper) and broken up (lower) corneal reflex images for participants #1 to #8. The number indicates the participant number.

In Fig. 4, the number of structures counted in the images after blinking is plotted versus time for participants #1 and #9. The blue dots correspond to the experimental data and the red line to a fitted exponential curve. The BUT, identified as the moment in which the number of structures increases, is marked with a red asterisk. As shown in the images themselves, it can be seen that, at first, the number of structures is stable, but when the image degrades, this number increases rapidly.

Table 1 summarizes the BUT and NIBUT results for all participants. The data from participants #4 and #7 was discarded as the measurements failed because of blinking prior to the breaking up of the tear film in the NIBUT (as explained before). The BUT measurement of participant #4 failed for the same reason. There was a mean difference between the two methods of 4.08 s (with shorter BUTs for the BUT method).

A. Simulation

Seven different cases were simulated. In the first case, no breakups were simulated. In cases 2 to 6, breakups with a diameter of 0.2 mm and a depth of $2.50 \pm 0.15\lambda$ ($\lambda = 780$ nm) distributed randomly along the pupil were simulated, with the total numbers of breakups being 1, 5, 10, 15, and 200. In case 7, an irregular breakups measuring 0.19 mm × 0.36 mm with a depth of 2 μm was simulated. In Fig. 5, for each simulated case, the images with the breakups located in the pupil plane, the image propagated to the focal plane of the lens (on focus), and the image propagated to the sensor plane (out of focus) are shown. The corneal reflex degradation was more notorious in the defocused images (sensor plane) than in the focused images (focal plane). While changes in the former plane (sensor) can be observed after the first breakup appears, they are more

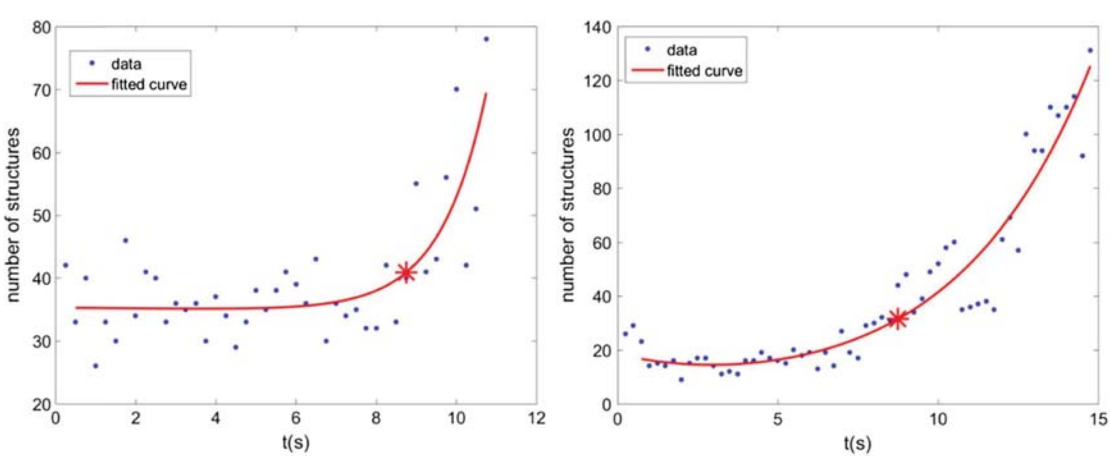

Fig. 4. Number of structures counted plotted against time after blinking for participants #1 (left) and #9 (right). Experimental data is plotted with blue dots, the fitted curve in red, and the BUT with a red asterisk.

Table 1. BUT and NIBUT Times for the Participants, and the Mean, Standard Deviation, and Median Values

Participant	BUT (s)	NIBUT (s)
#1	8.00	8.75
#2	10.00	12.75
#3	6.00	10.91
#5	5.00	5.25
#6	5.00	15.50
#8	49.00	57.25
#9	7.75	8.88
Mean	12.96	17.04
SD	15.99	18.03
Median	7.75	10.91

difficult to detect in the latter (focal) plane (in the focal plane the breakups affect the halo around the point spread).

As expected, the corneal reflex image degradation was proportional to the number of breakups simulated. Despite some limitations of the simulation, which are mentioned in Section 4, the simulated images showed some similarities with the real images.

4. DISCUSSION

BUT measurements are one of the most widely used methods for assessing tear film stability to diagnose dry eye. In this paper, we presented a new method for measuring the BUT in an objective and noninvasive way based on the degradation of the corneal reflex image.

The images recorded with the experimental setup, which are shown in Fig. 2, were stable for a short period of time after blinking, and image degradation occurred afterward. The degradation of the images, shown in Fig. 3, was generalized (except for two cases to be commented upon later), with the appearance of the breakups being the most likely reason. The broken-up tear film images shown in Fig. 3 present similar structures or patterns to those found by other authors using different interferometric methods and coherent light [4–6]. These authors have shown changes in the corneal reflex images, when using coherent light, after the breakups appear, similar to what occurred in our case. These authors used interferometric methods to assess tear film stability, while, in our case, the proposal is to simplify these methods by directly using the (defocused) first Purkinje image, without requiring complex optical setups. As presented in Section 3, the proposed method failed to detect the breakup of the tear film in two participants. This can be attributed to either the measured area or to spontaneous blinking. On the one hand, the diameter of the measured corneal area is limited to 3.7 mm in our method. Thus, if the breakup occurs in the periphery, it is not detected. To overcome this limitation, the optical setup could be modified by placing a lens with its focal plane at the center of curvature of the cornea so that the incident beam is normal to the tear surface. This is a similar configuration to those proposed by Licznerski *et al.* [4] and enables obtaining a measured area with a diameter of approximately 8 mm. On the other hand, although not frequently reported in breakup measurements, some authors have reported a high rate of spontaneous blinking before breakup [12]. In these cases, the breakup never happens and neither the NIBUT nor the BUT method is able to obtain an appropriate measurement. The fact that one of the participants failed at both the NIBUT and BUT tests supports the spontaneous blinking hypothesis. Because of the large area measured in the BUT method, the measured area should be discarded as a reason for the failing of the measurement, and it is logical to think that spontaneous blinking prior to breakup was the reason behind this particular case.

The way corneal reflex images degrade when the tear film breaks up varied from one participant to the other. In Figs. 2 and 3, which show images of broken up tear films, it can be seen that the effect of the breakups on the corneal reflex image is not always the same, and depends on the participant. The shape of the breakups is not always the same, and the nearly simultaneous appearance of several breakups is common. Thus, the cause of each type of image degradation (breakups) is not

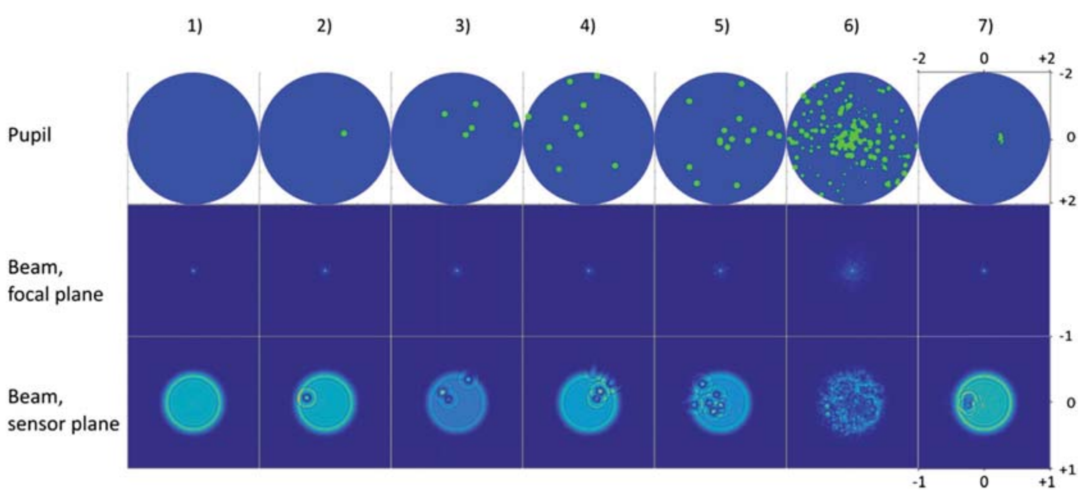

Fig. 5. Simulation of breakups on the pupil plane (top), the image in the focal plane (center), and the image in a defocused plane (bottom). The numbers on the top correspond to the simulation number described in the text. The axes are equal for all the simulations and are expressed in millimeters.

repeatable; therefore, corneal reflex image degradation is difficult to predict and, consequently, measure. In this sense, other metrics, which were not included in this paper, were preliminarily tested to determine the breakup of the films from the images, such as texture analysis [13], Fourier transform, and correlation. These failed, but the metric of counting for image fragmentation was found be the most robust, providing reasonable results.

Similarly to the recorded images, the performed simulations show that, when breakups appear, the image degrades. The simulations carried out have some limitations, such as the flat surface used as cornea, the speckle effect [14], or the aforementioned variety of breakups in real eyes. Nevertheless, despite the limitations, the images of the simulations show the impact of breakups in the corneal reflex images, and some of these images present similarities with the real raw images recorded. On the other hand, as seen in the simulations and the experimental images, working with defocused images facilitates the detection of broken up tear films. As expected, the image degrades proportionally with the number of breakups. When several breakups are present, there are interactions among the effects of each one and complex image structures are obtained as a consequence. The same happens when irregular breakups are simulated. These two effects, namely, the appearance of several and irregular breakups, could explain the variety of broken up images obtained and previously mentioned.

Regarding the BUT and NIBUT measurements, and keeping in mind the small sample size and the variability due to external factors, such as temperature or humidity, this study found that the mean values of the BUTs were in accordance with the data previously reported by other authors [15]. A mean difference of approximately 5 s was found between methods, which has also been explained by other authors, due to the effect of fluorescein instillation [16].

In summary, in this study, we investigated the suitability of a new method for measuring tear film BUT, based on the degradation of the corneal reflex images due to the appearance of breakups. We have shown that the corneal reflex image degrades when the tear film breaks up, and our results are in accordance with our simulations. However, the proposed method has some limitations, such as reduced measured area, which could be overcome with a new design of the optical setup. In conclusion, this simple, objective, and non-invasive method is affordable for implementation as a system to measure tear film BUT.

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