Current Topics in Tear Film Dynamics

Max Gould *

June 8, 2013

MAE C250G : Fluid Dynamics of Biological Systems

UCLA, Los Angeles, CA 90024

A review of current research topics in tear film dynamics was conducted. A selection of recent papers are discussed covering the current state of numerical modeling, recent experimental studies, and advanced techniques for tear film assessment. The difficulties of experimentally studying tear film dynamics are portrayed and an analysis of the validity of modern diagnostic techniques is proposed. While numerical modeling offers unprecedented understanding of the dynamics of the human tear film, the limitations of current efforts in this area are also presented. Dry eye syndrome, being the most common medical condition associated with tear film dynamics, is further discussed and presented in the context of the contributions made by the current field of research to its diagnosis and treatment.

*UID : 504.118.574

I. Introduction

The human tear film is a dynamic and complex fluid layer, extremely important to the health and proper functioning of the eye. It lubricates and protects the delicate ocular surface from diverse environmental factors we encounter every day. Every time we blink, the lacrimal gland on the upper eyelid secretes new tear fluid to replenish the tear film and maintain its depth and integrity across the entire ocular surface. Excess tear fluid gets drained away through the puncta, located at the nasal canthus, the part of the eye closest to the nose.[1]

The tear film has been characterized as being composed of three relatively distinct layers as shown in Figure 1. The mucous layer adheres to the epithelium coating the surface of the cornea itself, its viscous properties serving to reduce shear stresses acting on the ocular surface. This layer also provides a hydrophobic barrier between the cornea and the rest of the tear film, maintaining the integrity of the subsequent 'aqueous' layer. The aqueous layer comprises the majority of the tear film, being comprised mostly of water and various proteins, this layer serves a variety of purposes including waste removal and lubrication of motion between the ocular surface and the eyelids. This is also the primary protective layer for the ocular surface such that changes in its thickness or concentration can lead to ocular surface damage. Finally, a thin lipid layer forms the outer-most surface of the tear film, helping to maintain the tear film's integrity. It is also suggested that the lipid layer serves to protect the aqueous layer by retarding surface evaporation.[1] The accuracy of this model is still debated somewhat to this day. An alternative model which characterizes the mucous layer as a density gradient in the aqueous layer has received limited attention due to the difficulties of modeling the dynamics of such a system.[18] All of the papers reviewed in the following sections however are based on the more prevalent three-layer model.

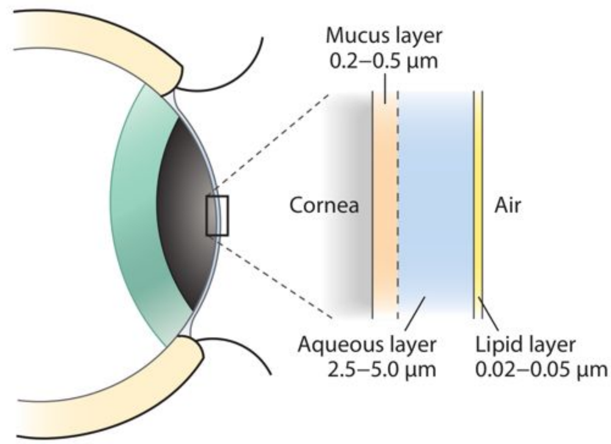

Figure 1. Classic characterization of the tear film as three distinct layers including approximate relative thicknesses.[1]

There are several parameters that are used to characterize tear film health. The most commonly used gauge is tear film osmolarity, which is a measure of the concentration of solutes present primarily in the aqueous layer. High tear film osmolarity can be caused by excess surface evaporation and is believed to be the primary cause of ocular surface damage. Another common diagnostic approach is to measure tear film breakup time. This is the time it takes for the tear film to thin to the point where it can no longer maintain integrity across the entire ocular surface and is reduced to diminishing patches of surface coverage.[1]

Surface evaporation is believed to be the primary cause of tear film thinning, however the complex geometry of the tear film prevents this from happening uniformly across its surface. Menisci form at the edges of the tear film where it comes into contact with the eyelids. Due to the decreased surface-area-to-volume ratio in these regions, surface evaporation is less effective, leaving these regions relatively intact as the tear film thins. The surface curvature at the menisci however creates a pressure differential that draws fluid away from the central portion of the tear film. This leads to the formation of what are known as the 'black line' regions that form around the entire tear film just inside of the menisci. The black line is a region that thins the fastest and experiences the highest osmolarity levels. As the black line forms, it creates a pressure barrier that insulates the central portion of the tear film from the menisci, helping to maintain the depth of tear fluid over the central portion of the cornea.[18]

Heightened tear film osmolarity is commonly associated with the medical condition known as 'dry eye' syndrome. Not just a single condition, dry eye encompasses a variety of symptoms and causes that all lead to ocular discomfort, reduced visual performance, and potentially ocular surface damage. Two primary classes of dry eye are identified as 'aqueous deficient dry eye', in which insufficient tear fluid is produced by the lacrimal gland, and 'evaporative dry eye', in which for one reason or another the surface evaporation rate is higher than usual leading to increased tear film thinning and osmolarity.[1] Improving diagnosis and treatment of dry eye syndrome is one of the primary goals of research in this area.

Experimental methods of studying the tear film have proven to be quite limited, such that significant effort has been put into modeling the tear film numerically. Most models of the tear film focus on modeling the dynamics of the aqueous layer, applying special boundary conditions at the free and ocular surfaces to account for the perceived effects of the mucous and lipid layers. The majority of these models simplify the geometry of the eye to a flat, semi-permeable corneal substrate due to the tear film's relatively small curvature and thickness. The fluid itself is generally treated as a Newtonian fluid under a lubrication theory approximation, ignoring flow in the direction normal to the ocular surface. Some models account for blink dynamics with moving boundaries representing the eyelids whose motion is prescribed by experimental observations, but most models simply analyze the static geometry associated with the inter-blink period. The direction of gravity in these models is often alternated between toward and normal to the corneal surface as in the case of a person lying down, and parallel to the corneal surface in the direction of the lower eyelid as is the case of a person standing or sitting up. Many studies explore the tear film dynamics associated with both positions and note the differences between them.

These and additional aspects of tear film dynamics are explored in the subsequent sections discussing the current state of research in the field. A variety of numerical models are presented including blink dynamics, flux boundary conditions, and heat dissipation through the corneal surface. Modern experimental and diagnostic techniques are discussed and their relevance to dry eye treatment is assessed. The review shows that while significant advances have been made in the field, we are still a long way off from having a good understanding of the complex dynamics of the human tear film.

II. Tear Film Thinning

The rate at which the tear film thins during the inter-blink period is a critical aspect of tear film dynamics. Heightened thinning rates can lead to increased tear film osmolarity, which is thought to be a good indication of overall tear film health. High thinning rates are also often observed in patients with dry eye syndrome, leading to ocular discomfort. Developing a better understanding of the phenomena that give rise to tear film thinning could therefore provide useful tools for the diagnosis and treatment of dry eye syndrome.

King-Smith et al.[2] hypothesized that surface evaporation is the primary cause of tear film thinning. Through experiments, they found thinning rates to be on the order of 20 $\mu\text{m} \cdot \text{min}^{-1}$, however this suggested surface evaporation rates four or five times that of previously reported values. King-Smith et al. suggested that this could partially be due to normal air currents that were prevented by the experimental environments used in previous studies, but nonetheless, this prompted further investigations into tear film dynamics.

1. Efforts in Numerical Modeling

In order to better understand the phenomena that give rise to tear film thinning, many attempts to model the fluid dynamics present in the human tear film have been made. Traditionally, the tear film is modeled simply as a thin film on a flat corneal surface. Berger and Corrsin[3] first postulated this form of analysis in 1974 through an order of magnitude analysis based on a spherical corneal geometry. However, pressure gradients due to surface curvature are a potential source of tear film thinning that was not considered in the analysis by King-Smith et al. Braun et al.[4] recently developed a model of the human tear film on a prolate spheroidal surface which is now considered to be a better approximation of the surface of the cornea than a simple spherical geometry. Their analysis confirmed however the negligible effect of surface curvature on tear film thinning rates, thus validating all of the other numerical models which are almost all based on a flat corneal substrate.

The high surface evaporation rates reported by King-Smith et al. suggests an increase in osmolarity well in excess of that typically measured in the meniscus region of the tear film. This supports the theory that hyperosmolarity is a major cause of ocular surface damage. Zubkov et al.[5] created a numerical model of the eye including blink dynamics in order to study the osmolarity across the ocular surface (see Figure 2). They were able to demonstrate that the osmolarity around the center of the eye is highly dependent on surface evaporation rates, while the osmolarity in the meniscus region remained relatively unaffected by surface evaporation. This provides a potential explanation for King-Smith et al.'s findings since measurements of the meniscus region cannot predict overall surface osmolarity, potentially leading to underestimates of surface evaporation rates. Zubkov et al.'s model suggests that significantly higher osmolarity is present in patients with evaporative dry eye syndrome than previously believed, which may account for symptoms of ocular discomfort and resulting ocular surface damage.

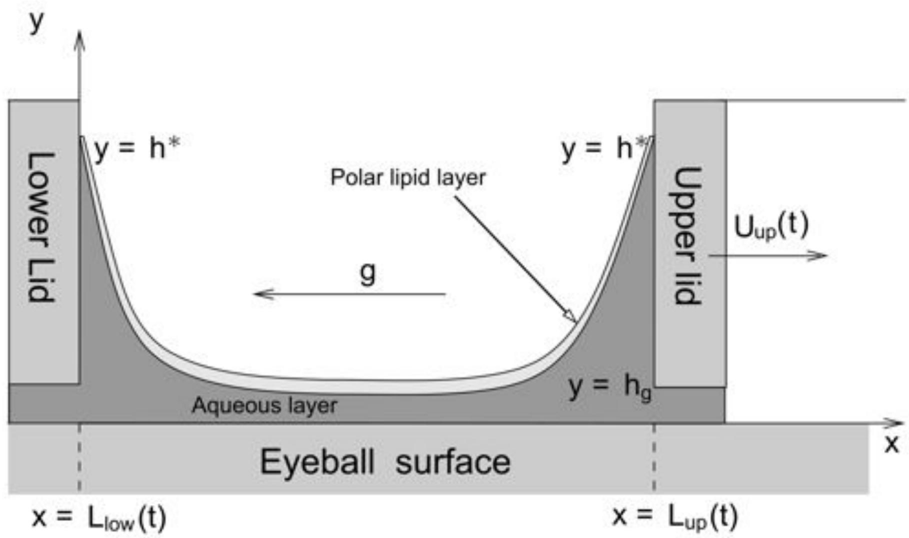

Figure 2. Diagram of the model developed by Zubkov et al. to study tear film dynamics including blink effects.[5]

2. Experimental Analyses

Aside from numerical modeling, a number of experimental studies have been conducted in order to gain further insight into tear film thinning. A study by Nichols et al.[6] was able to use different concentration levels of fluorescein present in the tear film to compare the relative influence of tangential flow to surface evaporation in tear film thinning. Fluorescein experiences a "self-quenching" effect at higher concentrations that actually causes the overall fluorescence to diminish (see Figure 3). The lower fluorescein concentration was chosen at a point in the spectrum where the resultant fluorescence was relatively independent of concentration. By measuring fluorescent decay at this concentration, Nichols et al. were able to measure the relative influence of tangential flow in tear film thinning. The fluorescent decay rate in the higher concentration case was approximately four times faster, suggesting a dominant self-quenching behavior as a result of increased fluorescein concentrations due to surface evaporation. Nichols et al. were able to show that tear film thickness was approximately proportional to the square root of the fluorescent intensity at this higher concentration level, which is the same relation predicted theoretically as a result of surface evaporation alone. This analysis clearly demonstrated the dominance of surface evaporation over tangential flow in tear film thinning.

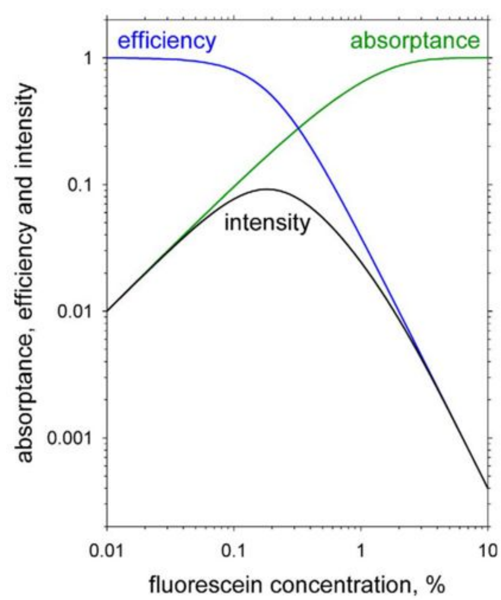

Figure 3. Calculated illumination absorptance, fluorescent efficiency, and intensity of fluorescence as a function of fluorescein concentration.[6]

Surface evaporation is also thought to be retarded by the outer lipid layer of the tear film. Rantamaki et al.[7] studied the evaporation retardation potential of a variety of lipid layer compositions intended to model the actual lipid layer of the human tear film. Evaporation retardation effects of lipid mono-layers are well known and Rantamaki et al. were able to demonstrate significant retardation due to layers of behenyl oleate and behenyl alcohol. However, the human tear film is a complex mixture of lipids and in all cases Rantamaki et al. found that evaporation retardation was significantly reduced in these multi-layer compositions. Lipid layer compositions that successfully mimicked other elements of the tear film lipid layer dynamics provided no significant retardation to surface evaporation. This suggests that the lipid layer of the human tear film actually does not retard evaporation as commonly believed. In order to demonstrate this conclusively however, the precise composition of the tear film lipid layer would have to be determined and tested under similar conditions.

Patients with dry eye syndrome often report ocular discomfort which is believed to be primarily caused by increased osmolarity due to high surface evaporation rates. Varikooty and Simpson[8] attempted to correlate ocular dryness with the blink response by having patients indicate their level of physical discomfort during extended interblink periods while simultaneously observing tear film integrity via fluorescein induced fluorescence of the tear fluid. As shown in Figure 4, they were able to show a triphasic response in both parameters with good correlation. After an initial constant period of relatively low levels of sensation and overall tear film dryness, a period of slow constant growth develops followed by a rapidly rising period leading to a blink incident. The symptoms experienced by dry eye patients are likely the result of a steeper second phase or the inability of the blink to fully reset these conditions, possibly eliminating the initial phase entirely. These phases also suggest that a similar triphasic structure exists in the tear film fluid dynamics following a blink. Further study of these relationships could lead to a better understanding not just of dry eye symptoms, but also of the changing fluid dynamics of the inter-blink period and their dependence on surface evaporation rates.

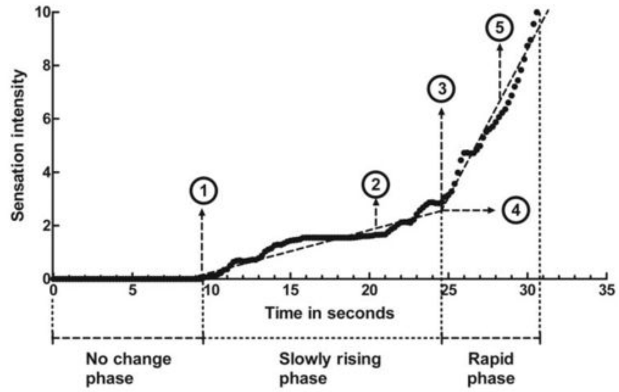

Figure 4. The three phases of sensation intensity rating accompanying ocular surface drying.[8]

3. Environmental Factors

King-Smith et al. originally suggested that air currents could have a significant effect on tear film evaporation rates. In a similar vein, a number of studies have attempted to correlate environmental parameters with tear film evaporation and osmolarity. A study by Abusharha and Pearce[9] recently explored the effects of relative humidity (RH) on surface evaporation rates. They demonstrated that sudden exposure to a 5% RH environment (typically 40%) can cause evaporative rates to more than double from around 0.13 $\mu\mathrm{L}\cdot\mathrm{min}^{-1}$ to 0.28 $\mu\mathrm{L}\cdot\mathrm{min}^{-1}$ during the course of an hour, effectively giving the patient dry eye syndrome, the cut-off for which occurs around 0.21 $\mu\mathrm{L}\cdot\mathrm{min}^{-1}$. Decreased lipid layer thickness was also observed in these patients, supporting the theory that the lipid layer serves to retard surface evaporation, though a direct correlation has yet to be found. A decrease in tear production was also observed for the low humidity environment. This is the primary cause of aqueous deficient dry eye, suggesting that there may be a relationship between this form of dry eye and evaporative dry eye. One thing that was not observed however was a significant increase in tear osmolarity, which is thought to be highly dependent on surface evaporation rates. This suggests that while environmental effects have a strong influence on tear film dynamics, their direct causal relationships are still not well understood.

Another study by Torricelli et al.[10] explored the effects of ambient levels of air pollution on tear film osmolarity. Ocular symptoms are frequently reported by individuals living in regions with high pollutant concentrations. Since tear film osmolarity is thought to be a good indicator of ocular surface health, we would expect exposure to high levels of pollutants to affect an increase in overall osmolarity levels. However, Torricelli et al. found that exposure to high levels of nitrogen dioxide and particulate matter actually lead to significant decreases in tear film osmolarity. The reason for this is unknown, but it does further suggest that a greater understanding of the tear film is required in order to determine good diagnostic techniques for assessing ocular surface health.

4. Diagnostic Techniques

Despite the current limits in our understanding of tear film dynamics, measurements of tear film osmolarity are still regarded as having the highest potential as a diagnostic tool for dry eye syndrome. Typical measurement techniques involve the comparison of the colligative properties of a solution via either a freezing-point osmometer or a vapor pressure osmometer. The presence of solutes in the tear film change the colligative properties of the solution, leading to a lower freezing point or vapor pressure which can be measured.[11] However, neither of these techniques have seen widespread use in clinical environments due to a variety of drawbacks. Collection techniques for acquiring samples of the tear film can cause minimal reflex tearing which throws off the results. In addition, transporting these samples to the actual osmometers gives rise to errors resulting from evaporation losses during transport. Finally, considerable technical expertise are required to take accurate measurements with either instrument.

A new measurement technique that shows strong promise for clinical use but which is still being verified has recently come on to the scene. Measurements of tear film osmolarity can be made through the measurement of a solution's conductivity. Microchips have been developed requiring minimal tear sampling and the ability to take direct *in situ* measurements which can determine the osmolarity of the tear film with minimal technical expertise. These measurements show a strong correlation both with freezing-point and vapor pressure osmometers. Gokhale et al.[12] demonstrated that a correlation coefficient of 0.9 with vapor pressure osmometers could be achieved by taking measurements of the same sample, however that coefficient dropped to 0.5 when using the impedance microchip *in situ*. This may suggest that evaporative losses during sample transport or reflex tearing are indeed responsible for significant errors in osmolarity measurements conducted with freezing-point or vapor pressure osmometers. The impedance microchip was also able to take osmolarity measurements of patients from whom sufficient tear samples could not be collected for vapor pressure analysis either due to dry eye symptoms or contact lenses. This makes the impedance microchip a promising new diagnostic tool for dry eye syndrome.

The study by Abusharha and Pearce[9] throws some doubt on the accuracy of the impedance microchip however. In their study of the effects of relative humidity on tear film dynamics, the measured no significant increase in tear osmolarity with the impedance microchip while evaporative rates more than doubled as a result of exposure to a low humidity environment. Theoretical analyses and numerical models however suggest that their should be a strong correlation between these two parameters. Since Abusharha and Pearce used the same impedance microchips to take their measurements as Gokhale et al., it is possible that these microchips are not as accurate or as reliable as the study by Gokhale et al. suggests. If, on the other hand, the impedance microchip is in fact a good measure of tear film osmolarity, this would imply that the mechanisms behind tear film osmolarity are still not well understood. A possible alternative interpretation provided by the numerical model developed by Zubkov et al., which informs us that the osmolarity of the menisci is not strongly correlated with surface evaporation rates as is the osmolarity across the surface of the tear film, suggests that the impedance microchip may be perfectly accurate if the study by Abusharha and Pearce took measurements exclusively from the menisci. This could also explain the low osmolarity levels measured by Torricelli et al. in their study of the effects of ambient levels of air pollution as their osmolarity measurements were taken from samples obtained from the lower meniscus region. The model developed by Zubkov et al. suggests that much of our data regarding tear film osmolarity may be inaccurate due to the common practice of taking tear samples from the meniscus. In order to properly assess tear film osmolarity, it will therefore be important for future studies to take measurements from the surface of the eye rather than from the menisci in order to obtain accurate data for the overall osmolarity of the tear film.

In addition to diagnosing dry eye, proper diagnostic tools for assessing tear film health could have more general applications as well. Fortes et al.[13] conducted a study into the use of tear film osmolarity measurements for the assessment of overall dehydration levels in the human body. Plasma osmolarity measurements are typically considered one of the best measurements of hydration status, but current assessment methods are time consuming, technically demanding, and invasive. Fortes et al. were able to show a strong correlation between tear film osmolarity and plasma osmolarity during an extended dehydration period after a workout. Measurement of tear film osmolarity with an impedance microchip may potentially offer a quick and easy method for assessing hydration levels. In addition, the standard practice of taking measurements from the menisci should actually serve this diagnostic technique well as the model developed by Zubkov et al. suggests that the tear film in the menisci is independent of surface evaporation rates and is more closely related to the composition of tear fluid secreted by the lacrimal gland, which should more closely correlate with bodily conditions as opposed to environmental ones.

III. The Blink Cycle

Studies of the surface evaporation rates during the inter-blink period are important for understanding tear film thinning, however, in order to understand how the tear film is renewed with each cycle, a study of blink dynamics is required. An inability to restore the tear film during a blink is believed to be one explanation for ocular surface discomfort in patients with dry eye syndrome. Furthermore, a better understanding of how the fluid dynamics involved during a blink could lead to more effective treatments for dry eye.

5. Efforts in Numerical Modeling

Zubkov et al.'s[5] study of the human tear film included detailed analyses of the blink cycle as well as saccadic eye motion, this being the fast motion of the eye when a subject looks up or down. They demonstrated not only that the meniscus regions are roughly independent of surface evaporation effects, but also that the upper and lower menisci are ultimately independent of each other. While the lower meniscus is governed primarily by the initial aqueous volume of the tear film, the upper meniscus was shown to be governed instead by the speed of the upper eyelid during a blink cycle and the flux of fluid coming from underneath the upper eyelid (see Figure 5). This suggests that measurements of either meniscus not only do not reflect the overall osmolarity of the tear film, but are not even necessarily representative of the salt concentrations in the other meniscus region. Zubkov et al. further discovered that the physiology of the lower black line and meniscus regions are radically altered during a 'look-down' vertical saccadic movement. Solute concentrations are significantly reduced in these regions as a result of the saccadic motion, suggesting that such eye movements could be used to help ameliorate lower black line hyperosmolarity.

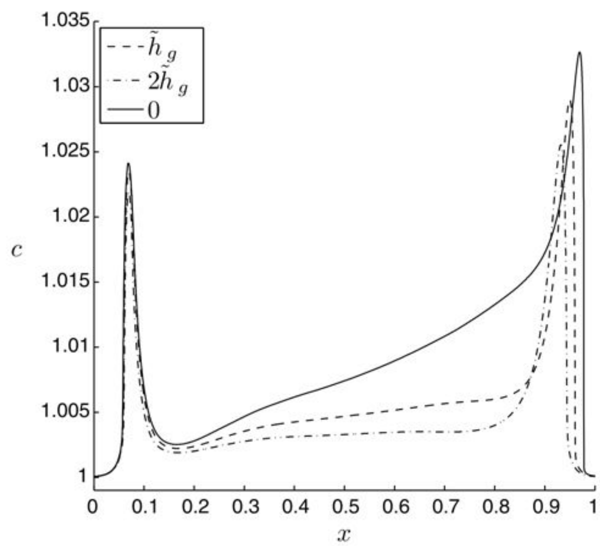

Figure 5. Numerical solutions for non-dimensional tear film osmolarity, c, at the end of the interblink period for three different variations in the gap size between the ocular surface and the upper eyelid during the upblink.[5]

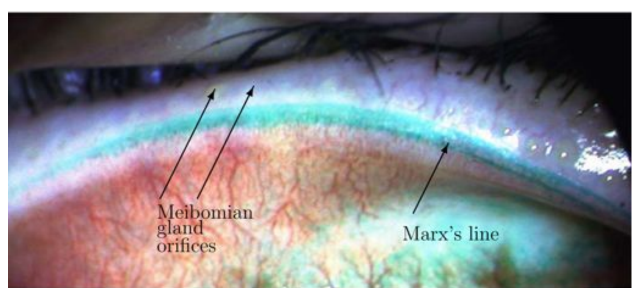

Figure 6. Vital staining of the upper eyelid revealing the high levels of cellular damage in the region known as Marx's line.[14]

In 2008, Jones et al.[14] produced a more detailed model of the blink cycle, incorporating eyelid geometry and elasticity, both of the eyelid and of the ocular surface itself. A fully elastic model of the blink cycle has yet to be developed, but Jones et al. were able to model the effect using a simple "mattress model" (see Figure 7), allowing the surfaces to deform in response to hydrodynamic pressure as a function of a spring constant. Experimental studies have used vital staining to reveal a high level of cellular damage in a region at the leading edge of the eyelid referred to as Marx's line (see Figure 6). Jones et al.'s model was able to predict levels of significant normal and shear stresses acting in this very region which are a likely cause of this cellular damage. The model also showed that a net flux of tear fluid onto the ocular surface from under the eyelid, which would be required to replace evaporative losses, is only possible if the cosing lid tension is higher than the lid tension during opening. Despite its successes, the model produced by Jones et al. lacks the experimental data needed to properly verify and tune its parameters enough to provide an accurate model of blink dynamics.

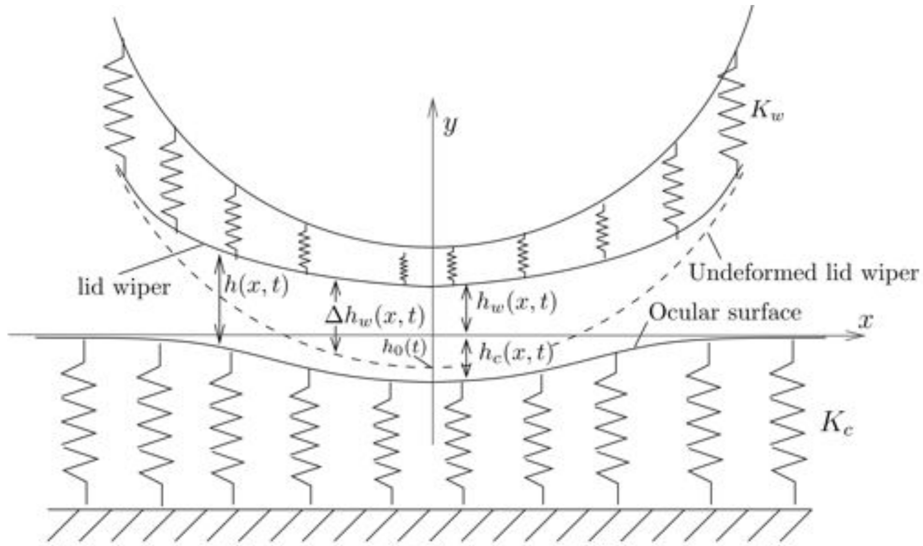

Figure 7. Mattress model of the elastic properties of the eyelid and ocular surface where K_w denotes the spring constant of the eyelid and K_c denotes the spring constant of the ocular surface.[14]

Significantly higher levels of cellular damage are observed across the under surface of the eyelid in patients with dry eye syndrome. Since the tear film acts as a surface lubricant, this may indicate the presence of an unusually thin tear film underneath the eyelid, leading to greater shear stresses and therefore to more extensive cellular damage. Once properly calibrated, the model developed by Jones et al. could prove to be a useful tool for determining the exact cause of this cellular damage and potentially derive the precise relationship between tear film thickness and eyelid surface stresses.

6. Experimental Analyses

Another study conducted by Harrison et al.[15] explored the dynamics of the menisci in both full and partial blinks. By instilling fluorescein directly under the eyelid near the lacrimal gland, they were able to show that the eyelid deposits a new layer of tear fluid onto the surface of the eye with each blink. A partial blink spread the fluorescein part way down the ocular surface (see Figure 8), but no fluorescein was observed spreading further downwards during the interblink period. Harrison et al. found that patients with dry eye syndrome exhibited significantly reduced meniscus heights and decreased film stability as a result. The tear film deposited by a partial blink in the dry eye patients was significantly more stable, likely due to the fact that the tear fluid was being deposited over a smaller surface area. The blink intervals between partial and full blinks were not significantly different however, suggesting that partial blinks may provide more stability over the sensitive central portion of the cornea and lead to overall improved vision in dry eye patients.

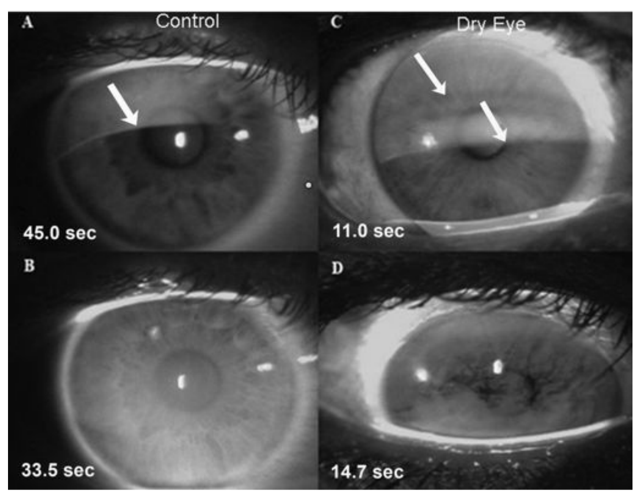

Figure 8. Incomplete and full blinks in normal and dry eye patients highlighted by the fluorescein deposited on the ocular surface.[15]

IV. Contact Lens Effects

The symptoms of ocular discomfort and dryness experienced by dry eye patients are also commonly experienced by habitual wearers of contact lenses. Understanding the effect of a contact lens on the fluid dynamics of the tear film could lead to improved contact lens design that would help to ameliorate these symptoms. Contact lens dynamics are complicated however by the formation of a thin fluid layer between the lens and the cornea in addition to the more regular tear film which forms on the surface of the lens.

7. *Efforts in Numerical Modeling*

Nong and Anderson[16] developed a numerical model for the outer tear film that develops in the presence of a semi-permeable contact lens. They ignore blinking and effects related to the inner tear film that develops between the contact lens and the ocular surface, but focus on attempting to develop a basis from which such dynamics can be explored in the future. Nong and Anderson were able to demonstrate that the addition of a permeable substrate (the contact lens) on top of the ocular surface has no significant effect on tear film thinning for expected interblink time scales and contact lens permeability values. Two slip models were considered at the surface of the contact lens, the first being a Beavers-Joseph boundary condition which allows free slip along a characteristic length, the second being a Le Bars-Worster boundary condition which allows slip into the porous layer of the contact lens itself over a characteristic depth (see Figure 9). Both slip conditions also served to increase tear film thinning rates, but neither had a significant effect at expected values of the slip constants. Ultimately, while the presence of a contact lens is expected to increase thinning rates, these effects are too small to affect a significant change in the outer tear film fluid dynamics. Since contact lens wearers often report similar symptoms to patients with dry eye syndrome, more elaborate models including evaporative effects and the coupled behavior between the outer and inner tear films formed by the presence of a contact lens must be necessary to study the true origin of these symptoms.

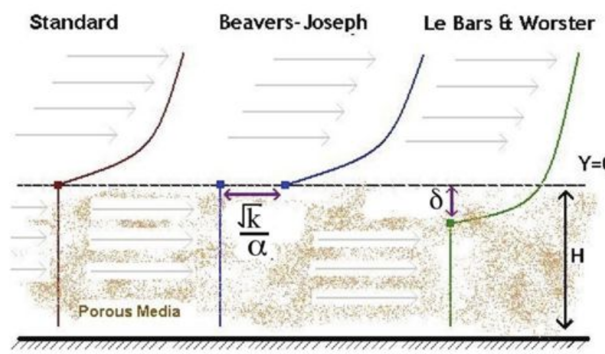

Figure 9. Velocity profiles for various fluid-porous interface slip conditions.[16]

8. *Experimental Analyses*

Optical coherence tomography (OCT) was recently used by Chen et al.[17] in the presence of a contact lens to measure the inner and outer tear films. Fluid boundaries were identified as peaks in the reflectivity profiles (see Figure 10), allowing for tear film thickness measurements with a resolution of approximately 3 μm. Three minutes after the insertion of a contact lens that was not prewetted with artificial tears, the inner tear film was too thin to detect via this method, meaning that it had to be less than 3 μm thick. The outer tear film also became undetectable in most subjects after three minutes, but successive measurements prior to this point indicated a clear trend, opening up the possibility of using a curve fit to predict the ultimate film thickness. Application of artificial tears to the interior of the contact lens prior to insertion allowed for visualization of the inner tear film for a short time, making it potentially possible to use curve fitting to predict the thickness of the inner tear film as well. Chen et al. did not go so far as to make these predictions in their study, but such a technique is clearly possible from their results. Dynamically, Chen et al. were able to demonstrate that application of artificial tears to the ocular surface after insertion of the contact lens had no influence on inner tear film thickness, meaning that none of the additional fluid was able to flow around the edge of the lens and into the space between the lens and the cornea. This limits the ability of artificial tears to improve comfort for contact lens wearers to relieving the friction between the contact lens and the eyelid.

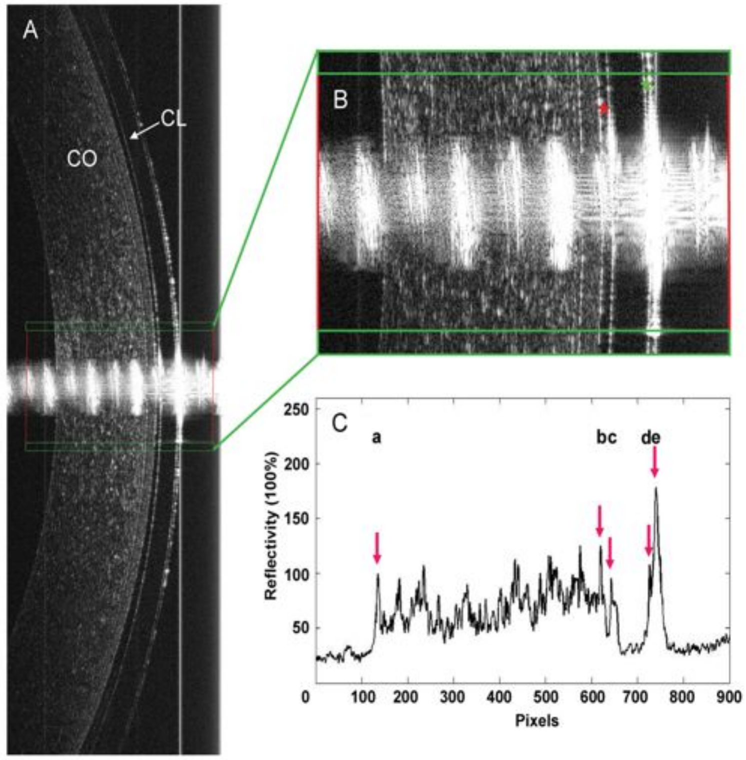

Figure 10. OCT image of the ocular surface in the presence of a contact lens. Peaks in the reflectivity profile shown in C correspond to: (a) the posterior surface of the cornea, (b) the anterior surface of the cornea, (c) the posterior surface of the contact lens, (d) the anterior surface of the contact lens, and (e) the anterior surface of the outer tear film.[17]

The study by Chen et al. offers a new diagnostic tool for the dynamics and geometries of contact lenses *in situ*. They were able to use optical coherence tomography to compare the fitting characteristics of lenses with different materials, back curves, and edge designs as they affected the fluid dynamics of the tear film. Chen et al. also found that application of artificial tears had no effect on the inner tear film thickness. By adopting optical coherence tomography as a diagnostic tool, improvements to the design of contact lenses could be made to promote fluid exchange around the edge of the contact lens and generally promote healthier tear film dynamics.

V. Tear Film Dynamics

While experimental data has provided some insight into parameters governing tear film dynamics and numerical models have been developed that characterize various portions of ocular surface flows, the overall fluid dynamics of the human tear film are still not well understood. Experimental efforts to fully characterize tear film fluid flow have been severely restricted by the limits of current measurement techniques and numerical models have focused on characterizing cross sections of the ocular surface in the interest of better understanding surface evaporation rather than overall flow dynamics. However, it is clear from these previous studies that our lack of understanding of the complex fluid dynamics present in the human tear film prevents us from developing better diagnostic techniques and treatments for ocular conditions such as dry eye syndrome.

9. Efforts in Numerical Modeling

While the limits of experimental techniques have made it difficult to verify many aspects of numerical models, they have also made these models our only real window into the complicated fluid dynamics inherent to the tear film. The models of tear film dynamics produced by Zubkov et al.[5] and Jones et al.[14] represent two of the more advanced tear film models produced to date. However, they are still fundamentally limited to a vertical cross-section of the ocular surface. Maki et al.[18] took a different approach to tear film modeling in their 2010 study of the flux boundary conditions. Rather than examine the cross section of the film, Maki et al. modeled the entire surface of the eye including influx from the lacrimal gland and puncta drainage (see Figure 11). These flux boundary conditions affect the local curvature of the menisci in these regions creating a pressure differential across the entire eye. Maki et al. demonstrated that this creates an overall flow towards the nasal canthus through the upper and lower menisci. The influence of gravity causes the film to flow primarily downward over the surface of the eye and the majority of flow towards the nasal canthus to occur through the lower meniscus. Unlike the models produced by Zubkov et al. and Jones et al. however, this model does not account for blinking behavior nor does it account for time dependent flux boundary conditions.

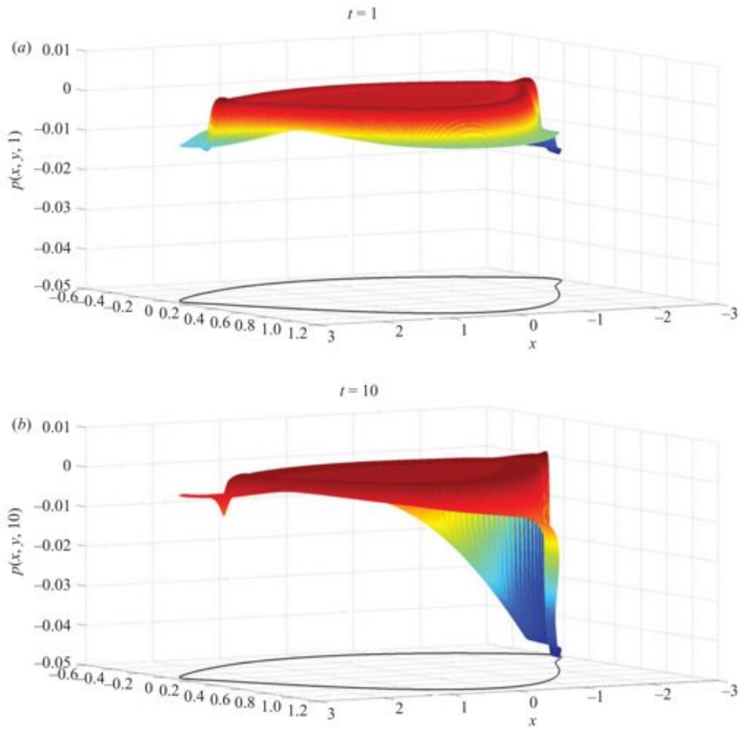

Figure 11. Ocular surface pressure at two different times after a blink with flux boundary conditions. Note the low pressure region that develops at the nasal canthus as a result of drainage through the punta.[18]

None of the aforementioned models take corneal heat dissipation into account. Models with fixed-temperature substrates predict that the tear film temperature will actually rise slightly after a blink. However, measurements of the ocular surface temperature reveal that the temperature actually drops after a blink. In 2012 Li and Braun[19] attempted to model this effect by including temperature variations in a thick substrate representing the cornea and part of the aqueous humor (see Figure 12). The substrate itself is modeled simply as a rectangular region below the tear film with continuity of temperature and heat flux maintained at the boundary between the two and body temperature ($T_B = 37°$ C) specified at the other three boundaries. Li and Braun were able to successfully demonstrate the tear film cooling effect as a result of heat dissipation into their thick substrate and found that a Biot number of $Bi = 0.0009$ best simulates experimental results. The Biot number here represents

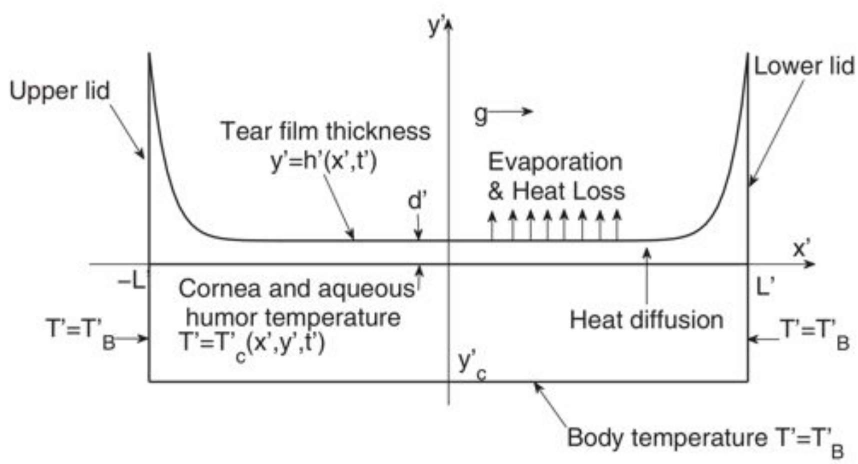

Figure 12. Tear film model including corneal heat dissipation through the inclusion of a thick substrate.[19]

the ratio of convective heat transfer inside the film to conduction between the film and the substrate. Li and Braun's model further revealed a strong dependence between Biot number and tear film evaporation as shown in Figure 13, providing a possible alternative explanation for the high evaporative rates postulated by King-Smith et al. However, these evaporative rates are also thought to depend on lipid layer thickness and composition, neither of which were modeled by Li and Braun. This model also fails to account for transient cooling throughout the blink cycle.

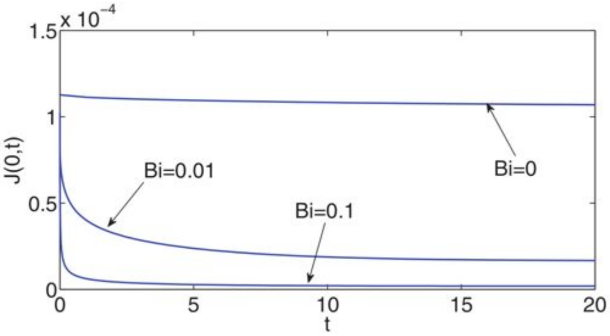

Figure 13. Evaporative mass flux, J, over time for several different Biot numbers.[19]

While modeling of the fluid dynamics of the human tear film has come a long way and made significant contributions to ophthalmology, a comprehensive model has yet to be designed. Few models study the full transient effects of the blink cycle, models of fluid flow across the entire surface of the eye are still in development, and heat dissipation effects have yet to be included in even the most advanced models of the human tear film. Many of these studies have focused on specific areas of tear film dynamics, but we are still a ways off from developing a model capable of predicting surface evaporation rates, which could play a critical role in diagnosing and treating evaporative dry eye disease. It has been suggested that measurements of tear osmolarity could serve as a gold standard for the diagnosis of dry eye syndrome,[11] however, it fails to provide an accurate benchmark for the severity of the condition and cannot properly distinguish between evaporative dry eye and aqueous deficient dry eye.[20] Well defined models of tear film osmolarity and surface evaporation rates could lead to better diagnostic tools capable of determining the exact nature of a patient's particular form and severity of dry eye.

10. Experimental Analyses

Historically, experimental data on the actual dynamics of the human tear film was limited due to the lack of good measurement techniques. Interferometry is limited to gathering static information regarding the surface of the tear film between blinks. Optical coherence tomography can be used to determine the thickness of the aqueous layer, but neither of these techniques shed any light on the actual fluid dynamics present in the human tear film. Organic dyes and radioactive tracers have been used to attempt to characterize these dynamics, but these tend to lose fluorescence rapidly and the volume of dye required to make these observations (2-5 μL) is large enough to potentially alter the dynamics of a typical tear film (4 μL).

Khanal and Millar[21] proposed to solve this dilemma through the use of quantum dots which remain fluorescent much longer than organic dyes and can be introduced in small enough quantities to avoid altering the actual dynamics of the tear film. In addition, quantum dots can be manufactured with either a hydrophilic or lipophilic outer coating providing the opportunity to study the dynamics of the aqueous layer and the lipid layer separately. Khanal and Millar were able to demonstrate the validity of a distinct, three-layer model as opposed to a density-gradient model by revealing three distinct dynamics present in the tear film.

Hydrophilic quantum dots introduced into the aqueous layer were swept away after a single blink and were subsequently transported through the menisci to the puncta. This suggests that the majority of the aqueous layer on the surface of the eye is distributed as the eyelid retracts directly from the secretions of the lacrimal gland. Khanal and Millar hypothesize that the eyelid draws the aqueous fluid into the menisci during a blink and high capillary forces within the menisci themselves prevent the fluid from redistributing over the ocular surface. A small percentage of these quantum dots did remain on the ocular surface, but apparently embedded in the mucin layer where they remained for a period of five to six blinks. The lipophlic quantum dots on the other hand did redistribute across the ocular surface with each blink. These quantum dots were slowly drawn onto the eyelids and into the nasal canthus, allowing for a more gradual replacement of the lipid layer.

The quantum dots analysis performed by Khanal and Millar[21] has provided a potential alternative resource for dry eye diagnosis. It is well known that the tear film dynamics of dry eye patients differ from those of healthy individuals. Quantum dots allow for these dynamics to be observed in unprecedented detail, so if these differences can be quantified and evaluated then quantum dot analysis of a patient's tear film could prove to be an invaluable diagnostic tool. Furthermore, these observations can be made with a slit-lamp biomicroscope, which is a standard clinical instrument, such that these techniques could be quickly and easily adopted for standard clinical use.

VI. Conclusions

As a complex and dynamic layer of fluid, the human tear film represents an aspect of biological fluid mechanics with which we continue to struggle for understanding. Its important role in protecting the corneal surface makes this a vital area of research in modern optholmology that continues to receive a lot of attention from the medical community. In order to develop better diagnostic techniques and treatment methods for related ocular conditions such as dry eye syndrome, a better understanding of tear film dynamics is required. To that end, significant efforts have been made in recent years in the field of numerical modeling to develop a better understanding of the precise fluid dynamic processes that influence commonly measured parameters such as tear film osmolarity and break up time.

Numerical models have been developed that account for thinning behavior, flux conditions, blink dynamics, and corneal heat diffusion. These models have already provided significant insights into the fluid dynamics of the human tear film. Most notably, the work by Zubkov et al.[5] and Maki et al.[18] revealed that tear film osmolarity varies widely across the ocular surface and the osmolarity in the lower meniscus, upper meniscus, and central portion of the tear film are all fairly independent of each other. Since osmolarity measurements are used as a standard gauge of overall tear film health and as the primary tool for diagnosing dry eye syndrome, it is extremely important to understand what dynamics the osmolarity in different regions of the tear film reflect. It is apparent from these studies that the surface evaporation rate primarily effects osmolarity in the central portion of the tear film, making measurements of the meniscus region less useful for diagnosing this particular dynamic of the tear film. Even in recent studies, experimental methodology in this area is not standardized or well documented, however it will be important to begin doing so for the validity of future research in this field.

Historically, efforts at analyzing the human tear film experimentally have been hampered by the limits of experimental techniques, however the recent study by Khanal and Millar[21] has provided a valuable new tool for future experimental research in this area. The use of quantum dots for nano-scale flow analysis represents the first detailed observations made of actual tear film fluid dynamics *in vivo* . Khanal and Millar were able to show three distinct flow behaviors, finally validating the commonly used three-layer model for tear film dynamics. Furthermore, they were able to demonstrate its viability as a potential new diagnostic tool for medical purposes. By focusing future research efforts on the characterization of the specific flow dynamics in various forms of dry eye, the accuracy and detail of dry eye diagnoses could be significantly improved. This method also has strong potential for validating numerical models with a more detailed and extensive study of the dynamics of healthy eyes.

The new impedance microchip also shows promise as a better tool for osmolarity measurements. It is not clear from the research whether this tool is capable of taking measurements of the osmolarity in the central region of the ocular surface, but it is potentially a far more accurate tool at least for measurements of meniscus osmolarity. However, due to the numerous sources of error present in older methods and in light of the numerical results showing significant osmolarity variations across the ocular surface, the accuracy of this techniques has yet to be fully validated. Nevertheless, researchers have already begun using the impedance microchip for measurements of tear film osmolarity in experimental studies and the continued use of this method in future studies will likely bear out its advantages over older forms of osmolarity measurement.

With these recent advancements in the field of opthalmology, future research into the dynamics of the human tear film looks promising. While numerical models have provided us with a better understanding of these dynamics and quantum dots promise to reveal even more, we still have a long way to go in our understanding of the human tear film. In order to better classify, diagnose, and treat dry eye syndrome, we will have to use these new experimental techniques to validate existing numerical models and help develop a more comprehensive model that can be used to better understand these dynamics and predict their effects on the overall health of the ocular surface.

References

[1]Braun, R. J., "Dynamics of the Tear Film," *Annu. Rev. Fluid Mech.*, Vol. 44, 2012, pp. 267–297.

[2]King-Smith, P. E., Nichols, J. J., Nichols, K. K., Fink, B. A., and Braun, R. J., "Contributions of Evaporation and Other Mechanisms to Tear Film Thinning and Break-Up," *Optom. Vis. Sci.*, Vol. 85, 2008, pp. 623–630.

[3]Berger, R. E. and Corrsin, S., "A Surface Tension Gradient Mechanism for Driving the Pre-Corneal Tear Film after a Blink," *J. Biomech.*, Vol. 7, 1974, pp. 225–238.

[4]Braun, R. J., Usha, R., McFadden, G. B., Driscoll, T. A., Cook, L. P., and King-Smith, P. E., "Thin Film Dynamics on a Prolate Spheroid with Application to the Cornea," *J. Eng. Math.*, Vol. 73, 2012, pp. 121–138.

[5]Zubkov, V. S., Breward, C. J. W., and Gaffney, E. A., "Coupling Fluid and Solute Dynamics within the Ocular Surface Tear Film: A Modelling Study of Black Line Osmolarity," *Bull. Math. Bio.*, Vol. 74, 2012, pp. 2062–2093.

[6]Nichols, J. J., King-Smith, P. E., Hinel, E. A., Thangavelu, M., and Nichols, K. K., "The Use of Fluorescent Quenching in Studying the Contribution of Evaporation to Tear Thinning," *Invest. Ophthalmol. Vis. Sci.*, Vol. 53, 2012, pp. 5426–5432.

[7]Rantamaki, A. H., Javanainen, M., Vattulainen, I., and Holopainen, J. M., "Do Lipids Retard the Evaporation of the Tear Fluid," *Ophthalmol. Vis. Sci.*, Vol. 53, 2012, pp. 6442–6447.

[8]Varikooty, J. and Simpson, T. L., "The Interblink Interval I: The Relationship between Sensation Intensity and Tear Film Disruption," *Ophthalmol. Vis. Sci.*, Vol. 50, 2009, pp. 1087–1092.

[9]Abusharha, A. A. and Pearce, E. I., "The Effect of Low Humidity on the Human Tear Film," *Cornea*, Vol. 32, No. 4, 2013, pp. 429–434.

[10]Torricelli, A. A. M., Novaes, P., Matsuda, M., Braga, A., Saldiva, P. H. N., Alves, M. R., and Monteiro, M. L. R., "Correlation between Signs and Symptoms of Ocular Surface Dysfunction and Tear Osmolarity with Ambient Levels of Air Pollution in a Large Metropolitan Area," *Cornea*, Vol. 32, 2013, pp. e11–e15.

[11]Stahl, U., Willcox, M., and Stapleton, F., "Osmolality and Tear Film Dynamics," *Clin. Exp. Optom.*, Vol. 95, No. 1, 2012, pp. 3–11.

[12]Gokhale, M., Stahl, U., and Jalbert, I., "In Situ Osmometry: Validation and Effect of Sample Collection Technique," *Optom. Vis. Sci.*, Vol. 90, 2013, pp. 359–365.

[13]Fortes, M. B., Diment, B. C., Felice, U. D., Gunn, A. E., Kendall, J. L., Esmaeelpour, M., and Walsh, N. P., "Tear Fluid Osmolarity as a Potential Marker of Hydration Status," *Med. Sci. Sports Exerc.*, Vol. 43, 2011, pp. 1590–1597.

[14]Jones, M. B., Fulford, G. R., Please, C. P., McElwain, D. L. S., and Collins, M. J., "Elastohydrodynamics of the Eyelid Wiper," *Bull. Math. Bio.*, Vol. 70, 2008, pp. 323–343.

[15]Harrison, W. W., Begley, C. G., Liu, H., Chen, M., Garcia, M., and Smith, J. A., "Menisci and Fullness of the Blink in Dry Eye," *Optom. Vis. Sci.*, Vol. 85, 2008, pp. 706–714.

[16]Nong, K. and Anderson, D. M., "Thin Film Evolution over a Thin Porous Layer: Modeling a Tear Film on a Contact Lens," *SIAM J. Appl. Math.*, Vol. 70, 2010, pp. 2771–2795.

[17]Chen, Q., Wang, J., Tao, A., Shen, M., Jiao, S., and Lu, F., "Ultrahigh-Resolution Measurement by Optical Coherence Tomography of Dynamic Tear Film Changes on Contact Lenses," *Invest. Ophthalmol. Vis Sci.*, Vol. 51, 2010, pp. 1988–1993.

[18]Maki, K. L., Braun, R. J., Ucciferro, P., Henshaw, W. D., and King-Smith, P. E., "Tear Film Dynamics on an Eye-Shaped Domain - Flux Boundary Conditions," *J. Fluid Mech.*, Vol. 647, 2010, pp. 361–390.

[19]Li, L. and Braun, R. J., "A Model for the Human Tear Film with Heating from within the Eye," *Phys. Fluids*, Vol. 24, 2012, pp. 062103.

[20]McGinnigle, S., Naroo, S. A., and Eperjesi, F., "Evaluation of Dry Eye," *Surv. Ophthalmol.*, Vol. 57, No. 4, 2012, pp. 293–316.

[21]Khanal, S. and Millar, T. J., "Nanoscale Phase Dynamics of the Normal Tear Film," *Nanotech. Bio. Med.*, Vol. 6, 2010, pp. 707–713.