© Journal for Modeling in Ophthalmology 2018;1:24-28
Meeting highlights article: ARVO 2017

Dynamics of fluorescent imaging in glob-driven breakup

Lan Zhong[1], Richard J. Braun[1], P. Ewen King-Smith[2], Carolyn G. Begley[3]

[1]Department of Mathematical Sciences, University of Delaware, Newark, DE, USA, [2]College of Optometry, The Ohio State University, Columbus, OH, USA, [3]School of Optometry, Indiana University, Bloomington, IN, USA

Key words: dry eye, fluorescence imaging, tangential flow, tear film breakup

1. Background and purpose

Fluorescent imaging has been widely used when imaging tear breakup (TBU) and diagnosing dry eye. However, the accuracy of using fluorescein images to quantify TBU is still an active area of research. Mathematical models have studied different mechanisms of tear film (TF) dynamics and dry eye.[1] Recent findings from mathematical models simulating evaporative TBU indicate that TF fluorescein concentrations higher than approximately 0.2% work well when visualizing TBU.[2]

In this work, we are more interested in imaging TBU caused by another mechanism: tangential flow. Our experimental results suggest that tangential flow can be responsible for rapid thinning, where TBU occurs in under a second. The tangential flow can be driven by a glob in the lipid layer; the glob is hypothesized to have more lipid than the surrounding area, which can cause Marangoni flow that rapidly thins the tear film and may cause TBU.[3] Due to a much shorter time scale and a different mechanism for rapid thinning, we expect the dynamics of fluorescein in the tears to be different. By building mathematical models which simulate the strong tangential flow, we studied solute movement inside the aqueous layer and its effects on fluorescent imaging. The results from the mathematical models suggest that a dilute TF fluorescein concentration may be the best for approximating TF thickness in rapid TBU.

2. Methods

We developed partial differential equation (PDE) models which capture the important dynamics in rapid thinning. The models include evaporative (J), tangential, and

Correspondence: L. Zhong, 501 Ewing Hall, University of Delaware, Newark, DE 19719, USA.
E-mail: lanzhong@udel.edu

osmotic flows. The evaporation is specified within experimental ranges based on the assumptions of the composition of globs. Tangential flow is driven by assuming that the surface tension at the glob is low; strong tangential flow is then induced by the Marangoni effect. Osmotic flow is assumed to be proportional to the osmolarity difference across the corneal surface. The TF is very thin, which allows us to use lubrication theory to non-dimensionalize the governing equations from fluid mechanics and reduce them to four PDEs.

The models are solved numerically in Matlab (MathWorks, Natick, MA, USA) using method of lines in time and Chebyshev spectral discretization in space. The resulting differential-algebraic equations are solved by ode15s in Matlab; this method is stable for the parameters we studied here. We solve the model for aqueous TF thickness (h), pressure (p), lipid concentration (Γ), osmolarity (c), and fluorescein concentration (f). We initialize our model to be a uniformly flat TF with a single glob in the center; the glob has a higher Γ than the surrounding area. The evaluated h help us track the thinning process of the TF. With h and f from the models, we can calculate the fluorescein intensity, (I).[4] I is the quantitative data usually measured directly for interpreting TF thickness in clinical settings. By comparing the computed I and h from our model, we estimate the accuracy to approximate h for rapid TBU.

3. Results

Within appropriate range of glob size (r_I), TBU can happen in about a second or less. Our model successfully captured the short time scale in rapid TBU. Figure 1 shows that h thins to 0.25 μm at 0.57 s, which is the threshold for TBU defined in our model. At the same time, Γ spreads to the region on the right, acting as a source that keeps driving the tangential flow. Due to the short time and our assumed evaporation profile (see Eq. 5 in the Appendix), c and f increased only slightly under the glob. We assume the evaporation rate is uniform. The concentration of solutes increases in percentage due to a thinner TF under the glob. Tangential flow does not change solute concentration in the aqueous layer. Comparing the first column with the last column, we see that I appears to be proportional to h when initial concentration f_0 = 0.2%.

When using higher concentrations of fluorescein in rapid TBU, the proportionality between I and h is lost. Figure 2 shows results with f_0 = 0.8%. Figure 3 summarizes results for various f_0. Here, $a = 1/\sqrt{I_0}$ is the constant that normalizes I to unity for $h = 1$ at $t = 0$.

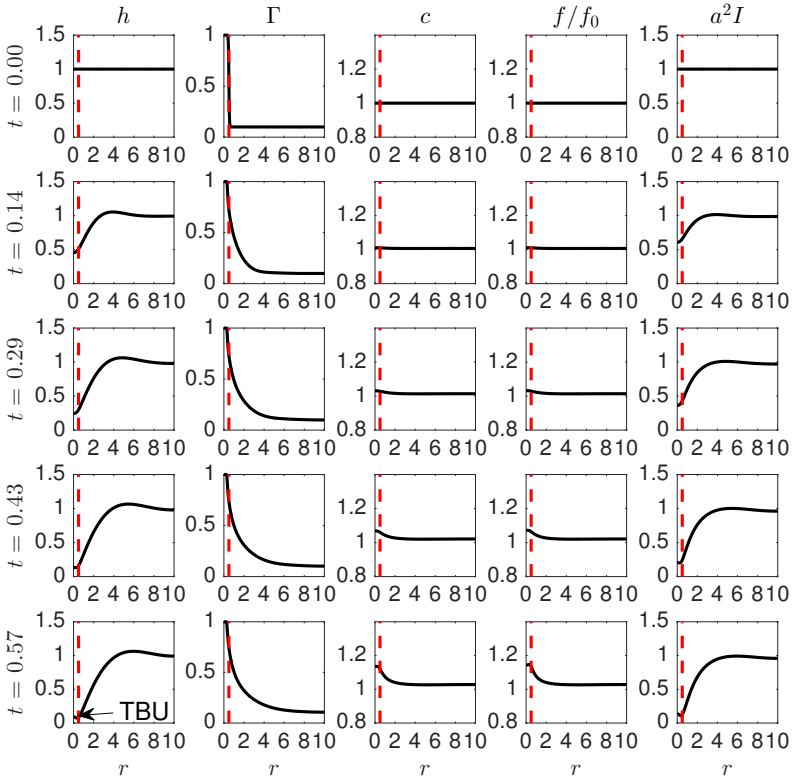

Fig. 1. Dynamics of the tear thinning. The vertical dashed line represents the edge of the glob. The dimensionless glob size in this figure is r_I= 0.5 (0.037 mm), the domain size is 0.74 mm, and the initial fluorescein concentration is f_0 = 0.2%.

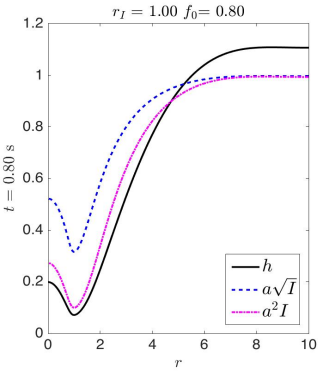

Fig. 2. TBU occurs in 0.80 s when r_I = 1. Fluorescein intensity does not accurately represent TF thickness when f_0 = 0.8% for rapid TBU.

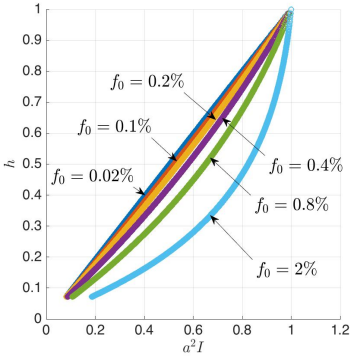

Fig. 3. Scatter plot of scaled fluorescein intensity and TF thickness with different f_0. When f_0 is lower than 0.2%, $a^2 I$ can roughly linearly indicate tear thinning.

4. Conclusions and future perspectives

Rapid TBU as described here occurs in about a second or less.[5,6] Evaporation only slightly increases fluorescein concentration in such a short time. Our models suggest that initial fluorescein concentration at the critical value or less is recommended when imaging rapid TBU. Concentrations beginning at 0.2% or higher are appropriate for evaporative TBU.[2,4,7]

Another hypothesis regarding rapid TBU is that it is caused by dewetting of the corneal surface; we did not study this case here.[5] Further work that isolates dewetting as a cause of rapid TBU would be highly desirable. A more comprehensive version of this work will be submitted elsewhere. In future work, the models discussed here should be extended to more realistic glob shapes and mobile globs.

Acknowledgements

This work was supported by US National Science Foundation (NSF) Grant 1412085 (Richard J. Braun), US National Institutes of Health (NIH) Grant R01EY17951 (P. Ewen King-Smith), and NIH Grant 1R01EY021794 (Carolyn G. Begley), and does not necessarily represent the official views of the NSF or NIH.

Appendix

Dimensionless model for circular-shape glob-driven TBU in axisymmetric cylindrical coordinates:

$$\partial_t h = -J + P_c(c-1) - \frac{1}{r}\partial_r(rh\bar{u}), \tag{1}$$

$$\partial_t \Gamma = \left[\mathrm{Pe}_\Gamma^{-1} \left(\frac{1}{r} \partial_r (r \partial_r \Gamma) \right) - \frac{1}{r} \partial_r (r \Gamma u_r) \right] B(r), \tag{2}$$

$$h \partial_t s = \mathrm{Pe}_s^{-1} \frac{1}{r} \partial_r (r h \partial_r s) + J s - P_c (c - 1) s - h \bar{u} \partial_r s, \tag{3}$$

where $s = c$ or f, $B(r)$ blends the glob and tear/air interfaces, and:

$$0 = p + \frac{1}{r} \partial_r (r \partial_r h) + A h^{-3}, \tag{4}$$

$$J = v \tag{5}$$

$$\bar{u} = \frac{-\frac{1}{3} \partial_r p h^2 [B(r) + \frac{1}{4} h (1 - B(r))] - \frac{1}{2} h B(r) \partial_r \Gamma}{B(r) + (1 - B(r)) h}, \tag{6}$$

$$u_r(r, h, t) = \frac{-\frac{1}{2} \partial_r p h^2 B(r) - \partial_r \Gamma B(r) h}{B(r) + (1 - B(r)) h}, \tag{7}$$

$$B(r; r_I, r_W) = 0.5 + 0.5 \tanh \left(\frac{r - r_I}{r_W} \right). \tag{8}$$

The constants in the equations are non-dimensional forms for the following quantities:

1. the uniform evaporation rate, v = 9.75$\times 10^{-4}$ (dimensionally, 10 μm/min);
2. the transition width for the blend function r_W = 0.05;
3. the Hamaker constant for wetting, A = 2.86$\times 10^{-4}$;
4. the permeability of the corneal surface to water, P_c = 3.82$\times 10^{-10}$;
5. the Peclet number for solutes in the aqueous layer, Pe_c = 168, Pe_f = 690; and
6. the surface Peclet number for polar lipid, Pe_Γ = 8.97.

References

1. Braun RJ. Dynamics of the tear film. Ann Rev Fluid Mech. 2012;44: 267–297.
2. Braun RJ, Driscoll TA, Begley CG, King-Smith PE, Siddique JI. On tear film breakup (TBU): dynamics and imaging. Math Med Biol. 2017. doi: 10.1093/imamb/dqw023.
3. King-Smith PE, Reuter KS, Braun RJ, Nichols JJ, Nichols KK. Tear film breakup and structure studied by simultaneous video recording of fluorescence and tear film lipid layer images. Invest Ophthalmol Vis Sci. 2013;54(7): 4900–4909.
4. Nichols JJ, King-Smith PE, Hinel EA, Thangavelu M, Nichols KK. The use of fluorescent quenching in studying the contribution of evaporation to tear thinning evaporation contribution to tear thinning. Invest Ophthalmol Vis Sci. 2012;53(9): 5426–5432.
5. Yokoi N, Georgiev GA. Tear-film-oriented diagnosis and therapy for dry eye. Dry eye syndrome: basic and clinical perspectives. London: Future Medicine Ltd, 2013; Chapter 7, p. 96–108.
6. Braun RJ, King-Smith PE, Begley CG, Li L, Gewecke NR. Dynamics and function of the tear film in relation to the blink cycle. Prog Ret Eye Res. 2015;45: 132–164.
7. Braun RJ, Gewecke NR, Begley CG, King-Smith PE, Siddique JI. A model for tear film thinning with osmolarity and fluorescein. Invest Ophthalmol Vis Sci. 2014;55(2): 1133–1142.