Bunsen–Roscoe law (BRL) is based on the Beer–Lambert law for UV light intensity without RF depletion, such that $S = akE$, which is a linear function of the dose E = (tI). In comparison, using a time-dependent "generalized" Beer–Lambert law[2–4], we obtain $S = \sqrt{(\frac{4kCo}{alo})\exp(A'z)}\ [1-\exp(-0.5aE)]$ which is a nonlinear function of E, and has a steady-state value $S = \sqrt{(\frac{Co}{alo})\exp(A'z)}$, for 0.5aE > 4, or UV exposure time t > 8a/I. Our nonlinear law predicts that high UV intensity requires longer exposure time than that calculated based on the BRL. In addition, for the same dose, higher intensity depletes the RF faster and reaches a lower steady-state efficacy than that of lower intensity, consistent with the recent clinical data.[5,8]

In the conventional Dresden protocol, the extra RF drops (with frequency F = 10 to 15) during the UV exposure will reduce the effective dose from 5.4 J/cm^2 to about 4.5 J/cm^2, calculated by a dose reduction of 0.06 J/cm^2 per drop for a surface layer of 100 μm. Modern protocols did not apply extra RF drops (with F = 0) to maximize the effective dose in the stroma. However, our nonlinear theory predicts that the optimal protocol (for fast and efficient CXL), F = 2 to 3 is required to compensate the fast depletion of RF, especially for the high-intensity cases (>9 mW/cm^2).

There are many debatable issues with CXL that require further basic studies to resolve. Examples are the role of oxygen and pulsing in the efficacy of type II CXL, dynamic corneal thinning during CXL, and the demarcation line depth related to CXL efficacy (or stiffness) profiles.

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REFERENCES

1. Caruso C, Epstein RL, Ostaacolo C, et al. Customized cross-linking—a mathematical model. *Cornea*. 2017;36:600–604.
2. Lin JT, Liu HW, Cheng DC. On the dynamic of UV-light initiated corneal cross linking. *J Med Biolog Eng.* 2014;34:247–250.
3. Lin JT. Combined analysis of safety and optimal efficacy in UV-light-activated corneal collagen crosslinking. *Ophthalmol Res.* 2016;6:1–14.
4. Lin JT, Cheng DC. Modeling the efficacy profiles of UV-light activated corneal collagen crosslinking. *PLoS One.* 2017;12:e0175002.
5. Kling S, Hafezi F. An algorithm to predict the biomechanical stiffening effect in corneal cross-linking. *J Refract Surg.* 2017;32:128–136.
6. Mooren P, Gobin L, Bostan N, et al. Evaluation of UVA cytotoxicity for human endothelium in an ex vivo corneal cross-linking experimental setting. *J Refract Surg.* 2016;32:596–605.
7. Schumacher S, Mrochen M, Wernli J, et al. Optimization model for UV-riboflavin corneal cross-linking. *Invest Opthamol Vis Sci.* 2012; 53:762–769.
8. Choi MJ, Kim J, Eung K, et al. Comparison of the conventional Dresden protocol and accelerated protocol with higher ultraviolet intensity in corneal collagen cross-linking for keratoconus. *Cornea*. 2017;36:523–529.

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***Reply*:**

We respectfully dispute the statement that the coupled equations of the ultraviolet (UV-A) light intensity were introduced for the first time in 2014 in the article "On the dynamic of UV-light initiated corneal cross linking" published in *J Med Biolog Eng* by Lin et al.

We disclosed the coupled equations in a recent article by Caruso et al,[1] respectively, (3) and (4) in our podium presentation.[2]

$$\frac{\partial I(z,t)}{\partial z} = -I(z,t)\times[(\varepsilon-\alpha)\times R_A(z,t) + \alpha\times R_A(z,0) + \beta]$$

$$\frac{\partial R_A(z,t)}{\partial z} = -\frac{\varepsilon\times P}{\gamma}\times I(z,t)\times R_A(z,t)$$

Our presentation, awarded as the best paper of the session by Prof. Cynthia Roberts, is enclosed per your perusal together with pictures taken at the Congress depicting also the Commission.

To participate as attending speakers to the ROLAND-SICSSO International Congress in July 2011, we had to submit our presentation earlier for acceptance; thus, it is clear that we had found our results quite earlier than that date.

Therefore, the coupled equations of the UV light intensity were published at least 3 years before the publication of the article of Lin et al.

Moreover, in our presentation dated 2011, we stressed the fact that the absorption coefficient of the Lambert-Beer law $(\varepsilon-\alpha)\times R_A(z,t)$ is time dependent in cross-linking treatments because of riboflavin consumption, as demonstrated by the experimental data published in another article of ours.[3] Our experimental data, and even clinical results,[4] have confirmed the theory based on our equations published in 2011 that the coefficient of absorption is time dependent. Therefore, it is clear that using a time-independent absorption coefficient may lead to relevant errors.

Lin et al state that the derivation of our Equation 4 is based on the work of Schumacher et al[5] published in 2012 and cited in our article.[1] Clearly, we could not use this work for drafting our presentation held in July 2011 because the article of Schumacher had not been published yet.

Moreover, this statement of Lin et al cannot be shared because Schumacher et al[5] start from a time-dependent $c(z,t) = c_0\cdot\mathrm{erfc}(\frac{z}{2\sqrt{Dt}})$ diffusion model based on the Fick second law of diffusion (Equation 1) $\frac{\partial c}{\partial t} = D\frac{\partial^2 c(z,t)}{\partial z^2}$, to obtain a time-dependent UV intensity distribution (Equations 5 and 6).

$$I(z,t) = I_0(t)\cdot\exp\left(-\varepsilon_r \times \int_0^z c(x,t)dx\right)\cdot\exp(-\mu_c z)$$

$$\int_0^z c(x,t)dx = c_0 z - c_0\left[\frac{2}{\sqrt{\pi}}\left(e^{\frac{z^2}{4Dt}}-1\right)\sqrt{Dt} + z\cdot\mathrm{erf}\left(\frac{z}{2\sqrt{Dt}}\right)\right]$$

The mathematical model proposed by Schumacher is relevantly different from the coupled equations of the UV light intensity disclosed in our article[1] because Schumacher et al tried to explain the time-dependent absorption coefficient in the Lambert-Beer law with a phenomenon of diffusion (immediately

recognizable for the presence of the mathematical Erf function) and not of photolysis.

As far as our approximation $\varepsilon_2 = 0$ is concerned, we are aware that assigning a null absorption coefficient to photolysis products leads to an underestimation of the value of the absorption coefficient A'(z). We did this purposely because we have not found reliable sources in the literature providing an accurately estimated value of the absorption coefficient of these photolysis products. We stress the fact that underestimating the value of the absorption coefficient A'(z) is in favor of the patient's safety because the mathematical model will overestimate the UV intensity at the endothelium; thus, according to calculations, the safety threshold for the UV intensity at the endothelium is attained earlier than in a real cross-linking treatment.

By contrast, even slightly overestimating the value of the absorption coefficient A'(z) means exposing the treated patient to the danger of receiving an excessive dose of UV-As.

It seems that in the article of Lin et al,[6] different possible values for ε_2 are assumed. Until enough experimental data on the type of photolysis products, on their rate of production during a real cross-linking treatment, and on their absorption coefficient are collected, assuming $\varepsilon_2 = 0$ seems advisable to perform cross-linking treatments in the topmost safety conditions for patients.

In the numerical simulations, not in the mathematical equations that are general, we assumed a flat profile of the riboflavin distribution because we are unable to determine in vivo the exact distribution of riboflavin within the cornea of a patient to be treated. Moreover, patients are not identical to each other. Thus, it seems unlikely that a single distribution profile of riboflavin can be adopted to describe what really happens in the stroma of each patient.

We have not found any publication in which the exact riboflavin distribution within the corneal stroma is experimentally measured in vivo in a patient to be treated.

Schumacher et al assumed that the distribution of riboflavin within the stroma is determined according to an error function (Erf), whereas Lin et al assumed a decreasing profile; both hypotheses are reasonable, although claiming that a chosen distribution profile of riboflavin is the exact and appropriate profile should be substantiated by a relevant amount of experimental data collected in vivo.

We respectfully remark that the article[6] by Lin et al does not provide any detailed explanation of the proportionality factor γ, $\gamma = \frac{h \cdot c}{\lambda} \times \frac{N}{W_{mol}}$ in our Equation (4)[1] nor is it derivable from the cited work of Schumacher et al.

We further remark that, according to the article of Lin et al, it would be possible to irradiate corneal stroma with a UV-A intensity of 10 mW/cm^2 or more. We cannot agree on this point because our experimental data[3] show that this intensity is too great and causes a UV-A intensity at the endothelium exceeding the safety limit of 0.35 mW/cm^2. We know that certain authors believe that it is possible to irradiate the cornea with a UV-A intensity of 10 mW/cm^2, or even more, but our experimental results are in sharp contrast with this assumption. Our figure 1 clearly disproves the possibility of treating patients with UV-A intensity of 10 mW/cm^2 within published safety limits.[1]

We would respectfully remark that we correctly cite the article by Schumacher et al being highly visible and properly listed in one of the most popular search engines in the field of medical sciences, such as PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=Optimization+model+for+UV-riboflavin+corneal+cross-linking).

Contrariwise, the article by Lin et al "On the dynamic of UV-light initiated corneal cross linking" is not listed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=On+the+dynamic+of+UV-light+initiated+corneal+cross+linking) and has been self-cited 2 times (Source: Scopus) since 2014. Thus, not receiving the visibility it probably deserves.

Similarly, the article entitled "Optimal focusing and scaling law for uniform photo-polymerization in a thick medium using a focused UV Laser" is not listed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=Optimal+focusing+and+scaling+law+for+uniform+photo-polymerization+in+a+thick+medium+using+a+focused+UV+Laser) and after accurate reading, it is focused on slightly different topics (6 self-citations, source: Scopus).

Finally, the article "Combined analysis of safety and optimal efficacy in UV-light-activated corneal collagen crosslinking" is not listed in any of the most trusted scientific data banks such as PubMed, Scopus, and WOS.

It seems to us that our work adds a significant contribution to the present knowledge and may call attention to the patients' safety during cross-linking treatments.

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REFERENCES

1. Caruso C, Epstein RL, Ostacolo C, et al. Customized corneal cross-linking—a mathematical model. *Cornea*. 2017;36:600–604.

2. Barbaro G, Caruso C, Troisi S, et al. A mathematical model of corneal UV-a absorption after soaking with a riboflavin solution during transepithelial cross-linking. Paper presented at: 1st Joint International Congress Refractive online and SICSSO; July 7–9, 2011; Grosseto, Italy. Available at: http://sicsso.org/Programma2011.pdf.
3. Caruso C, Barbaro G, Epstein RL, et al. Corneal cross-linking: Evaluating the Potential for a lower Power, Shorter Duration treatment. *Cornea*. 2016;35:659–662.
4. Caruso C, Ostacolo C, Epstein RL, et al. Transepithelial corneal cross-linking with vitamin e-enhanced riboflavin solution and abbreviated, low-dose UV-a: 24-month clinical outcomes. *Cornea*. 2016;35:145–150.
5. Schumacher S, Mrochen M, Wernli J, et al. Optimization model for UV riboflavin corneal cross-linking. *Invest Ophthalmol Vis Sci.* 2012;53:762–769.
6. Lin JT, Liu HW, Cheng DC. On the dynamic of UV-light initiated corneal cross linking. *J Med Biolog Eng.* 2014;34:247–250.

Visual Outcomes After SMILE, LASEK, and LASEK Combined With Corneal Cross-Linking for High Myopic Correction

To the Editor:

In the past few years, small-incision lenticule extraction (SMILE) has been proposed as a promising alternative to laser in situ keratomileusis (LASIK) and laser-assisted subepithelial keratomileusis (LASEK) for correction of myopia. For this reason, we have read with great interest the article by Hyun et al[1] about the visual results of SMILE compared with LASEK and LASEK combined with corneal collagen cross-linking for the treatment of high myopia. However, we have some concerns about this study. Hyun et al[1] reported that SMILE induced no postoperative corneal haze, whereas 18% of patients treated with LASEK and 25% of patients treated with LASEK + cross-linking had corneal haze at 6 months postoperatively, thus explaining the better visual results obtained with SMILE in terms of higher-order aberrations. It is noteworthy that what the authors really compare are the results obtained by SMILE versus LASEK without intraoperative use of mitomycin C (MMC), and it is well accepted that MMC, by its cytotoxic and antimitotic effects on the keratocytes, inhibits corneal haze that may appear after surface ablation, especially in deep ablations.[2] In fact, the incidence of haze after LASEK without MMC in the study by Hyun et al[1] (18%) is clearly worse than the results reported previously by our team, using LASEK + MMC for correction of myopia from −7.00 to −13.75 diopters,[3] in which no eye of 114 eyes included developed haze greater than 1+. For this reason, we believe that the main conclusion of the study by Hyun et al[1] is clearly biased, that is, no adjuvant use of MMC in LASEK (and not the less epithelial trauma after SMILE suggested by Hyun et al) might be the reason why the authors found more incidence of haze, and subsequently, worse visual results after LASEK compared with SMILE for correction of high myopia.

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REFERENCES

1. Hyun S, Lee S, Kim JH. Visual outcomes after SMILE, LASEK, and LASEK combined with corneal cross-linking for high myopic correction. *Cornea*. 2017;36:399–405.
2. Teus MA, de Benito-Llopis L, Alió JL. Mitomycin C in corneal refractive surgery. *Surv Ophthalmol.* 2009;54:487–502.
3. de Benito-Llopis L, Teus MA, Sánchez-Pina JM. Comparison between LASEK with mitomycin C and LASIK for the correction of myopia of −7.00 to −13.75 D. *J Refract Surg.* 2008;24:516–523.