

1-2016

On the probability summation model for laser-damage thresholds

Clifton D. Clark

Fort Hays State University, cdclark@fhsu.edu

Gavin D. Buffington

Fort Hays State University, gbuffing@fhsu.edu

Follow this and additional works at: http://scholars.fhsu.edu/physics_facpub



Part of the [Physics Commons](#)

Recommended Citation

Clark, Clifton D. and Buffington, Gavin D., "On the probability summation model for laser-damage thresholds" (2016). *Physics Faculty Papers*. Paper 1.

http://scholars.fhsu.edu/physics_facpub/1

This Article is brought to you for free and open access by the Physics at FHSU Scholars Repository. It has been accepted for inclusion in Physics Faculty Papers by an authorized administrator of FHSU Scholars Repository.

Journal of Biomedical Optics

BiomedicalOptics.SPIEDigitalLibrary.org

On the probability summation model for laser-damage thresholds

Clifton D. Clark, III
Gavin D. Buffington

SPIE.

On the probability summation model for laser-damage thresholds

Clifton D. Clark III* and Gavin D. Buffington

Fort Hays State University, Department of Physics, 600 Park Street, Hays, Kansas 67601, United States

Abstract. This paper explores the probability summation model in an attempt to provide insight to the model's utility and ultimately its validity. The model is a statistical description of multiple-pulse (MP) damage trends. It computes the probability of n pulses causing damage from knowledge of the single-pulse dose–response curve. Recently, the model has been used to make a connection between the observed $n^{-1/4}$ trends in MP damage thresholds for short pulses ($<10 \mu\text{s}$) and experimental uncertainties, suggesting that the observed trend is an artifact of experimental methods. We will consider the correct application of the model in this case. We also apply this model to the spot-size dependence of short pulse damage thresholds, which has not been done previously. Our results predict that the damage threshold trends with respect to the irradiated area should be similar to the MP damage threshold trends, and that observed spot-size dependence for short pulses seems to display this trend, which cannot be accounted for by the thermal models. © The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: 10.1117/1.JBO.21.1.015006]

Keywords: laser damage modeling; multiple-pulse exposures; probability summation model; microcavitation.

Paper 150411RR received Jun. 18, 2015; accepted for publication Dec. 17, 2015; published online Jan. 18, 2016.

1 Introduction

The probability summation model (PSM) provides a statistical description of multiple-pulse (MP) damage.¹ In recent years, it has been increasingly used to analyze the observed reduction in damage threshold with multiple short ($<10 \mu\text{s}$) pulses, which cause damage by producing a microcavitation bubble, and the apparent independence of this reduction on the duty cycle. It has been shown that, for short pulses, this model can provide an explanation for the observed $n^{-1/4}$ MP ED_{50} trends.

In this paper, we develop the application of the PSM to laser-damage thresholds in greater detail than in previous works and consider the consequences of assuming its validity. We do not attempt to prove or disprove the model, rather we develop a set of predictions that must all be considered when using or assessing the model against experimental data. The model has been used to make a connection between the $n^{-1/4}$ trend and experimental uncertainties,^{2,3} which we wish to address. We will also show that the model can account for the dependence of the MP ED_{50} trends on spot size and that it may also provide an explanation for the single, short-pulse ED_{50} dependence on spot size.

Important note: The PSM relates the dose–response curve for a single pulse (SP) to the dose–response curve for MPs, and this paper contains a great deal of discussion about dose–response curves and their shape. One very important property of a dose–response curve is its “sharpness,” i.e., the difference between a dose for which damage is virtually impossible and a dose for which damage is virtually guaranteed. Unfortunately, there are two quantities that are in common use to characterize this property, and both are often called “slope.” The first definition, which is used in this paper and denoted as SL, refers to the slope of the best fit line obtained with probit analysis. The second

definition is the ratio of the ED_{84} over the ED_{50} ($s = \text{ED}_{84}/\text{ED}_{50}$). For our definition, a “large slope” corresponds to a steep dose–response curve. For example, in Fig. 1, the slope of the dose–response curves is increasing from right to left. For log-normal dose–response curves, the two are directly related and one can be obtained from the other $\text{SL} = \frac{1}{\log(\text{ED}_{84}/\text{ED}_{50})}$.⁴

2 Model

The PSM refers to a statistical-based description of MP laser exposures first proposed by Menendez et al.¹ The model is based on the assumption that MPs in a laser exposure are statistically independent events, so that the probability of the exposure causing damage is given by the cumulative probability of any SP causing damage. Let p_i be the probability that the i 'th pulse in the exposure causes damage. The total probability that damage is caused during the exposure is given by

$$P = 1 - [(1 - p_1)(1 - p_2) \cdots (1 - p_n)]. \quad (1)$$

In general, each p_i may be different. In the case of identical pulses, each pulse has the same probability of causing damage ($p_i = p$), and the total damage probability simplifies to

$$P = 1 - (1 - p)^n. \quad (2)$$

The probability of an SP resulting in damage depends on the dose administered, so the probability, p , will depend on the dose, $p \rightarrow p(d)$. The total probability, P , of damage occurring will also depend on dose, $P \rightarrow P(d)$. Note that this is the dose delivered in an SP, so the MP exposure is expressed as a dose per pulse (i.e., energy/pulse or peak power). Equation (2) is just the relation between the dose–response curve of an SP to the dose–response curve of n pulses. Figure 1 illustrates this for the log-normal distribution that is used in laser retinal damage threshold experiments.

*Address all correspondence to: Clifton D. Clark III, E-mail: cdclark@mail.fhsu.edu

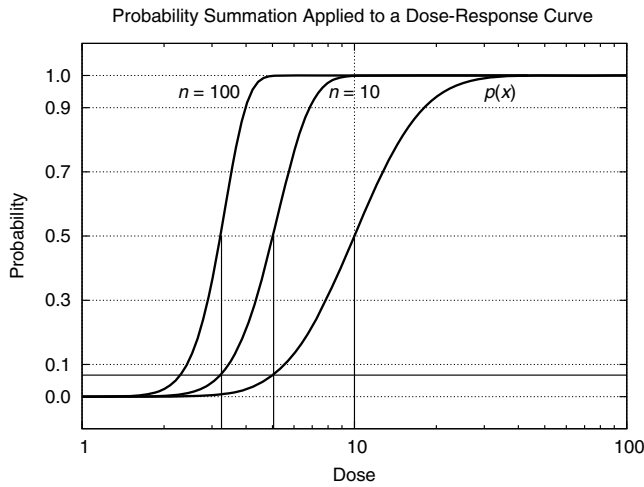


Fig. 1 Two multiple-pulse (MPE) dose–response curves (for 10 and 100 pulses) generated by probability summation applied to the same SP dose–response curve. Note that the ED_{50} for 10 pulses is equal to the ED_6 for an SP and that the ED_{50} for 100 pulses is equal to the ED_6 for 10 pulses. This shows that the 100-pulse dose–response curve can also be produced by applying probability summation to the 10-pulse dose–response curve since a 100-pulse exposure can be treated as 10 10-pulse exposures.

In their original paper, Menendez et al.¹ considered the PSM as a test for statistical independence of multiple exposures separated by space or time. The idea is that one can compare actual damage threshold trends for MP exposures to the predictions of the PSM to identify interaction effects between pulses and even determine if a positive (sensitizing) or negative (desensitizing) effect exists. Lund⁵ has suggested that the discovery of the microcavitation damage mechanism has provided a physical justification for the statistical independence assumption made by the PSM. The probability of damage occurring is just the probability of a microcavitation event occurring and therefore does not depend on the thermal addition between pulses.

2.1 Link to Single-Pulse Dose–Response Curve

Solving Eq. (2) for p ,

$$p = 1 - (1 - P)^{1/n}, \quad (3)$$

gives the SP damage probability required to cause a given MP damage probability for n pulses. By definition, the ED_{50} dose will elicit a response in 50% of the population. In order for an MP exposure to have a 50% probability of producing damage, it is necessary for the probability of any SP in the exposure to have less than a 50% chance of causing damage. Setting $P = 0.5$ gives

$$p = 1 - (0.5)^{1/n}, \quad (4)$$

which relates the SP dose–response curve to the MP ED_{50} trends.

Equations (2–4) hold, in general, for exposures consisting of identical pulses, regardless of the specific dose–response curves used for p and P . A particularly interesting feature of Eq. (4) is that it suggests that the SP dose–response curve could be determined by measurement of the MP ED_{50} . For example, $n = 4$ gives $p = 0.16$, so the ED_{50} for a four-pulse exposure

corresponds to the ED_{16} for an SP exposure. Assuming a log-normal response, the SP probit slope can be calculated from these values since,⁴

$$SL = 1 / \log(ED_{84}/ED_{50}) = 1 / \log(ED_{50}/ED_{16}). \quad (5)$$

2.2 Application to Spot Size Dependence

Menendez et al.¹ mentioned that the PSM would also apply to exposures separated in space as well as time. The authors were referring to separate laser exposures to different areas of the retina, but the model can also be applied to the spatial distribution of a single exposure. An irradiated area can be considered as a collection of smaller subareas. If each subarea within the irradiated area is statistically independent from the others, then the probability of damage occurring at each subarea will sum to give the net probability of damage occurring. This requirement of statistical independence certainly does not exist for long exposures in which heat can conduct through the irradiated volume. But, if the exposure time is short enough, such that heat does not have time to conduct through the volume during the exposure, then these points can be considered statistically independent from each other during the time of the exposure. It is generally accepted that microcavitation causes damage for exposure durations $<10 \mu\text{s}$ and that heat does not significantly conduct through the irradiated volume during this time.

Therefore, if a laser exposure covers an area A that contains m possible microcavitation sites, the probability of the exposure causing damage should just be the probability that one of the sites produces microcavitation. Assuming that the density, σ , of microcavitation “seeds” (sites which are capable of producing microcavitation) is uniform, the number of seeds exposed by a uniform laser beam with area A will be $m = \sigma A$. The probability of damage occurring within the irradiated area will be

$$P = 1 - (1 - p)^{\sigma A}, \quad (6)$$

where now p represents the probability of a single microcavitation seed responding to the dose. Note that here the exposure is expressed as a dose per area (i.e., retinal radiant exposure or retinal irradiance). This is identical to the MP case except that n has been replaced with σA . We would expect the dependence of the ED_{50} on the irradiated area to be similar to the dependence on MPs. In fact, for every spot size, there should be an “effective pulse number” that produces the same ED_{50} , when expressed as an irradiance. The exact relationship between A and n will depend on the microcavitation seed density σ .

2.2.1 Nonuniform beams

For nonuniform beam profiles, Eq. (6) must be modified since microcavitation seeds at different positions in the beam will receive different doses. We start by breaking the irradiated area into N elements. Let the area of the j 'th element be denoted as a_j . The partitioning of the elements is arbitrary, we only require that the dose delivered to the j 'th element, d_j , be uniform over the element. Circular beams, for example, could be broken up into thin rings.

The probability of damage occurring within the j 'th element is then given by Eq. (6),

$$P_j = 1 - (1 - p(d_j))^{\sigma a_j},$$

and the total probability of damage occurring within the irradiated area is given by Eq. (1):

$$P = 1 - \prod_j^N (1 - P_j) = 1 - \exp\left(\sum_j^N \ln(1 - P_j)\right) \\ = 1 - \exp\left(\sum_j^N \sigma a_j \ln(1 - p(d_j))\right). \quad (7)$$

This gives the probability of an exposure causing damage based on the dose–response curve of a single microcavitation seed and is the most general case. If all elements are exposed to the same dose, $d_j = d$, then Eq. (7) reduces to Eq. (6).

Consider the important case of a circular Gaussian beam profile:

$$d = H(r) = H_0 e^{-r^2/\omega^2}, \quad (8)$$

where H_0 is the peak radiant exposure and ω is the $1/e$ beam radius. We break the irradiated area up into thin circular rings of thickness Δr , each with a radius r_j and area $a_j = 2\pi r_j \Delta r$. The probability of damage occurring then is

$$P = 1 - \exp\left(\sigma 2\pi \Delta r \sum_j^N r_j \ln(1 - p(H_0 e^{-r_j^2/\omega^2}))\right). \quad (9)$$

To obtain a threshold from this probability, we would need to numerically evaluate this summation for multiple values of H_0 until the value producing $P = 0.5$ is found. This will depend on the value of ω ; therefore, the threshold will depend on the beam diameter. However, we do not consider this case any further in this work.

2.3 Effect on Probit Slope

A closer look at Eq. (3) indicates that the dose–response curve will become sharper with more pulses. For log-normal distributions, the probit slope is given by Eq. (5). If we consider the case of $n = 4$, then the SP ED_{16} gives the MP ED_{50} , and the SP ED_{37} gives the MP ED_{84} . Therefore,

$$\frac{MP:ED_{84}}{MP:ED_{50}} = \frac{SP:ED_{37}}{SP:ED_{16}} < \frac{SP:ED_{50}}{SP:ED_{16}} = \frac{SP:ED_{84}}{SP:ED_{50}}, \quad (10)$$

and the MP slope must be larger than the SP slope:

$$MP:SL = \frac{1}{\log\left(\frac{MP:ED_{84}}{MP:ED_{50}}\right)} > \frac{1}{\log\left(\frac{SP:ED_{84}}{SP:ED_{50}}\right)} = SP:SL. \quad (11)$$

This is also seen in Fig. 1, where the dose–response curves for 10 and 100 pulses become “sharper,” indicating a larger slope. The slopes for the three curves shown are 5.0, 9.4, and 13.6 for the $n = 1, 10,$ and 100 cases. Equation (3) also applies to the spot-size dependence, so the probit slope for larger beams should be greater than the slope for smaller beam, based on the PSM.

3 Discussion

We will now apply the PSM to a few problems in laser retinal damage. This model can only be applied to short-pulse cases, when microcavitation is responsible for the damage threshold,

where the assumption of statistical independence is valid. For longer pulses, significant interaction occurs between exposures separated by space and time due to heat conduction. Thermal models, based on the Arrhenius damage model, are well established and can correctly predict the damage thresholds for these longer exposures. We will note that the PSM and Arrhenius model make different predictions for the damage threshold trends, which could be used to identify when microcavitation is in play, as is done when identifying photochemical damage.⁶ A subtle but important point is that the PSM cannot predict the damage threshold for a single data point as the Arrhenius damage model can. Rather, it can only predict the damage threshold trends.

3.1 Probit Slope for Small-Spot In-Vivo Data

Note: In this section, we will use “actual” and “measured” to refer to the true physical value of a statistical quantity and the value obtained for the quantity by measurements, respectively. The measured value is an approximation of the actual value.

We have shown in Sec. 2.1, that the slope of the SP dose–response curve is directly related to the MP ED_{50} trends. For example, based on Eqs. (5) and (10), the ED_{50} for a four-pulse exposure could be written in terms of the SP slope directly:

$$MP:ED_{50}(n = 4) = SP:ED_{50} 10^{-1/SL}. \quad (12)$$

If the dose–response curve is very sharp, then the MP reduction will be very small. This is shown in Fig. 2, where the MP reduction based on a slope of one is much greater than the reduction based on a slope of 20. Lund^{5,7} has shown that the PSM can be used to derive the $n^{-1/4}$ trend that has been repeatedly observed. The PSM predicts (after a few approximations) that the MP ED_{50} trend should be $n^{-1/\beta}$, where β is the SP dose–response slope minus 1 ($\beta = SL - 1$). Based on the measured slopes from several (small-spot) data sets, Lund concluded that the most probable value for SL is five, which gives the $n^{-1/4}$ trend that is observed.

Sliney and Lund^{3,7} have argued that the observed $n^{-1/4}$ trend may simply be an artifact of experimental method. They have stated that the PSM supports this based on the relationship

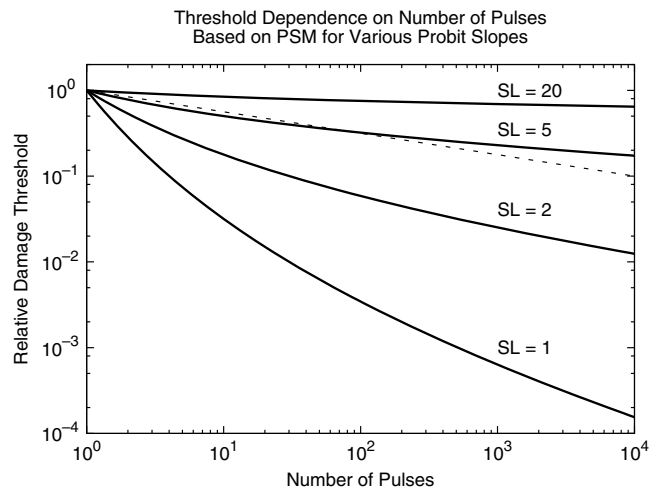


Fig. 2 The MP damage threshold reduction predicted by the PSM applied to log-normal dose–response curves with various slopes. The reduction is greatest when the slope is small and diminishes for larger slopes. Dashed line indicates the $n^{-1/4}$ trend.

between the SP probit slope and the MP reduction. However, this specific claim (involving the PSM) is invalid, and we wish to correct it here.

They argue that it is very difficult to detect small retinal lesions in the eye and that because of this, the SP dose–response curve for small-spot exposures is affected by experimental uncertainties more so than large-spot exposures. Experimental uncertainties will cause a measured dose–response curve to have a lower probit slope (and higher ED_{50}) than the actual dose–response curve.⁸ They point to the large-spot *in-vivo* and small-spot explant data in which both have larger probit slopes and smaller MP effects, as evidence that the small-spot *in-vivo* MP reduction would be much smaller if the actual probit slope could be measured.^{3,7} However, if a measured probit slope is smaller than the actual probit slope, it does not follow that the observed MP reduction would be larger.

The PSM determines the actual MP dose–response curve from the actual SP dose–response curve because it is the actual probabilities that are being summed. Equation (2) is a relationship between the underlying probability distributions. Experimental uncertainties limit the ability to observe these underlying distributions, but they do not change this relationship. Therefore, one cannot suggest that if the actual SP probit slope was determined, β would be larger and the observed MP reduction would be smaller. If anything, the PSM would suggest that the actual probit slope is small based on the observed MP reduction.

For example, imagine that two different methods are used to observe the same experiment in which the SP damage threshold and the 1000-pulse damage threshold are measured. One includes significant experimental uncertainties, the other does not. The two methods will not agree on the ED_{50} values for each exposure, the inaccurate method will measure a higher ED_{50} for both the SP and 1000-pulse exposures. However, the actual ED_{50} does not depend on the measurement method and is the same for both methods. Now assume that the accurate method measures no difference between the SP and 1000-pulse ED_{50} . We would not expect the inaccurate method to measure a significant decrease in the 1000-pulse ED_{50} simply because the probit slope obtained by it for the SP exposure is small.

At this point, we would like to explicitly state that we are not disputing the conclusions of Lund and Sliney,^{3,7} specifically that the observed MP reduction in small-spot *in-vivo* data is an effect caused by the difficulty in observing small-spot lesions. We only wish to clarify that the PSM does not play a role in this. The problem is that this would not be a probit-slope effect but an ED_{50} effect. In the example given above, Lund and Sliney² would argue that the inaccurate method will not measure a significant decrease in the 1000-pulse ED_{50} , but instead will measure a significant increase in the SP ED_{50} . Therefore, it will appear as if a significant reduction in threshold has occurred from an SP exposure to a 1000-pulse exposure, even if none exists.

If this is in fact the case, then the MP effect is caused by the inability to detect small lesions causing measured ED_{50} values to be larger than the actual values. The continued reduction in ED_{50} with more pulses must be due to an increased ability to detect lesions (so that the measured ED_{50} is closer to the actual, lower ED_{50}) and the apparent connection between the small-spot *in-vivo* probit slope and $n^{-1/4}$ is purely coincidental.

Finally, we note that the PSM predicts that the actual probit slope for MP dose–response curves should increase with the

number of pulses, but it does not require that the measured slope do so. Again, experimental uncertainties may severely limit the ability to measure an accurate slope, but the PSM will still predict a decrease in ED_{50} based on the actual SP probit slope. If, on the other hand, the experimental uncertainties are directly responsible for the MP reduction, then the measured probit slope would necessarily depend on the number of pulses. Any observed decrease in ED_{50} due to an increased lesion visibility should be accompanied by an increase in probit slope. It would be interesting to examine the MP dependence of the measured probit slope to see if a strong correlation has been observed.

3.2 Single-Pulse Threshold Dependence on Spot Size

The dependence of the SP ED_{50} on spot size should be similar to that of MPs, but direct application of the PSM is more difficult. Equation (6) requires both the dose–response curve for a single microcavitation seed ($\sigma A = 1$) and the microcavitation seed density (σ) to be known.

However, just as a 100-pulse exposure can be treated as ten 10-pulse exposures, an irradiated area can be treated as multiple smaller irradiated areas. And just as the PSM can be applied to the 10-pulse dose–response curve to produce the 100-pulse dose–response curve, we can apply the PSM to the dose–response curve for any irradiated area to produce the dose–response curve for larger irradiated areas.

Let A_0 be some irradiated area for which the dose–response curve, $P_0(d)$, has been measured. From Eq. (6), we get:

$$P_0(d) = 1 - (1 - p(d))^{\sigma A_0}. \quad (13)$$

The dose–response curve for larger areas, $A = \alpha A_0$, based on the PSM will be

$$P(d) = 1 - (1 - P_0(d))^\alpha, \quad (14)$$

which can be checked by plugging Eq. (13) into Eq. (14) to obtain Eq. (6). The area A_0 cannot be smaller than the area containing a single microcavitation seed, but this should not present a problem in practice. The microcavitation seeds are most likely melanin granules in the retinal pigment epithelium cells and Thompson et al.⁹ noted that the melanin granule density is probably >100 granule/cell for a $20 \times 20 \times 15 \mu\text{m}$ cell based on their melanin granule thermal model. So, even a $25 \mu\text{m}$ diameter beam should irradiate hundreds of granules.

Figure 3 shows the threshold dependence on irradiated diameter, based on the PSM, for uniform beam profiles (flat top). However, an interesting comparison to experiment can be made if we follow the work of Menendez¹ and Lund^{5,7} to derive a “correction factor” for the irradiated diameter analogous to the MP $n^{-1/4}$ correction factor. Starting with Eq. (6) and applying the approximations used by Menendez and Lund leads to the following relationship:

$$ED_{50}(A) \approx ED_{50}(A_0) \left(\frac{2}{A_0} \right)^{-1/\beta} A^{-1/\beta}, \quad (15)$$

where β is related to the slope of the probit curve for the irradiated area A_0 , $\beta = \text{SL} - 1$. The value of β implicitly depends on σ , because the value of the probit slope will depend on σ . If σ

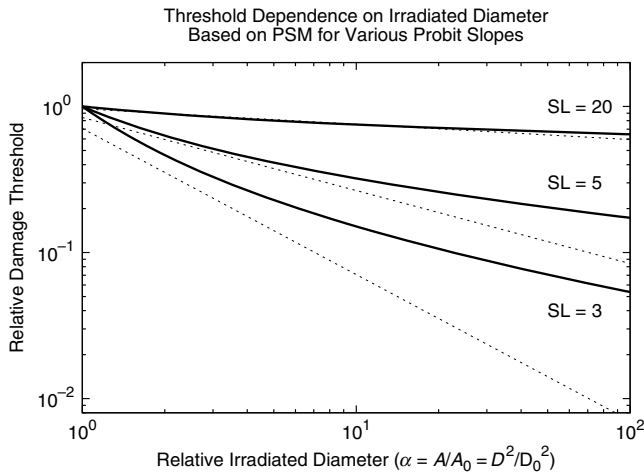


Fig. 3 The threshold dependence on irradiated diameter, predicted by the PSM applied to log-normal dose–response curves with various slopes. Note that the x axis is the relative diameter, for a 25 μm baseline, the right end of the x axis would correspond to 2500 μm . Dashed lines indicate the correction factor approximation from Eq. (15) for each slope.

is very large, then Eq. (6) indicates that the slope will be very large.

Lund et al.¹⁰ re-examined the relationship between the damage threshold retinal radiant exposure (J cm^{-2}) and retinal irradiated area, analyzing all available data in the literature, and noted that thermal models could not account for the threshold dependence on irradiated area for short pulses ($<20 \mu\text{s}$). For thermal damage, the threshold retinal radiant exposure is expected to increase for smaller beams because heat can conduct out of the irradiated volume. However, if the energy is delivered in a shorter time than it takes heat to conduct out (the thermal confinement time), there should be no increase in threshold for small beams. The experimental data examined by Lund indicate that the retinal radiant exposure threshold does increase for smaller irradiated areas, even for very short exposure times.

This is puzzling, even though we now expect the damage to be caused by microcavitation, because for short-pulse exposures, there should not be enough time for the exposure at the edge of an irradiated area to influence the threshold at the center of the irradiated area. The threshold for causing microcavitation at the center of the area should not depend on the size of the area. The PSM may provide an explanation for this, which is that the probability of damage occurring at the center of the area does not increase, but that the overall probability of damage occurring somewhere in the beam does.

In their re-examination, Lund et al.¹⁰ showed that if the damage thresholds, expressed as a radiant exposure, were plotted versus irradiated diameter on a log-log plot, then a linear line could be fit to most datasets. In other words, each dataset could be approximated by the equation $H_r = kD^S$, where H_r is the threshold radiant exposure at the retina and D is the retinal irradiance diameter. S is the slope of the best fit line, on log-log scale, and the value of S that best fit each set depended on the exposure time. Longer exposure times tended to have a large negative value (indicating a large decrease in threshold with increasing diameter) while shorter exposure times tended to have a smaller negative value (indicating a small decrease in threshold with increasing diameter).

For pulses longer than 20 μs , the value of S for any given exposure time was approximated well by the function $S(t) = (-0.233 \log(t) + 1)$. However, for pulses shorter than 20 μs , no such trend appeared. In addition, the dependence on retinal irradiated diameter for exposures longer than 20 μs was consistent with thermal model predictions, while the dependence for shorter exposures was not. The thermal model predicted no dependence on the irradiated diameter ($S = 0$), but the data showed a decrease in threshold with diameter ($S < 0$).

The observed threshold trends for exposure durations below 20 μs do not match the predictions made by thermal models because microcavitation is responsible for damage for these short times, and the PSM would apply. Rewriting the approximate function for H_r in terms of the retinal irradiance area A gives $H_r \propto A^{S/2}$. Comparing this to Eq. (15) implies that $-1/\beta = S/2$. The values for S observed by Lund et al.¹⁰ for exposures below 20 μs ranged between 0 and -1 . This would require the probit slope for P_0 in Eq. (14) to be 3 or greater. This is not a very narrow range but is certainly in the range of observed values. For example, a slope of 11 would give a value of $S = -0.2$. More important than the specific value of S is the fact that the damage threshold radiant exposure still depends on the irradiated diameter, even for short pulses where the thermal model predicts no dependence. Now, it should be noted that there are other possible explanations for this (for example, the minimum beam diameter may actually be much larger than is assumed), but this is consistent with the PSM.

Lund et al.¹⁰ also noted that the thermal model predictions agreed with the shorter pulse data better when the irradiated area was large but was increasingly less predictive for irradiance diameters $<100 \mu\text{m}$. This too is consistent with our understanding of microcavitation damage. It is still possible to cause thermal damage during short-pulse durations. It is just that the threshold for causing microcavitation is lower, and the observed damage threshold will be the lesser of the two. Therefore, if the thermal damage threshold (as a radiant exposure) is somehow lowered, it can be observed. This can be achieved by increasing the thermal relaxation time, the time it takes the irradiated tissue to cool back down after an exposure. Increasing the irradiated diameter will increase the thermal relaxation time, which can bring the thermal damage threshold below the microcavitation threshold. If the thermal relaxation time is increased, the thermal damage threshold will be observed at lower exposure durations.

3.3 Multiple-Pulse Thresholds for Large Spot Sizes

In the PSM, the reduction in ED_{50} for an MP exposure is directly related to the slope of the SP dose–response curve. If the (actual) slope of the SP dose–response curve increases, the MP reduction will be smaller.

The observed ED_{50} trends for large spot MP exposures exhibit this behavior. The MP effect on damage thresholds seems to be reduced for large spot size, and in some observations, there appears to be no reduction in the damage threshold.² The PSM provides an explanation for this. As the irradiated area increases, the SP dose–response curve will become more sharp (see Sec. 2.3), and the MP effect will decrease. Note that this prediction is counter to that of thermal damage models, which predict that the MP effect should be stronger for larger spot sizes.¹¹ This may provide an additional test (along with the independence of MP thresholds on duty cycle) to differentiate microcavitation and thermal damage mechanisms. The observed $n^{-1/4}$

trend was based on small-spot exposures (collimated beam into the eye), which are more likely to show an MP effect.

4 Conclusions

At this point, it is not certain that the PSM is valid. Our intention here is not to prove or disprove the model. Our primary objective is to communicate the correct application of the model to MP exposures, specifically the relationship between experimentally observed probit slopes and the MP reduction factors. In addition, we have developed a new application of the model to the threshold dependence on retinal spot size that, if the assumptions of the model are to be accepted, must also be considered. These predictions provide new ways in which the model can be tested in order to prove or disprove its validity. Observations suggesting that the model cannot describe the relationship between threshold and spot size would also suggest that the model cannot describe the relationship between threshold and number of pulses.

In summary, if one assumes that the PSM is valid, then the following predictions must be taken into consideration for short pulse exposures:

- The actual slope of the probit curve should increase with spot size.
- The actual slope of the probit curve should increase with MPs.
- The MP effect, i.e., a reduction in the damage threshold with MPs, should diminish for larger spot sizes.
- The retinal radiant exposure required to cause damage can decrease when the irradiated area is increased, even for cases that the thermal models do not predict a decrease.

The model's application to retinal spot size requires a more detailed investigation. A large amount of experimental data already exists for this. We have found that the model predictions are generally consistent with the data, but a more thorough comparison of model predictions to this data is needed. There are many unknowns that must be considered in this analysis, such as the microcavitation "seed" density and the effects of nonuniform beam profiles. One important factor that must be considered is the choice of dose–response curve. The use of the log-normal distribution is standard for laser-damage experiments, but it is possible to use other distributions (such as the logit distribution). Slight changes to the dose–response curve can cause significant changes to the predicted threshold trends. All of this work is important and will need to be addressed in the future.

Acknowledgments

The authors would like to thank Shawn Denton and Sheila Clark for help with editing this paper.

References

1. A. R. Menendez et al., "Probability-summation model of multiple laser-exposure effects," *Health Phys.* **65**, 523–528 (1993).
2. D. J. Lund and D. H. Sliney, "A new understanding of multiple-pulsed laser-induced retinal injury thresholds," *Health Phys.* **106**, 505–515 (2014).
3. D. H. Sliney and D. J. Lund, "Do we over-state the risk of multiple pulsed exposures?," in *ILSC Conf. Proceedings*, pp. 93–98 (2009).
4. B. J. Lund, "The probitfit program to analyze data from laser damage threshold studies," Technical Report, United States Army Medical Detachment (2006).
5. D. J. Lund, "Repetitive pulses and laser-induced retinal injury thresholds," *Proc. SPIE* **6426**, 642625 (2007).
6. M. L. Denton et al., "In-vitro retinal model reveals a sharp transition between laser damage mechanisms," *J. Biomed. Opt.* **15**(3), 030512 (2010).
7. B. J. Lund, D. J. Lund, and P. R. Edsall, "Damage threshold from large retinal spot size repetitive-pulse laser exposures," *Health Phys.* **107**, 292–299 (2014).
8. D. Sliney and M. Wolbarsht, *Safety with Lasers and Other Optical Sources: A Comprehensive Handbook*, 4th ed., Plenum Press, New York (1985).
9. C. R. Thompson et al., "Melanin granule model for laser-induced thermal damage in the retina," *Bull. Math. Biol.* **58**(3), 513–553 (1996).
10. D. J. Lund et al., "Laser-induced retinal injury thresholds: variation with retinal irradiated area," *Proc. SPIE* **5688**, 469–478 (2005).
11. C. D. Clark, III, Micael L. Denton, and Robert J. Thomas, "Mathematical model that describes the transition from thermal to photochemical damage in retinal pigment epithelial cell culture," *J. Biomed. Opt.* **16**, 020504 (2011).

Clifton D. Clark III is an assistant professor at Fort Hays State University (FHSU). He received his BS in physics from FHSU in 2004. After graduating, he began working in the United States Air Force's directed energy bioeffects research lab in San Antonio, TX, as a contractor. He received his MS and PhD degrees in physics from the University of Texas at San Antonio in 2008 and 2011, respectively. He has been a faculty member in the Department of Physics at FHSU since 2011. His current research interests include modeling damage mechanisms in the retina and laser propagation in the eye.

Gavin D. Buffington is a professor at Fort Hays State University (FHSU), where he has been a member of the Department of Physics faculty since 1997. He received his BS and MS in physics from Pittsburg State University in 1989 and 1991, respectively. He received his PhD in physics from the University of Missouri-Rolla in 1997. His PhD research was focused on atomic physics, but he began working on computational laser bioeffects soon after arriving at FHSU.