Broadband radiometry for photodynamic therapy

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ABSTRACT

The effective irradiance is a useful measure to compare performances of different broadband light sources and to more precisely predict the outcome of a topical photodynamic therapy. The effective irradiance (or effective fluence rate) and the exposition time of the optical radiation usually determine the light dose. The effective irradiance (E_{eff}) takes into account the spectral irradiance of the source as well as the action spectrum, where the wavelength dependence of both optical diffusion through tissue and photosensitizer are considered. In practice there are no standard action spectra for the currently used photosensitizers. As a consequence, measured values of effective irradiance using different action spectra can not be compared. In order to solve this problem, the basis of the calibration theory developed for the broadband ultraviolet radiometry can be applied, where an experimental radiometer is compared with a standard radiometer. Here is presented a simple set of linear relations in the form $E_{eff} = k \,.\, E$, where E is the source irradiance and k a real positive value, here denoted as a characteristic of the radiometer, as valuable tools for correction of effective irradiances measured according to different action spectra. As a result, for two effective radiometers with different characteristics k_1 and k_2, measured values are E_{eff} and Q_{eff} respectively, and it is easily shown that the value $E_{eff} = Q_{eff} \cdot k_1 / k_2$.

Keywords: Effective irradiance, Effective light dose, PDT radiometry

1. INTRODUCTION

Topical photodynamic therapy (PDT) is an effective treatment of a class of skin cancers.[1,2] For this purpose clinical protocols have been suggested in terms of the drug dose, the time interval drug-illumination and of the irradiance or radiant exposure, among other parameters.[1,2]

While the concept of drug dose is well established for pharmacology, the same is not valid for the light dose, where the spectral irradiance (or the spectral radiant exposure) of the light source and the action spectrum should be considered. The action spectrum is the spectrum of interest.[3] Here the spectrum of interest is related to the spectral dependence of the process (drug photo-activation). In this way the effective exposure, defined as the (spectrally) integrated spectral radiant exposure, weighted by the action spectrum is a measure for the photon dose.[3]

The action spectrum should take into account the spectral dependence of both light propagation through tissue and absorption by the photosensitizer.[4]

In practice there is no standard action spectrum even for a particular photosensitizer and application and frequently the light dose is approximated by the incident radiant exposure. As a consequence, light dose comparison from different studies is not possible.[1]

Here we adapted to the PDT radiometry, the basis of the broadband radiometry, firstly established to the photometry and further developed to the ultraviolet radiometry. As a consequence, a set of relevant parameters intended to characterize the light source and the radiometer is suggested, making it possible comparisons of light doses from different studies.

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2. BROADBAND RADIOMETRY: THEORETICAL BASIS

The effective irradiance in a certain distance from a source S1 (E_{eff1}) is a radiometric quantity defined as

$$E_{eff1} = \int_0^\infty S_p(\lambda) \cdot E_1(\lambda) d\lambda \tag{1}$$

where $S_p(\lambda)$ is the action spectrum (usually normalized for maximum value equal to one), and $E_1(\lambda)$ is the spectral irradiance of the light source S1 in absolute values, usually expressed in W/(cm^2.nm).

There is not a unique definition for the action spectrum yet. However, a desirable possibility is $S_p(\lambda)$ meaning the efficiency of singlet oxygen formation when photosensitizer is irradiated. In this case it was suggested an approach where $S_p(\lambda)$ considers the excitation spectrum of the photosensitizer and the relative irradiance as a function of tissue depth.[4]

In order to measure the effective irradiance, a spectroradiometer can be used (to know the spectral irradiance), and then one can calculate E_{eff1} using the Equation (1). Nevertheless, a radiometer is frequently used, whose spectral response should follow $S_p(\lambda)$, where the construction is less expensive and more robust.

Usually a specific radiometer to measure the effective irradiance is constructed using an approximation of $S_p(\lambda)$ (due to limitations of current technology to construct optical filters), here expressed as $S_a(\lambda)$ (also normalized), and give as output a quantity Q proportional to E_{eff1} . In this case there is an error in measuring the effective irradiance, although it is possible to calibrate the radiometer, correcting this kind of error[5], using the relation

$$c_1 = \frac{Q}{E_{eff1}} = \frac{Q}{\int_0^\infty S_p(\lambda) \cdot E_1(\lambda) d\lambda} \tag{2}$$

or

$$c_1 = \frac{\int_0^\infty S_a(\lambda) \cdot E_1(\lambda) d\lambda}{\int_0^\infty S_p(\lambda) \cdot E_1(\lambda) d\lambda} \ . \tag{3}$$

where c_1 is a calibration factor.

In order to calibrate a radiometer according to the Equation (2), it is necessary to measure or to know the spectral irradiance of the source S1. To calibrate a radiometer according to the Equation (3), it is necessary to measure or to know $S_a(\lambda)$ and $E_1(\lambda)$, or alternatively to know the relative spectral irradiance of the source and the spectral responsivity of the detector in absolute values.[6]

According to the Equation (2) or (3), a detector can be calibrated (resulting in no error) by using any responsivity $S_a(\lambda)$, even if $S_p(\lambda)\cdot S_a(\lambda)=0$ (there is no overlap). However, the calibration is only valid to measure sources that have the same spectrum used for calibration.

In the case the same detector, with action spectrum $S_a(\lambda)$, measures a source S2, with spectral irradiance $E_2(\lambda)$, the Equation (3) result c_2 and

$$\frac{c_1}{c_2}=\frac{\int_0^\infty S_a(\lambda)\cdot E_1(\lambda)d\lambda\cdot\int_0^\infty S_p(\lambda)\cdot E_2(\lambda)d\lambda}{\int_0^\infty S_p(\lambda)\cdot E_1(\lambda)d\lambda\cdot\int_0^\infty S_a(\lambda)\cdot E_2(\lambda)d\lambda}=c_3 \quad . \tag{4}$$

It must be noticed in the Equation (4) that, to compute the value c_3, there is no need to know absolute values. That is, the constant c_3 can be calculated from the relative values of spectral irradiances and action spectra. Thus, the measurement of the effective irradiance from a source S2 made with a detector with an approximate action spectrum $S_a(\lambda)$ and calibrated to the source S1 can be obtained by multiplying the value measured by c_3.

The Equations (2) and (3) have been used as the basis of radiometric calibration and the Equation (4) has been used to transfer the calibration of a radiometer calibrated with a particular source to measure another source.[5,6] Thus, the principles of broadband ultraviolet radiometry available in the literature can be applied to PDT radiometry.

In the sequence, a new approach to broadband radiometry will be presented, where the relation between the source irradiance and radiometer output is evident, and not between detectors responses as above. The new approach facilitates the understanding of the calibration theory and calibration transference to another source. The approach also sets the following: i) the error due to mismatch in the action spectrum of a detector (useful to know the impact on the measurements when the action spectrum changes) and ii) the error when a detector (with an approximated action spectrum) measures a source with a spectral irradiance different of that used for the calibration (useful for quantifying this common kind of error).

Considering the cases when the spectral irradiance of a source or the action spectrum (or both) has limited spectral support (functions are limited in the range $\lambda_1 \le \lambda \le \lambda_2$ and zero elsewhere), then the Equation (1) can be expressed as

$$E_{eff1}=\int_{\lambda 1}^{\lambda 2} S_p(\lambda)\cdot E_1(\lambda)d\lambda \ . \tag{5}$$

Considering, for a moment, that $S_a(\lambda)=1$ into the range $\lambda_1 \le \lambda \le \lambda_2$ and zero elsewhere, the denominator in the Equation (3) becomes

$$\int_{\lambda 1}^{\lambda 2} S_a(\lambda)\cdot E_1(\lambda)d\lambda = E_1 \tag{6}$$

where E_1 is the source irradiance S1 in the range $\lambda_1 \le \lambda \le \lambda_2$, and the Equation (3) can be expressed as

$$k_{p,S1} = \frac{\int_{\lambda 1}^{\lambda 2} S_p(\lambda)\cdot E_1(\lambda)\, d\lambda}{\int_{\lambda 1}^{\lambda 2} E_1(\lambda)\, d\lambda} = \frac{E_{eff1}}{E_1} \tag{7}$$

where $k_{p,S1}$ is a constant for the source S1, here denoted as characteristic of the detector for the source S1, meaning the useful fraction of the irradiance of the source S1, and assumes values in the range $0 \le k_{p,S1} \le 1$. Similarly, for a detector with an approximate action spectrum, the Equation (7) can be rewritten as

$$Q_1 = \int_{\lambda 1}^{\lambda 2} S_a(\lambda)\cdot E_1(\lambda)\, d\lambda = k_{a,S1}\cdot E_1 \tag{8}$$

where Q_1 is the irradiance of the source S1 when measured with a detector with an approximate action spectrum. Combining the Equations (7) and (8) we obtain

$$E_{eff1} = \frac{k_{p,S1}}{k_{a,S1}}\cdot Q_1 \tag{9}$$

i.e., a measurement made with a detector with an approximated action spectrum can be corrected according to the Equation (9), as long as the source spectral irradiance is the same.

Using the Equations (7) and (8), it is possible to express the relative error in percentage $\varepsilon(\%)$ in a measurement of a source due to the mismatch of the approximated action spectrum as

$$\varepsilon(\%) = \left|\frac{E_{eff1} - Q_1}{E_{eff1}}\right|\cdot 100 = \left|1 - \frac{k_{a,S1}}{k_{p,S1}}\right|\cdot 100 \tag{10}$$

The error expressed in the Equation (10) is corrected when a radiometer is calibrated. However, the calibration expressed in the Equation (9) is valid only when the spectra of both calibration and target light sources are the same. For a radiometer with an approximate action spectrum, calibrated with a source S1, to be used to measure a source S2 with different spectrum, another correction is required, as follows.

For a source S2, the Equation (9) becomes

$$E_{eff2} = \frac{k_{p,S2}}{k_{a,S2}}\cdot Q_2 \tag{11}$$

where $E_{eff\,2}$ is the effective irradiance of a source S2 measured by a radiometer with characteristic $k_{p,S2}$ and Q_2 is the irradiance measured by a radiometer with characteristic $k_{a,S2}$ (approximated action spectrum).

Using the Equations (9) and (11), the transference function of the calibration of a radiometer with a calibration source S1 for measurements of a source S2 is

$$E_{eff\,2} = \frac{k_{a,S1} \cdot k_{p,S2}}{k_{p,S1} \cdot k_{a,S2}} \cdot Q_2 \tag{12}$$

Using the Equations (9) and (11), it is also possible to express the relative error in percentage $\varepsilon(\%)$ due to measurements of a source S2 using a radiometer with an approximated action spectrum calibrated with the source S1 (when the transference of calibration in the Equation (12) is not performed) as follow

$$\varepsilon(\%) = \left| 1 - \frac{k_{p,S1} \cdot k_{a,S2}}{k_{p,S2} \cdot k_{a,S1}} \right| \cdot 100 \tag{13}$$

Certainly, when the action spectrum of the detector is not approximated, the error expressed in the Equation (13) is zero for any source.

3. RECALIBRATION

Portable spectrometers equipped with linear sensors, integrated to personal computers, are now popular, making it possible to construct a calibrated spectroradiometer with a relative low cost. In this case the desired action spectrum could be numerically implemented by the end user for a specific application. However, radiometers are still largely used because they are more robust, easier to use and cheaper. Therefore, generally the spectral responsivity of a radiometer designed to the PDT radiometry and the desired action spectrum are not the same one. Thus, it is necessary to recalibrate the detector.

To exemplify a recalibration process, we considered the relative spectral responsivity $S_R(\lambda)$, showed in the Figure (1), from a radiometer R for the PDT radiometry (close to responsivity of the IL1400BL photometer equipped with a SEL033 detector head with a red filter, International Light Technologies, Peabody, Massachusetts, USA). The relative spectral irradiance $E_1(\lambda)$ shown in the Figure (1) is from a source standard S1 (OL 220, Optronics Laboratories Inc., Orlando, USA).

Consider the relative spectral irradiances $E_2(\lambda)$ and $E_3(\lambda)$, shown in the Figure (1), from two PDT irradiation sources, S2 and S3 respectively. Both sources are halogen lamps followed by dichoic filters (MSR 1200 and PAR30S-75W230-30 respectively, Philips B.V., Eindhoven, The Netherlands).

The efficiency spectrum $S_{PDT}(\lambda)$ shown in the Figure (1) is an approximation to the efficiency spectrum for ALA-PDT at 2mm depth to the treatment of the ulcered nodular basal cell carcinoma with normal oxygen level, as suggested by Nielsen K. P. *et al.*.[4] Here $S_{PDT}(\lambda)$ is approximated by a Gaussian function with maximum value equal to one at 630nm (meaning maximum efficiency for the considered depth) and bandwidth of 20nm (FWHM). The ALA absorption spectrum occupies a large spectral range, but other factors (hemoglobin and other chromophores) when considered, they result into a considerably narrow action spectrum that is the case of the action spectrum for the specific sensitizer, application and depth considered.

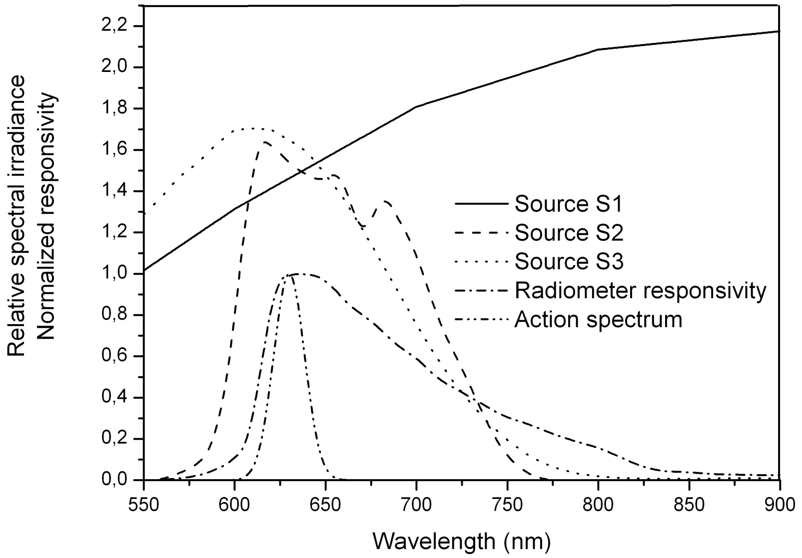

Figure 1: Spectral irradiances from a source standard S1, two PDT irradiance sources S2 and S3, spectral respoponsivity $S_R(\lambda)$ of a radiometer R and an action spectrum $S_{PDT}(\lambda)$ for a specific PDT treatment.

In this specific example, the goals are: a) to compute the resulting error when the radiometer R measures the sources S1, S2 and S3 and the desired action spectrum is $S_{PDT}(\lambda)$; b) to recalibrate the radiometer R against S1 for the desired action spectrum $S_{PDT}(\lambda)$; c) to transfer the recalibration in (b) to measure the source S2 and; d) to compute the resultant error when process (b) is not performed and S2 and S3 are measured, even if the process (a) is performed.

By using the Equations (7) and (8), the characteristic values (*k*) of the radiometer R with spectral responsivity $S_R(\lambda)$ and of a detector with spectral responsivity equal to the action spectrum $S_{PDT}(\lambda)$, for the sources S1, S2 and S3 are shown in the Table (1).

It must be noticed that for computation of the characteristic values (*k*) it is not necessary to know absolute values of either the spectral irradiances of the sources or the radiometer spectral responsivity. Only the respective relative values are needed (only the spectral shapes are required). The radiometer calibration in absolute values is out of the scope of this work, and can be performed by using one of the known methods.[5,6] Here a source standard S1 with a known spectral irradiance (furnished by the manufacturer) is used to characterize the radiometer R against the source S1 according to the Equation (7). The radiometer manufacturer normally performs this process.

Table 1: Characteristic values (*k*) of the radiometer R and of the efficiency spectrum $S_{PDT}(\lambda)$.

	Source 1	Source 2	Source 3
Radiometer R $S_R(\lambda)$	$k_{a,S1} = 0.31$	$k_{a,S2} = 0.69$	$k_{a,S3} = 0.49$
Efficiency spectrum $S_{PDT}(\lambda)$	$k_{PDT,S1} = 0.05$	$k_{PDT,S2} = 0.19$	$k_{PDT,S3} = 0.14$

Taking the results in Table (1), according to the Equation (10), one can verify that the resulting relative errors when S1, S2 and S3 are measured by the radiometer R with spectral responsivity $S_R(\lambda)$ are, respectively, 520%, 263% and 250%.

Here such type of error means the deviation of the measured value *Q*, by the radiometer R, relative to the value that would be measured for the desired action spectrum $S_{PDT}(\lambda)$. In this specific example one can verify that this kind of error is high and source dependent, as expected.

The recalibration of the radiometer R to respond according to the action spectrum $S_{PDT}(\lambda)$ is accomplished by multiplying the measured quantity Q by the value $k_{PDT,S1}/k_{a,S1} = 0.05/0.031$, according to the Equation (9). In this case the measurement error of S1, with the recalibrated radiometer R, is zero. In order to transfer this calibration process, only valid to S1, to measure S2, according to the Equation (12), it is necessary to multiply the measured Q value by $(k_{a,S1} \cdot k_{PDT,S2})/(k_{PDT,S1} \cdot k_{a,S2}) = (0.31 \cdot 0.19)/(0.05 \cdot 0.69)$. In this way the measurement error of S2 with the recalibrated radiometer R is zero.

Computing the relative errors according to the Equation (13) when S2 and S2 are measured by R and the recalibrating transfer from S1 to S2 and to S3 are not performed, we have respectively, $\varepsilon = 41\%$ and $\varepsilon = 44\%$. This kind of error is also high for the specific example, and source dependent.

One can verify in the above example that, in radiometric measurement in PDT, errors can be high when a correct radiometer recalibration is not performed. In order to make it possible a radiometer recalibration, the instrument manufacturer should furnish its spectral responsivity. Alternatively, the manufacturer should inform the used calibration source, and the characteristic value of the detector (*k*) for the used calibration source. Furthermore, to make it possible comparisons between different sources, the manufacturer of a source should furnish its spectral irradiance.

4. CONCLUSION

The mismatch between a radiometer spectral responsivity and a desired action spectrum can result into high measurement errors. Thus, it is of fundamental importance the correct recalibration of the radiometer for a specific action spectrum and source.

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