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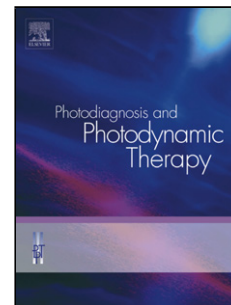
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SmartPDT[®]: smartphone enabled real-time dosimetry via satellite observation for daylight photodynamic therapy

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Highlights

- dPDT is an effective treatment for field change actinic keratosis (AK).
- dPDT light dose is not routinely monitored due to demanding measurement techniques.
- SmartPDT[®] is a novel method of delivering dPDT using a smart-phone and web portal.
- SmartPDT[®] accurately determines light dose received during dPDT without a detector.
- SmartPDT[®] forecasts expected light dose 24 and 48 hours prior to treatment.

Abstract

Background: Actinic keratosis (AK) affects one quarter of over 60s in Europe with the risk of transforming into invasive squamous cell carcinoma. Daylight photodynamic therapy (dPDT) is an effective and patient preferred treatment that uses sunlight to clear AK. Currently, there is no standardised method for measuring the light received during treatment.

Methods: SmartPDT[®] is a smartphone-based application and web-portal, developed by siHealth Ltd, enabling remote delivery of dPDT. It uses satellite imagery and computational algorithms to provide real-time determination of exposure to PpIX-effective solar radiation ("light dose"). The application also provides forecast of expected radiant exposures for 24- and 48-hours prior to the treatment period. Validation of the real-time and forecasted radiant exposure algorithms was performed against direct ground-based measurement under all weather conditions in Chilton, UK.

Results: Agreement between direct ground measurements and satellite-determined radiant exposure for 2-hour treatment was excellent at $-0.1\% \pm 5.1\%$ (mean \pm standard deviation). There was also excellent agreement between weather forecasted radiant exposure and ground measurement, $1.8\% \pm 17.7\%$ at 24-hours and $1.6\% \pm 25.2\%$ at 48-hours. Relative Root Mean Square of the Error (RMSE_r) demonstrated that agreement improved as time to treatment reduced (RMSE_r = 22.5% (48-hours), 11.2% (24-hours), 5.2% (real-time)).

Conclusion: Agreement between satellite-determined, weather-forecasted and ground-measured radiant exposure was better than any existing published literature for dPDT. The

SmartPDT[®] application and web-portal has excellent potential to assist with remote delivery of dPDT, an important factor in reducing risk in an elderly patient population during the Covid-19 pandemic.

Keywords

Daylight Photodynamic Therapy; Photodynamic Therapy; Dosimetry; Live Dosimetry

Introduction

Field change carcinogenesis, as a result of chronic sun exposure, manifests as actinic keratosis (AK). It is extremely common, affecting 11% to 26% of individuals over 60-years-old in the USA, Europe and the UK, with prevalence increasing linearly between 60 and 80 years of age [1–4]. If left untreated, there is a reported 0.1% to 20% annual risk that individual AKs will develop into invasive squamous cell carcinoma [5,6]. Furthermore, most affected individuals will have multiple AKs which, along with increased severity, increases the risk of progression to skin cancer. For example, multiple severe AK (≥ 10) on the scalp raises the cumulative risk of developing squamous cell carcinoma by 13.6% [6]. Hence, there is a need for treatment.

Daylight photodynamic therapy (dPDT) is widely used in Europe, Australia and South America as an effective, patient preferred treatment for superficial AKs affecting field areas on the face and scalp [7–9]. It is also becoming an increasingly popular therapy in Northern America [10] due to its effectiveness and association with high levels of patient satisfaction [7,11,12]. Complete clearance rates of 70% were reported by Lacour *et al.* following a single dPDT treatment in a multicentre European study [13] and Rubel *et al.* reported a complete clearance rate of 89% in an equivalent study in Australia [7]. dPDT involves topical application of a photosensitiser pro-drug to the area of diseased skin. The pro-drug is absorbed and metabolised to the photosensitiser, protoporphyrin-IX (PpIX), in the dysplastic cells [14–16]. The PpIX is photoactivated when exposed to the visible and long-wavelength ultraviolet radiation components of natural daylight. A photochemical reaction then takes place in the presence of oxygen, producing oxidative stress, inflammation and subsequent cell death. The outcome is effective clearance of diseased tissue [14].

In dPDT, it is common practice to define the effective light dose as the PpIX-weighted effective irradiance combined with the treatment time [10,17]. Exposure is administered over a 2-hour period when weather conditions are favourable and a minimum PpIX-weighted radiant exposure (“light dose”) of 8 Jcm^{-2} can be achieved [8,9,18–23]. A lack of control of the received light dose could result in under-exposure, particularly in geographical locations with, and during periods of, variable weather conditions [10,20,24]. These issues necessitate the need for procedural improvement incorporating reliable and accurate monitoring of AK-received light dose.

SmartPDT[®] is a smartphone-based application and a web-portal that aims to improve the reliability and simplicity of dPDT delivery. The application uses satellite-based near real-time monitoring of PpIX accumulated effective dose received by the patient. It also accounts for the impact of sunscreen on effective dose and reduces the risk of sunburn during dPDT by monitoring erythema effective solar UV exposure. Additionally, the web-portal, a tool

developed for the clinician, will predict radiant exposures both 48- and 24-hours prior to a potential treatment. It will also be used to monitor ongoing therapy sessions via an automatic connection to the active patients' application.

The objective of this study was to determine the accuracy of the algorithms used in the commercial SmartPDT[®] application by comparison of real-time and forecasted PpIX-effective radiant exposure with direct ground measurements. Validation of algorithms for erythema effective exposures was reported previously [25] and not included in this paper.

Methods

Satellite Imagery Determination of PpIX-effective irradiance

The method developed by siHealth Ltd. (Harwell Campus, UK) is based on near real-time determination of the PpIX-effective irradiance by acquiring the optical imagery from several Earth Observation satellite sensors (geostationary and low earth orbit) [25]. These multi-source satellite data are fused, and a downscaling model is applied to achieve a temporal resolution of 1 minute, a spatial resolution in the range 1 - 12 km depending on latitude. Using more than one satellite source as an input for clouds, ozone and aerosols allows the expansion of existing models [26–29] to the PpIX action spectrum and all weather conditions which is particularly important for climates with highly variable weather such as the UK. This model is further development of a previously reported method for the near real-time monitoring of erythema effective ultraviolet radiation [25].

Certain elements of this approach are similar to Wald [30] who extended methodology for the computation of site-specific solar irradiance (ESRA) by using satellite-based total shortwave solar irradiance and substituting the sunshine duration input with a new input, the satellite-based “clearness factor” (expressing the turbidity of the atmosphere) calculated by using Meteosat Second Generation data. In contrast, the proprietary method developed by siHealth Ltd. applies radiative transfer model directly to the PpIX action spectrum and the relevant atmospheric components (clouds, ozone, aerosols). The PpIX action spectrum used in this research is the spectral absorption of PpIX dimethyl ester in chloroform [31].

Weather Forecast Determination of PpIX-effective irradiance

The determination of forecasted PpIX-effective irradiance for 24- and 48-hours in advance of the 2-hour treatment period is achieved by utilising the above model, replacing satellite imagery with meteorological numerical weather predictions of cloudiness, ozone density and aerosols optical depth; forecast of cloudiness is provided by MetOffice (Exeter, UK), while the prediction of ozone and aerosols optical depth is provided by the Copernicus Atmosphere Monitoring Service (CAMS) (<https://atmosphere.copernicus.eu/>). The temporal resolution of the forecasted PpIX effective irradiance in this case is hourly, the spatial resolution is approximately 4 km in Europe and about 17 km worldwide. The same methodology could also be used to estimate the PpIX effective irradiance in clear-sky conditions on a larger timescale

(e.g. weeks or months) by using archived data on the ozone and aerosols optical depth derived from the weekly average in the last 5 years.

Real-time and forecasted data were determined in 15-minute intervals during the UK dPDT treatment season from 1st August to 26th October 2018 and 31st March to 31st May 2019 under all weather conditions for Chilton (51.575N, 1.318W), UK.

Ground-based measurement

Ground-based measurements of PpIX effective irradiance were performed by Public Health England at the same location as indicated above (Chilton, UK) using Glacier X TE-cooled CCD array spectroradiometer (BWTek, Newark, NJ, USA), coupled by optical fibre to a D7-SMA diffuser (Bentham Instruments, Reading, UK).

Comparison

Two-hour PpIX-weighted radiant exposures (“light dose”) produced by satellite imagery and weather forecasting were compared to the ground-based measurements using a custom MATLAB script. Data below 2 Jcm^{-2} , significantly lower than the International guidelines minimum criteria for dPDT [32], were excluded and only data from 0800 to 1700, representing clinical operating hours, were considered.

Ground measured radiant exposure was set as the reference and the percentage differences from the SmartPDT[®] application calculated. To evaluate performance of satellite imagery algorithms, Mean Bias Error MBE, relative Mean Bias Error MBE_r , Standard Deviation STDE, relative Standard Deviation STDE_r , Root Mean Squared Error RMSE, relative Root Mean Squared Error RMSE_r , Mean Absolute Error MAE, relative Mean of Absolute Error MAE_r and Goodness-of-fit R^2 were calculated.

Results

Real-time radiant Exposure (“light dose”)

Figure 1a shows scatter plot of satellite imagery vs direct ground measurements for 2-hour dPDT, statistical analysis is given in Table 1 for all data and as a detailed breakdown for treatment at different times of the day.

Satellite imagery demonstrated excellent correlation with direct ground measurements under all weather conditions and range of exposures. The goodness-of-fit is above 98% for the whole dataset and all treatment periods; average percentage difference is -0.13% with absolute average percentage difference of 4.00% and there is substantially no bias ($\text{MBE}_r < 0.6\%$).

24h and 48h forecasted light dose

Figure 1b shows the scatter plot of satellite imagery vs direct ground measurements for 24-hour forecast and Figure 1c for 48-hour forecast; statistical analysis is given in Table 2 for the 24-hour forecast and Table 3 for 48-hour forecast.

The mean percentage difference between 24-hour forecasted data and ground is 1.77% with an absolute average percentage difference of 11.7%. Goodness-of-fit is above 93% for all data and all treatment periods. 48-hour forecast is marginally poorer with mean percentage difference from ground measurement of 1.57% and absolute percentage difference of 19.4%. Goodness-of-fit for all data is 80% and is above 74% for each treatment period. It should be stressed that performance of forecasted dPDT model depends on weather forecast and not on live data, therefore its outcome is unavoidably linked to the accuracy of weather forecasting.

Discussion

dPDT is an effective treatment for the common pre-malignant condition of chronic photodamaged skin and AK. However, the light dose received by the patient is not routinely monitored in clinical practice due to the lack of a simple standardised method. It is, therefore, not known what solar ultraviolet radiation exposure the patient has received or whether the minimum effective PpIX radiant exposure has been reached. Indeed, the proposed minimum effective light dose has not been robustly determined in the literature due to limited data and inaccurate dosimetry [24].

The most accurate dosimetry approaches are often costly, require expertise to operate and are appropriate for environmental rather than personalised measurement [7]. Personalised approaches are less accurate, do not determine the radiant exposure at the treatment site and require post-acquisition processing [24,33].

Manley *et al.* [34] estimated the experimental errors associated with four different methods of dosimetry, including the O'Mahoney *et al.* method [18]. They concluded that use of spectroradiometers results in the lowest total error on effective light dose calculation, provided the patient is in the vicinity of the spectroradiometer. Therefore, for practical reasons Manley *et al.* recommended the O'Mahoney *et al.* method, with a 95% confidence interval of $\pm 14.3\%$ and a maximum error of $\pm 28\%$ [34]. SmartPDT[®] has a lower error than the O'Mahoney *et al.* method (95% confidence interval $\pm 10.2\%$ and a maximum error of 18% for dPDT doses $\geq 8 \text{ Jcm}^{-2}$) and is more convenient requiring only a smartphone without additional measurement device.

The importance of a simple non-detector based determination of radiant exposure has also been identified by LaRochelle *et al.* who developed a model determining effective dose based on easily accessible local weather data [10]. Their practical solution is aimed at delivery of dPDT indoors, through glass, to negate low temperatures and wind chill. La Rochelle *et al.* model showed strong correlation between the meteorological factors and the PpIX-weighted irradiance ($R^2 = 87\%$) but was not as strong as our model ($R^2 > 98\%$). We believe that the model we present here is the most accurate and practical method available for PpIX-weighted radiant exposure determination.

To our knowledge, SmartPDT[®] is also the only system to forecast the PpIX-effective light dose, which will greatly assist with treatment planning. Determining the future light dose relies

upon weather forecast information, which becomes less accurate the further in the future one tries to predict. Inaccuracies in weather prediction are represented by the increase in $RMSE_r$ at 24-hours (11.2%) and 48-hours (22.5%). The goodness-of-fit also deteriorates with increasing time to treatment ($R^2 = 94\%$ at 24-hours and 80% at 48-hours). Precision of forecast data is not as critical as real-time determination of light dose as forecasted light dose will be used, along with additional factors such as predicted rainfall and ultraviolet exposure, to select potentially appropriate treatment times. Additional and improved forecast information may help improve the precision of the model.

Currently, the SmartPDT[®] algorithm is similar to many of the other reported dPDT dosimetry techniques, determining radiant exposure in the horizontal plane (i.e. pointing directly upwards). This cannot be regarded as the true light dose to the surface of the lesion because the orientation of the lesion(s) will vary in relation to the solar position. Manley *et al.* demonstrated that, in extreme circumstances, measurement in the horizontal plane could under-represent the true received radiant exposure by 78% [34]. Further work is required to consider the position of the lesion and determine radiant exposure on the surface of the affected area.

The current application is also limited in its spatial resolution of 1 – 12 km; higher spatial resolution is achieved at the equator and decreases towards northerly latitudes. The analysis presented here results in agreement that is acceptable clinically in the UK.

In conclusion, we present a verification of the satellite-imagery and weather-forecast determination of PpIX-weighted radiant exposure by SmartPDT[®] application. SmartPDT[®] has the potential to assist with treatment planning and deliver accurate real-time dosimetry for dPDT creating a more convenient and reliable therapy. This may lead to further improvement in the accuracy of forecasted data, the geographical resolution and the light dose received in any treatment plane. Importantly, in a therapy where there is no standardised simple dosimetry measure, SmartPDT[®] offers accurate and accessible technology to increase confidence in the delivery of effective dPDT.

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Declaration of Interest

M. M is a board director and CTO of siHealth Ltd. and E. S is founder and CEO of siHealth Ltd.

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Figure 1: Satellite predicted PpIX-effective radiant exposure for 2-hour dPDT versus direct ground measurements. Data below 2 Jcm⁻² excluded due to lack of clinical relevance. a) Real-time b) 24-hour forecasted and c) 48-hour forecasted.

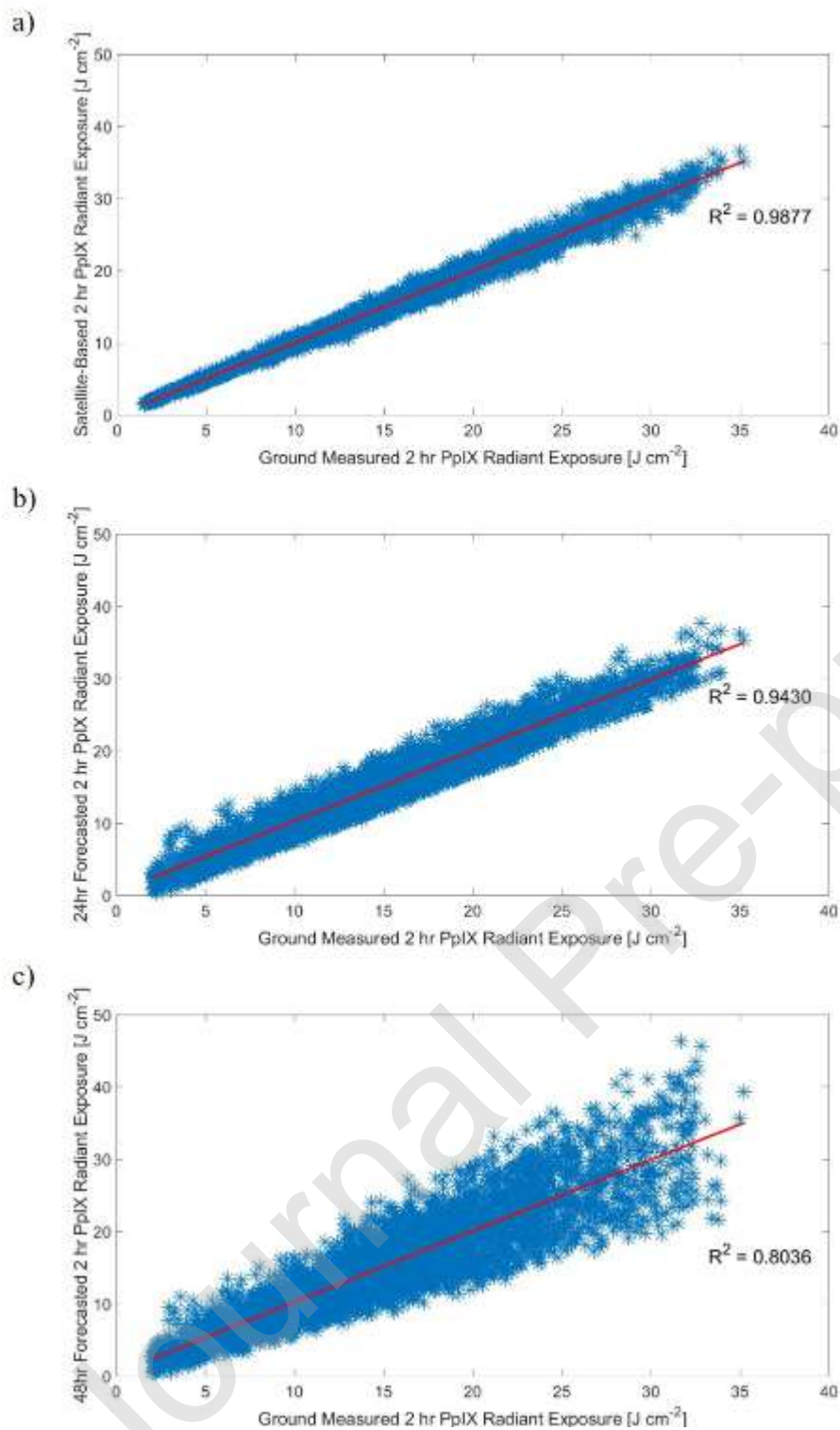


Table 1 Statistical indexes of PpIX-weighted dose calculated by real-time satellite imagery and measured ground data under all weather conditions for dPDT at different time of the day.

	<u>All data</u>	<u>2h treatment period</u>							
		<u>08:00 - 10:00</u>	<u>09:00 - 11:00</u>	<u>10:00 - 12:00</u>	<u>11:00 - 13:00</u>	<u>12:00 - 14:00</u>	<u>13:00 - 15:00</u>	<u>14:00 - 16:00</u>	<u>15:00 - 17:00</u>
Number of data points	3913	263	530	532	525	525	521	520	497
Mean radiant exposure (Jcm ⁻²)	15.6	12.7	14.9	17.2	18.4	18.4	16.7	14.0	10.9
MBE (Jcm ⁻²)	-0.0247	0.036	0.0301	-0.073	-0.096	-0.046	-0.0178	0.0070	-0.0065
MBE _r	-0.16%	0.29%	0.20%	-0.42%	-0.52%	-0.25%	-0.11%	0.05%	-0.06%
STDE	0.81	0.68	0.85	0.97	1.00	0.88	0.77	0.63	0.53
STDE _r	5.20%	5.37%	5.68%	5.62%	5.44%	4.77%	4.63%	4.47%	4.84%
RMSE	0.81	0.68	0.85	0.97	1.01	0.88	0.77	0.63	0.53
RMSE _r	5.21%	5.38%	5.69%	5.64%	5.46%	4.78%	4.63%	4.47%	4.84%
MAE	0.60	0.50	0.62	0.74	0.77	0.67	0.59	0.47	0.38
MAE _r	3.84%	3.91%	4.14%	4.31%	4.19%	3.66%	3.52%	3.37%	3.43%
R	0.994	0.994	0.993	0.991	0.991	0.993	0.994	0.995	0.995
R ²	0.988	0.988	0.985	0.983	0.982	0.987	0.989	0.990	0.990

Table 2 Statistical indexes of PpIX-weighted dose calculated by 24-hour forecasted satellite imagery and measured ground data under all weather conditions for dPDT at different time of the day.

	<u>All data</u>	<u>2h treatment period</u>							
		<u>08:00 - 10:00</u>	<u>09:00 - 11:00</u>	<u>10:00 - 12:00</u>	<u>11:00 - 13:00</u>	<u>12:00 - 14:00</u>	<u>13:00 - 15:00</u>	<u>14:00 - 16:00</u>	<u>15:00 - 17:00</u>
Number of data points	3892	261	525	532	524	525	520	515	490
Mean radiant exposure (Jcm ⁻²)	15.7	12.8	15.0	17.2	18.5	18.4	16.7	14.1	11.1
MBE (Jcm ⁻²)	0.147	-0.35	0.035	0.46	0.56	0.49	0.294	-0.094	-0.52
MBE _r	0.93%	-2.74%	0.24%	2.65%	3.04%	2.63%	1.76%	-0.66%	-4.65%
STDE	1.75	1.56	1.69	1.91	1.96	1.92	1.75	1.59	1.44
STDE _r	11.15%	12.22%	11.22%	11.11%	10.63%	10.43%	10.45%	11.27%	12.95%
RMSE	1.76	1.60	1.69	1.96	2.04	1.98	1.77	1.59	1.52
RMSE _r	11.19%	12.52%	11.22%	11.42%	11.05%	10.76%	10.60%	11.29%	13.76%
MAE	1.41	1.24	1.36	1.53	1.63	1.56	1.39	1.29	1.15
MAE _r	8.95%	9.68%	9.05%	8.91%	8.80%	8.47%	8.28%	9.14%	10.42%
R	0.971	0.972	0.969	0.966	0.966	0.967	0.971	0.971	0.972
R ²	0.943	0.944	0.940	0.934	0.934	0.934	0.944	0.943	0.945

Table 3 Statistical indexes of PpIX-weighted dose calculated by 48-hour forecasted satellite imagery and measured ground data under all weather conditions for dPDT at different time of the day.

	<u>All data</u>	<u>2h treatment period</u>							
		<u>08:00 - 10:00</u>	<u>09:00 - 11:00</u>	<u>10:00 - 12:00</u>	<u>11:00 - 13:00</u>	<u>12:00 - 14:00</u>	<u>13:00 - 15:00</u>	<u>14:00 - 16:00</u>	<u>15:00 - 17:00</u>
Number of data points	3892	261	525	532	524	525	520	515	490
Mean radiant exposure (Jcm ⁻²)	15.7	12.8	15.0	17.2	18.5	18.4	16.7	14.1	11.1
MBE (Jcm ⁻²)	0.133	-0.55	0.272	0.231	0.40	0.39	0.51	-0.120	-0.46
MBE _r	0.85%	-4.28%	1.81%	1.35%	2.16%	2.10%	3.08%	-0.85%	-4.13%
STDE	3.5	2.86	3.31	3.9	3.9	4.1	3.6	3.18	2.70
STDE _r	22.44%	22.36%	22.01%	22.76%	21.18%	21.96%	21.77%	22.55%	24.39%
RMSE	3.5	2.91	3.32	3.9	3.9	4.1	3.7	3.18	2.74
RMSE _r	22.46%	22.77%	22.08%	22.80%	21.29%	22.07%	21.99%	22.57%	24.74%
MAE	2.75	2.20	2.61	3.09	3.11	3.20	2.87	2.52	2.11
MAE _r	17.53%	17.22%	17.36%	18.00%	16.82%	17.32%	17.14%	17.84%	19.08%
R	0.897	0.907	0.898	0.866	0.868	0.861	0.898	0.897	0.900
R ²	0.804	0.823	0.806	0.749	0.753	0.742	0.806	0.804	0.809