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Objective Assessment of Psoriasis Lesion Thickness for PASI Scoring using 3D Digital Imaging

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***Abstract*—**Psoriasis is a chronic inflammatory skin condition which affects 2-3% of population around the world. Psoriasis Area and Severity Index (PASI) is a gold standard to assess psoriasis severity as well as the treatment efficacy. Although a gold standard, PASI is rarely used because it is tedious and complex. In practice, PASI score is determined subjectively by dermatologists, therefore inter and intra variations of assessment are possible to happen even among expert dermatologists. This research develops an algorithm to assess psoriasis lesion for PASI scoring objectively. Focus of this research is thickness assessment as one of PASI four parameters beside area, erythema and scaliness. Psoriasis lesion thickness is measured by averaging the total elevation from lesion base to lesion surface. Thickness values of 122 3D images taken from 39 patients are grouped into 4 PASI thickness score using K-means clustering. Validation on lesion base construction is performed using twelve body curvature models and show good result with coefficient of determinant (R^2) is equal to 1.

***Keywords*—**3D digital imaging, base construction, PASI, psoriasis lesion thickness.

I. Introduction

PSORIASIS is a chronic inflammatory skin condition which is caused by speed-up replacement of human skin cell. Psoriasis can affect any stage of life, but it usually occurs during second and third decades of life. Psoriasis also occurs in any gender or race with equal amount of male and female; 2 to 3% of population is living with psoriasis [1].

There are seven types of psoriasis based on the symptom and appearance which are plaque psoriasis, pustular psoriasis, exfoliative psoriasis, guttate psoriasis, flexural psoriasis, erythodermic psoriasis, and psoriasis arthritis. About 80% of psoriasis case is plaque psoriasis [2]. Plaque psoriasis appears with silvery-white scales on top of red and thick patches. Silvery-white scales are skin shedding as the result of speed-up growth of the skin cell. Red patches are due to increasing amount of blood vessels to support the speed-up growth.

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Dermatologists use 4 types of treatments to cure psoriasis: topical therapies, ultraviolet lights, systemic medication and the latest one is biological injection [3]. Treatment applied depends on psoriasis severity level and patient condition. For mild to moderate psoriasis, dermatologists apply topical therapies. For moderate to severe psoriasis, dermatologists apply UV light therapies and systemic medication. Dermatologists have to monitor patient's condition as the UV light therapies and systemic medication give side effects. The latest treatment found, biological injection, is only for severe psoriasis where topical therapies, ultraviolet lights, and systemic medication treatments can not cure the psoriasis. This injection blocks certain immune cell (T cell) to act, as this speed-up growth of skin cell is the cause of psoriasis. Biological injection also alters the immune response to the skin cell's growth.

Dermatologists use their knowledge and experience to decide which treatment to be applied. Patient's physical condition which differs from one another also needs to be noted. Treatment may include combination of several treatments to increase the treatment efficacy and reduce side effects. Dermatologists also change dosage and rotate the treatment. In every visit, dermatologists need to assess patient's psoriasis severity as well as monitor the treatment efficacy.

The gold standard to assess psoriasis is Psoriasis Area and Severity Index (PASI) [4]. In PASI calculation, human body is divided into 4 regions: head, trunk, upper extremities and lower extremities. Each body region has 4 parameters that need to be determined which are psoriasis area, erythema (redness), thickness, and scaliness. Each body region is weighted differently regarding the proportion of Body Surface Area (BSA). Head is weighted 0.1, trunk is 0.3, upper extremities is 0.2 and 0.4 for lower extremities. PASI scoring is calculated using (1).

$$PASI = 0.1(R_h + T_h + S_h)A_h + 0.2(R_u + T_u + S_u)A_u + 0.3(R_t + T_t + S_t)A_t + 0.4(R_l + T_l + S_l)A_l \quad (1)$$

A is for area (score 0-6), R is redness (score 0-4), T is thickness (score 0-4), S is scaliness (score 0-4), h is for head

body part, u is upper extremities, t is trunk and l is lower extremities.

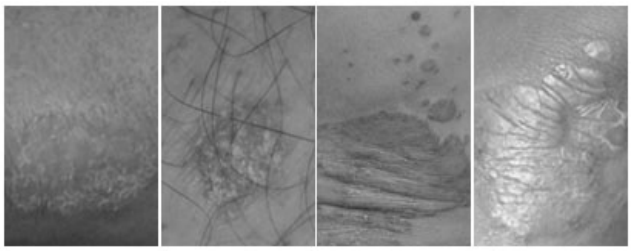
PASI scoring is used in clinical practice. Dermatologists examine the lesions by visual and tactile assessment then assign it to the PASI scores based on the PASI description. Although PASI is a gold standard to assess the treatment efficacy, this method is rarely used in daily practice. It is a tedious and complex task to do since dermatologist has to assess all lesions in every body regions and score them for each of four PASI parameters. Concerning the issue, this research objective is to develop an algorithm to measure PASI parameter objectively using 3D digital imaging technology. PASI measurement and scoring will be conducted easily and no prior knowledge is involved. Quantitative value derived from the measurement allows the scoring to be objective.

This research focuses on psoriasis lesion thickness measurement for PASI scoring. From the PASI description, thickness scoring is based on the assessment of two parameters which are elevation and edge shape. Elevation is considered as the most significant parameter to determine the lesion thickness compare to edge shape. This definition is based on the dermatologist technique during the clinical assessment which uses their forefinger to touch the lesion from its surrounding normal skin. Dermatologists run their forefinger several times on the lesion and use various directions to reassure how thick the elevation compare to surrounding normal skin is. Dermatologists do not examine the edge. Based on this observation, PASI thickness parameter is defined as 0 for no elevation, 1 for slight plaque elevation, 2 for moderate elevation, 3 for marked elevation, and 4 for very marked elevation. This description is shown in Table 1.

TABLE I
PASI THICKNESS DESCRIPTION

Score	Description
1	slight plaque elevation
2	moderate elevation
3	marked elevation
4	very marked elevation

Psoriasis lesion which is assigned by a dermatologist to PASI score 1, score 2, score 3 and score 4 is shown in Fig. 1a, Fig. 1b, Fig. 1c and Fig 1d, respectively.



(a) (b) (c) (d)

Fig. 1 Psoriasis lesions and its score, assigned by dermatologist (a) score 1, (b) score 2, (c) score 3 and (d) score 4

Researches have been developed algorithms to measure and assess the psoriasis thickness. The early lesion thickness measurement is by examining hystopathological image of psoriasis lesion. In the image, epidermal layers of lesion is segmented from other layers hence the thickness can be determined. Olympus BX50 microscope has been used to take the hystopatholigal image of psoriasis lesion [5]. Image is transferred to computer and analysed to examine the image and perform the measurement. Thickness of epidermal layer is determined by measuring the distance between the top and the bottom of rete. Unfortunately, histhopathological image is obtained from patient using biopsy method, hence it is an invasive method and discomfort the patient.

Ultrasound has also been used as an imaging technology for measuring the skin thickness [6]. In psoriasis case, ultrasound with 15MHz frequency is applied on lesion area to quantify the lesion thickness in percentage compare to the normal [7]. The ultrasound renders several subcutaneous layers under the skin. The boundary between epidermal thickness where psoriasis occurs and other fat layers is hard to be distinguished, therefore an expert is needed. The expert is needed to perform such visual segmentation on the ultrasound images.

In 3D digital imaging, the image obtained shows elevation of psoriasis lesion on top of healthy skin surface. The issue is that 3D images only shows information of lesion surface while the elevation is the distance between lesion surface and lesion base. The lesion base needs to be constructed. On a flat surface, lesion base can be constrcuted as a straight line connecting psoriasis lesion from edge to edge. The challenge is that psoriasis lesion occurs on top of human skin which has certain degree of curvature. The lesion base constrcuted has to be able to folow the curvature of surrounding healthy skin.

II. METHODOLOGY

A total of 122 3D surface images of skin with psoriasis lesions are taken from 39 male patients with varying ages from 21 to 60 years old. The patients are registered with Dermatology Department of General Hospital Kuala Lumpur, Malaysia. Several lesions are taken from each patients from different body regions which are head, trunk, upper extremities, and lower uptremities. In this research, distribution of lesions thickness condition ranges from mild,

moderate to severe condition of plaque psoriasis.

The steps to measure lesion thickness and to determine PASI thickness score is shown in Fig. 2. The process involves 3D surface image capture, lesion segmentation from normal skin, lesion base construction, calculating lesion thickness value, and assigning lesion to PASI thickness score.

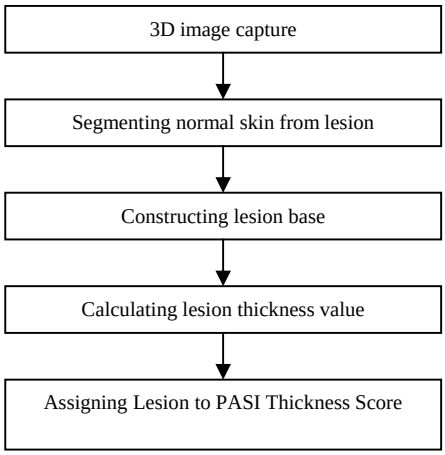
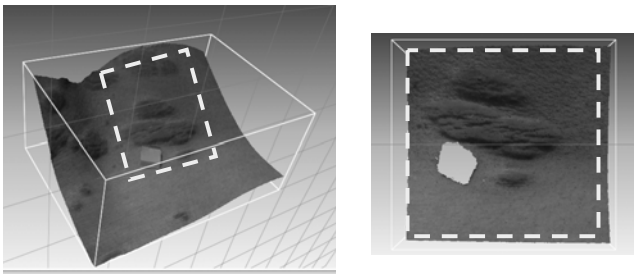


Fig. 2 Algorithm to measure psoriasis lesion thickness

A. 3D Image capture

The 3D skin surface images are obtained using a laser scanner, Konica Minolta Non-Contact 3D Digitizer VIVID 910. An object is scanned using laser triangulation as a basic principle by a plane of laser light coming from the source aperture [8]. The image is captured using middle lens with focal length distance f = 14 mm. It captures 198 to 823 mm in X direction, 148 to 618 mm in Y, and 70 to 800 mm in Z. Acquisition accuracy is up to 0.10 mm to the reference plane. The camera is placed minimum 1 meter from the skin surface to maintain the focus of image obtained. An example of image taken from patient used for PASI thickness scoring is shown in Fig. 3a. Dermatologist assesses the lesion thickness of Fig. 3a as severe condition. The image is then cropped to contain only one lesion as the region of interest. This region is indicated by dash square in Fig. 3b. The sticker which is non-lesion elevation is taken out from the surface.



(a) (b)

Fig. 3 (a) The 3D surface image captured by 3D scanner, (b) region of interest after cropping

The 3D image of Fig. 3b is then converted to STL format which only takes the height information. The color information is omitted. The 3D STL file of Fig. 3b is shown in Fig 4.

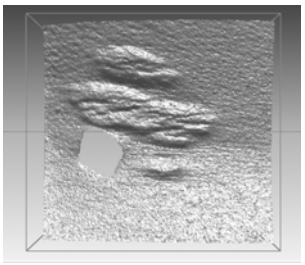
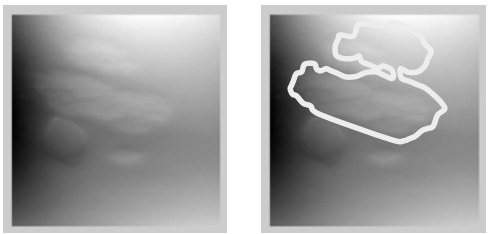


Fig. 4 3D STL format which only inform the elevation values

B. Segmenting Normal Skin from Lesion

The segmentation process is intended to separate surrounding normal skin elevation values from the lesion. The segmentation is conducted manually. Each 3D STL file of surface images as shown in Fig. 4 is then converted to 2D elevation map which shows the elevations in the x-y coordinate. Elevations are shown as gray-level intensity (black to white for low to high elevation).

Fig. 5a shows the 2D elevation map of Fig. 4. The normal skin is segmented manually by user as normal skin's gray-level intensity can be distinguished visually from surrounding normal skin. The white line shown in Fig. 5b indicated user selection of lesion according to the intensity difference. Once the border has been selected, the normal skin and lesion coordinate are known.



(a) (b)

Fig. 5 Psoriasis lesion segmentation;
(a) the 2D elevation map shown in gray-level intensity,
(b) manual lesion segmentation by user

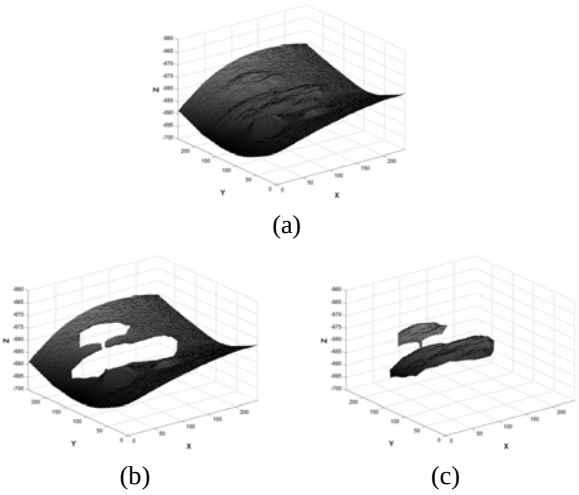
C. Constructing Lesion Base

Thickness is defined as the elevation between surface and its base. As mentioned in the end of introduction part, the 3D surface images only provide lesion surface information hence its base needs to be constructed.

Psoriasis lesion forms irregular shape above healthy skin. Thicker lesion means higher surface's elevation which is formed above its healthy skin. This leads to an assumption that lesion base is the healthy skin under lesion surface. The lesion base is therefore constructed using surrounding healthy

skin information as the reference.

Once the normal skin is segmented from the lesion on 2D elevation map, the coordinate belonging to normal skin and lesion are known. The respective elevation values of normal skin and lesion can be determined which correspond to each coordinates on the 3D surface. The surface containing elevation values of 3D image, normal skin and lesion on 3D image is shown in Fig. 6a, Fig. 6b and Fig. 6c, respectively.



(a) (b) (c)

Fig. 6 The surface containing elevation value of: (a) 3D image, (b) normal skin, (c) lesion

The lesion base is constructed by an interpolation method using the normal skin information. An interpolated surface is created and the lesion base is the elevation value on its lesion coordinate. The interpolation method to construct lesion base from surrounding healthy skin has also been developed to create the top for ulcer wounds for volume measurement [9]. Opposite to psoriasis lesion which elevates the skin, ulcer hollows it down.

Human skin is a non-flat surface hence the interpolated lesion base must able to follow the skin curvature. Least square surface fitting using polynomial function is chosen for the interpolation as it is a best-fitting method that shows the trend of surface [10]. Function for second, third and fourth order polynomial used in the surface fitting are shown in (2), (3) and (4) respectively.

$$Z = D(x,y) = (a_1 + a_2 x + a_3 x^2)y + (a_4 + a_5 x)y^1 + (a_6)y^2 \quad (2)$$

$$Z = D(x,y) = (a_1 + a_2 x + a_3 x^2 + a_4 x^3)y + (a_5 + a_6 x + a_7 x^2)y^1 + (a_8 + a_9 x)y^2 + (a_{10})y^3 \quad (3)$$

$$Z = D(x,y) = (a_1 + a_2 x + a_3 x^2 + a_4 x^3 + a_5 x^4)y + (a_6 + a_7 x + a_8 x^2 + a_9 x^3)y^1 + (a_{10} + a_{11} x + a_{12} x^2)y^2 + (a_{13} + a_{14} x)y^3 + (a_{15})y^4 \quad (4)$$

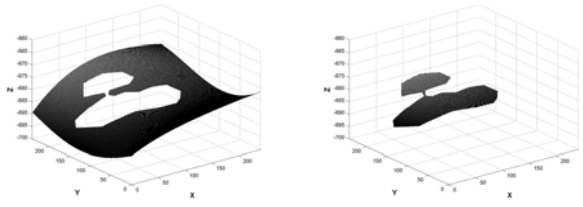
There are two steps to perform polynomial interpolation. First is to find polynomial coefficient using matrix equation as shown in (5) using every coordinate $[X_s, Y_s]$ and elevation value $[Z_s]$ of surrounding surface.

$$[a] = [X_s, Y_s]^{-1}[Z_s] \quad (5)$$

After obtaining the polynomial coefficients matrix $[a]$, the elevation values of interpolated surface $[Z_i]$ in every coordinates $[X_i, Y_i]$ can be determined using (6).

$$[Z_i] = [X_i, Y_i][a] \quad (6)$$

The order of polynomial function used is based on the interpolated surface which gives smallest error to fit the normal skin. The interpolated surface of normal skin shown in Fig. 6b is shown in Fig. 7a, while the lesion base resulting in the interpolated surface is shown in Fig. 7b.



(a) (b)

Fig. 7 (a) Interpolated surface of normal skin, (b) lesion base

D. Calculating Lesion Thickness Value

After the lesion base is constructed using polynomial interpolation, the elevation at every point can be calculated as the subtraction value between the lesion surface and the lesion base at the respective coordinates. During the lesion base construction, some lesion base value can be higher than the

lesion surface. This condition creates negative subtraction result. Higher lesion base can occur since the interpolation attempts to find the trend of human skin curvature instead of fit exact to each elevation. The negative results are then excluded from total elevations value. A representative thickness value is taken by averaging the thickness values from every lesion coordinates such determining the thickness of sea ice [11].

E. Assigning Lesion Thickness Value to PASI Thickness Score

The next step after determining the representative thickness value is assigning the value into PASI thickness score. The score ranges from 0 to 4 where 0 is for no elevation and 4 is for very marked elevation. Since 0 means no elevation occurs, hence the PASI thickness score is only determined from 1 to 4. A clustering method is used to group all 122 thickness values from 122 3D images to the scores. The clustering gathers thickness values with similar pattern. The clustering is based on prior statistical information extracted from data. Clustering is unsupervised classification where prior knowledge is not available.

K-means method is a clustering algorithm well known for its simplicity. Given a set of n data points, the algorithm assigns each point into k cluster based on the nearest distance to the cluster's center. The initial center is chosen randomly and updated until the process is stabilized. K-means clustering has been widely used in image processing [12] and computational biology [13].

III. ALGORITHM VALIDATION

Skin curvature model is created to validate polynomial interpolation on lesion base construction step. Objective of the validation is to test whether the interpolated lesion base is able to follow the normal skin curvature accurately. There are 7 types of curvature which are peak, pit, ridge, flat, valley, saddle ridge, minimal surface, and saddle valley [14]. Each type is classified based on the sign of Gaussian curvature (K) and mean curvature (H). Gaussian curvature (K) determines convex regions of surface. Given surface function, $S = f(x, y, Z)$, the Gaussian curvature of every point is calculated using (7).

$$K(x,y) = \frac{2 f_{xx} f_{yy} - {f_{xy}}^2}{\left(1 + {f_x}^2 + {f_y}^2\right)^2} \tag{7}$$

Mean curvature determine graph surface if boundary curve is specified. Given surface function, $S = f(x, y, Z)$, the mean curvature of every point is calculated using (8).

$$H(x,y) = \frac{\left(1 + {f_y}^2\right) f_{xx} - 2 f_x f_y f_{xy} + \left(1 + {f_x}^2 f_{yy}\right)}{2\left(1 + {f_x}^2 + {f_y}^2\right)^{3/2}} \tag{8}$$

Where f_x is first derivative of f in x; f_y is first derivative of f in y; f_{xx} is second derivative of f in x; f_{yy} is second derivative of f in y and f_{xy} is second derivative of f in (x, y).

A representative value of Gaussian curvature and mean curvature of a 3D image is determined by taking the integral of all the values in every coordinates (x, y). K positive - H negative is peak, K positive - H positive is pit, K zero - H negative is ridge, K zero - H zero is flat, K zero - H positive is valley, K negative - H negative is saddle ridge, K negative - H zero is minimal surface, and K negative - H positive is saddle valley. The curvature classification of 3D image based on K and H sign is listed in Table 2.

TABLE II
HK CLASSIFICATION

K / H	-	0	+
-	Saddle ridge	Ridge	Peak
0	Minimal surface	Flat	None
+	Saddle valley	Valley	Pit

The sign and value of Gaussian and mean curvature of the 122 3D images captured during data acquisition are determined. There are 4 types of curvature found, which are pit, peak, saddle ridge and saddle valley. Apparently, the sign does not depend on body location only but also depend on image position during capturing.

Skin curvature models are created by taking the surface function, $f(x, y)$ from each peak, pit, saddle valley, and saddle ridge image curvature. Surface function used is fourth order polynomial. The skin curvature model is shown in Fig. 8. Curvature model is taken from 12 different body regions and different patients. One pit curvature is shown in Fig. 8a, one peak curvature is Fig. 8b, one saddle valley is Fig. 8c, and one saddle ridge is shown in Fig. 8d.

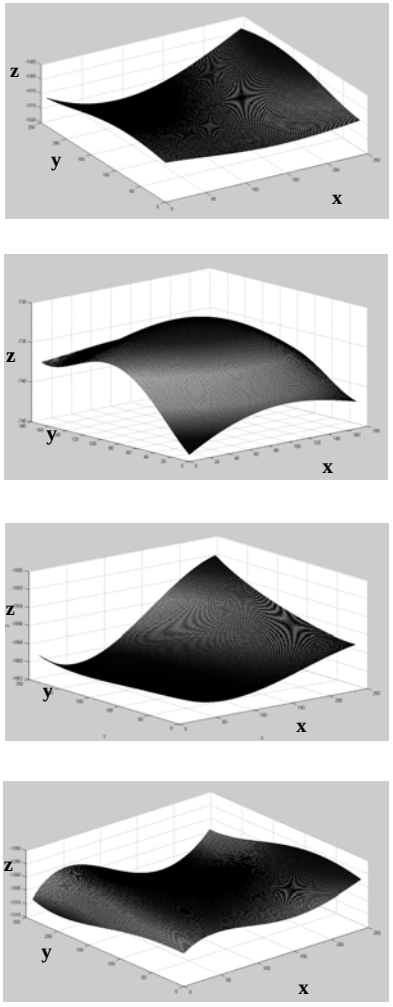


Fig. 8 Four types of Human Skin Curvature
Pit (a), peak (b), saddle valley (c), and saddle ridge (7d)

The model is then cropped in center. The cropping is tested with surrounding healthy skin's availability varies from 75% and 25%. Varied normal skin availability is to test whether the polynomial interpolation can still construct the center's surface accurately in 75% and 25% of surrounding healthy skin's availability. The cropping process is performed manually in the 2D elevation map of the respective 3D surface model.

Coefficient of determinant (R^2) between the cropped center's surface and the constructed center's surface value is calculated to define how good is the fitting. R^2 value varies from 0 to 1, where 1 means the constructed center's surface value is fit precisely to the cropped center's surface value. R^2 is determined by (9).

$$R^2 = 1 - \frac{\sum_i (y_i - f_i)^2}{\sum_i (y_i - \bar{y})^2} \quad (9)$$

where y_i is data set of the cropped center's surface value, f_i is data set of the constructed center's surface value, while $\bar{y}$ is mean of y_i data set. The coefficient of determinant (R^2) of 12 skin curvature models are shown in Table 3.

TABLE III
R^2 OF LESION BASE CONSTRUCTION VALIDATION

Surface Number	Surface Curvature Type	R^2	
		75% of normal skin availability	25% of normal skin availability
1	peak1	1	1
2	peak2	1	1
3	peak3	1	1
4	pit1	1	1
5	pit2	1	1
6	pit3	1	1
7	saddle valley1	1	1
8	saddle valley2	1	1
9	saddle valley3	1	1
10	saddle ridge1	1	1
11	saddle ridge2	1	1
12	saddle ridge3	1	1

From the coefficient determinant (R^2) listed in Table 2, it is shown that polynomial interpolation is able to fit the constructed center's surface exactly to the cropped center's surface. The result is robust for 75% to only 25% of surrounding healthy skin's availability. This result also ensures that polynomial interpolation creates interpolated lesion base that follows normal skin curvature as well as answers the objective the algorithm validation.

IV. Result and Analysis

The thickness value of 122 3D images which contain psoriasis lesion surrounded by healthy skin are then calculated using the proposed algorithm. The result is shown in Fig. 9.

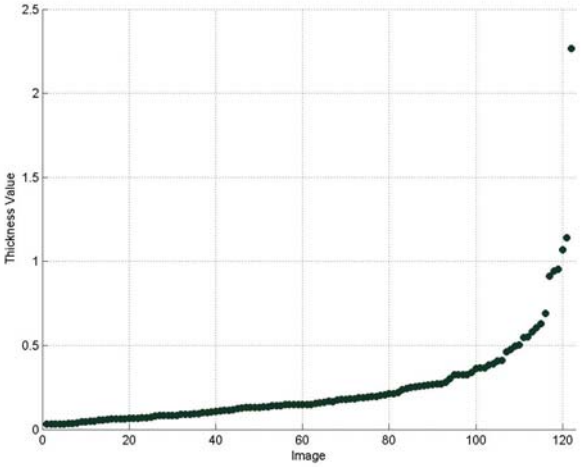


Fig. 9 Thickness Values of 122 3D skin image with psoriasis

All the thickness values are then clustered into 4 groups of PASI-thickness scores using K-means clustering. Each cluster has its own centre such that every point in the cluster is closer to it than to centre of any other cluster. Thickness values of Fig. 9 after the clustering process are shown in Fig. 10.

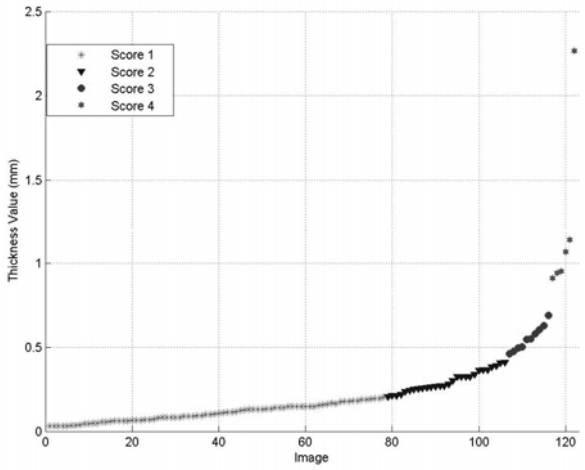


Fig. 10 Thickness values classification of group 1, 2, 3, and 4

The score 1 has thickness value of 77 images ranging from 0.032mm to 0.202mm. The score 2 has thickness value of 33 images ranging from 0.208mm to 0.410mm. The score 3 has thickness value of 9 images ranging from 0.463mm to 0.689mm. The score 4 has thickness value of 6 images ranging from 0.911mm to 2.268mm.

Hair on human skin in some persons can be really thick and dense. The psoriasis lesion can occur in every body regions which sometimes covered by such hair condition. The algorithm is not designed to handle this type of situation. The non-skin elevation value distracts the polynomial interpolation in determining its coefficients. This lead to a non-accurate construction of lesion base. To overcome this problem, the patient hair in the area of interest has to be removed before the 3D surface capture.

V. Conclusion

This paper develops an algorithm to measure psoriasis lesion thickness objectively. The algorithm uses 3D imaging technology which capture 3D image of psoriasis lesion surrounded by healthy skin. Psoriasis lesion thickness is measured by constructing the lesion base then averaging every distance from lesion base to lesion surface. The lesion base is constructed using polynomial interpolation.Thickness psoriasis lesions from 122 surface images of patients are determined. Moreover, K-means clustering as non-supervised classification is used to grouped all the thickness values into 4 group of PASI-thickness score ranging from 1 to 4. By using the algorithm developed in this research, objective assessment of psoriasis lesion thickness can be perfomed in daily practice. Inter and intra variation result between deramatologists can be avoided. The proposed algorithm is validated using skin curvature model which fits exactly to body curvature model. The validation show good fitness with coefficient of determinant (R^2) is equal to 1. This result ensures that polynomial interpolation is able to construct the unknown lesion base which follows the curvature of surrounding healthy skin. The algorithm has limitation in skin covered with hair.

Acknowledgment

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References

[1] Peter van de Kerkhof, *Textbook of Psoriasis*, 2003, Blackwell Publishing: Massachussetts
[2] The Psoriasis Association, *What is Psoriasis?*, 2008, The Psoriasis Association: UK
[3] Lionel Fry, *An Atlas of Psoriasis*, 2005, Taylor&Francis: London
[4] T. Frederiksson, U. Pettersson, Severe Psoriasis: Oral Therapy with a New Retinoid, *Dermatologica*, 1978, 157(4), pp: 238-44
[5] M. Alper, A. Kavak, A.H. Parlak, R. Demirici, I. Belenli, N. Yesildal, Measurement of Epidermal Thickness in a Patient with Psoriasis by Computer Supported Image Analyisis, *Brazilian Journal of Medical and Biological Research*, 2004, 37, pp: 111-117.
[6] Harold Alexander, D.L. Miller, Determining Skin Thickness with Pulsed Ultra Sound. *The Journal of Investigative Dermatology*, Vol 72, pp: 17-19. 1979.
[7] Serup, J.: Non-invasive quantification of psoriasis plaques–measurement of skin thickness with 15 MHz pulsed ultrasound. *Journal of Clinical and Experimental Dermatology*, Volume 9 Issue 5, 502 -- 508 (2006)
[8] Konica Minolta Vivid 910 Non Contact 3D Digitizer Manual Handbook, Japan (2001)
[9] Bryan F. Jones, Peter Plassman, An Instrument to Measure the Dimension of Skin Wounds, *IEEE Trancastion on Biomedical Engineering*, Vol. 42, No.5 1995, pp: 464 - 470
[10] Zhilin Li, Qing Zhu, Christopher Gold, *Digital Terrain Modeling: Principle and Methodology*,2005, CRC Press: Florida
[11] J. P. Luntama, S. Koponen, M. Hallikainen, Analysis of Sea Ice Thickness and Mass Estimation with a Spaceborne Laser Altimerer, *Geosciense and Remote Sensing*, 1997, Volume 3. pp: 1314-1316
[12] Frederic Gibou and Ronald Fedkiw. "A fast hybrid k-means level set algorithm for segmentation". In 4th Annual Hawaii International Conference on Statistics and Mathematics, pages 281–291, 2005.
[13] R. Herwig, A.J. Poustka, C. Muller, C. Bull, H. Lehrach, and J O'Brien. Large-scale clustering of cdna-fingerprinting data. *Genome Research*, 9:1093–1105, 1999.
[14] Paul J. Besl, Ramesh C. Jain, Three-Dimensional Object Recognition, *Annals of Discrete Mathematics-ACM*, Vol. 17, 1985, pp: 75-145