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Inter- and intra-variability of pigmented skin lesions: could the ABCD rule be influenced by host characteristics?

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Background/purpose: Many differences in color, shape and dimension exist between different moles even in the same individual. Major differences might be accounted for anatomical location, genetic factors and by environmental factors, mainly sunlight exposure. Therefore, it would be of great value, when evaluating skin lesions, to take into account the degree of intra- and inter-variability of several diagnostic parameters. In order to assess the morphologic and chromatic differences between lesions belonging to different patients and between lesions belonging to the same individual, we examined objective digital parameters obtained with dermatoscopic analysis, using the DBDermo MIPS system (BIO MIPS Engineering, S.R.L, siena, Italy).
Methods: The automatic classifier inside the software is based on a 'match by similarity' algorithm, based on the measurement of the Euclidean distances of all variables considered from the reference image. Two-hundred and four clinically benign pigmented lesion, belonging to 18 patients were examined, stored and automatically processed. For each lesion objective parameters related to geometry, color and texture were automatically evaluated.
Results: We found skin color (healthy skin) is objectively different from subject to subject and the lesion color is more similar among different lesions of the same patient than among lesions belonging to different individuals both in their darkest and slightly dark component. We also observed that lesion dimensions are individual correlates, i.e. the probability for a lesion to be large is higher when the other, in the same patient, is large.
Conclusion: Many parameters of pigmented skin lesions evaluated by digital dermoscopy analysis are similar in the same patient and different from those belonging to different individuals. This indicates that, when considering a lesion, we should take into account the peculiar patient's characteristics.

Key words: digital dermatoscopy – epiluminescence microscopy – melanoma – nevus

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DERMATOSCOPY, ALSO called dermoscopy or epiluminescence light microscopy, is a microscope-based technique which allows, using a substrate of oil placed between the skin and the optics, to observe subcutaneous patterns not visible to the naked eye. In this way, it is possible to evaluate the *in vivo* morphologic features that have been demonstrated to be determinants of the differentiation of pigmented skin lesions (PSL) (1–8). The digital technology allows the transformation, using well-defined algorithms, of dermoscopic images into matrices of numbers, i.e. digital pictures, allowing the numeric evaluation of colors and shapes of the represented PSL (9, 10). Many differences in color, shape and dimension exist between different moles, even in the same individual. Major differences might be accounted for both by genetic factors such as skin color and other pigmentary characteristics of the subject, and by environmental factors, mainly sunlight exposure (11). Therefore, it would be of great value, when evaluating PSL of a patient, to take into account the degree of intra- and inter-individual variability of several dermoscopic diagnostic parameters.

Shapes and colors play a key role in the early detection of cutaneous malignant melanoma

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(MM) using digital algorithms to classify and automatically analyze pigmented lesions (12–14). Each PSL is, in fact, different from the other and its uniqueness is due to the distribution of the pigment below the skin. The clusters of melanocytes may originate darker zones or peripheral dark areas. Superficial pigmentation leads to black dots, and many other factors contribute to the pigmented network aspect originating the unique aspect of a lesion. Many attempts to evaluate the colors and patterns by subjective interpretative algorithms or numeric computerized methods have been made (9–14). The science of object recognition and analysis allows to numerically evaluate shapes and colors on the basis of previously defined rules (15–17). An algorithm consists of a series of simple instructions starting from initial data and leading to unambiguous results in a finite numbers of steps, allowing the implementation of a reliable mechanistic model using digital analysis. Once the problem is known and the algorithms defined, a computer-based system may translate the subjective perceptions into measurement values. Clusters of parameters can be statistically analyzed in order to classify different groups of lesions. Subsequently, artificial neural network (ANN) classifiers or multivariate mathematical models may serve to differentiate groups of different lesions (18).

The aim of this study was to examine objective digital parameters, obtained by dermatoscopic analysis of pigmented lesions taken from subjects with high mole counts, in order to assess the morphologic and chromatic differences between lesions belonging to different patients and between lesions belonging to the same patient.

Methods

Instrumentation

The DB-MIPS$^{(r)}$ System (Fig. 1) consists in a handle microscope, which provides different magnifications $\times 6$ through $\times 40$ allowing a horizontal field of view (FOV) ranging from 45.3 mm (17 pels/mm) to 6.8 mm (113 pels/mm). The illumination is provided by a 3200 K tungsten lamp. A 3 CCD (charge coupled device) is connected to a digitizing board placed in a Personal Computer. The 768×576 Pal Broadcast video signal is digitized directly into the three RGB components in order to avoid noise problems and to allow the maximum available quality.

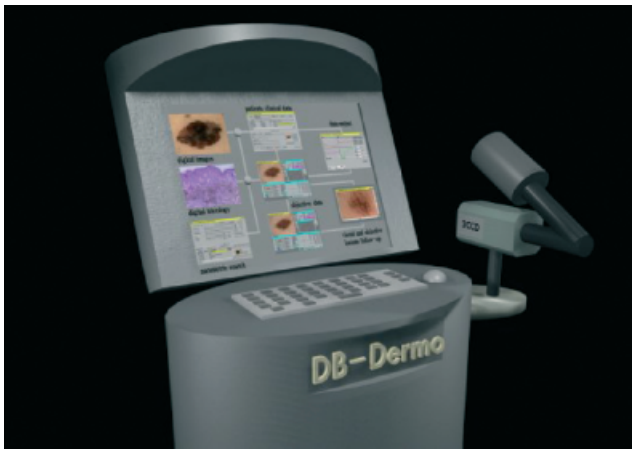

Fig. 1. DB-MIPS System.

TABLE 1. The objective geometries: some parameters

Geometries		
Name	Description	Measurement unit – range
Area	Area inside the outline	mm^2
D_{min}	Maximum diameter of the lesion	Mm
D_{max}	Minimum diameter of the lesion	Mm
D_{ratio}	Ratio between the D_{min} and D_{max}	0–100
Symvar	Normalized variance of the symmetry respect to 180 axes	0–100
Circ	Normalized differences in overlapping zones with a circle having the same area of the lesion	0–100
Shape	Normalized evaluation of the indentation of the border	0–100

The 24 bits/pixel, i.e. true color, PSL image is automatically processed by the DDA Software (BIO MIPS Engineering, S.R.L., Siena, Italy) module which automatically evaluates the outline of the lesion giving 50 objective parameters subdivided into three categories: geometries, colors, and textures and islands of colors (Tables 1–3). Each series of parameters is stored along with the coded image of the corresponding lesion. A proper, artificial intelligence-based database module permits to store images and patient's data. During 6 years of daily PSL observation, 45769 lesions have been framed and stored in magneto optical drives by three standardized DBDermo Systems (Fig. 2). The automatic classifier inside the DDA-Mips software is based on a 'match by similarity' algorithm based on the measurements of Euclidean distances of all the studied variables with respect to those of the reference image. The ordered list of images (sorted by ascending order of properly weighted sums of distances) show the most similar lesions.

The similarity analysis is based on 630 samples of melanoma and 1800 other benign lesions stored in eight different centers equipped with the same system.

Patients

A series of 18 consecutive patients, referring to the Digital Epiluminescence Service of the Istituto Dermopatico dell'Immacolata for checking their PSL between March 1999 and February 2000, was included in the study. For each patient, the images of all the lesions having a diameter greater than 2 mm were taken at a magnification of $\times 16$, stored and subsequently processed as described above in this section.

Statistical analysis

The following repeated measures analysis of variance model (random effects ANOVA model) was used to estimate the variance components: $X_{ij} = S_i + \varepsilon_{ij}$, where S_i is the random variable $N(\mu, \sigma_b^2)$ for variation between subjects, and ε_{ij} is white noise error term $N(0, \sigma_w^2)$. For each subject k_i nevi were measured ($i = 1, \ldots, 18$). We indicated with X_{ij} the value of variable X on the jth nevi on subject i, with $\bar{X}_i$ the mean for subject i, and with $\bar{X}$ the overall mean.

The ANOVA table is as follows:

Source of variance	Sum of squares (SS)	Degrees of freedom (df)	Mean squares (MS = SS/df)	Expected mean squares
Between subjects	$\bar{k}\sum_{i=1}^{18}(\bar{X}_i - \bar{X})^2$	$18-1$	MS_b	$\sigma_w^2 + \bar{k}\sigma_b^2$
Within subjects	$\sum_{i=1}^{18}\sum_{j=1}^{k_i}(X_{ij} - \bar{X}_i)^2$	$18(\bar{k}-1)$	MS_w	σ_w^2
Total	$\sum_{i=1}^{18}\sum_{j=1}^{k_i}(X_{ij} - \bar{X})^2$	$18\bar{k}-1$		

Estimates of within-person or intra-individual variation $\hat{\sigma}_w^2$, and between-person or inter-individual variation $\hat{\sigma}_b^2$ were calculated by setting mean squares equal to their expected values. The values for $\hat{\sigma}_b^2$ were calculated from the following relationships:

$$MS_w = \hat{\sigma}_w^2$$

$$MS_b = \hat{\sigma}_w^2 + \bar{k}\hat{\sigma}_b^2$$

$$\hat{\sigma}_b^2 = \frac{MS_b - \hat{\sigma}_w^2}{\bar{k}}$$

TABLE 2. The objective colors and textures: some parameters

Colors and texture analysis		
Name	Description	Measurement unit – range
SkinRA, SkinGA, SkinBA	R,G,B median values of the healthy skin surrounding the lesion's outline	0–32
Grad	Skin-Lesion gradient	0–100
Grad10n	Decile of Skin-Lesion's gradient histogram	0–100
Grad25n	Quartile of Skin-Lesion's gradient histogram	0–100
Grad50n	50 percentile of Skin-Lesion's gradient histogram	0–100
Grads	Normalized variance of the Skin-Lesion's gradient histogram	0–100
Gradp	Peaks of the Skin-Lesion's gradient histogram	0–100
RedAve, GreenAve, BluAve	R,G,B median values of the colors inside the lesion's outline	0–32
RedQua, GreenQua, BluQua	R,G,B lesion's histogram quartiles	0–32
RedTen, GreenTen, BluTen	R,G,B lesion's histogram deciles	0–32
Contrast	Co-occurrence matrices contrast	0–4
Entropy	Co-occurrence matrices entropy	0–4
Idm	Contrast's ratio at different steps	0–100

In addition, we tested the hypothesis $S_i = S$, $i = 1,\ldots,18$, with the F-statistic:

$$F = \frac{MS_b}{MS_w}$$

Because of the differences in the number of nevi examined among the study subjects, the analysis was actually based on an unbalanced model.

Results

A total of 204 clinically benign pigmented lesions belonging to 18 patients were examined, stored and automatically processed by DB-Mips system. For each lesion a number of objective parameters related to geometry, colors, textures and islands (i.e., internal color clusters distribution) have been automatically evaluated (Tables 1–3). The

TABLE 3. The 'Islands of colors' objective values: some parameters

Islands (clusters of colors)		
Name	Description	Measurement unit – range
TransVal	The percentage and balanceness of the area inside the lesion's border closer to the surrounding skin colors	0–100
BackVal	The percentage of areas between the mean color of the lesion and the darker areas	0–100
BackMom	The unbalance of BackVal areas respect to the center of gravity of the lesion	0–100
RHom, GHom, Bhom	The homogeneity of textures evaluated on the Red, Green and Blue bands	0–100
BluVal	The percentage of areas with gray–blue dominance	0–100
BluMom	The unbalance of the Blue–Gray Areas respect to the center of gravity of the lesion	0–100
DarkVal	Percentage of Dark Areas inside the lesions (evaluated by means of segmentation)	0–100
DarkMom	The unbalance of the Dark Areas respect to the center of gravity of the lesion	0–100
Pdark	Normalized Gradient of the dark areas from the center to the periphery of lesion	0–100
Unbal	Weighted chromatic unbalance respect to the center of gravity of the lesion	0–100

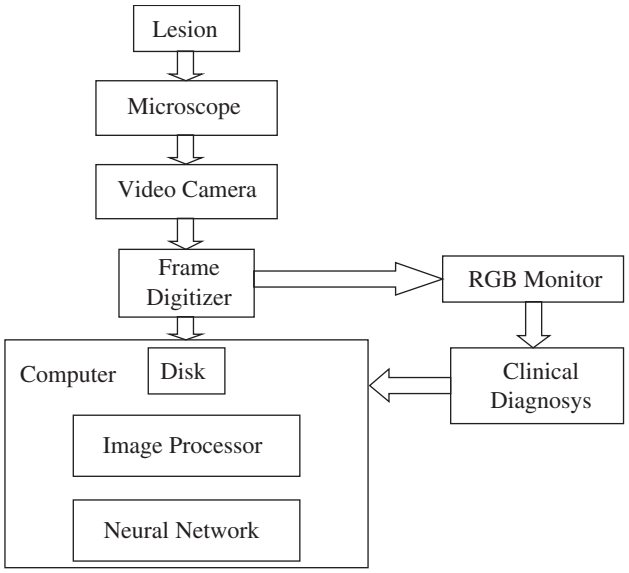

Fig. 2. The System's lay-out.

TABLE 4. Description of the study patients by age, sex and number of nevi

Patient	No. of naevi	No./total percentage	Sex	Age
1	9	4.43	F	28
2	10	4.93	F	25
3	11	5.42	M	29
4	17	8.37	M	40
5	10	4.93	M	61
6	10	4.93	F	33
7	10	4.93	M	37
8	10	4.93	M	29
9	10	4.93	M	35
10	10	4.93	M	29
11	12	5.91	F	32
12	10	4.93	F	28
13	10	4.93	M	24
14	17	8.37	M	16
15	9	4.43	F	30
16	18	8.87	F	35
17	10	4.93	F	31
18	10	4.93	M	20

demographic characteristics of the study patients and number of examined nevi for each patient are shown in Table 4. The results of the statistical analysis of the variance components, based on a random effect model, are reported in Table 5. The proportion of the total variance due to inter-individual variance is a measure of the part of the total variability that can be accounted for by differences between individuals. For a given ELM parameter, high values of this proportion indicate a high homogeneity of the values of that specific parameter among the PSL of individual subjects. In our series of patients, several ELM parameters measuring skin color, geometry, colors and texture of PSL show a high degree of similarity among different lesions of the same individual. Among the geometrical variables, the parameters that show a higher intra-individual homogeneity are those related to the lesion's size. For minimum and maximum diameter, the proportion of the total variability explained by inter-individual differences is 29%. As expected, the lesion's area shows a similar tendency, with a proportion of variability explained by inter-individual differences of 26%. A lower degree of intra-individual consistency is observed in circularity, shape, and symmetry variance, which are variables dealing with the roundness, the irregularity of the edges, and the lack of symmetry of the PSL. In other words, among the geometric variables, the PSL size seems to represent a unique characteristic of an individual, whereas the shape and the characteristics of the edges tend to vary in the same individual.

The parameters related to colors and texture include a subset of parameters (red median, blue median, and green median) related to the color of

TABLE 5. Mean values, intra-individual variance, inter-individual (residual) variance, and total variance of ELM parameters for 204 PSL of 18 subjects by random effect analysis

Parameter	Intra-individual variance	Inter-individual variance	Total variance	% of the total variance due to inter-individual variance	% residual variance
Geometries					
Minimal diameter	2.307	0.934	3.241	**28.8**	71.2
Maximum diameter	7.032	2.838	9.870	**28.8**	71.2
Area	498.639	174.185	672.824	**25.9**	74.1
Circularity	0.009	0.002	0.011	15.6	84.4
Shape	0.007	0.001	0.007	9.9	90.1
Symmetry variance	3.335	0.328	3.663	9.0	91.0
Colors and texture					
Skin red median	3.590	3.858	7.448	**51.8**	48.2
Skin blue median	2.317	2.092	4.409	**47.4**	52.6
Skin green median	2.772	1.564	4.337	**36.1**	63.9
Lesion red median	6.404	4.391	10.795	**40.7**	59.3
Lesion blue median	2.265	1.300	3.565	**36.5**	63.5
Lesion green median	3.868	1.806	5.674	**31.8**	68.2
Color islands					
gradient	29.678	7.514	37.192	20.2	79.8
rhomn_	0.025	0.007	0.032	21.7	78.3
entropyn	0.056	0.004	0.060	7.2	92.8
asmn	0.001	0.000	0.002	23.6	76.4
contrast	0.024	0.007	0.032	23.5	76.5
transval	0.007	0.001	0.008	18.3	81.7
darkvaln	0.001	0.000	0.001	24.2	75.8
bluvaln	0.009	0.003	0.011	23.9	76.1
blumomn	0.006	0.001	0.008	16.6	83.4
backvaln	0.001	0.000	0.002	16.4	83.6
umbaln	0.003	0.000	0.003	6.9	93.1
pdarkn7	0.010	0.001	0.010	6.4	93.6
darkmomn	0.001	0.000	0.001	6.4	93.6
backmomn	0.002	0.000	0.002	4.4	95.6
transmom	0.034	0.001	0.035	3.1	96.9

normal skin, and a subset related to the lesion color. Both subsets of parameters present a high degree of homogeneity among different body sites and different lesions of the same individual, with the colors of normal skin showing, as expected, the lowest degree of intra-individual variability (Fig. 3).

Among the parameters included in the color islands group, the ones that show a high degree of intra-individual homogeneity are those referring to the skin-lesion gradient (gradient, transval), texture quality (rhomn, contrast), and color uniformity (darkval, bluval, blumomn, backvaln). By contrast, the parameters measuring the color homogeneity with respect to the lesion barycentre and the parameter 'entropy', measuring the lesion irregularity, show a variability unexplained by inter-individual differences.

These results have been confirmed by the similarity check, integrated in the DB-Mips software. The similarity check, in fact, permits to see the stored lesions that are similar to the lesion

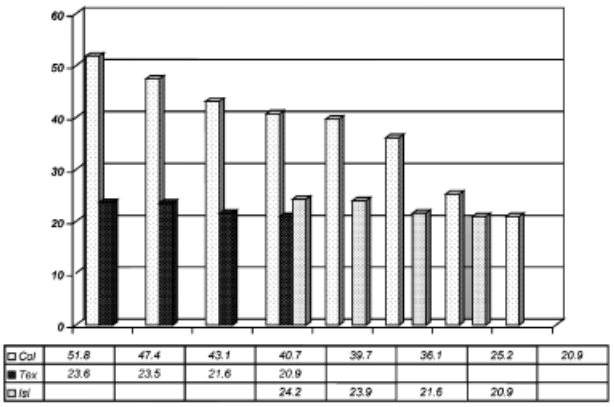

Fig. 3. IC values plotted by groups. The greatest homogeneity is given by colors.

under analysis, by means of the nearest-neighbor algorithm, properly modified for the purpose of PSL analyses. A similarity matching album, given on the basis of the most similar lesions found, indicated, in fact, a strong probability of having the same patient's lesions on the first matched.

Discussion

In this study we have shown how the healthy skin color components (SkinRA, SkinGA, SkinBA) are in the first places sorted by similarity scores, and so the most intra-similar. This means that the skin color is, objectively, different from subject to subject and this apparently obvious result represents a sort of proof of measurements. We can observe that even the lesion colors are more similar among different lesions of the same patients, both in their darkest components (Redten, GreenTen, BluTen) and in the slightly dark components (RedQua, GreenQua and BluQua), than among lesions belonging to different individuals. This observation indicates that, when considering the lesion color, we should take into account the fact that the patient's genetics in some way contributes and thus influence the darkness of the lesions. Subsequently, we observe the dimensions of the lesion ($D_{\min}$, $D_{\max}$, Area), indicating the fact probability for PSL being higher is large when the other in the same patient is of higher dimensions. The subsequent parameter is the abruptness of the border when considering it in the darker areas (Grad10), immediately followed by the darker areas themselves, going toward the border's periphery (Darkval). Subsequently, we can note Blue Dominant colors (BluVal) and the homogeneity in the distribution of colors clusters inside the lesion's border (Rhom, Ghom, Bhom). The above-mentioned objective parameters are known to be very important for the differentiation of MM from other lesions, and is worthy of deepening. It is a remarkable fact that the verification of the similarity matching is influenced up to 8% (58% represents 8% more than the casuality) when objectively analyzing these data. An immediate comment refers to the automated machine diagnostic processes, which could be influenced by these factors. If it was possible to detect which factors (skin type, age, history of sunburns, etc.) influence the appearance of a lesion, then it should be easy to correct and calibrate the statistical classification of the PSL in a sort of 'rebalancing equation'. It should emphasized that a certain percentage of error (in terms of diagnostic accuracy) could be avoided if some parameters could be considered inside the patient's context. When diagnosing a PSL, a clinician focuses his attention on the peculiar caracteristics of the host. A proof of this situation is the necessity of building proper databases owning the cutaneous properties of a patient, his familiarity vs. the MM, his young sunburns and many other factors, like colors of the eyes and hair. The statistical results show the reasons for collecting this data, because they must be considered of paramount importance in the diagnostic context. The rebalancing values can be probably detected if considering a very large number of cases whithin the patient's history and data. We are collecting cases and working in this direction hoping to achieve a statistically significant result.

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