Claridge E, Cotton S, Moncrieff M, Hall P (2006)Spectrophotometric Intracutaneous Imaging (SIAscopy): Method and clinical applications. Chapter 37 in *Handbook of Non-Invasive Methods and the Skin* (2nd ed). Serup J, Jemec GBE, Grove G (Eds), 315-325: CRC Press.

SPECTROPHOTOMETRIC INTRACUTANEOUS IMAGING (SIASCOPY): METHOD AND CLINICAL APPLICATIONS

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1. INTRODUCTION

SIAscopy – Spectrophotometric Intracutaneous Analysis – is a new optical skin imaging method in which computer reconstructed images reveal a number of aspects of skin histology, namely the concentration of epidermal melanin, the concentration of dermal blood, the thickness of the papillary dermis and, in pathological cases, the presence of dermal melanin. Due to its ability to provide a unique insight into the skin histology *in vivo*, SIAscopy is becoming a preferred tool for the diagnosis of pigmented skin lesions and early melanoma detection. Other applications, both clinical and not, are in the experimental stage of development.

2. BACKGROUND

The study of any clinical dermatology textbook will reveal that colour is an important diagnostic indicator (e.g. [1]). This is because the colours seen on the skin surface reflect many aspects of its internal structure and composition. For example, the reddening of the skin, erythema, indicates increased amounts of dermal blood.

If the skin is considered as a physical system comprising components with particular optical properties, then its colour can be analysed by using the principles of physics. Considered in this way, skin colour is a function of the spectral characteristics of light remitted from the skin. This, in turn, is the result of the interaction of light with the structures in the skin and depends on the optical properties of the skin components and the spectral composition of the light shone on the skin surface (the incident light).

Given information about the optical properties of the skin, the colour of the remitted light can be computed using physics equations describing a light transport theory [2-3]. In this way it is possible to predict the skin colours corresponding to a given particular skin structure. This approach has been used in a number of applications [4-6]. However, in SIAscopy the process is reversed, allowing predictions of the skin structure to be made from skin colours captured by a digital camera. From calibrated images captured in the red, green, blue and near-infrared parts of the spectrum,

the computer reconstructs four images showing respectively the concentration of epidermal melanin, the concentration of blood within the papillary dermis, the thickness of collagen of in the papillary dermis, and the presence of dermal melanin. These quantities are represented as *parametric maps* (SIAgraphs) which can be either viewed directly or subjected to further image analysis. Information contained in these images is complementary to that obtained through normal visual examination and thus it is likely to help in differential diagnosis. The method is totally non-invasive as it uses only visible and near-infrared light. As an example, Figure 1 shows an advanced melanoma and a set of SIAgraphs showing the concentration of dermal and epidermal melanin, blood and collagen thickness across the imaged lesion and its surrounding skin. A detailed description and interpretation of the maps is given in section 5.1.

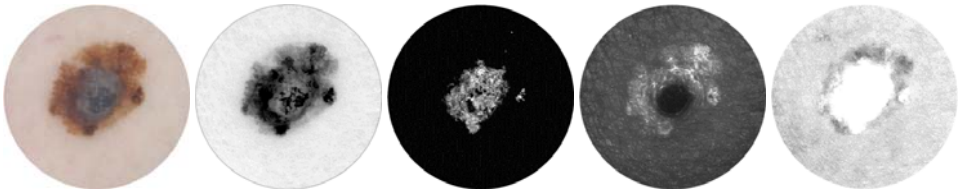

Figure 1. (a) A colour image of a melanoma together with parametric maps showing: (b) total melanin (darker = more); (c) dermal melanin, whose presence suggests abnormality (brighter = more); (d) papillary dermis, showing that collagen was displaced by melanocytes and the melanin they produce; also a peripheral increase indicating fibrosis in the region where cancer is developing actively (brighter = more); (e) dermal blood, showing an absence in the centre, suggesting necrosis; also an increase on the periphery, suggesting inflammation and vasodilatation in the area of active cancer growth (darker = more). These features are typical for melanoma and can be easily seen in the maps.

3. THE SCIENCE OF SIASCOPY

3.1 GENERAL OUTLINE OF THE METHOD

The key concept underpinning SIAscopy is a *model of skin colouration*. It is a set of correspondences between the parameters characterising the skin and its colours. The model is constructed by computing the spectra remitted from the skin from parameters specifying its structure and optical properties, and then computing equivalent RGB colours. This step needs to be carried out only once. The model is then used to perform the inversion process, i.e. to infer the combination of histological parameters which lead to a particular colour of tissue. Figure 2 shows schematically the process of image formation. As a final step, semi-quantitative information about the histological parameters is represented in a form of parametric maps (SIAgraphs). These are grey-scale images showing the magnitude of the parameters at each pixel of the original skin image.

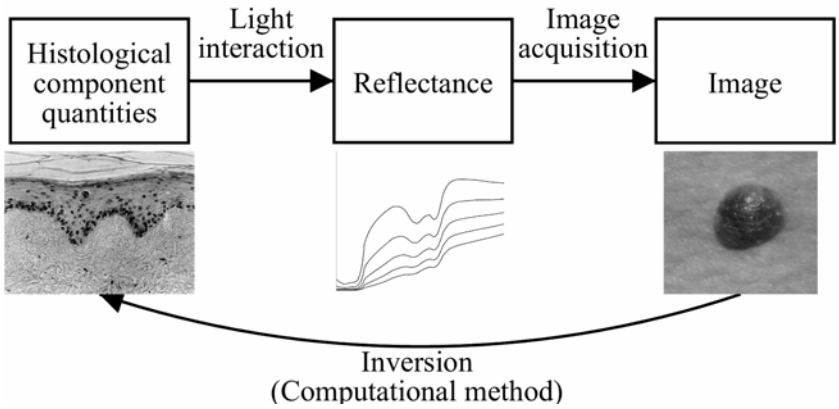

Figure 2. The process of image formation. Histological components present in the skin give rise to a reflectance spectrum as a result of the light interaction with the tissue. The spectrum is specific to the particular skin composition. The remitted light is captured by a camera and stored as a digital image. The digital image is normally composed of three (red, green and blue) or more spectral bands. SIAgraphs are derived by a computational method which takes the digital image as input and from it derives the quantities of the histological components present in the tissue.

3.2 OPTICAL MODEL OF THE NORMAL SKIN

The normal skin can be optically modelled as five layers, each with different optical properties.

The stratum corneum is the most superficial layer of the epidermis, consisting of keratinocytes full of keratin. Its thickness varies considerably between individuals as well as between different sites on the body. Optically it scatters the light forward, but it does not change its spectral characteristics.

The remaining part of the epidermis is mostly cellular, containing dividing keratinocytes and basal cells, in addition to immune cells and melanocytes, all of which are transparent to the visible light. The melanocytes produce melanin, a pigment which strongly absorbs light in the blue part of the visible spectrum and in the ultraviolet (see Figure 3).

All light not absorbed by melanin can be assumed to pass into the dermis, a distinct, deeper layer of the skin separated from the epidermis by a basement membrane known as the dermal - epidermal junction . The dermis consists of two structurally different layers, papillary and reticular, which also differ optically. The papillary dermis consists of loosely-packed collagen fibres with a small diameter. This arrangement makes this layer highly back-scattering so that a large proportion of incoming light is directed back towards the skin surface. The reticular dermis is composed of significantly larger collagen fibres arranged into tightly-knit and highly organised bundles. The diameter of these bundles is comparable to or greater than the wavelengths of visible light. Structures of this size cause scattering which is highly forward-directed. Thus any light which reaches this layer is passed on deeper into the subcutis, where it is absorbed and does not contribute to the spectrum remitted from the skin. The papillary dermis contains an extensive network of fine blood vessels and the haemoglobins present in blood act as selective absorbers of light in both blue and green part of the spectrum (see Figure 3).

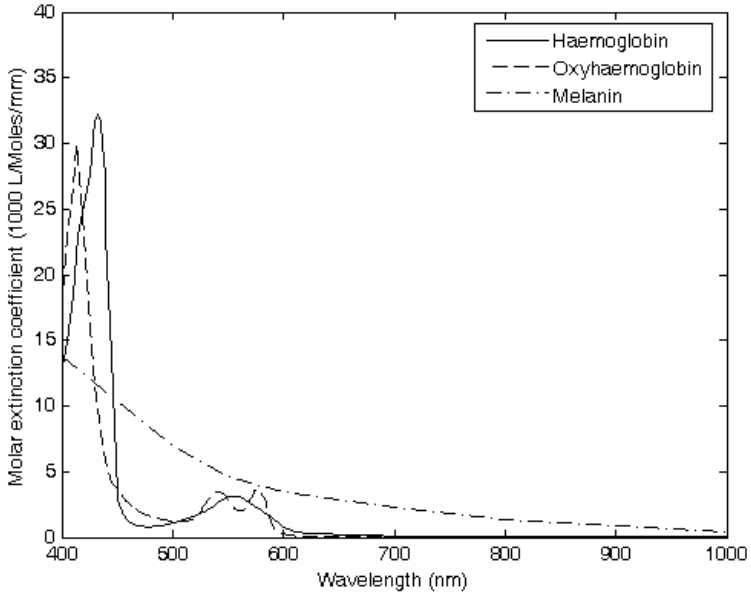

Figure 3. The absorption spectra for melanin, haemoglobin and oxyhaemoglobin. In the model a mixture of 50% haemoglobin and 50% oxyhaemoglobin has been used.

For the above description of the skin structure, the following parameters are required to model the optical properties of the normal skin:

- a set of wavelength (λ) dependent absorption coefficients for melanin, $\mu_a^m(\lambda)$
- the melanin concentration, c^m
- the absorption coefficients for haemoglobin, $\mu_a^h(\lambda)$
- the haemoglobin concentration, c^h
- the scatter coefficient for collagen in the papillary dermis, μ_s^{pd}
- the thickness of the papillary dermis collagen layer, d^{pd}
- the scatter coefficient for collagen in the reticular dermis, μ_s^{rd}
- the thickness of the reticular dermis collagen layer, d^{rd}

3.3 FORWARD PREDICTIVE MODEL OF SKIN COLOURATION

Given the above parameters, a remitted light spectrum can be computed using physics-defined light transport equations. The optical characteristics of the skin tissue are such that a number of different methods can be used. This work implements a two-flux method [7] based on Kubelka-Munk theory [2]. It computes the remitted (R) and transmitted (T) light separately for each layer i: R_i and T_i.

$$R_i = \frac{(1-\beta^2)(e^{Kd} - e^{-Kd})}{(1+\beta)^2 e^{Kd} - (1-\beta)^2 e^{-Kd}}$$

$$T_i = \frac{4\beta}{(1+\beta)^2 e^{Kd} - (1-\beta)^2 e^{-Kd}}$$

where $K = \sqrt{k(k+2s)}$, $\beta = \sqrt{\frac{k}{k+2s}}$, d is a layer thickness, k $\propto \mu_a$ and s $\propto \mu_s$.

For an n layered system, values for $R_{12...n}$ and $T_{12...n}$ are computed recursively [8]:

$$R_{12...n} = R_{12...n-1} + \frac{T^2_{12...n-1} R_n}{1 - R_{12...n-1} R_n} \quad \text{and} \quad T_{12...n} = \frac{T_{12...n-1} T_n}{1 - R_{12...n-1} R_n}$$

The method requires that the incident light is diffuse. This condition is fulfilled because, as explained in section 3.1, light is diffused as it passes through stratum corneum.

A complete model of colouration for the normal skin is computed by considering all the possible values of parameters defining the skin. In the set of parameters given in section 3.2, the absorption and scatter coefficients ($\mu_a^m(\lambda)$, $\mu_a^h(\lambda)$, μ_s^{pd}, μ_s^{rd}) are treated as constants because they characterise the entire tissue type rather than a specific instance of the tissue. Their specific values are based on published data (e.g. [9]). The thickness of the reticular dermis, d^{rd}, can be assigned an arbitrary value because due to its strong forward scattering properties even a thin layer will prevent any remission of light. The parameters characterising a specific instance of the skin are the melanin and blood concentration c^m and c^h, and the thickness of the papillary dermis, d^{pd}. Thus the model of skin colouration computes a colour vector for each combination of the above three parameters, where the parameters are drawn from the entire range of histologically valid concentrations and thicknesses. In this way a cross-reference between histology and colour is formed.

The range of wavelengths used for computing the remitted spectra, from λ = 400 to 1300 nm, covers the whole visible spectrum and a small range of near infrared radiation. The wavelengths used for the computations are taken at equal intervals of 30nm, giving 30 discrete points for each spectrum. The incident light is white, i.e. it has equal contributions from each discrete wavelength. The [*r g b nir*] vectors are derived from the computed spectra using a set of filter response functions equivalent to the physical filters used by the SIAscope.

Table 1 The range of histological parameter values corresponding to the normal skin

Parameter	Symbol	Range from	Range to
Epidermal melanin concentration (10^{-1} mMol/l)	c^m	0.00	8.69
Haemoglobin concentration (in dermal blood) (mMol/l)	c^h	0.00	4.34
Thickness of the papillary dermis (10^{-4} m)	d^{pd}	0.05	0.40

3.4 INVERSION AND COMPUTATION OF SIAGRAPHS

Figure 4 illustrates the relationship between the two reference systems: colour, [*r g b*]; and histological parameters: melanin concentration, blood concentration and thickness of the papillary dermis, [c^m c^h d^{pd}]. These relationships constitute the model of skin colouration. Since there is a one-to-one mapping between the colours and the parameters [10], the parameter values can be retrieved from the model, given the colour vector obtained from each point in a colour image of the skin. The magnitude of each parameter is then displayed at each pixel location in a separate image, giving three SIAgraphs: melanin, haemoglobin and papillary dermis, as shown in figures 1 and 6, (b), (d) and (e).

3.5 MALIGNANT MELANOMA

The model of colouration described above represents *all* the instances of the normal skin. Differences related to racial type, age or gender are all in terms of the quantities of pigments and thicknesses of the layers and hence are all represented in the model. However, certain pathologies change the structure of the skin in such a way that it is no longer represented by the normal model. An example is malignant melanoma where malignant melanocytes have penetrated into the dermal layer and created melanin deposits there. Optically, this not only increases the overall melanin concentration at the site of the deposit, but also decreases the total scatter as melanin replaces the highly back-scattering collagen in the papillary dermis. The colours of the skin with melanin deposits in the dermis no longer fit the model of normal colouration. In the schematic representation shown in Figure 4 such colours appear outside the “surface” which corresponds to a particular thickness of the papillary dermis. This non-conformance to the model identifies colours as “abnormal” and provides a highly sensitive diagnostic sign. The presence of dermal melanin is represented in the fourth SIAgraph (figures 1 and 6 (c)).

There are also a number of histological changes associated with melanoma, such as angiogenesis and fibrosis, which induce colour changes within the bounds of the normal colouration. These secondary signs have been found diagnostically important, as will be described in section 5.1.

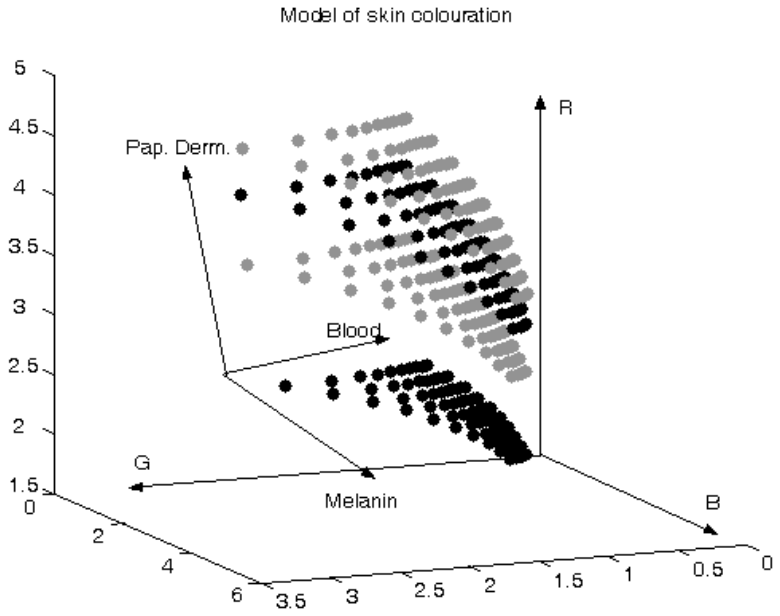

Figure 4. A graphical representation of the model of skin colouration which encodes the relationships between the quantities of histological components and the RGB colours. The main axes labelled R, G and B represent the colour system. The histological parameter system is represented by smaller axes labelled Melanin, Blood and Pap.Derm. Each dot represents a specific instance of the skin tissue. It is characterised by the specific quantities of melanin, blood and thickness of the papillary dermis, as indicated by its position in the histological parameter system; and by the specific colour, as indicated by its position in the colour system. During the model construction the colours are computed from the parameters using light transport equations. During the image interpretation, the parameters corresponding to the image colours are "looked up" from the model.

3.6 VALIDATION

One of the advantages of physics based methods is that it is possible to estimate the accuracy of their results if errors on the input data can be estimated. The two main sources of error associated with the computation of the parametric maps are the uncertainties in the absorption and scatter coefficients (σ_{spec}) [9] and the camera digitisation error (σ_{cam}), derived from the signal-to-noise ratio (SNR) characteristics of a particular camera. As the two sources are independent, the respective errors can be combined to give the overall error estimate [10]

$$\sigma_{pk} = \sqrt{\sigma_{spec}^{\ 2} + \sigma_{cam}^{\ 2}}$$

Errors associated with each of the skin parameters can then be calculated using standard error propagation [11]. Table 2 shows the percentage errors derived in this way.

Table 2 Percentage errors associated with the recovery of the three main parameters, excluding zero concentrations of blood and melanin

	mean	st dev	median
Melanin	14.0	14.0	13.9
Blood	5.0	8.2	3.4
Papillary dermis	3.3	3.4	3.2

Practical validation has established that, firstly, the skin colours predicted by Kubelka - Munk equations were consistent with skin colours measured from the skins of volunteers of various racial origins (Cotton and Claridge, 1996). The validity of parametric maps was established through indirect comparisons and measurements [12-13].

4. IMAGE ACQUISITION USING A SIASCOPE

The SIAscope is a commercial, clinically approved device [14] operating according to the principles of the imaging method described above. Images of the skin can be taken over an area of 24 x 24 mm or 12 x 12 mm, corresponding to spatial resolutions of 40 μm or 20 μm per pixel respectively. Images are acquired using a lightweight handset connected to a laptop via a IEEE-1394 connection. A number of spectrally filtered images are obtained in the range between 400 nm to 1000 nm, calibrated and processed to compute the parametric maps. These are then displayed in the form of SIAgraphs on the screen together with the colour image of a lesion. SIAscope II is shown in figure 5.

Figure 5. The SIAscope II – a commercial device for skin imaging and computation of SIAgraphs. Images are acquired using a handset (at the bottom right of the case) connected to a laptop computer. The image interpretation is implemented on the computer and SIAgraphs are displayed on its screen.

5. APPLICATIONS

5.1 CLINICAL APPLICATIONS

The main current application area for SIAscope is as an aid for diagnosis of pigmented skin lesions, and in particular for early detection of cutaneous melanoma. It is particularly suited for this role because the SIAgraphs make explicit a number of primary and secondary signs associated with this cancer. Table 3 lists the features together with their sensitivity and specificity as melanoma predictors.

Table 3 Diagnostic features shown in SIAgraphs and their individual sensitivity and specificity as melanoma predictors

Diagnostic feature	SIAgraph	Sensitivity (%)	Specificity (%)
Presence of dermal melanin	Dermal melanin	96.2	56.8
Areas within the lesion with no blood present (“blood displacement”)	Dermal blood	75.0	70.3
Increase in blood level on the lesion periphery (“erythematous blush”)	Dermal blood	75.0	65.5
Blood displacement with erythematous blush		63.5	84.8
Areas within the lesion with no collagen present (“collagen holes”)	Collagen	78.8	74.0
Asymmetry	Total melanin	76.9	62.2

The lesion shown in figure 1 shows all the characteristic signs of invasive cutaneous melanoma. The presence of melanin in the dermis is a very sensitive sign, indicating invasion into the papillary dermis. Also coinciding with dermal melanin is a “collagen hole”, an area with no papillary collagen present, indicating destruction or replacement of the papillary dermis by melanoma. The blood distribution map shows the increase in blood levels on the lesion periphery (“erythematous blush”), which is indicative of inflammation and vasodilatation, often

associated with invasive skin tumours. In addition, there is a total lack of blood in the centre of the lesion in the area which coincides with the dermal melanin, further indicating destruction or replacement of the papillary dermis. Whilst other benign skin lesions may demonstrate either erythematous blush or blood displacement, it is the presence of the two signs together in the same lesion that is highly specific for invasive melanoma. The collagen map also shows fibrosis (the increase in collagen thickness and irregularity) on the lesion periphery, often associated with early, invasive melanoma [1].

The lesion in figure 6 is small and fairly pale. However, the SIAgraphs strongly suggest that it is a malignant case. Many significant features are present, including dermal melanin, blood displacement with erythematous blush together with evidence of fibrosis. Both lesions were histologically diagnosed as melanomas.

Figure 6. (a) A colour image of an early stage melanoma; Parametric maps showing (b) total melanin (darker = more); (c) dermal melanin (black = none, brighter = more); small speckles of dermal melanin can be seen in the centre of the lesion; (d) thickness of the papillary dermis (brighter = more); note the increased amount in all areas of increased epidermal melanin and one very distinct nest in the vicinity of the dermal melanin deposits; (e) blood (darker = more); note an erythematous reaction in the area corresponding to dermal melanin and a small decrease in the area corresponding to the dermal melanin deposits.

A number of larger studies have demonstrated that SIAscopy is an excellent diagnostic aid. Diagnosis using three SIAscopy features (dermal melanin, blood displacement and peripheral blush) together with the assessment of the lesion size yielded sensitivity of 80% and specificity of 83% on a set of 348 lesions [15]. Diagnosis using a simple scoring method that considers two SIAscopy features (dermal melanin, and blood displacement with peripheral blush) together with the assessment of the lesion size and the patient's age yielded on the same lesion set sensitivity of 90.4% and specificity of 74.0% [12]. Another study, using a scoring method which incorporates patient's age, lesion diameter, the presence of dermal melanin, collagen hole and blood displacement with peripheral blush, achieved specificity of 87% (78%) for sensivity level of 80% (100%) respectively, on a set of 214 lesions [16].

The most recent study [17] have shown that the SIAscope outperforms dermatoscopy in the diagnosis of melanoma producing a sensitivity of 91% and specificity of 91% compared with a sensitivity of 91% and specificity of 54% for a panel of experts using dermatoscopy. This study introduced the assessment of the dermal - epidermal junction to the analysis of a pigmented lesion and produced a simple clinical checklist:

A lesion is suspicious if it has

- An irregular dermal epidermal junction

OR

- Dermal melanin with any of
    - Irregular dermal melanin
    - Presence of linear vessels or dots
    - Regression structures

The use of the SIAscope has also been investigated in the assessment of psoriasis and eczema [18-19] where it has been shown to be useful in both differential diagnosis and the assessment of treatment regimes.

5.2 NON-CLINICAL APPLICATIONS

Although the imaging method was designed with clinical applications in mind, the generic nature of the underpinning science means that it is potentially applicable in many different areas. For example, in a cosmetics application, a modified method was used to image facial skin in order to detect spots and blemishes [20]. Images

in figure 7 show the original image together with SIAgraphs of blood and melanin. The blood image shows the increased levels in the lips and also clearly shows a number of "spots". The melanin image highlights a number of small moles (common naevi).

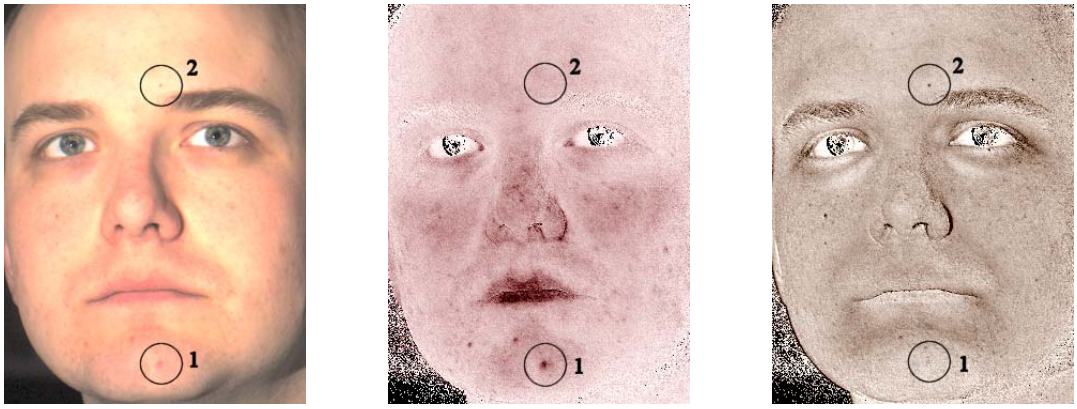

Figure 7. (a) A colour image of the face; (b) a blood SIAgraph showing haemoglobin concentration across the image; (c) a total melanin SIAgraph showing melanin concentration across the image. The region if interest 1 shows the location of a skin "spot", note that it is clearly visible in the blood image, but not in the melanin image. The region of interest 2 shows the location of a small "mole (common naevus), note that it is clearly visible in the melanin image but not in the blood image.

In a sport sciences application, a small study was carried out in which the blood supply levels at various body locations were measured as a function of time during strenuous exercise. In this application SIAscopy provided the scientists with a non-invasive indirect method of studying a thermoregulatory mechanisms in the human body. Figure 8 shows four blood SIAgraphs of two subjects.

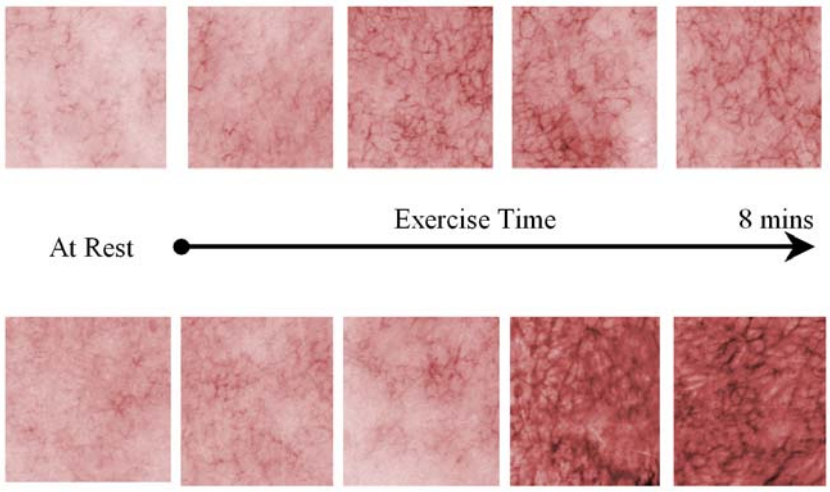

Figure 8. Four blood SIAgraphs from two subjects showing the effect of exercise on superficial blood supply.

5.3 FUTURE POTENTIAL

Due to its physical and physiological underpinnings, SIAscopy is a truly generic imaging method. The range of its applications is growing steadily. In the medical field the use of the method to determine excision margins for Basal Cell Carcinoma [21] is currently under investigation. Preliminary studies have also begun on the monitoring of wound healing (see figure 9), the development of ulcers and the assessment of Port Wine Stains prior to laser treatment. The ability to understand the composition and structure of the skin has also been of interest in the assessment of cosmetic treatments for the skin.

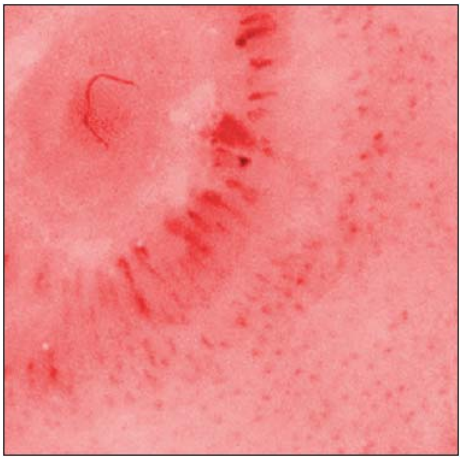

Figure 9. A blood SIAgraph taken around the edge of a healing punch biopsy wound (top left). Small punctate blood vessels can be seen in the surrounding skin. They have formed due to the release of angiogenic stimulants in the wound vicinity. As the wound heals these dots can be seen "stretching" into linear vessels around the wound edge.

6. DISCUSSION

The method in its current form is principally two-dimensional, and SIAgraphs show the surface distribution and the magnitudes of individual tissue components. This aspect makes it different from tomographic methods (e.g. OCT [22] and confocal microscopy [23]) which are capable of showing three-dimensional structure of the skin. The depth resolution of SIAscopy is limited by both absorption and scatter within the skin tissue. Its resolution within-the-surface varies depending on scatter, so that small details are not always resolved. However, the maps showing the gross distribution of histological parameters are still providing useful diagnostic insight into the tissue properties.

The detection of the presence of dermal melanin *in vivo* is one of the unique features of SIAscopy which in principle can detect melanin penetration at depths smaller than 30 μm from the dermal – epidermal junction. However, the accuracy of measurement decreases with increase in depth and increase in melanin concentration. Although this is a limitation in a general sense, it does not adversely affect the method's capability to detect the very thin, early melanomas which are still a challenge to other methods.

The encouraging diagnostic results achieved with the aid of SIAscopy can be attributed to the inclusion of the clinically appropriate variables in the scoring methods. For instance, increased diameter of a pigmented lesion is a risk factor for early melanoma actively enlarging; the presence of dermal melanin and blood displacement with erythematous blush are strong risk factors for early, invading melanoma; and, like most cancers, the risk of developing melanoma increases with age. Further advantage of these features is that they are rapidly identifiable in a repeatable and reproducible manner. Studies comparing intra- and inter-observer error of SIAscopy features demonstrated "excellent" or "almost perfect" scores in their identification [12]. This, together with the speed with which these features can be learnt, is in direct contrast with the identification of features employed by other methods in the diagnosis of cutaneous melanoma [26][27].

7. CONCLUSIONS

SIAscopy is a novel skin imaging method showing significant promise as a tool for *in vivo* inspection of the normal and abnormal skin. Unlike traditional image analysis methods, which operate primarily on the image itself, this method adds and exploits a physics based model of skin colouration. SIAgraphs reconstructed from colour images using the model of colouration, characterise the internal structure and composition of the skin rather than its external appearance and thus are far more informative than images obtained by simpler imaging methods. In clinical applications, the model can explain the skin appearance and thus increase understanding as to why various skin diseases manifest themselves through particular visual signs. As SIAgraphs show views directly related to histology, they can be easily understood by medical personnel and their interpretation does not require much training. A substantial body of experimental work showed that the method can help improve the diagnosis of melanoma. A range of further applications, in skin imaging and beyond [24-25], is currently being investigated.

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