Three dimensional modeling of bruise evolution for improved age determination

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Introduction

Child abuse

Child abuse has a severe effect on the mental and physical health of affected individuals, on both the short and the long term [1-3]. Although the phenomenon has long been present in our society, the spread of this problem has been denied for decades [4]. Recognizing child abuse has become increasingly important, as evidenced by the growing annual number of publications on child abuse that appeared in recent years (figure 1.1), and the instatement of Child Protection Teams in hospitals (Chapter 6).

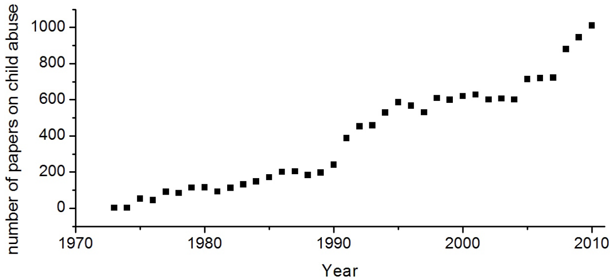

Figure 1.1. Annual number of publications on child abuse, approximately increasing as nr = 0.625*(Year-1970)^2. From: ISI web of knowledge, topic=child abuse.

This increase in scientific attention has also boosted the recognition in hospitals and family practices, but as Goren et al showed, many cases of child abuse are missed and if recognized often the follow up is lacking [5]. Each form of child abuse has its own characteristics of which physicians should be aware. In physical abuse for example, the presence of multiple bruises should raise questions, particularly in combination with a delay in the presentation of the injury and an unconventional interaction of the child with its parents. Upon examining bruises, several more factors can indicate abuse, for example bruises at unusual locations such as the back or buttocks, multiple bruises of uniform shape or bruises on immobile infants [6-10]. Another important factor in child abuse is the age of the bruise(s). When the age can be determined accurately, the time of injury can be established and, if needed, legal actions taken. However, despite extensive research [11-15], accurate age determination of bruises is not yet possible [16-18].

Bruise pathophysiology

In concordance with Randeberg et al [19] our hypothesis was that a clear understanding of bruise pathophysiology is a prerequisite for identifying methods that allow accurate age determination. A bruise is formed when a mechanical force causes the formation of a pool of blood in the subcutaneous layer (figure 1.2) [13-14, 19-20].

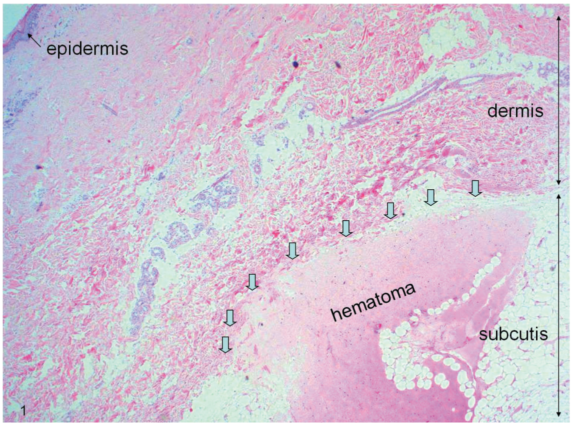

Figure 1.2. Histological image of a hematoma located in the subcutaneous layer. Arrows point to edge of hematoma in dermis.

The erythrocytes in the blood are phagocytosed by macrophages, and inside the macrophages the hemoglobin in the erythrocytes is converted to bilirubin, which is released into the interstitial fluid [21-22]. Both erythrocyte/macrophage complexes and the bilirubin diffuse in the skin upward into the dermis and outward in all skin layers. Because of the tight basal membrane, there is no diffusion into the epidermis. When sufficient amounts of these chromophores have reached the upper dermis, the bruise becomes visible as a blue/red hemorrhage (from the hemoglobin) or yellow hemorrhage (from the bilirubin), depending on the depth, amount of chromophore, oxygenation of the hemoglobin and skin pigmentation [13, 20, 23-24]. As a consequence of the size difference between the erythrocyte/macrophage complexes and the free bilirubin, the diffusion of the bilirubin is faster, causing a ring of yellow surrounding the red/blue hemoglobin part, or filling gaps between hemoglobin areas (figure 1.3).

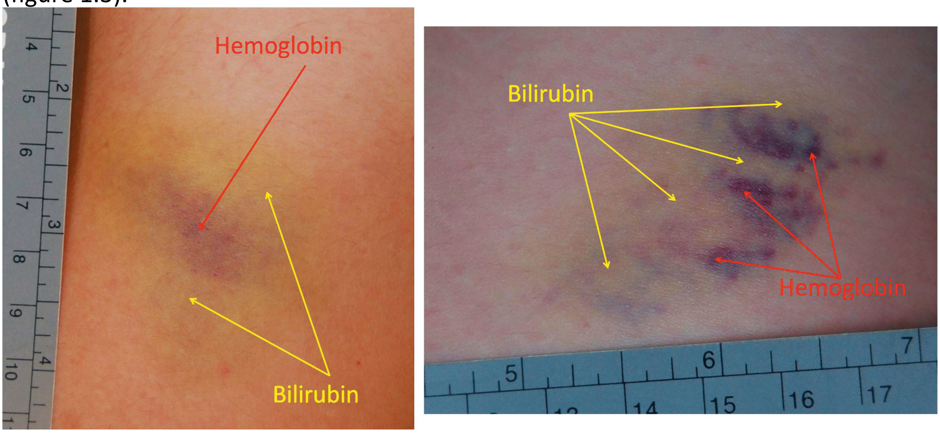

Figure 1.3. Bilirubin surrounds the hemoglobin (left) and fills the gaps between the hemoglobin areas (right).

Color of a bruise

Color changes and time dependent presence of bilirubin in bruises in slaughtered animals (cattle and rabbits) has first been shown in 1957 by Hamdy et al [12]. Since then, several groups have shown time dependent changes in bruises using different histological and histochemical approaches; based on apoptotic cell activity [25], based on chemokine increases [26] and based on expression of Heme-Oxygenase, the enzyme that converts hemoglobin to biliverdin in the bruise [27]. At autopsy, histological investigation may also give clues about the age of a bruise, but the time intervals given for this form of age estimation are such that using these age estimations is unreliable [28-32].
Although these invasive, histological methods show promise, in dealing with abused children a non-invasive method is obviously preferred. The current, non-invasive, method to determine the age of bruises is based on the changing colors in the bruise (figure 1.4) [13, 15, 17].

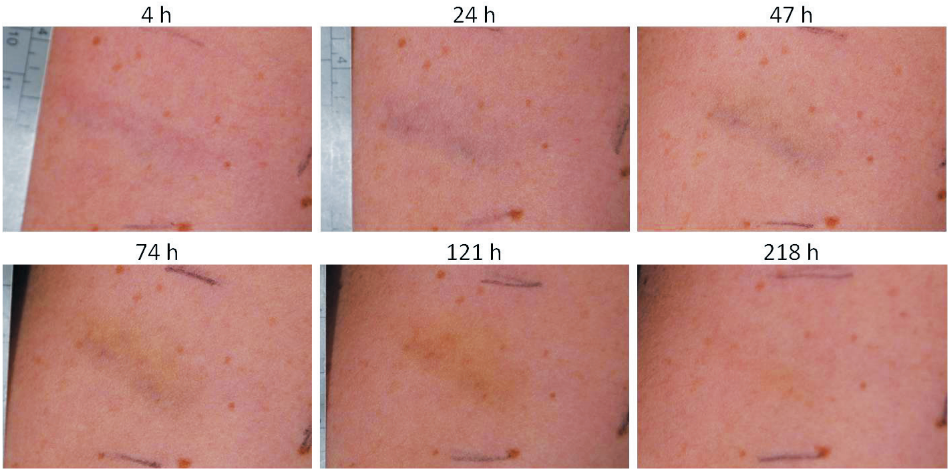

Figure 1.4. Changing colors in a bruise. At 4 hours, only redness is visible. At 24 h the predominant color is blue, where a day later yellow is also visible. After 72 h yellow is the predominant color, but blue is still visible. After 121 h only yellow is present. At 218 h, still a small amount of yellow is visible. At 264 h, no yellowness is visible anymore (not shown). Bruise located on upper arm of a 27 year old woman, resulting from a blow with a small cane.

These colors are described in lookup tables which state e.g. that a blue/brown bruise is between 1-3 days old, and a yellow/green bruise about 1 week old (table 1.1) [15, 17]. However, the variation in color and color description is such that legal use is not possible [15, 18, 33-34]. In fact, Langlois and Gresham argued that the *only* conclusion that can be drawn from the color of the bruise is that if the bruise contains the color yellow, the bruise is at least 18 h old [13]. Yet, Mosqueda et al challenged this conclusion when they showed that bruises can already be predominantly yellow on the first day [35]. The cause of the wide range in color description is twofold; firstly, color description is subjective and large inter observer differences occur [32-33, 36-37], secondly, the color of the bruise is not only dependent on the age of the bruise, but also on e.g. the size and depth of the bruise, and on the age and sex of the child [24, 28, 38].

	Adelson	**Rentoule and Smith**	**Camps**	**Polson and Gee**	**Spitz and Fisher**
Initial	Red/blue	Violet	Red	Red, black	Blue/red
1-3 days	Blue/brown	Dark blue	Purple/black	Purple/black	Dark purple
1 week	Yellow/green	Green	Green	Green	Green/yellow
8-10 days		Yellow	Yellow		Brown
2 weeks		Normal	Normal	Yellow	Normal

Table 1.1. Color of bruise according to different authors [17].

Reflectance spectroscopy

To overcome the subjective nature of color descriptions, several groups have proposed the use of reflectance spectroscopy to objectively determine the color of the bruise [23, 39-48]. Reflectance spectroscopy has been used to measure skin optical properties as well as oxygenation and hemoglobin content [49-51]. In bruise research, it has been used to show that hemoglobin and hemoglobin breakdown products can be detected [40], and to differentiate between superficial and deeper bruises [23]. Several groups have shown a change in chromophore concentrations over time [19, 40-41, 44-45, 52]. The validity of using reflectance spectroscopy in bruise research was shown when histology confirmed the presence of hemoglobin and derivatives measured with reflectance spectroscopy [53-54].

Modeling of bruises

Although the color can now be measured objectively, the complex and non-linear pathophysiology of bruises makes it impossible to intuitively estimate the influence of size, depth etc. on the color development and the age of the bruise. Under such circumstances, a model to predict the behavior of bruises during their lifetime and that incorporates depth, size, shape, different tissue types etc. is necessary. Randeberg et al developed the first model describing bruise formation and healing and combined it with objective color measurement [19, 41]. This model uses Darcy's law of convection and Fick's law of diffusion to describe fluid transport in tissue including the distribution of hemoglobin and its breakdown products. Although their model equations allow a full 3D numerical solution, 1D analytical expressions were derived that calculate the temporal distribution of hemoglobin and its breakdown products integrated over the whole bruise area. They successfully applied this model to assess the age of bruises that were caused by surgical intervention [19]. However, as the 1D analytical solutions do not account for the spatial variations that are present in bruises [40] (and figure 1.3), there is a need to extend this model, adding Michaelis-Menten enzyme kinetics for the conversion of hemoglobin to bilirubin and adding diffusion of bilirubin, and solving the equations numerically. This model then allows calculating the behavior of bruises of all shapes and sizes [55], and identifying how parameters like bruise size and shape, skin thickness and diffusivity of hemoglobin and bilirubin all affect the rate of healing. Importantly, such a model likely confirms that the temporo-spatial behavior of hemoglobin and bilirubin are different, as observed in figure 1.3, and hence carries information on the age of the bruise. Thus, also this model will show potential for accurate age determination of bruises, as will be demonstrated in this thesis.

As modeling seems the way forward, knowledge of the parameters involved in bruise modeling is crucial. These parameters are likely to vary between individuals, but also between body sites, skin depths of the bruise and degree of activity of the subject. Investigating these parameters requires a large heterogeneous database of bruises. One of our goals is to create such a database containing bruises at different body sites on different people at the injury consulting hour at the municipal health service in Amsterdam. The subjects that present here are victims of abuse, robbery, bar fights etc, and referred to the consulting hour by the police after filing a report regarding a criminal complaint. A second group of subjects that may be measured at the Biomedical Engineering and Physics department in the Academic Medical Centre, Amsterdam, may result of bumping into furniture, falling of bikes etc.

Hyperspectral imaging

The introduction of hyperspectral imaging in bruise research has opened up new possibilities compared with single fiber reflectance spectroscopy. The latter method measures the remitted spectrum at a single location only, and spectral information of the whole bruise requires frequent repositioning of the fiber. The spectral information of the whole bruise can also be measured with an integrating sphere, but this approach averages out the spatial differences. In hyperspectral imaging, the whole bruise is imaged spectrally; with the use of a filter different wavelengths λ in the (visible) spectrum are selected and at each wavelength an image of the bruise is taken. Stacking the images results in a data cube with dimensions x, y, λ, where a spectrum can be obtained from each point in the image, resulting in a large increase in available data from the bruise (figure 1.5).

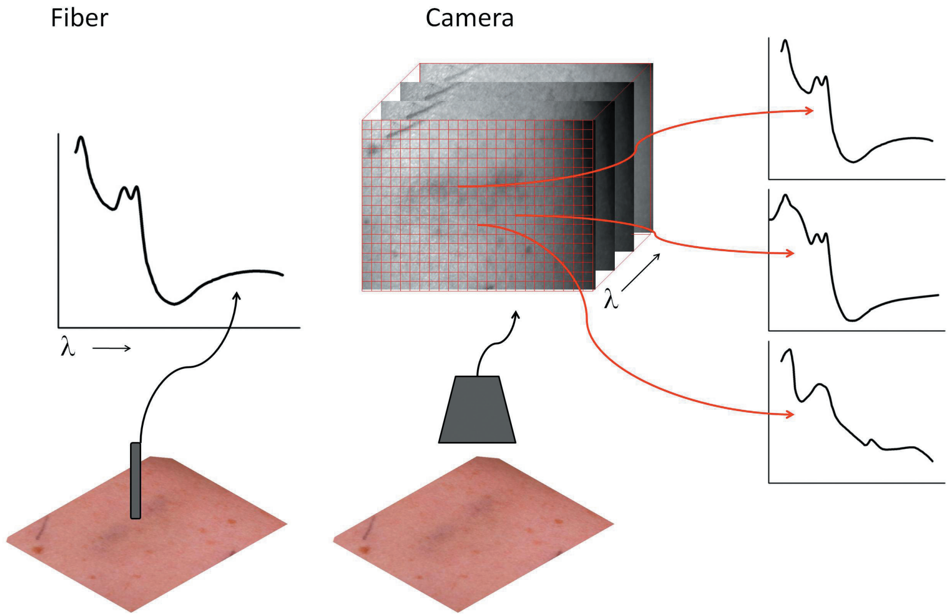

Figure 1.5. A fiber measurement provides a single spectrum for a single point. A hyperspectral measurement provides spectra for each pixel in the image.

With hyperspectral imaging, depth information can be derived, and differentiation between different areas in the bruise has become possible [20, 46, 56]. Changes in chromophore concentration that occur during the lifetime of a bruise, as shown with fiber based or integrating sphere measurements, can also be measured with hyperspectral imaging [20, 56]. With this increase in spectral information, it is possible to determine the localization of hemoglobin and bilirubin in the bruise and thus determine the size of the hemoglobin and bilirubin areas. We hypothesized that this area information allows age determination of bruises. We also hypothesized that by following the areas in the bruise over time, the model parameters of the bruise can be determined [20, 55].

Thesis

The goal of the work presented in this thesis is to better understand the spatial and temporal aspects of the healing of a bruise, knowledge that is needed for accurate age determination of bruises. First, based on the pioneering work of Randeberg et al, we extend the existing 1D analytical bruise model into a numerical 3D model, while including the above mentioned Michaelis-Menten enzyme kinetics for the conversion of hemoglobin to bilirubin and diffusion of both chromophores in all directions (chapter 2). The key output parameters of our 3D model are the concentrations and areas of hemoglobin and bilirubin during healing. We use the model to assess the

influence of hemoglobin diffusivity, skin thickness and bruise size on the bruise healing. As the 3D model allows simulation of bruises of any shape and size, we can also simulate clinical bruises with non symmetric shapes. In chapter 3 we measure such non symmetric clinical bruises, using a hyperspectral imaging system. We can determine the areas of hemoglobin and bilirubin from these measurements, and simulate these non symmetrical bruises with our model. Based on the temporal behavior of the areas of hemoglobin and bilirubin, a first attempt is made to develop a method to determine the age of a bruise.
The input parameters used in the 3D model influence the spatial and temporal behavior of the hemoglobin and bilirubin distributions in the skin. In chapter 4, the influence of the bruise parameters shape, size and concentration distribution of the initial blood pool on the spatial and temporal behavior of the bruise is assessed. The influence of the configuration of the initial blood pool on the age determination of bruises is discussed.
Knowledge of the tissue specific input parameters as the hemoglobin diffusivity, the concentration of Heme Oxygenase-1 and the relaxation time of bilirubin is another prerequisite for further clinical application of bruise age determination. In chapter 3 we determine these parameters for 3 bruises based on the temporal behavior of the areas of hemoglobin and bilirubin.
In clinical practise it is not always practical to measure bruises multiple times in order to determine model parameters. If bruises on the same anatomical position would have the same or very similar parameters, fewer measurements may be necessary.
In chapter 5 we measure the hemoglobin and bilirubin areas in 3 groups of bruises in a first attempt to determine these important model input parameters in a large and heterogeneous group of bruises. We also investgate if bruises on the same anatomical position have similar spectral properties (chapter 6).
Age determination of bruises will only be useful if physicians recognize the signs of child abuse, after which the technique may aid the diagnosis. The recognition and handling of abuse in a clinical setting is discussed in chapter 7. Finally, in chapter 8 we discuss the implications and limitations of our results and give a future perspective of bruise research.

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