Simulation Pipeline for Virtual Clinical Trials of Dermatology Images

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ABSTRACT

Skin cancer is the most common cancer in the US; one in five Americans will develop it by the age of 70. Early diagnosis offers more favorable treatment options; currently available diagnostics, however, shows large reader-dependence. The simulation approach (virtual trials) to development and validation offers advantages in terms of quantitative and objective assessment of system performance in the design of novel imaging methods, and validation of clinical trial designs prior to execution of real clinical trials.

We have designed a pipeline for performing Virtual Clinical Trials of optical imaging of skin lesions. This pipeline includes modules to simulate healthy skin and subcutaneous tissue, to create skin lesions and insert those in the skin models, and to simulate the acquisition of optical images resulting in simulated/virtual images of skin. The last module of the pipeline performs virtual reading of simulated images, which is based on the clinical task-based performance analysis. The physical properties of the skin and lesions used in our simulations were selected to represent clinically plausible conditions. Skin lesion images were simulated assuming the ambient white light, and a linear camera model. We have utilized the standards for optimal data representation based upon the XML schema, adopted from the VCT pipeline developed for breast imaging research.

This paper describes the principles used for designing the proposed VCT pipeline and presents preliminary simulation results, including visual and quantitative evaluation. Integration of pipeline modules and its validation is ongoing.

KEYWORDS

Skin lesion imaging, skin cancer, melanoma, lesion, computer simulation of skin anatomy, virtual clinical trials, Blender.

1. INTRODUCTION

Skin cancer is one of the most common cancers in Western countries. More people are diagnosed with skin cancer each year in the U.S. than all other cancers combined[1]. One person dies of melanoma every hour in the U.S.[1] Worryingly, the incidence of cutaneous melanoma among young adults is rapidly increasing[2].

In skin lesion diagnostics, traditional optical dermatoscopes are still the standard equipment used by dermatologists, which allows the inspection of skin lesions unobstructed by skin surface reflections. Dermatoscopes can be either contact or non-contact, based on the type of lesion that is to be examined; open wound lesions tend to require non-contact based dermatoscopes. Most traditional dermatoscopes are analogue devices, relying on the subjective examination of the medical examiner present. Some companies have introduced basic digital dermatoscopes[3] though these are mostly limited to attaching a digital camera to an otherwise analogue dermatoscope to enable the acquisition of digital images. There are also present a few dermatoscope add-ons to the smartphone which provide patients the ability to snap their own pictures of lesions and have them sent / checked across the corresponding application on the smartphone[4].

Digital dermatoscopes allow the dermatologist to have a second look at the lesion without the burden of having the patient present at all times, as well as to be able to monitor the evolution of a lesion over time. There are current efforts

to develop a novel digital dermatoscope optimized for skin cancer imaging[5]. Apart from benefits of digital imaging, they provide multispectral lighting[6] as well as possible embedded decision support which is something yet to be found in other dermatoscope models. Multispectral lighting provides the ability to view lesions and their effects at various depths. Different wavelengths of light penetrate to different depths into the skin, thus able to give spectral characteristics and concentrations of various chromophores in the skin[7].

Bringing such novel devices into the market would require multiple clinical trials with a large number of patients imaged repeatedly to compare the performance of different systems or system settings. Optimization and validation of such a dermatology imaging system is therefore very challenging. The associated cost, duration, and the burden to patient volunteers participating in the trials, represent a significant impediment to the introduction of novel imaging technologies into clinical practice.

In this paper we propose an efficient alternative for the optimization and validation, in the form of Virtual Clinical Trials (VCTs) of dermatology imaging.. VCTs allow quantitative and objective assessment of the imaging system performance, and the performance of novel imaging methods. This computer simulation pipeline proposed for VCTs of dermatology imaging (hereafter VCT-Derma) is described in Section 2.1.

One section of the VCT-Derma pipeline requires a software model of the skin. This model represents a skin volume of interest, containing simulated normal skin anatomical structures, as well as (optionally) simulated abnormalities (malignant or non-malignant lesions, and/or other clinically relevant findings). There are models of the skin that are available in literature, some of which are the Breault's Advanced Systems Analysis Program (ASAP) model[8], which takes several parameters (the anisotropy factor, the scattering coefficient, the absorption coefficient, and the fractional obscuration per unit area) as input and provides us with a simulation skin model on which ray tracing could be run, and a simplified model of the skin available in the breast imaging VCTs proposed by Bakic et al.[9] The skin model used in our VCT-Derma pipeline is described in Section 2.2.1

VCT-Derma also requires an optical simulation of light propagation within the skin model. A BioSpec model by Krishnaswamy, A et.al[10] describes light propagation in terms of ray optics, and is simulated as a random walk process. Funamizu et.al[11] shows how certain ray tracing tools could also be used to obtain a rough 3 layer model of the skin, each layer characterized by four optical properties: refractive index, absorption coefficient, scattering coefficient and scattering anisotropy, and thickness. Some of the basics of the light propagation model used in our VCT-Derma pipeline is described in Section 2.2.3

While raytracing software like ASAP[12] and LightTools[13] do help us produce images from skin models, they all have a serious disadvantage in that the simulation time is extremely long due to the algorithms being CPU-based. There are also certain GPU based Monte Carlo Simulations(MCS) which achieve speed increases of up to 3 orders of magnitude over a CPU-based MCS[11], but since the VCT-Derma implementation in Blender[14] is mainly CPU-based, these GPU implementations were not delved into.

In order to be able to run virtual trials of a dermatascope, the images that are obtained should resemble dermatoscopic images upto a sufficient level of accuracy (luminance/colour errors lower than 10%). Through the above mentioned methods, we may obtain models that may have the properties of the skin lesion but not the appearance, the latter of which is what we aim to achieve with our model.

A generally observed problem in the skin imaging simulations (including ASAP model) is the fact that the model and software are proprietary, which limits cross-validation of results and impedes development of the field by, and considering the novel nature of the research, any changes that are unique to our dermatoscope or our application. Therefore our composite skin tissue model is an extension of the basic skin model included in the breast anatomy simulation[15,16]. While sufficient for requirements of breast imaging VCTs, this basic model lacked detail layered structure of human skin, needed for the efficient simulation of dermatological imaging. A look at a possible model with multiple layers and skin structures is what is detailed in this paper. The model in question has been developed in a tool akin to a game engine (Blender), which has not been looked into before for similar applications. Results of some

preliminary tests / simulations have been discussed in the respective sections. Below is a more in depth discussion on the pipeline developed, which includes a skin model as a separate module.

2. METHODOLOGY

2.1. The VCT-Derma pipeline

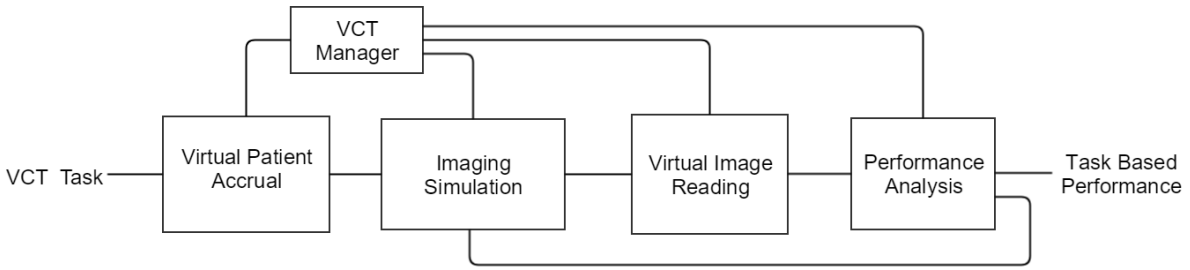


Figure 1: Flow chart showing individual simulation modules of the proposed VCT-Derma pipeline for running virtual trials on optical images of skin lesions.

The use of a virtual pipeline in the process of designing and developing a medical imaging system is motivated by the success with breast imaging VCTs. The VCT open source pipeline[8] has been used for the development of novel clinical-grade displays, testing the new generation of tomosynthesis systems, and the development of novel search observer models[17]. VCTs can help simulate hyperspectral images.

The dermatoscopy pipeline introduced in this paper is based on this open source pipeline[8] and includes modules for the simulation of skin and subcutaneous tissue, insertion of lesion models, and the simulated acquisition of optical images, followed by the virtual reading of simulated images, and the analysis of the task-based system performance (see Figure 1). These tasks could be anywhere from lesion dependent, e.g. melanoma, basal cell carcinoma, to specific parameter dependent, e.g. looking at only the lesion asymmetry or the color etc. An advantage of this pipeline is that the blocks / modules can be modified to suit user specified tasks. In case of dermatology, we have detailed a brief description of the modules here in this section.

Individual modules in the pipeline perform the simulation of corresponding VCT components, and based upon the appropriately selected computer platform, lists of parameters describing physical properties of simulated objects, and appropriate list of header parameters, are used for VCT management. Our computer platform will utilize the standards for optimal data representation based upon the XML schema, adopted from the breast imaging VCTs.

As can be seen from Figure 1, the pipeline's performance depends on the task that has been designated. The Virtual Patient block contains parameters from the patient data (reference numbers for identification purposes etc.), to the data about the skin volume of interest (VOI) in question. The latter parameters include the number of lesions to be added to our skin model, the thickness of the skin layers, whether the borders between skin layers would be flat or irregular, whether to include the subcutaneous tissue or not, etc.

The Virtual Patient Block also contains the lesion parameters from the stage, type, shape of the lesion, to their size, shape, and composition. This particularly relates to the various types of skin cancers and how the vascular structures vary with each one[14]

The Imaging Simulation Module contains the light propagation model, which will contain any device specifications; in our experiments the device is assumed to be similar to a dermatoscope system that will involve hyperspectral imaging[5].

The Virtual Image reading Module contains the display model as well as the reader model. The display model applies the appropriate post-acquisition processing so as to simulate how an image will appear on a given dermatoscopic display.

The reader model will be either a CAD or AI model whose purpose is to be able to simulate the image analysis and classification, performed by a clinical dermatologist.

The final block is the Performance Analysis block and it contains parameters required to run task-based criteria tests and compute the corresponding figures of merit, such as the area under the receiver operating characteristic (ROC) curve, or the percent correct score.

All these blocks/modules are controlled by the VCT Manager block. Thanks to the XML schema data representation, the VCT-Manager Block can access / call the headers from each of the modules. So depending on the task to be performed, a certain set of modules are called to perform the task.

The Virtual Image Reader and Performance Analysis modules have been designed based upon the Medical Virtual Imaging Chain (MeVIC)[17] also used as a part of the breast imaging VCTs pipeline.

For this paper, we have performed preliminary proof-of-concept tests of the proposed VCT pipeline to assess the effect of varying skin, and lesion, thickness, and position on the appearance of simulated images. Preliminary tests did not include virtual readings and performance analysis.

2.2. Virtual Patient Accrual

2.2.1. Skin Model

Human skin tissue can roughly be divided into three layers, as illustrated in Figure 2: (1) epidermis, the outermost layer, (2) dermis, the middle one, and (3) hypodermis, the subcutaneous tissue.

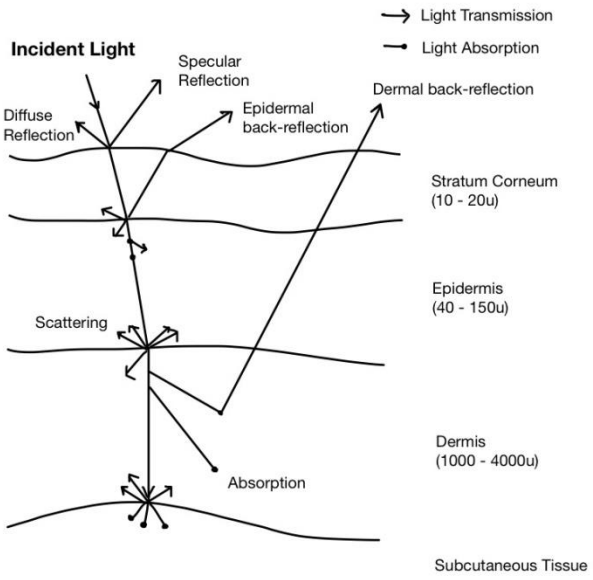


Figure 2: Schematic Diagram of Optical Pathways in skin[16]

The thickness of the skin layers has been documented in literature (and can also be seen in the Figure 2). In order to create a reliable skin model for the VCT-Derma, it is vital to understand the interaction of radiation, such as visible light, with human skin. The optical properties of the layers of the skin are elaborated in great detail in literature[20], but are summarized below.

Human skin contains light-absorbing and scattering molecules – otherwise known as chromophores – including eumelanin, pheomelanin, hemoglobin, bilirubin, beta carotene, and water, the properties of which change with the wavelength of light incident upon them. They are responsible for complex elastic and inelastic[20] scattering events that

can be wavelength dependent. Volume components such as blood vessels, glands etc. also affect the optical properties of the skin, and are in fact quite important in determining the severity of a skin lesion, or even in classifying the type of cancer[18].

Models such as the ASAP model utilizes the Henyey-Greenstein approximation[21] to volumetric light-scattering simulations. In this software, four parameters are necessary to create a volumetric-scattering model: the anisotropy factor, the scattering coefficient, the absorption coefficient, and the fractional obscuration per unit area. The ASAP model allows researchers to simulate light interactions in the stratum corneum, epidermis, dermis, and hypodermis of human skin – with provisions for hair, blood vessel, dermal papillae (refers to the finger like projections that create the uneven boundaries between consecutive skin layers), and fluorescence characterization – as well as single and multilayer tissue models based on bulk-scattering approximations[20].

A simple model of the skin was also developed for the breast imaging VCT model[16]. This model varies from the current VCT-Derma in the sense that the model in the latter is the skin and it's interaction with visible light, while the former involves a breast model and it's interaction with x-rays. The basic skin layer in the breast imaging VCT model was represented by a layer of a certain thickness to prove a barrier for the x-rays. This is not the case in the VCT-Derma, where the skin and its multiple layers and structures are of vital importance. The skin model is expected to have multiple influencing characteristics (light absorbing chromophores, blood vessels etc.) which determine the severity of the cancer / lesion.

On comparing these two models in question, we see that the ASAP model has the advantage in that it provides us the options to model the layers of the skin, and their properties; therefore, the work left to be done is on selecting optimal values of these optical properties (the anisotropy factor, the scattering coefficient, the absorption coefficient, and the fractional obscuration per unit area). With these values, the ASAP software should be able to generate a skin phantom. The breast imaging VCT model on the other hand, requires more extensive work to be done with regards to the layers and their respective chromophore content, apart from also obtaining their optical properties from research.

The pitfalls on raytracing methods with CPU/GPU have already been mentioned in the introduction which brings about the need for a much faster and more visually acceptable skin model that could be passed to a dermatologist. Realistic rendering of human skin and light has always been a very important aspect in the computer graphics industry. There exist a number of computer graphics based software (Unity[22], Unreal[23], Maya[24] etc.) that are available which can realistically render human skin. The software that has been decided on is called Blender[14] which will be explained further in section 2.2.3.

In this paper we have created a basic two layer skin model; the layers being the epidermis and the dermis. The layer specifications can be seen in section 2.2.3. Since this paper is a proof of concept and a preliminary implementation, this will be a good starting point. There is a possible third layer that could have also been included which is the hypodermis / subcutaneous tissue layer below the dermis, but this was deemed unnecessary because the depth at which it is located has little influence on the lesion or the dermatologist's diagnosis.

Since the VCT pipeline has the goal of being adapted for dermatology, it makes sense to assume the skin model to be one form of skin cancer prevalent today1. A lesion is therefore inserted into the model.

2.2.2. Lesion Model

In general, a skin lesion refers to an abnormal lump, bump, ulcer, sore or colored area on the skin[25]. They can be either benign or malignant.

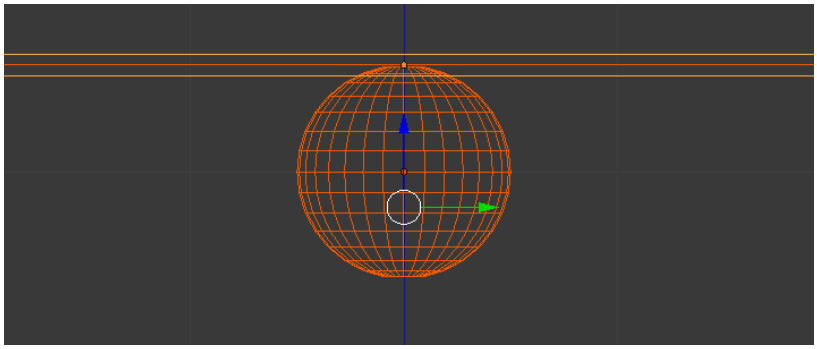


Figure 4: Cross Section of the two layer skin model with a simulated lesion inserted (The arrows denote the axes; blue z axis, green y axis, red x axis)

Our work is currently focused on the simulation of melanoma[25]. There have been several papers detailing the structure and evolution of melanoma over time[26], and even the evolution / progression of cancerous cells in biological tissue[27], but for the scope of this paper, we have approximated the shape of simulated skin lesions by the sphere. This was in order to obtain a preliminary understanding of how the lesion in VCT-Derma would react when it's size, position / depth varies in the skin.

A spherical lesion has thus been inserted into the two-layer model of the skin. Since Melanomas most often start from the border between the epidermis and dermis, where the melanoma is most densely located[28] (at the boundary between the epidermis and dermis), the spherical lesion has been inserted with its top surface just touching the boundary between the epidermis and the dermis. The tests / simulations that were run can be seen in the Results and Discussion section below.

2.2.3. Simulating Images

For the simulation of skin anatomy, we have used open source software Blender (v. 2.79; Stichting Blender Foundation, Amsterdam, the Netherlands). We simulated skin as composed of two layers: epidermis and dermis, of thickness 0.1mm and 1-3mm, respectively[29].

Simulating different size and depth of inserted lesions is our first step towards simulating malignant lesions at different diagnostic stages. Lesions were modeled as oblate spheroids of thickness 0.5-2mm. Each lesion was inserted, with its top surface just touching the epidermis-dermis border.. Optical properties of the skin and lesions were selected based upon the reports in literature[29]; we used 1.34, 1.4, and 1.7 for the index of refraction of epidermis, dermis, and lesion, respectively

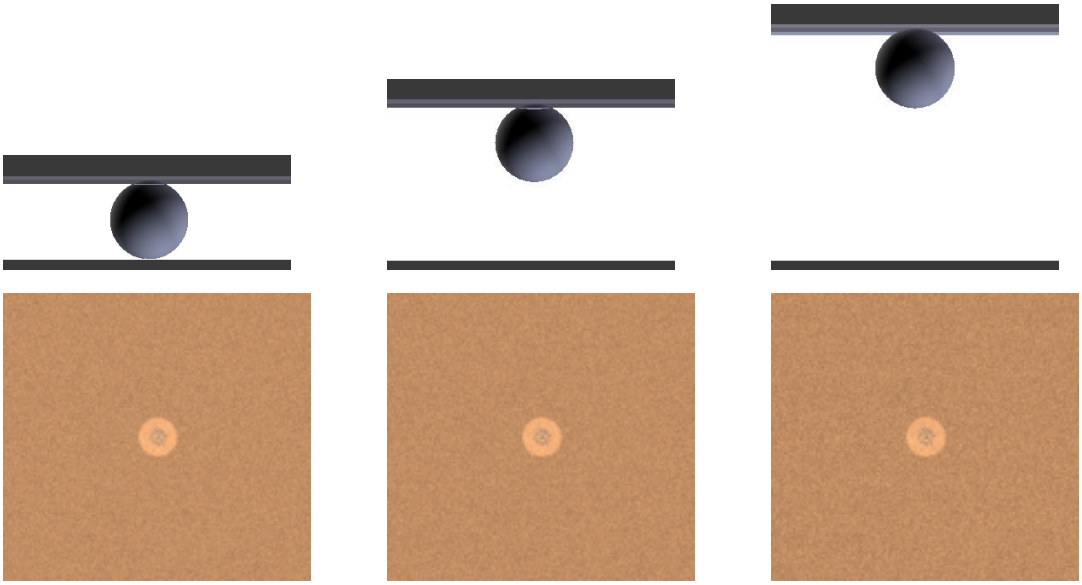
Simulated images were generated using a linear camera model available in Blender renderer LuxCore. The LuxCore renderer is based on physically based rendering (pbrt)[30] which looks to render graphics in a way that more accurately models the flow of light in the real world. The default camera parameters were selected: Gain=0.5 (with Auto Brightness ON); F stop=2.8; Shutter=0.01s; ISO=100. The light propagation in the model follows ray tracing that is used to determine the depth of lesion. We have assumed ambient white lighting, with 6mm distance to the camera. The 6mm distance relates to the distance between the glass of the Barco dermatoscope and the sensor, while ambient white light is selected to best approximate normal lighting under which a dermatologist would examine a patient.

We have also selected the light absorption settings to approximate the chromophore content of the skin, and achieve a clinically plausible appearance.

3. RESULTS AND DISCUSSION

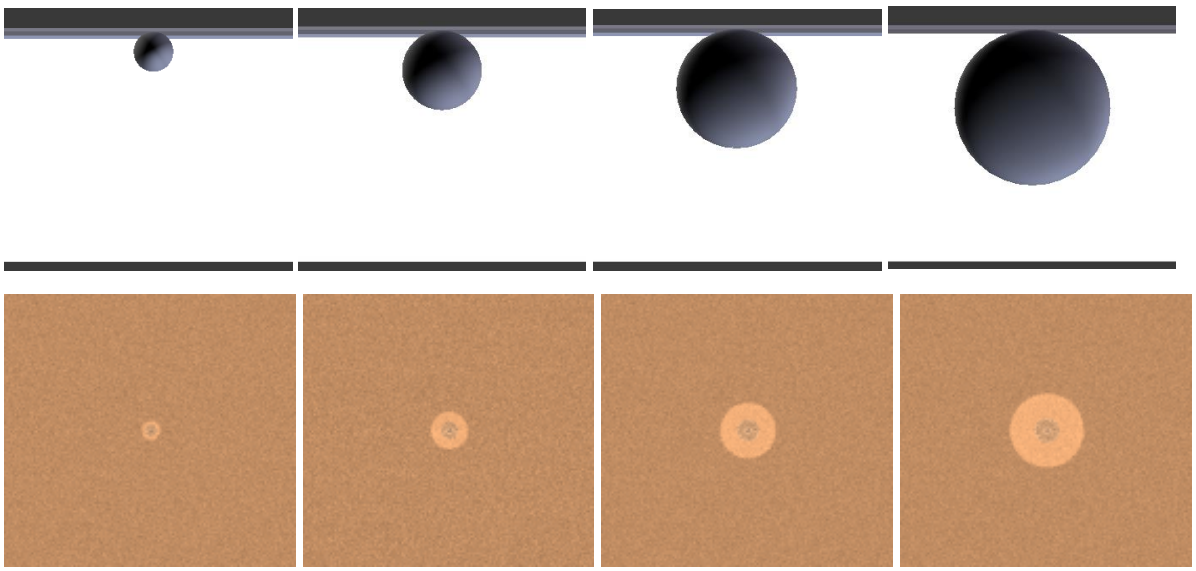
In our preliminary simulations of dermatoscopy images, we have varied the thickness of simulated dermis (between 1mm and 3mm). Figure.5 shows the skin sections and corresponding simulated images in the case of a 1mm uniform spherical lesion inserted in the dermis area and touching the epidermis. We have also varied the size of simulated lesions (between

0.5mm and 2mm diameter). Figure.6 shows the skin sections and corresponding simulated images, for the lesions of different size inserted into a skin model with 3mm thick dermis. Lastly, we varied the depth of lesion insertion (from just touching the epidermis to 1.75mm from the epidermis-dermis border. Figure.7 shows the skin sections and corresponding simulated images.



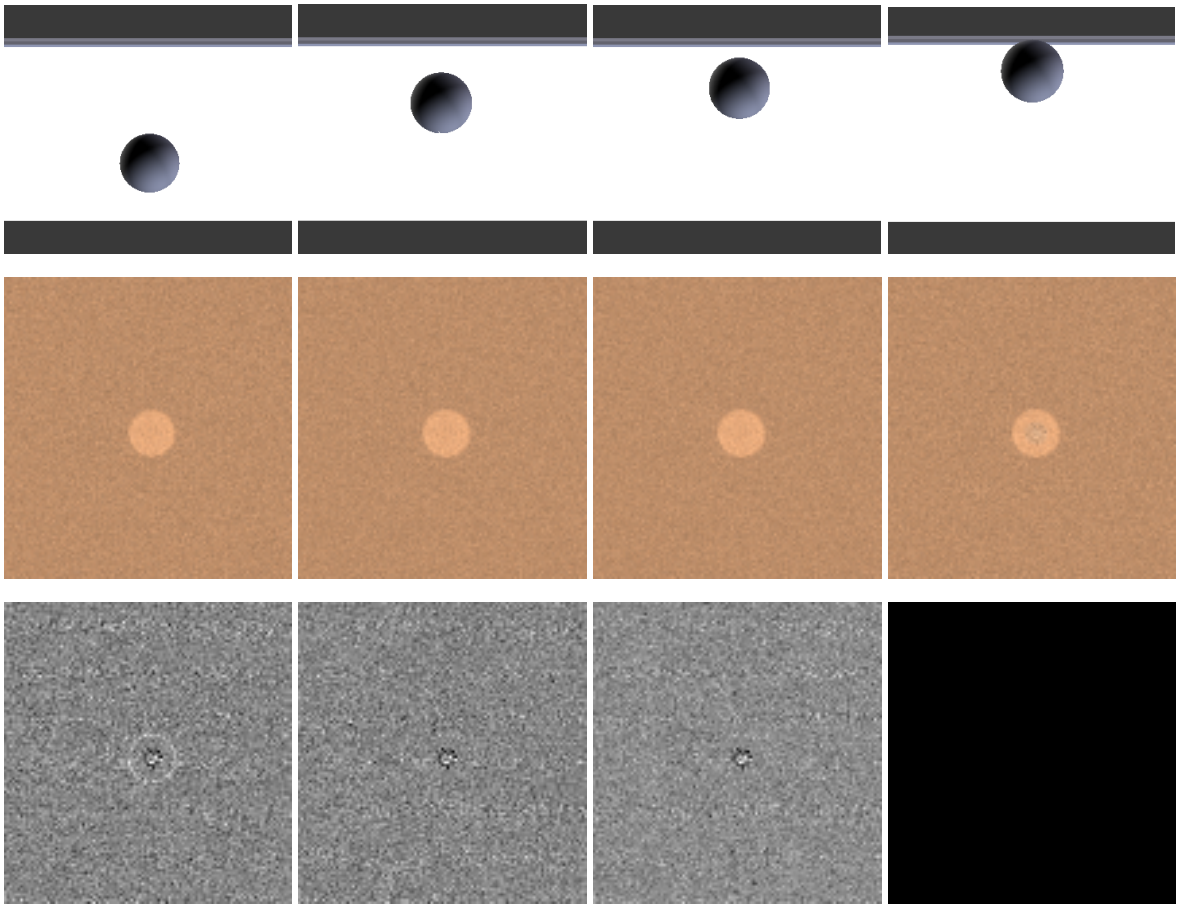
(a) (b) (c)

Figure 5: Simulated skin sections (top) and rendered images (bottom) of a spheroidal lesion (1mm diameter and 1mm thickness) inserted into skin models with the dermis thickness of: (a) 1mm; (b) 2mm; and (c) 3mm. (The Epidermis is denoted by the narrow grey band above the lesion, while the dermis is denoted by the white band. The Black bands above the epidermis and below the dermis are not part of the model, and hence should not be considered)



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

Figure 6: Simulated skin sections (top) and rendered images (bottom) of a skin model with 3mm thick dermis, and inserted lesions of diameter: (a) 0.5mm; (b) 1.0mm; (c) 1.5mm; (d) 2.0mm.



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

Figure 7: Simulated skin sections (top) and rendered images (middle) of a skin model with 3mm thick dermis, and 1mm diameter lesions inserted at depth (measured from the lesion top to from the epidermis-dermis border): (a) 1.75mm; (b) 0.5mm; (c) 0.25mm; (d) 0mm. 3rd row images represent mathematical difference between each image and the image with the lesion at the 0mm depth.

Overall, our preliminary simulated images with lesions have plausible visual appearance. Varying the thickness of the dermis layer did not significantly affect simulated images (see Figure. 5). The appearance of lesions with different size is affected by their position within the skin (see Figure. 6). All the lesions were touching the epidermis-dermis border; thus, by increasing the lesion size, their center was moved deeper in the skin. The effect of lesion depth is more evident when we compare the results with the lesion at 0mm depth (touching the epidermis-dermis border) (see Figure. 7); the deeper the lesion, the darker it appears in simulated images – which matches the observation from clinical images.

Currently we are working with a simplified two-layered skin model, but there are in fact multiple sub-layers to each of these two layers themselves, as was mentioned earlier in the skin model section. Each of these sublayers have their own optical properties decided by their own chromophore content and vascular structures. This makes it very important to extend the two-layer model in the future in order to further improve the realism of the simulated skin volume of interest. The future work could include adding more layers to the skin model such as the stratum corneum and the living epidermis, instead of just the epidermis, while splitting up the dermis into four layers as well: Papillary dermis, upper blood net dermis, dermis, lower blood net dermis.

The current work also has a notable lack of local variations in the skin texture. Our future work will include surface skin grooves and septated border between the epidermis and dermis, and between other intermediate layers as well. The skin wrinkle network / texture affects the vascular structures[18] present which, as mentioned before, are important for

dermatology diagnosis[31]. Meglinky et.al[29] discussed the optical and physical properties for each of these layers, as well as the significant role in skin optics of rough boundaries between layers of different refractive index. The wavy layer interfaces produce a deeper and more homogeneous distribution of photons within the skin and tend to suppress the direct channeling of photons from the source to detector.

Another notable lack in the current model has to do with a blood network. Future work will include a reasonable network of blood capillaries to be able to better simulate the appearance of skin. Different vessel morphologies are associated with different melanocytic or non-melanocytic skin tumors; thus, the recognition of distinctive vascular structures may be helpful for diagnostic purposes[18].

Future work with regards to the lesion will be to move from a regular spherical shape to one that better reflects the randomness of a malignant lesion, as mentioned earlier. Some of the main factors on which dermatologists classify / diagnose lesions have to do with the ABCD parameters[31] which account for the asymmetry, border, color and dermatoscopic structures present in the lesion. Hence future work could also include some of these factors taken into account

4. CONCLUSION

We propose a simulation pipeline for VCTs of skin lesion imaging, named VCT-Derma. The pipeline is based upon our previously developed VCTs of breast imaging. Simulated images from a proof-of-concept test show visually plausible appearance. In this paper we detail the first of the pipeline modules for Virtual Patient accrual, which includes the Skin, and Lesion Models. Integration of these models with the remaining pipeline modules, as well as the detailed simulation of skin tissue structure is ongoing.

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