IVUS Simulation Based on Histopathology

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Abstract

The purpose of this research was to develop a realistic IVUS simulator based on histopathology images as input. Although IVUS is currently the reference method to visualize human coronary plaques, little is known about the capabilities of IVUS with respect to the determination (qualitatively and quantitatively) of the different tissue components as found inside such plaques. This was the main motivation for developing the simulator. The outcome of this work is an IVUS simulator capable of producing highly realistic IVUS images as compared to real IVUS images. It could therefore act as a tool to study the qualitative and quantitative capabilities of IVUS.

The IVUS simulator uses histopathology images as input. Different methods used in existing simulators have been studied, such as analytical methods, ray tracing and the finite element method. This research led to the development of a simulator based on a hybrid approach combining analytical methods with ray tracing. This allows the simulation of phenomena such as refraction, which was not being taken into account by other published simulators.

Validation of our simulator proved to be a difficult task, although matching histopathology and real IVUS images where available. Comparison of images generated by the simulator compared to real IVUS images was done by experts, who where impressed by the level of detail. A number of analytical phantoms were tested in different analysis tools, yielding results that correlated with expectations.

1.   Introduction

Intravascular ultrasound (IVUS) is an important imaging tool in the study of cardiovascular diseases. It allows studying the structures of the vessel wall in living individuals by using ultrasound. The main advantage over other diagnostic imaging techniques, such as angiography, is that IVUS not only visualises the lumen (the blood filled structures) but also plaques inside the vessel wall.

The images generated with IVUS are greyscale images, based on the reflection of ultrasound. One of the major challenges is distinguishing different types of tissue within the coronary plaque. Usually, only histopathology can be used for this. This entails that the vessel is cut up in thin slices (approximately 5mm thick) and stained with dye to differentiate tissue types. If an IVUS image was created before the histopathology is performed, these two modalities could be compared. The problem is that histopathology is a costly and time-consuming method. Since it is also a post mortal method, it can't be used for plaque progression-regression studies for example.

Our main objective was to create an IVUS simulator that is able to produce accurate IVUS images from histopathology images. The input of this simulator should be fully adjustable. This way a large collection of cases can be created and investigated in an easy and low costly manner. This would be impossible using traditional methods, since real samples are difficult to obtain. An IVUS simulator would be an important contribution to facilitate research towards a better understanding and quantification of cardiovascular diseases.

1.1.   Ultrasound

The most important property of ultrasound in medical imaging is scattering. Discontinuities smaller than the wavelength cause the sound wave to reflect in every direction. This means that a part of the wave is transmitted back to the transducer (which also acts as a receiver). Since most tissue types have a grainy structure, scattering occurs over the entire depth of the tissue. This results in a continuous echo. Different types of tissue have different ultrasound properties, which results in a different echo. At low rates of scatterers, the amount of backscattering is proportional to the amount of scatterers.

Other important properties are the speed of sound, attenuation and refraction. The speed of sound is the speed at which a sound wave travels through a certain material. This speed differs per material and influences the duration of the delay of the echo, altering dimensions in an ultrasound image. Attenuation is the decrease in power of the sound wave over distance as it travels through the material. This is caused by reflection, scattering and absorption. A boundary of two different

materials will reflect as well as refract the sound wave. This can also cause deformations in an ultrasound image.

2. Method

Based on previous studies the choice was made to use a method that employs a combination of scatterers and ray tracing. Scatterers are used to model the scattering that occurs in tissue. This method uses the fact that the echo's created by scattering can be summed, so that they form the complete echo signal. A scatterer in the model represents an amount of scattering and is used to determine the reflection and transmission of the sound signal.

Ray tracing is used the by simulator for the transmission of the sound wave through the tissue components. A sound wave can change direction due to boundaries in the materials. By using rays to simulate the path of the wave, this can be modeled.

An important factor was the possibility to fully modify the input of the simulator. It should be possible to construct any vessel shape as input for the simulator. Furthermore, the simulator should be able to simulate the common types of tissue found in vessels. In addition, the simulator should be able to be tuned in a way that it can support multiple types of catheters, which means different types of frequencies (e.g. 20-, 30- or 40MHz).

The algorithm is at first summarized here shortly in pseudo code. The full procedure is explained in more detail thereafter.

```
PRE-PROCESS INPUT IMAGE
FOR EACH SCANLINE
FOR EACH SUBSCANLINE
    GET POSITION AND DIRECTION
    TRACE TROUGH BOUNDARIES
    STEP LINE, FOR EACH STEP
        CALCULATE BACKSCATTER INTENSITY
        UPDATE ATTENUATION
        UPDATE POSITION USING SOUNSPEED
CREATE FINAL IMAGE
```

The simulator uses modified histopathology images so that a large variety of pathologies can be simulated. Different colors in the input image represent different types of material components, each having their own specific ultrasound properties.

The pre-processing consists out of three steps. The first is to create a material map, which makes it easy to look up the material settings of a certain coordinate. Secondly, a scatter map is created. Each scatterer is a point on the map with certain properties. The scatterers are distributed randomly. The type and amount are based on the material map. At last, the boundaries that are specified are pre-processed. These boundaries cause the simulated ultrasound wave to refract.

The generated pulse is a short sound wave that penetrates the tissue in a specific direction. This way, a beam is formed which generates echoes only from a specific area. The shape of the beam will widen the further it penetrates the tissue. The beam is simulated using ray tracing. Many traces (lines) are fired into the direction of the pulse. By using enough lines, the complete area of the pulse is covered (Figure 1).

Figure 1: Example of simulated beam

These lines are processed one by one. Firstly the line is traced trough possible boundaries. The line is refracted were it crosses a boundary, depending on the tissue found on both sides of the boundary. Then the line is scanned. While the simulator steps along the line, it keeps track of two different variables. First is the position of the pulse (depth). This is incremented with a fixed step size. For each step, the current material is scanned and the attenuation is taken into account. The second variable is the time that has passed before reaching the current point. The time added per step depends on the speed of sound in the material that is currently being traversed. Since the pulse also has to travel back to the transducer, the elapsed time is the doubled value. The total time is used to add an echo to the total response. This makes sure that the simulator works the same way as the ultrasound console. The intensity is affected as the simulator steps the line. Because of the attenuation of the propagated materials, this variable decreases. The intensity of the echo, which is a combination of the material and the current pulse intensity, is visualised by the grey value in the final image. When all the sublines are scanned the result is summed up in order to form the final scanline. This is repeated for all directions, in order to gather all the necessary data for an IVUS image.

The final image is created by arranging scanlines radially according to their trajectories through the input data, akin to the spokes in a wheel. The space between the different scanlines is interpolated to create the complete image.
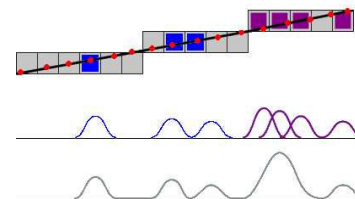

Figure 2: Illustration of the simulated echo as a result from the propagation of a single scanline

3. Evaluation

For the evaluation of the simulator several methods where used. Our main goal was to test the accuracy of the simulator as compared to a real IVUS ultrasound-console.

A collection of IVUS images and matching histopathology images were available for the validation of the simulator. By using the (modified) histopathology images as input, the output could be compared to the real IVUS images. Differences between the histopathology cross sections and the real IVUS images complicated the evaluation. First of all, the images differ in shape because of deformations due to the histopathology sectioning process and to the pressurizing of the vessel during the IVUS-scan. Another problem is the difference in slice thickness (5µm compared to 120µm), which can cause IVUS to have visualisations of tissues that do not exist in the histopathology image. To overcome these problems, the comparison between the generated images and the real images had to be done by IVUS experts instead of by automated comparison. Several regions of interest are selected from the available data (Figures 3 and 4) that shows several capabilities of the simulator.
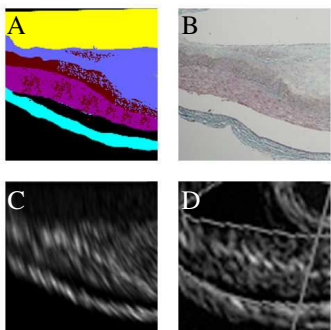

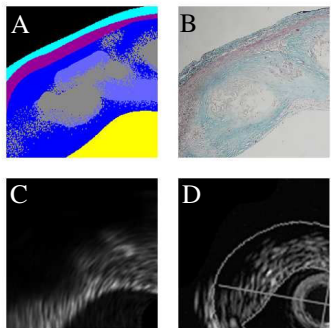Figure 3: A) input image B) histopathology image C) simulated IVUS real IVUS

Figure 4: A) input image B) histopathology image C) simulated IVUS D) real IVUS

Further evaluation was performed using different phantoms and theoretical test cases. These cases were designed to test specific properties of the simulator against the theory. Tests include checking the speed of sound as the pulse propagates through different materials, as well as other artefacts such as attenuation and refraction.

4. Results

The simulator is capable of generating realistic looking images. Its flexibility enables one to generate a large variety of pathologies with different aspects of ultrasound behaviour.
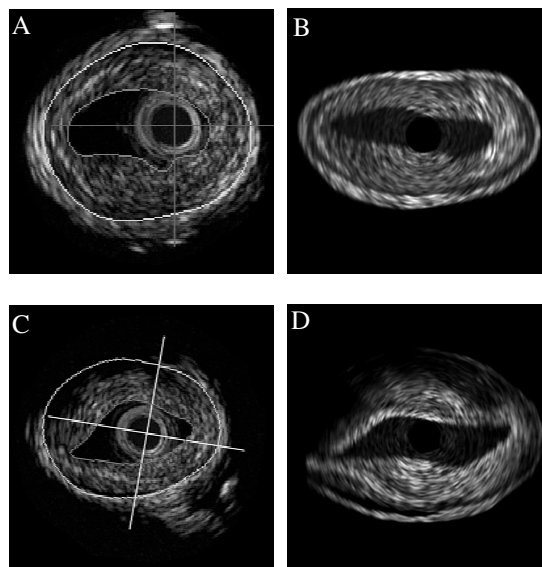

Figure 5: A,C) real IVUS B,D) simulated IVUS

Tests with the speed of sound showed significant changes in dimensions. The example presented in **Figure 6** shows two artificial plaques of similar size but different composition. The difference in plaque area was 10.3% in this typical case, while in fact the real areas are the same. Studies using area measurements by IVUS images should keep in mind that dimensions might alter due to changing tissue material, which is a common process in real cases.
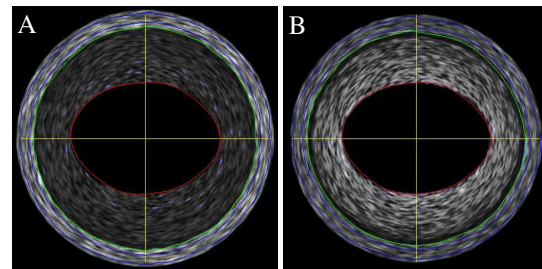

Figure 6: A) fibrofatty plaque B) fibrosis plaque

5. Discussion and conclusions

The purpose of this research was to develop a realistic IVUS simulator based on histopathology images as input. Although IVUS is currently the reference method to visualize human coronary plaques, little is known about the capabilities of IVUS with respect to the determination (qualitatively and quantitatively) of the different tissue components as found inside such plaques. The outcome of this work is an IVUS simulator that is capable of producing highly realistic IVUS images as compared to real IVUS images. It could therefore act as a tool to study the qualitative and quantitative capabilities of IVUS.

The simulator is capable of visualizing several of the most commonly found tissue components inside human coronary plaques. However, the simulator has been developed so that several parameters of the tissue components can be adjusted, which makes it possible to add new tissue components. In addition, changes can be made to simulate different types of catheters and/or ultrasound console settings.

The input of the simulator consists of pre-processed real or "mocked-up" histopathology images. The mocked-up images can be easily created using a drawing program of choice. The advantage of this is a great deal of flexibility. Furthermore, rare pathologies that are only seldom found can now be simulated.

Features like scattering, attenuation, sound speed and refraction are fully implemented. Other features such as reflection will be addressed in future work. Our simulator framework has been developed with these changes in mind.

Validation of our simulator proved to be a difficult task, although matching histopathology and real IVUS images were available. Experts in IVUS and histopathology have compared generated images to real IVUS images and were impressed by the level of detail. In addition, generated images, also using basic and more analytical phantoms, have been tested in different analysis tools, showing results as could be expected theoretically. Unfortunately, a semi-realistic phantom mimicking a real coronary vessel containing plaque was not available at present.

Such a phantom would need to exist out of materials with exactly known ultrasound properties and dimensions, which lie in the same range as found in reality. This would greatly benefit future research and would be useful for final evaluation and fine-tuning of the developed simulator, also when new ultrasound consoles or catheters (operating at other frequencies) are added.

IVUS is most often used for coronary plaque dimensional measurements. Since the simulator uses histopathology images as input, the exact dimensions and the different tissue components are known. This can be useful for the evaluation or development of available quantitative software.

The simulator could also be used to perform certain predictions about a research or experiment. By performing the experiment in the simulator, possible results could be obtained before the actual experiment is finished or has actually started. These results could than be used to develop or test specific algorithms.

It can be questioned why there is so little research performed to the way IVUS images are generated. This line of research could be very useful to gather a greater understanding of what is and can actually be determined by applying IVUS in clinical practice. This is especially urgent, as IVUS is the reference method to study human coronary plaques and is being used in large clinical trials to evaluate new treatments in the field of human coronary artery diseases.

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