Computer Assisted Coronary CT Angiography Analysis
Disease-Centered Software Development

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Cover picture: Coronary CTA data visualized in 3D using volume rendering. The right coronary artery, the left anterior descending artery and the left circumflex artery are segmented with the presented software and shown in different colors.

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The substantial advances of coronary CTA have resulted in a boost of use of this new technique in the last several years, which brings a big challenge to radiologists by the increasing number of exams and the large amount of data for each patient. The main goal of this study was to develop a computer tool to facilitate coronary CTA analysis by combining knowledge of medicine and image processing.

Firstly, a competing fuzzy connectedness tree algorithm was developed to segment the coronary arteries and extract centerlines for each branch. The new algorithm, which is an extension of the “virtual contrast injection” method, preserves the low density soft tissue around the coronary, which reduces the possibility of introducing false positive stenoses during segmentation.

Secondly, this algorithm was implemented in open source software in which multiple visualization techniques were integrated into an intuitive user interface to facilitate user interaction and provide good overviews of the processing results. Considerable efforts were put on optimizing the computational speed of the algorithm to meet the clinical requirements.

Thirdly, an automatic seeding method, that can automatically remove rib cage and recognize the aortic root, was introduced into the interactive segmentation workflow to further minimize the requirement of user interactivity during post-processing. The automatic procedure is carried out right after the images are received, which saves users time after they open the data. Vessel enhancement and quantitative 2D vessel contour analysis are also included in this new version of the software.

In our preliminary experience, visually accurate segmentation results of major branches have been achieved in 74 cases (42 cases reported in paper II and 32 cases in paper III) using our software with limited user interaction. On 128 branches of 32 patients, the average overlap between the centerline created in our software and the manually created reference standard was 96.0%. The average distance between them was 0.38 mm, lower than the mean voxel size. The automatic procedure ran for 3-5 min as a single-thread application in the background. Interactive processing took 3 min in average with the latest version of software.

In conclusion, the presented software provides fast and automatic coronary artery segmentation and visualization. The accuracy of the centerline tracking was found to be acceptable when compared to manually created centerlines.
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LIST OF PAPERS

This thesis is based on the following original papers, which are referred to in the text by Roman numerals:


# Abbreviations

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<td>Coronary Angiography</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CPR</td>
<td>Curved Plane Reformatting</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>IVUS</td>
<td>Intravascular Ultrasound</td>
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<td>LAD</td>
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1. INTRODUCTION

Despite worldwide efforts to investigate and control cardiovascular risk factors, coronary artery disease (CAD) remains currently the primary cause of death worldwide and in particular among Western nations [1]. Approximately one in five deaths is currently related to cardiac disease in Europe and the US. Nearly 500,000 deaths caused by CAD are reported every year in the US, and over 600,000 in Europe [2]. The lifetime risk of developing CAD after 40 years of age is 49% for men and 32% for women [3]. In Sweden, although the age-standardised mortality of myocardial infarction (MI, an acute manifestation of CAD) decreased from 1987 to 2004 with an average of 3.5% per year, and the age standardised MI incidence from 1987 to 2000 with 1-2% per year [4], CAD is still the most common cause of death and the case fatality of MI is still high. During 2006, 17,000 out of 91,000 total deaths were caused by CAD-related ischemic cardiac disease [5]. It is expected that from 1990 to 2020, the global burden of cardiovascular disease will rise with 55% in the developing countries. The highest rise is foreseen in India and China [6]. These alarming statistics highlight an acute need for tools to diagnose cardiac and coronary artery disease. Presently, the gold-standard modality for diagnosis of CAD is invasive selective coronary angiography (CA). The greatest advantage of this method is that interventions can be performed immediately after the lesion has been located with X-ray. More than 2.5 million diagnostic coronary angiograms are performed every year in Europe and the US, but only about 40% of them are followed by subsequent interventional treatment [7]. Moreover, a recent study has questioned the usefulness of interventional treatment in non-acute cases [8]. These data show the significant need for and importance of reliable non-invasive imaging for early and preventive diagnosis of CAD and other cardiac diseases.

Since the introduction of contrast-enhanced CT angiography, it has been established as a reliable and widely used non-invasive imaging modality for vascular diagnosis. Early in the 1980s, researchers started to dream about performing CTA on coronary arteries [9]. It was only after the introduction of helical CT, especially multidetector helical CT (MDCT), that coronary CTA became more realistic. Although there were several major limitations of this new techniques in the beginning, like high X-ray exposure and low temporal resolution, requiring a heart rate below 70 beats per minute for diagnostic images (which can be obtained by administering a beta-blocker) [10], most of them have been overcome or at least attenuated by improvements of the imaging technique. With current state-of-the-art CT scanners, motion free images can be acquired from most patients without any heart rate control, and techniques have been developed to reduce the X-ray exposure to 1.1-3.0mSv [11], which is no more than the average annual background radiation (about 3mSv) for each individual. Thanks to these dramatic improvements of scanning techniques and some obvious benefits of CT, such as the low cost, shorter acquisition time and non-invasive
nature, the acceptance of coronary CTA has continuously proceeded in the last 5
years. It is generally believed that in the near future, the use of coronary CTA may
replace a substantial proportion of CA examinations, especially for assessing the
degree of stenosis and patency of grafts [12].

However, unlike CA, the information supplied by coronary CTA is distributed
in hundreds of transverse images. Radiologists and cardiologists still largely
depend on viewing original slices, oblique multiplanar reformatting (MPR) and
curved plane reformatting (CPR) images, sometimes complemented by a thin-slab
maximum intensity projection (MIP) image. Evaluating the coronary artery in
such a large stack of time-resolved images is rather time-consuming. Taking into
account the increasing number of examinations per day, it is an important goal for
medical image science to find efficient and accurate ways of viewing large
volumes of images. Encouraged by this clinical requirement, we have been
devoting our knowledge and enthusiasm to develop coronary CTA processing
software from a radiologist’s perspective to facilitate the diagnosis procedure and
improve the accuracy of the stenosis assessment in coronary CTA data. In this
disease-centered study, we have attempted to combine our experience from
medical practice and understanding of image processing techniques to build a
“Swiss army knife” for coronary CTA analysis. Thanks to generous help from
clinical and technical colleagues, an open-source software module for coronary
CTA post-processing was developed. New functionalities, including thus far rib
cage removal, tracing of the ascending aorta, coronary artery segmentation and
centerline tracking and quantitative 2D cross-section measurement, were added
underway, and the quality and performance of the software were also consistently
improved in the last two years. This thesis will report studies describing and
evaluating this software from a technical as well as a clinical point of view.
2. BACKGROUND

2.1. Coronary Artery Disease and Diagnostic Methods

CAD occurs when the coronary arteries supplying blood to myocardium become hardened and narrowed, which is usually caused by the buildup of atherosclerotic plaques on their inner walls. Plaques are made up of fat, cholesterol, calcium, and other substances found in the blood. As the buildup grows, most individuals with coronary artery disease show no evidence of disease for decades before the stenosis caused by plaques severely reduces the blood flow through the arteries and the first onset of symptoms finally arises. A common symptom is chest pain known as angina, indicating that the heart muscle cannot get the blood or oxygen it needs. The resulting ischemia, i.e. oxygen shortage, if left untreated for a sufficient period, can cause reversible damage and/or infarction of the myocardium. After decades of progression, some of the atherosclerotic plaques may rupture and form an embolus that suddenly cuts off the heart’s blood supply, causing permanent heart damage. If this happens in a main branch, it often leads to sudden death.

Over time, CAD can also weaken the heart muscle and contribute to heart failure and arrhythmias. Heart failure means the heart is unable to pump blood well to the rest of the body. Arrhythmias are changes in the normal beating rhythm of the heart.

Diagnosis of CAD is a relatively complicated procedure. Many tests are available for this purpose. The choice of which, and how many, tests to perform depends on the patient’s risk factors, history of heart problems, and current symptoms. Usually the tests begin with the simplest and may progress to more complicated ones. Several often used diagnostic techniques are listed below.

Electrocardiogram (ECG): An electrocardiogram records electrical signals as they travel through the heart. When the heart muscle is damaged (reversibly or irreversibly), the electrical signals passed will also be affected, and in turn cause changes in the ECG pattern. ECG can thus often reveal evidence of a previous heart attack or one in progress. But since a routine 12-lead ECG is mostly targeting on the left ventricle, MI on the right ventricle or posterior basal wall can be overlooked [13]. If the coronary insufficiency is not very severe, a rest ECG could be normal as the damage to myocardium is only temporary, and sometimes the ECG pattern can be very complicated and uninterpretable. The degree of inter-observer variation can be significant in these cases [14]. However, as ECG is a widely accepted, non-invasive and convenient procedure, it is still one of the most important diagnostic tools for CAD.

Biochemical tests: After myocardial necrosis, certain biochemical markers, such as cardiac troponin I or T, will be released into patients’ blood. A blood test can reveal an elevation of such markers that starts 2-4 hours after onset of symptoms. Troponin testing in primary care has shown to be helpful in the triage of chest
pain patients [15]. However, in some situations, such as unstable angina, myocardial ischemia is not associated with an elevated level of cardiac troponin. Further, there are several reasons for cardiac troponin elevation in the absence of ischemic heart disease [16].

**Echocardiography:** An echocardiogram is a sonogram of the heart. Also known as a cardiac ultrasound, it uses standard ultrasound techniques to image 2D slices of the heart. The latest ultrasound systems now employ 3D real-time imaging [17]. Since the spatial resolution of echocardiography is not sufficient to evaluate coronary arteries directly, the method can only be used in an indirect manner, like the other diagnostic methods mentioned above. During echocardiography, the examiner can determine whether all parts of the heart wall are contributing normally to the heart’s pumping activity. Parts with impaired motility may have been damaged by a myocardial infarction or be receiving too little oxygen. This may indicate CAD or various other conditions.

**Stress test:** In patients showing normal results from ECG or echocardiography, but signs and symptoms mostly after exercise, an alternative is to let the patient walk on a treadmill or ride a stationary bike during an ECG, known as an exercise stress test. In other cases, medication to stimulate the patient’s heart may be used instead of exercise. Some stress tests are done using an echocardiogram. Another type of stress test, known as a nuclear stress test, measures blood flow to the myocardium at rest and during stress. It is similar to a routine exercise stress test, but with images in addition to the ECG. Using single photon emission computed tomography (SPECT), myocardial perfusion imaging can be performed by tracing amounts of radioactive material injected into the patient’s circulation system to reveal areas that receive inadequate blood flow.

**Coronary angiography:** CA is a minimally invasive procedure to access the coronary circulation. A radio-contrast agent is injected into the coronary arteries through a long, thin, flexible tube (catheter) that is inserted through an artery, usually in the leg, to the heart. X-ray images are then taken while the contrast agent is flushed through the coronary tree, and the presence and extent of a stenosis can directly be judged from these images. This is in contrast with the other methods summarized above which rely on indirect phenomena caused by a stenosis. In complex cases, intravascular ultrasound (IVUS) can be used to closely inspect the atherosclerotic plaque burden, using a specially designed catheter with a miniaturized ultrasound probe attached to the distal end. One great advantage of CA is that, if narrow parts or blockages are revealed during the procedure, a balloon can be pushed through the catheter and inflated to remove the stenosis. A stent may then be used to keep the dilated artery open. Despite several well-known drawbacks, such as high expense, various complications and absence of direct plaque evaluation (unless IVUS is used), CA is currently the “gold standard” diagnostic technique for CAD, due to its ultra-high spatial and temporal resolution and the possibility to simultaneously perform interventional treatment.
**Coronary CTA:** Coronary CTA, also known as cardiac CTA, is a non-invasive technique that can directly capture 3D images of a beating heart using a CT scanner. During coronary CTA, the patient will receive a contrast agent injected intravenously through the arm, and while the contrast agent arrives in the heart, CT images are acquired continuously or triggered by ECG signals until the whole heart is covered. Acquired images can then be registered together using the recorded ECG to show a “frozen” image of the heart at a certain phase of the cardiac cycle. Compared to CA, coronary CTA not only can determine the severity of blockages, but it also directly visualizes the atherosclerotic plaque deposited in the vessel wall. It can identify the early stages of soft (fatty and fibrous) plaque formation even before the stenosis caused by the plaque can be visualized on X-ray angiography images [18]. It also visualizes calcified plaque, which occurs in more chronic coronary artery disease. Besides coronary arteries, the structure and function of other parts of the heart, like the myocardium and valves, can also be evaluated with coronary CTA. This technique is currently undergoing rapid development. A more detailed review of coronary CTA technique will be given in the next chapter.

**Magnetic resonance imaging (MRI):** The procedure using cardiac MRI technology is often combined with an injected contrast medium, to check for areas of narrowing or blockages. Although direct imaging of coronary arteries is possible with MRI, the limited temporal and spatial resolution are still the bottleneck of this technique. The strengths of magnetic resonance cardiovascular imaging, compared to CT, include superb definition of tissue characteristics, perfusion, valvular function, absence of ionizing radiation, and lack of need for potentially nephrotoxic contrast media. Limited temporal and spatial resolution, partial volume artifacts (due to slice thickness limitations), reliance on multiple breath-holds, and poor visualization of the left main coronary artery [19] all reduce the clinical applicability of MR coronary angiography.


2.2. **Coronary CTA**

2.2.1. The development of Coronary CTA

Since its introduction by G. Hounsfield in 1972, CT scan has become a reliable and widely used non-invasive imaging modality for various diagnostic usages. The first attempts to image the heart were in the very early days of CT in the 1970’s [20]. However, due to the rapid motion of the heart and relatively long acquisition times (more than 10 seconds per slice) of early equipment, only large pathological lesions such as tumors along the surface of the heart could be detected.

In the early 1980s, Electron beam computed tomography (EBCT), so-called “Ultrafast CT”, was introduced [9]. With non-mechanical control and movement of the X-ray source, fixed detector system and ECG-correlated sequential scanning, EBCT enabled extremely short image acquisition times to virtually freeze cardiac motion. However, the limited application spectrum of EBCT in general purpose use, high cost of acquisition and very limited industry support have restricted distribution of the technology. Despite coronary calcium evaluation reports since 1989 [21], and non-invasive coronary angiographic imaging reports with EBCT since 1995 [22], these applications did not gain widespread appeal until studies with multi-detector CT (MDCT) became available. The first sub-second single-slice scanner appeared in the late 1980s with the introduction of the “slip ring” technique, which allows continuous rotation of detectors and X-ray source around the patient. The preliminary studies with single-slice spiral CT in the early 1990’s had very limited cardiac applications and significant motion artifacts. It became possible to visualize the coronary arteries but not with reliability to diagnose blockages.

During the 1990’s there were rapid advancements in detector, X-ray tube generators, circuitry, and computers, which allowed the development of multi-row CT scanners. In 1998, mechanical multi-slice CT systems with simultaneous acquisition of four slices were introduced by all major CT manufacturers. For the first time, these scanners enabled ECG-correlated multi-slice acquisition at considerably faster volume coverage and higher spatial and temporal resolution for cardiac applications compared to single-slice scanners. Then 16-row, 64-row and now 320-row CT scanners are available commercially with the speed of image acquisition and volume coverage continuing to increase rapidly with each next generation of CT. The current state-of-the-art dual-source 64-slice CT scanners can achieve a temporal resolution of < 100 ms at all heart rates. In a dual-source CT system, two X-ray tubes and two corresponding detectors are mounted on the rotating gantry with an angular offset of 90°. Thus a complete data set of 180° of parallel-beam projections can be generated from two 90° data sets (“quarter-scan segments”) that are simultaneously acquired by the two independent measurement systems.

While the scanner hardware has evolved, the image reconstruction techniques have also improved in the last decades. On the initial CT systems of the 1970’s, researchers tried to use a prospective triggering method, also known as “step-and-
“shoot”, to capture the beating heart. The tube was turned off after acquisition of a single axial slice, and the patient table incremented to the next slice position, where scanning was triggered to specific cardiac phases. Despite gradual improvements in tube rotation time, these single-slice systems were too slow to image mobile organs.

After implementation of two key technical advances, spiral scanning and multi-slice technology, data can be acquired throughout the entire cardiac cycle during simultaneous recording of the ECG signal. Subsequently, data from specific periods of the cardiac cycle (most commonly late diastole) are reconstructed by retrospective referencing to the ECG signal. This technique is known as retrospective ECG gating. Since data are acquired throughout the cardiac cycle, spiral imaging allows reconstruction from multiple cardiac phases into cine-loops, which is required for functional assessment. However, an obvious drawback is the continuous X-ray exposure during the entire cardiac cycle. Based on the consideration of patient radiation dose, a dose modulation technique has been introduced to reduce the tube current outside the selected phase. Most recently, a new developed “step and shot” protocol for MDCT has successfully reduced the mean radiation dose to $2.1 \pm 0.6 \text{mSv}$ (range 1.1–3.0 mSV) [11]. Besides ECG triggering techniques, a few other advanced image reconstruction techniques, such as half-scan reconstruction and multi-segment reconstruction have also been developed to improve the temporal resolution further.

2.2.2. Advantages of Coronary CTA

Coronary CTA provides a quick and non-invasive diagnostic technique for CAD. The technological advances that have occurred in CT have been directed towards non-invasive coronary angiography. Many clinical studies have proved that the ability of modern coronary CTA to detect significant CAD (stenosis with more than 50% diameter reduction) is very close to CA [12, 23]. Although it might not be able to replace coronary angiography (CA) for diagnosis and assessment of CAD totally, its high sensitivity for patient-based detection of CAD and high negative predictive value suggest its ability to rule out significant CAD. There are several widely recognized advantages that make coronary CTA preferred over invasive CA for a selected patient spectrum [12, 18, 23-26].

Non-invasive: CA is an invasive procedure that might cause some complications to the patients. Although the risk of severe complications such as death is relatively low, around 0.1-0.2% [27], a combined risk of all major complications such as MI, stroke, renal failure, or major bleeding is around 2% [28]. Minor complications such as local pain, ecchymosis, or hematoma at the catheterization site can be even more frequent [28]. Coronary CTA, on the other hand, is a non-invasive diagnostic technique. Although the possibility of allergy and nephrotoxicity still exists, the total risk of complications is much lower than for CA [29, 30].

Time and cost efficient: Thanks to the advanced imaging techniques, performing a coronary CTA exam is currently much less complicated than invasive CA. The cost for coronary CTA is a small fraction of the cost of a diagnostic
catheter in most countries. The high sensitivity of 64-slice CT avoids the costs of unnecessary CA in those patients referred for investigation who do not have CAD. Although diagnostic strategies involving 64-slice CT will still require invasive CA for CT test positives to identify CT false positives, several studies have proved the cost efficiency of coronary CT for rapid disposition of the low risk population in emergency department [26, 31]. If the associated death rate, although small, with the unnecessary CA is considered, the use of 64-slice CT may also result in a small immediate survival advantage in the presenting population.

**Three-dimensional modality:** Contrary to CA, coronary CTA is a three-dimensional modality and is not limited to any particular two-dimensional projections/slice orientation. This allows assessment of structures in any desired plane or angle, and offers volumetric information on vessel stenosis and other structures such as cardiac chambers. Although there is still no evidence suggesting that coronary CTA is more accurate at evaluating stenosis than CA, the possibility should be kept in mind.

**Plaque imaging:** Diagnostic CA (without IVUS) only gives the images of the contrasted-filled lumen, which can only be used for estimating the stenosis caused by plaques at those lesions. On the other hand, with the extraordinary contrast resolution of CT, physicians can closely investigate the composition of plaques and perform quantitative measurements on them [32].

**“Triple Rule Out” for chest pain diagnosis:** Besides the coronary arteries, specially designed coronary CTA protocols with a wider field of view (FOV) can simultaneously visualize the pulmonary and systemic arteries of the chest, thereby excluding two other important causes of chest pain: pulmonary embolism and aortic dissection. This is known as a “triple rule out” study [33]. CT images acquired with this protocol can also give accurate information of other structures in the chest, which cannot be otherwise visualized by other coronary artery modalities, such as lung and bony tissue.

**Four-dimensional modality for function analysis:** The image reconstruction in coronary CTA has been optimized for coronary artery visualization. However, with ECG-gated spiral acquisition, image data are available for any phase of the cardiac cycle, which makes coronary CTA a 4D modality that can give accurate information about cardiac muscle and valve function and is less operator dependent than echocardiography [34].

### 2.2.3. Limitations of Coronary CTA

In comparison with invasive CA and other non-invasive cardiac imaging techniques, coronary CTA has some inherent limitations, which physicians should consider when requesting this examination. These disadvantages have restricted the usage of coronary CTA to selected patients who have atypical symptoms and are of intermediate risk for coronary artery disease [35].
Radiation Exposure: Radiation exposure is a major drawback of CTA. The average background radiation one experiences in a year is about 3 mSv, and the estimated radiation dose from chest X-ray is 0.04 mSv, while the radiation of a coronary CTA examination currently is 6.4±1.9 and 11.0±4.1 mSv for 16- and 64-slice CTA [36]. In view of the potential benefits, this is probably within acceptable limits, but still higher than a conventional coronary angiogram, with effective doses of 5.6±3.6 mSv [37]. This has severely restricted the indications of coronary CTA examination.

Limited temporal resolution and cranio-caudal coverage: Studies have indicated that temporal resolutions of 35 ms are needed to be able to obtain motion-free images from a beating heart [38]. A modern 64-slice CT can achieve a temporal resolution of 175-200 ms, and a cranio-caudal (z-axis) coverage of 40 mm [39]. This makes coronary CTA highly dependent on the ECG-gating technique that calibrates images from different parts of the heart to the same phase of the cardiac cycle. Thus coronary CTA has difficulty in patients with tachycardia and arrhythmia, where the images can suffer from registration artifacts and blurring.

Nephrotoxic contrast medium: Coronary CTA requires iodinated contrast and often additional medication such as beta-blockers [40]. Although the risk of these drugs is minimal, and CTA exams are usually performed in a hospital under close supervision of medical staff, it does limit the usage of this technique among patients with renal insufficiency [41].

Difficulty with calcifications: The degree of luminal narrowing may be difficult and even impossible to quantify if heavy calcification presents, due to the blooming artifacts. One study shows that the area of calcified plaque measured on MDCT was severely overestimated compared to the histopathologic examination [42]. In addition to calcifications, certain types of stents and bypass grafts with heavy metal content and multiple clips may also cause severe artifacts and make the images non-evaluable.

Relatively high rate of false positives: Sixty-four-slice CT is almost as good as invasive CA in terms of detecting true positives (negative predictive value range 86-100%, median 100% [12]). However, its rate of false positives is relatively high (positive predictive value range 64-100%, median 93% [12]). One study showed that the percentage of stenosis measured on MDCT was systemically overestimated by 12% [12]. Several studies have suggested that a stenosis found with coronary CTA still requires confirmation from invasive CA [12, 25, 26].

Inadequate scientific documentation and clinical guidelines: As with other newly developed techniques, clinicians’ acceptance of coronary CTA varies considerably depending on their personal understanding of the technique. The proper use of this technology may not yet be fully understood by cardiologists, and there is inadequate scientific literature with strong evidence of its true value in diagnostic testing in various clinical scenarios. More evidence-based multidisciplinary evaluation studies are needed to understand the role of coronary CTA in the diagnosis and treatment of early and advanced stages of coronary artery disease.
2.3. Image Visualization and Post-processing for Coronary CTA Analysis

Images produced from coronary CTA are volume data usually consisting of 300-500 slices of 512x512 (pixel) images. To achieve high accuracy and efficiency in evaluating the coronary artery system from such volume data, proper visualization techniques are needed. In order to give prominence to certain structures, hide unwanted information or derive additional information, post-processing techniques may also be required. Image visualization and post-processing are essential for diagnostic accuracy of coronary CTA. As the American Heart Association has recommended, a workstation that allows for interactive manipulation and post-processing of the acquired dataset is crucial, and at least two types of image displays should be used.

In this section, several common visualization and post-processing techniques often used for coronary CTA analysis are briefly explained.

Trans-axial image slices: Trans-axial image slices are the basic outcome of a multi-slice CT scan and include all of the acquired information. Looking through these original source images is recommended in all cardiac CT examinations [35]. This is usually performed in the first step, before any other techniques are used, to get a quick overview of the relevant cardiac structures, including the coronary arteries.

Multi-planar Reformatting (MPR): MPR is a visualization method that allows reconstruction of a 2D slice at any plane defined in a 3D volume of the stacked axial slices. Sagittal and coronal views, usually called orthogonal MPR, are two simple examples. Modern software allows reconstruction in non-orthogonal (oblique) planes, so that the optimal plane can be chosen to display a particular branch of the coronary tree (Figure 1). In practice, however, a stack of oblique planes is needed for each branch. Two often used MPR stacks in coronary CTA are the one parallel to the left anterior descending artery (LAD) and the one parallel to the right coronary artery (RCA) and the left circumflex artery (LCX) [39]. Scrolling through these stacks allows better overview of the atherosclerotic plaque burden and vessel narrowing of each vessel. More accurate segment-based lesion evaluation will require interactive MPR, where the viewer can manipulate the cut plane to be parallel or perpendicular to the centerline of the affected segment [43].

Curved MPR: MPR images cannot present an entire vessel in one slice because of the tortuous course of coronary arteries. Alternatively, instead of using a straight cut plane, a smooth curved surface can be used to fit into the winding vessel and cut open the volume along the centerline of a vessel (Figure 1). This allows bends in a vessel to be ‘straightened’, so that the entire length can be visualized in one image. Once a vessel has been straightened in this way, quantitative measurements of length and cross-sectional area can be made. The centerline used for creating curved MPR images can be defined manually by the user or created from an automatic or semi-automatic program as mentioned later. In most post-processing software, once a centerline is specified, curved MPR can
be produced in real-time and allow users to rotate the curved plane around the centerline to provide complete information of the vessel lumen.

**Maximum Intensity Projection (MIP):** MIP is a computer visualization method that presents 3D information of a volume in one 2D image. Each pixel of the 2D MIP image represents the voxel with maximum intensity that falls in the way of parallel rays traced from the viewpoint to the plane of projection [44]. A MIP image looks very similar to an X-ray image, which makes it a good way to mimic CA images with coronary CTA. However, this is not usually done in coronary CTA because of the inevitable overlay between heart chambers and coronary arteries. Instead, so-called thin-slab MIP, combining MIP with MPR, is normally used. In a thin-slab MIP, the maximum CT number within a given distance orthogonal to the MPR plane is displayed for every ray (Figure 1). For evaluation of the coronary arteries, typical slab thicknesses range from 3 to 10 mm [39], according to the diameter of the vessel. MIP can also be combined with the curved MPR technique to produce curved MIP images along the warped vessel. The oblique MIP or curved MIP usually provides a better overview of the vessel than oblique MPR or curved MPR. On the other hand, the depth information is sacrificed, as everything in the slab is projected onto one plane, which sometimes may affect the interpretation of a lesion.

**Volume Rendering Technique (VRT):** VRT is a 3D visualization technique that mimics how a camera captures images. By using a transfer function that converts the intensity of pixels into colors and opacity, VRT computes each desired pixel by summing up the weighted opacities and colors of all voxels on a ray starting at the center of projection of the camera (usually the eye point) and passing through the image pixel on the imaginary image plane hanging between the camera and the volume to be rendered [45]. The ray usually stops at voxels with 100% opacity or the boundaries of the volume. VRT gives a vivid 2D image like a picture taken in front of a 3D object (Figure 1). In coronary CTA, whole heart VRT is often used to provide an overview of the heart from the outside, with the coronaries visible on the outer surface of the myocardium. This is very helpful in the evaluation of aberrant coronary anatomy, as VRT provides good insight into the 3D relationship of anatomical structures. However, for stenosis assessment, thin-slab VRT is used instead just as thin-slab MIP.

**Four-dimensional visualization and function analysis techniques:** To be able to analyze cardiac valve function and heart wall motion, clinicians and diagnosticians usually need 4D visualization techniques to navigate an anatomical structure’s changes throughout the cardiac cycle. This is typically done by playing MPR/thin-slab MIP images from different cardiac phases in an ordered loop. Usually, the plane defining the MPR/thin-slab MIP images is fixed, and the multiple-phase 3D volumes are reconstructed using retrospective ECG gating with a step of 5 or 10% of the RR-interval [46]. In some software modules, 4D datasets can be rendered with dynamic VRT in a continuous loop, but this requires very powerful hardware support. More advanced software also provides automatic or semi-automatic segmentation of the left ventricle and myocardium, which allows
Background

Calculating the left ventricle ejection fraction and constructing a wall thickening map [39].

**Vessel segmentation, centerline tracking and plaque analysis:** Thin-slab MIP and thin-slab VRT provide intuitive ways to assess segments of the coronary arteries. It is, however, time-consuming to manipulate the position and direction of the sample plane to investigate all branches. Using vessel segmentation, the user can hide all unwanted structures in a whole volume MIP or VRT images by setting them to be transparent. As only coronary arteries are shown in the view, the images look very similar to invasive CA images, with which cardiologists are familiar. Moreover, MIP and VRT techniques allow viewing the vessel from any projection even after the acquisition. Centerline tracking is also very useful for coronary CTA, as it is the foundation of curved MPR techniques. Most advanced medical workstations are able to semi-automatically find a centerline between two points specified by the user. More recently, fully automatically coronary artery centerline tracking and tree modeling have become available on some workstations [39]. Automatic segmentation techniques are also used for calcium score calculations, which have been widely used to evaluate the CAD risk factor [39]. More advanced plaque analysis tools are also under development, which are believed to be able to provide more comprehensive quantitative information about the patient’s plaque burden and to monitor the therapy response of patients undergoing medical treatment [32].

![Figure 1. Comparison of image visualization methods in patient with multiple atherosclerotic plaques of the LAD. A. Transverse images, at the level of left coronary ostium. B. Visualization of stenosis in an oblique MPR. C. Visualization of stenosis in an oblique thin-slab MIP. D. Curved MPR of left main and LAD. E Three-dimensional reconstruction using volume rendering. Calcification can clearly be seen.](image-url)
3. AIMS

Although coronary CTA sometimes can be evaluated without any post-processing, e.g. using interactive MPR or thin-slab MIP, more and more physicians are convinced that using proper post-processing methods may greatly enhance the efficiency of the diagnostic workflow and improve the diagnostic reliability. This clinical need has encouraged the development of modern advanced medical image processing software, and it is also the starting point of this project. The main goal of our study is to develop a computer tool to facilitate coronary CTA analysis by combining knowledge of medicine and image processing. More specifically, the aims of this thesis were:

- to propose a new algorithm for fuzzy connectedness segmentation of the coronary arteries and perform a preliminary evaluation of its speed and visual credibility
- to present a software module implementing this algorithm in an open-source software environment and perform a visual evaluation of its results
- to develop, implement and preliminarily evaluate a method for automating the analysis using the proposed software module

Clinical evaluation of the proposed algorithm and software module falls outside the scope of this thesis, but is planned to be covered in its continuation as a doctoral dissertation.
4. SUMMARY OF THE PAPERS

Paper I

Methods

We propose a new segmentation algorithm based on a competing fuzzy connectedness theory, also called “virtual contrast injection”, which is then used for visualizing coronary arteries in 3D CTA images. The strength of connectedness from each voxel to two sets of seeds, artery seeds and ventricle seeds defined by the user, is calculated and compared to decide which object a voxel should belong to. The strength is calculated by finding the strongest among all possible connecting paths. The strength assigned to a particular path is defined as the lowest gray-scale value of voxels along the path. The membership of every voxel is then calculated by comparing its connectedness value to different seeds, assigning the voxel to the seed yielding the highest connectivity. Applying this strategy to all voxels in the image, a natural segmentation by “virtual contrast injection” is achieved. The whole concept can be likened to contrast agents of different color being injected in the seed regions and circulating within the cardiovascular system while competing with each other. The propagation procedure for a seed is somewhat similar to Region Growing, but uses a non-local propagation criterion.

The major difference compared to other fuzzy connectedness algorithms is that an additional data structure, the connectedness tree, is constructed at the same time as the seeds propagate. Using this tree structure not only speeds up the computational speed, but also improves the segmentation results by solving an ambiguity problem that may arise when propagation from different seeds occurs along the same path. In addition to that, the fuzzy connectedness tree algorithm also includes automated extraction of the vessel centerlines, which can be used for creating curved MPR images along the arteries’ long axes.

Results

The proposed method was compared with a previously reported method [47] in 33 clinical coronary CTA datasets. Using only basic seed planting (with one root seed placed in each coronary artery) resulted in all visible branches being completely segmented in 18 cases, compared to 12 cases when using the same seeds with the previous algorithm ($p<0.05$; McNemar’s test). In total, visually correct centerlines were obtained automatically in 95.3% (262/275) of the visible branches.
Figure 2. A. Segmentation result shown in 3D with volume rendering, arrow indicating a severe stenosis in LCX. B. Segmentation result of left coronary artery shown in 3D with MIP, arrow indicating the same stenosis. C. Segmentation result shown as a mask in color on a 2D transverse image. Circle indicates the cross-section of the same lesion in A and B. The red mask proves that the stenosis seen in 3D was not caused by errors in segmentation. D-F. Curved MPR, oblique MPR and oblique MIP of the LCX, arrow indicating the same stenosis.

Paper II

Methods

A new software module for coronary artery segmentation and visualization in CTA datasets is presented, which aims to interactively segment coronary arteries and visualize them in 3D with MIP and VRT.

The software was built as a plug-in for an advanced open-source PACS workstation - OsiriX. The main segmentation function is based on an optimized “virtual contrast injection” algorithm, which uses fuzzy connectedness of the vessel lumen to separate the contrast-filled structures from each other. In contrast to many other algorithms, our approach does not aim to define the exact border of the vessel, but rather to keep a sufficient amount of myocardial tissue surrounding the vessel in the segmentation result, which facilitates preservation of detailed information about the coronary artery tree.
The software was evaluated in 42 clinical coronary CTA datasets acquired with a 64-slice CT using isotropic voxels of 0.3–0.5 mm.

**Results**

The median processing time was 6.4 min, and 100% of the main branches (right coronary artery, left circumflex artery and left anterior descending artery) and 86.9% (219/252) of visible minor branches were intact, as judged by visually checking if there was at least one voxel of soft tissue surrounding the contrast-enhanced lumen (Figure 2). Visually correct centerlines were obtained automatically in 94.7% (321/339) of the intact branches.

**Paper III**

*Methods*

To provide an efficient method to extract useful information from the increasing amount of coronary CTA data, a quantitative coronary CTA analysis tool was built on OsiriX, which integrates both fully automatic and interactive methods for coronary artery extraction. The image processing in the software can be divided into three phases: image reception and classification; automatic coronary artery tree extraction; and interactive coronary artery extraction and visualization (summarized in Figure 3).

During the image reception and classification, the software checks all received images and decides which should enter the automatic processing pipeline.

Automatic coronary artery tree extraction starts with rib cage removal using a minimum-cost-path searching method to close the heart contour at the anterior and posterior mediastinum. The ascending aorta is then detected using a Hough-transform-based 2D circle detection method, and extracted using a 3D cross-section growing method. The coronary arteries are finally segmented and skeletonized with the “virtual contrast injection” method performed on the vessel structure enhanced data using the detected aorta as start seed.

In the interactive coronary artery extraction and visualization phase, the user can correct the automatically created results by adding new seeds or an endpoint for a branch. For quantitative analysis, a 2D level-set method is used to segment the vessel’s contour on the cross-section and longitudinal-section images.

The computational power of an ordinary PC is exploited by running the non-supervised coronary artery segmentation and centerline tracking in the background as soon as the images are received. When the user opens the data, the software provides a real-time interactive analysis environment.

**Results**

Standardized evaluation methodology and a reference database for evaluating coronary artery centerline extraction algorithms (publically available at [http://coronary.bigr.nl](http://coronary.bigr.nl)) were used for evaluating its performance. The average
overlap between the centerline created in our software and the reference standard was 96.0%. The average distance between them was 0.38 mm. The automatic procedure ran for 3-5 min as a single-thread application in the background. Interactive processing took 3 min in average.

Figure 3. The workflow of the presented software. The non-supervised coronary artery segmentation and centerline tracking starts in the background as soon as the images are received. When the user opens the data, the software provides a real-time interactive analysis environment.
5. DISCUSSION AND CONCLUSION

5.1. The Clinical Role of Coronary CTA and Its Future

The substantial advances of coronary CTA have resulted in a boost of use of this new technique in different clinical scenarios in the last several years. But in view of its inherent limitations and unavoidable disadvantages, the medical community must balance the diagnostic information against the risks of radiation and iodinated contrast agents. Considerable controversy about its role in clinical practice has been raised. The discussion of the appropriateness and validation of coronary CTA has drawn much attention from practitioners who wonder how they should incorporate coronary CTA into their practice. Although there is still no universal consensus at this time, the picture of coronary CTA has become clearer as more and more study results regarding different aspects of coronary CTA have become available. In June 2008, the American Heart Association published a scientific statement on noninvasive coronary artery imaging by MRA and MDCT [35], which gives a systematic review of the coronary CTA history and clinical research papers related to this technology and offers six recommendations regarding clinical use. The six recommendations are summarized here:

(1) Neither coronary CTA nor MRA should be used to screen for CAD in asymptomatic populations; (2) Both multivendor and additional multicenter validation studies are needed; (3) The potential benefit of noninvasive coronary angiography is likely to be greatest for symptomatic patients with intermediate risk for CAD after initial risk stratification. Coronary CTA is not recommended for high-risk patients who are likely to require intervention and invasive catheter angiography for definitive evaluation; (4) MRA, when it is available, is preferred over CTA for anomalous coronary artery evaluation; (5) Reporting of coronary CTA and MRA results should describe technical quality, coronary findings, and significant non-cardiac findings; (6) Continued research is encouraged to non-invasively detect, characterize, and measure atherosclerotic plaque burden, as well as its development over time.

This guideline highlights the role of coronary CTA as a potential alternative CAD diagnosis tool to invasive CA in carefully selected populations. However, it is noticeable that these recommendations compromising the advantages and disadvantages of coronary CTA are based on a review of current knowledge of coronary CTA. Encouraged by the widely interests in this non-invasive method for CAD diagnosis, new developments of imaging technique, scanning protocol and post processing methods are still underway that will further enhance the reliability and expand the spectrum of CT in cardiac imaging in the near future. A few important trends of the future are discussed below.

Low X-ray dose: The biggest issue of coronary CTA is the radiation exposure involved in the procedure. Although ionizing radiation from natural sources is
Discussion And Conclusions

part of our daily existence (background radiation including air travel, ground sources, and television), it is important for a healthcare professional involved in medical imaging to understand potential risks of a test and balance those against the potential benefits. This is particularly true for diagnostic tests that will be applied to healthy individuals as part of a disease screening or risk stratification program. Recent studies using prospective ECG-gating technique, so-called “step and shoot”, to limit the X-ray exposure have achieved radiation doses as low as 1.1-3 mSv with acceptable diagnostic image quality [11]. Although the cardiac function analysis is sacrificed as images are acquired only during one selected cardiac phase, these promising results might eventually stimulate introduction of modern protocols to lower radiation doses and widen the indications of coronary CTA, for example to improve the “triple rule out” exam protocol used to triage chest-pain patients in the emergency departments [33].

Higher temporal resolution and scan speed: The spatial resolution of coronary CTA is 0.24-0.6 mm, which is roughly comparable to the 0.20-0.25 mm of CA. However, the temporal resolution of coronary CTA is much lower than CA (83-175 ms of CTA compared to 5-20 ms of CA) [39]. This implies that the image quality is strongly related to the patient’s heart rate. However, the technical evolution keeps updating these numbers. The record of high temporal resolution has just improved to 75 ms by the introduction a new generation of DSCT (Somatom Definition Flash, Siemens Healthcare). This allows to reliably display a heart with a fast or irregular heart rate without using beta blockers. An additional benefit from higher temporal resolution is shorter scanning time, which is inversely related to the X-ray dose. The new scanner allows an entire heart scan to be performed in less than half a heart beat, resulting in a dose of less than 1 mSv [48]. Wider coverage is another way to reduce the scanning time. The coverage of the new 320-slice CT is now 16 cm, which allows whole heart imaging during one heart beat without moving the bed. It is foreseen that in the near future the innovations of the imaging technique will eventually free coronary CTA from ECG-gating and provide even higher spatial resolution [49].

Quantitative measures of coronary stenosis severity: Visual interpretation of the coronary CTA is an important factor that contributes to the intra- and inter-observer variability of visual estimates and assessment of lesion severity. Recent developments of CT imaging techniques have greatly improved the image quality and spatial resolution of coronary CTA images. This makes more precise evaluation of coronary stenosis possible. Several studies addressing the possibility of quantitative measurements of vessel lumen and stenosis severity have revealed good correlation between coronary CTA and IVUS and good inter-observer agreement [50, 51]. However, it should be noticed that the image display setting (window setting) has important influence on the CT-derived measurements of lumen [52]. Software that can auto-adapt display setting according to local attenuation distribution is needed to further improve the intra- and inter-observer agreement and reduce user interaction.

Function assessment: Cardiac function assessment is an important part of CAD evaluation. As coronary CTA acquired with retrospective ECG-gating produces
4D data throughout the cardiac cycle, with the help of certain post-processing software, it is possible to quantitatively evaluate the patient's global cardiac function, like ejection fraction, and regional function, like wall thickening [34]. Studies have revealed a good correlation between coronary CTA and transthoracic echocardiography, and a moderate correlation against SPECT [53, 54]. Quantitative myocardial CT perfusion remains a big challenge because of the rapid cardiac motion and considerable X-ray exposure. Although a few animal studies have proved the feasibility [55], no clinical study on a large number of patients has been reported so far. The “iodine map” created with the dual energy CT imaging technique highlights an alternative method to evaluate the blood flow of myocardium [56]. Another application of CT’s 4D ability is cardiac valve evaluation. With the introduction of dual source CT (DSCT), the increased spatial and temporal resolution of the latest 64-slice CT scanners makes functional valve-defect visualization possible [57]. It should be pointed out that pure ventricular function analysis is not the focus of multi-slice CT, since other non-invasive imaging modalities, like MRI and echocardiography, which do not require ionizing radiation or administration of potentially nephrotoxic contrast media, are available. In most cases, functional assessment will be carried out complementary to coronary CTA, and the imaging protocols are the same.

**Plaque imaging and analysis:** Coronary CTA is the most sensitive test in detection of soft and hard plaques, except for IVUS, which requires invasive catheterization and inserting the IVUS probe into every major branch with all its inherent risks. Coronary artery calcium (CAC) score calculated from the calcified plaque area and calcium lesion density is one of the successful applications of CT plaque imaging. Recent data provide support for the concept that the CAC score is a reliable risk assessment tool for CAD, especially in terms of the incremental prognostic value for populations with intermediate risk [58]. More recently, with the increasing spatial resolution of CT scanners, clinicians have started to pay more attention to the soft plaques, as some of them, so-called vulnerable plaques, may rupture in the future and cause sudden death of the patient [32, 59, 60]. The developing coronary CTA technique may allow more accurate prediction of such events and better treatment planning on these segments, as some studies based on IVUS exams have suggested that most myocardial infarctions occur at areas with extensive atheroma within the artery wall, but very little stenosis of the arterial lumen [61].

### 5.2. Contributions and limitations of the current study

Several other software tools have been developed for coronary artery segmentation [62, 63]. Due to the complicated structure of the coronary artery tree, most of them either yield imperfect segmentation results or are computationally too expensive to be clinically useful. Until present, their spread into the clinical routine appears to have been rather limited. In contrast to such tools, our approach does not aim to define the exact border of the vessel, but rather to segment each coronary with some surrounding tissue from other vascular
structures, each with its surrounding tissue. This may seem to contradict the definition of segmentation, but since the results are shown with MIP or VRT, the exact delimitation of the lumen is left to the eye of the user, who may interactively adjust the window setting or VRT transfer function whenever needed. This approach facilitates preservation of detailed information about the coronary artery tree, e.g., the tips of minor branches, which may otherwise be lost as a result of under-segmentation. Moreover, it may prevent the introduction of false stenoses arising from imperfect segmentation, which may be crucial for the diagnostic accuracy (e.g., Figure 2). The preliminary experiments in Paper II showed promising results regarding the reliability of the segmentation method. This might eventually change the role of 3D VRT images in coronary CTA assessment. In an earlier study, Maros Ferencik et al. reported that the accuracy of coronary CTA for stenosis detection using pre-rendered 3D VRT images is much lower than using other post-processing methods (accuracy for detecting stenosis were 88% for transverse, 91% for oblique MPR, 86% for oblique MIP, 83% for curved MIP, 81% for curved MPR, and 73% for VRT) [43]. However, the 3D datasets in their experiments were prepared very cursorily. Only the rib cage, pulmonary arteries and liver were cut away, and no user interactivity was allowed during the evaluation. With our software, a much clearer coronary tree can be interactively viewed from any desired angle. Future studies will, however, be needed to ascertain whether the accuracy of stenosis evaluation on MIP/VRT 3D images could be higher using this new method than reported previously. It also remains to be studied whether the negative predictive value of 3D images prepared with our method equals that of other methods (Ferencik reported 97% with free oblique MPR and 85% with 3D VRT [43]). As 3D VRT images are obviously more time-efficient than 2D MPR images, a new protocol combining 3D images and 2D images for the evaluation might bring about both accuracy and time efficiency. Experiments to test this hypothesis are going to be performed in the near future.

By introducing the automatic seeding function, the user interaction time has, in average, been cut into half compared with the completely interactive procedure (3 min in Paper III vs. 6 min in Paper II). Moreover, with the automatic processing method, about 80 percent of major coronary branches were detected without any user interaction. About one third of the branches achieved more than 99% overlap with the reference centerline in segments with diameter 1.5 mm or larger (which is believed to be clinically relevant), and two thirds achieved 90% overlap or higher (Paper III). In the manual correction procedure, more than 80% of the branches needed none or only one extra seed region. From our experience thus far, the automatic procedure can substantially speed up the review procedure in cases where there are no severe motion artifacts or stenoses present. This is a big proportion of the population undergoing coronary CTA examination, as the examination is usually applied to patients with intermediate or low pre-test probability of CAD [35].

Introducing automatic background pre-processing on image receiving to the PACS workstation is another contribution of our study. Letting the workstation software “think ahead” saves the users waiting time after they open the CTA
exam. Although 4 or 5 minutes of auto-processing time may seem too long to be clinically applicable, a workstation serving one CT scanner will still have ample time to perform the whole procedure, as the interval between two exams sent from the scanner is rarely shorter than 10 minutes. Since the automatic coronary artery extraction pipeline is designed as a single-thread program in the background, the user can simultaneously carry out most 2D image viewing tasks on other exams without noticeable delay in performance on our dual-core Mac system. Further development will focus on pausing or stopping the automatic processing thread when computation-intensive tasks, like 3D rendering, are initiated.

A major limitation of the current version of software is the lack of a calcification segmentation function, which makes stenosis evaluation very difficult in segments with heavy calcification. Centerline tracking does not perform very well in these segments either. Although a threshold filter set at 650 HU is used in the latest version to eliminate the influence from calcium, more sophisticated filters or segmentation algorithms will be needed to correct the distorted segment. Another shortcoming is the fact that the quantitative measurement is based on 2D segmentation, which means that the evaluation results will depend strongly on the location and direction of the MPR plane chosen. This may cause problem if the centerline is not well centered in some segments, which in turn may cause the cross-sectional plane not to be perpendicular to the vessel’s direction. Using 3D morphological measurement based on a more advanced 3D segmentation algorithm may potentially not only prevent such errors but also provide the user with a more intuitive 3D model. Other minor limitations like low computational performance and high memory usage will also be addressed in the future.

5.3. Software development from a radiologist’s perspective

As coronary CTA has become an area of great interest in medical imaging, many medical image workstation vendors have been attracted into the coronary artery analysis software development competition. There are already several commercial software systems available that can perform most of the tasks described in the last chapter, such as Syngo Circulation from Siemens Healthcare, Brilliance Workspace from Philips Medical Systems and AW Workstation from GE Healthcare. Among numerous differences between our software and the others, one factor distinguishing it from commercial workstations is that it is developed mainly from a radiologist’s perspective, where radiologists are involved in the whole development procedure. Classical software development starts with software requirement analysis, and then software design, coding and testing. Usually software requirement analysis is done together by physicians and engineers. Once the requirements have been “clearly” specified, the technician will work on the remaining steps according his understanding of the requirements. However, due to limitations of the clinician’s knowledge about image processing, the defined goal may be difficult to achieve. Conversely, because of lacking medical background, technicians seldom question the definition of the users’ requirement
Discussion And Conclusions

Once it has been defined, even though they may have practical difficulties in achieving that. However, in a team where most members have both a solid medical background and good overview of medical image processing and visualization techniques, it is possible to work together on the defined software requirements and the chosen method. Sometimes the definition of the requirement can be changed after a thorough understanding of the chosen algorithm. So, instead of focusing on finding the right answer to the question, as most developers do, we are trying to find the right answer to the right question.

A typical example in our project is the coronary artery segmentation. Traditional vessel segmentation focuses on defining the exact area of the vessel, which means detecting the edges of the contrast-enhanced lumen in coronary CTA. Many software modules have chosen a region-growing method, which iteratively classifies neighbor pixels/voxels with an intensity-threshold-based criterion. Due to the complicated structure of the coronary artery tree and inhomogeneous CT values from segment to segment in coronary CTA, many of them yield imperfect segmentation results that are not likely to be trusted for diagnostic purposes. Although there are more sophisticated algorithms available, such as the level-set method, these are generally computationally too expensive to be clinically useful. Still, the accuracy of the segmentation results is questionable. In our project, we considered, as the eventual goal of coronary artery segmentation, to provide an intuitive and reliable 3D visualization of coronary artery tree for diagnosis purpose.

In MRA and in most abdominal CTA cases, vessel segmentation is seldom needed for visualization purpose, because there are no high intensity structure blocking the view of users, and with MIP or VRT the low density tissue can be set to transparent by interactively adjusting the window setting or VRT transfer function whenever needed. In such cases, the exact delimitation of the lumen is left to the eye of the user, a very accurate and efficient image processing system. Based on this consideration, we modified the goal of the coronary artery segmentation to separating the coronary artery tree from the other high intensity structures. This allowed us to borrow the “virtual contrast injection” method that has been developed for separating contrast-enhanced arteries and vein in MRA images [47]. A few extensions on this method (Paper I) helped us to achieve very promising results on coronary CTA data. Also, this segmentation strategy itself brings a reconsideration of the diagnostic value of 3D MIP/VRT images as discussed in section 5.2.

Another example of choosing proper image processing tools for right application in our project is using multi-layer QuickTime Virtual Reality (QTVR) Object Movies to visualize high-dimensional datasets and their post-processing results [64] (abstract publishing, not included in the paper list). QTVR technique is a relatively old technique that was introduced as an alternative to VRT. In QTVR movies, images in different projections are pre-rendered and arranged in a grid, so that users can rotate the object around two axes by moving the grid horizontally or vertically relative to current view window. Most technicians have abandoned it as real-time VRT has become increasingly practical on ordinary PCs with the
evolution of software and hardware. However, we noticed the clinical needs to transfer information between radiographer and radiologist or between radiologist and cardiologist. The most common practice is to save sequences of projections as movie clips, thus sacrificing most of the interactivity.

This becomes even more problematic when high-dimensional datasets or post-processing results are involved, as at most time visualization of those data is highly depending on particular software and hardware settings. In one study, we extended the QTVR format to a high dimension visualization method by including multiple layers in each projection and adding a “sprite” track that is programmed to control the visibility of each layer [65]. By grouping the layers, a 5D dataset can also be presented. The preliminary results tested on 3.5D datasets (3D volume with segmentation information), 4D datasets (multiple-phase cardiac CT datasets) and 5D datasets (multiple-phase PET-CT datasets) show that multi-layer QTVR movie is an attractive solution for sharing high-dimensional post-processing results, offering the user a high degree of interactivity at low cost. The fast interaction at review may exceed the interaction speed at a high-end workstation, and the compact file size facilitates data transfer.

Another advantage of programming as a radiologist is that medical knowledge sometimes also helps us to improve the algorithm design. For example, in the ascending aorta tracking method mentioned in Paper III, we decided to let the aorta tracking stop when the aortic valve is reached, as detected by an increased intensity variation in the center of the cross-section. In order to make sure the valve will appear in the center of the 2D cross-section images, the direction of the cross-section plane is calibrated every 10 mm by linear regression of the centers of the last ten cross-sections. This design is based on the anatomical character of aortic valve and the fact that most coronary CTA is acquired during diastole. (The algorithm also works on data acquired during systole, as the valves will not totally disappear from the aorta cross section.) Compared to other authors’ algorithms that use one-direction slice-by-slice region growing and apply a stop criterion if the size of this intersection area between the segmented region and the one in the preceding slice drops below a defined minimum, our method is more robust in certain extraordinary cases, as shown in Figure 4.

However, there are also limits to perform programming as a radiologist. Most prominent is the limited knowledge of various image-processing techniques, which prevents the programmer from using more sophisticated techniques. It may also take longer time to choose proper algorithms for a certain task than for experts in image processing. Another drawback is that lack of training in software engineering may make maintenance of the software more difficult. We have been aware of these problems and tried to minimize the negative effects by enrolling experienced technicians in our group, consulting with image processing experts and consistent training and self-learning. The goal, after years practicing and training, is to break the knowledge fence between medicine and image processing.
Figure 4. A special case on which the one-direction slice-by-slice region growing failed to find the right coronary ostium due to the unusual angle between the ascending aorta and left ventricle (the upper images). Our method can avoid this error by adjusting the growing direction (the bottom images).

5.4. Disease-Centered Software Development

A technician is more often disposed to develop software centered by methods, which means finding different medical applications of one or several methods. That is important because one improvement in the image-processing field will benefit many aspects of medical practice. On the other hand, researchers in the field of medicine often like to collect as many image processing tools as possible to help them study, analyze and understand one particular disease. However, disease-centered software development should not only be understood as simply studying, understanding and implementing each individual method or algorithm, but also a procedure of systemically integrating different methods, knowledge and experience into one functional system that can serve as a powerful tool for the research goal. This can be explained at three different levels:

Firstly, integrating different visualization techniques and image processing methods can provide a clearer picture of the targeted lesion. For example, combining MIP/VRT images with MPR or Curved MPR images for stenosis analysis will improve the accuracy of the diagnosis [35, 43]. By introducing quantitative measurements, the problem of inter-observer variation will hopefully be reduced.

Secondly, integrating different software modalities or even imaging modalities gives a thorough evaluation of the targeted disease. Diagnosis and assessment of a disease usually involves many factors. In order to investigate and control the cardiovascular risk of CAD patients, cardiologists need to look into not only the vessel narrowing measurement but also the atherosclerotic plaque burden analysis.
and the cardiac function studies like myocardial perfusion from SPECT or CT perfusion imaging. Instead of listing them separately, disease-centered software should be able to fuse the information from different modalities to provide an intuitive visualization of the linkage between morphological changes and function changes [66].

Thirdly, integrating the knowledge learned from different aspects of image processing may help us understand the targeted disease better. Some pioneers in the coronary CTA research field have attempted to extend our knowledge about the progress of CAD by combining the blood flow simulation with atherosclerotic plaque modeling. Ufuk Olgac et al. reported a study of using coronary CTA data and blood flow simulation to study the transport of low-density lipoprotein (LDL) from blood into arterial walls [59]. This highlights the possibility of using imaging techniques to predict the development of atherosclerotic plaques. In their study, at least three different kinds of knowledge — image segmentation, blood flow simulation and LDL transport modeling — were required, which can be seen as a typical example of disease-centered study served by interdisciplinary knowledge.

In our study about CAD, we have been trying from the very beginning to integrate knowledge from different fields. Although at the current stage we have not be able to achieve the second and third level, due to limited time and human resources, the long-term goal is to explore all possibilities to expand our limited knowledge of CAD.

5.5. Open Source

To benefit more users and contribute more to the academic society, we decided to distribute our software as an open-source plug-in for OsirIX, an open-source medical workstation platform developed also by a radiologist [67]. The abundant feedback from users and developers within the open-source society, which was experienced also in this project, may help considerably in improving different aspects of the software. Compared to commercial software vendors, the feedback circle in open source development may be more efficient and healthy, as users not only share their experience with the software but also explain their research interests and their opinion about research plans. It may also facilitate finding research collaboration partners.

5.6. Future Work

The continuing evolution of coronary CTA imaging technique brings both opportunities and challenges to medical image processing researchers. While the introduction of 320-row CT scanners and dual-source CT scanners keep increasing physicians’ faith in this technique [57, 68], there are still questions regarding accuracy and short-/long-term prognosis that need to be answered. Our future goals include providing an accurate and efficient quantitative measure tool for stenosis evaluation by extending current 2D segmentation to 3D segmentation. Plaque segmentation and characterization will also be the focus of future studies.
In addition to this technological development, an important task for future research is to clinically evaluate the developed methods by determining their diagnostic value in terms of specificity and sensitivity, e.g. by using the concept of receiver operating characteristic (ROC) curves. Plans for such studies are underway in our group.

The development of another non-invasive coronary angiography technique, coronary MRA, has also drawn our attention. According to an early feasibility study and feedback of users, most functionalities of our current software will still work on MRA data. However, future studies are needed to achieve optimal results. More importantly, the possibility of integrating information from different imaging modalities, such as CT and MR, CTA and SPECT, or CTA with invasive CA, will be more valuable to extend the view of radiologists and cardiologists.

Multi-discipline cooperation projects, such as atherosclerotic plaque modeling, are another natural continuation of the work reported in this thesis.

5.7. Conclusion

In this thesis, we have presented an open-source software environment for coronary CTA analysis, which aims to facilitate the coronary artery stenosis evaluation in coronary CTA datasets. The software is based on a competing fuzzy connectedness tree algorithm, which can yield both coronary artery segmentation and skeletonization. The computational speed is acceptable on ordinary PCs after optimization. Multiple visualization techniques are integrated into the user interface to facilitate user intervention on the results and provide good overviews of the coronary artery. Integrating an automatic seeding method into the interactive segmentation workflow further minimizes the requirement of user interactivity during post-processing. In our preliminary experience, visually accurate segmentation results have been achieved with limited user interaction. The accuracy of the centerline tracking was found to be acceptable when compared to manually created centerlines.
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