Quantitative analysis of coronary artery from computed tomography angiography images

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Quantitative Analysis of Coronary Artery from Computed Tomography Angiography Images

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Abstract

Coronary artery diseases (CAD) have been the major cause of death worldwide, accounting for about 17% of total US deaths. Automatic and accurate reconstruction of coronary arteries has been one of the aims of medical imaging, which is used to detect and quantify the potential stenosis. In clinical practice, there exist numerous ways of quantifying coronary artery lumen for stenosis detection [1]. To evaluate the severity of a coronary stenosis, two main different approaches at present can be used: by evaluating longitudinal diameter reduction (angiography imaging) or by measuring the reduction of lumen (Computed Tomography (CT) imaging) [2, 3].

Most commonly, diameter stenosis is measured because of the popularity of projection-based invasive angiography, which is measured as the ratio of the reduction in vessel diameter to the proximal normal diameter [4]. The estimate of area stenosis has distinct advantages and priorities, i.e., less dependency on reference site and viewing angle. When correlating with myocardial perfusion assessment or coronary blood flow, lumen area evaluation is expected to be preferable to diameter quantification [5, 6, 7, 8]. It is intuitive that diameter assessment is difficult when considering irregular arterial lumen shapes at lesion sites [9]. Since lumen shapes of the lesion are irregular, diameter assessment may distort the true extent of stenosis in many cases [10].

An automated, robust and efficient method to approach most Computed Tomography Angiography (CTA) images is still in demand due to the intrinsic ill-posedness and the external stenosis quantification difficulties such as manual

measurement, low contrast and huge processing time, which motivates the studies in this thesis. This thesis includes several works addressing three challenging issues in the stenosis quantification topic. The proposed stenosis quantification framework used in this thesis generalizes the framework used in earlier methods. It not only preserves all theoretic merits of existing methods, but also adapts to numerical solvers in current segmentation and centerline extraction methods. In three studies, novel mathematical models are proposed and validated for the quantification purpose; efficient minimization and shortest path tools are developed; potential applications are suggested through a wide spectrum of 3D CTA images. The methods not only outperform existing methods on common stenosis quantification problems, but also first address cross sectional lumen planes cutting over vessel surface mesh.

Firstly, it is a prerequisite to precisely segment coronary arteries for the quantitative evaluation of the severity of potential stenosis. An automatic coronary artery segmentation approach based on Hessian filter and connected components is proposed. A model-based vesselness filter is first used to segment coronary arteries in CTA images. Next a threshold operation based on the intensities of coronary artery is performed to create the binary representations of these structures. Besides, post-processing steps such as filling hole and surface smoothing are also performed to accurately extract the centerline.

Secondly, a fast and accurate technique for coronary centerline extraction is developed. The fast marching method is first applied to calculate the time-crossing map. In the second step, a branch tracking procedure based on the Runge-Kutta method is performed. The proposed method can reduce the processing time by about 10% and achieve higher accuracy compared to the existing approaches. In addition, the application of this new approach is demonstrated on various CT images. The subvoxel precise centerlines are shown to be reliable and accurate.

At last, an accurate and reproducible coronary artery cross sectional lumen

area measurement algorithm at sub-voxel accuracy from human cardiac CTA images is developed. The proposed algorithm depends on centerline extraction and coronary artery surface mesh generation. Moreover, the approach is applied over morphometric data of real patients and the accuracy of the obtained cross sectional lumen area (CSLA) is validated against intravascular ultrasound (IVUS).

In summary, the new approach for coronary artery stenosis quantification consists of three steps, 3D segmentation, centerline extraction and cross sectional lumen plane cutting. The application of this new algorithm is demonstrated on various CT images and the accuracy of the obtained lumen area is validated based on IVUS. This approach will facilitate quantitative evaluation of the severity of potential stenosis and help in clinical diagnosis of CAD.

Notations and Abbreviations

Common Notation

$\mathbb{R}$	Set of all real numbers
$\mathbb{N}$	Set of all nonnegative integers, i.e., $\{0, 1, 2, \dots\}$
$\mathbb{C}$	Set of all complex numbers

Pixel and Voxel Spaces

N_4	4-connected neighborhood in 2D image
N_8	8-connected neighborhood in 2D image
N_6	6-connected neighborhood in 3D image
N_{18}	18-connected neighborhood in 3D image
N_{27}	27-connected neighborhood in 3D image
$N_6(p)$	Voxel p and its 6-connected neighbors
$N_{18}(p)$	Voxel p and its 18-connected neighbors
$N_{27}(p)$	Voxel p and its 27-connected neighbors

Distance

$d_4(x, y)$	Distance in 4-connected neighborhood
$d_8(x, y)$	Distance in 8-connected neighborhood
$d(x, y)$	Euclidean distance
T_P	Distance map
d_{power}	Power distance

Physical and Straightened Spaces

$\mathcal{P}$	Original physical space
$\mathcal{V}$	Vessel space defined by the moving frame
$\mathcal{S}$	Straightened space produced by the vessel reformation
$\mathbf{t}_i$	Normalized tangent
$\mathbf{n}_i$	Unit normal
$\mathbf{b}_i$	Unit binormal
$p_i^{\mathcal{P}}(0, 0)$	Skeleton point i

Abbreviations

<i>CAD</i>	Coronary artery disease
<i>CTA</i>	Computed Tomography Angiography
<i>CSLA</i>	Cross sectional lumen area
<i>IVUS</i>	Intravascular ultrasound
<i>CVD</i>	Cardiovascular disease
<i>MRA</i>	Magnetic Resonance Angiography
<i>MSCT</i>	Multi-slice computed tomography
<i>PSF</i>	Point spread function
<i>MIP</i>	Maximum intensity projection
<i>MinIP</i>	Minimum intensity projection
<i>ROI</i>	Region of interest
<i>MAT</i>	Medial axis transform
<i>VED</i>	Vessel enhancing diffusion
<i>MHT</i>	Multiple hypothesis tracking
<i>LAD</i>	Left anterior descending
<i>LCX</i>	Left circumflex artery
<i>RCA</i>	Right coronary artery

Introduction

1.1 Background

Cardiovascular diseases (CVDs) have been one of the leading reasons of death worldwide in modern society. In 2012, approximately 31% of all global deaths are caused by CVDs, representing 17.5 million people globally. Of these deaths, an estimated 7.4 million people died from coronary heart disease [11]. In the US-A, for example, while approximately 4% of women deaths are caused by breast cancer, about 50% are related to heart disease or stroke [12]. Coronary heart disease is mainly caused by coronary artery stenosis, which represents an abnormal narrowing of arteries. It is important to extract the lumen boundary from cardiac images for diagnosis and treatment of CAD. Similarly, effective stenosis grading requires the accurate vascular structures visualization and quantification. It is also the basis for blood flow modeling and vessel wall dynamics [13].

Currently, human vascular images are acquired using various medical imaging techniques, for example, 3D Computed Tomography Angiography (CTA), 3D Magnetic Resonance Angiography (MRA) or 3D Ultrasound (US). With the development of high and spatial resolution combined with electrocardiographic (ECG) gating, multi-slice computed tomography (MSCT) has become a clinically important non-invasive diagnostic technique in cardiac image analysis [14, 15].

Current MSCT coronary angiography studies are based on the visual estimation of the degree of stenosis. Prior to imaging, often a contrast agent is intraarterially or intravenously injected to enhance the contrast of blood vessels w.r.t. the surrounding tissue, i.e. yielding contrast-enhanced (CE) MRA and CTA images. The resulting enhancement of the vessel contrast is determined by the local concentration of the agent within a vessel. Usually, the contrast agents are based on gadolinium and iodine in the case of MRA and CTA, respectively.

As an example, Figure 1.1 shows maximum intensity projection (MIP) of 3D CTA images of human cardiac anatomy. The vessels generally have a higher contrast compared to other anatomical structures. However, it can also be seen that the contrast of some vessels varies in different parts of the image, and can even be relatively poor. The reason is that the contrast agent is transported within the blood, and therefore, the local concentration of the agent depends on the spatial distance from the locus of injection of the agent. As a consequence, the timing in CE angiography is crucial to ensure a similar concentration level in all considered vessels.

The intensity distribution within a vessel mainly depends on the size of the vessel as well as the imaging technique. For 3D CTA images, for example, typical intensity distributions are shown in Figure 1.2 as 2D axial sections through three vessels of different sizes. It can be seen that the shape of a thin vessel (left) is approximately Gaussian-like, whereas the vessels of medium and large widths (middle and right) have quite a different shape, which is plateau-like.

Coronary artery stenosis quantification is crucial for the diagnosis of cardiovascular diseases [16]. Recent development of medical imaging techniques can be able to monitor coronary heart disease status and treatment effects. Due to the properties of noninvasive and economical, CTA has become a commonly used imaging technique for quantification of coronary arterial stenosis [16, 17, 18, 19, 20]. In the literature, a large number of approaches have been developed for coronary artery tree segmentation [21, 22, 23, 24, 25] and coronary stenosis quantification

Figure 1.1: MIP of 3D CT images of human cardiac anatomy.

[26, 27, 28, 29] via CTA.

Segmentation and quantification of coronary arteries, for example, measurement of the width, from 3D CTA and MRA images is essential for diagnosis and treatment of CAD. However, it is usually difficult and challenging to segment the vessels from 3D medical images. The main reasons are: 1) different types of vessel have different widths. 2) the width even varies along the branch. 3) medical images are noisy and vessel boundaries are difficult to be determined due to surrounding tissues. 4) curved 3D structures are much more difficult to be segmented.

There exist large numbers of ways for quantifying coronary artery luminal information for stenosis evaluation. The most commonly used measure is diameter stenosis. However, evaluating cross sectional lumen area becomes preferable to diameter measurement when correlating with myocardial perfusion assessment or coronary flow [5, 6, 7, 8]. More specifically, diameter evaluation is challenging and not accurate at lesion sites where arterial lumen shapes are irregular [30, 9]. Due to these irregular lumen shapes, diameter measurement may not represent true lumen narrowing [10, 1]. Lumen area measurement is not dependent on the selection of reference site, seems suitable in several ways. However, diameter assessment is the gold standard for coronary stenosis evaluation due to historical popularity of invasive coronary angiography. Similarly, coronary lumen evaluation

Figure 1.2: 2D axial sections through a thin vessel of small RCA (left), medium RCA (middle), and the aorta (right) in 3D CTA images displayed as intensity image (top) and intensity plot (bottom).

is mainly based on diameter evaluation by MSCT. But lumen area evaluation is expected to be more frequently used once its superiority and feasibility can be demonstrated.

1.2 Motivation

One of the aims of medical imaging is to automatically and accurately reconstruct coronary arteries, which may be subject to stenosis [31]. In clinical practice, it is usually crucial to extract certain information from 3D medical images of heart vascular system for coronary artery diseases diagnosis, surgical planning and treatment. However, such 3D data are quite large (e.g., $512 \times 512 \times 480$), while the useful vessel information contains only about 5% of the whole volume. Therefore, a manual analysis is usually quite time consuming, in particular, for achieving the required accuracy. In addition to this sparseness, varied width of different types of vessels, curved 3D structures and general presence of surrounding noise make

the analysis a challenging task. In order to increase performance, it is desirable to automatically analyze the 3D image data.

Currently, there exist numerous approaches for the segmentation and quantification of vessels from 3D image data. Previous work on vessel segmentation can be divided into two main classes: deformable models (e.g., [32, 33]) and differential measures (e.g., [34, 35]). Deformable models are often used to exploit contour information. We can refer to McNerney and Terzopoulos [36] for a review of deformable models in medical images analysis. For instance, Ruechert *et al.* [37] have applied extended geometrically deformable models (GDM), where the contour of the model is formed by connecting a set of vertices, and model fitting is represented by an energy-minimizing process. However, these approaches generally section through vessel structures in order to exploit contour information. Approaches based on differential measures often exploit the image gradient or the Hessian matrix [38, 39, 40], which are computationally efficient.

Skeletonization [41] is generally a process of extracting a 1D centerline from volume data while preserving their geometrical features. As a concise and reliable representation, curve-skeleton is useful in computer graphics and visualization, such as virtual navigation, shape reconstruction, animation, shape matching, etc [41]. Currently, numerous 3D skeletonization algorithms have been developed and applied on a variety of synthetic 3D shapes [42]. Each algorithm is tuned with different thresholds and parameters for its own specific application and for good visual result. As a consequence, it is difficult to evaluate the performance of these 3D skeletonization approaches and replicate the algorithm on general medical image processing.

In clinical practice, the vessel diameter is commonly used to evaluate coronary stenosis due to the historical popularity of projection-based invasive angiography. Generally, traditional radiographic assessment of arterial disease severity depends on the ratio of a focal minimum diameter to a proximal normal diameter, namely as diameter stenosis [4]. The percentage stenosis is widely used to measure the

severity of a potential stenosis [43, 44, 45]. But unfortunately, the focal minimum, which depends on reference site and projection plane, is challenging to be accurately measured even for trained medical specialists [46, 1]. Compared to diameter measurement, the cross sectional lumen area is expected to be more significant and suitable since it is directly related to the hemodynamic properties of vessels. Quantitative analyses of the cross sectional profile based on 3D curve-skeleton of coronary artery will facilitate the severity assessment of stenosis in a straightforward and accurate way [47]. Therefore, extraction of curve-skeleton of coronary artery tree, which is centered in and represents the complete topology of blood vessels, is of utmost importance in clinical practice [48].

Particularly, inter-observer variability for the quantification of CAD with visual estimates is also substantial. For example, when quantifying intermediate grade (40% to 70%) stenoses, differences of $\pm 20\%$ are common among readers even performed by experienced cardiologists [49]. Even evaluation with conventional angiography may produce substantial variability due to the software algorithm and parameters [50]. Therefore, accurate evaluation of length of the 3D vessels and cross sectional lumen area (CSLA) is required for computational modeling of cardiovascular disease. With the ease of stenosis detection by MSCT, quantitative CSLA evaluation may garner wider clinical potential as the routine assessment.

1.3 Major Contributions of the Thesis

In this thesis, the coronary artery segmentation and centerline extraction problems have been addressed within a unified framework. The major contributions of the thesis are summarized as follows.

- A new anisotropic diffusion filter is proposed, which is able to enhance the vessel structures with a diffusion strength function based on the vesselness measure. To achieve this, we develop a novel diffusion tensor for the

purpose of steering main diffusion along the vessel and inhibiting diffusion perpendicular to the vessel. The proposed diffusion filter, which reduces noise and background objects and improves vessel delineation, can be used to facilitate visual analysis and improve vessel segmentation results. Based on this, an automatic coronary artery segmentation approach that depends on Hessian filter and connected components is proposed.

- A hybrid strategy for coronary centerline determination is developed. The first step of this new method is to calculate the time-crossing map using the fast marching method. We propose a new speed image function that is based on the distance map and employs the magnitude of Gaussian gradient of the vessel image. In the second step, a branch tracking procedure based on the Runge-Kutta method is performed. Compared with Van's approach, the proposed method can achieve high accuracy even with large step size, which reduces the computational time dramatically.
- An accurate and reproducible coronary artery cross sectional lumen area measurement algorithm at sub-voxel accuracy is proposed from human cardiac CTA images. The new approach consists of four steps: 3D segmentation, smoothing, centerline determination and cross sectional lumen plane cutting. In addition, the application of this new algorithm is demonstrate on various CTA images and validate the accuracy of obtained lumen area based on intravascular ultrasound (IVUS). This approach will facilitate quantitative evaluation of the severity of coronary stenosis and help in clinical diagnosis of CAD.

1.4 Organization of the Thesis

The main contents and contributions of this dissertation are highlighted as follows.

- In Chapter 1, the coronary artery segmentation and centerline extraction problems are introduced as well as their background and motivation. Main contributions are summarized and the thesis organization is listed.
- In Chapter 2, background knowledge and existing works of coronary artery segmentation and centerline extraction are reviewed. For coronary artery segmentation, both differential measures and deformable models are provided. For centerline extraction, three main categories of existing methods are presented.
- In Chapter 3, an automated coronary artery segmentation method is proposed. Our method presented in Chapter 3 is based on differential measures and hybridizes with graph-cuts method. The new segmentation approach is able to extract small vessel branches even from low-quality CT images, with minimal user interaction. Various examples of CTA images are shown to indicate the accuracy and efficiency.
- In Chapter 4, a novel coronary artery centerline extraction method is presented. A new speed image function that is based on the distance map and integrates the magnitude of Gaussian gradient of the vessel image is proposed to drive the wave propagation. Then the branch tracking procedure based on the Runge-Kutta method is performed. Various examples of CTA images from human patients are included to demonstrate the robustness and effectiveness.
- In Chapter 5, an accurate and reproducible cross sectional lumen area measurement algorithm at sub-voxel accuracy is proposed. The proposed 3D cross sectional lumen area measurement algorithm, which is based on centerline extraction and coronary artery surface mesh generation, is performed over a variety of CTA images from human patients and validated against IVUS. Its clinical potential and effectiveness to facilitate quantitative assessment of the anatomic severity of coronary stenosis are also demonstrated.

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- In Chapter 6, a novel approach for coronary lumen area evaluation with 3D centerline-centric straightening method is developed. The proposed method consists of four steps: vessel segmentation, surface smoothing, fast marching (FM) method and central cutting. Their effectiveness and properties are analyzed. Differences of area stenosis in a human patient with suspected CAD are tested by varying the combination of methods.
 - Chapter 7 concludes this thesis, and future research direction on coronary artery segmentation and centerline extraction are suggested.

Part I

Coronary Artery Segmentation and Centerline Extraction

General Framework of Coronary Artery Segmentation and Centerline Extraction

In this chapter, we provide an overview of existing approaches related to our work, focusing on 3D approaches of coronary artery segmentation and centerline extraction. First, some background knowledge of medical image processing are briefly reviewed in Section 2.1.

After the review of the background [51], the segmentation framework used in the thesis is presented in detail in Section 2.2. Current approaches based on vesselness measure and parametric intensity model are reviewed. It can be shown that under certain CT image quality assumption, differential measures based segmentation approaches have some advantages and priorities. The most desirable advantage of differential measures is that these approaches are computationally efficient. In this thesis, a more robust segmentation approach is established, which is capable of handling low quality CT images. The theoretical guarantee of Hessian matrix and vesselness measure is examined and proved in Subsection 2.2.1.

Next existing techniques for vessel centerlines extraction are reviewed in Section 2.3. Most of the present approaches can be divided into three different categories, thinning method, voronoi method and distance transform method.

2.1 Background

In this thesis, we mainly deal with 3D tomographic images acquired by using different imaging techniques. For 3D tomographic images, the intensities represent a different meaning that depends on the imaging modality (e.g., 3D MR or 3D CT), the imaging parameters (e.g., T_1 - and T_2 -weighted 3D MR images), and additional scanning techniques (e.g., injection of contrast agents for 3D MR or 3D CT angiography). The general framework of 3D image processing consists of four steps: data acquisition, 3D image generation in voxel space, digital image processing for 3D image, and 3D image display (see Figure 2.1).

For data acquisition, Suetens *et al.* [52] have provided a detailed overview of the image formation process for 3D tomographic images. Among all the imaging techniques, X-ray computed tomography or CT is an imaging modality that produces cross-sectional images representing the X-ray attenuation properties of the body. Image formation of a cross-section is based on the following procedure. X-rays are produced by an X-ray tube, attenuated by the patient and measured by an X-ray detector. Using thin X-ray beams, a set of lines is scanned covering the entire field of view. This process is repeated for a large number of angles, yielding line attenuation measurements for all possible angles and for all possible distances from the center. Based on all these measurements, the actual attenuation at each point of the scanned slice can be reconstructed.

Next the computer calculates the CT number, which is expressed in *Hounsfield units* (HU). The CT number is defined as

$$\text{CT number (in HU)} = \frac{\mu - \mu_{H_2O}}{\mu_{H_2O}} * 1000 \quad (2.1)$$

where μ is the linear attenuation coefficient. Based on this definition, air and water have a CT number of, respectively, -1000 HU and 0 HU. Bone falls on the positive side of the scale, but has no unique CT number. This value ranges from several hundreds to over 1000 HU. The reason is that μ of bone (and all other tissues) depends on its composition and structure, e.g., cortical or trabecular, as

well as on the energy of the absorbed X-rays.

The CT numbers can be printed as a numerical image. This image must be converted into a gray-scale image because it is more useful to the radiologist. For each 2D CT slice, the size of the matrix is chosen by the technologist before the CT scan and depends on the anatomy under study. The technologist must select the field of view (FOV) or reconstruct circle, which is a circular region from which the transmission measurements are recorded during scanning. This region is specifically referred to as the *scan FOV*. The pixel size can be computed from the FOV and the matrix size through the following relationship:

$$\text{Pixel size, } d = \frac{\text{field of view}}{\text{matrix size}} \quad (2.2)$$

Because the slice to be scanned has the dimension of depth, the pixel is transformed into a voxel, or volume element. The radiation beam passes through each voxel and a CT number is then generated for each pixel in the displayed image. The voxel size depends not only on the thickness of the slice but also on the matrix size and the FOV.

In modern CT scanners, the images consist of 512×512 pixels representing the CT number. The numerical value of the pixel represents the brightness of the image at that pixel position. In a digital image, the gray levels are integers. Although brightness values are continuous in real life, in a digital image we have only a limited number of gray levels at our disposal. Most digital medical images today use 4096 gray values (-1000 to 3095).

In general, blurring effect as well as image noise will be introduced during the image acquisition process. The point spread function (PSF) for many existing imaging modalities is normally complicated but can be well approximated by an isotropic Gaussian. Also, the image noise is often well approximated by additive zero-mean white Gaussian noise, which does not depend on the image data.

In clinical practice, CT images are often post-processed by using several image reformatting approaches (e.g., sagittal/coronal, maximum intensity projection, curved reforming), to help radiologists view particular vessel structures from a

Figure 2.1: The general framework of 3D image processing consists of four steps: data acquisition, 3D image generation in voxel space, digital image processing for 3D image, and 3D image display.

different perspective [53]. Other useful image-processing techniques for CT images consist of volume rendering, surface rendering, and virtual CT endoscopy. In this section, each method is briefly introduced, and actual clinical examples are provided.

2.1.1 Reformatting Approaches

Sagittal and Coronal Reformatting

A sequence of CT images can be reformed into standard orthogonal, sagittal, and coronal views following the routine in Figure 2.2. For an axial image plane, the x direction is generally along the patient's left-right axis, the y direction is along

Figure 2.2: Sagittal and coronal views reformation from a sequence of axial images (see [53]).

the anterior-posterior axis, and the z direction is along the superior-inferior axis (see [54]). An orthogonal view is able to view a sequence of CT images from the conventional axial acquisition plane (Figure 2.3(a)). A sagittal view is constructed by sampling in the y and z directions from a stack of CT images (Figure 2.3(b)). Similarly, a coronal view can be formed by sampling in the x and z directions (Figure 2.3(c)).

Maximum- and Minimum-Intensity Projections

3D images can be displayed by using different techniques on the image processing workstations. Maximum intensity projection (MIP) and minimum intensity projection (MinIP) are two most commonly used viewing techniques. In MIP, only the tissues with the great attenuation are detected and displayed for viewing along each ray path. This method is able to display contrast material-filled structures and bone, and other lower attenuation structures will not be displayed. Similarly, the MinIP technique is used to detect the tissues with the minimum or

Figure 2.3: A sequence of CT images can be reformed into standard orthogonal, sagittal and coronal views.

lowest attenuation along each ray path. Both techniques are used to offer radiologists additional information to the original axial sequence and alternate view of the anatomy condition. For example, in Figure 2.4(a) we show the maximum intensity projection image in orthogonal view from the CTA dataset of a real patient. Besides, the MIP image in Figure 2.4(b) shows the vascular structures quite clearly after performing Frangi’s vesselness filter.

Figure 2.4: MIP of 3D CTA images of a real patient in orthogonal view.

Curved Reformatting

Sometimes, if there exists narrowing of tortuous tubular structures, sampling a 3D stack of CT images along a curved plane is also necessary. Generally, this desired curve plane is defined along some anatomic structure, such as the curve of the mandible. Moreover, some other curves can be defined for this application along the spinal cord, or along the midline of a vessel.

2.1.2 Surface Rendering

Surface rendering techniques usually identify the edge voxels by intensity thresholding. These voxels are often enhanced with morphologic operations and then can be displayed. The other voxels are generally invisible. This technique is often used to evaluate tubular structures (blood vessels). The advantage of surface rendering techniques is that they only require contour information instead of all the voxel information.

2.1.3 Volume Rendering

Volume rendering techniques can produce 3D images of better quality and provide more information, compared with surface rendering. Volume rendering techniques assign the CT numbers that make up the image either visible or invisible. Moreover, they are often displayed with varying colors and opacity levels (transparency). Volume rendering uses the entire 3D data set and therefore it displays the object structure with better quality.

2.1.4 Virtual CT Endoscopy

The CT image data from 3D space can be processed in such a way by using sophisticated algorithms to generate what has been referred to as virtual endoscopic images. This technique has received much attention since it allows the operator to "fly through" and examine hollow structures.

2.1.5 Sampling

In medical imaging, original CT images can be downsampled to improve the processing efficiency. Consider the 2D image $F_{(x,y)}$

$$F_{(x,y)} = \begin{bmatrix} f_{\Delta x \cdot (x-1)+1, \Delta y \cdot (y-1)+1} & \cdots & f_{\Delta x \cdot (x-1)+1, \Delta y \cdot y} \\ \vdots & & \vdots \\ f_{\Delta x \cdot x, \Delta y \cdot (y-1)+1} & \cdots & f_{\Delta x \cdot x, \Delta y \cdot y} \end{bmatrix} \quad (2.3)$$

This image F can be divided into many 2×2 sub-regions:

$$F = \left[\begin{array}{cc|cc} f_{11} & f_{12} & f_{13} & f_{14} \\ f_{21} & f_{22} & f_{23} & f_{24} \\ \hline f_{31} & f_{32} & f_{33} & f_{34} \\ f_{41} & f_{42} & f_{43} & f_{44} \end{array} \right] \quad (2.4)$$

Taking the mean of each 2×2 sub-matrix produces the downsampled 2D image G

$$G = \left[\begin{array}{c|c} g_{11} & g_{12} \\ \hline g_{21} & g_{22} \end{array} \right] \quad (2.5)$$

where $g_{11} = (f_{11} + f_{12} + f_{21} + f_{22})/4$.

Consider the original 3D CT image of size 512×512 (Figure 2.5(a)), the input 3D image is first downsampled by a factor 2, which is reduced to 256×256 (Figure 2.5(b)). This procedure is able to reduce the running time without a corresponding loss in accuracy.

2.1.6 Mathematical Morphology

In binary images, an object is usually represented by a connected set of pixels or voxels. For two-dimensional images, connectivity can be either 4-connectivity or 8-connectivity. In 4-connectivity, each pixel (P) has four connected neighbors. In 8-connectivity, each pixel (P) has eight connected neighbors, including the diagonally touching pixels (see Figure 2.6). For three-dimensional images neighborhoods can be 6-connected, 18-connected or 26-connected.

Figure 2.5: CT image downsample using average filter.

Figure 2.6: Connectivity in two-dimensional images. (a) 4-connectivity. (b) 8-connectivity.

Different cases of connectivity lead to different ideas of distance. In a 4-connected neighborhood, N_4 , the distance is known as the city-block, taxicab or Manhattan distance by analogy with a city based on an orthogonal grid of

roads. It is the distance a taxicab would drive in Manhattan. The distance in a 4-connected neighborhood is defined as

$$d_4(x, y) = |x_1 - x_2| + |y_1 - y_2| \quad (2.6)$$

A diagonal step has a distance of two since it requires a horizontal and a vertical step. Equal distances from a certain position would form diamonds centered on it. In an 8-connected neighborhood, N_8 , the distance is known as the Chebyshev or chessboard distance, by analogy with the moves available to a king in chess. The distance in an 8-connected neighborhood is defined as

$$d_8(x, y) = \max\{|x_1 - x_2|, |y_1 - y_2|\} \quad (2.7)$$

A diagonal step has a distance of one, the same as a horizontal or vertical step. Equal distances from a certain position would form squares centered on it. The most commonly used distance is Euclidean distance

$$d(x, y) = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2} \quad (2.8)$$

A diagonal step is given by a distance of $1/\sqrt{2}$, and equal distances from a certain position form circles centered on it. Alternating the two metrics ($N_4 - N_8$ or $N_8 - N_4$) is an approximation to Euclidean distance.

In binary images, dilation operation is used to increase the size of foreground objects, generally taken as white pixels. The connectivity needs to be established prior to operation, or a structuring element defined. In contradistinction, erosion is used to increase the size of background objects (and shrinks the foreground objects) in binary images. Based on erosion and dilation, other mathematical morphology operators, e.g., opening and closing, are defined by using the set operators (intersection and union). Opening is defined as erosion followed by dilation using the same structuring element. The erosion part is used to remove some edge pixels from the foreground (bright) regions, while the dilation part is used to add foreground pixels. The foreground features remain about the same

size, but their contours are smoother. Normally, the shape of the structuring element leads to different effects of opening operation. For example, foreground regions similar to the structuring element will be preserved. While for foreground regions of dissimilar shape, opening will eliminate these kinds of regions. Closing is defined as dilation followed by erosion using the same structuring element for both operations. Closing smoothes the contours of foreground objects but, in contradistinction to opening, it merges narrow breaks or gaps and eliminates small holes.

2.1.7 Geometry

In computer graphic applications, it is important to compute a measure of distance from a set of points. Generally, a distance map is used to assign a value that represents the shortest distance from a given set of source points to each point in the domain. Assume we have a given set of points P , that might just as well represent a curve. Then, the distance map $T_P : \mathbb{R}^2 \rightarrow \mathbb{R}_+$ assigns a value to each point in the domain such that

$$T_P(q) = \inf_{p \in P} d(p, q) \quad (2.9)$$

where $d(p, q) = \|p - q\|_{L_2}$.

Consider a 2D weighted flat domain (isotropic non-homogeneous domain), the distance is defined via the arclength, which is written as a function of the x and y coordinates of the planar domain

$$ds^2 = \mathcal{F}^2(x, y)(dx^2 + dy^2) \quad (2.10)$$

where the function $\mathcal{F}(x, y) : \mathbb{R}^2 \rightarrow \mathbb{R}_+$ defines a weight for each point.

The distance map $T(x, y)$ from a given point p_0 assigns a scalar value to each point in the domain that corresponds to its distance from p_0 . It can be shown [55] that like in the 1D case, the gradient magnitude of the distance map is inversely proportional to the weight function at each point

$$|\nabla T(x, y)|\mathcal{F}(x, y) = 1 \quad (2.11)$$

where $|\nabla T| = \sqrt{T_x^2 + T_y^2}$. This is an Eikonal equation in 2D. The viscosity solution to the Eikonal equation coupled with the boundary condition $T(p_0) = 0$ results in the desired distance map. Consider the following upwind approximation to the gradient, given by

$$((\max\{D_{ij}^{-x}T, -D_{ij}^{+x}T, 0\})^2 + (\max\{D_{ij}^{-y}T, -D_{ij}^{+y}T, 0\})^2)^{1/2} = \frac{1}{\mathcal{F}_{ij}} \quad (2.12)$$

where $D_{ij}^{-x}T = (T_{ij} - T_{i-1,j})/h$ is the standard backward derivative approximation, and $T_{ij} = T(i\Delta x, j\Delta y)$.

Assume the set S contains all vertices for which the T value is decided, and G represents the set of all vertices. That is, $\forall i, j \in S$, T_{ij} either satisfies (2.12) or is given as a fixed boundary condition. The algorithm updates all the adjacent vertices of S . First the T values of all the adjacent vertices are entered to a priority queue called Q . Each iteration, a vertex $u = i, j$, whose T_{ij} is the smallest, is extracted from Q and moved to S , and all its neighboring vertices that are not in S are updated. An updated vertex that changed its value can either enter the queue Q if it is the first time it is updated, or change its location in Q if it is already there. The queue, Q , can be implemented as a binary heap. Algorithm 2.1 explains this fast marching procedure.

Algorithm 2.1 Fast marching algorithm

- 1: Fast Marching($\mathcal{F}$, G , S , Q)
 - 2: $\forall v \in G \setminus S$ **do** $T_v \leftarrow \infty$
 - 3: **while** $Q \neq \emptyset$ **do**
 - 4: $u \leftarrow \text{ExtractMin}(Q)$
 - 5: $S \leftarrow S \cup u$
 - 6: **for** each vertex $v \in \text{Adj}[u]$ **do**
 - 7: $\text{Update}(Q, v)$
 - 8: **end for**
 - 9: **end while**
-

2.2 Automatic Coronary Artery Segmentation

In the literature, there exist many research efforts for segmenting and quantifying of coronary arteries from 3D image data. Previous work on vessel segmentation can be divided into two main classes: deformable models (e.g., [32, 33]) and differential measures (e.g., [34, 35]). Deformable models are often used to exploit contour information. However, these approaches generally section through vessel structures in order to exploit contour information. Approaches based on differential measures often exploit the image gradient or the Hessian matrix [38, 39, 40], which are computationally efficient.

2.2.1 Differential Measures

The 3D vessel segmentation approaches based on differential measures have been proposed, which exploit the image gradient or the Hessian matrix. The approach described in this thesis is mainly based on the Hessian analysis proposed by Frangi [40]. The Hessian matrix is obtained by taking second order partial derivatives of the filtered image I that can be first convolved with a 1D Gaussian kernel G in each dimension,

$$H = \begin{bmatrix} I_{x,x} & I_{x,y} & I_{x,z} \\ I_{y,x} & I_{y,y} & I_{y,z} \\ I_{z,x} & I_{z,y} & I_{z,z} \end{bmatrix} \quad (2.13)$$

In the context of vessel detection, this second order information provides an intuitive justification. Eigenvalues of the Hessian H are used to explore the local second order structure (principal directions) of the image. For the convolved image I , consider its Taylor expansion at point x_o ,

$$I(x_o + \delta x_o, \sigma) \approx I(x_o, \sigma) + \delta x_o^T \nabla_{o,\sigma} + \delta x_o^T \mathcal{H}_{o,\sigma} \delta x_o \quad (2.14)$$

The last term in (2.14) represents the second order directional derivatives,

$$\delta x_o^T \mathcal{H}_{o,\sigma} \delta x_o = \left(\frac{\partial}{\partial \delta x_o} \right) \left(\frac{\partial}{\partial \delta x_o} \right) I(x_o, \sigma) \quad (2.15)$$

Now let $\lambda_{\sigma,i}$ denote the eigenvalue that corresponds to the i -th normalized eigenvector $\vec{v}_{\sigma,i}$ of the Hessian $\mathcal{H}_{o,\sigma}$ (computed at scale σ). From the definition of eigenvalues:

$$\mathcal{H}_{o,\sigma}\vec{v}_{\sigma,i} = \lambda_{\sigma,i}\vec{v}_{\sigma,i} \quad (2.16)$$

and it follows that

$$\vec{v}_{\sigma,i}^T \mathcal{H}_{o,\sigma} \vec{v}_{\sigma,i} = \lambda_{\sigma,i} \quad (2.17)$$

By combining (2.15)-(2.17), a valid geometric interpretation is proposed. The main idea of Hessian analysis is to explore the eigenvalues $|\lambda_1| \leq |\lambda_2| \leq |\lambda_3|$ as well as the corresponding eigenvectors v_1 , v_2 and v_3 , respectively. The three eigenvectors are used to define an orthogonal coordinate system where v_1 and v_3 are pointing in the direction of minimal and maximal curvatures of the intensity function I , respectively. Now consider a single voxel on the centerline of a thin vessel, since the intensity is approximately constant along this vessel, the second order partial derivative of I in the direction of the vessel is approximately zero, as well as the curvature of I . On the other hand, assuming the isotropic Gaussian shaped intensity profile of the thin vessel in the orthogonal direction, the magnitude of the second order partial derivatives of I in the orthogonal directions is relatively large. In addition, vessels normally emerge as bright tubular structure on a dark background in MRA and CTA. Therefore, for an ideal thin vessel, we have the following relationships between the eigenvalues:

$$|\lambda_1| \approx 0 \quad (2.18)$$

$$|\lambda_1| \leq |\lambda_2| \quad (2.19)$$

$$\lambda_2 \approx \lambda_3 \quad (2.20)$$

where the sign of λ_2 and λ_3 indicates whether the intensity of the vessel is bright (negative) or dark (positive) compared to the background intensity. Different relations between eigenvalues can represent other image structures. For instance, for blob-like structures the magnitude of all three eigenvalues is relatively large, and for plate-like structures the magnitude of λ_1 and λ_2 is approximately zero

whereas λ_3 is relatively large. The relations between the eigenvalues of the Hessian and different structures are presented in Table 2.1.

Table 2.1: Eigenvalues and image structure orientation (L low, H+ high positive, H- high negative).

λ_1	λ_2	λ_3	Structure orientation
L	L	L	Noise (no preferred noise)
L	L	H+	Dark sheet-like structure
L	L	H-	Bright sheet-like structure
L	H+	H+	Dark tubular structure
L	H-	H-	Bright tubular structure
H+	H+	H+	Dark blob-like structure
H-	H-	H-	Bright blob-like structure

In order to quantitatively discriminate the different image structures, a measure based on the eigenvalues is often defined. In [40] Frangi *et al.* defined three measures:

$$A = \frac{|\lambda_2|}{|\lambda_3|} \quad (2.21)$$

$$B = \frac{|\lambda_1|}{\sqrt{|\lambda_2\lambda_3|}} \quad (2.22)$$

$$S = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \quad (2.23)$$

It is noted that B is maximal for a blob-like structure as well as zero for a line-like and a plate-like structure. Besides, A is used to discriminate between line-like and plate-like structures. The measure S discriminates between background and high contrast regions. Lorenz *et al.* [56] and Sato *et al.* [57] propose similar measures that only use two eigenvalues. Moreover, the eigenvalues in Sato's vessel filter are sorted in increasing value (not absolute value), and only the two largest are used. Following this filter, bright and dark lines are treated in a different way. Now given the model of the desired structures and the theoretical behavior of

the eigenvalues, the probability of being a vessel for each voxel can be calculated. The vesselness function proposed by Frangi is given by:

$$\mathcal{V}_F(\vec{\lambda}) = \begin{cases} 0 & \text{if } \lambda_2 > 0 \text{ or } \lambda_3 > 0 \\ (1 - e^{-\frac{A^2}{2\alpha^2}}) \cdot e^{-\frac{B^2}{2\beta^2}} \cdot (1 - e^{-\frac{S^2}{2\gamma^2}}) & \text{otherwise} \end{cases} \quad (2.24)$$

Here the parameters α , β and γ are weighting factors. The multiscale vesselness response is usually computed by calculating the Hessian with Gaussian derivative filters with multiple standard deviations. At each voxel position, the vesselness response with the largest value is selected.

Although differential measures are relatively efficient, they exploit only local information of the image data, which makes these approaches sensitive to image noise. Particularly, when exploiting second order derivatives of the image, Hessian-based approaches are more sensitive to image noise compared to approaches that only require the image gradient. To increase the robustness of these approaches, a multi-scale approach where the different scales are used by performing the Gaussian smoothing [39]. However, a larger number of scales can induce a higher computation cost.

2.2.2 Deformable Models

Deformable models approaches have been proposed to increase the accuracy and to increase the robustness against image noise.

Free-Form Deformable Models

Free-form deformable, or active contour models, can represent arbitrary shapes of a given topology, which are only constrained by a regularization term (e.g., minimization of the deformation energy). These techniques are used to find object contours, which is defined by parametric curves and controlled by internal and external forces. During the dynamic fitting procedure, the model is iteratively deformed until the deformation energy is maximized or minimized.

Physically, a snake is defined as a set of connected control points [58]. Its associated energy either can rise or fall, depending on snake's internal and external forces. Generally, internal forces are used to impose smoothness constraints while external forces can pull the snake towards the desired image features (edges). For 3D case, a contour is equivalent to the object surface. Thus the main idea of snakes is to adapt an active contour to a certain image structure representing an object. The shape of the contour is formulated as the functional

$$E_{snake} = \int_0^1 (E_{int}(\mathbf{v}(s)) + E_{image}(\mathbf{v}(s)) + E_{ext}(\mathbf{v}(s)))ds \quad (2.25)$$

where $s \in [0, 1]$ is the parameter and $\mathbf{v}(s) = (x(s), y(s))^T$ are coordinate functions along the contour. This functional represents the energy of the contour where the final shape of the contour corresponds to the minimal deformation energy. The energy term E_{int} represents the internal deformation energy. The energy E_{image} is defined by some potential due to image forces. In addition, the energy E_{ext} is often used to model external constraints. Different numerical approaches can be applied, for example, finite differences or finite elements, to solve for the minimization of the functional E_{snake} in (2.25). The deformable models are guaranteed to be robust to the noise by imposing the smoothness constraint. However, initial user interaction and parameters are required to initialize the snake.

Tang *et al.* [59] have developed a new deformable model which applies new edge measures for coronary arteries segmentation. The newly proposed edge measures combined multi-scale filtering responses and the vesselness measures. The vessel region and boundary were initialized by the multi-scale filtering responses. The brightness measure was computed by collecting the statistical information of vessel. The refined vesselness measures were able to effectively preserve vessel-like structure and suppress non-vascular background, compared with the multi-scale filtering responses. Finally, the deformable model that incorporates the new edge measures could produce better segmentation results.

Oliveira *et al.* [60] proposes a method for retinal vessels segmentation without

supervision, which applies Frangi's filter, Gabor Wavelet filter and a combined matched filter for enhancing the images. To improve the segmentation results, two different approaches, weighted mean and median ranking, are investigated to perform the filter combination. After the vessel enhancement, segmentation approaches are then tested.

Yu *et al.* [61] have developed a vessel segmentation approach that depends on region-based active contour. The main advantage is that the problem caused by gray intensity inhomogeneity can be avoided since the morphology measure of regions is introduced as stop criterion of curve instead of gray intensity or its gradient.

Tian *et al.* [62] presented a vessel active contour model, which is based on a vessel vector field and local intensity weighting.

However, the model is not able to incorporate prior knowledge about the vessel shape. Besides, the approach is often sensitive to image noise since only local information is included in the energy term E_{snake} . In addition, the segmentation result of this approach is also vulnerable to the positions of the initial contour.

Parametric Intensity Models

To further increase the segmentation robustness and accuracy, parametric intensity models have been developed by incorporating more prior image information compared to contour-based approaches. Objects of interest are defined parametrically by parametric models approach. For instance, tubular structures are often represented by a set of overlapping ellipsoids. The original image can be used to estimate the model parameters. For 2D case, Gaussian-shaped intensity models are often used [32]. In 3D approaches, the intensity profile of vessel axial sections can be modeled by a 2D Gaussian [63]. Therefore, the model is extended to a 3D Gaussian blob model

$$g_{GaussianBlob}(\mathbf{x}) = a_0 + (a_1 - a_0)e^{-\frac{x^2}{2\sigma_x^2}}e^{-\frac{y^2}{2\sigma_y^2}}e^{-\frac{z^2}{2\sigma_z^2}} \quad (2.26)$$

where σ_z is the standard deviation in the direction of the main axis, which is relatively large, or to a 3D Gaussian line model

$$g_{GaussianLine}(\mathbf{x}) = a_0 + (a_1 - a_0)e^{-\frac{x^2}{2\sigma_x^2}}e^{-\frac{y^2}{2\sigma_y^2}} \quad (2.27)$$

where intensity level in z -direction is constant. In both models, parameters a_0 and a_1 represent background and vessel intensity levels, respectively. The parameters σ_x and σ_y describe the shape of the orthogonal intensity profiles. A branch of vessel can be segmented by fitting the parametric intensity model to the image data with a 3D region of interest (ROI).

Spiegel *et al.* [64] have proposed a new approach for 3D vessel segmentation and validation based on 2D digital subtraction angiography (DSA). Clinically, when measurements of vessel diameter are required, 2D DSA projections are treated as gold standard. An ellipsoid vessel model can be used to initialize 3D segmentation. Then a global optimization function is used to adjust 3D vessel segmentation toward the 2D vessel contours based on local vessel discrepancies.

Delibasis *et al.* [65] proposed an automatic method for detecting the overall vessel tree and computing vessel orientation and diameter. A parametric vessel model based on any complex shape is proposed in the algorithm. Moreover, a simple measure of match is introduced, which is used to quantify how well the parametric model matches the image data. Then an automatic approach for vessel tracing can be developed to exploit and detect the geometric vessel model. The vessel diameter at each medial axis pixel can be determined by the proposed algorithm.

Worz *et al.* [66] have also introduced a new approach for accurate 3D thin vessels segmentation and quantification. This new approach introduces a model fitting scheme and develops a 3D curved tubular intensity model, which is constructed by using the principles of the image formation process. Besides, an analytic solution can be derived for the model function. The proposed model can be used to measure the local curvature and track curved vessel structures by model fitting.

2.3 Centerline

Generally, curve-skeleton is not precisely defined. In this work, we can define curve-skeleton as a reduced representation of a foreground object with the following properties [67]:

- **Homotopy:** The curve-skeleton is homotopy equivalent to the original 3D object [68].
- **Thinness:** The skeleton should be one voxel wide.
- **Medialness:** The skeleton is centrally located within the 3D object.
- **Reliability:** Reliability [69] refers to the property that every boundary point can be reached directly from at least one skeleton point.
- **Junction detection:** The curve-skeleton is able to distinguish the different components of the original object. In other words, each logical component of the original object has one-to-one correspondence with the logical component of the curve-skeleton [70].

A large number of approaches have been proposed for 3D skeletonization of volumetric objects. Most of them can be divided into three main different categories [71, 72]: Voronoi method, topological thinning, and distance transform method.

2.3.1 Voronoi Method

Voronoi method is usually used to explore the medial information of 3D objects [73, 74, 75]. First, the Voronoi diagram can be constructed by the 3D polygon vertices or directly by discrete points [76]. Second, internal edges and faces are used to extract the approximated medial surface [77]. This medial surface is able to describe a 3D object by the set of maximal balls inside the object, rather than by the set of boundary points. The complete topology of the object is accurately

preserved. Finally, a further pruning step is needed to extract a 1D centerline from this medial surface approximation.

Definition 2.1. *The medial axis transform (MAT) of surface P is the set of medial balls. The centers of the medial balls form the medial axis of P ; the MAT includes the radii as well [78].*

Let Q be a bounded open region. The Voronoi diagram is a partition of space into cells that are closer to a sample point than to any other such point. Let $S \subset Q$ be the set of seed points. For each sample $s \in S$, there is a corresponding region consisting of the points $x \in Q$ closest to seed s (see Figure 2.7(a)). These regions are called Voronoi cells, and the vertices of these cells are the Voronoi vertices. For each Voronoi vertex v , there is a corresponding Voronoi ball centered at v having seed points on its boundary, but no seed points in its interior. Thus the medial axis can be approximated by the Voronoi vertices [77, 79]. For 2D case, Voronoi vertices can approach the medial axis as the sampling is arbitrarily dense. However, 3D Voronoi diagram usually contains some special vertices that are close to the surface and far from the medial axis. Even if the sampling is dense and surface P is smooth, this problem still cannot be avoided.

In order to better approximate the medial axis, Edelsbrunner [80] used power diagram. Each ball $B_{o,r}$ can be thought of as a point o with weight r^2 . The power distance between a point x in $\mathbb{R}^3$ and $B_{o,r}$ is

$$d_{power}(x, B_{o,r}) = d^2(o, x) - r^2 \quad (2.28)$$

where d is the usual Euclidean distance. Formally, the power diagram is a partition of Q into regions consisting of the points $x \in Q$ closest, in power distance, to a particular point $s \in S$. Figure 2.7(b) shows a two-dimensional example.

The Voronoi based algorithm can therefore be proposed [77]. First, the Voronoi diagram of the sample points S is generated. Second, the poles for each sample point are computed, as well as the power diagram based on the poles. Moreover, each pole should be labelled either inside or outside. The power

Figure 2.7: (a) 2D example of the Voronoi diagram of S , with the Voronoi ball centered at one Voronoi vertex. (b) The power diagram. A point o with weight r^2 is represented by a ball centered at o with radius r .

diagram faces can be saved as the power crust and the regular triangulation faces are saved as the power shape. Finally, a further simplification of medial axis is usually conducted in computer graphics for the purpose of preserving geometrical features but removing redundant points.

2.3.2 Topological Thinning

Generally, topological thinning method yields the most accurate skeletonization result [81]. Thinning method starts to remove boundary voxels and continues inward until the required thinness is achieved, without changing the object topology. At every iteration, each boundary voxel is examined against a set of matching templates ($3 \times 3 \times 3$ or larger). Parallel thinning methods remove a set of simple points [82]. The thinning process is repeated with a period of n ($n \geq 2$). Only certain kind of border points are removed during each iteration of a period (subiteration). Therefore, a thinning process performs like a 3D reduction operation on binary image changing some 1's to 0's.

Assume p is a voxel in 3D discrete space $\mathbb{Z}^3$. The collection of j -neighborhood voxels to p is denoted by $N_j(p)$ (for $j = 6, 18, 26$). Each 3D binary image I can be described by a quadruple $I = (\mathbb{Z}^3, m, n, B)$ [83]. Each voxel in $B \subset \mathbb{Z}^3$ represents a black (object) voxel, and each voxel in $\mathbb{Z}^3 \setminus B$ represents a white (background) voxel. The pair (m, n) indicates connectivity for black and white points respectively. Here we focus on $(26, 6)$ digital images. Different sets of neighborhood voxels to p are defined in Figure 2.8.

Figure 2.8: The set $N_6(p)$ contains points p and its neighbors marked U, D, N, S, E and W. The set $N_{18}(p)$ contains the set $N_6(p)$ and the 12 points marked “□”. The set $N_{26}(p)$ contains the set $N_{18}(p)$ and the 8 points marked “*”.

In this paper, a 3-subiteration thinning method [84] is applied for coronary artery thinning. The three deletion directions are denoted by NS, UD and WE. Then the 3-subiteration thinning method can be proposed (Algorithm 2.2):

A set of matching templates are defined to decide deletable points in a subiteration. If a black point at least matches one of the templates, it will be deleted. Each opposite pair of border points can be deleted simultaneously in each subiteration. The proposed thinning algorithm will terminate until there are no more deletable black points.

However, the deletion of all simple points may make the obtained centerlines excessive shorter, since all the end points are simple points themselves. To maintain the geometrical features, further constraints are applied to prevent removal of the endpoints. Besides, extracted centerlines by using thinning method is not

Algorithm 2.2 3-subiteration thinning method

```
1: Input: Image  $I = (\mathbb{Z}^3, 26, 6, B)$ 
2: Output: Image  $I' = (\mathbb{Z}^3, 26, 6, B')$ 
3: 3-subiteration thinning ( $B, B'$ )
4: while There exist deletable points do
5:    $B' = B$ 
6:   repeat
7:      $B' = NS\_deletion(B')$ 
8:      $B' = UD\_deletion(B')$ 
9:      $B' = WE\_deletion(B')$ 
10: end while
```

smooth and even tends to zigzag back and forth, since all surface irregularities propagate to the curve-skeleton through the erosion process. This hence makes the thinning approach more sensitive to boundary noise. As there are no parameters to control for this approach, the centerline can only be improved by branch pruning and smoothing to remove extraneous branches.

2.3.3 Distance Transform Method

The distance transform is often used to determine the centerlines of tubular structures [85, 86]. Let O denote a 3D object and ∂O denote its boundary. For each interior point P , the distance transform is defined as the shortest distance from P to ∂O :

$$DT(P) = \min_{Q \in \partial O} (d(P, Q)) \quad (2.29)$$

where d is a distance function. Different distance functions are often used such as the Manhattan distance or Euclidean distance, etc [87]. In the first step, a 3D filtering operation can be conducted over the original 3D binary data set. This can be treated as a pre-pruning process. Second, we classify each object voxel into boundary and interior. Moreover, we can compute distance value

for each interior voxel and then generate a distance field inside the object. In addition, we need to find the ridge points (local maximum) of this distance field corresponding to voxels that are centrally located within the object. The last step will be connecting these ridge points by using minimum spanning tree [88].

Distance transform method has the advantage of low complexity. However, a mass of false skeleton bifurcations appear at the end of the tubular objects such as blood vessels [89, 90].

2.4 Summary and Conclusions

In this chapter, we first gave an overview of some basic medical imaging analysis techniques related to our work. Next, we reviewed existing approaches for coronary artery segmentation from 3D images in general. The first class of approach is based on the differential measures, which exploits the image gradient or the Hessian matrix. The second class of approach depends on the deformable models. We also reviewed existing approaches for vessel centerline extraction from CTA images, which can be divided into three different classes: thinning method, voronoi method and distance transform method [91].

Connected Components Based Coronary Artery Segmentation

3.1 Introduction

In this chapter, a new approach is developed for coronary artery segmentation from 3D CTA images, which depends on the Hessian filter and connected components. To increase the segmentation efficiency and accuracy, vessel enhancement is first performed as a pre-processing step. A novel diffusion tensor is presented which fulfills all the requirements for diffusion tensor and enables multiscale approaches to vessel analysis.

Subsequent to coronary artery segmentation, the corresponding centerlines can be extracted by using three different algorithms: Voronoi method, topological thinning and distance transform method. We compare these three different categories of 3D skeletonization methods in terms of several desired properties of curve-skeleton, as required by a number of applications in visualization and clinical practice. The 3-subiteration thinning method with smoothing and pruning operation at sub-voxel level is advised as the most suitable method. The obtained centerline is reliable and accurate for vessels of different sizes. The main objective of this work is to provide an overview of curve-skeleton implementations over 3D

CTA images, in order to help medical image visualization and processing. Based on the obtained curve-skeletons of coronary arteries, we also propose and validate a 3D cross sectional lumen area measurement algorithm, which is based on centerline extraction and coronary artery surface mesh generation.

This chapter is organized as follow. Section 3.2 presents the methodology for coronary artery segmentation. In Section 3.3, the results of our segmentation approach and 3D skeletonization methods over the coronary CTA datasets are shown. Conclusions are presented in Section 3.4.

3.2 Methodology

3.2.1 Vesselness Detection

As already described in Subsection 2.2.1, the segmentation approach is mainly based on the Hessian analysis proposed by Frangi [40], in which three measures are defined to capture different structures:

$$A = \frac{|\lambda_2|}{|\lambda_3|} \quad (3.1)$$

$$B = \frac{|\lambda_1|}{\sqrt{|\lambda_2 \lambda_3|}} \quad (3.2)$$

$$S = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \quad (3.3)$$

and the vesselness function is formulated as:

$$\mathcal{V}_F(\vec{\lambda}) = \begin{cases} 0 & \text{if } \lambda_2 > 0 \text{ or } \lambda_3 > 0 \\ (1 - e^{-\frac{A^2}{2\alpha^2}}) \cdot e^{-\frac{B^2}{2\beta^2}} \cdot (1 - e^{-\frac{S^2}{2\gamma^2}}) & \text{otherwise} \end{cases} \quad (3.4)$$

where the parameters α , β and γ are weighting factors. The multiscale vesselness response is usually computed by calculating the Hessian with Gaussian derivative filters with multiple standard deviations.

3.2.2 Scale Space Theory

Generally, MIP images are often generated by clinicians for visual analysis of 3D images. However, the existence of overlapping non-vascular structures has a great impact on vascular visualization. Moreover, small vessel branches with low contrast are usually invisible in MIP images. In many existing vessel analysis approaches, original CTA images are first preprocessed for vascular structures enhancement, which is usually performed to improve the delineation of small vessel branches and suppress non-vascular structures [92].

Original image can be evolved according to the diffusion equation to generate a family of images. The diffusion equation uses original image as the initial condition, and its divergence form can be expressed as:

$$L_t = \nabla \cdot (D \nabla L) \quad (3.5)$$

The diffusion tensor D is used to drive the flow for the purpose of preserving or blurring that features of interested. For example, the simplest form of D (identity matrix) can be used to reduce the diffusion equation to the linear isotropic heat equation. Perona and Malik [93] proposed the first nonlinear variant, in which a function of the gradient magnitude is used to define the diffusion tensor.

Unfortunately, due to its nonsmoothness at the origin, Frangi's vesselness function $\mathcal{V}_F$ defined in (3.4) can not directly be used in (3.5). This issue can be remedied by proposing the following modifications. First, the domain definition is updated by changing from $\lambda_{2,3} > 0$ to $\lambda_{2,3} \geq 0$. The function is thus continuous when $\lambda_2 \rightarrow 0$ and $\lambda_3 \rightarrow 0$. Now the function approaches zero when $\lambda \rightarrow \mathbf{0}$, since the first two terms are bounded while the last goes to zero. In addition, the resulting function is still not smooth due to the existence of the ratio of polynomial functions in λ_i in the first two terms of the vesselness function $\mathcal{V}_F$, which has the same order in the numerator as well as in the denominator. Consider the second order partial derivative of λ_1

$$\mathcal{V}_{F\lambda_1\lambda_1} = \frac{\partial^2 \mathcal{V}_F}{\partial \lambda_1^2} \quad (3.6)$$

Now suppose $\lambda_2 = \lambda_3 \triangleq \alpha\lambda_1$ with $\alpha \in \mathbb{R}$ and $\alpha \geq 1$ and consider $\lambda_1 \rightarrow 0$, we obtain

$$\mathcal{V}_{F\lambda_1\lambda_1} = (2 + 4\alpha^2)(1 - 1/e)e^{-1/\alpha^2} \quad (3.7)$$

It can be verified that a similar argument applies for the first order derivative in λ_1 in the 2D case. The diffusion tensor defined in [94] is therefore not smooth. It can be observed that both $\mathcal{V}_F$ and $\mathcal{V}_F^{(n)}$ include terms of the form

$$T(\boldsymbol{\lambda}) = \left(\frac{M}{N}\right) e^{-\left(\frac{U}{V}\right)} \quad (3.8)$$

with M, N some polynomial functions in $\boldsymbol{\lambda}$, and U, V some polynomial functions in $\boldsymbol{\lambda}$ without any constant terms. Obviously, after taking any order derivative, only M, N change while U, V remain the same. Therefore, T is not well defined when $\boldsymbol{\lambda} \rightarrow \mathbf{0}$ ($U, V \rightarrow 0, 0$). We can multiply T with $e^{(-1/S)}$

$$T'(\boldsymbol{\lambda}) = \left(\frac{P}{Q}\right) e^{-\left(\frac{R+1}{S}\right)} \quad (3.9)$$

which always approaches zero if $\boldsymbol{\lambda} \rightarrow \mathbf{0}$. Therefore, T' is well defined.

It can be observed that the smallest common denominator for all the exponential terms of $\mathcal{V}_F$ is $|\lambda_2|\lambda_3^2$. Therefore, a smoothed version of the vesselness function can be obtained by multiplying $\mathcal{V}_F$ with

$$e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)} \quad (3.10)$$

where c is some constant that is chosen as small value to ensure that it only has influence when $\boldsymbol{\lambda} \rightarrow \mathbf{0}$. Intuitively, Frangi's vesselness function should be multiplied by a term which rapidly approaches zero in a small neighborhood around the origin and is one everywhere else. It follows that the new vesselness function $\mathcal{V}_s$ can be proposed

$$\mathcal{V}_s(\sigma) = \begin{cases} 0 & \text{if } \lambda_2 \geq 0 \text{ or } \lambda_3 \geq 0 \\ e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)} (1 - e^{-\frac{A^2}{2\alpha^2}}) \cdot e^{-\frac{B^2}{2\beta^2}} \cdot (1 - e^{-\frac{S^2}{2\gamma^2}}) & \text{otherwise} \end{cases} \quad (3.11)$$

with range $\mathcal{V}_s \in [0, 1]$. Following Frangi's vesselness function, a multiscale approach can be performed. By taking second order Gaussian derivatives at multiple scales and normalizing each by σ^2 , the Hessian $\mathcal{H}$ is obtained. Then the maximum vesselness response is selected at each voxel location

$$\mathcal{V} = \max_{\sigma_{min} \leq \sigma \leq \sigma_{max}} \mathcal{V}_s(\sigma) \quad (3.12)$$

The eigensystem of the Hessian is commonly used for geometrical interpretation of vessel analysis. The eigenvectors are used to store the second order image information (curvature), which represent the direction in which curvature takes extreme values. The eigenvalues store the curvature extreme values. For example, Frangi's [40] vesselness measure can be used to drive the diffusion procedure. In [94] Canero and Radeva have explored the combination of vessel enhancing diffusion (VED) and the vesselness measure. However, this approach is only applicable to 2D case. In this chapter, it motivates us to extend the diffusion process by proposing a new diffusion tensor D , which integrates the image's Hessian matrix. The proposed diffusion tensor D satisfies a smoothness constraint and ensures that the diffusion process is well-posed by imposing a necessary condition. Also it is able to include non-linear behavior on vesselness measure and perform stronger diffusion for non-vessel structures to reduce background noise. Besides, a parameter is introduced in between the extremes of anisotropic and isotropic diffusion, to control the sensitivity on the vesselness response. Finally, the method is extended to 3D case compared to [94].

3.2.3 Vessel Enhancing Diffusion

It is worth noting that the diffusion equations are generally required to be well-posed, regular and to satisfy a maximum-minimum principle. To achieve these, the diffusion tensor D must be smooth, symmetric and uniformly positive definite [95].

There are three advantages of vessel enhancement. First, it is used to enhance

the continuity of vessels. Second, it improves the separation of vessels in MIPs. Third, it enables suppression of background noise. Enhanced continuity of vessels is important for vessel and centerline tracking or vessel segmentation algorithms based on region growing. VED is able to overcome significant intensity drops due to the strong anisotropic diffusion along the vessel. Moreover, VED is able to improve vessel separation in MIPs, since the intensity distribution of each filtered vessel becomes more homogeneous while the gap between vessels becomes smaller. In clinical case, VED can be used to suppress non-vessel structures before vessel segmentation.

Our goal is to develop a vessel enhancement diffusion tensor D that satisfies these three requirements and enables multiscale approaches to vessel analysis. In the literature, smoothed vesselness function $\mathcal{V}$ in (3.12) has been used to construct several scale spaces based on the eigensystem of the Hessian [95, 96]. In this chapter, a novel anisotropic diffusion filter is developed, which uses the vesselness measure to determine the diffusion strength to be applied for each pixel. More specifically, the diffusion tensor D is defined for the purpose of steering main diffusion along the vessel and inhibiting diffusion perpendicular to the vessel. The diffusion tensor is therefore given by [97, 98]:

$$D \triangleq Q\Lambda'Q^T \quad (3.13)$$

where Q represents the eigenvectors of the Hessian $\mathcal{H}$, and Λ' is a diagonal matrix whose diagonal entries are given by:

$$\lambda'_1 \triangleq 1 + (\omega - 1) \cdot \mathcal{V}^{\frac{1}{s}} \quad (3.14)$$

$$\lambda'_2 \triangleq 1 + (\epsilon - 1) \cdot \mathcal{V}^{\frac{1}{s}} \quad (3.15)$$

$$\lambda'_3 \triangleq 1 + (\epsilon - 1) \cdot \mathcal{V}^{\frac{1}{s}} \quad (3.16)$$

with $\mathcal{V} \in [0, 1]$ and parameters $\omega > \epsilon$, $\epsilon > 0$ and $s \in \mathbb{R}^+$. Normally, ω is used to control the diffusion strength, which should be a large value (larger than one). To ensure the tensor's positive definiteness, ϵ should be a small positive value.

In addition, small values of time discretization step should be chosen to prevent instabilities. Based on the eigenvalues λ_i^t of the diffusion tensor D , a Diffusion Ellipsoid (DE) can be constructed and fractional anisotropy (FA) [99] can be calculated, which is defined as:

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1^t - \hat{\lambda}^t)^2 + (\lambda_2^t - \hat{\lambda}^t)^2 + (\lambda_3^t - \hat{\lambda}^t)^2}}{\sqrt{\lambda_1^{t^2} + \lambda_2^{t^2} + \lambda_3^{t^2}}} \quad (3.17)$$

where $\hat{\lambda}^t = (\lambda_1^t + \lambda_2^t + \lambda_3^t)/3$ being the average value of the eigenvalues. For tubular structures ($\mathcal{V} \rightarrow 1$), the diffusion strength is maximal (ω) in the direction along the vessel. And the diffusion is high and isotropic for non-vessel structures ($\mathcal{V} \rightarrow 0$), which reduces background noise. The 3D diffusion ellipsoids can be visualized in Figure 3.1. Figure 3.2 demonstrates the sensitivity on the vesselness response $\mathcal{V}$ by adjusting the parameter s . It is noted that the smoothness property will not be altered by introducing parameter s . Figure 3.3 shows one 2D slice of the computed Fractional Anisotropy. Figure 3.4 presents a comparison between original data and diffusion filter result. It can be observed that VED is able to enhance main branch and suppress background non-vessel structures.

It follows that the proposed diffusion tensor satisfies the above conditions. Compared with the vesselness measure based vessel tracking algorithms, the proposed diffusion filter incorporates image coherence. For instance, if a voxel belongs to a vessel, its neighbor voxel in the direction along the vessel is also likely to be part of a vessel. Therefore, the enhanced image provides a better response to the vesselness measure and allows better segmentation results.

By evolving the image according to (3.5), vascular structures will be enhanced. Compared with segmentation results without diffusion, VED can be used to smooth vessels and suppress non-vessel structures, which produces better segmentation results. In Figure 3.5(a) one slice of Frangi's vesselness image is shown. Figure 3.5(b) shows the obtained vesselness measure after applying the smoothed vesselness filter. In Figure 3.5(c) the obtained image after applying diffusion filter is given. An example of vessel enhancement and non-vessel structures suppression

Figure 3.1: Different 3D diffusion ellipsoids spanned by the eigenvectors $\mathbf{v}^t$.

can be clearly seen.

3.2.4 Morphological Operations

Next some morphological operations were conducted over the filtered image at each scale, to segment the two main coronary arteries. Before that, each slice of the original CT images was separated from the outer boundary by using a threshold operation with a disk-shaped structuring element. In addition, a morphological opening operation was conducted over the original CT data with a ball-shaped structuring element to preserve certain shapes and avoid connecting background noise to the vessel object. To avoid the influence of the surrounding organs (lungs), another threshold operation was conducted to isolate the part of interest, which was operated over the filtered image at increasing scales. By

Figure 3.2: The eigenvalues are functions of the vesselness function $\mathcal{V}$ with parameter $s > 1$ specifying the sensitivity on $\mathcal{V}$ (see [98]).

Figure 3.3: One 2D slice of the computed fractional anisotropy.

combining these thresholded images at each analyzed scale, the overall structure can be obtained. Finally, further threshold operation was needed to extract the two main coronary arteries by manually locating and choosing the correct index value. The final result is a 3D binary dataset. Those voxels with value of 1 belong

(a) Original data (b) Filtered result

Figure 3.4: A comparison between original data and diffusion filter result. (a) Original data. (b) The filtered result after 10 iterations.

(a) Frangi's vesselness (b) Enhanced vesselness (c) Diffusion

Figure 3.5: A comparison between smoothed vesselness function and diffusion filter. (a) Original Frangi's vesselness. (b) The result of smoothed vesselness filter. (c) The filtered result after 4 iterations.

to the coronary artery tree.

3.2.5 Graph Cuts

Moreover, we assess the robustness of the graph cuts method for optimal boundary and region segmentation of coronary arteries in 3D CT images [100, 101, 102]. Let $\mathcal{P}$ be the 3D voxel dataset and $\mathcal{N}$ be the neighborhood system of all unordered pairs $\{p, q\}$ of neighboring elements under a standard 26-neighborhood system. Similarly, the original image I was first filtered at each analyzed scale, producing $I_{\sigma=1}$, $I_{\sigma=3}$, $I_{\sigma=5}$ and $I_{\sigma=7}$, with corresponding critical values c_1 , c_3 , c_5 and c_7 respectively when conducting threshold operations. Let $\mathcal{O} \subset \mathcal{P}$ and $\mathcal{B} \subset \mathcal{P}$ denote the subsets of pixels marked as ‘object’ and ‘background’ seeds respectively, thus we have $\mathcal{O} \cap \mathcal{B} = \emptyset$. In this study, the subset $\mathcal{O}$ is defined as:

$$\mathcal{O} = \{p \in \mathcal{P} : (I_{\sigma=1}(p) > c_1) \cup (I_{\sigma=3}(p) > c_3) \cup (I_{\sigma=5}(p) > c_5) \cup (I_{\sigma=7}(p) > c_7)\} \quad (3.18)$$

while the subset $\mathcal{B}$ is given by:

$$\mathcal{B} = \{p \in \mathcal{P} : (I_{\sigma=1}(p) = 0) \cap (I_{\sigma=3}(p) = 0) \cap (I_{\sigma=5}(p) = 0) \cap (I_{\sigma=7}(p) = 0)\} \quad (3.19)$$

More specifically, all pixels in subset $\mathcal{O}$ are marked as ‘object’ while all in subset $\mathcal{B}$ are marked as ‘background’. In addition, those pixels satisfying $p \in \mathcal{P}$, $p \notin \mathcal{O} \cup \mathcal{B}$ are treated as ‘crust’. Our task is to extract the two main coronary arteries by performing graph cut method over the filtered image. The set of edges $\mathcal{E}$ contains two different types of undirected edges: n -links (neighborhood links) and t -links (terminal links). In order to construct the dual graph, the 3D binary dataset I_{log} obtained above is used here to set up the t -links. Those voxels with value of 1 in the binary image, which indicates that they belong to the vessel, will be connected to the S node. While those with value of 0 in the binary image will be connected to the T node. Each voxel is connected to both terminals S and T , which gives two t -links $\{p, S\}$ and $\{p, T\}$. Besides, each pair of neighboring voxels $\{p, q\}$ in $\mathcal{N}$ is connected by an n -link. For simplicity, we use $\{p, q\}$ to denote this n -link. Thus we have

$$\mathcal{E} = \mathcal{N} \bigcup_{p \in \mathcal{P}} \{\{p, S\}, \{p, T\}\} \quad (3.20)$$

Table 3.1: Weight of edges.

edge	weight (cost)	for
$\{p, q\}$	$C_{\{p,q\}}$	$\{p, q\} \in \mathcal{N}$
$\{p, S\}$	C	$p \in \mathcal{O}$
$\{p, T\}$	0	$p \in \mathcal{O}$
$\{p, S\}$	0	$p \in \mathcal{B}$
$\{p, T\}$	C	$p \in \mathcal{B}$
$\{p, S\}$	0	$p \in \mathcal{P}, p \notin \mathcal{O} \cup \mathcal{B}$
$\{p, T\}$	0	$p \in \mathcal{P}, p \notin \mathcal{O} \cup \mathcal{B}$

Table 3.1 presents the weight of edges in $\mathcal{E}$. Here C is a large enough positive number and $C_{\{p,q\}}$ is defined by using an *ad-hoc* function

$$C_{p,q} \propto \exp\left(-\frac{(I_p - I_q)^2}{2\sigma^2}\right) \cdot \frac{1}{\text{dist}(p, q)} \quad (3.21)$$

Now the graph $\mathcal{G}$ can be constructed. The segmentation boundary between the object and the background can be drawn by finding the minimal cost cut on $\mathcal{G}$. Based on the obtained 3D segmentation result, the two main coronary arteries can be extracted.

3.2.6 3D Cross Sectional Lumen Area Measurement and Area Stenosis

As described in Section 2.3, coronary centerlines can be determined by using three different algorithms: Voronoi method, topological thinning and distance transform method. Now assume the discrete centerline is extracted. Let $\mathbf{P}_0 = (x_0, y_0, z_0)$ denote one skeleton point. The tangent vector to the centerline at $\mathbf{P}_0$ can be calculated by finite difference approximation and denoted as $\mathbf{N} = (a, b, c)$. Assume $\mathbf{P} = (x, y, z)$ is any point in the normal plane at $\mathbf{P}_0$. This plane is given by

$$\mathbf{N} \cdot (\mathbf{P} - \mathbf{P}_0) = 0 \quad (3.22)$$

Plugging in gives the general equation of the normal plane,

$$a(x - x_0) + b(y - y_0) + c(z - z_0) = 0 \quad (3.23)$$

The intersection of this normal plane and the coronary artery surface will be a series of vertices forming a circular disk-like polygon. However, cutting the normal plane over the segmented coronary arteries may not produce a complete circular disk-like polygon. This is because all the three main categories of 3D skeletonization algorithms are performed in voxel-based domain. It is challenging to obtain accurate and complete cross sectional profile for voxel-based shape representation in graphical practice. To improve the geometric accuracy, the mesh for the original 3D volumetric shape is generated. Based on the skeleton points extracted by thinning method, normal plane can be cut at each skeleton point over the remeshed data instead of the voxelized data, eventually yielding a polygon contour which is formed by a set of boundary vertices. When cutting a set of vertices, V_i ($i = 1, 2, \dots, n$), at the skeleton point $\mathbf{P}_0$, the geometric centroid of this polygon formed by these vertices can be calculated and denoted by C . Besides, a set of n triangles that decompose the polygon can be constructed by connecting each pair of adjacent vertices and each vertex V_i to the centroid C . Based on the original CT images resolution, the 3D coordinates of each triangle can be computed and thus its area can be obtained. Therefore, the 3D cross sectional lumen area of this normal plane can be approximated by

$$\text{area}(S) = \sum_{i=1}^n \text{area}(T_i) \quad (3.24)$$

Instead of using the conventional diameter stenosis, the area stenosis can be calculated as

$$\text{Area stenosis} = \left(1 - \frac{s}{S}\right) \times 100\% \quad (3.25)$$

where s measures the focal minimum area at the site of the stenosis, and S measures the “normal” area.

3.3 Results

3.3.1 3D Segmentation

Frangi's vesselness filter was first implemented to access its robustness to detection of coronary arteries in 3D CT images ($512 \times 512 \times 560$). Parameters of vesselness were set to $\alpha = \beta = 0.5$ and $\gamma = 500$. Furthermore, vesselness diffusion was performed with $\omega = 25$ and $S = 5$ (3.14), $\epsilon = 10^{-2}$ (3.15), and time step $\Delta t = 10^{-3}$. With the aim of performing a multi-scale Hessian analysis, we set scales $\sigma \in [1, 8]$, with step size of 2. Figure 3.6 shows MIPs of the vesselness at four different scales. The last image depicts the final result of maximum vesselness over all analyzed scales, eventually yielding a combination of both the small and large vessels. In addition, the filtered vascular structures in three different views are presented in Figure 3.7.

Second, some morphological operations were conducted to extract two main coronary arteries for further medical purpose. A ball-shaped structuring element with radius 10 and height 10 was first constructed. Morphological erosion operation with this structuring element was then conducted over the original CT dataset (Figure 3.8). Subsequent to the erosion operation, another dilation operation was conducted with the same structuring element. This opening operation was used to preserve certain shapes and avoid connecting noise to the main object (Figure 3.9).

Figure 3.10 shows the plots of the connected components at increasing scales. Figure 3.11 gives the overall normalized intensity measure of the connected components after the threshold operation based on the intensities of coronary arteries. Furthermore, by manually locating the pixels and choosing the correct critical values, we can extract the desired vessel structures. The classical Marching Cubes algorithm [103] is used to reconstruct 3D surface mesh of the vessel from segmentation result. Several isosurface plots of the two main coronary arteries corresponding to different critical values are shown in Figure 3.12.

Figure 3.6: MIP of filtered images at 4 scales. (a) $\sigma = 1$. (b) $\sigma = 3$. (c) $\sigma = 5$. (d) $\sigma = 7$. (e) $\sigma \in [1, 8]$.

Next the proposed coronary artery segmentation approach was applied into 5 cardiac CTA datasets, namely Dataset 22, Dataset 23, Dataset 24, Dataset

Figure 3.7: MIP of 3D CTA images of a real patient in orthogonal, sagittal and coronal views.

27 and Dataset 29. The coronary artery segmentation results are presented in Figure 3.12. To obtain more reliable lumen geometry, post-processing steps such as smoothing and filling hole were performed.

3.3.2 Centerline

In this section, three different categories of 3D skeletization algorithm were applied over two patient CTA datasets, namely, Data 1 and Data 2, and discussed in terms of the desired properties described in Section 2.3. These DICOM files represented the coronary CT angiography images of two patients, which

Figure 3.8: Morphological erosion operation with a ball-shaped structuring element with radius 10 and height 10.

Figure 3.9: The morphological opening operation is used to preserve certain shapes and avoid connecting noise to the main object

were acquired using 320-slice CT scanner (Toshiba AquilionOne) with ECG gating. For Data 1, the data size was $512 \times 512 \times 560$, and the data resolution was $0.427\text{mm} \times 0.427\text{mm} \times 0.25\text{mm}$. While for Data 2, the data size was $512 \times 512 \times 480$, and the data resolution was $0.46\text{mm} \times 0.46\text{mm} \times 0.25\text{mm}$. For these two datasets, Frangi's vesselness filter was first used to detect coronary arteries in 3D CT images. Additionally, the curve-skeleton and cross sectional lumen area were explored to quantify the anatomic significance of coronary artery stenosis [46].

Figure 3.10: Normalized intensity measures at 4 increasing scales. (a) $\sigma = 1$. (b) $\sigma = 3$. (c) $\sigma = 5$. (d) $\sigma = 7$.

Homotopy

Figure 3.13 presents the isosurface plot and curve-skeletons extracted by three different algorithms of Data 1 and Data 2. Thinning method can ensure homotopy since during the deletion procedure, only those voxels that do not change geometric topology are removed. Figure 3.14(a) gives the left coronary artery tree segmented from the original 3D CT angiography data. Figure 3.14(b) shows the corresponding curve-skeleton, obtained using 3-subiteration thinning method. The obtained curve skeleton is seen to capture the topology, when overlaying the skeleton over the 3D rendering of left coronary artery tree (Figure 3.14(c)). It

Figure 3.11: Overall normalized intensity measure after combining 4 different scales.

can be found that the thinning method performs well in this case. However, the resulting curve-skeleton is not smooth and even tends to zigzag back and forth. Further smoothing and pruning steps are necessary in order to remove extraneous branches. The centerline becomes much smoother, and most of the zigzags can be eliminated (Figure 3.14(d)).

The thinning method sometimes leads to excessive shortening of the centerline when deleting all simple points, since all the end-points themselves are simple points. Therefore, additional post-processing steps are needed to maintain the geometrical features. For distance transform method, topology preservation is in relation to post-processing steps, i.e., subsequent pruning and connecting. For instance, minimum spanning tree based connectivity techniques are not able to maintain topology because they cannot produce loops if there exist loops in the original object. Fortunately, no loops exist for our left coronary artery tree cases so distance transform method can preserve the necessary topology. The power shape can be used to accurately approximate of the medial surface of the original 3D object. However, correct subsequent simplification steps should be taken to maintain the topology of the power shape. Moreover, sampling density is also an important factor in discrete space case. For example, some small topological features may not be preserved when the the sampling is too sparse. If the sampling

Figure 3.12: Segmented RCAs and LAD by using the proposed method. (a) Dataset 22. (b) Dataset 23. (c) Dataset 24. (d) Dataset 27. (e) Dataset 29.

is too dense, it may lead to high computational cost.

Thinness

Topological thinning method can directly produce 1D curve-skeleton by using thinning deletion templates. Parallel thinning algorithm is not guaranteed to extract 1D curve-skeletons due to homotopy constraints. However, this issue does exist for directional thinning methods: one column of voxels will be deleted when processing the left-right direction, and the second column can be preserved

Figure 3.13: Centerlines of left coronary artery tree obtained using three different 3D skeletonization algorithms. All three algorithms are implemented over two DICOM data sets, Data 1 and Data 2.

Figure 3.14: Left coronary artery tree: (a) 3D rendering of original CT data. (b) 3D skeleton obtained using 3-subiterative thinning method. (c) Overlay of the 3D skeleton over the original 3D data. (d) Skeleton after pruning.

in subsequent steps.

Distance transform method is also able to produce 1D curve-skeleton directly. We just need to find the ridge points (local maximum) of the distance field, which corresponds to the centrally located voxels within the object. The last step will be connecting these ridge points by using minimum spanning tree.

Voronoi method is not able to produce 1D curve-skeletons directly. Therefore, additional post-processing is required to extract a 1D curve-skeleton based on the

generated medial surface. Amenta's power shape [77] algorithm is implemented in this study. It is noted that only the coronary artery surface voxels were provided as input for the power shape algorithm, and the results shown here are the obtained inside poles. Figures 3.15(a) and 3.15(b) show the original coronary artery isosurface plot and the medial surface obtained by Amenta's power shape algorithm separately. By conducting the simplifying and pruning operation, the redundant voxels were removed and the underlying topology was preserved. Figure 3.15(c) shows the simplified medial surface. Finally, the curve-skeleton can be determined from point cluster of medial surface. In [104] a simple method is proposed to compute curve-skeletons based on an explicit advection of the medial surface in the implicitly-computed gradient of its distance transform field.

Figure 3.15: Left coronary artery tree: (a) Original surface. (b) Medial surface obtained by using Voronoi method. (c) Simplified medial surface by choosing optimal parameter values for noise threshold and redundancy threshold.

Medialness

Voronoi method can achieve medialness because it directly computes the boundary points where the maximal balls contact the surface [105]. However, the sampling density of the vessel surface also affects the medialness of curve-skeletons.

Generally, a denser sampling can produce a more centered centerline [77] but it leads to longer running time. Thinning method does not maintain medialness. For example, medialness of curve-skeletons obtained by directional thinning algorithm depends on the order in which the different deletion directions are applied. Distance transform method is able to achieve medialness because this kind of medialness information can be directly reflected by the ridge points in distance field.

Normally, 3D image resolution affects medialness measurement of curve-skeleton in the discrete domain. For example, the curve-skeleton of a 2D rectangle with width of an even number of voxels must be one voxel closer to one of the sides than to the other. Therefore, the quality of CT medical images has a great impact on the curve-skeleton's medialness.

Reliability

In clinical applications, reliable curve-skeleton is a prerequisite for quantitative assessment of each normal plane cutting at skeleton point. Reliability is often checked using the visibility test by overlaying the obtained centerline over the original object. We notice that all three methods can produce a reliable curve-skeleton. Sometimes, for distance transform method, small branches need to be added to the overall centerline tree if it is necessary.

Junction Detection

The skeletonization algorithm should be able to accurately detect the junction points, i.e., the points where two or more curves intersect, in order to distinguish the different components of the obtained curve-skeleton. Based on this, the corresponding branch structure of the original coronary artery tree is easily identified.

Topological thinning method is able to directly identify the junction points during thinning procedure. In addition, Voronoi method directly identifies the

joints as the locus of the maximal ball at each bifurcation. But for distance transform method, junction placement is quite sensitive to noise. Figure 3.16 depicts a comparison of curve-skeletons obtained by thinning and distance transform method. We can see that junction points detected by thinning method are relatively accurate. While for distance transform method, junction placement is not visually appealing.

Figure 3.16: A comparison of curve-skeletons by thinning and distance transform method. Curve-skeleton by thinning method is in red line, while curve-skeleton by distance transform method is in blue line.

3.3.3 Validation of Cross Sectional Lumen Area Measurement Algorithm

In order to verify the present cross sectional lumen area measurement algorithm, which is based on coronary arteries centerline extraction and surface mesh generation, we artificially constructed several 3D shapes and compared the obtained cross sectional lumen areas with the true areas. The centerlines were first extracted by 3-subiteration thinning method and refined by smoothing and pruning at

voxel level. The Matlab toolbox iso2mesh [106] was applied in this study for the purpose of generating surface mesh and cutting the normal plane. The proposed algorithm was implemented over four basic geometric shapes to demonstrate its validity. In Figure 3.17(a) we plot the 3D isosurface of a Block voxelized at a $34 \times 9 \times 54$ resolution with its skeleton points obtained by topological thinning method embedded into it. Figure 3.17(b) shows the volumetric mesh and the normal plane cut at one landmark skeleton point. Figure 3.17(c) depicts the real normal plane cut at the same skeleton point in 3.17(b). By simple calculation, we know that the real cross sectional lumen area is 150. Figure 3.17(d) gives the set of polygon vertices (blue) and the geometric centroid (red). The approximated cross sectional lumen area can be obtained by using our algorithm, which is 149.5. Similarly, we can apply this algorithm for the other three geometric shapes. Final results of Ball, Ice cream and Ellipsoid are presented in Figures 3.18-3.20, respectively. In Table 3.2 we summarize the real and approximated cross sectional lumen areas for these four models. The percent of error for each object which is computed as $(A_{real} - A_{appro})/A_{real} * 100$ is also presented. The approximated cross sectional lumen areas are found to be accurate and reliable for different 3D volumetric shapes.

Table 3.2: A comparison of real and approximated cross sectional lumen areas for the 3D models.

Cross sectional lumen area	3D models			
	Block	Ball	Ice Cream	Ellipsoid
Resolution	$34 \times 9 \times 54$	$70 \times 70 \times 70$	$100 \times 100 \times 100$	$256 \times 256 \times 256$
Real area	150.0	2826.0	1287.6	25132.7
Approximated area	149.5	2824.0	1281.2	25101.8
Percent of error	0.33%	0.07%	0.50%	0.12%

Figure 3.17: Cross sectional area approximation for a block. (a) Isosurface plot with skeleton points. (b) Mesh and normal plane. (c) Real cross sectional profile. (d) Approximated cross sectional profile.

3.3.4 3D Cross Sectional Profile in A Coronary Artery Model

In this part, we cut the normal planes at six landmark skeleton points L_1 , L_2 , L_3 , L_4 , L_5 and L_6 , along one specific branch of the obtained left coronary artery tree (see Figure 3.21(a)). A pre-remeshing operation was conducted over the original 3D binary data set of coronary artery surface, while keeping the parameters the same as those for 3D geometric shapes. Figure 3.21(b) depicts the corresponding contours when each normal plane intersects the coronary artery surface mesh. At

Figure 3.18: Cross sectional area approximation for a ball. (a) Isosurface plot with skeleton points. (b) Mesh and normal plane. (c) Real cross sectional profile. (d) Approximated cross sectional profile.

landmark L_1 , the obtained contour is a polygon with 9 vertices, v_1 to v_9 . The geometric centroid can be computed, which is denoted by C . The polygon is therefore decomposed into 9 triangles. Figure 3.22 shows this obtained polygon. Table 3.3 gives the 3D coordinates of these 9 vertices and the centroid C . In Table 3.4 we show the cross sectional profiles. For each landmark skeleton point, we count the number of vertices of the polygon when normal plane intersects the original coronary artery, and then approximate its corresponding cross sectional lumen area (in mm^2). In addition, the calculation outcome of the cross sectional lumen areas can be plotted against the positions of the curve-skeleton, which is presented as a line chart.

At Figure 3.23 the corresponding cross sectional lumen area and the average diameter are depicted. In Figure 3.23(a), the horizontal direction measures the distance of each landmark from the initial point, while the vertical direction

Figure 3.19: Cross sectional area approximation for an ice cream. (a) Isosurface plot with skeleton points. (b) Mesh and normal plane. (c) Real cross sectional profile. (d) Approximated cross sectional profile.

measures the corresponding cross sectional lumen area at each landmark. It can be seen that from L_5 the coronary artery cross sectional lumen area drops dramatically to a minimum at the position of L_6 . Afterwards the cross sectional lumen area increases and reaches the initial values. This drop in the lumen area reflects the coronary artery stenosis. The length of the stenosis can be obtained by measuring the distance between two landmark points. Therefore, the coronary artery lumen area and diameter changes can be displayed and length and degree of coronary artery stenosis can be measured on this chart in a quantitative manner. Furthermore, the proposed lumen area evaluation approach can process the segment of Left Anterior Descending (LAD). The corresponding centerline was first extracted by topological thinning method and refined by smoothing and pruning at sub-voxel level. There were a total of 286 skeleton points along the

Figure 3.20: Cross sectional area approximation for an ellipsoid. (a) Isosurface plot with skeleton points. (b) Mesh and normal plane. (c) Real cross sectional profile. (d) Approximated cross sectional profile.

segment of LAD. In Figure 3.24 we show the vessel surface mesh, the corresponding centerline, and normal planes at 29 landmark skeleton points. Furthermore, the variation was also calculated to determine the variability of the proposed algorithm. A total of 286 cross-sections were measured twice along the segment of LAD in both Data 1 and 2. Figure 3.25 shows scatterplots with regression line between two replicates for both datasets. The least square fit for two datasets were given by $y = 1.01x + 0.29$ ($R = 0.947$) and $y = 0.88x + 0.96$ ($R = 0.939$), respectively. Area stenoses were measured as 37.5% and 37.9% respectively. The variation for two datasets were $7.8\% \pm 2.7\%$ and $8.1\% \pm 2.9\%$, respectively. The accuracy of the proposed lumen area measurement algorithm will be validated based on intravascular ultrasound (IVUS) in our future work.

Figure 3.21: Cross-sectional lumen plane cutting at six landmarks. (a) Six landmarks L_1 , L_2 , L_3 , L_4 , L_5 and L_6 . (b) Corresponding contours at the vessel boundary.

Figure 3.22: Obtained polygon when cutting the cross section at landmark L_1 . We have 9 vertices, v_1 - v_9 . Geometric centroid C can be calculated.

Table 3.3: 3D coordinates of the nine polygon vertices and the geometric centroid.

Vertices	Coordinates		
	x	y	z
v_1	338.0424	159.8646	185.9575
v_2	338.3765	159.8514	185.6234
v_3	338.6155	159.4158	185.3844
v_4	338.7952	158.3011	185.2047
v_5	338.4915	157.7357	185.5084
v_6	337.6983	157.5017	186.3016
v_7	337.2956	158.0384	186.7043
v_8	336.8149	159.2199	187.1850
v_9	336.8648	159.2920	187.1351
C	337.8884	158.8023	186.1116

Table 3.4: 3D cross sectional profiles at six landmarks.

Cross sectional	Landmark name					
	L1	L2	L3	L4	L5	L6
Number of vertices	9	12	13	15	18	14
Area (mm^2)	0.6710	1.1785	1.1217	1.4614	2.0966	1.4764
Average Diameter (mm)	0.9245	1.2253	1.1954	1.3644	1.6343	1.3714

3.4 Remarks

In this chapter, a non-linear vesselness measure based diffusion filter has been proposed to perform vascular structures enhancement. Frangi's vesselness function is first modified to guarantee smoothness on its domain and can be directly applied in the diffusion equation. The approach has been applied to CTA datasets and it demonstrates very strong vessel enhancement and background noise suppression, which outperforms previous vessel filtering techniques. However, due to

Figure 3.23: 3D cross sectional profiles at 6 landmark skeleton points. (a) Cross sectional area. (b) Average diameter.

the non-linear and multiscale character of the diffusion filter, this technique has a high computational cost. In clinical practice, a region of interest may be selected to speed up the diffusion process.

For complete coronary artery tree segmentation, the present approach is based on Hessian filter and connected components [107]. For different CTA datasets, all parameters and thresholds need to be tuned to fit the data, and the computational cost is high. Moreover, small vessels may not be detected because of low contrast in original CT images or smoothing operation prior to segmentation. In our future work, some other automated coronary artery segmentation approaches can be performed, i.e., multiple hypothesis tracking (MHT) algorithm [108] or knowledge-based 3D segmentation approach [23].

Moreover, three main categories of 3D skeletonization approaches were investigated to determine the centreline of segmented coronary arteries from human cardiac CTA images. Among these three algorithms, Voronoi method can only produce medial surface directly, therefore, additional pruning steps especially at the locations of branches and dilatations are required to obtain 1D skeleton.

Figure 3.24: Cross sectional profiles of LAD. The left frame shows the segmented left coronary artery and centerline for LAD. The right frame shows the vessel surface mesh, the centerline, and the cross sectional profiles at 29 landmark skeleton points.

Topological thinning method has no parameters to control since at every iteration, some topology preserving templates are used at each iteration to check whether the boundary voxels are going to be deleted or not. The obtained skeleton is continuous and one voxel wide, but its smoothness and centeredness is worse in comparison to other results. Distance transform method is sensitive to the thickness of the vessel, which may cause unwanted clusters of voxels or disconnections of the curve at narrow locations. The simplicity of algorithm however leads to faster execution. It is necessary to improve distance transform method or use thinning method to prune the skeletons obtained by performing distance transform method.

Figure 3.25: Scatterplots with regression line between two replicates. (a) Data 1. (b) Data 2.

In the last part, the proposed cross sectional lumen area measurement algorithm can be performed only on a straight vessel branch without bifurcation. Therefore, small branches from the target vessel are manually removed. It is noteworthy that this step of removing bifurcations in measurement of cross sectional area has little effect on the accuracy of the entire vessel. Subsequently, for every single branch, the centerline can be extracted and the quantitative assessment can be conducted. Since our proposed cross sectional area measurement algorithm is based directly on coronary artery surface mesh generation and centerline extraction, the quality of surface mesh is significantly important to the accuracy of the algorithm. In this study, the tetrahedral mesh of the segmented coronary artery surface is generated. It is noted that denser coronary artery surface mesh can produce more nodes and elements of the tetrahedral mesh, which can better approximate the original vessel contour. On the other hand, it leads to a higher computational cost.

Fast Marching and Runge-Kutta Based Coronary Artery Centerline Extraction

4.1 Introduction

In clinical practice, fast and accurate coronary centerline computing is an essential prerequisite for coronary stenosis evaluation [47]. Generally, precise quantification of coronary stenosis is important to the diagnosis of cardiovascular diseases [4, 46]. Therefore, the centerline is required to be smooth for accurate normal vector calculations, centrally located for precise measurement, and fully connected for the entire branch.

In the literature, several centerline extraction approaches for CTA images have been developed [67, 107, 109, 110], most of which can be divided into three different categories. In the first category, the approach is based on topological thinning methods [81]. The thinning process starts from the vessel's boundary. Some topology preserving templates ($3 \times 3 \times 3$) are used at each iteration to check whether the boundary voxels are going to be deleted or not. Once all the simple points are deleted, the thinning procedure terminates. Due to the massive rules and iterations, these methods lead to a high computational cost. For 3D volume

dataset, the obtained centerlines may contain spurious branches and medial surfaces. Therefore, further post-processing is required to obtain a refined centerline. The second class of approach uses the shortest paths techniques [111], which are usually applied in virtual endoscopy. First, the start and end points are selected and an initial path can be defined along the vessel. Next the path is iteratively adjusted toward the true centerline. However, the obtained centerlines are not accurate and thus further refinement of the skeleton points is required. Besides, it is a challenging task to manually select the start and end points for complex vessel structures. The last class of approach is based on the distance transform (DT) [112]. For instance, Van Uiter *et al.* [91] propose a centerline determination algorithm, which calculates the distance transform and applies the fast marching method. In the first step, a subvoxel distance field of the vessel object can be computed. The largest distance value point is then selected as source point for the fast marching propagation, which gives the geodesic distance field. The furthest geodesic point is defined as the start point for the first branch. From the start point, the remaining discrete centerline points can be backtracked along the gradient descent. The whole centerline tree can be obtained by repeating this procedure for each vessel branch. Many of these approaches have limitations such that they are sensitive to boundary noise, depend on threshold values and parameters, require manual placement of seed points, or are computationally expensive.

In this chapter, a new algorithm for fast and accurate extraction of coronary artery centerlines with minimal user interaction is proposed. First of all, the fast marching method [55, 113] is applied to calculate the time-crossing map. The proposed speed image function is based on the distance map and integrates the magnitude of Gaussian gradient of the vessel image. In the second step, a branch tracking procedure based on the Runge-Kutta method [114] is performed. Compared with Van's approach, the proposed method can achieve high accuracy even

with large step size, which reduces the processing time dramatically. The application of this new algorithm is demonstrated on a variety of CT images, which shows that the obtained subvoxel precise centerlines are reliable and accurate.

This chapter is organized as follow. Section 4.2 presents the methodology. In Section 4.3 we construct four 3D vessel models and validate the method accuracy by comparing three overlap measures between the ground truth centerlines and the obtained centerlines. The results over different CTA datasets of patients are presented in Section 4.4. Section 4.5 discusses the advantages of the proposed method.

4.2 Methodologies

The shortest path technique can be applied to extract the centerline. Assume $S(t) : [0, \infty] \rightarrow \mathbb{R}^n$ is a path from point O to position x in $\mathbb{R}^n$. The shortest path problem minimizes the total cost H . Assume the cost function is a function of position x :

$$C(x) = \min_{S_{Ox}} \int_0^L H(S(t)) dt \quad (4.1)$$

where S_{Ox} represents the set of paths connecting O and x , and L is the total distance. Generally, several wave propagation techniques have been developed to extract the centerline between two nodes. Provided a cost function (e.g., distance field), a front propagation can be driven from one node until the other node is reached, and a backtracking procedure can be used to extract the centerline. The solution of (4.1) satisfies [115]:

$$|\nabla T(x)|\mathcal{F}(x) = 1 \quad (4.2)$$

where $\mathcal{F}(x)$ represents the speed and $T(x)$ is the time crossing map. However, the employed cost function and its parameters need to be set heuristically, which prevents these techniques from automation. In [116] Hassouna *et al.* derived a closed-form solution for the energy function and its controlling parameters.

Let $\mathcal{O} \subset \mathbb{R}^3$ be an object. The medial function $\lambda(x) : \mathcal{O} \rightarrow \mathbb{R}_+$ is defined to assign medial points higher weights than nonmedial ones, that is, $\lambda(p) > \lambda(q)$ where p is a medial point and q is any nonmedial point. The speed function $F(x) = g(\lambda(x)) : \mathcal{O} \rightarrow \mathbb{R}_+$ is a function of $\lambda(x)$. Let Δx , Δy , and Δz be the grid spacing, δ be the minimum absolute difference in medialness of two neighbor voxels.

Theorem 4.1. *The minimum cost path between two skeleton points inside an object is a centerline, if the cost function over the object is defined as*

$$u(x) = \exp(-\alpha\lambda(x))$$

where

$$\alpha > \frac{1}{\delta} \ln \left(\frac{\sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z}}{\min(\Delta x, \Delta y, \Delta z)} \right) > 0$$

Proof. Consider the vessel in Figure 4.1. Let p_s and p_e be two medial points. Assume that p_s be a point source that transmits a monotonic wave front W , whose speed is proportional to some medial function $\lambda(x)$. If the curve skeleton between p_s and p_e is the minimum cost path, then the time taken by W to cover the distance between two consecutive medial points p_{i-1} and p_i (i.e., t_p) must be less than the time required by the same front to travel from p_{i-1} to its nonmedial neighbor $q_{j,j \neq i}$ (i.e., t_q). This can be mathematically formulated as

$$t_p = \frac{\varepsilon(\mathbf{p}_{i-1}, \mathbf{p}_i)}{F(\mathbf{p}_i)} < t_q = \frac{\varepsilon(\mathbf{p}_{i-1}, \mathbf{q}_j)}{F(\mathbf{q}_j)} \quad (4.3)$$

or

$$\frac{\varepsilon(\mathbf{p}_{i-1}, \mathbf{p}_i)}{\varepsilon(\mathbf{p}_{i-1}, \mathbf{q}_j)} < \frac{F(\mathbf{p}_i)}{F(\mathbf{q}_j)} \quad (4.4)$$

The medial function $\lambda(x)$ assigns medial points higher weights than nonmedial ones, so

$$\lambda(\mathbf{p}_i) = h, \lambda(\mathbf{q}_j) = h - \delta_j \quad (4.5)$$

where h and δ_j are the real positive numbers. Since the ratio $\varepsilon(\mathbf{p}_{i-1}, \mathbf{p}_i)/\varepsilon(\mathbf{p}_{i-1}, \mathbf{q}_j)$ is maximum when

$$\varepsilon(\mathbf{p}_{i-1}, \mathbf{p}_i) = \sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z} \quad (4.6)$$

Figure 4.1: 3D wave propagation: The red line represents a curve skeleton connecting p_s with p_e while the envelope of a 3D wave front is represented by an arrow.

and

$$\varepsilon(\mathbf{p}_{i-1}, \mathbf{q}_j) = \min(\Delta x, \Delta y, \Delta z) \quad (4.7)$$

Then the speed function F will be designed such that

$$\frac{F(\mathbf{p}_i)}{F(\mathbf{q}_j)} > \frac{\sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z}}{\min(\Delta x, \Delta y, \Delta z)} \quad (4.8)$$

in order to satisfy (4.4). Recall that $F(x) = g(\lambda(x))$, inequality (4.8) implies that

$$r = \frac{\sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z}}{\min(\Delta x, \Delta y, \Delta z)} < \frac{g(h)}{g(h - \delta_j)} \quad (4.9)$$

$$r g(h - \delta_j) - g(h) < 0 \quad (4.10)$$

Applying Taylor series expansion to $g(h - \delta_j)$ and substituting into (4.10), we obtain

$$r \left(g(h) - \delta_j \frac{dg(h)}{dh} + \epsilon(\delta_j) \right) - g(h) < 0 \quad (4.11)$$

By rearranging 4.11 by ignoring higher order terms, we get

$$\frac{dg(h)}{g(h)} > \frac{r - 1}{r \delta_j} dh \quad (4.12)$$

Since δ_j varies from one point to another, δ_j will be fixed over $\mathcal{O}$ to its lowest positive value such that (4.12) is satisfied:

$$\delta_j = \delta = \min_{\mathbf{p} \in \mathcal{O}, \mathbf{q} \in \eta_{\mathbf{p}}} \{|\lambda(\mathbf{p}) - \lambda(\mathbf{q})|, \lambda(\mathbf{p}) \neq \lambda(\mathbf{q})\} \quad (4.13)$$

where $\eta_{\mathbf{p}}$ is the nearest neighborhood of $\mathbf{p}$. Now define

$$\alpha_1 = \frac{r-1}{r\delta} = \frac{1}{\delta} \left(1 - \frac{\min(\Delta x, \Delta y, \Delta z)}{\sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z}} \right) > 0 \quad (4.14)$$

By integrating both sides of (4.12) for a given x , we get

$$\int_{\lambda_{\min}}^{\lambda(\mathbf{x})} \frac{dg(h)}{g(h)} > \int_{\lambda_{\min}}^{\lambda(\mathbf{x})} \alpha_1 dh \quad (4.15)$$

$$\ln F(\mathbf{x}) > \alpha_1 \lambda(\mathbf{x}) - (\alpha_1 \lambda_{\min} - \ln F_{\min}) \quad (4.16)$$

where $\lambda_{\min}$ is the minimum medialness and $F_{\min} = g(\lambda_{\min})$. Let

$$\varsigma = \alpha_1 \lambda_{\min} - \ln F_{\min} \quad (4.17)$$

Then

$$F(\mathbf{x}) > \exp(\alpha_1 \lambda(\mathbf{x}) - \varsigma) = \exp(-\varsigma) \exp(\alpha_1 \lambda(\mathbf{x})) \quad (4.18)$$

One possible choice for $F(\mathbf{x})$ that allows neglecting $\epsilon(\delta_j)$ without altering the inequality is

$$F(\mathbf{x}) = \exp(\alpha_2 \lambda(\mathbf{x})) \exp(\alpha_1 \lambda(\mathbf{x})) \quad (4.19)$$

which requires

$$\exp(\alpha_2 \lambda(\mathbf{x})) > \exp(-\varsigma) \quad (4.20)$$

$$\alpha_2 \lambda(\mathbf{x}) > \ln F_{\min} - \alpha_1 \lambda_{\min} \quad (4.21)$$

Now let's find the condition that satisfies $\epsilon(\delta_j) \rightarrow 0$. By restricting the minimum value of the speed to be unity, the equation always holds. Therefore, (4.19) reduces to

$$F(\mathbf{x}) = \exp(\alpha \lambda(\mathbf{x})) \Rightarrow \mu(\mathbf{x}) = \exp(-\alpha \lambda(\mathbf{x})), \quad (4.22)$$

$$\alpha = \alpha_1 + \alpha_2 \quad (4.23)$$

By substituting the proposed speed (4.22) into (4.11), we obtain

$$r \left(\exp(\alpha h) - \delta \alpha \exp(\alpha h) + \frac{\delta^2 \alpha^2}{2!} \exp(\alpha h) - \dots \right) - \exp(\alpha h) < 0 \quad (4.24)$$

$$r \exp(\alpha h) \left(1 - \delta \alpha + \frac{\delta^2 \alpha^2}{2!} - \dots \right) - \exp(\alpha h) < 0 \quad (4.25)$$

It can be observed that $(1 - \delta \alpha + \frac{\delta^2 \alpha^2}{2!} - \dots)$ is the Taylor expansion of $\exp(-\delta \alpha)$, so we have

$$r \exp(-\delta \alpha) - 1 < 0 \quad (4.26)$$

Therefore,

$$\alpha > \frac{1}{\delta} \ln(r) = \frac{1}{\delta} \ln \left(\frac{\sqrt{\Delta^2 x + \Delta^2 y + \Delta^2 z}}{\min(\Delta x, \Delta y, \Delta z)} \right) > 0 \quad (4.27)$$

which is the necessary condition to satisfy 4.12. $\square$

4.2.1 Speed Image

The speed image [117] used in the level set methods is usually defined to store the curve evolution velocity at each voxel location. For example, Van's speed image [91] is defined as:

$$F = \left(\frac{D}{\max D} \right)^2 \quad (4.28)$$

with the distance field D and its global maximum value $\max D$. However, no theoretical evidence is provided for F to ensure centeredness. Additionally, the tracking procedure is guaranteed along the gradient descent direction only for small value of step size (0.01) in Van's method. Besides, Van's method is not able to adequately handle sudden vessel enlargements.

In this chapter, the distance field D from the vessel boundary and its global maximum value $\max D$ are first computed. Next the derivatives of 3D image can be obtained by convolving the original image I with Gaussian gradient filter in each dimension. The first order derivative of Gaussian function is given by

$$G'(x) = -\frac{x}{\sigma^2} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{x^2}{2\sigma^2}} \quad (4.29)$$

where σ is the standard deviation. Therefore, the Gaussian gradient filter $G'(x)$ is applied along x , y and z directions for 3D vessel image to locate the medial voxels.

Then a hybrid distance field function is proposed by integrating the magnitude of Gaussian gradient of the vessel image, which is defined as:

$$I_{distance} = \frac{(\frac{D}{maxD})^4}{(0.5 - |\nabla I|)^2} \quad (4.30)$$

where ∇I is computed by convolving 3D vessel image I with $G'(x)$ along x , y and z directions. The gradient magnitude field $|\nabla I|$ is a slowly varying field that has smaller values at central voxel positions of 3D vessel image. Thus the strong medial function $I_{distance}$ is defined to give higher distance responses at those centerline points. Therefore, a new speed image [118] is proposed

$$\mathcal{F}(x) = \begin{cases} 0 & \text{if } I_{distance} = 0, \\ e^{\frac{D}{\tau * maxD}} & \text{if } I_{distance} > t, \\ e^{\frac{D}{maxD}} & \text{otherwise} \end{cases} \quad (4.31)$$

where t is the threshold value experimentally determined in the new medial function $I_{distance}$, and τ is the parameter. The speed is defined as $e^{\frac{D}{\tau * maxD}}$ for those points with larger values than t . The parameter τ is introduced to enhance the image speed and drive the front moving along the center within the vessel. The proposed speed image employs a new medial function $I_{distance}$ that avoids forming medial surfaces and is theoretically supported because all of its parameters are analytically derived in [116]. The accuracy and efficiency of this hybrid technique for robust coronary centerline extraction will be demonstrated.

It is noted that the centerlines can be directly extracted from the medial function using some classical techniques [119, 120]. However, these techniques lead to large metrication errors since the obtained centerline is discrete.

4.2.2 Source Point Determination

First of all, the distance field $D(x)$ of the 3D vessel object can be computed. The source point P_s is defined as the largest distance value point in $D(x)$:

$$P_s = \arg \max_x D(x) \quad (4.32)$$

Then a front can be propagated from P_s using the proposed speed image $\mathcal{F}$, which results in a modified distance map T that assigns medial voxels higher values using a non-Euclidean metric. This T can be used to determine the start point and then extract the first branch.

4.2.3 Start Point Determination

The point m_0 with maximum T value is selected as the start point [121]:

$$m_0 = x \mid T(x) \geq T(y) \forall x, y \in O \quad (4.33)$$

Then the shortest path can be extracted by backtracking from m_0 along the gradient descent direction until source point P_s is reached. This is guaranteed to be found since the shortest path is the only global minimum cost path [116]. All the detected points from m_0 to P_s at this step belong to the entire centerline S_f . Therefore, the first branch starting at P_s can be extracted.

4.2.4 Branch Tracking

The first branch is determined by tracking along the gradient descent in the time crossing map T . More specifically, the centerline is extracted by tracking discrete points along ∇T , which is formulated as:

$$\frac{dS}{dt} = -\frac{\nabla T}{|\nabla T|}, \quad S(0) = m_0 \quad (4.34)$$

where $S(t)$ represents the centerline and m_0 denotes the furthest geodesic point.

Assume the current skeleton point is $\mathbf{P}_c$, in [91] the next skeleton point $\mathbf{P}_n$ along the branch is computed using the following equation

$$\mathbf{P}_n = \mathbf{P}_c - 0.01 \frac{\mathbf{g}}{\|\mathbf{g}\|} \quad (4.35)$$

where $\mathbf{g}$ is the gradient. This tracking technique is only suitable for small value of step size. For example, a step size of 0.01 was selected to simulate a continuous curve. If the step size is increased, this approach will not be applicable to the solution of (4.34). Moreover, the previous fast marching method starts at the global maximum point of the distance field, which may induce a singularity in the gradient field at that point. For example, when the branch is tracked near this point, further gradient descent cannot be computed and the solution may not intersect the end point. Therefore, the implicit method is explored to solve this stiff ordinary differential equation.

Again the centerline determination process can be treated as an initial value problem given by

$$\frac{dS}{dt} = f(t, S), \quad S(t_0) = m_0 \quad (4.36)$$

where

$$f(t, S) = -\frac{\nabla T}{|\nabla T|} \quad (4.37)$$

Now select a step size $h > 0$

$$t_{n+1} = t_n + h \quad (4.38)$$

The classical implicit Runge-Kutta method is defined as

$$S_{n+1} = S_n + \sum_{i=1}^s b_i k_i \quad (4.39)$$

where

$$k_i = hf(t_n + c_i h, S_n + \sum_{j=1}^s a_{ij} k_j) \quad (4.40)$$

The Gauss-Legendre method with 2 stages (order of 4) is explored in this study. By exploring the Butcher tableau [122], we can obtain

$$\begin{array}{c|cc} \frac{1}{2} - \frac{1}{6}\sqrt{3} & \frac{1}{4} & \frac{1}{4} - \frac{1}{6}\sqrt{3} \\ \frac{1}{2} + \frac{1}{6}\sqrt{3} & \frac{1}{4} + \frac{1}{6}\sqrt{3} & \frac{1}{4} \\ \hline & \frac{1}{2} & \frac{1}{2} \end{array} \quad (4.41)$$

Then we get

$$k_1 = hf(t_n + (\frac{1}{2} - \frac{1}{6}\sqrt{3})h, S_n + \frac{1}{4}k_1 + (\frac{1}{4} - \frac{1}{6}\sqrt{3})k_2) \quad (4.42)$$

$$k_2 = hf(t_n + (\frac{1}{2} + \frac{1}{6}\sqrt{3})h, S_n + (\frac{1}{4} + \frac{1}{6}\sqrt{3})k_1 + \frac{1}{4}k_2) \quad (4.43)$$

Given the start point m_0 , initial guesses of k_1 and k_2 , denoted as k_1^0 and k_2^0 , are computed as the linear interpolation of 8 nearest neighbors of m_0 in the gradient field ∇T . Therefore, an iterative method [123] is applied to solve this system of nonlinear equations. Assume k_1^* and k_2^* are the final solutions, the next skeleton point can be computed by

$$S_{n+1} = S_n + \sum_{i=1}^s b_i k_i = S_n + (\frac{1}{2}k_1^* + \frac{1}{2}k_2^*) \quad (4.44)$$

4.2.5 Multiple Branch Centerline Formation

Further branches can be extracted by repeating the above procedure to obtain the entire centerline tree. Now all the centerline points of the first branch are treated as source points, instead of using a single point. A wave front is propagated from this initial set of source points to compute the geodesic furthest point m_1 , which will be the start point of the new branch. To extract another branch, the backtracking procedure is repeated from the start point m_1 among the remaining unreached branches S_b . Once there is one point in S_f can be detected, the backtrace procedure terminates. The whole extraction procedure is finished when all the remaining branches are reached. All the points m_i are called extreme points, and all the backtraced points reached in S_f represent bifurcations.

The proposed method ensures that the overall centerline tree is connected. Every single branch is guaranteed to be connected due to the constant step size used during the tracing process. Furthermore, the branches are connected to each other because the centerline points detected along the gradient descent path are guaranteed to intersect the prior skeleton, since the fast marching field is strong monotonic with its minima at the prior skeleton points. The proposed algorithm automatically determines the number of branches. When the length of the branch is less than the maximum diameter of the object, the multiple branch formation procedure terminates and this new branch is not added to the skeleton. Algorithm 4.1 gives the pseudo-code of this procedure.

Algorithm 4.1 Centerline extraction algorithm

```

1: Input: Binary segmentation result  $V$ 
2: Output: Discrete centerline  $S_f$ 
3:  $S_f = \emptyset, \text{linelength} = \infty$ 
4:  $P_s = \arg \max_x D(x)$ 
5:  $i = 0$ 
6: while  $\text{linelength} > 2 * \max D$  do
7:    $T = \text{FastMarching}(P_s, \mathcal{F})$ 
8:    $m_i = x \mid T(x) \geq T(y) \forall x, y \in O$ 
9:    $S = \text{backtrace}(m_i, P_s)$ 
10:   $\text{linelength} = \text{length}(S)$ 
11:   $P_s = P_s + S, S_f = S_f + S$ 
12:   $i = i + 1$ 
13: end while

```

4.2.6 Time Complexity

In this chapter, the distance field images were computed by applying the multi-stencils fast marching method (MSFM) [124]. The time complexity of the entire

algorithm for subvoxel centerline extraction is $O(kn \log n)$, where k is the number of branches and n is the number of voxels in the data set. The $n \log n$ factor comes from the use of the FM method in the centerline determination algorithm. The centerline extraction procedure is able to operate automatically and without user dependent delays.

4.3 Validation

In this study, several 2D and 3D synthetic vessel models were constructed to validate the accuracy of the centerline extraction method. Figure 4.2 presents its application on a 2D vessel image. The distance field of the vessel is shown in the left frame. The middle frame shows the gradient of Gaussian filter over the 2D image. The extracted centerline is presented in the right frame. It is observed that the final centerline is continuous, smooth and centrally located.

In addition, several training datasets downloaded from the online evaluation framework [48] are used to compare the overlap scores between two different methods. Dataset 0, which included four different segments (Vessel 0-3), was selected as the reference vessel data. Besides, the discrete ground truth centerline and the corresponding radius at each skeleton position were provided. The digital synthetic vessel model was generated by placing a sphere ball with given radius at each skeleton point for each reference centerline. Therefore, the distance field and the centerline were computed by applying the proposed method for each phantom coronary artery.

In Figure 4.3 we show the obtained centerline for Vessel 0, using the proposed method and for visual comparison, with the provided ground truth centerline. According to visual inspection, the obtained subvoxel centerline was centrally located within the vessel object. Moreover, the centerline obtained by our approach was naturally smooth due to the subvoxel precision of the algorithm; no post-processing smoothing was performed on the centerline. The presence of main

Figure 4.2: Validation of the proposed method for 2D vessel image. Left: distance field of the 2D vessel image. Middle: Gaussian gradient filter with $\sigma = 2$ is applied to localize the medial pixels. Right: obtained centerline.

differences can be found in the high curvature areas of the branch. It is noted that different values of parameter τ between 0.01 and 0.5 have been tested, which gave similar results. The results shown here are computed using $\tau = 0.02$. Both the proposed and Van's approaches were performed over Vessel 0. The comparison of boundary distance for a segment of centerline is shown in Figure 4.4. It is observed that Van's centerline has much smaller boundary distance at several skeleton points, which indicates that Van's centerline deviates more from the medial axis. Moreover, the method and ground truth centerlines for Vessel 1-3 are presented in Figure 4.5.

The dataset sizes and processing time for different digital reference datasets

Figure 4.3: A comparison of method centerline and the ground truth centerline for Vessel 0.

are summarized in Table 4.1, with step size of 0.01. Table 4.2 presents a comparison of processing time, overlap measure, average error and maximum error for the centerlines extracted from Vessel 0 by using both methods, with different values of step size. It can be found that both methods achieve high overlap measure and small average and maximum error when the step size h is small (0.01). The proposed method is more accurate and reliable due to the smaller average error. Besides, Van's method leads to a higher computational cost by using small step size. The proposed method is still able to obtain higher overlap measure and smaller average error when the step size increases. Particularly, the backtracking process in Van's method halts near the start point when the step size increases to 2. The proposed method, however, is able to extract the complete centerline with high accuracy and reliability. In addition, this improvement in centerline's reliability and accuracy does not incur larger running time. Finally,

Figure 4.4: A comparison of the boundary distances of both centerlines for a segment of Vessel 0.

the proposed method is more efficient because less computations are required (two distance maps), and the shortest path determination is also faster using the modified speed image.

4.3.1 Centerline Accuracy

To demonstrate the accuracy of the obtained centerline, the average error L_2 in millimeters and maximum error L_∞ in millimeters from the ground truth centerline are measured for Vessel 0. The comparison of quantitative results between two methods is presented in Table 4.2. Now assume the step size was selected as 0.01, L_2 was only 0.48 mm. The proposed procedure was able to provide subvoxel precise solutions since the L_2 error was less than a voxel unit. The maximum error, which tended to occur in areas of high curvature in the centerline, was less than the diagonal of a voxel (1.10 mm). Also, the L_2 and L_∞ errors of the present algorithm never exceeded 0.99 mm and 2.14 mm, respectively. Therefore, we can

Figure 4.5: A comparison of the obtained centerlines and ground truth centerlines for Vessel 1-3. Up: Vessel 1. Middle: Vessel 2. Down: Vessel 3.

Table 4.1: Dataset size and running time required for centerline extraction by both methods.

	Size	Time (s)	
		Van's Method	Our Method
Vessel 0	512×512×272	39.5	34.8
Vessel 1	512×512×260	37.2	32.3
Vessel 2	512×512×262	37.8	33.2
Vessel 3	512×512×270	38.6	33.9

Table 4.2: A comparison of running time, overlap, average distance and maximum distance (measured in mm) for Vessel 0.

	Van's method				Our method			
h	time (s)	overlap (%)	L_2	L_∞	time (s)	overlap (%)	L_2	L_∞
1/100	39.5	93.4	0.57	1.29	34.8	97.6	0.48	1.10
1/50	37.9	92.1	0.60	1.34	33.6	96.3	0.49	1.21
1/10	36.1	87.2	0.65	1.55	32.9	91.5	0.59	1.49
1/2	34.7	80.5	0.78	1.79	31.4	89.4	0.61	1.53
1	33.6	75.8	0.85	1.82	30.7	86.9	0.68	1.63
2	—	—	—	—	30.3	85.2	0.99	2.14

Note: L_2 -Average error, L_∞ -Maximal error.

conclude that the obtained centerlines are reliable and accurate based on these quantitative results.

4.3.2 Overlap Evaluation

Moreover, the overlap measures between the obtained centerline and the ground truth centerline were compared using the online evaluation methodology and reference database [48]. Three different overlap measures are used to measure the overlap between the obtained centerline and the reference centerline, which are

overlap (OV), overlap until first error (OF) and overlap with clinically relevant part (OT). The scores are scaled so that 0 indicates complete failure, 50 is a normal result and 100 corresponds to a perfect result. Table 4.3 presents a comparison of three overlap measures between the present method and Van’s method for Vessel 0-3. The proposed method is shown to be more accurate and reliable with a 4.3% higher OV score compared with Van’s approach. In addition, the proposed method outperforms Van’s method in terms of average overlap measures (Figure 4.6).

Table 4.3: Computed three overlap measures between the obtained centerline and the ground truth centerline.

	Our Method						Van’s Method					
	OV		OF		OT		OV		OF		OT	
	%	Score	%	Score	%	Score	%	Score	%	Score	%	Score
Vessel 0	97.6	58.8	94.9	89.8	97.6	48.9	93.4	51.2	91.5	80.7	92.1	43.5
Vessel 1	99.4	95.5	93.6	64.3	98.6	49.7	95.7	85.2	90.2	61.3	92.9	41.1
Vessel 2	96.8	78.6	95.2	79.6	97.8	68.5	92.3	61.4	92.6	70.9	93.4	53.2
Vessel 3	98.2	69.4	96.3	85.7	96.2	58.4	94.1	64.5	92.8	79.5	91.8	49.6

Note: OV–Overlap, OF–Overlap until first error, OT–Overlap with clinically relevant part.

4.4 Results

The CT data provided in [125] were used in this study. Both the proposed and Van’s methods were applied on four different cardiac CTA datasets in DICOM format (Figure 4.7). The Hessian filter method proposed in [107] was used to segment the complete 3D digital coronary artery trees. Table 4.4 summarizes the size, resolution and computation time of each CTA dataset. The proposed method can reduce the average computation time by approximately 18.2%, which demonstrates its clinical potential and higher efficiency.

Figure 4.6: A comparison of average overlap measures between two centerlines.

Figure 4.8(a-d) gives the obtained centerlines of RCAs by both methods from 3D CTA image dataset 22, dataset 23, dataset 27 and dataset 29, respectively. It is observed that the extracted centerlines were continuous, complete and centrally located within the vessels. However, Van's centerlines were not thin enough at non-smooth locations (Figure 4.8(a), (b), (d)). This is because Van's speed image is based on distance field forms medial surfaces of constant travel costs for non-tubular structures. The obtained centerlines are therefore not ensured to be centrally located when the cross sections deviate too much from a circle. Moreover, Van's method sometimes produces some undesired small branches since it is sensitive to boundary noise (Figure 4.8(c)). The step size is selected as 0.01 for both methods to plot the results here. Van's method cannot guarantee that the skeleton points are extracted along the center of the vessel object. Besides, the backtrace procedure halts near the start point when the step size is too large. On the other hand, the proposed approach outperforms Van's method by applying a new speed image function. Even the step size is large, the proposed method can

Figure 4.7: Coronary CTA images. (a) Dataset 22. (b) Dataset 23. (c) Dataset 27. (d) Dataset 29.

compute smooth centerlines with high accuracy.

Moreover, the CTA lumen area based on the obtained centerline was computed to compare with the IVUS area, in order to demonstrate the accuracy of the centerline extraction algorithm. In this chapter, the CTA lumen areas were calculated following the method in [125], and the IVUS lumen areas provided in [125] were used as reference. Both Van's method and our method were applied to determine the centerline for each CTA dataset. Subsequent to centerline determination, cross sectional lumen contours and corresponding lumen areas can be evaluated. The obtained cross sectional lumen contours and the comparison

Table 4.4: Size, resolution and computation time of each dataset.

	Size	Resolution (mm ³)	Time (min)	
			Van's method	Our method
Dataset 22	512×512×211	0.283×0.283×0.700	28	23
Dataset 23	512×512×206	0.328×0.328×0.750	26	21
Dataset 27	512×512×54	0.391×0.391×2.000	21	17
Dataset 29	512×512×266	0.305×0.305×0.450	30	25

of lumen areas with IVUS lumen area are presented in Figure 4.9(a-d). Compared with the plots of areas obtained by Van's centerline method, the majority of our plots of areas are observed to be closer to IVUS area plots. It is also worth noting that almost all the plots of areas by Van's method are above those of our method. This is because if the computed skeleton point deviates too much from the real centerline point, the approximated tangent vector will shift from the real position. Therefore, the obtained lumen area is larger since the corresponding cross sectional lumen contour deviates from the circle.

4.5 Discussion

Although the centerline extraction approach presented in [91] has several advantages, some limitations do exist as well. First, the computational cost required for computing the distance field becomes increasingly large for large datasets. Second, the obtained centerlines for 3D non-tubular objects follow the shortest paths since distance field forms medial surfaces. In addition, the tracking process in Van's method is along the gradient descent direction only for small value of step size. Strong oscillations are present in the obtained centerlines when the step size increases.

In this study, the proposed speed image distinguishes from the one in Van's

Figure 4.8: A comparison of coronary artery centerline overlayed over the 3D rendering of RCA between our method (left panel) and Van's method (right panel). (a) Dataset 22. (b) Dataset 23. (c) Dataset 27. (d) Dataset 29.

Figure 4.9: Cross sectional lumen contours and the comparison of cross sectional lumen areas with IVUS area. (a) Dataset 22. (b) Dataset 23. (c) Dataset 27. (d) Dataset 29.

work, which integrates the magnitude of Gaussian gradient [126] of the vessel image to force the tracking process along the centerline. The new speed image has several advantages over the previous one. First, it is able to substantially reduce the processing time by using larger step size during the tracking procedure. Second, the new speed image employs a centerline strength function for the purpose of giving higher responses at central voxel positions. Therefore, the vessel centerline is guaranteed to be extracted along the medial axis of the vessel object.

4.6 Remarks

In this chapter, we developed and validated a new coronary centerline extraction approach. The proposed method proved to be efficient and accurate for the determination of centerline from cardiac CT images. There were several advantages of the proposed method with respect to Van's method. First, the tracking procedure was guaranteed along medial axis of the vessel, even for large step size. Moreover, the efficiency of our method was higher since a lower number of computations was required. Given the speed, accuracy and automation, this approach may garner wider clinical potential as a real-time coronary stenosis evaluation tool.

Part II

Cross Sectional Lumen Area Quantification

IVUS Validation of Cross Sectional Lumen Area

5.1 Introduction

Coronary artery stenosis is currently one of the major reasons of cardiovascular diseases. One of the aims of computational modeling of CAD is automated and accurate reconstruction of coronary arteries, which is used to quantify the potential stenosis [6, 31, 127, 128]. Currently, coronary artery stenosis can be evaluated by measuring longitudinal diameter reduction or by evaluating lumen reduction [3].

In clinical practice, the percentage stenosis is widely used to measure the severity of a coronary stenosis [4]. Unfortunately, it is a challenging task to accurately measure the focal minimum even for trained medical specialists, as it depends on the reference site and projection plane [1, 46]. Moreover, biased reference site selection significantly affects the resulting coronary artery stenosis value. Lumen area is less frequently evaluated for quantification of coronary artery stenosis at present. However, lumen area measurement is less dependent on reference site and viewing angle. Moreover, lumen area is directly related to coronary blood flow or myocardial perfusion assessment, and is therefore expected

to be more significant and more consistent [30].

In this chapter, an accurate, noninvasive and reproducible approach for quantification of CAD with limited user interaction is developed. To effectively quantify the cross sectional lumen area of coronary artery, a novel centerline extraction method is proposed, which can accurately reproduce the vessel axis sub-voxel level. After that, the CSLA along the centerline is calculated by the proposed approach and then validated by IVUS [125].

This chapter is organized as follow. Section 5.2 presents our method for coronary artery cross sectional lumen area measurement, which is described in three parts: segmentation, centerline extraction, cross sectional lumen area measurement. In Section 5.3, we show the results of our approach over the coronary CTA datasets from 4 patients, and validate the obtained cross sectional lumen area against IVUS. Conclusions are presented in Section 5.4.

5.2 Methodologies

5.2.1 Coronary Artery Segmentation

In this chapter, the whole coronary artery tree can be segmented from CTA data by using a connected components based segmentation technique. Frangi's vesselness filter is first used to segment coronary arteries in 3D CT images. After that, morphological operations are performed to extract all the remaining contrast filled structures within the heart. Then a threshold operation based on the intensities of coronary artery is conducted to create the binary representations of these structures. Finally, classical Marching Cubes algorithm [103] is used to reconstruct the 3D surface mesh of the vessel. More detailed information about the segmentation approach can be found in our previous work [107]. In this work, post-processing steps such as filling hole and surface smoothing are also performed to accurately determine the centerline.

5.2.2 Centerline Extraction

As already described in Section 4.2, we propose a fast and accurate approach for coronary centerline extraction with minimal user interaction, which uses the distance transform from the vessel boundaries to drive a fast marching propagation. First, a hybrid distance field function can be proposed as follows:

$$I_{distance} = \frac{(\frac{D}{maxD})^4}{(0.5 - |\nabla I|)^2} \quad (5.1)$$

where D is the distance field and $maxD$ is its global maximum value. ∇I is computed by convolving 3D vessel image I with $G'(x)$ along x , y and z directions. Then a new speed image [118] is proposed and given by:

$$\mathcal{F}(x) = \begin{cases} 0 & \text{if } I_{distance} = 0, \\ e^{\frac{D}{\tau * maxD}} & \text{if } I_{distance} > t, \\ e^{\frac{D}{maxD}} & \text{otherwise} \end{cases} \quad (5.2)$$

where t is the threshold value experimentally determined in the new medial function $I_{distance}$, and τ is the parameter.

Next, the largest distance value point in $D(x)$ is defined as the source point. Then a wave front is propagated from the source point using the speed image $\mathcal{F}$, which gives a modified distance map T . Second, the start point m_0 is selected as the point with maximum T value. Based on the time crossing map T , the first branch can be extracted by tracking discrete points along ∇T , which is the solution of the ordinary differential equation

$$\frac{dS}{dt} = f(t, S), \quad S(t_0) = m_0 \quad (5.3)$$

with

$$f(t, S) = -\frac{\nabla T}{|\nabla T|} \quad (5.4)$$

where $S(t)$ represents the centerline and m_0 denotes the furthest geodesic point.

The classical implicit Runge-Kutta method is chosen to solve (5.3) and defined as:

$$S_{n+1} = S_n + \sum_{i=1}^s b_i k_i \quad (5.5)$$

where

$$k_i = hf(t_n + c_i h, S_n + \sum_{j=1}^s a_{ij} k_j) \quad (5.6)$$

The theoretical guarantee of the proposed speed image and the backtrace procedure is examined in Section 4.2. This tracking procedure described above can be repeated to extract further branches which can form the entire centerline. The proposed method is able to guarantee that the entire centerline tree is connected.

5.2.3 3D Cross Sectional Lumen Area Measurement

Current cross sectional lumen areas are mainly computed on each single 2D slice at voxel level. Deconvolution is usually performed in order to provide more accurate edge feature. Besides, interpolation is required. In this chapter, provided the 3D segmentation result and connected centerline, lumen area can be automatically and accurately obtained from the geometrical aspects of vessel structures.

In order to analyze the coronary centerline, one skeleton point is defined as $\mathbf{P}_0 = (x_0, y_0, z_0)$. The tangent vector to the centerline at $\mathbf{P}_0$ can be calculated by one-sided or central finite difference approximation and denoted as $\mathbf{N} = (a, b, c)$. Assume $\mathbf{P} = (x, y, z)$ is any point in the normal plane at $\mathbf{P}_0$. This plane can be defined as:

$$a(x - x_0) + b(y - y_0) + c(z - z_0) = 0 \quad (5.7)$$

The intersection of this normal plane and the coronary artery surface will be a series of vertices forming a circular disk-like polygon. However, it is challenging to obtain accurate and complete cross sectional lumen contour for voxel-based shape representation in graphical practice. To improve the geometric accuracy, the mesh for the original 3D volumetric shape is generated. Based on the extracted centerline, cross sectional plane can be cut at each skeleton point over

the remeshed data instead of the voxelized data, eventually yielding a polygon contour which is formed by a set of boundary vertices. When cutting a set of vertices, V_i ($i = 1, 2, \dots, n$), at the skeleton point $\mathbf{P}_0$, the geometric centroid of this polygon formed by these vertices can be calculated and denoted by C . Besides, a set of n triangles that decompose the polygon can be constructed by connecting each pair of adjacent vertices and each vertex V_i to the centroid C . Based on the original CT images resolution, the 3D coordinates of each triangle can be computed and thus its area can be obtained. Therefore, the 3D cross sectional lumen area of this normal plane can be approximated by

$$\text{Area}(S) = \sum_{i=1}^n \text{Area}(T_i) \quad (5.8)$$

5.2.4 IVUS Validation

In this chapter, a total of 10 major coronary arteries (left anterior descending artery, LAD; left circumflex artery, LCX; and right coronary artery, RCA) with coronary lesions were scanned with CT [129]. The CT images were used to reconstruct 3D structure by our previous segmentation method. Then the image segmentation results were validated by IVUS [125], which provided the 2D cross sections along the centerline. The angiography data were saved as JPEG format while the CT and IVUS data were saved as DICOM format. To overlap the CT and IVUS data, the distance from the start frame to its nearest bifurcation location in angiography data is used to identify the landmarks.

In order to validate the lumen area obtained by our approach, we apply our segmentation method to segment RCA for dataset 22, 23, 27 and 29. After that, the corresponding centerline is extracted by the proposed method for each dataset. Subsequent to centerline extraction, cross sectional lumen planes are cut along the centerline based on the provided IVUS start and end frames. The step size of the centerline is manually adjusted in order to match the IVUS frame position, which generates reasonable comparison between the CSLA from CTA and IVUS. Percentage of error is defined as

$$\text{Percentage of error} = \left| \frac{\text{Area}_{\text{IVUS}} - \text{Area}_{\text{CT}}}{\text{Area}_{\text{IVUS}}} \right| \times 100\% \quad (5.9)$$

5.3 Results and Discussion

In this study, a connected components based coronary artery segmentation approach was applied into four cardiac CTA datasets acquired by a MDCT scanner with ECG gating in DICOM format. Morphometric data of 4 patient CT scans with 10 arteries from IVUS were reconstructed as the reference including the cross sectional lumen area, diameter and length. Moreover, the centerline and CSLA were explored by the proposed algorithm to evaluate the anatomic significance of coronary artery stenosis [46].

The coronary artery segmentation results, obtained centerlines and cross sectional lumen contours from four CTA datasets are shown in Figure 5.1(a-d), respectively. To obtain more reliable centerline and lumen geometry, post-processing steps such as smoothing and filling hole were performed. In addition, we present the centerline obtained by the proposed method overlayed over the 3D rendering of RCA for each dataset. It is observed that the obtained centerline is smooth and accurate at a sub-voxel level and can accurately reproduce the vessel axis. Moreover, we show an example of cross sectional lumen plane cutting for one segment of RCA for each dataset. Each cross sectional lumen contour is plotted in different color for easier visualization.

Table 5.1 presents the size, resolution and computation time of each DICOM image data. The average computational time per dataset is approximately 23.5 minutes, which demonstrates our method's clinical potential as a real-time cardiac assessment tool. In Figure 5.2(a-d) we present the obtained cross sectional lumen contours, angiography data, IVUS start frame and the comparison between CT and IVUS lumen area for each dataset. The IVUS start frame was used to identify landmarks to overlap the CT and IVUS data. The comparison of cross sectional

Figure 5.1: RCA segmentation results, obtained centerlines and cross sectional lumen contours. (a) dataset 22, (b) dataset 23, (c) dataset 27 and (d) dataset 29.

Table 5.1: Size, resolution and processing time of each dataset.

	Size	Resolution (mm ³)	Time (min)
Dataset 22	512×512×211	0.283×0.283×0.700	25
Dataset 23	512×512×206	0.328×0.328×0.750	23
Dataset 27	512×512×54	0.391×0.391×2.000	19
Dataset 29	512×512×266	0.305×0.305×0.450	27

Table 5.2: A comparison between CT and IVUS lumen area for each dataset.

	Lumen area (mm ²), mean $\pm$ SD	
	IVUS	CT
Dataset 22	4.579 $\pm$ 0.878	4.587 $\pm$ 0.864
Dataset 23	4.857 $\pm$ 0.292	4.802 $\pm$ 0.333
Dataset 27	7.152 $\pm$ 1.304	7.222 $\pm$ 1.311
Dataset 29	4.831 $\pm$ 0.805	4.838 $\pm$ 0.807

lumen areas between CT and IVUS for 4 CTA datasets are shown in Table 5.2.

We evaluated 1,950 cross-sections within 4 arteries of 4 patients. Correlation coefficients between CT and IVUS lumen area for 4 CTA datasets were, respectively, up to 0.99, 0.96, 0.99 and 0.95. Figure 5.3 shows scatterplots with regression line, and Bland-Altman plots and comparison of differences between areas measured with IVUS vs coronary CTA. The least square fit was given by $y = 1.01x - 0.07$ ($R = 0.993$). Bland-Altman analysis showed a systematic bias of lumen area overestimation by coronary CTA by 0.008 mm².

Table 5.3-5.6 present the comparison of cross sectional lumen area of five frames between CT area and IVUS area for dataset 22, 23, 27 and 29, respectively. The obtained centerline is resampled in order to match the given IVUS frame position. It can be seen that the percentage error of the method CSLA is not greater than 2% for each frame. In this study, we focused on direct validation of

Figure 5.2: Cross sectional lumen contours, angiography data, IVUS start frame and the comparison between CT and IVUS lumen area. (a) dataset 22, (b) dataset 23, (c) dataset 27 and (d) dataset 29.

Figure 5.3: Scatterplots with regression line, and Bland-Altman plots and comparison of differences between areas measured with coronary CTA vs IVUS for all 4 datasets.

CSLA and found the error to be $<20\%$ for all the segments of RCA. The average percent errors from all 4 segments of RCA were 1.7%, 2.1%, 1.9% and 3.6%, respectively.

Receiver-operating characteristic (ROC) curves showing the sensitivity and specificity of CT lumen areas given different IVUS cut-off areas (5 mm², 6 mm², 7 mm² and 8 mm², respectively) were compared (Figure 5.4). The obtained CT

Table 5.3: A comparison of cross sectional lumen area of five frames between CT area and IVUS area for dataset 22.

Frame	Position	IVUS area (mm ²)	CT area (mm ²)	Error (%)
1	0.05	5.032	4.962	1.379
2	0.1	5.001	4.969	0.648
3	0.15	5.001	4.975	0.521
4	0.2	5.059	4.981	1.545
5	0.25	5.080	4.988	1.817

Table 5.4: A comparison of cross sectional lumen area of five frames between CT area and IVUS area for dataset 23.

Frame	Position	IVUS area (mm ²)	CT area (mm ²)	Error (%)
1	0.05	5.520	5.502	0.327
2	0.1	5.525	5.506	0.334
3	0.15	5.529	5.510	0.340
4	0.2	5.533	5.514	0.346
5	0.25	5.526	5.518	0.131

Table 5.5: A comparison of cross sectional lumen area of five frames between CT area and IVUS area for dataset 27.

Frame	Position	IVUS area (mm ²)	CT area (mm ²)	Error (%)
1	0.017007	5.303	5.305	0.028
2	0.034014	5.281	5.313	0.602
3	0.05102	5.282	5.321	0.756
4	0.068027	5.281	5.329	0.910
5	0.085034	5.282	5.337	1.063

Table 5.6: A comparison of cross sectional lumen area of five frames between CT area and IVUS area for dataset 29.

Frame	Position	IVUS area (mm ²)	CT area (mm ²)	Error (%)
1	0.016611	5.994	5.903	1.515
2	0.033223	5.982	5.908	1.249
3	0.049834	5.982	5.913	1.165
4	0.066445	5.982	5.918	1.080
5	0.083056	5.982	5.923	0.995

Figure 5.4: Comparison of receiver-operating characteristic curve for CT lumen area given different IVUS cutoff areas.

areas showed a high diagnostic accuracy since the area under the curve (AUC) for each IVUS cut-off area is >0.99 .

In this study, the vessels were segmented directly from original CT images and converted into surface mesh. The centerlines were extracted by the proposed approach at sub-voxel level and found to accurately represent the medial axis. To improve the smoothness, filtering operations on both image and geometry domain are performed. One of the limitations is that the proposed cross sectional lumen area measurement algorithm can be performed only on a straight vessel branch without bifurcation. Therefore, manual operation is needed to remove branches from the target vessel of interest. It is noteworthy that this step of removing bifurcations in measurement of cross sectional area has little effect on the accuracy of the entire vessel. Subsequently, for every single branch, the centerline can be extracted and the quantitative assessment can be conducted. Since our proposed cross sectional area measurement algorithm is based directly on coronary artery surface mesh generation and centerline extraction, the quality of surface mesh

is important to the accuracy of the approach. In this work, we generate the triangular mesh for the segmented coronary artery surface. Denser coronary artery surface mesh can produce more nodes and elements of the triangular mesh, which can better approximate the original vessel contour. On the other hand, it leads to a higher computational cost.

5.4 Remarks

In this chapter, complete coronary artery trees were automatically segmented via connected components based method from CTA images. Based on the segmentation results, the corresponding centerlines were extracted using our proposed approach, which uses a new speed image to drive a fast marching propagation. The proposed 3D cross sectional lumen area measurement algorithm, which is based on centerline extraction and coronary artery surface mesh generation, was applied over morphometric data of 4 patients and was validated against IVUS. The accuracy and efficiency proved that our approach will be able to facilitate quantitative evaluation of the severity of coronary stenosis.

Quantification of Coronary Artery Cross Section Lumen Area with 3D Centerline-Centric Straightening

6.1 Introduction

As described in Chapter 5, it is a challenging task to accurately measure the focal minimum even for trained medical specialists, which depends on the reference site and projection plane [46]. Besides, biased reference site selection significantly affects the resulting coronary artery stenosis value. On the other hand, lumen area evaluation does not depend on reference site and viewing angle. In addition, lumen area measurement is expected to be more significant since it is directly related to coronary blood flow or myocardial perfusion assessment [30].

In this chapter, we develop an accurate, noninvasive and reproducible approach for quantitative analysis of CAD with limited user interaction. To effectively quantify the cross sectional lumen area of coronary artery, the concept of vessel straightening along its centerline is introduced and a new method for generating straightened segment of coronary artery is proposed. The method is able to evaluate coronary stenosis in a straightforward manner.

This chapter is organized as follow. Section 6.2 describes the method for generating straightened segment of coronary artery, which consists of three steps: centerline extraction, cross sectional lumen area measurement and 3D straightening. In Section 6.3, the result of the proposed approach over a coronary CTA dataset is presented. Conclusions are presented in Section 6.4.

6.2 Methodologies

6.2.1 Centerline Extraction

Numerous approaches have been developed for computing coronary artery centerlines, both from geometric and volumetric data. Many of them have shortcomings such that they are sensitive to boundary noise, depend on parameters and threshold values, require selection of seed points, or are computationally expensive. In Chapter 4, we develop a fast and accurate algorithm for coronary centerline extraction at subvoxel precision. To demonstrate the effect of centerline extraction techniques on lumen area, we employ an approach based on 3-subiteration thinning algorithm [84] for the purpose of comparison. A further smoothing and pruning operation at sub-voxel level is performed. The final centerline can be formed by connecting the set of discrete skeleton points with the minimum spanning tree algorithm. More detailed information about centerline extraction can be found in [107]. Both techniques are applied over the CTA dataset to extract the centerline.

6.2.2 3D Cross Sectional Lumen Area Measurement

In order to analyze the coronary centerline, one skeleton point is defined as $\mathbf{P}_0 = (x_0, y_0, z_0)$. The tangent vector to the centerline at $\mathbf{P}_0$ can be calculated by finite difference approximation and denoted as $\mathbf{N} = (a, b, c)$. Assume that $\mathbf{P} = (x, y, z)$

is any point in the normal plane at $\mathbf{P}_0$. This plane can be defined as:

$$\mathbf{N} \cdot (\mathbf{P} - \mathbf{P}_0) = 0 \quad (6.1)$$

The intersection of this plane and the coronary artery surface will be a set of vertices forming a circular disk-like polygon. However, cutting the normal plane over the segmented coronary arteries may not produce a complete circular disk-like polygon. This is because almost all the 3D skeletonization algorithms are performed in voxel-based domain. In order to obtain accurate and complete cross sectional profile at sub-voxel level, the mesh for the original 3D volumetric shape is generated. Based on the skeleton points extracted by thinning method, normal plane can be cut at each skeleton point over the remeshed data instead of the voxelized data, eventually yielding a circular disk-like polygon. When cutting a set of vertices, V_i ($i = 1, 2, \dots, n$), at one skeleton point, the geometric centroid of this polygon formed by these vertices can be calculated and denoted by C . Besides, a set of n triangles that decompose the polygon can be constructed by connecting each pair of adjacent vertices and each vertex V_i to the centroid C . Based on the original CT images resolution, the 3D coordinates of each triangle can be computed and thus its area can be obtained. Therefore, the 3D cross sectional lumen area of this normal plane can be approximated by

$$\text{Area}(S) = \sum_{i=1}^n \text{Area}(T_i) \quad (6.2)$$

6.2.3 3D Centerline-Centric Straightening

In this chapter, the vessel straightening technique is developed based on the concept of moving frame. Three different spaces are formally introduced [130]. Original image data, the centerline and the obtained normal planes are defined in the original physical space, $\mathcal{P}$. The vessel space $\mathcal{V}$ is constructed by the moving normal planes along the centerline. The straightened space $\mathcal{S}$ is produced by the vessel reformation, which is a Cartesian grid.

Assume there are $n+1$ evenly spaced skeleton points $\mathbf{p}_i^{\mathcal{P}}(0,0)$ in the $\mathcal{P}$ coordinates along the centerline, which divides the centerline into n segments of equal length. For each i , $0 \leq i \leq n$, the $\mathbf{u}\mathbf{v}\mathbf{n}$ basis $\mathbf{B}_i$ of the moving frame at $\mathbf{p}_i^{\mathcal{P}}(0,0)$ is given by

$$\mathbf{u} = \mathbf{b}_i, \mathbf{v} = \mathbf{n}_i, \mathbf{n} = \mathbf{t}_i \quad (6.3)$$

where $\mathbf{t}_i$ is the normalized tangent, $\mathbf{n}_i$ is the unit normal and $\mathbf{b}_i$ is the unit binormal. Moving frames can thus be calculated following the traditional Frenet-Serret frame [131], given the obtained centerline.

Definition 6.1. *Let C be a parametric curve with position vector $\mathbf{r}(s)$. The unit tangent vector $\mathbf{t}(s)$, the unit normal vector $\mathbf{n}(s)$ and the binormal vector $\mathbf{b}(s)$ are defined to be*

$$\mathbf{t}(s) = \frac{\mathbf{r}'(s)}{\|\mathbf{r}'(s)\|} \quad (6.4)$$

$$\mathbf{n}(s) = \frac{\mathbf{t}'(s)}{\|\mathbf{t}'(s)\|} \quad (6.5)$$

$$\mathbf{b}(s) = \mathbf{t}(s) \times \mathbf{n}(s) \quad (6.6)$$

It can be verified that $\mathbf{b}(s)$ is also a unit vector and perpendicular to both $\mathbf{t}(s)$ and $\mathbf{n}(s)$.

However, the Frenet-Serret frame is only applicable to twice continuously differentiable curves. To solve this issue, Daae Lampe *et al.* [132] applied a constant up vector $\mathbf{u}$ and defined a new binormal and normal as follows:

$$\mathbf{b}_m(s) = \frac{\mathbf{u} \times \mathbf{t}(s)}{\|\mathbf{u} \times \mathbf{t}(s)\|} \quad \text{and} \quad \mathbf{n}_m(s) = \mathbf{t}(s) \times \mathbf{b}_m(s) \quad (6.7)$$

It is noted that when the tangent is parallel to $\mathbf{u}$, this technique is not applicable any more. When $\mathbf{t}(s) \parallel \mathbf{u}$, the cross product $\mathbf{u} \times \mathbf{t}(s)$ is zero. This technique can be extended by using a user-specified up vector $\mathbf{u}$ only at those points where the tangent is not parallel to $\mathbf{u}$ and using the normal in the previous position to compute the binormal for those points where $\mathbf{t}(s) \parallel \mathbf{u}$.

The vessel grid of resolution t and radius r can be generated by using this normal plane, which induces space $\mathcal{V}$. The grid points around each $\mathbf{p}_i^{\mathcal{P}}(0, 0)$ lying in the normal plane $\mathbf{P}_i$ can be defined as

$$\forall x, y \in \mathbb{Z} : -t \leq x, y \leq t, \mathbf{p}_i^{\mathcal{P}}(x, y) = \mathbf{p}_i^{\mathcal{P}}(0, 0) + \frac{r}{t}x\mathbf{b}_i + \frac{r}{t}y\mathbf{n}_i \quad (6.8)$$

Based on (6.8), a mapping from $\mathcal{P}$ to $\mathcal{S}$ of a point $[x, y, z]_i^{\mathcal{P}}$ lying on plane $\mathbf{P}_i$ is given by

$$[x, y, i]^{\mathcal{S}} = \mathbf{B}_i^{-1}([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0)) + [0, 0, i] \quad (6.9)$$

Equation (6.9) can be induced as follows:

$$\begin{aligned} [x, y, i]^{\mathcal{S}} &= \mathbf{B}_i^{-1}([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0)) + [0, 0, i] \\ &= \begin{bmatrix} \mathbf{b}_i & \mathbf{n}_i & \mathbf{t}_i \end{bmatrix}^{-1} ([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0)) + [0, 0, i] \\ &= \begin{bmatrix} \mathbf{b}_i & \mathbf{n}_i & \mathbf{t}_i \end{bmatrix}^T ([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0)) + [0, 0, i] \\ &= \begin{bmatrix} \mathbf{b}_i \\ \mathbf{n}_i \\ \mathbf{t}_i \end{bmatrix} ([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0)) + [0, 0, i] \\ &= [x', y', 0] + [0, 0, i] \\ &= [x', y', i] \end{aligned} \quad (6.10)$$

where $x' = \mathbf{b}_i([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0))$ and $y' = \mathbf{n}_i([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0, 0))$. The basis matrix $\mathbf{B}_i$ can be treated as the columns $(\mathbf{u}|\mathbf{v}|\mathbf{n})$, which is in fact $(\mathbf{b}_i|\mathbf{n}_i|\mathbf{t}_i)$. The columns of this matrix are mutually perpendicular unit vectors: an orthonormal basis of $\mathbf{R}^3$. The transpose of $\mathbf{B}_i$ is therefore equivalent to the inverse of $\mathbf{B}_i$. The third component is i since $\mathbf{t}_i$ is the unit tangent vector to the centerline, which is perpendicular to any vector lying in the normal plane $\mathbf{P}_i$. The basis matrix is calculated using finite difference approximation given the discrete skeleton points.

Moreover, (6.8) defines a mapping from $\mathcal{S}$ to $\mathcal{P}$, $f : \mathcal{S} \rightarrow \mathcal{P}$ as

$$f(x, y, i) = \mathbf{p}_i^{\mathcal{P}}(0, 0) + x\mathbf{b}_i + y\mathbf{n}_i \quad (6.11)$$

It can be shown that this transformation is able to preserve distances orthogonally out from the center. Consider two points $\mathbf{p}_1, \mathbf{p}_2$ in the i -th orthogonal plane in reformed volume, $\mathbf{p}_1$ can be decomposed to $[x_1, y_1, i]$ and $\mathbf{p}_2$ can be decomposed to $[x_2, y_2, i]$, then the distance in $\mathcal{P}$ is

$$\begin{aligned} \|f(\mathbf{p}_2) - f(\mathbf{p}_1)\| &= \|(\mathbf{p}_i^{\mathcal{P}}(0, 0) + x_1 \mathbf{b}_i + y_1 \mathbf{n}_i) \\ &\quad - (\mathbf{p}_i^{\mathcal{P}}(0, 0) + x_2 \mathbf{b}_i + y_2 \mathbf{n}_i)\| \\ &= \|(x_2 + y_2) - (x_1 + y_1)\| \end{aligned} \quad (6.12)$$

since two points ($\mathbf{p}_1$ and $\mathbf{p}_2$) share their i component, and $\mathbf{b}_i$ and $\mathbf{n}_i$ are constants for each normal plane. On the other hand, the distance in $\mathcal{S}$ is

$$\begin{aligned} \|\mathbf{p}_2 - \mathbf{p}_1\| &= \|[x_1, y_1, i] - [x_2, y_2, i]\| \\ &= \|(x_2 + y_2) - (x_1 + y_1)\| \end{aligned} \quad (6.13)$$

Therefore, two distances can be trivially reduced to the same term.

From (6.11) it follows that the Z plane denoted by i in space $\mathcal{S}$ equals to a plane in space $\mathcal{P}$ defined by the skeleton point $\mathbf{p}_i^{\mathcal{P}}(0, 0)$ and the tangent vector $\mathbf{t}_i$. We utilize this planar coherence to create a fast implementation of curve-centric straightening by slice-by-slice-based integration along the centerline. It is worth noting that no smoothing is performed to the curve's position since these positions are strictly enforced as the center of the resulting volume.

6.2.4 Modified Centerline-Centric Straightening

In this part, the centerline is also obtained by connecting a sequence of discrete skeleton points at subvoxel level, which is not assumed to be of equal length for each segment. Without loss of generality, we assume that the 0-th and n -th skeleton points are located at two end points of the coronary artery segment. Let L denote the total arc-length of the centerline. As we are dealing with discrete skeleton points, the arc-length parameter s defines a mapping from the set $[0, 1, \dots, n]$ to a set of distances of arc-length in $[0, L]$, $g : [0, 1, \dots, n] \rightarrow [0, L]$, as

$$s_i = \sum_{j=0}^{i-1} \|\mathbf{p}_j^{\mathcal{P}}(0,0) - \mathbf{p}_{j+1}^{\mathcal{P}}(0,0)\| \quad \text{for } i = 1, 2, \dots, n \quad (6.14)$$

here the norm is defined by Euclidean distance. At the two end points of the centerline, we have

$$s_0 = 0 \quad \text{and} \quad s_n = L \quad (6.15)$$

Therefore, the slice offset Δ_i in the reformed space can be obtained by calculating the distance from point $\mathbf{p}_i^{\mathcal{P}}(0,0)$ to $\mathbf{p}_{i+1}^{\mathcal{P}}(0,0)$

$$\Delta_i = \|\mathbf{p}_i^{\mathcal{P}}(0,0) - \mathbf{p}_{i+1}^{\mathcal{P}}(0,0)\| \quad (6.16)$$

Now the mapping from $\mathcal{P}$ to $\mathcal{S}$ of a point $[x, y, z]_i^{\mathcal{P}}$ lying on the normal plane $\mathbf{P}_i$ is defined as follows:

$$[x, y, s_i]^{\mathcal{S}} = \mathbf{B}_i^{-1}([x, y, z]_i^{\mathcal{P}} - \mathbf{p}_i^{\mathcal{P}}(0,0)) + [0, 0, s_i] \quad (6.17)$$

And the mapping from $\mathcal{S}$ to $\mathcal{P}$, $f : \mathcal{S} \rightarrow \mathcal{P}$ is extended to

$$\begin{aligned} f(x, y, s_i) &= \mathbf{p}_i^{\mathcal{P}}(0,0) + x\mathbf{b}_i + y\mathbf{n}_i \\ &= r(s_i) + x\mathbf{b}_i + y\mathbf{n}_i, \quad \text{for } s \in [0, L] \end{aligned} \quad (6.18)$$

Based on the present centerline extraction and cross sectional planes cutting technique, a sequence of simple closed lumen contours can be obtained, each of which is formed by a set of discrete boundary points in $\mathcal{P}$. In this study, we can perform a resampling operation on these contours. Assume each contour C_i consists of the same number of boundary points, denoted as m . Then the set of contour points can be denoted as $\{(x_1, y_1), (x_2, y_2), \dots, (x_m, y_m)\}$. Based on 6.18, a new boundary approximation can be suggested. For each cross sectional plane $\mathbf{P}_i$, we have the set of contour points $\{C_1, C_2, \dots, C_m\}$ and another discrete set of skeleton points along the centerline $\{r(s_1), r(s_2), \dots, r(s_n)\}$, and then compute the Frenet frame at $r(s_i)$, say $(\mathbf{b}_i, \mathbf{n}_i, \mathbf{t}_i), i = 1, 2, \dots, n$. Then the points

$$\{r(s_i) + x_j\mathbf{b}_i + y_j\mathbf{n}_i \mid i = 1, 2, \dots, n; j = 1, 2, \dots, m\} \quad (6.19)$$

constitute a grid which can be used to define bicubic patches or to create an approximation boundary of triangles.

Besides distance preservation, arc length is still can be preserved following the modified transformation (6.18). Consider two skeleton points $\mathbf{q}_1$, $\mathbf{q}_2$ in the z_1 -th and z_2 -th orthogonal plane in reformed volume $\mathcal{S}$ ($z_1 < z_2$), $\mathbf{q}_1$ can be decomposed to $[0, 0, z_1]$ and $\mathbf{p}_2$ can be decomposed to $[0, 0, z_1]$, then the distance of arc length from z_1 to z_2 in $\mathcal{S}$ is $z_2 - z_1$. On the other hand, these two skeleton points $\mathbf{q}_1$, $\mathbf{q}_2$ in reformed volume $\mathcal{S}$ can be transformed back to space $\mathcal{P}$, based on (6.18)

$$f(0, 0, z_1) = r(z_1) \quad (6.20)$$

$$f(0, 0, z_2) = r(z_2) \quad (6.21)$$

Thus the distance of arc length from z_1 to z_2 in $\mathcal{P}$ is also $z_2 - z_1$. Figure 6.1 illustrates a 2D example of this property.

Figure 6.1: An example of arc-length preservation in 2D. Two points in space $\mathcal{S}$, $[0, 0, z_1]$ and $[0, 0, z_2]$, can be transformed to $r(z_1)$ and $r(z_2)$, respectively, in space $\mathcal{P}$. The distance of arc-length is $z_2 - z_1$ for both spaces.

6.3 Experimental Results

In this study, a 3-subiteration thinning method with smoothing and pruning operation at sub-voxel level was performed into a cardiac CTA dataset in DICOM format to determine the coronary artery centerline. The data size was $512 \times 512 \times 560$, and the resolution was $0.427\text{mm} \times 0.427\text{mm} \times 0.25\text{mm}$. Frangi's vesselness filter was first used to detect coronary arteries. Next morphological operations were conducted over the filtered vessels to extract the coronary artery tree based on the intensities of coronary artery. Additionally, the curve-skeleton and cross sectional lumen area were explored to quantify coronary artery stenosis [46].

Figure 6.2(a) gives the obtained segment of LAD in physical space. Figure 6.2(b) depicts the skeleton points obtained by using the 3-subiteration thinning algorithm with smoothing and pruning operation at sub-voxel. Connecting them by minimum spanning tree algorithm produces a set of segments. Besides, a bounding tube object can be constructed by the moving frame with same radius along the centerline. Figure 6.2(c) shows the lumen contours and the generated curvilinear grid. Finally, the straightened space $\mathcal{S}$ can be defined by the curvilinear grid points expressed with respect to their basis $\mathbf{B}_i$. The lesion site and the proximal reference site (two arrows) can be found in Figure 6.2(c). The area stenosis is therefore given by $(Area_{ref} - Area_{les})/Area_{ref} * 100\%$.

In Table 6.1 we summarize the different method combinations for quantitative evaluation of coronary area stenosis. Group 1 was formed by combining connected components based segmentation, surface smoothing, fast marching based centerline extraction, and cross sectional plane cutting by using central finite difference, which gave the best visual results of the centerline and lumen contour. Besides, the remaining four groups of CSLA were sampled by changing only one factor and keeping the other factors fixed compared to Group 1. The cross sectional lumen profile trends along the branch for five different groups of data are presented in Figure 6.3. At almost all the skeleton points, Group 2 is found to produce larger

Figure 6.2: (a) Segment of LAD. (b) Obtained centerline by 3-subiteration thinning method. (c) Obtained lumen contours and selection of lesion and reference sites.

CSLA. This can be explained that the centerline and the cross sectional plane are explored over the coronary artery surface mesh without smoothing. In addition, Group 5 is observed to have the CSLA with larger oscillation since one-sided finite difference approximation of tangent vector is less reliable and accurate.

Five 3D lumen contours defined in original space $\mathcal{P}$ coordinates are displayed in Figure 6.4(a). The corresponding reformed 3D contours produced by centerline-centric reformation are given in Figure 6.4(b). Table 6.2 summarizes a comparison of the obtained proximal area, minimal area and area stenosis between five groups. It can be observed that Group 2 overestimates the cross sectional lumen areas at both reference site and lesion site, but with larger proportion at lesion site (Figure 6.3). As a result, the area stenosis is underestimated. Besides,

Table 6.1: Different method combinations for CSLA evaluation.

	Segmentation		Smoothing		Centerline		Cutting	
	Original	Denser	Yes	No	Thinning	FM	One-Sided	Central
Group 1	✓		✓			✓		✓
Group 2	✓			✓		✓		✓
Group 3	✓		✓		✓			✓
Group 4		✓	✓			✓		✓
Group 5	✓		✓			✓	✓	

Note: CSLA–Cross sectional lumen area, FM–Fast marching method.

Figure 6.3: A comparison of cross sectional profile along the segment of LAD.

Group 5 overestimates the area stenosis since larger CSLA at reference site is obtained due to the gradient vector approximation by one-sided finite difference. Table 6.3 was obtained by repeating exactly the same procedure as in Table 6.2. Area stenosis in Group 1 has the least intra-observer variation. Group 4 also has small intra-observer variation but it underestimates the area stenosis.

Figure 6.5 shows the obtained lumen contours for different groups at the same

Figure 6.4: Centerline-centric reformation. (a) Original cross sectional contours at five landmark skeleton points. (b) Corresponding centerline-centric reformed contours.

Table 6.2: Proximal area, minimal area, and area stenosis.

Cross Sectional Lumen Area - 1st time			
	Area _{pro} (mm ²)	Area _{min} (mm ²)	Area stenosis
Group 1	4.8646	3.0396	37.5%
Group 2	5.3313	3.6099	32.3%
Group 3	4.9645	3.1357	36.8%
Group 4	4.9137	3.3401	32.0%
Group 5	5.6540	3.0753	45.6%

Note: Area_{pro}—Proximal area, Area_{min}—Minimal area.

lesion site. It is noted that the geometric shape of the lumen contour at lesion site for Group 5 is totally changed. In addition, due to the fact that the obtained centerline at voxel level may change the approximated tangent vector, the lumen contour of Group 3 is shifted. In Figure 6.6 we plot the straightened segments of LAD for different groups near the lesion site. Group 2 and 4 are found to give less reliable straightened segments and may cause inaccurate severity of coronary

Table 6.3: Proximal area, minimal area, and area stenosis.

Cross Sectional Lumen Area - 2nd time			
	Area _{pro} (mm ²)	Area _{min} (mm ²)	Area stenosis
Group 1	4.9483	3.0727	37.9%
Group 2	5.6254	3.7170	33.9%
Group 3	5.2441	3.5436	32.4%
Group 4	5.3800	3.6061	32.9%
Group 5	6.2047	3.0704	50.5%

Note: Area_{pro}—Proximal area, Area_{min}—Minimal area.

Figure 6.5: A comparison of lumen contours at lesion site.

artery stenosis.

6.4 Remarks

In this chapter, we developed a new approach for coronary stenosis evaluation based on area stenosis index. This approach includes original coronary artery segmentation, surface smoothing, fast marching (FM) method and central cutting. The application on real patient data demonstrates that the proposed approach carries very minimal intra-observer variation in time-efficient manner. However, investigation on larger population is necessary before making a final conclusion.

Figure 6.6: A comparison of straightened segments at lesion site. (a) Group 1. (b) Group 2. (c) Group 3. (d) Group 4. (e) Group 5.

This approach holds potential for downstream computational fluid dynamics analysis of coronary flow simulation in clinical bedside.

Conclusions and Future Work

In this chapter, we give a summary of the works done in this thesis and explore some relevant topics for further investigation.

7.1 Conclusions

In this thesis, three challenging issues regarding coronary artery stenosis quantification are addressed within a unique framework. The effectiveness of the framework, i.e. quantitative analysis of coronary CTA, is justified in Chapter 2.

- (i) In Chapter 3, the coronary artery segmentation problem is discussed. An automatic coronary artery segmentation approach based on Hessian filter and connected components is proposed. Furthermore, the method is extended by hybridizing with graph-cut method, for the purpose of segmenting small vessels from CTA images of low contrast.
- (ii) In Chapter 4, the coronary artery centerline extraction problem is discussed. The main idea is to use a time-crossing map to drive a front propagation from a source point until the other node is reached, and a backtracking procedure can be used to extract the centerline. In the first step, the fast marching method is applied to compute the time-crossing map based on a

new speed image function. In the second step, a branch tracking procedure based on the Runge-Kutta method is performed. The proposed method is able to achieve high accuracy even with large step size, which reduces the computational time dramatically.

- (iii) In Chapter 5, the coronary artery cross sectional lumen area measurement problem is addressed. The proposed algorithm is based on centerline extraction and coronary artery surface mesh generation. The approach is applied over morphometric data of real patients and the accuracy of the obtained CSLA is validated against IVUS.
- (iv) In Chapter 6, a novel approach for coronary lumen area evaluation with 3D centerline-centric straightening method is developed. Differences of area stenosis in a human patient with suspected CAD are tested by varying the combination of methods.

In this thesis, the proposed coronary artery stenosis quantification methodology is shown to be able to quantitatively evaluate the severity of coronary stenosis. Compared with the existing methods, the advantages and disadvantages of our methods are summarized as follows.

- (i) Automatic. The proposed approaches for centerline extraction and lumen area measurement are highly automatic and with minimal user interaction.
- (ii) Robustness. From the aspect of robustness of segmentation, our current method is as good as differential measures, but segments less small vessels than deformable models for CTA images of low quality. Our centerline extraction approach outperforms existing methods by applying a new speed image function that is based on the distance map and integrates the magnitude of Gaussian gradient of the vessel image.
- (iii) Efficiency. The proposed segmentation method performs as fast as other

differential measures, and slightly faster than deformable models. Our centerline extraction method is much faster than existing fast marching based method since a new speed image function is applied, which allows to use larger step size, and at the same time, achieve high accuracy. The last step of coronary artery stenosis evaluation, coronary lumen area measurement, is fully automatic and much efficient compared to manual measurement in current clinical practice.

7.2 Future works

We explore some relevant topics for further investigation in this section. In the following, some directions of future researches on quantification of coronary artery stenosis are provided.

- (i) In Chapter 3, the Hessian filter based approach is used to segment complete coronary artery tree. One of the future works is to develop some automatic 3D segmentation techniques, e.g., multiple hypothesis tracking algorithm, for coronary artery segmentation. Moreover, knowledge-based 3D segmentation, such as region probability or region classification, will be another research topic in the future.
- (ii) In Chapter 4, the coronary artery centerline is extracted by fast marching method. The tracking procedure was performed on distance transform based time-crossing map. It is quite generic to integrate the vesselness measure or gradient vector flow with current time-crossing map. These could be explored as well in the future.
- (iii) In Chapter 5, the proposed lumen area measurement algorithm was performed on straight branch without bifurcations. In the future, the proposed approach will be improved for the purpose of measuring branch with bifurcations by exploring balloon and knowledge about the body shape.

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List of Publications

Journal paper

- (i) H.F. Cui, D.S. Wang, M. Wan, J.M. Zhang, X.D. Zhao, R.S. Tan, W.M. Huang, W. Xiong, Y.P. Duan, J.Y. Zhou, T. Luo, G.S. Kassab and L. Zhong. Fast Marching and Runge-Kutta Based Method for Centreline Extraction of Right Coronary Artery in Human Patients. *Cardiovascular Engineering and Technology*, 7(2), 159-169, 2016.

Conference paper

- (i) H.F. Cui, D.S. Wang, M. Wan, J.M. Zhang, X.D. Zhao, S.Y. Tan, , A.S.L. Wong, R.S. Tan, W.M. Huang, W. Xiong, Y.P. Duan, J.Y. Zhou and L. Zhong, 2014, December. Coronary artery segmentation via Hessian filter and curve-skeleton extraction. In Biomedical Engineering and Sciences (IECBES), 2014 IEEE Conference on (pp. 93-98). IEEE.
- (ii) H.F. Cui, D.S. Wang, M. Wan, J.M. Zhang, X.D. Zhao, S.Y. Tan, , A.S.L. Wong, R.S. Tan, W.M. Huang, W. Xiong, Y.P. Duan, J.Y. Zhou, Y.L. Chi and L. Zhong, 2015, December. Quantification of Coronary Artery Cross Section Lumen Area and Area Stenosis with 3D Centerline-Centric Straightening. In International Conference for Innovation in Biomedical Engineering and Life Sciences (pp. 306-309). Springer Singapore.

Paper in progress

- (i) H.F. Cui, D.S. Wang, M. Wan, J.M. Zhang, X.D. Zhao, R.S. Tan, W.M. Huang, W. Xiong, Y.P. Duan, J.Y. Zhou, T. Luo, G.S. Kassab and L. Zhong. Validation of Right Coronary Artery Lumen Area from Cardiac Computed Tomography against IVUS. *Medical Physics*, 2016.

- (ii) H.F. Cui, D.S. Wang, M. Wan, J.M. Zhang, X.D. Zhao, R.S. Tan, W.M. Huang, W. Xiong, Y.P. Duan, J.Y. Zhou, T. Luo, G.S. Kassab and L. Zhong. Coronary Arteries' Curve-skeleton extraction and Cross-sectional lumen area measurement from CT angiography images, for severity assessment of Coronary stenosis. *Journal of Mechanics in Medicine and Biology*, 2016.