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Development of an image-based model for capillary vasculature of retina

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ABSTRACT

The paper presents a method of development of a detailed network model to represent retinal capillary vasculature. The capillary model is a circular mesh consisting of concentric rings with an increasing diameter. Each of the rings has uniformly distributed bifurcation nodes to represent capillary vessels. The model is customized using the data that has been measured from confocal microscopic images of a mouse retina. The capillary model developed can be connected to networks of larger vessels of the vasculature such as arterial and venous networks to form a complete model of the retinal network. A method to automate such interface connections between capillary and other vascular networks using connecting vessels (i.e., pre-capillary and post-capillary) is also presented in the paper. Such a detailed image-based capillary model together with the arterial and venular networks can be used for various circulation simulations to obtain accurate information on hemodynamic quantities such as the spatial distribution of pressure and flow in the vasculature for both physiological and pathological conditions. The method presented for the development of the capillary model can also be adopted for vasculatures of other organs.

1. Introduction

The growing need to understand the relationship between the hemodynamic parameters in microcirculatory network during the progression of pathological conditions has enhanced the importance of detailed and anatomically based network analysis. One of the basic requirements is the understanding of the pressure and flow distribution in the microvasculature network [1–6]. As a main component of microvasculature, the capillaries are the main location where the transport of nutrients between blood and tissue takes place. Capillary vessels are also the first to be affected during the progression of a disease and circulation changes in these vessels are immediately sensed by pre-capillary vessels (i.e., arterioles) and post-capillary vessel (i.e., venules). Therefore, a detailed and flexible capillary model describing the specific capillary structure in question should prove useful for the accurate prediction of circulations in a complete network of a microvasculature including arterial and venous networks.

A relatively good understanding of the retinal anatomy and vascular network has been developed through extensive studies using staining and perfusion techniques to reveal the vasculature [7–17]. The structure of retinal vasculature can be described using three distinct layers, namely the superficial layer, the intermediate layer, and the deep layer. The superficial layer is close to the vitreous side and the deep layer is close to the photoreceptor side. The larger vessels such as arteries, arteriolar branches and veins lay in the superficial layer, whereas plexus of capillaries is distributed in the inter-

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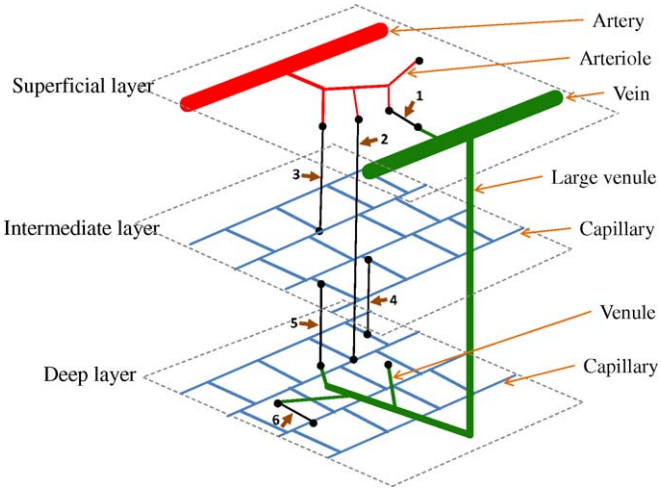

Fig. 1 – Schematic presentation of the vascular distribution of the retina. Arrows and numerals show the various types of connecting vessels.

mediate layer and the deep layer. Venular branches, located in the deep layer, move transversely to connect the veins in the superficial layer. The pre-capillary arterioles and post-capillary venules link capillaries to larger vessels. Fig. 1 shows a simplified schematic presentation of the structure of retinal vasculature.

The understanding of retinal vascular circulation has significantly benefited from invasive and non-invasive optical measurement techniques and digital imaging, which have provided quantitative information on retinal hemodynamics for both normal and pathological conditions. Examples include the use of dye dilution technique (DDT) to determine mean transit time of blood cells through the retinal network [18] and the measurement of the movement of florescent stained blood cells to quantify velocities of blood cells [15,16]. In addition, bidirectional laser Doppler velocimetry has been used to measure the centerline velocity from which the mean flow rate has been estimated [19,20]. The developments in computing and image processing have also enabled the development of automated measurements and monitoring of the vascular network especially large retinal blood vessels. Examples include online and continuous measurement of retinal vessel diameters by the developed retinal vessel analyser (RVA) [21].

Notwithstanding the aforementioned development in the understanding of the topology and circulation of retinal vasculature, there is a lack of modelling studies of retinal vascular and circulation in literature. We have recently carried out a detailed vascular and circulation modelling study of a mouse retina and presented the hemodynamic details such as pressure and velocity in the retinal vasculature in Ganesan et al. [17,22]. The focus of the current paper is to describe in detail the methodology of the model of capillary network developed in the study which has enabled a good prediction of the retinal microvascular circulation. The method developed combines methodology and modelling techniques which have been previously developed and used for other organs such as pulmonary and coronary vasculatures, in which detailed studies on capillary vasculature and the development of anatomically based capillary models have been carried out [23–25].

The primary objective of this paper is to describe a method for the development of an image-based capillary model of retinal vasculature for detailed circulation simulations of the retinal microvascular network. The secondary objective is to propose an automated method to connect the capillary model developed to arterioles (i.e., pre-capillary feeding vessels) and venules (i.e., post-capillary draining vessels) using connecting vessels. Confocal microscopic images of a mouse retina prepared using a flat-mount technique will be used. The methodology presented can also be adopted for the development of capillary vasculatures of other organs.

2. The retinal vasculature and its modelling

2.1. *Morphology and topology of retinal vasculature of a mouse retina*

Confocal images of retinal flatmounts of three healthy female C57BL/6 mice have been prepared as described in Ganesan et al. [17]. The method of the animal preparation for confocal microscopy (LSM510 META, Carl Zeiss) has been described in detail in that paper. Images of a single mouse retina have been the main source of the morphometric data collection. The images of other mice have been used to further improve our understanding about the distribution of the vasculature and for the purpose of comparison. Following the conventional terminology, the retina is classified into three main regions, namely the pre-equator (closer to the optic disc), the equator (middle) and the periphery (near to the outer edge of the retina).

Fig. 2 shows topological images of a single mouse retinal vasculature obtained, which have been used as the basis of the development of a detail network representing mouse retina. The retina contains six arteries and six veins which are labelled as A1 to A6 and V1 to V6, respectively. The mainstream vessels which run from the optic disc to the periphery are referred to as artery and vein and vessels that branches out from the mainstream vessels are referred to as arteriole and venule, respectively, in this study. Fig. 2a and b are images of the superficial and deep layers of the network topology of the mouse retina. The retinal arteries and veins are sequentially distributed around the optic disc (in the centre) and they are distinguished based on the branching pattern and the size of the vessels. Basically, arteries give rise to side-arm branches, which then, progressively divide into dichotomous branches of arterioles. Arterioles form a 'non-uniform delivering type' of branching pattern and give rise to capillaries (Fig. 2d). As in arteries, side-arm branches also arise from veins and give rise to venule branches. Unlike arterioles, venules are more likely to have a 'conveying type' branching pattern (Fig. 2e). Fewer numbers of arteriolar and venular branches have been observed at the pre-equator region (near the optic disc) of the retina.

As described previously, the vascular distribution in the mouse retina layer is tri-dimensional with a superficial layer, an intermediate layer and a deep layer overlain on top of each other. Blood flow of the arterioles in the superficial layer is