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Integrated geometric and mechanical analysis of an image-based lymphatic valve

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ABSTRACT

Lymphatic valves facilitate the lymphatic system's role in maintaining fluid homeostasis. Malformed valves are found in several forms of primary lymphœdema, resulting in incurable swelling of the tissues and immune dysfunction. Their experimental study is complicated by their small size and operation in low pressure and low Reynolds number environments. Mathematical models of these structures can give insight and complement experimentation. In this work, we present the first valve geometry reconstructed from confocal imagery and used in the construction of a subject-specific model in a closing mode. A framework is proposed whereby an image is converted into a valve model. An FEA study was performed to identify the significance of the shear modulus, the consequences of smoothing the leaflet surface and the effect of wall motion on valve behaviour. Smoothing is inherent to any analysis from imagery. The nature of the image, segmentation and meshing all cause attenuation of high-frequency features. Smoothing not only causes loss of surface area but also the loss of high-frequency geometric features which may reduce stiffness. This work aimed to consider these effects and inform studies by taking a manual reconstruction and through manifold harmonic analysis, attenuating higher frequency features to replicate lower resolution images or lower degree-of-freedom reconstructions. In conclusion, two metrics were considered: trans-valvular pressure required to close the valve, ΔP_c, and the retrograde volume displacement after closure. The higher ΔP_c, the greater the volume of lymph that will pass through the valve during closure. Retrograde volume displacement after closure gives a metric of compliance of the valve and for the quality of the valve seal. In the case of the image-specific reconstructed valve, removing features with a wavelength longer than four μm caused changes in ΔP_c. Varying the shear modulus from 10 kPa to 60 kPa caused a 3.85-fold increase in the retrograde volume displaced. The inclusion of a non-rigid wall caused ΔP_c to increase from 1.56 to 2.52 cmH_2O.

1. Background

The lymphatic system is responsible for maintaining fluid balance within the tissues (Carola et al., 1990). The collecting lymphatics drain fluid from the interstitial tissues, transport this fluid through valved contractile tubular structures - called lymphangions - before emptying into the venous system (Alitalo, 2011). The valve behaviour is poorly understood and essential for efficient fluid transport against gravity. Insufficient transport can lead to lymphœdema, i.e. inflammation and an accumulation of lymph fluid in the tissues. This results in swelling leading to fibrous tissue formation and compromised immune function (Penzer, 2003; Bellini and Hennekam, 2014). Several authors have commented on the potential benefit of a lumped model of the lymphatic system and attempts to that end have been made (Margaris and Black, 2012; Rahbar and Moore, 2011; Macdonald, 2008). Sensitivity analysis of lumped models has revealed that valve resistance is a determinant of lymphatic pumping function (Jamalian et al., 2013) as is the trans-valvular pressure required to close the valves (Bertram et al., 2013).

As far as the authors are aware no numerical analysis greater than 1-D has been performed to study lymphatic valve closure. A finite volume approach to flow around a 2-D valve has been considered (Macdonald, 2008). Studies have looked at the opening

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behaviour of three-dimensional parametric valves through mixed finite element and finite volume methods (Wilson et al., 2015).

However, reconstruction from confocal imagery (Rahbar et al., 2012) reveals geometric features on the valve that have not been included in previous parametric models (Wilson et al., 2015). Reconstruction, spectral analysis and finite element analysis of these structures may elucidate their role and allow their inclusion in parametric models. Manifold harmonic analysis of triangulations is analogous to Fourier analysis in signal processing, as it allows a controlled removal of features, that is not possible in other smoothing algorithms.

Confocal scans allow for a geometric characterisation of lymphatic valves. This information can be used as a basis for building idealised models, which are well-suited for parametric studies to elucidate a representative valve behaviour with the construction of a lumped model of the lymphatic system as a final goal. This process is intensive, and an idealised representative model would allow large parametric studies to find the relationships necessary to construct a lumped model of the lymphatic system. The presence of wavy features on the surface of the valve poses a problem as they can only be captured with higher order geometric models, which requires more information. Smoothing is inherent to imaging and meshing, but the sensitivity of lymphatic models to surface smoothness has not been established.

This work aimed to provide the first image-specific lymphatic valve geometry and to use a mechanical analysis for studying the closure of these compliant valves. The sensitivity of this model is assessed against smoothing, the shear modulus of the leaflet and the inclusion of a non-rigid wall.

2. Methods

2.1. Image processing and segmentation

The image set used was produced by confocal imagery of a lymphangion isolated from the mesentery of a rat. A section of lymphatic vessel was extracted and placed in a calcium-free solution to prevent contraction. The vessel was cannulated and loaded intra-luminally with Cell Tracker Green. The lymphangion was pressurised to a trans-mural pressure of 5 cmH_2O and scanned with a Leica AOBS SP2 confocal-multiphoton microscope with an U APO 40.0 × 1.15 W CORR objective. A 100 mW 488 nm laser was attenuated with an acousto-optical modulator, and acousto-optical beam-splitters were used to select the wavelengths from the emission spectrum between 510 and 525 μm. A single *x-y* confocal slice was acquired perpendicular to the axial direction of the vessel, after which the focal plane was advanced along the *z*-axis before acquiring the next *x-y* image. The scans represent a pack of 195 2D slices containing 512-by-512 pixels at a resolution of 0.6-by-0.6 μm. The distance between consecutive images was 1 μm. A 307 micron length of wall was segmented from the image set. The valves length was 230 μm from the middle of the bases to the middle of the commissures. The diameter at the commissures was 160 μm, and the diameter at the base was 90 μm. The average thickness of the wall was 14 μm and the average thickness of the leaflet was deemed 5 μm by inspection. The valve had a sinus-to-root ratio of 1.78, larger than the mean of 1.65, but still within the observed range of 1.20–2.66 (Wilson et al., 2015).

As can be seen in Fig. 1A, the images were noisy, the objects blurred and the intensity was non-uniform. Intensity decayed

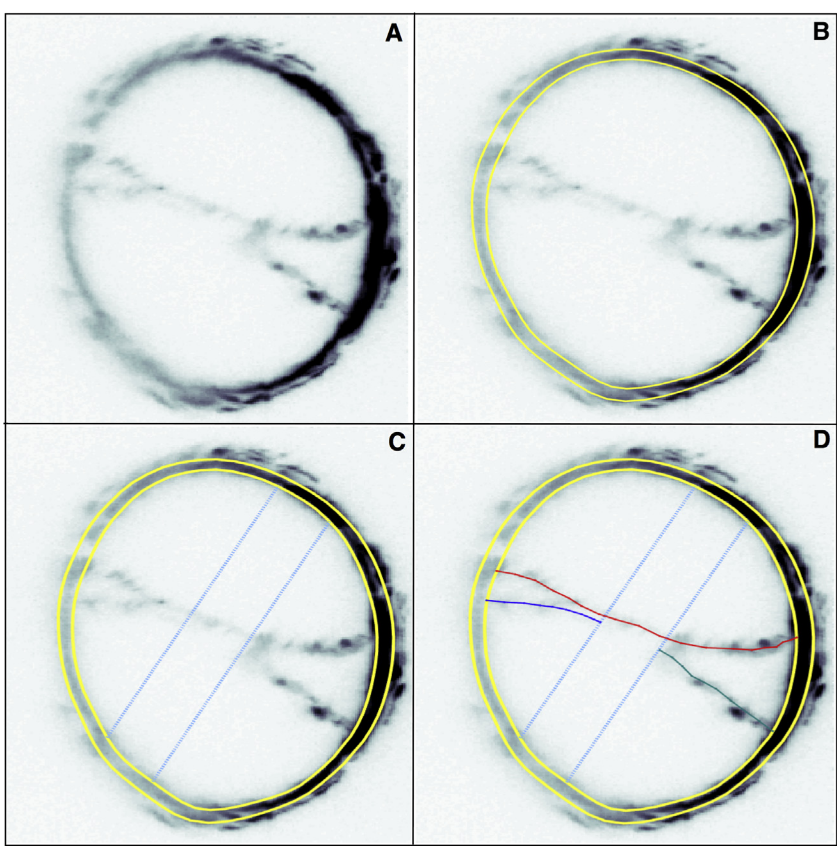

Fig. 1. A series of z-y slices illustrating a step by step overview of the segmentation process. (A) A z-y image slice. (B) A segmentation of the wall (yellow). (C) The guidelines of leaflet edges used in reconstruction (cyan). (D) Manual reconstruction of the leaflet structures (red and blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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