

Generation of three-dimensional models suitable for computational mechanical analysis, based on a population of endothelial cells

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Computational analyses of cell mechanical behaviour are sensitive to cell morphology, in particular the spatial distribution of sub-cellular components. The majority of cell mechanical studies fall into two categories: idealised geometry or cell-specific approaches. Both approaches are unable to capture the spatial variation found in cell populations, nor can they assess how these variations affect model outputs. Hence we have developed a framework for quantifying morphological variation in a population of endothelial cells.

A population ($n = 15$) of human-microvascular endothelial cells were cultured, stained and imaged, using a combination of immunofluorescence and confocal microscopy. Various subcellular components were imaged including the nucleus, actin and tubulin components of the cytoskeleton, the primary cilium, focal adhesions, and cell-cell junctions. We developed shape descriptors for each subcellular component (see figure for example of cell membrane shape descriptor). These descriptors provided numerical representation of three-dimensional spatial distribution of each component, and were employed to quantify shape variation across the population.

Using these shape variations, we generated virtual cells with morphologies that were characteristic of the overall population. Compared to cell-specific mechanical models, the generated virtual cells are more likely to yield mechanical behaviour that is representative of the whole cell population. Furthermore, we employed our framework to characterise the “uniqueness” of shape of a particular cell in the population. We found little variation in nuclei morphology in the population. However, 5 out of the 15 total cells had non-typical shapes: having first shape modes more than one standard deviation away from the average. We intend to extend our study to include shape analysis of diseased cells or cells that have undergone flow-induced remodelling, which will aid future studies examining morphological implications of endothelial related disease.

Keywords: Cell modelling, morphology, generative models, image analysis, cell population, endothelial cells, spatial statistics, cytoskeleton, shape descriptors.

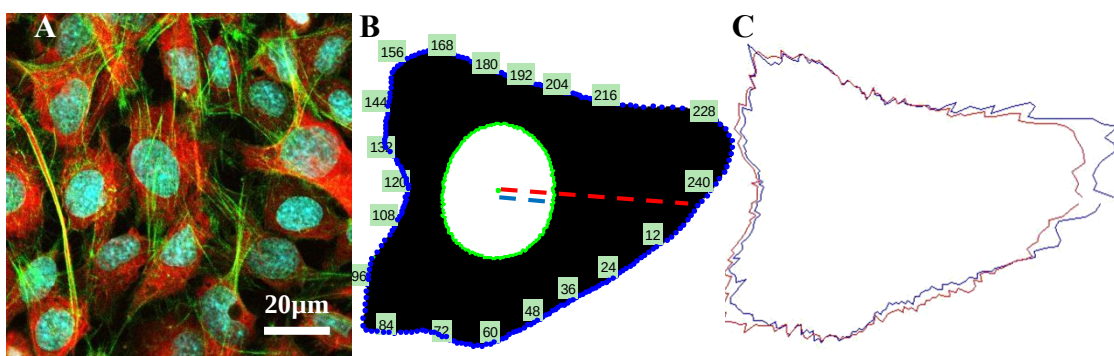


Fig 1. A) Confocal microscope image of human microvascular endothelial cells, with F-actin (green), acetylated alpha-tubulin (red) and nucleus (blue). **B)** Illustrative spatial descriptor of cell membrane; each cell outline is described as a 240-element vector consisting of the ratio of nuclei length (blue dashed line) to cell membrane length from centre of the nucleus (red dashed line). **C)** Quantifying uniqueness of a single cell compared to the entire population. Blue outline is original cell shown in **B**. Red outline is a reconstruction of that cell using shape modes found from principle component analysis of the entire cell data set (shape modes fitted using a genetic algorithm). Each shape mode used to reconstruct the cell is within one standard deviation of the entire population, indicating that this cell has a “typical” morphology. These approaches have been extended to three-dimensions, using confocal image stacks.