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Probability density functions for axial ratios of sectioning profiles of anisotropically arranged elliptical microvessels

R.A. Krasnoperov *, A.N. Gerasimov

Proxima Technology Ltd., 5-2-64, General Karbyshev Blvd., Moscow 123154, Russia

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ABSTRACT

The article theoretically regards probability density functions (PDFs) for axial ratio (X/Y) of sectioning profiles of elliptical microvessels (MVs) arranged with anisotropy in a biological tissue volume. A technique for the $PDF_{X/Y}$ calculations in anisotropy of the elliptical MVs is described. The essence of this technique is introducing anisotropy in $PDF(\alpha, \varphi)$, i.e. the function of the joint distribution of the polar and planar angles α and φ, which define mutual orientation of the elliptical MVs and sectioning planes. With the aid of this technique, the anisotropy cases are studied with $PDF(\alpha, \varphi)$ given by pair combinations of the following distributions: (i) a uniform distribution of the angles α and/or φ, (ii) the angle α distribution with $PDF_\alpha = \sin\alpha$ ($\alpha \in [0, \pi/2]$), and (iii) Gaussian distributions of the α or φ values. Specifically, $PDF_{X/Y}$ curves are obtained for MVs with the true, or three-dimensional, axial ratio $X_0/Y_0 = 2.0$, and the anisotropy effects on the X/Y expected frequencies are analysed. Conclusions of this analysis, the $PDF_{X/Y}$ calculation technique, and the $PDF_{X/Y}$ curves obtained are useful for stereological reconstruction of anisotropically organised microcirculatory networks, with an ellipticity of their MVs being taken into consideration.

1. Introduction

Cross-sectional sizes belong to the most useful characteristics of blood and lymphatic microvessels (MVs). Knowledge of these sizes is needed in developing structural and functional models of microcirculatory networks. The sizes of MVs are often estimated on their profiles found on sections for light and electron microscopy. Because MVs are randomly orientated in a tissue volume, a majority of their profiles obtained by planar sectioning in any direction usually have the sizes, which differ from the perpendicular sectioning sizes. To derive these 3D sizes of MVs from their two-dimensional (2D) sectioning profiles, a model of an MV shape has to be employed. This model should provide required accuracy in describing a characteristic MV shape and should be tractable at the same time. With the shape model, the 3D sizes of MVs can be calculated from the sizes of their 2D profiles, with appropriate functions being used for giving relations between the 2D and 3D sizes (hereafter 2D/3D-functions).

A conventional method for MV modelling is based upon approximating an MV shape on its limited lengths by a straight circular cylinder [2,17,18,33]. The 2D/3D-functions for this shape model are simple (e.g., [17,18]) and the model accuracy is high enough to study MVs with nearly circular perpendicular sectioning profiles. Nevertheless, in analysis of MVs with elliptical perpendicular sectioning profiles (hereafter – elliptical MVs), this shape model does not meet modern requirements and only rough estimates are obtainable for the MV sizes. An additional drawback of the conventional method is that the researcher does not generally know whether circular or elliptical MVs are studied – all these MVs can produce circular and elliptical profiles on random sections. Therefore, in most cases an extent remains unknown to which the circular cylinder model is applicable for the MVs under investigation.

It follows from general considerations that an ellipticity can be acquired by MVs in places of relatively low blood or lymph hydraulic pressure, as well as in regions of elevated outer pressure put on by the surrounding tissue. Mathematical equations governing microhemodynamics, microrheology, transmural mass transfer, and other physiological processes in microcirculatory beds contain variables that depend on that the MVs are circular or elliptical in their perpendicular sectioning profiles. All this implies the need in microangiology for the elliptical cylinder model and for methods based upon this shape model.

Taking this into account, the authors designed a stereological method for determining 3D sizes of elliptical MVs on their random sectioning profiles [13,14]. The following 3D sizes can be defined by the method: the major (X_0) and minor (Y_0) radii, the axial ratio (X_0/Y_0), the area (S_0), and the perimeter (P_0) of MVs. The obtainable estimates of the MV sizes are length-weighted because probability of an MV being sectioned by a plane depends on the MV

* Corresponding author. Tel.: +7 495 410 3994.
E-mail address: info@proxima-t.com (R.A. Krasnoperov).

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Nomenclature

Notation	
2D	two-dimensional
3D	three-dimensional
CDF	cumulative distribution function
Gd	Gaussian distribution
$j_{2.01-2.10}$	portion of microvessel profiles with axial ratios in the range [2.01,2.10]
MV	microvessel
P_0	perimeter of a microvessel
PDF	probability density function
$PDF_{X/Y}$	probability density function of the microvessel profile axial ratio
PDF_α	probability density function of the angle α
PDF_φ	probability density function of the angle φ
$PDF(\alpha,\varphi)$	probability density function for the joint distribution of the angles α and φ
S_0	area of a perpendicular sectioning profile of a microvessel
X	major radius of a microvessel sectioning profile
X_0	major radius of a microvessel
Y	minor radius of a microvessel sectioning profile
Y_0	minor radius of a microvessel
X/Y	axial ratio of a microvessel sectioning profile
X_0/Y_0	axial ratio of a microvessel
α, φ	the angles of planar MV sectioning in spherical coordinates

length. The 2D/3D-functions derived by the authors are used in the method for the stereological reconstruction; these functions correspond to the elliptical cylinder model, which describes characteristic MV shape on its limited lengths in the vicinity of sectioning planes. The method requirements to the structure under study and their biological relevance are thoroughly discussed in [13]. Some additional explanation on the requirements to the structure in stereology of MVs can be found in [20].

With the help of the method designed, it was shown that the elliptical cylinder model is good enough to yield high confidence probability in fitting empirical results [13,14,16]. Specifically, perifollicular blood capillaries in the normal rat thyroid were studied by the method. The best fit of the model to an empirical distribution of the axial ratios of the capillary sectioning profiles (X/Y) was found at $X_0/Y_0 \approx 1.6$ in 72.7%, $X_0/Y_0 \approx 1.0$ in 17.6%, and $X_0/Y_0 \approx 3.2$ in 9.7% of the studied capillaries [13,14]. In hypercalcaemia, the rat thyroid capillaries were also heterogeneous: their 3D axial ratios were estimated as $X_0/Y_0 \approx 1.3$ in 79% and $X_0/Y_0 \approx 2.7$ in 21% of the capillaries [16]. These findings, taken together with scarce data of other investigators on an ellipticity of MVs in heart and skeletal muscles [the data were obtained by means of (i) optical sectioning of smaller MVs through thickness of a thick histological section [9], (ii) measuring corrosion casts of bigger MVs [9], and (iii) approximate calculations using the results of assessing the MV perimeters P_0 by model-based and model-free stereological methods, with the clearly ideal assumption being made that all the MVs in the organ have the same X_0/Y_0 values [23]], strongly suggest that the MV ellipticity is not a single case. To all appearances, the ellipticity is a typical state for certain MVs, perhaps even for a majority of blood capillaries, sinusoids, postcapillaries, venules, and microlymphatics. The elliptical cylinder model is more general anyway – it treats MVs having nearly circular cross-sectional profiles as elliptical cylinders of zero ellipticity, and therefore it should be chosen if there is no preliminary information on a characteristic MV shape. All this leads to the conclusion that the elliptical cylinder model is indispensable for further progress in microangiology, especially in decreasing computational cost that happens systematically.

In addition to the stereological approach based on the stochastic 2D/3D reconstruction, modern methods can also be employed for studying MVs and generating their 3D images. Among these methods are such modern facilities as confocal laser scanning microscopy (CLSM), X-ray computer microtomography (μCT), X-ray synchrotron microtomography, and multiphoton excitation microscopy, which can give useful qualitative and quantitative information about MVs (e.g., [3,7,27,29]). These facilities have a great potential in estimating ellipticity of MVs and developing mathematical description of physiology of microcirculation, but nowadays their use in this issue is restricted by some technical limitations. In particular, the minimal voxel volume achieved is typically about 15 μm^3, which is too big for reliable assessment of moderate ellipticity of capillaries with a small diameter less than 5–6 μm. This fact can explain the absence of publications devoted to studying MVs' ellipticity with the help of CLSM, μCT, and other similar methods. Hence, the stereological approach is of continuing use as it can derive 3D information on MVs from their planar sections observed for example by transmission electron microscopy. At the same time, the modern facilities can readily be used for measuring bifurcation angles and other orientational information on MVs, and in combination with our stereological method based upon the elliptical cylinder model they can yield sound structural models of microcirculatory networks.

Until now our stereological method was used only in the analysis of the sizes of the rat thyroid capillaries, which are isotropic in their 3D organisation, i.e. they have no preferential orientations in tissue space. For isotropic MVs, the method is thoroughly developed. In particular, probability density functions (PDFs) of sectioning profile sizes are plotted for isotropic elliptical MVs with the 3D axial ratios fixed on various X_0/Y_0 values [13,14]. One may thus expect that isotropic MVs in other organs and tissues will be soon studied with paying proper attention to their ellipticity. At the same time, application of the elliptical cylinder model to anisotropically arranged MVs is not yet clear in all substantial detail. This application will be of considerable importance because MVs are evidently anisotropic in many organs and tissues (e.g., in skeletal muscles, myocardium, tubular bones, eye tunics, pleura, meninges, some regions of brain [23,25,30,32]). For these MVs, employing three-dimensionally isotropic sets of cylinders, the same as for the thyroid capillaries, can result in serious errors even provided the adequate MV ellipticity is used in modelling. In order to apply the elliptical cylinder model in anisotropy, the appropriate technique for calculations of the PDFs of the MV profile sizes should be described. Quite substantial is also exploring effects of different anisotropy cases on expected size distributions of the MV sectioning profiles. The present theoretical article deals with these issues, the 3D axial ratio (X_0/Y_0) being under study as the size parameter, which is commonly used for defining an MV ellipticity. More specifically, the article is devoted to the calculations and analysis of the $PDF_{X/Y}$ curves for elliptical MVs arranged with anisotropy in tissue space. These curves are applicable in fitting X/Y empirical distributions with the help of the designed method, which is based upon the elliptical cylinder model. Hence, this fitting can further be employed in the stereological reconstruction of the X_0/Y_0 values, other 3D sizes, and their weights in microvascular networks [13,14] as well as in the assessment of 3D