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Modelling capillary oxygen supply capacity in mixed muscles: Capillary domains revisited

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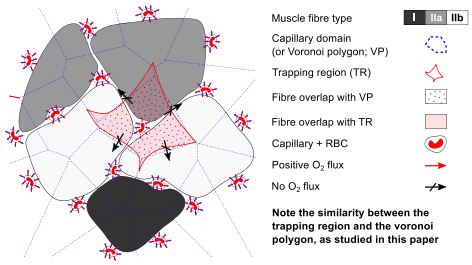
HIGHLIGHTS

- We assess the effectiveness of Voronoi Polygons (VP) in predicting capillary supply.
- VP are found to generally agree with biophysical predictions of capillary supply regions.
- Thus VP often provide a simple means of characterising capillary supply regions.
- We demonstrate the use of VP provides insights into capillary regulation.
- We also identify when VP do not coincide with biophysical capillary supply regions.

GRAPHICAL ABSTRACT



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ABSTRACT

Developing effective therapeutic interventions for pathological conditions associated with abnormal oxygen transport to muscle fibres critically depends on the objective characterisation of capillarity. Local indices of capillary supply have the potential to identify the onset of fine-scale tissue pathologies and dysregulation. Detailed tissue geometry, such as muscle fibre size, has been incorporated into such measures by considering the distribution of Voronoi polygons (VP) generated from planar capillary locations as a representation of capillary supply regions. Previously, detailed simulations have predicted that this is generally accurate for muscle tissue with uniform oxygen uptake. Here we extend this modelling framework to heterogeneous muscle for the assessment of *capillary supply capacity* under maximal sustainable oxygen consumption. We demonstrate for muscle with heterogeneous fibre properties that VP theoretically provide a computationally simple but often accurate representation of trapping regions (TR), which are predicted from biophysical transport models to represent the areas of tissue supplied by individual capillaries. However, this use of VP may become less accurate around large fibres, and at the interface of fibres of largely different oxidative capacities. In such cases, TR may provide a more robust representation of capillary supply regions. Additionally, given VP can only approximate oxygen delivery by capillaries, we show that their generally close relationship to TR suggests that (1) fibre type distribution may be tightly regulated to avoid large fibres with high oxidative capacities,

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(2) the anatomical fibre distribution is also tightly regulated to prevent a large surface area of interaction between metabolically dissimilar fibres, and (3) in chronically hypoxic tissues capillary distribution is more important in determining oxygen supply than the spatial heterogeneity of fibre demand.

1. Introduction

The objective assessment of anatomical capillary supply to striated muscle fibres is contingent on using methods that can accurately capture tissue capillarity while also unambiguously linking the local capillary distribution to the global supply. A survey of recent literature on the quantitative assessment of capillary supply in striated muscle identifies two general morphometric methods for analysing tissue capillarisation in an effort to assess functional consequences (Hoofd et al., 1985; Hudlická et al., 1992; Degens et al., 1992; Egginton and Ross, 1992; Egginton, 2002; Ahmed et al., 1997; Suzuki et al., 2000; Wüst et al., 2009a,b, 2012). First, global methods use average values of structural composition or functional activity to represent the tissue uniformly, e.g. mean intercapillary distance (ICD), mean capillary density (CD), mean capillary-to-fibre ratio (C:F), and mean oxygen uptake (MO_2). However, average indices cannot capture the spatial heterogeneity in capillary supply generated by the local metabolic environment and the distribution of fibre size (Ahmed et al., 1997), and the scale-dependency inherent in such indices may explain why data on capillarity is variable, if not conflicting (Egginton, 1990). Second, area-based methods, such as those based on Krogh cylinders (Krogh, 1919) or Voronoi polygons (equivalently known as capillary domains, Hoofd et al., 1985), are used to avoid the spatial limitations of models based on global indices. A capillary domain is defined to be the area of a muscle cross section surrounding an individual capillary and closer to its centre than all neighbouring capillaries. The resulting polygonal tessellation potentially captures the local environment of capillaries, with each 2-dimensional domain contained in the cross section approximating the supply region of the capillary it encloses.

Krogh cylinders, however, are inadequate for this role since they lead to nonphysiological tissue voids and overlaps. In contrast, Voronoi polygons (Fig. 1B) generate a space-filling alternative (Egginton and Ross, 1989, 1992) thereby allowing the exploration of the local influences associated with microvascular remodelling, as well as any mismatch between angiogenesis and local O_2 demand (Degens et al., 1992, 2002, 2006, 2008; Egginton et al., 2001; Wüst et al., 2009a). This gives Voronoi polygons an advantage in assessing the efficacy of applications to pathological scenarios, such as ischaemia, where potential therapeutic interventions include strength training (Deveci and Egginton, 2002; Suzuki et al., 2000), endurance exercise (Ahmed et al., 1997; Scott et al., 2009), electrical stimulation (Ebina et al., 2002), and alterations in muscle temperature (Egginton et al., 2001; Egginton, 2002). In addition to their ability to reproduce robust versions of the aforementioned global measures, Voronoi polygons have the capacity to provide indices of capillary supply to individual fibres, with both direct contact and indirect influence, and to fibres of different metabolic activities. For instance, the local capillary-to-fibre ratio (LCFR) and the local capillary density around fibres (LCD, also known as the capillary fibre density, CFD) are obtained from the cumulative overlap of Voronoi polygons with individual muscle fibres (Egginton and Ross, 1989). These indices have continuous distributions that are based on both adjacent and remote capillaries, thus allowing for the experimental observation of fibres that are supplied by capillaries with no direct contact (Egginton, 1990; Wüst et al., 2009a).

Although experimental studies of muscle tissue capillarity that are based on Voronoi polygons have revealed intricate details about the regulatory process of microvascular remodelling, there

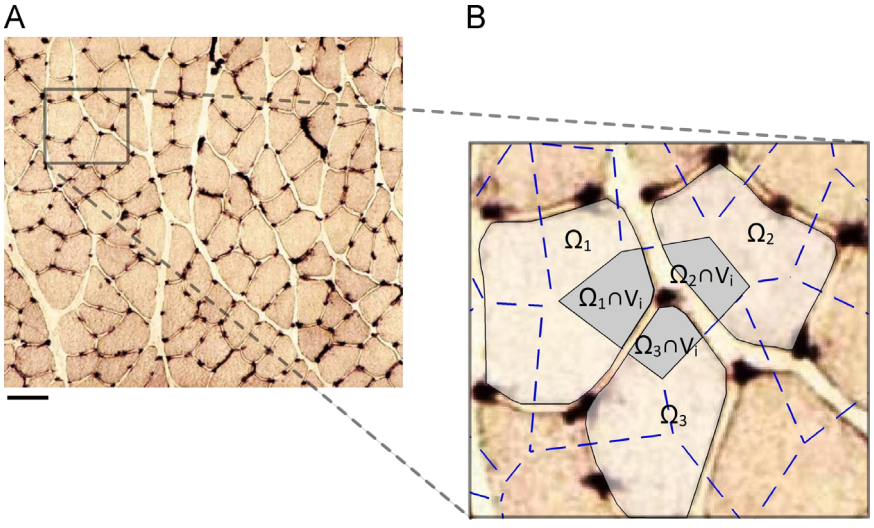

Fig. 1. (A) Typical tissue cross section of rat skeletal muscle (*m. extensor digitorum longus*) with capillary location identified by alkaline phosphatase staining. The dark structures are capillaries, the lighter objects are muscle fibres, and the lightest region is the interstitial space. Note the heterogeneity of intercapillary distances between adjacent vessels, in part reflecting heterogeneity of cell size in the host tissue (Egginton et al., 1988; Egginton and Ross, 1989). The scale bar corresponds to 50 μm. (B) An expanded region of the original image on which a Voronoi tessellation is superimposed by dashed (blue) lines. A central Voronoi polygon, V_i, is highlighted in *dark gray* and overlaps adjacent fibres denoted by Ω_1, Ω_2, and Ω_3 (*light gray*) with the overlapping regions $\Omega_1 \cap V_i$, $\Omega_2 \cap V_i$, and $\Omega_3 \cap V_i$ representing the fractional supply area of this Voronoi polygon to each fibre. The symbol $\cap$ denotes the intersection of or overlap between two regions. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)