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Tissue capillary supply – it's quality not quantity that counts!

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This article explores how common misunderstandings about the microcirculation – that capillary supply varies directly with O_2 demand, that local capillary supply in muscle is determined by fibre type and that it is appropriate to model capillary distribution as either random or in a fixed geometric pattern – arise from quantifying capillarity by simple measures of quantitative extent, rather than the more functionally relevant qualitative distribution. We show that the latter approach reveals exquisite control of angiogenesis that determines the location of new vessels with astonishing accuracy, motivating a reappraisal of the physiological remodelling process and a new approach to computational investigations into peripheral O_2 transport.

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Background

Capillaries are the terminal delivery points for cardiovascular delivery of oxygen to and removal of metabolites from respiring tissue, hence the assumption has always been that 'more is better'. Indeed, a survey of the literature readily supports a correlation between capillary density (CD) and the proportion of oxidative fibres or average mitochondrial volume density among different skeletal muscles (Hudlická *et al.* 1992). For example, endurance exercise training significantly increases the capillary supply to active skeletal muscle and leads to a parallel increase in oxygen extraction capacity in both humans and rats (Yang *et al.* 1994; Richardson *et al.* 1999). If either supply or demand is already limiting then it is logical that an adaptive response would involve an apparent covariance. However, some glycolytic muscles have a higher CD than oxidative muscles (Schmidt-Nielsen & Pennycuik, 1961), suggesting this is not always the case. Indeed, CD is proportional to oxygen consumption ($\dot{M}_{O_2}$) in red (soleus) muscles, but proportional to lactate clearance in white (gracilis) muscles of the cat (Hudlická *et al.* 1987). Interestingly, capillarity may increase prior to mitochondrial enzyme activity in various disease states and some models of exercise (Skorjanc *et al.* 1998).

Angiogenesis (the growth of new capillaries by expansion of an existing capillary bed) may result from a mismatch in microvascular supply and metabolic demand, or in response to an altered haemodynamic environment. The heterogeneity in angiogenic response within a given muscle may therefore reflect either differences in fibre type composition or mechanical load, and it is possible to experimentally dissociate an angiogenic stimulus from any increase in oxidative capacity (Egginton & Hudlická, 2000). That control is exerted at a local level is evident by the specificity in location of new capillaries adjacent to glycolytic fibre types following indirect muscle stimulation (Badr *et al.* 2003), whereas angiogenesis differentially occurs around oxidative fibres following endurance training (Mai *et al.* 1970), presumably as a result of the different motor programme recruitment.

The variable, sometimes conflicting data on capillarity may, in part, be due to artefacts introduced by the method of analysis (Egginton, 1990). For example, as capillarity is highly dependent on fibre size it is necessary to move from a number-based to an area-based analysis of capillary supply, in order to avoid bias due to scaling effects. This allows a capillary-by-capillary and a fibre-by-fibre analysis of the angiogenic response to physiological challenges such as training, ischaemia and myopathic atrophy (Ahmed *et al.* 1997). In doing so, it allows the spatial limitations inherent in some models of tissue oxygenation to be overcome, generating a space-filling alternative to Krogh's

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cylinder, termed the capillary domain (Egginton & Ross, 1989*a*,*b*). This allows the influence of changes in extent and location of angiogenesis to be explored, though further refinements are required to incorporate the consequences of detailed muscle fibre and intracellular geometries for oxygen tension.

Mathematical modelling is used to undertake theoretical analysis of processes difficult to examine experimentally, and to predict behaviour within biological systems. One of the first theoretical analyses of oxygen supply within tissue was developed by the Nobel prize winner August Krogh in collaboration with the mathematician Agner Erlang, with the formulation of a model to predict the oxygen tension (P_{O_2}) distribution around a capillary. The original study envisioned a simplified solution that is conceptually similar whether diffusion over eccentric (Fig. 1*A*) or concentric geometries (Fig. 1*B*) are considered. Despite its numerous shortcomings, such as the lack of differential extraction, it is still widely used (Egginton & Ross, 1992).

Interestingly, most modelling of the functional consequences relies on averaged values of structural composition or functional activity across a tissue, e.g. mean intercapillary distance (ICD) and mean $\dot{M}_{O_2}$. In contrast, it is evident that capillary supply is spatially heterogeneous (Fig. 2*A*), which reflects local variations in both cell size and metabolic characteristics of the host tissue (Fig. 2*B*), and requires an approach that takes account of consequential differences in O_2 diffusion (Fig. 2*C*).

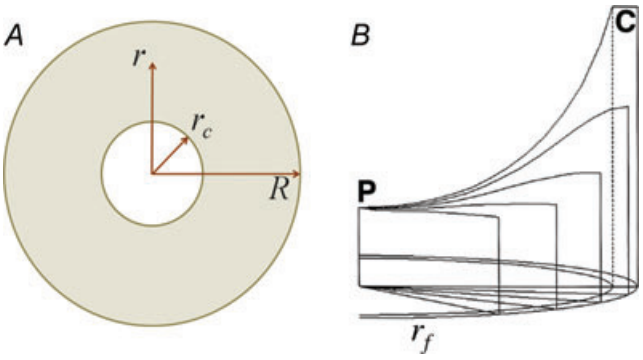

Figure 1. Models of tissue P_{O_2}
A, the estimation of tissue P_{O_2} within a cylinder of tissue surrounding a capillary of radius r_c. Let r be the distance of the point from the centre of the capillary. With R denoting the cylinder radius where oxygen flux becomes zero (Krogh, 1919), M the rate of tissue uptake ($\dot{M}_{O_2}$), P_c the capillary partial pressure (P_{O_2}) and D the oxygen diffusion coefficient, the partial pressure in any plane perpendicular to the capillary is given by $P = P_c - \frac{MR^2}{4D}[\ln(\frac{r^2}{r_c^2}) - \frac{r^2-r_c^2}{R^2}]$. *B*, P_{O_2} at capillary C declines montonically both around and within a fibre of radius r; P is the minimum P_{O_2} at the centre of a fibre (see Egginton & Ross, 1992).

Spatial heterogeneity

In order to resolve the outstanding issues concerning the developmental and dynamic link between capillary supply and cellular demand, we need to consider how best to measure spatial heterogeneity in tissue capillarity (Fig. 3*A*). We and others have digitized images like Fig. 2*A*, viewing capillaries as point sources of O_2. This allows the division of the tissue section (two-dimensional space) into a tessellation of polygons (termed capillary domains) representing that area of tissue closer to one capillary than another (Hoofd *et al.* 1985; Egginton & Ross, 1989*b*). This may be thought of as a space-filling equivalent of the Krogh cylinder. Unlike other attempts at objective segmentation of sections into structural elements, this also allows an unambiguous identification of adjacent capillaries and thus a robust estimate of ICD (Fig. 3*B*).

Using the area-based approach leads to the surprising finding that capillary supply in skeletal muscle is qualitatively the same between regions of a muscle with different fibre type composition (Fig. 4*A*), between muscles of different metabolic character (Fig. 4*B*), among homologous muscles of different species with widely differing capillary densities (e.g. fish *versus* mammals; Egginton *et al.* 1988), and even within a muscle in terms of perfusion over time (Fig. 4*C*; Egginton & Ross, 1989*a*). This means that the separation of physical capillaries and

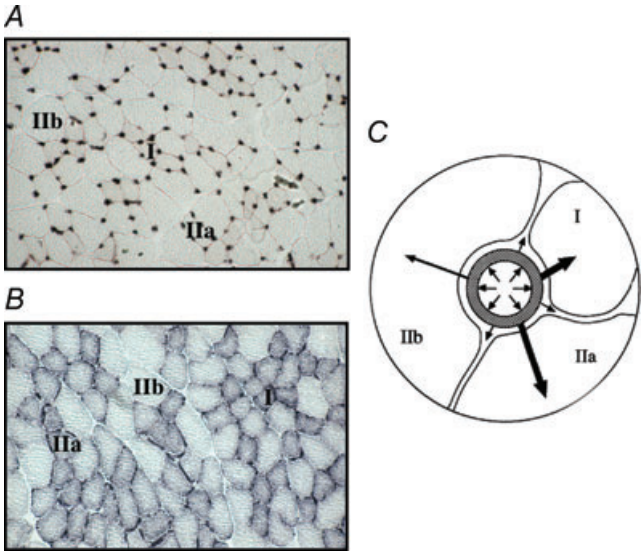

Figure 2. Heterogeneities in supply and demand
Frozen sections of rat hindlimb muscle stained for capillary supply (alkaline phosphatase reaction; *A*) and oxidative fibre content (succinate dehydrogenase activity; *B*). Note that the local density of capillaries varies according to level of succinate dehydrogenase stain, which in turn varies inversely with fibre size. Within skeletal muscle any given capillary may be surrounded by up to three distinct fibre types; it follows that O_2 diffusion (flux density) will then depend on local extraction pressures established by differences in consumption (*C*). From Egginton (1998), with permission.

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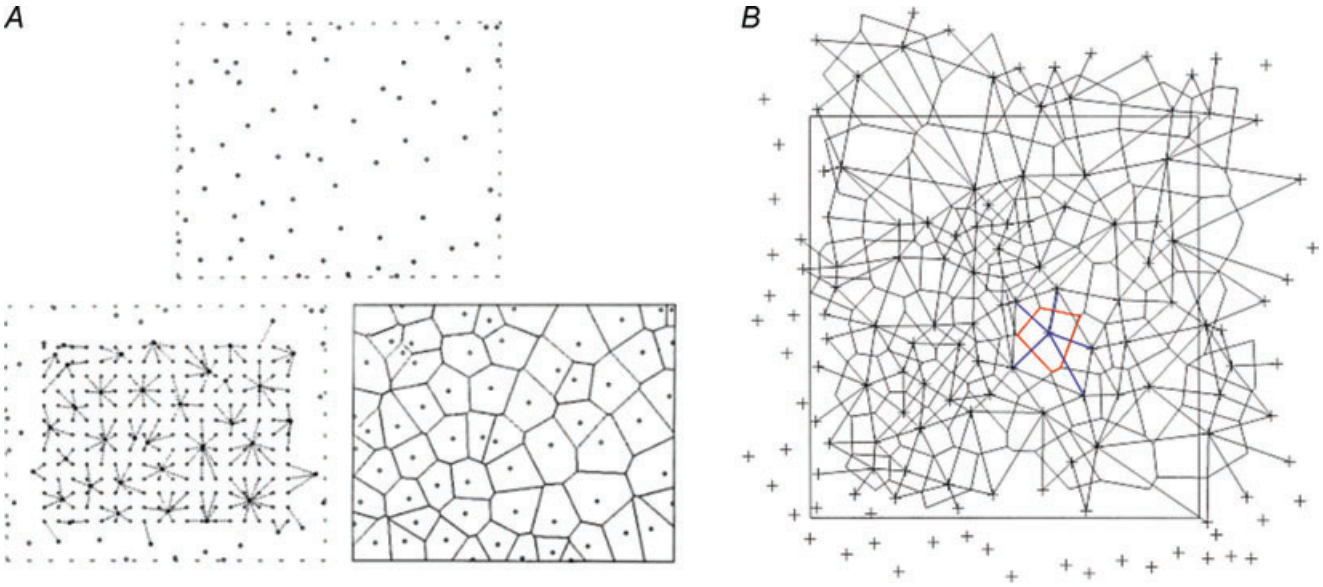

Figure 3. Quantifying capillary separation
A, quantifying the extent of unequal, non-random capillary distribution (top panel) may employ a variety of statistical approaches, such as nearest-neighbour analysis of capillary separation (bottom left panel) or calculation of the area of tissue potentially supplied by a single capillary (bottom right panel). Construction of the domain of influence for each capillary is based on a Voronoi tessellation, with the extent of capillary domain overlap for each fibre providing an estimate of capacity in terms of 'capillary equivalents' of supply. From Egginton & Ross (1992), with permission. *B*, a complimentary, Delaunay tessellation (blue lines) provides an unambiguous measure of all intercapillary distances between contiguous capillaries, defined by adjacent capillary domains (red polygon).

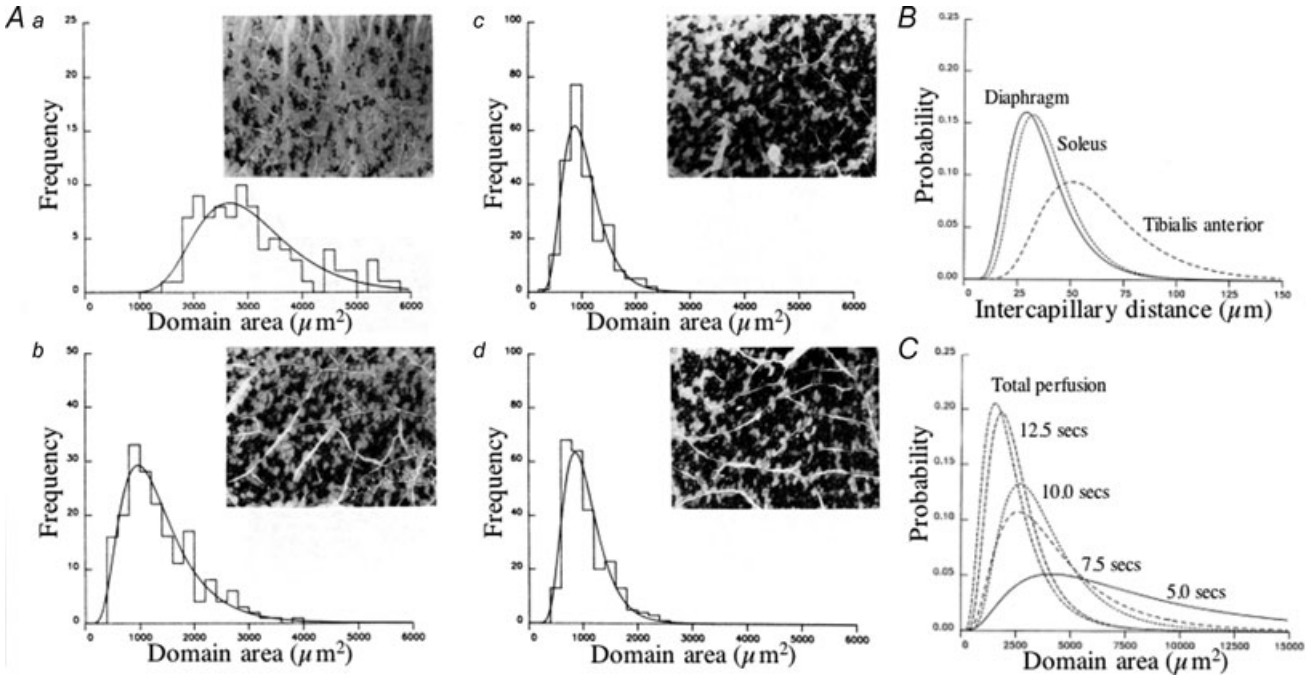

Figure 4. Qualitatively similar capillary distributions
A, capillary domain distribution along the glycolytic–oxidative transect (represented by panels *a*–*d*) within rat tibialis anterior; insets show histochemical staining for succinate dehydrogenase as an index of the varying metabolic character. *B*, intercapillary distance distribution for uniform (soleus) and mixed oxidative muscles (diaphragm), compared with a glycolytic muscle (outer cortex of tibialis anterior). *C*, distribution of domain areas for perfused capillaries following timed injection of a plasma marker (thioflavin S) in a mixed hindlimb muscle of the rat (extensor digitorum longus). After Egginton (1990).

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of capillary perfusion appears to be tightly regulated in four dimensions. How is growth of such a self-similar system regulated?

Targeted angiogenesis

In order to produce a qualitatively similar (though quantitatively variable) distribution of capillaries in both space and time, the placement of capillaries cannot be regulated on a tissue or organ level, as is often implicitly assumed, nor even on a regional or zonal basis within a tissue, but on the scale of individual cells. This implies an impressive degree of spatial localisation, quite at variance with the usual stochastic (random event) models of angiogenesis. For example, during normal or adaptive muscle growth the capillary supply will be expanded in order to minimise any metabolic error signal (mismatch of supply and demand), leading to hypertrophy-induced angiogenesis, but at a rate that leads to an approximately exponential fall in CD with increasing fibre area (Egginton, 1990). Nevertheless, ontogenetic growth maintains a qualitatively similar capillary distribution within a given muscle in old and young rats (Degens *et al.* 2006). These and other data lead us to conclude that the location of new capillaries is a non-random event, in part dictated by the physical exclusion of sprouts from the space occupied by muscle fibres (Fig. 5*A*), resulting in a remarkable site specificity (Fig. 5*B*) that is evident even within a muscle of mixed fibre type (Fig. 5*C*).

Functional consequences

Previous assumptions about the covariance of capillary supply and oxygen demand may result, in part, from the use of indices that are scale dependent, applied to situations where part of the remodelling process involves a

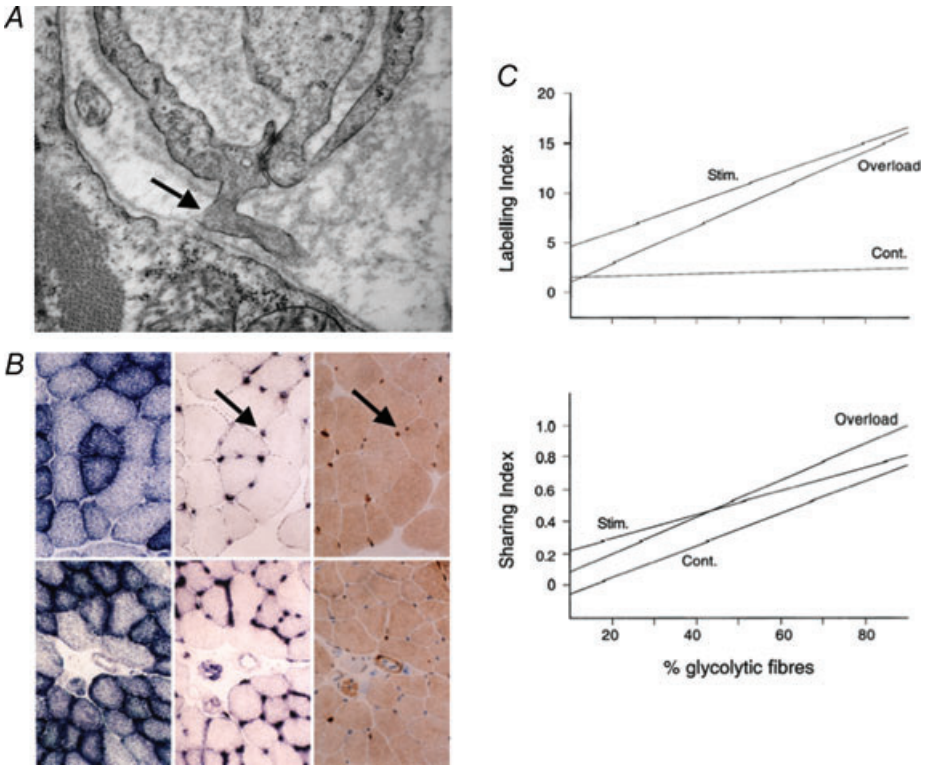

Figure 5. Spatial specificity of angiogenesis
A, endothelial sprout (arrow, approximately 0.5 μm long) during the initial stages of angiogenesis apparently deflected by the adjacent muscle fibre, thus ensuring a non-random orientation of the subsequent new capillary (see also Zhou *et al.* 1998). *B*, localisation of cellular proliferation during sprouting angiogenesis (arrow, approximately 50 μm long), with fibre oxidative capacity indicated by extent of succinate dehydrogenase staining (left panels), capillaries identified by alkaline phosphatase reaction (middle panels) and sites of proliferation located by proliferating cell nuclear antigen (PCNA) reactivity; upper row from the outer cortex of rat tibialis anterior, lower row from aerobic core. *C*, specificity of growth determined by local metabolic environment, showing scaling of labelling index (labelling index, number of PCNA-positive capillaries as a proportion of total capillary supply; top panel) and sharing index (the proportion of glycolytic fibres surrounding a capillary; bottom panel) in rat hindlimb extensor digitorum longus muscle subjected to stimulation (Stim.) or overload relative to the proportion of glycolytic fibres in both oxidative and glycolytic regions (shown as a percentage of the glycolytic fibre content). From Badr *et al.* (2003), with permission.

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change in scale, e.g. fibre size. The use of capillary domains allows calculation of a scale-independent measure of local capillary supply, which shows that the major determinant is fibre size, not fibre type (Fig. 6*A*). A component of the variance associated with such data is the location of the angiogenic foci. Given the unusual length of muscle fibres, the depletion of O_2 down a capillary length would significantly impair diffusive exchange, hence O_2 flux is maintained in the face of a reduced gradient by increasing CD towards the venular end of the microvascular unit (Fig. 6*B*). If the capillary domain has any physiological relevance for oxygen transport, then the mitochondrial content (an index of O_2 consumption) would be independent of domain area, which is the case in rat skeletal muscle (Fig. 6*C*).

Modelling oxygen transport

One limitation of Krogh's approach was that lack of close packing of tissue cylinders represents non-physiological voids or overlaps in supply from adjacent capillaries, situations that are avoided by the use of the space-filling domains (Fig. 7*A*). The original model made a number of unrealistic assumptions, such as: straight

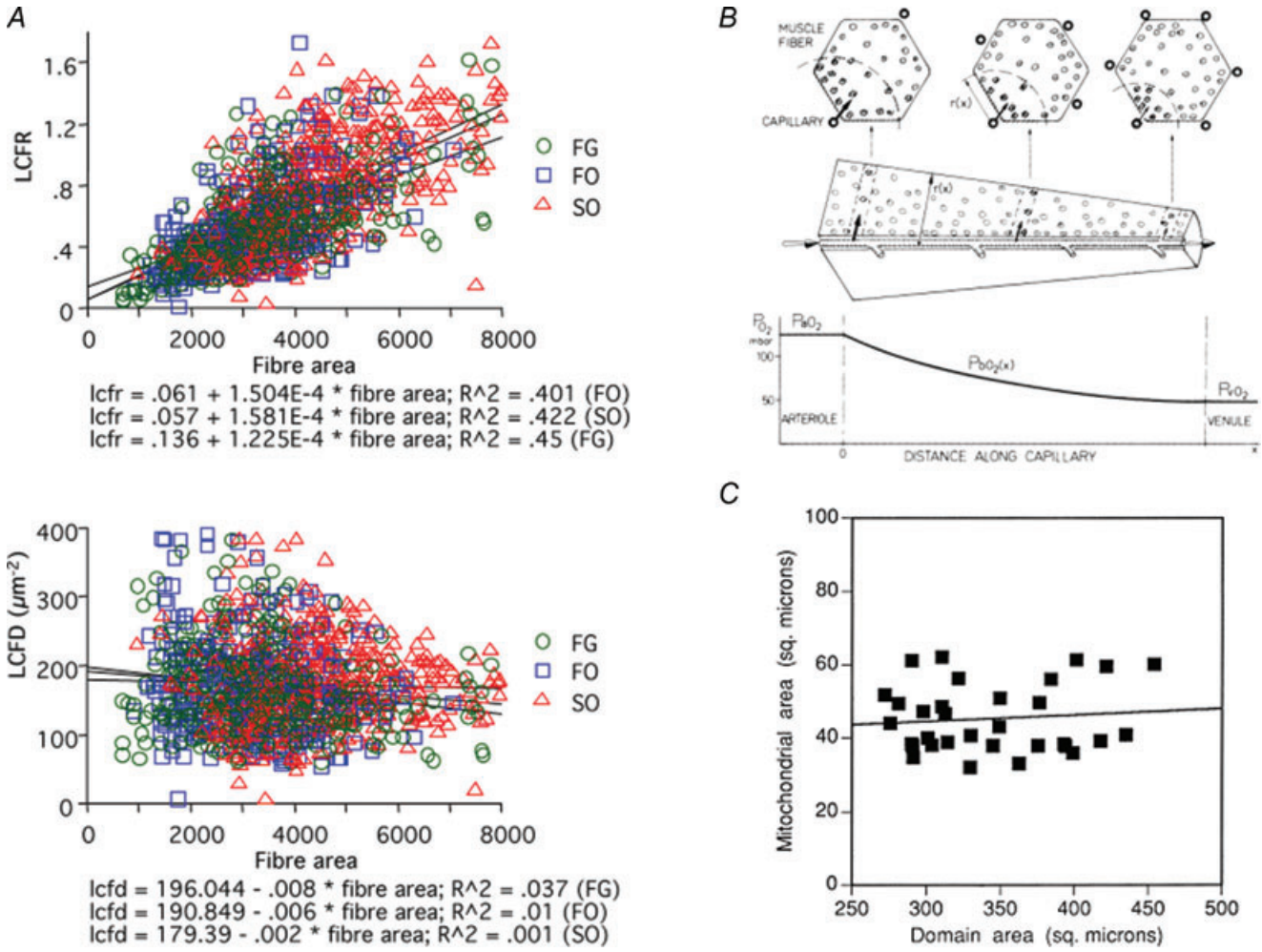

Figure 6. Functional relevance of capillary domains
A, local capillary supply indices in the human lateral quadriceps, split according to fibre type: type I (red triangles), type IIa (blue squares) and type IIb (green circles); top panel shows local capillary-to-fibre ratio (LCFR), bottom panel local capillary-to-fibre density (LCFD; Ahmed *et al.* 1997). *B*, conceptual visualization of the need to increase capillary density in order to adequately supply a consistent mitochondrial demand along muscle fibres, allowing for the exponential decrease in oxygen tension driving oxidative phosphorylation (Weibel 1984). Reprinted by permission of the publisher from THE PATHWAY FOR OXYGEN: STRUCTURE AND FUNCTION IN THE MAMMALIAN RESPIRATORY SYSTEM by Ewald R. Weibel, p. 202, Cambridge Mass.: Harvard University Press, Copyright © 1984 by the President and Fellows of Harvard College. *C*, analysis of electron micrograph montages in a mixed mammalian muscle (rat extensor digitorum longus) illustrating the constancy of total mitochondrial volumetric content, irrespective of capillary domain size (from Egginton & Ross, 1992, with permission).

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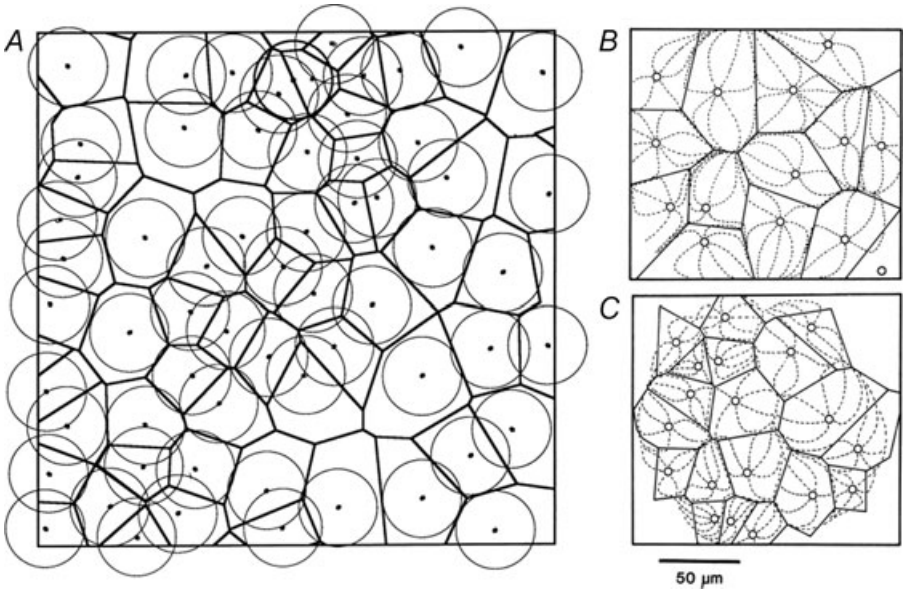

Figure 7. Capillary domains and oxygen flux
A, a representative section of rat extensor digitorum longus, digitised to show capillary locations (black dots) and their associated domains (polygons), and the Krogh cylinders (circles). *B*, if capillaries (open circles) are assumed to have identical transport capacity and supply tissue with homogeneous oxygen consumption, such as rat myocardium, the O_2 flux lines (dotted lines) coalesce at points of minimal P_{O_2} (zero O_2 flux) that match domain boundaries (continuous lines). *C*, heterogeneity in fibre composition and oxygen consumption make the fit less good for skeletal muscle. From Egginton & Ross (1992), with permission.

capillaries running parallel with homogeneous distribution; constant capillary radius and length; no resistance to O_2 flux at the capillary wall; constant capillary flow and venous O_2 concentration; cylindrical symmetry in O_2 efflux from capillaries; no diffusion of O_2 outside of the tissue cylinder; no axial or longitudinal diffusion; no O_2 exchange in arterioles or venules; chemical equilibrium within the blood; $\dot{M}_{O_2}$ is independent of P_{O_2}; O_2 transfer is by diffusion only; no facilitated diffusion of O_2; homogeneous O_2 diffusion coefficient across the tissue; homogeneous $\dot{M}_{O_2}$ within tissue; and the system is in steady state (independent of time) (Kreuzer, 1982). Many studies have explored relaxing these approximations, as reviewed by Goldman (2008). In calculating O_2 flux lines, the domain boundaries coincide with regions of zero exchange in tissue with homogeneous consumption (cardiac muscle; Fig. 7*B*), but not where spatial heterogeneity of capillaries and metabolic demand are found (skeletal muscle; Fig. 7*C*).

To understand these observations, consider a tissue with uniform consumption where the capillaries are arranged with a periodic symmetry, such as the centres of regular hexagons close-packing (tessellating) the plane of a biopsy section (Fig. 8). Each Voronoi polygon represents the capillary domain associated with the capillary it encloses. Extending any one of the hexagon edges indefinitely will reveal a line of symmetry of the tessellation, as

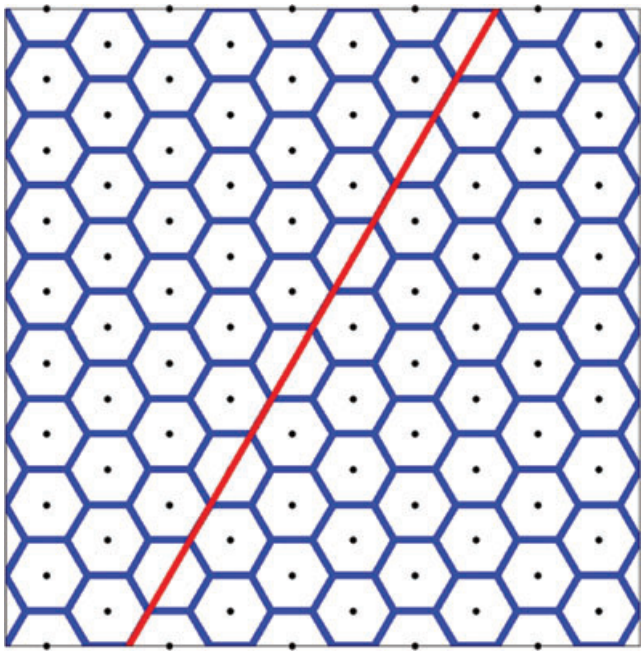

Figure 8. The concept of oxygen supply regions
An illustration of the symmetry for the idealization of an array of identical capillaries (black dots) within homogeneous tissue, arranged such that the associated Voronoi polygons (blue) are regular hexagons. In particular, extending any edge of one of these hexagons to a line, as illustrated in red, reveals a line of symmetry, which enforces an absence of a diffusive flux through the hexagons in the absence of symmetry-breaking physiology, as discussed in the main text.

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illustrated in red (Fig. 8). Without further physiological features to break this symmetry, the partial pressures of oxygen will be the same either side of this line. The geometrical distribution of capillaries is such that there is no gradient of partial pressure, and consequently no diffusive oxygen transport, across the red line. As this argument applies for any edge of the Voronoi polygons, there is no transport across any Voronoi tessellation edge and thus the capillary domains depict the region of supply for all capillaries. Furthermore, the underlying physical processes vary continuously with perturbations of the physiological geometry so that, for sufficiently small deviations from a homogeneous, highly symmetric tissue, one may expect the capillary domains to define approximately the regions that are supplied by individual capillaries.

However, for highly heterogeneous tissue such reasoning is inappropriate, and the observed discrepancy between the Voronoi polygons and the regions which do not exchange oxygen is not surprising. That such predictions will differ among tissues of different composition can be anticipated due to the unphysiological limit that there is no feedback between the flux across a capillary and the local tissue oxygen tension. Then, the flux of oxygen supplied by each capillary is the same; hence, for uniform oxygen uptake the region of tissue supplied with oxygen by each capillary is the same, even if the intercapillary distance varies markedly. The area distribution of the capillary domains will fail to capture this behaviour in this simplified regime, and cautions that using indices based on Voronoi tessellations will not be reliable in all cases.

Such observations also highlight the importance of the influence of global capillary distribution within a tissue in determining the regions supplied by individual capillaries, and a number of studies have explored this, both analytically (Hoofd, 1995; Titcombe & Ward, 2000) and numerically (e.g. Secomb *et al.* 1993). In particular, the fluxes due to surrounding capillaries dictate the feedback between local tissue oxygenation and any given capillary. These fluxes are generally not insignificant, and this feature of tissue cannot be captured by the Krogh cylinder model of an isolated capillary.

Incorporating this physiology into analytical generalizations of the Krogh model designed to capture the influence of inhomogeneous distributions of

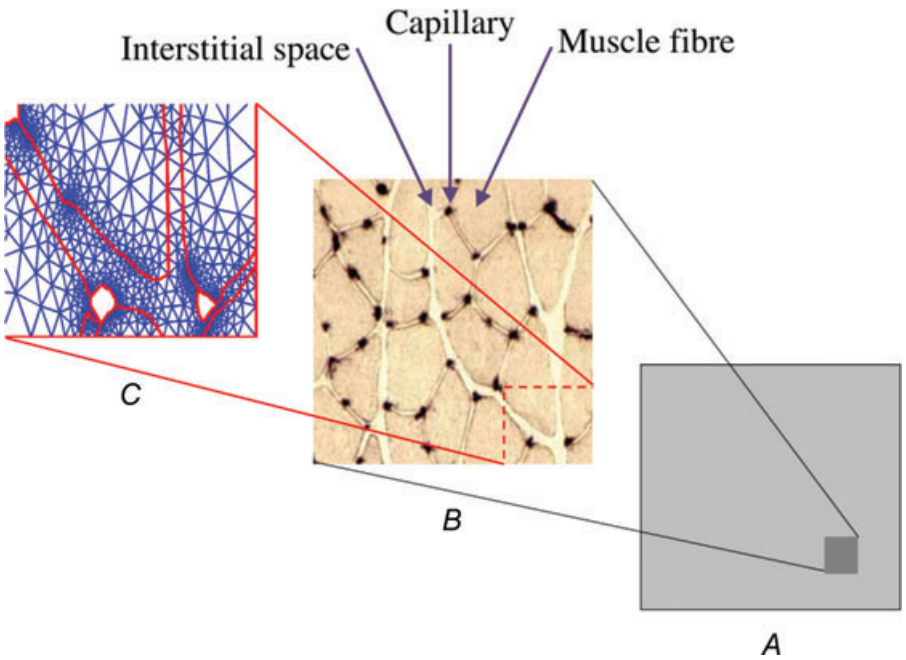

Figure 9. Modelling detailed anatomical geometry and the multiscale paradigm
A direct numerical exploration of the oxygen transport problem within tissue cross-sections (*A*) can be pursued via image capture, overlaying a mesh which is faithful to the geometry captured from biopsies (*B*) and refined within regions of complex geometry (*C*). This allows a numerical solution of oxygen transport equations, which capture the biophysics of oxygen delivery while accounting for histological detail. However, the complexity at the microvascular level limits the length scales which may be readily explored in this manner, especially for three-dimensional simulations, or for simulations within a large parameter space. A current theme running throughout the application of mathematical methods to the life sciences is the use of controlled approximations to capture the important small-scale features that are inherited by equations which capture global dynamics at larger scales. In this context, such developments are anticipated to enable efficient modelling explorations of the links between the capillary bed and tissue scales, as schematically illustrated by the cascade from *A* to *C*.

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capillaries requires careful consideration. It is relatively straightforward to determine approximations that are accurate for sufficiently small values of the parameter ε, where:

$$\varepsilon = \frac{\text{capillary diamater}}{\text{domain size}}$$

as illustrated by Hoofd (1995). However, further studies have revealed that relative errors scale with minus the reciprocal of the logarithm of ε (Titcombe & Ward, 2000); thus, while these will always be negligible if ε is sufficiently small, this is often unachievable in practice. For example, restricting relative errors to approximately 10% requires:

$$\frac{-1}{\ln(\varepsilon)} = 0.1$$

that is:

$$\varepsilon = \exp(-10) = 4.5 \times 10^{-5}$$

For a capillary diameter of 8 μm, one is therefore forced to consider domains sizes of about 15 cm for the analytical solution to reach 10% accuracy, though of course the modelling assumptions may not be uniformly valid for such large scales. Analytical approaches necessary for the consideration of the typical scale of tissue cross-sections have been derived at the expense of substantial additional complexity (Titcombe & Ward, 2000), though based on the mathematics of the Green's function method used for efficient numerical simulation of tissue oxygen transport (Secomb *et al.* 2004). This highlights that extensive and counter-intuitive complications in general emerge on considering the global features of a tissue, such as the distribution of the capillaries, even before anatomical details, such as the influence of interstitial spaces, are considered.

Consequently, understanding the origins and exploring the potential interactions between different spatial heterogeneities requires development of models that take into account realistic anatomical data, e.g. from biopsies in normal physiological conditions, and from pathological situations, such as tissue ischaemia. The coupling of anatomical geometries and the complications associated with the slow decay of P_{O_2} away from capillaries requires the development of finite elements models, with computational intensity concentrated on regions of likely greatest O_2 change (Fig. 9*A* and *B*). This will allow heterogeneities of fibre composition to be accommodated, e.g. intracellular lipid will improve O_2 diffusivity and may compensate for impaired flux in hypothermia (Hoofd & Egginton, 1997), and implementation of rules regarding different metabolic behaviour. Tests of Krogh's assumptions show that when zero-order (P_{O_2}-independent) kinetics of $\dot{M}_{O_2}$ are assumed, then tissue O_2 tension distribution is sensitive to spatial or flow heterogeneities in capillary O_2 delivery, an effect that is markedly reduced if Michaelis–Menten kinetics is combined with additional resistance (capillary barrier) to O_2 efflux (Turek *et al.* 1989).

Generalizations to accommodate large-scale geometries or three-dimensional geometries, such as the increased capillary density along a muscle and capillary anastomoses, will be computationally extremely demanding. Thus, considering such tissue-level complications also requires a framework for accurately approximating the detailed geometry that dictates tissue uptake, as well as feedback between the capillary supply and the tissue within large-scale models. This also provides the ideal framework for testing, generalizing and implementing mathematical frameworks (e.g. Chapman *et al.* 2008) that are being developed in response to the increasing importance of multiscale problems associated with functional capillary supply, as schematically illustrated in Fig. 9. It is anticipated that such explorations will facilitate the coupling of the microvasculature with the tissue level in the next generation of multicapillary models.

Summary

It is usually assumed that capillary supply varies directly with O_2 demand, but as a general statement this is clearly wrong. Another common idea is that local capillary supply in muscle is determined by fibre type; again, this is not supported by experimental evidence. These and other misconceptions arise from the erroneous approach of modelling capillary distribution as either random or in a fixed geometric pattern. New approaches have focused on more anatomically realistic models, leading to the appreciation that capillary distribution is similar across differing scales and biological function. Future implications for this work will encourage development of multiscale simulations and approximations to explore influences of the microvasculature at the tissue level, such as regional specializations or functional compartmentalization for metabolite recycling, and inform new avenues to explore the exquisite control of capillary growth required for effective angiotherapy.

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