ELSEVIER

Calculation of Oxygen Pressures in Tissue with Anisotropic Capillary Orientation. II. Coupling of Two-Dimensional Planes

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ABSTRACT

The mathematical descriptions of oxygen transport in terms of two-dimensional diffusion in planes perpendicular to the capillaries can be coupled for an ensemble of planes to yield a three-dimensional description. In tissue with a distinct orientation of the oxygen supplying structures, the capillaries, this leads to a description of oxygen pressure in a whole tissue volume. Muscle tissue is an example of such tissue. The method allows calculation of oxygen pressure (pO_2) at any location in the volume. Tissue volume oxygen status can be assessed by constructing a pO_2 histogram, gathering pO_2's at a large number of locations in the tissue.

1. INTRODUCTION

The complicated task of calculation of oxygen pressures in tissue is simplified considerably when a description in terms of two-dimensional diffusion is allowed [5]. Such a description seems appropriate for tissue with a distinct orientation, like muscle tissue, where the oxygen supplying capillaries run largely in parallel [1]. Under certain conditions, in any plane perpendicular to the capillaries oxygen partial pressure can be described by means of a single mathematical formula. Such a description can serve as a solution by itself [5, 9] or be extended to a three-dimensional description. The parameter constants in the two-dimensional description are derived from the boundary conditions in that plane. These parameters include the oxygen supply area of each individual capillary, which allows calculation of the amount of oxygen withdrawn from the capillary. By coupling consecutive planes, a three-dimensional description can be constructed along the same lines as for the simple Krogh model [10]. In each plane and for each capillary, the oxygen distributed into the corresponding surrounding tissue area is subtracted from the amount in the flowing capillary blood. From the

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resulting next-plane O_2 content new capillary pO_2's can be calculated. Then, these values can serve as boundary conditions for that next plane. In this way, a number of planes can be overlaid to describe a tissue volume, containing several capillaries (or, capillary segments). Since the two-dimensional solution was explicitly solved for a rectangle or a circle, the resulting tissue volumes of a block and a cylinder are treated most readily. Additionally, tests can be provided concerning the validation of this three-dimensional approach.

2. THEORY

2.1. *PLANE COUPLING*

The two-dimensional approach [5] describes oxygen distribution in a plane through a composed quantity, the "driving pressure" p^*:

$$\mathscr{P}\nabla^2 p^* = \dot{Q}, \tag{2.1}$$

where $\mathscr{P}$ is oxygen permeability constant of the tissue and $\dot{Q}$ is its oxygen consumption rate, per tissue volume. p^* is a composed quantity, $p^* = p + p_F s$, where p is oxygen partial pressure, p_F is a constant called facilitation pressure [9], and s is oxygen saturation of the myoglobin (Mb) in the tissue; p_F depends on Mb concentration and mobility in the tissue. For N oxygen sources in a flat plane and for the two-dimensional equivalent of (2.1), the formula was derived:

$$p^* = \frac{\dot{Q}}{4\mathscr{P}}\left[\Phi(\vec{r}) - \sum_{i=1}^{N} \frac{A_i}{\pi} \ln\left(\frac{|\vec{r} - \vec{r}_i|^2}{r_{ci}^2}\right)\right], \tag{2.2}$$

where Φ was termed "background function," a function of location $\vec{r}$ obeying (2.1) for the plane without sources, and $A_i, \vec{r}_i, r_{ci}$ are O_2 supply area, location and characteristic measure of the ith capillary, respectively. This description was in terms of point-like sources and the O_2 supply area A_i is that of the ith point source, which is infinitesimally small. When dealing with capillaries, of finite dimensions, part of this O_2 supply flows into the capillary and will be passed to the next plane. The net oxygen release of the kth capillary has to be found by integration of oxygen flux leaving the capillary across the capillary outline (rim k)[1]:

$$\sigma_k O_2 = \oint_{\text{rim } k} J_{nk}\, dr',$$

[1] Symbols and notation follow the same guidelines as in [5].

where $\sigma_k O_2$ is the amount of oxygen released into the plane (so, per unit time and per unit tissue length) and J_{nk} is the oxygen flux perpendicular to the capillary outline and is equal to $-\mathscr{P}\partial p^*/\partial \vec{n}$, where $\vec{n}$ is the vector normal to the outline. The outline is around a capillary area A_{ck} and we could apply Green's law were it not that the integral is around a singularity, at $\vec{r} = \vec{r}_k$. The singularity can be removed by isolating a small area $A_{\varepsilon k}$ around the singularity, with outline rim ε. Applying Green's law for the remaining "area with a hole":

$$\sigma_k O_2 = \oint_{\text{rim } \varepsilon} J_{nk}\, dr' - \iint_{A_{ck} - A_{\varepsilon k}} \mathscr{P} \nabla^2 p^*\, dA'.$$

Now in the limit for $\varepsilon \to 0$ the first integral is that of the point source whereas for the second integral the substitution of (2.1) is allowed:

$$\sigma_k O_2 = \dot{Q}(A_k - A_{ck})$$

so that the capillary area has to be subtracted from the point source supply area. This amount of O_2 extracted from the capillary per unit of time and per plane leads to a decrease in capillary O_2. The O_2 is transported by the flowing blood in the z-direction perpendicular to the x, y-plane. Consequently, there is a gradient in blood O_2 flow equal and opposite to the extraction $\sigma_k O_2$:

$$\frac{d}{dz}(F_k c_{tk} O_2) = -\sigma_k O_2$$

where F_k is the capillary blood flow (volume/time) and $c_{tk} O_2$ the total O_2 content (moles/volume) of the kth capillary; this total amount encompasses O_2 both free and reversibly bound by chemical reactions with the blood hemoglobin (Hb). Under the assumption that no fluid leaves the capillary, the flow F_k is independent of plane position z so that:

$$\frac{d}{dz} c_{tk} O_2 = -\frac{\dot{Q}}{F_k}(A_k - A_{ck}). \tag{2.3}$$

The above derivation is a generalization of that of [10] but it should be noted that in that publication **F** is the specific blood flow, i.e., per unit of tissue volume, whereas F_k here is the blood volume flowing through the kth capillary only.

2.2. *CAPILLARY OXYGEN*

For the two-dimensional solution [5] only the value of the kth capillary pO_2, p_{ck}, had to be known, but here also its relation to the O_2 content $c_{tk}O_2$ has to be found. Most of the capillary oxygen is contained in the erythrocytes so that it is straightforward to take p_{ck} as the erythrocyte pO_2. Due to intracapillary transport, however, plasma pO_2 will be lower than erythrocyte pO_2 and consequently average capillary pO_2, $\bar{p}_{ck}$, will be also. The total capillary O_2 content is expressed as:

$$c_{tk}O_2 = \bar{\alpha}_k \bar{p}_{ck} + \bar{B}_k s_{ck}, \tag{2.4}$$

where α is oxygen solubility, B is oxygen binding capacity, and s_c is Hb oxygen saturation. The overbars indicate average values, averaged over the whole capillary, erythrocyte, and plasma, and the index k indicates the kth capillary. These values may be different for each capillary since hematocrit values can be different and all quantities have to be evaluated for each respective erythrocyte/plasma mixture. The O_2 binding groups in the hemoglobin molecule are the four heme groups, so when all these groups are available for oxygen (none blocked by, e.g., CO or oxidation) the oxygen binding capacity B_k is equal to the heme concentration, i.e., four times the average Hb concentration of the kth capillary. The saturation s_{ck}—the erythrocyte saturation—is related to p_{ck} through the equilibrium relation the oxygen dissociation curve (ODC) assuming chemical reactions to be fast (these are of the order of milliseconds [2]). There are several equations available for the description of this chemical equilibrium, the easiest one being the so-called Hill formula [4]:

$$s_c = \frac{p_c^n}{p_{50,c}^n + p_c^n}, \tag{2.5}$$

where $p_{50,c}$ is the Hb half-saturation O_2 pressure and n is called the Hill constant. The subscripts k have been dropped since the equation is general, holding for all capillary blood. There is vast literature about the topic of $Hb-O_2$ interaction. Depending on capillary blood conditions, such as pCO_2, pH, temperature, etc., the half-saturation pressure can be different for each capillary situation whereas such differences for n are so small that they can be neglected. The Hill formula is an empirical equation lacking chemical background but describes most ODCs very well above $\sim 10\%$ saturation. For the remaining part, extensions by other formulations are available [2, 13, 14] but they rarely will be needed because capillary saturations in this range are quite unphysiological.

When elaborating (2.3), the difference between the $\bar{p}_{ck}$ of (2.4) and "capillary" p_{ck} as in (2.5) is irrelevant if that difference is independent of z. In other words, $p_{ck} - \bar{p}_{ck}$ may be different for different capillaries but that does not matter when it is a constant along the capillary trajectory for any particular capillary. In that case $d\bar{p}_{ck}/dz$ is equal to dp_{ck}/dz and (2.3), (2.4) can be combined:

$$\left(1 + p_{\beta,k}\frac{ds_c}{dp_c}(p_{ck})\right)\frac{dp_{ck}}{dz} = -\frac{\dot{Q}}{\bar{\alpha}_k F_k}(A_k - A_{ck}), \tag{2.6}$$

where $p_{\beta,k} = \bar{B}_k/\bar{\alpha}_k$ is the pressure equivalent of the amount of chemically bound O_2 present in 100% saturated blood. Equation (2.6) relates oxygen supply to axial gradient in capillary pressure, i.e., between the planes.

In the calculation algorithms for the parameters in (2.2), r_{ci} was taken as the effective capillary radius, $r_{ci}^2 = A_{ci}/\pi$. Note, however, that this does not imply that the capillary outline is circular. Instead, (2.3) and (2.6) are derived generally. Moreover, capillary outlines are allowed to be different in each plane.

3. CALCULATION ALGORITHMS

3.1. *LAYER STEP*

For solving a particular situation, it is obvious that for each capillary a value of p_{ck} must be assumed in one of the planes. Say, that for all capillaries this is the plane at $z = 0$. In each consecutive plane, the capillary values follow from (2.6). Going from the plane at $z = z_m$ to $z = z_{m+1}$ the left side can be easily integrated and as a first approximation the right side can be considered (approximately) constant:

$$\begin{aligned}(p_{ck} + p_{\beta,k}s_{ck})\big|_{z=z_{m+1}} &\simeq (p_{ck} + p_{\beta,k}s_{ck})\big|_{z=z_m} \\ &\quad - \frac{\dot{Q}}{\bar{\alpha}_k F_k}\left(\big|A_k\big|_{z=z_m} - A_{ck}\right)(z_{m+1} - z_m),\end{aligned} \tag{3.1}$$

where the relation in fact is for p_{ck} because of its one-to-one relationship with s_{ck}, the ODC. When A_k is overestimated by taking the value at $z = z_m$, p_{ck} will be estimated too low at $z = z_{m+1}$. Such low p_{ck} results in less supply, i.e., too low a value calculated for A_k in that plane. Then, according to (3.1) the next pressure drop is underestimated. Consequently, this scheme with a first-order approximation for

A_k is expected to be sufficient. It can be improved by repeating the calculation of (3.1) now with an averaged value of A_k:

$$\begin{aligned}(p_{ck} + p_{\beta,k}s_{ck})\big|_{z=z_{m+1}} &\simeq (p_{ck} + p_{\beta,k}s_{ck})\big|_{z=z_m} \\ &\quad - \frac{\dot{Q}}{\overline{\alpha}_k F_k}\left(\frac{1}{2}A_k\Big|_{z=z_m} + \frac{1}{2}A_k\Big|_{z=z_{m+1}} - A_{ck}\right)(z_{m+1} - z_m),\end{aligned}$$

and this procedure might be iterated. Whether and how many iterations are needed will depend on the step size $z_{m+1} - z_m$.

3.2. *ELABORATION OF THE LAYER STEP*

The layer step yields a formula for a combination of p_{ck} and s_{ck} in the plane at $z = z_{m+1}$ (see (3.1)) which generally can be written as:

$$p_{ck} + p_{\beta,k}s_{ck} = G_k. \tag{3.2}$$

Commonly, the term $p_{\beta,k}s_{ck}$ will be the larger term and an iterative method should be set up correcting s_{ck}. However, this quantity is bounded between 0 and 1 and corrections either must be restricted to that range or applied to a mathematically transformed value. An appropriate transformation seems to be

$$p_c = p_{50,c}\exp(t) \tag{3.3}$$

and a corresponding expression for s_c according to the ODC, e.g., (2.5). Initial estimates $p_{ck}^{(0)}, s_{ck}^{(0)}, t^{(0)}$ can be found by using the values of the former plane (at $z = z_m$) and the estimates of the next step come from linearization of (3.2), worked out in terms of (2.5):

$$\left\{p_{ck}^{(j)} + p_{\beta,k}ns_{ck}^{(j)}\left(1 - s_{ck}^{(j)}\right)\right\}\Delta t^{(j)} = G_k - p_{ck}^{(j)} - p_{\beta,k}s_{ck}^{(j)},$$

allowing calculation of $\Delta t^{(j)} = t^{(j+1)} - t^{(j)}$. According to (3.3) the next-step pressure is found from

$$p_{ck}^{(j+1)} = p_{ck}^{(j)}\exp(\Delta t^{(j)}),$$

but it was found that the procedure becomes even faster when the exponent is linearized:

$$p_{ck}^{(j+1)} = \begin{cases} p_{ck}^{(j)}(1 + \Delta t^{(j)}) & \Delta t^{(j)} > 0 \\ \dfrac{p_{ck}^{(j)}}{1 - \Delta t^{(j)}} & \Delta t^{(j)} < 0. \end{cases}$$

Also note, that the above formulas are applicable for other schemes of the relationship between p_c and s_c than stated in (2.5) if an appropriate value for n is used [13, 14]. Furthermore, iteration may be speeded up by combining the steps for calculation of $p_{ck}^{(j+1)}$ and averaging A_k over the planes at $z = z_m$ and $z = z_{m+1}$.

4. RESULTS OF AN EXEMPLARY CASE

As a calculation example, a tissue block was considered with parallel capillaries running from bottom ($z = 0$) to top plane ($z = z_M$) where capillary location in each plane was according to the situation of Figure 1. The cross-section is square and distances will be expressed as fractions of the width/height (0–1). The square field was divided into four zones of equal size with different conditions of capillary spacing/capillary flow, as indicated by the letter combinations in Figure 1. The first letter **E** or **H** indicates equally or heterogeneously spaced

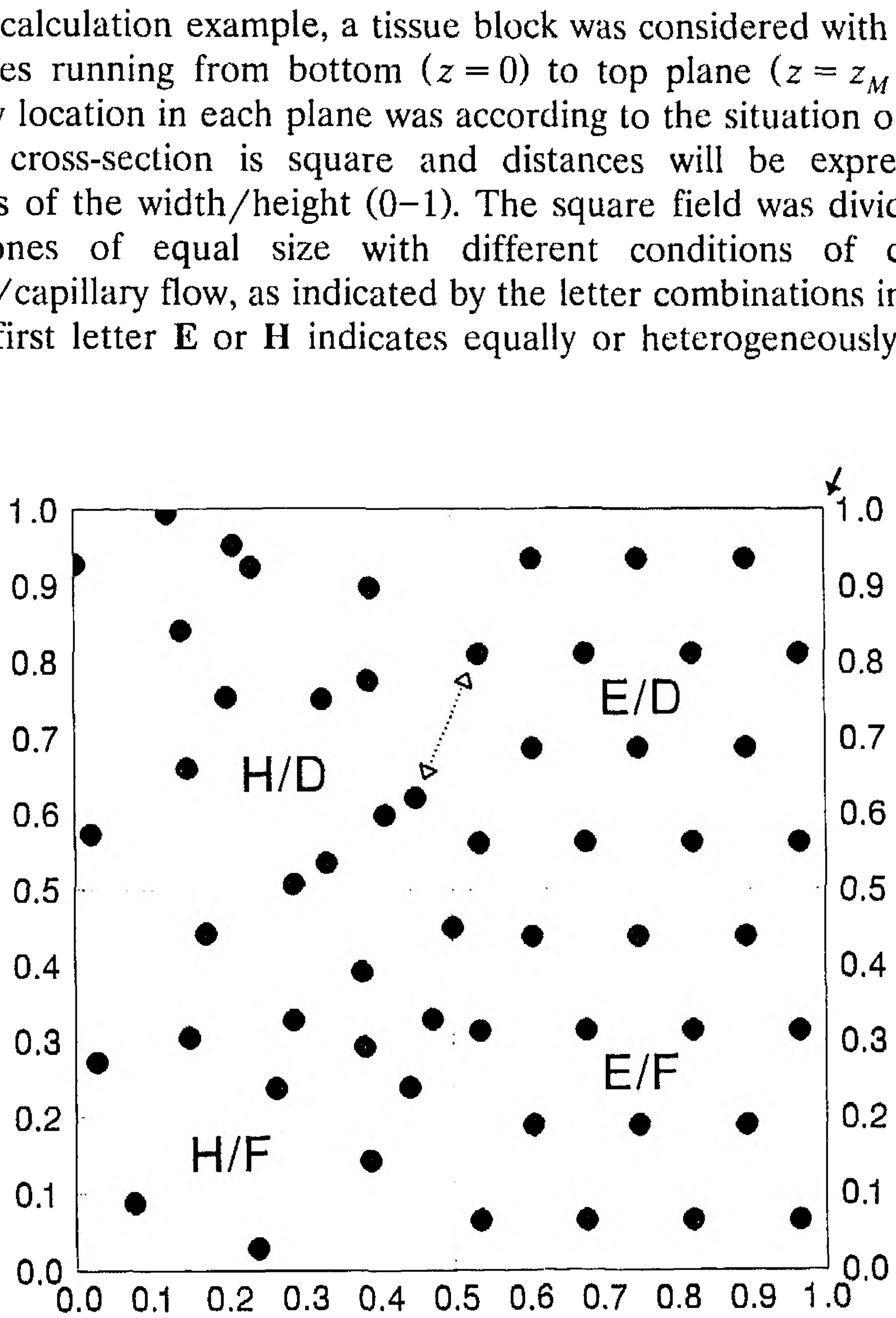

FIG. 1. Capillary locations of the example, a square field of four square zones with different capillary properties as indicated by the two-letter coding. The first letter indicates equal (**E**) or heterogeneous (**H**) capillary spacing, the second identical flow (**F**) or randomly distributed flow (**D**). Distances are given as fractions of the maximum. The thick arrow top right is the viewpoint direction of Figure 2; the dotted arrow points to the two capillaries indicated there.

capillaries and the second letter **F** or **D** identical (F_k equal to the average value of all capillaries) or randomly distributed capillary flow respectively. The example is to elucidate some effects of heterogeneities in capillary spacing and capillary flow. The equally spaced capillaries were placed in a filled hexagonal grid whereas the heterogeneous distances were as for realistic rat heart [9] (combined with a square side of 152 μm). Random flow was distributed with a standard deviation of 0.2 and all the other capillary data (r_{ck}, initial p_{ck}, $p_{50,ck}$, $p_{\beta,k}$) were identical for each capillary. There was no facilitation by myoglobin and no difference between capillary and capillary-rim pressure ($p_F = 0$ and all $\gamma_k = 0$; see [5]). The remaining data are summarized in Table 1 and are taken also from [9], combined with a layer spacing of 5 μm. The $\dot{Q}/\bar{\alpha}_k F_k$ needed for the evaluation of (3.1) come from combination of the $\dot{Q}/\mathscr{P}$ needed for the calculations within each plane and the dimensionless parameter $\mathscr{P} z_M/(\alpha F)$, where $\alpha F = \bar{\alpha}_k F_k$, which was identical for each capillary.

4.1. *OXYGEN PRESSURE IN EACH PLANE*

The resulting pO_2 fields were calculated for two planes, at $z = 0$ (high pO_2) and at $z = z_M$ (low pO_2), reached in 60 equidistant steps ($M = 60$). In-field values were calculated using (2.2) as described in [5], whereas the steps were taken according to (3.1). Both pO_2 fields are shown in Figure 2, together with the capillary pO_2s indicated as solid dots—note, that these capillary pO_2's in the top profile are identical ($p_{ck} = 2.5$). Pressure drop between the planes is different for different supply-area/flow combinations; a good example is seen for the capillaries indicated by the arrow in the lower ($z = z_M$) field. In contrast, in the **E/F** region seen at the left the drop is equal for each capillary.

4.2. *TISSUE VOLUME OXYGEN HISTOGRAM*

Usually, the oxygen status of a whole piece of tissue is expressed in terms of a pO_2 histogram, where the oxygen pressure is sampled at a

TABLE 1

Parameter Values Used for the Calculations of Figure 2 and Figure 3*

Quantity	r_{ck}	$\dot{Q}/\mathscr{P}$	$\mathscr{P} z_M/(\alpha F)$	$p_{ck,z=0}$	$p_{\beta,k}$	n
Unit	l	p·l^{-2}	—	p	p	—
Value	0.0158	115.5	30	2.5	169	2.7

*All values are relative to field width (length, unit l) and $p_{50,c}$ (pressure, unit p); $\mathscr{P} z_M/(\alpha F)$ and n are dimensionless. Dimensional values of r_{ck} and $p_{ck,z=0}$ were 2.4 μm and 12.5 kPa respectively.

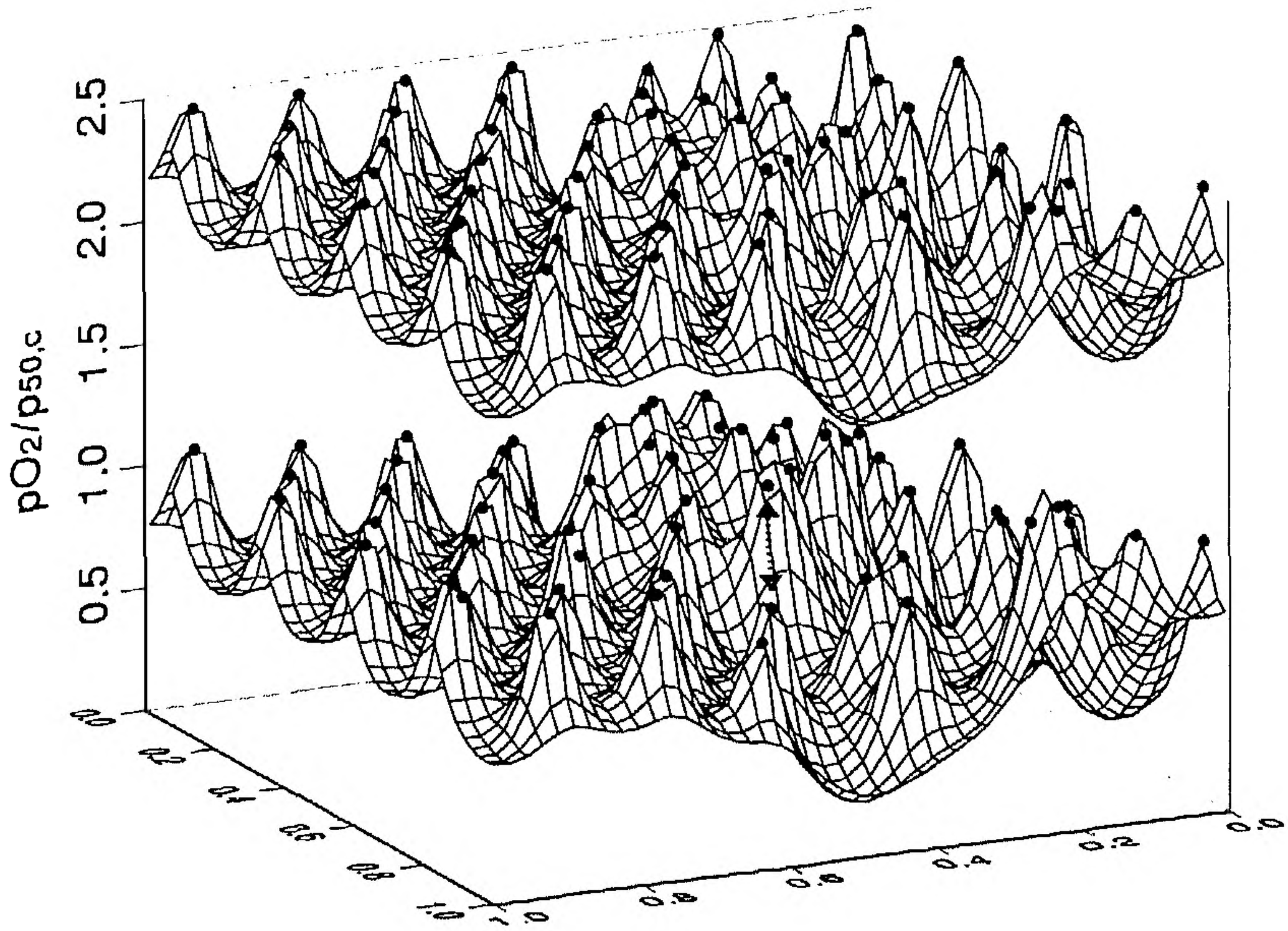

FIG. 2. Tissue pO_2 (vertical axis; relative units) fields calculated for the capillary arrangement of Figure 1; base plane shown with the same axes as in this figure (**E**/**D** zone in front); viewpoint 65° in (see solid arrow in Figure 1) and 15° above the x, y-plane. Top field is for homogeneous starting capillary pO_2 ($z = 0$); bottom field is for end-capillary conditions ($z = z_M$). Solid dots indicate capillary pressures; the arrow points to a clearly visible case of difference between end pressures.

number of locations and gathered into pO_2 classes. This can be simulated here by calculating pO_2 in a cubic grid with a lattice distance equal to the distance between the planes, i.e., identical square grid in each plane. This resulted in 56120 grid points (grid points inside a capillary were omitted, of course). Values were gathered in classes of $0.1\,p_{50,c}$ width and shown as fraction **f** of the total number in Figure 3. Also, the cumulative histogram (Cum) is shown as black dots interconnected by solid lines; these dots indicate the percentage of values calculated below the corresponding pO_2 threshold. This type of histogram is utilized in literature as well. In both ways, a good impression can be obtained of the oxygen status of the tissue block.

5. DISCUSSION

The present method provides a straightforward way to calculate pO_2 in a whole volume. The basis for this calculation is the two-dimensional method [5] and the individual planes are coupled as described above.

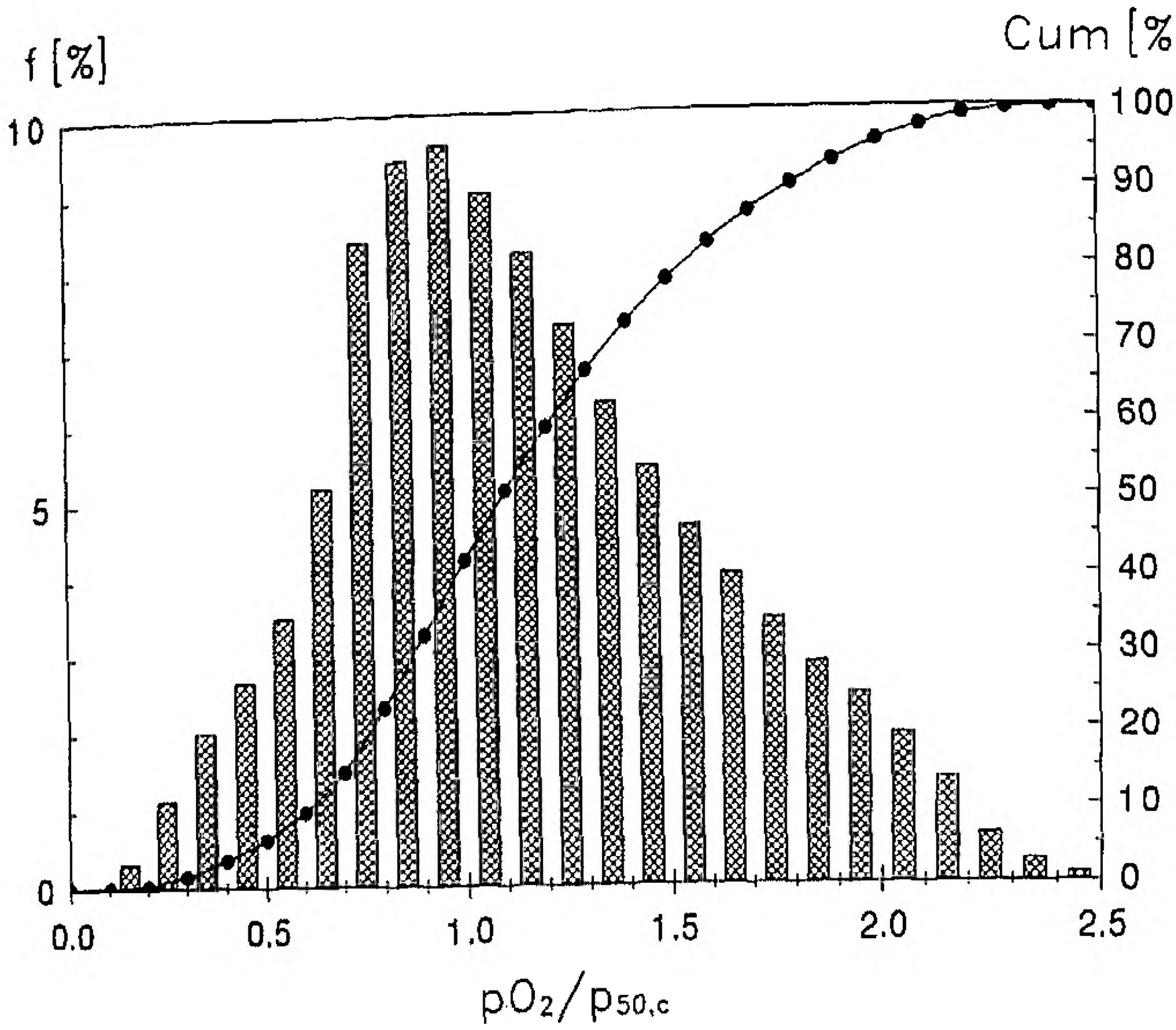

FIG. 3. pO_2 histogram calculated for the example at 56120 locations in the tissue block. Bars are frequency (f; left axis) of occurrence of tissue pO_2 in the classes as shown on the horizontal axis (relative units); dots connected by solid line are cumulative frequency (Cum; right axis).

The assumption involved, consequently, is that the influence of adjacent planes on the calculation within a plane is negligible. It comes down to a constraint already stated for the two-dimensional solution, that the term $\partial^2/\partial z^2$ in the Laplacian of (2.1) must be negligible. This can be judged numerically by approximating the second derivative $\partial^2 p^*/\partial z^2$ at $(x, y, z = z_m)$ by the corresponding difference equation. This $\partial^2 p^*/\partial z^2$ is a part *fr* of $\nabla^2 p^*$ and $\nabla^2 p^*$ is equal to $\dot{Q}/\mathscr{P}$ so that

$$fr = 2\frac{\mathscr{P}}{\dot{Q}}\left|\frac{(z_m - z_{m-1})p^*_{m+1} - (z_{m+1} - z_{m-1})p^*_m + (z_{m+1} - z_m)p^*_{m-1}}{(z_m - z_{m-1})(z_{m+1} - z_{m-1})(z_{m+1} - z_m)}\right|,$$

where $p^*_{m''}$ is the value evaluated at $(x, y, z_{m''})$, respectively. The fraction *fr* should have a negligible influence on the calculations; consequently, *fr* should be small. When tissue pO_2 largely follows capillary pO_2 (only gradual shifts in oxygen supply areas and only little desaturation of the myoglobin in the tissue) the estimation of *fr* can be restricted to the capillary pO_2s(fr_c). In the above example, the maximum value found was 0.13; this occurs in the $(z = 0)$-plane, and after that initial plane both the maximum (0.035 for $z = z_5$) and the average value rapidly

decrease so that in large regions of the tissue block fr was far below 1%. For fr_c, a formula can be derived using (2.6):

$$fr_{ck} = \mathscr{P}\dot{Q}\left(\frac{A_k - A_{ck}}{\overline{\alpha}_k F_k}\right)^2 \left.\frac{p_{\beta,k}\left|\dfrac{d^2 s_c}{dp_c^2}\right|}{\left(1 + p_{\beta,k}\dfrac{ds_c}{dp_c}\right)^3}\right|_{p_c = p_{ck}}$$

and indeed fr_c will become small when the ODC becomes involved, i.e., $p_{\beta,k}(ds_c/dp_c)$ is large. Also, where the ODC is approximately linear, $s_c \approx s_{ck} + \{ds_c/dp_c(p_{ck})\}(p_c - p_{ck})$, the second derivative $d^2 s_c/dp_c^2$ is almost zero and consequently fr_c is. Therefore, especially for the physiologically interesting range where the Hb is active the above method seems to be appropriate.

The picture is not complete for a situation where capillaries are not straight and parallel to the z-direction, or when they start or end in one of the planes between $z = 0$ and $z = z_M$. There is no constraint in the above derivation that capillary locations must be the same for all planes, so slanting, tortuous, and even branching capillaries and capillary pieces of limited length are not excluded beforehand [6]. The constraint still is that the term $\partial^2/\partial z^2$ in the Laplacian can be neglected. This should be tested for the whole piece of tissue under consideration.

For capillaries branching from an arteriole (or draining into a venule) the situation is even more complicated because of the presence of the larger blood vessel, which can extend in any direction and might distribute oxygen itself. The arteriole has the highest pO_2 so gives rise to a local large value of $\partial^2 p/\partial z^2$ but that is not so relevant since the vessel is at that very location distributing oxygen. So, capillary ends should be handled with some caution, more so since the high values of fr_c are expected there, as found in the above example. Possibly, the highest pO_2 values found in the calculations should be disregarded. This concerns only a small portion of the total tissue, as can be seen from the example, Figure 3, where the tissue fractions close to the highest pressure of $2.5p_{50,c}$ are very small.

It is just one of the features of the treatment presented here that all capillary data can be different for the individual capillaries. Not only capillary location $\vec{r}_i$ but also its outline, flow, Hb content (hematocrit), initial pO_2 drop (γ_k, see [5]) and internal conditions determining $p_{50,ck}$ (like pCO_2 and pH) can be chosen individually. Outline, γ_k, and internal conditions can be different even for each different plane. This opens the way for investigation of the effects of capillary redistributions of flows and erythrocytes on tissue pO_2.

The method is semi-analytical, where the pO_2 within a plane is directly described by mathematical formulas [(2.2)] and the planes are coupled numerically. In order to solve the situation for a whole piece of tissue, first the conditions of each individual plane must be calculated, i.e., $\Phi(\vec{r}_0)$ and A_k must be known, where $\vec{r}_0$ is any location in the plane. This means that the number of calculations is restricted to the number of capillaries plus one, where a purely numerical method would need a much denser grid in each plane (certainly more than 100 grid points per capillary [6]). The block is the readiest form of tissue piece especially for calculation of a pO_2 histogram since it is apt to be overlaid with a cubic grid. It is to be expected that a regular grid is random with respect to the tissue since capillary locations are not regular in a tissue. When it is regular nevertheless, as in the above example in the **E/F** and **E/D** zones, the grid spacing must be chosen cautiously to avoid calculation of pO_2 systematically at the same distance of the capillaries, as is done in the above example by choosing the quotient of grid spacing and capillary distance equal to 0.2647. In judging the effects of heterogeneity of capillary spacing this should be—and has been [5]—a point of concern.

Since flow can be chosen negative, modeling of countercurrent flows is also possible [7]. This was done in literature also using different models or configurations [12]. There is a problem in choosing the boundary conditions since now a low value of capillary pO_2 must be found in the initial ($z = 0$) plane and will increase in each following plane such that it ends at the correct, e.g., arterial, value. This may be a bit tricky because a small overestimation of this initial pO_2 can lead to "exploding" (increasing very fast) capillary pO_2's in the last planes. The reason is that with high pO_2 the Hb becomes loaded with oxygen and can store hardly any more. This causes the next-plane pO_2 to be much higher, which in turn leads to a high supply area so a high flux from the capillary; the high O_2 outflow implies a higher added amount for the next plane. It is just the opposite of the argument following (3.1). For oxygen pressures staying within the physiological range, one should always be able to find an appropriate initial value.

Subtracting A_{ck} from A_k as in (2.3) seems an unimportant correction because the total space occupied by capillaries is mostly only a small fraction of the tissue volume. This might be true considering the tissue, but it can be important for the capillaries. Equation (2.2) allows for very small individual capillary O_2 supply areas A_k—these can even become negative [5]. Let us assume a supply area A_k that is half the size of the capillary area A_{ck}. Then, neglecting A_{ck} in (2.3) would predict decreasing capillary pO_2 whereas actually this value would increase.

The coupling of planes can be considered as an extension of the method of [10]. Plane coupling can be done for any two-dimensional

description (see [12]). Here, it is laid out in terms of capillary oxygen supply areas A_k and it could be combined with any two-dimensional method that allows calculation of such supply areas. The net O_2 release is calculated also considering the actual capillary shape [(2.3)]. Also, the further derivations are quite general, allowing for differences between erythrocyte and apparent capillary pO_2s ($\bar{p}_{ck}$ and p_{ck}). An area might be negative which would imply real oxygen shunting, from adjacent capillaries to the one under consideration [3]. Capillary flow cannot only be heterogeneous but also countercurrent flow is allowed, as done by [11].

In the example of Figures 1 and 2, heterogeneity in capillary flow leads to heterogeneity in tissue pO_2. This is best seen in the **E/D** zone of Figure 1. In Figure 2, this is the front middle part, where the top profile starts homogeneous and bottom profile ends heterogeneous. Heterogeneity in pO_2, however, is much less than in the adjacent zones with heterogeneous capillary locations. Actually, there is a mitigating effect. A rapidly decreasing capillary pO_2, either due to a large supply area or to low blood flow, will lead to a smaller supply area A_k in the following planes and consequently to less oxygen release there. Eventually, the resulting heterogeneity in capillary pO_2 will increase only slightly [7,8]. In the example of Figure 2, the capillaries indicated by the arrow have very different supply areas in the starting plane (top profile); that of the front capillary is 58% larger than the other one. In the bottom plane, it is only 24% larger. Capillary pO_2's both start at $2.5p_{50,c}$, half-way they differ by $0.29p_{50,c}$ and in the bottom plane by slightly more, $0.32p_{50,c}$. Half the bottom-plane pO_2 difference, $0.16p_{50,c}$, is reached in the first 15% of the capillary length. When starting from heterogeneous capillary pO_2's (in the top plane) the deviation in pO_2 decreases, as found by others [3, 11, 12].

Summarizing, the method presented here is considered to be a powerful tool in the modeling of oxygen transport to tissue. It is directly applicable to tissue models with straight and parallel capillaries, while the other capillary data can be chosen freely. Several extensions to other situations are open (see also [5]) but these should be considered individually.

APPENDIX: NOMENCLATURE

A_i A_k	capillary supply area
A_{ci} A_{ck}	capillary cross-sectional area
$A_{\varepsilon k}$	infinitesimal area
B_k	oxygen binding capacity of hemoglobin
$c_{tk}O_2$	total capillary oxygen content

F_k	capillary blood flow
fr	estimated three-dimensional error in Laplacian
fr_c fr_{ck}	capillary estimate of fr
G_k	equivalent combined pressure O_2 + Hb
Hb	hemoglobin
J_{nk}	flux across capillary outline
M	number of layers
Mb	myoglobin
N	number of capillaries
n	Hill constant
$\vec{n}$	vector normal to capillary outline
ODC	oxygen dissociation curve of hemoglobin
$\mathscr{P}$	oxygen permeability constant
p	oxygen partial pressure, pO_2
$p_{50,c}$ $p_{50,ck}$	hemoglobin half-saturation pressure
p_c p_{ck}	capillary oxygen pressure
p_F	facilitation pressure
$p_{\beta,k}$	equivalent hemoglobin pressure
p^*	oxygen driving pressure
$\dot{Q}$	oxygen consumption rate
$\vec{r}$	two-dimensional coordinate vector
$\vec{r}_0$	reference location in plane
r_{ci}	effective capillary radius
$\vec{r}_i$ $\vec{r}_k$	capillary location
rim k	capillary rim
rim ε	outline of infinitesimal area
s	myoglobin saturation
s_c s_{ck}	hemoglobin saturation
t	transformed variable ((3.3))
x y z	cartesian coordinates
z_m	location of the mth plane

GREEK SYMBOLS

α_k	oxygen solubility
γ_k	pressure drop proportionality factor
Δt	step in t
ε	infinitesimal distance
$\sigma_k O_2$	capillary oxygen release per plane
$\Phi(\vec{r})$	background function

SUPERSCRIPTS

(0) (j) (j+1)	iteration index
′ ″	dummy variable
overbar	average value

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