

## Three-dimensional morphometry of mammalian cells II. Areas, volumes, and area-volume ratios

Morfometría tridimensional de células de mamíferos.  
II. Areas, volúmenes y cuocientes área-volumen

ENRIQUE MORGADO<sup>1</sup>, CATHERINE OCQUETEAU<sup>1</sup>,  
MONICA CURY<sup>1</sup>, LILIAN BECKER<sup>2</sup>, URCESINO GONZALEZ<sup>3</sup>,  
LUIS MUXICA<sup>3</sup> and BRUNO GÜNTHER<sup>4</sup>.

<sup>1</sup>Departamento de Preclínicas, Facultad de Medicina, División Oriente,  
Universidad de Chile, Casilla 16.038, Santiago, 9, Chile.

<sup>2</sup>Departamento de Ciencias Exactas, Facultad de Ciencias y Humanidades,  
Universidad del Bío-Bío, Concepción. <sup>3</sup>Departamento de Matemática,  
Facultad de Ciencias, Universidad de Concepción, and

<sup>4</sup>Departamento de Ciencias Fisiológicas, Facultad de Ciencias Biológicas  
y de Recursos Naturales, Universidad de Concepción, Chile.

From three-dimensional diameter measurements of eleven kinds of cells pertaining to five different organs, which were excised from eleven adult mammals (nine species) whose body weight range was 40 g to 450 kg, we calculated the corresponding cell soma areas (A), volumes (V), and finally their area-volume ratios (A/V). The dissimilarities among these eleven cell types could be established quantitatively by means of a cluster analysis. The dendrograms for cell areas (A), volumes (V), and their corresponding area-volume ratios (A/V), yielded similar groupings when cell areas and volumes were compared, yet the grouping of the area-volume ratios (A/V) for the eleven types of cells was different. These results were corroborated by means of the principal components analysis, where five distinct cell groupings could be established. The relationship between cellular morphometry, oxidative metabolism, and body mass, was established by means of the fractal geometry of the transport systems (respiration and circulation), which provides the tools for the scale-dependent analysis of the surfaces across which the transport of metabolites is performed.

In a previous study (Ocqueteau *et al.*, 1989) we determined the three-dimensional cell diameters of eleven types of cells from five different organs that were subjected to standardized fixation and staining methods. The numerical data (7260 diameter measurements) were obtained from cells of mammals of different body sizes, i.e., from 40g mouse to a 450 kg cow. Subsequently these figures were submitted to a descriptive statistical analysis, then to a cluster analysis (city-block metric), and finally to a principal component analysis. The aim was to compare—in a quantitative manner—eleven different cell types by taking into account their three mean diameters (length, height, and width). In order to reduce cell variability we arranged the original data in such a way that all cell comparisons were made in accordance with the same spatial orientation, i.e., the mean cell diameter values were classified in three groups: major, medium, and minor. From these mean cell diameters values (see Table I) we calculat-

ed the corresponding mean cell areas (A), the somatic volumes (V), as well as the respective area/volume ratios (A/V), with the purpose of numerical evaluation relationships between the exchange areas (A) and volumes (V) of the corresponding cell somas.

### MATERIAL AND METHODS

The detailed description of the different organs whose cell diameters were investigated, the histological methods utilized, and the statistical criteria that were applied, can be found in the above mentioned publication (Ocqueteau *et al.*, 1989). The main topics of the latter study may be summarized as follows:

The mammalian *species* studied were (body weight, in grams, are given in parenthesis): Rockefeller mouse (40); male hamster (135); female hamster (168); female rat (189); male rat (200); cat (2.700); dog (5.300); sheep (12.000); pig (120.000); horse (270.000); and cow (450.000).

The *organs* studied were: 1) liver; 2) large intestine; 3) kidney; 4) cerebellum; and 5) skin.

The *cell types* measured were: 1) glomerular epithelium (kidney); 2) proximal convoluted tu-

TABLE I

Each number corresponds to the mean value of 20 individual measurements of the diameters of eleven different types of cells, which were obtained from eleven mammals, from the mouse (1) to the cow (11). The mean cell diameters were arranged in accordance to their sizes:  $D_1$  = major diameter;  $D_2$  = medium diameter; and  $D_3$  = minor cell diameter. In each column, the mean values ( $\bar{X}$ ) and the standard errors (SE) are indicated.

## CELL TYPES

N	1	2	3	4	5	6	7	8	9	10	11
MAJOR DIAMETER ( $D_1$ )											
1	12.05	14.00	10.60	3.60	9.80	31.00	15.00	16.70	4.95	20.20	18.90
2	21.25	16.10	11.90	6.00	14.25	47.50	13.30	19.20	5.90	16.00	15.90
3	25.75	17.00	12.15	6.30	14.30	45.25	14.80	17.50	5.75	17.15	16.65
4	24.00	16.90	14.00	6.70	12.65	33.55	14.45	17.35	6.00	15.85	17.70
5	18.00	15.65	13.20	6.00	14.00	56.50	14.45	18.80	6.60	15.40	16.65
6	23.25	16.45	14.75	6.40	14.75	50.50	14.20	27.70	6.65	16.00	15.75
7	21.75	16.00	12.95	6.40	14.10	52.50	16.05	18.45	5.40	16.10	17.20
8	20.05	16.85	13.50	4.50	10.90	46.75	16.05	42.75	7.45	23.80	15.90
9	17.20	16.00	12.30	6.90	11.55	71.75	19.20	37.00	7.60	18.85	14.40
10	34.00	18.95	13.50	4.90	12.70	42.50	17.30	41.50	7.35	18.35	18.55
11	18.30	16.85	14.60	7.80	10.60	85.50	18.95	46.60	7.40	18.75	16.40
$\bar{X}$	21.42	16.43	13.04	5.95	12.69	51.21	15.80	27.60	6.46	17.86	16.73
SE	1.70	0.36	0.37	0.36	0.52	4.76	0.59	3.61	0.28	0.76	0.39
MEDIUM DIAMETER ( $D_2$ )											
1	10.30	12.80	10.40	3.45	5.90	27.75	14.10	13.00	4.45	15.50	15.70
2	13.85	15.35	10.60	4.00	6.20	35.50	12.55	16.35	5.60	13.85	15.30
3	14.50	15.30	11.15	5.25	5.45	37.75	12.30	16.00	4.70	15.15	16.10
4	14.85	15.80	12.10	5.60	6.55	30.45	14.10	15.90	5.20	15.30	16.00
5	11.85	14.05	7.90	4.30	5.05	36.25	14.40	15.65	5.90	15.15	15.70
6	13.45	16.40	10.00	4.95	6.35	39.50	14.00	21.55	6.25	14.90	15.50
7	11.80	15.70	12.25	4.70	6.05	40.75	13.95	17.95	5.00	16.05	15.70
8	14.75	15.20	10.55	4.50	8.80	35.50	14.30	28.70	7.10	19.75	15.50
9	16.20	15.25	10.70	5.55	5.65	51.25	16.60	30.20	7.00	17.15	13.20
10	12.20	15.40	11.30	3.90	7.00	38.25	14.70	30.80	7.34	17.60	16.30
11	14.40	15.05	10.60	5.50	5.55	67.50	17.55	25.55	6.90	17.20	16.40
$\bar{X}$	13.47	15.12	10.69	4.70	6.23	40.04	14.41	21.06	5.95	16.15	15.64
SE	0.52	0.29	0.35	0.22	0.31	3.29	0.46	1.99	0.31	0.50	0.27
MINOR DIAMETER ( $D_3$ )											
1	2.40	11.95	9.80	3.00	2.75	24.35	13.70	12.85	3.80	15.25	15.60
2	3.40	13.80	7.55	3.10	3.40	22.20	11.35	16.20	5.30	11.35	14.70
3	5.00	13.35	10.00	4.65	3.95	23.75	11.00	15.00	4.55	14.10	15.80
4	5.70	13.70	9.90	4.15	3.00	26.15	13.60	15.90	4.40	13.85	15.80
5	3.05	13.55	7.75	3.80	3.45	23.95	12.05	15.35	5.30	14.35	14.85
6	5.20	14.80	9.80	4.55	3.40	30.00	10.90	20.50	5.80	14.50	14.65
7	4.75	12.50	10.50	3.75	3.25	31.50	13.20	15.55	4.55	12.70	14.70
8	3.10	14.10	7.85	3.90	2.75	35.00	14.00	23.55	7.10	17.05	14.65
9	3.20	14.70	7.65	3.60	2.85	35.50	11.75	17.00	6.85	14.20	12.85
10	3.80	13.80	8.20	3.55	3.35	33.55	14.45	17.75	6.95	16.40	16.20
11	3.60	14.85	8.90	3.65	3.10	39.25	12.45	18.50	6.15	17.00	14.95
$\bar{X}$	3.93	13.74	8.90	3.79	3.20	29.56	12.59	17.10	5.52	14.61	14.98
SE	0.32	0.28	0.34	0.16	0.11	1.75	0.38	0.88	0.34	0.53	0.27

bule (kidney); 3) Henle-loop cell; 4) fibrocytes; 5) fibroblast (kidney); 6) adipocyte (skin); 7) goblet cell (large intestine); 8) Pankinje cell (cerebellum); 9) granule cell (cerebellum); 10) sebaceous gland cell (skin); and 11) hepatocyte (liver).

*Cellular diameter measurements:* The mean values of 20 individual cell diameter measurements (given in micrometers) were summarized in Table I, where the 7260 individual diameter measurements were arranged in accordance with their spatial orientation: major, medium, and minor diameters.

*Statistical analysis:* The mean values of the 20 cell diameter measurements were submitted to three independent statistical procedures, namely a) descriptive analysis; b) cluster analysis; and c) principal component analysis. The hierarchical grouping were based on the simple means methods, and the cell dissimilarities were established in accordance to the corresponding Euclidean distances.

## RESULTS

### Somatic cell areas

When the mean three cell diameters are known ( $D_1, D_2, D_3$ ) as summarized in Table I, then the surface area ( $A$ ) can be determined by assuming that each cell soma is roughly a parallelepiped ( $A=2(D_1 \times D_2 + D_1 \times D_3 + D_2 \times D_3)$ ). From the numerical data obtained for eleven different cell types it is possible to obtain a dendrogram (Fig. 1) which illustrates that the area ( $A$ ) of the proximal convoluted tubule cell N° 2, the hepatocyte (N° 11), the sebaceous gland cell (N° 10), and the goblet cell (N° 7), are very similar. The next group is formed by the glomerular epithelium cell (N° 1) and the Henle-loop cell (N° 3), while the remaining cells (8, 6, 4, 5, 9) are increasingly dissimilar.

### Somatic cell volumes

The cell soma volumes were obtained from the product of the three diameters of each cell type ( $V = D_1 \times D_2 \times D_3$ ). The corresponding dendrogram (Fig. 2), obtained by means of the cluster analysis, shows that the volumes of cell type 2 and 11 are the most similar. These are followed by cell types N° 10 and N° 7, as well as by N° 1 and 3.

### The area-volume ratios

The relationships between the cell surfaces ( $A$ ) and corresponding volumes ( $V$ ) are

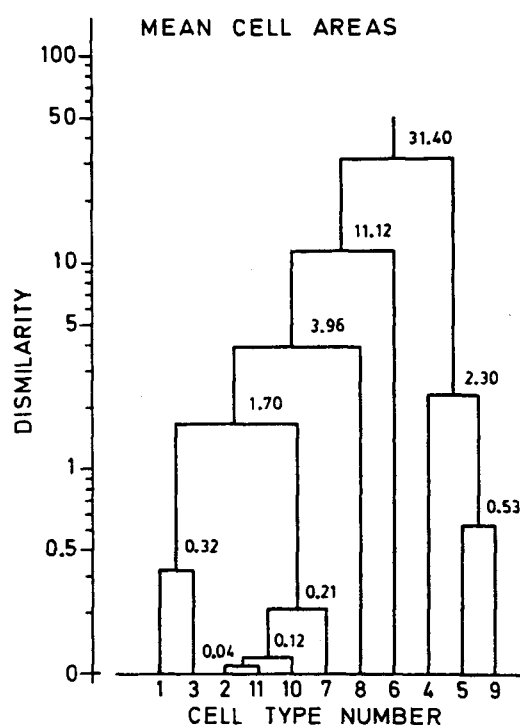


Fig. 1: Dendrogram based on the simple means and on the Euclidean distances for the calculated areas ( $A$ ) for cell somas corresponding to eleven types of mammalian cells. Ordinate: logarithm of dissimilarities. Abscissa: cell type numbers.

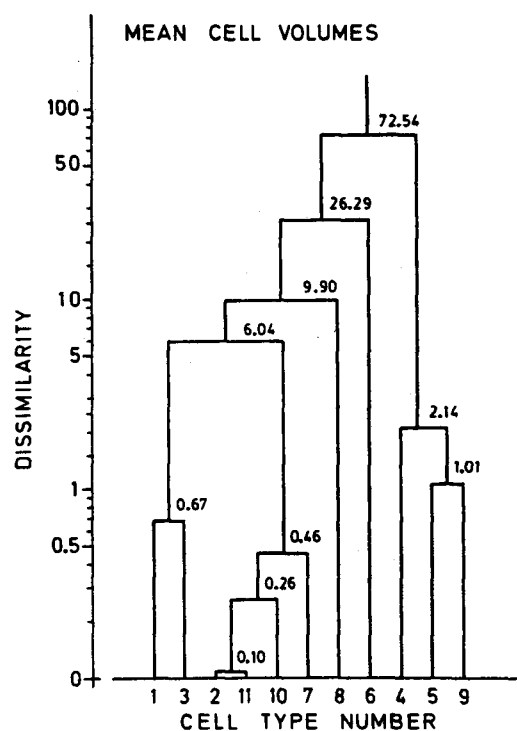


Fig. 2: Dendrogram for the calculated volumes ( $V$ ) of the somas of eleven types of mammalian cells. Ordinate: logarithm of dissimilarities. Abscissa: cell type numbers.

illustrated in Fig. 3. The greatest similarities are between cell types N° 2 and N° 11, and slightly less between N° 10 and N° 7.

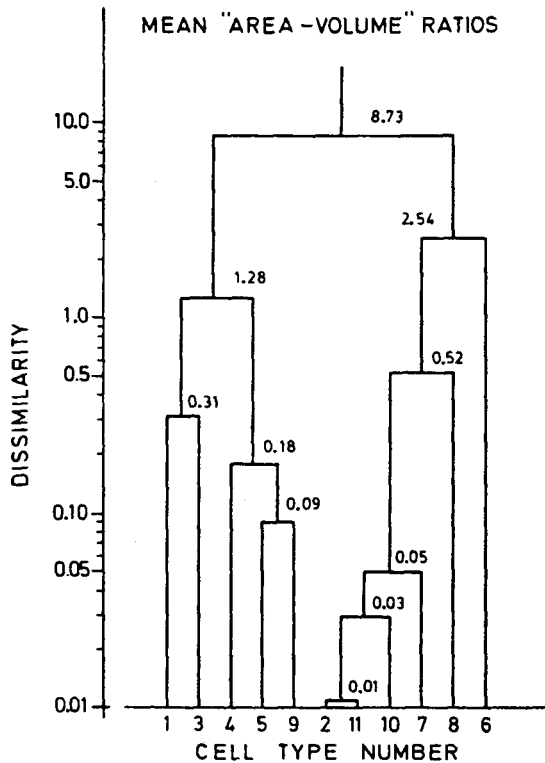


Fig. 3: Dendrogram of the calculated area-volume ratios (A/V) of mammalian cell somas. Ordinate: logarithm of dissimilarities. Abscissa: cell type numbers.

#### Principal components analysis

The first and second principal components were calculated for log area, log volume, and log area/volume, for the eleven different types of cells (Fig. 4). The cell grouping yielded five distinct entities; where three groups were represented by a single type of cells (6, 8, 9), another one by two very similar cell types (4, 5), and a separate cluster was conformed by the remaining cell types (1, 2, 3, 7, 10, 11).

#### DISCUSSION

The paramount feature of the organization of mammalian bodies is their "cellular" structure. For this reason, the morphometric analysis of the different cell types, pertaining to organisms of various sizes,

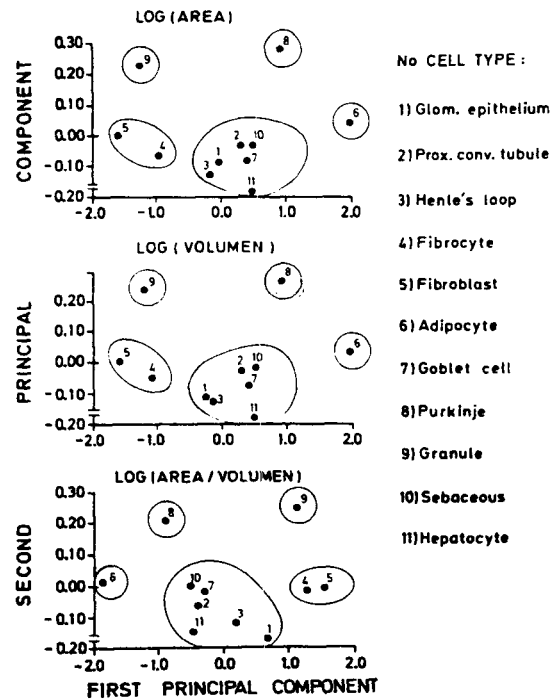


Fig. 4: Principal components analysis of log(area), log(volume), and log(area/volume ratios), for eleven different types of cells.

may help answering the following questions: first, which are the most common cell sizes in the different organs and tissues? Second, does the cell size change when small and large animals are compared: and third, which cell types are similar with regard to their areas (A), volume (V), and area-volume ratios (A/V)?

The literature on cell sizes in different organs, excised from various mammalian species, is extensive (Teissier, 1939; Thompson, 1917; Szarski, 1976; Altman & Dittmer, 1964; Spector, 1956). Nevertheless, most of the available data is incomplete because:

- 1) Only one cell diameter was commonly measured;
- 2) The numerical data were obtained from different organs of a single animal; and
- 3) Different authors used multifarious fixation and staining methods.

Maldonado *et al.* (1973) have been the only ones to utilize the same fixation and staining procedures in their studies. Unfortunately, they only measured one cell diameter of different cell types in homeotherms and poikilotherms of various sizes.

Consequently, in our previous communication (Ocqueteau *et al.*, 1989) we measured the three diameters of cells from five organs, excised from mammals of a wide body weight range, i.e., from 40g mouse to a 450 kg cow, which were submitted to identical fixation and staining procedures. Furthermore, and in order to avoid discrepancies due to idiosyncratic measuring criteria, all microscopic measurements (7260 in all) were performed by the same observer (C.O.) The three-dimensional cell diameters ( $D_1$ ,  $D_2$ , and  $D_3$ ) thus obtained were tabulated in accordance with the same orientation of the cells, i.e., the first diameter ( $D_1$ ) corresponds to the major cell axis; the second diameter ( $D_2$ ) to the medium size dimension, and the third diameter ( $D_3$ ) to the minor dimension of each cell. These mean cell diameters were submitted to a cluster analysis (group average method), and subsequently cell similarities or dissimilarities were established by applying the cityblock metric which is commonly known as the "Manhattan metric", and finally to the principal components analysis.

The aim of the present study was to calculate from the numerical data of the three mean cell diameters ( $D_1$ ,  $D_2$ ,  $D_3$ ), the corresponding cell areas ( $A$ ) by assuming a parallelepipedal form for each cell soma, the corresponding cell volumes ( $V$ ), and the area-volume ratios ( $A/V$ ) of the eleven different cell types. The similarities or dissimilarities of the latter three cell parameters ( $A$ ,  $V$ ,  $A/V$ ) are illustrated in the corresponding dendrograms (Figs. 1, 2 and 3). In all instances the greatest similarity was found between cell types N° 2 and N° 11, i.e., proximal convoluted tubule cells and hepatocytes, a conclusion which can hardly be expected from the direct microscopic examination of the histological specimens.

The calculations of the somatic areas ( $A$ ), volumes ( $V$ ), and of the  $A/V$  ratios for the majority of the different cell types were unambiguous, due to the fact that the geometric forms of these cells corresponded to either a sphere, a cube, or a parallelepiped. The latter statement is not valid for two cell types analyzed in this study, i.e., the

Purkinje and granule cells from the cerebellum. These two neuron-type cells have both dendrites and long axons, and in consequence, the total cell volumes ( $V$ ) and the total surface areas ( $A$ ) are significantly greater than the values we have calculated, which were based only on the somatic measurements of the three cell diameters ( $D_1$ ,  $D_2$  and  $D_3$ ). Delbrück (1986) has recently emphasized, that the Purkinje neuron (cell type N° 8) appears to be the central integrative element of the cerebellum, and that the granule cells (type N° 9), which are structurally and functionally related with the Purkinje cells, have increased in number during mammalian evolution (in the rat about 300 granule cells are associated with one Purkinje cell, while in humans this ratio is ten times greater), which seems to indicate an increasing complexity of the informations delivered by the granule cells to each Purkinje neuron. Another exceptional cell type is the adipocyte (type N° 6). Its soma is comparatively larger (mean diameter between 30 and 50  $\mu\text{m}$ ). Each of these fat-cells represents a central microscopic lipid reservoir, surrounded by a thin protoplasmatic surface layer. Di Girolamo *et al.* (1971) studied the cell diameters ( $D$ ), the areas ( $A$ ), and the volumes ( $V$ ) of adipocytes from *ad libitum* fed rats, hamsters, guinea-pigs, and dogs, at different stages of developments. The values these authors found, agree with the encountered heterogeneity in size of fat-cell populations.

Finally, the principal component analysis (Fig. 4) enabled us to establish five different cell groups. Three are represented by a single type of cells (N° 6, 8 and 9). A fourth was conformed by two very similar cells (fibroblast and fibrocytes, N° 4 and 5), and a fifth group of cells N° 1, 2, 3, 7, 10 and 11) which together formed a separate cluster, either for  $\log(\text{area})$ ,  $\log(\text{volume})$ , as well as for  $\log(\text{area}/\text{volume})$ .

In sum, cluster analysis (dendrograms) and principal components analysis yielded similar results. Moreover, the different methods of statistical analysis of the quantitative data concerning mammalian cells agree with the results drawn qualitatively from the microscopic examinations of the corresponding histological specimens.

From the present morphometric analysis of mammalian cells, we can conclude that the diameter of all cell somas are of much the same order of magnitude, and consequently, their relative areas, volumes, and area/volume ratios are practically the same. These conclusions are in agreement with the following statement of D'Arcy Thompson (1952): "In short, Nature has her materials of predeterminate dimensions, and keeps to the same bricks whether she built a great house or a small".

As discussed in our previous paper (Ocqueteau *et al.*, 1989), the main limiting factor, and the probable reason for cell dimension invariance, is the diffusion distance of oxygen delivery. The diffusion time for O<sub>2</sub> is in the millisecond range only when the diffusion distance is in the microscopic realm ( $\mu\text{m}$ ).

One of the classical concepts of scaling deals with the oxygen consumption or organisms of different body mass. A first relationship was established by Rubner at the beginning of this century. He found that the basal metabolic rate ( $\dot{V}\text{O}_2$ ) was proportional to (body mass)<sup>0.66(6)</sup>. Kleiber (1947), on the other hand, insisted that the best fit between both variables (oxygen consumption and body mass) was obtained when another exponent of body mass was applied, namely (body mass)<sup>0.75</sup>. This small, but significant difference between body mass exponents, has been the cause of a long lasting and vivid controversy between these two points of view.

Conversely, oxygen consumption per cell and per hour of isolated mononuclear leucocytes, obtained from mammals of different body masses (from a 0.3 kg rat to a 552 kg horse), measured under standardized conditions (Langer, 1985), was practically the same in all cases ( $1.132 \times 10^{-12}$  L/h/cell). Thus the oxidative metabolic differences between unicellular and multicellular organisms must be associated to the complex structural organization of the latter. Furthermore, large organisms are characterized by a massive endoskeleton and abundant connective tissues, with reduced oxygen requirements, as well as with long and wide arterial and venous systems, whose walls of smooth musculature do not consume much

oxygen when compared with parenchymatous organs. An increase in body mass means: a) more supporting structures (skeleton and connective tissues); and b) greater lengths and larger diameters of the transport systems (circulatory and respiratory systems, digestive apparatus, and renal excretory system).

The final common pathway of the circulatory transport system is represented by the capillaries which are surrounded by a Krogh-cylinder of cells. The capillary membranes correspond to the exchange area of gases, liquids, electrolytes, substrates, and catabolytes; among the latter we must mention "heat", which is originated in the mitochondria (Himms-Hagen, 1976).

A general feature of the respiratory and circulatory systems is their dichotomic treelike geometry; in both cases they reach the microscopic level (alveoli, capillaries, and cells) only after more than twenty consecutive generations.

The exchange areas between alveoli and capillaries, as well as between capillaries and cells, do not obey the rules of an "Euclidean geometry", but rather to "fractal geometry" (West and Goldberger, 1987), which was introduced by Hausdorff in the early 1900's, and actualized by Mandelbrot (1982). The term "fractal" is equivalent to "fractional" (non-integer exponents for length L). Thus, the dimension of a geometric or topological surface is  $D_T = L^2$ , whereas the fractal dimension ( $D_F$ ) of the capillary exchange surface is equivalent to  $L^{2.25}$  (Sernetz *et al.*, 1985), which is in fact nearer to a topological surface ( $D_T = L^2$ ), and significantly different from a topological volume ( $D_T = L^3$ ).

Sernetz *et al.* (1985) have assumed that all organisms are open, multiphase catalytic systems, which dissipate energy to maintain their organization, and in consequence, mammalian organisms are surface-volume-hybrids, with a fractal dimension ( $2 < D_F < 3$ ) of 2.25, which seems to be the determining factor of Kleiber's power law for the basal metabolic rate of mammals ( $\dot{V}\text{O}_2 = M^{0.75}$ ). If  $x$  is a characteristic length, then, at constant density of the organisms,  $x = M^{1/3}$ , and the basal metabolism is equal to

$M^{2.25/3}$  and from which one finally obtains Kleiber's power law ( $M^{0.75}$ ). In this manner cellular morphology (dimensions) and physiology ( $\dot{V}O_2$ ) are integrated to conform the whole organism, which includes a highly organized and complex transport system (respiration and circulation), whose exchange surfaces obey a fractal geometry.

Finally, it is worth mentioning that the half century-old dilemma, Rubner's surface law ( $M^{0.67}$ ) versus Kleiber's 3/4 power law ( $M^{0.75}$ ), can be expressed as the ratios between two exponents; in one case between the body mass exponents, i.e.,  $0.75/0.66(6) = 1.126$ , and in the other by the characteristic length exponent of a fractal geometry ( $D_F$ ) and of a topological geometry ( $D_T$ ), or  $2.25/2.00 = 1.125$ . In both instances we obtain the same value for the corresponding ratio, in the sense that a fractal interpretation of the main exchange surfaces of the oxygen transport systems (respiration and circulation) with all parenchymatous cells of the organism is concordant with the basal oxygen consumptions ( $\dot{V}O_2$ ) as a function of (body mass) $^{0.75}$ , a fractional power law first postulated by Kleiber.

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So I was recently thinking about the similarity in formulae between spheres volume ( $\frac{4\pi r^3}{3}$ ) and their surface area. ( $4\pi r^2$ ) Firstly, I noticed that the surface area looks like its the derivative of volume with respect to radius which come to think of it makes sense as the rate of chan... So I was recently thinking about the similarity in formulae between spheres' volume ( $\frac{4\pi r^3}{3}$ ) and their surface area. ( $4\pi r^2$ ). Firstly, I noticed that the surface area looks like it's the derivative of volume with respect to radius which come to think of it makes sense as the rate of change in volume at a point in time is that outer spherical shell being added times its thickness. But secondly I also noticed that the ratio of the two is  $r/3$ .