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ON THE MODELLING OF FRACTAL TREE-LIKE STRUCTURES IN BIOLOGY

by

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On the modelling of fractal tree-like structures in biology

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The fractal tree-like structures can be divided into three classes, according to the value of the similarity dimension D_s: $D_s < D$, $D_s = D$ and $D_s > D$, where D is the topological dimension of the embedding space. An important characteristic of the trees with $D_s > D$ is the self-overlapping exponent. As an example, we study the model of the human blood-vessel system with $D_s \approx 3.4$

1 Introduction

The fractal tree-like systems can be met rather often in biology [1]. The most obvious examples are ordinary trees. The physiological tree-like structures — such as a blood-vessel system, a lung, nerve tissues, a lymphatic system — are "hidden" by tissues. For this reason, it is quite a complicated task to study the fractal properties of them. The constituent parts of these tree-like systems (single blood vessels, neurons and bronchial tubes) have been studied for a long time and the physical properties of them are known in great details. Meanwhile, the global properties of the respective "trees" have been the object of systematic studies only during the last decade.

Several papers have been devoted to cite the airway tree of a lung (c.f. [2–4]) and to the tree of blood-vessels (c.f. [5–8]). They include extensive experimental measurements and concern mainly the geometrical arrangement of the branches. Also, mathematical models have been proposed to match the experimental data. However, they do not provide a complete consistent fractal description of the system. A good consistent model should satisfy the following criteria:

a) it should be in accordance with the simplest physical laws, such as the

flow continuity and the Poiseuille law in the case of the blood-vessel system;

b) it should satisfy certain physiological requirements, e.g. ensure a complete (homogeneous) blood supply of the organism;

c) it should be in accordance with our knowledge about the processes governing the growth and formation of the "trees";

d) it should be self-similar within a wide range of scales;

e) the result of many iterations of a generation-to-generation relation specifying the model should not be very sensitive to the subtleties of the model;

f) the model should not contradict empirical data.

Some comments are needed here. First, it is possible that a tree is not self-similar. Instead, it can be multifractal [1]. Besides there can be a a transition scale between two different scale-invariant regions. Item *d)* here means that as soon as an exponent of a scaling law is claimed to be a fractal dimension, the system should be self-similar.

Second, in most cases the consequence of the item *b)* is that the spatial distribution of the branches of the tree should be quasi-homogeneous, i.e. the tree should be space-filling. For instance, in the case of the blood-vessel system, the homogeneous blood supply implies that in the vicinity of each point of the organism there is a blood-vessel. Analogously, the alveoli fill almost all the space of the lung. Perhaps in a less extent this is true for a neural network; however, within distinct regions of the organism, the distribution of neurons is also quasi-homogeneous. Thus, the box-counting and Hausdorff-Besicovitch dimensions of these trees are equal to the dimension of the embedding space, $D_b = D_{HB} = D = 3$. However, the similarity dimension D_s may be larger [2]. This issue is discussed in the Sec. 3.

[1] Multifractality is the most general scale-invariant behaviour.

[2] D_s is defined by the logarithm of similarity factor base the branching ratio. Alternatively, it can be defined via the scaling law $M \propto l_s^D$, where M is the (average) mass of a branch of length l. The second definition is applicable to the random fractals, as well

2 Trees with $D_s = D$. The model of bronchial tree.

Bronchial tree is a good example of a space-filling fractal tree, the similarity dimension of which equals to the dimension of the embedding space. A characteristic feature of this kind of trees is that a distinct branch (together with its sub-branches) forms a compact space-filling structure, so that overlapping of different branches of the same generation is insignificant.

In Ref. [9], a simple regular 3D model of lung has been presented. According to that model, all the bronchial tubes are similar to each other; each tube branches into two smaller tubes which are perpendicular both to the given tube and to the tube of the previous generation.

Sometimes a confusion has been caused by the fact that the experimental dependencies are not power laws (as would be expected in the case of self-similarity). Thus, in Ref. [2] it has been pointed out that the plot of the logarithm of the average diameter of the bronchial tubes versus the generation number differs notably from the straight line. It has been shown in Ref. [10] that the experimental curves can be modeled fairly well, if we take into account the presence of the small-scale cut-off at the alveoli size. Indeed, for real lung, the two branches of a bronchial tube are always of a different size. Thus we can modify the model of the paper [9] by introducing the distribution function of the diameter ratio of the branches. Due to such an unequal branching, the generation number of the alveoli (the alveoli are assumed to be approximately of the same size) can vary several times. The power laws can be expected only by the generation numbers, smaller than the smallest generation number among the alveoli.

Another example (though not biological) of the trees with $D_s = D$ is the river networks. The network is space-filling, if we assume that the sources are distributed quasi-homogeneously. The compactness is caused by the two-dimensional topology: two branches cannot intersect.

3 Trees with $D_s > D$. The model of blood-vessel system.

It can be easily understood that the Hausdorff-Besicovitch and box-counting dimensions of a space-filling fractal set D_{HB} and D_b are equal to the topological dimension of the embedding space D. It is generally accepted [1] that the similarity dimension D_s coincides with the Hausdorff-Besicovitch dimension D_{HB}. Thus it may seem that always $D_s \leq D$. However, the equality $D_s = D_{HB}, D_b$ can be applied only if all the dimensions are less than the dimension of the embedding space. One can imagine that the tree with $D_s > D$ is obtained as a projection of a tree embedded into a space of higher dimensionality. Indeed, as a result of such a projection, the dimensions D_{HB} and D_s become equal to the new value of D, whereas the similarity dimension will remain unchanged.

The similarity dimension exceeds the topological dimension if the ratio δ_n/l_n of the average distance between the branches of n-th order δ_n and average length of the branches l_n vanishes towards higher generation numbers n, i.e. towards smaller values of l_n. This is possible in two cases:

1. the tree is not self-similar, but instead, self-affine; [3]

2. the branches of the same generation number have significant overlapping regions.

Being guided by the assumption of self-similarity, the similarity dimension of the blood-vessel system can be easily assessed using the following empirical data: the length of the capillaries (i.e. the vessels of the last generation) $\lambda_0 \approx 0.5$mm (cf. [11]), the length of the largest vessels (aorta) $l_0 \approx 0.5$m and the total length of the capillaries, $L \approx \lambda_0 N \approx 100,000$km. The total number of capillaries N can be expressed via the effective number of generations n_{eff} as $N = 2^{n_{eff}}$; the similarity factor a can be expressed as $a = (\lambda_0/l_0)^{1/n_{eff}}$. Using the definition of the similarity dimension we can easily find

$$D_s = -1/\log_2 a \approx 3.4. \tag{1}$$

In fact it is not surprising that the similarity dimension of the blood-vessel system exceeds the dimension of the space. Indeed, in order to provide an

[3] A set is called (statistically) self-affine, if an affine transformation of a subset and the set itself are (statistically) equivalent.

homogeneous blood supply of the organism, the distance between capillaries should be less than the effective diffusion radius $\delta_{diff} \approx 100\mu$m. Thus the relative distance between capillaries is smaller than between large vessels.

Recently, several papers have been reported that the fractal (box-counting) dimension of retinal and subcutaneous vascular networks is close to $d_b \approx 1.7$ ([6,12,13]). Note that both networks are effectively two-dimensional. The obtained value is very close to the fractal dimension of diffusion-limited aggregates (DLA), $d_{DLA} = 1.75$. This coincidence has been lead to the thought ([13]) that the growth of the blood-vessels is indeed governed by the diffusion-limited aggregation.

The growth of the vascular network is controlled by several chemical mechanisms. The generally accepted model (c.f.[13,14]) of this process can be outlined as follows. In the growing organism, the tissue cells grow at a certain rate and subdivide when a maximum size is reached. The existing vascular structure grows with all the other tissues. The distance between capillaries grows as well; this can cause ishemia of the most distant cells. Ishemic cells generate chemical substances which lead to angiogenesis (angiogenic factors, AF). The particles of AF diffuse in all the directions. These particles can be captured by blood vessels; when captured, they cause new vessel sprouting towards the ishemic cell (actually, towards the higher concentration of AF). Some purely perfused vessels undergo regression and disappear.

Despite the fact that diffusion plays an important role in such a model, it seems that in most cases the growth is not diffusion-limited. Instead, diffusion is faster than the growth of the tissues: the time between the subsequent emergence of two ishemic regions is longer than the characteristic diffusion time. Such a growth model leads to a space-filling statistically self-similar vascular tree. If we assume that the average distance between the capillaries is constant during all the growth process and that the regression of vessels is negligible, there would be a fractal tree of $D_s = 3$ with slightly overlapping branches. Besides, the relative distance between the large vessels would be equal to the relative distance between capillaries.

If we admit that the regression of vessels can be significant, we obtain a tree with $D_s > 3$. The higher the regression rate is, the higher the similarity dimension will be. Such an unequality has two observable consequences. First, the relative distance between vessels increases with the size of vessels. Second, there will be a significant overlapping of the same-generation branches. This is rather important from the physiological point of view: the

damage of a vessel will not lead to the complete cease of the blood supply: in a vicinity of every cell fed by a capillary belonging to the damaged branch there are capillaries belonging to healthy branches. In order to describe this effect quantitatively, we introduce the overlapping exponent of a fractal tree. Let us draw around a branch of size l a sphere [4] of diameter l. We repeat this procedure with all the branches, the size of which is between L and $2L$, i.e. $L < l < 2L$. Further, let the maximum number of spheres of non-zero intersection scale with size L as

$$N_{max} \propto L^{-\beta}. \tag{2}$$

Then we say that β is the overlapping exponent. It is easy to see that

$$\beta = D_s - D. \tag{3}$$

Indeed, in the case of vascular system the average distance between the vessels of size l with $L < l < 2L$ can be calculated as $d \approx [l_0^3/(2^m L)]^{1/2}$. Here m denotes the effective generation number of the vessels of given size; it can be eliminated using the expression for the similarity factor $a = (L/l_0)^{1/m} = 2^{-1/D_s}$. Finally, the number of overlapping spheres can be assessed as $N_{max} \approx L^3/(d^2 L) \approx (l_0/L)^{D_s-3}$.

Due to the lack of experimental data, it is impossible to check directly the applicability of our model. In fact, it is a very difficult technical task to make three-dimensional measurements of vascular tree and cover a wide range of scales. However, detailed data are available concerning the correspondence between blood pressure, flux of blood and diameters of the vessels. Particularly, the diameter of the vessels scales with the flux w of blood as $d \propto w^{1/\alpha}, \alpha \approx 2.7$ (see Ref. [15]). According to the model and Poiseuille law, this scaling law corresponds to the dependence $p(d) = p_0 - cd^\gamma$ with $\gamma \approx -0.5$ (the exponent γ can be expressed via α and D_s), where $p(d)$ denotes the average blood pressure in the vessels of diameter d (see Ref. [10]). This law is in accordance with the experimental data (c.f. [11]) and can be considered as an indirect argument supporting our model.

Now let us return to the experiments reporting fractional values of the box-counting dimension. The fractional values seem to be in most cases artifact and caused by one of the following reasons: *a)* the range of scales

[4] In the case of self-affine trees, we would have to draw an ellipsoid.

used in analysis is too short, *b)* the vessels have a specific spatial distribution (this is the case for the retinal vessels in the vicinity of fovea), *c)* the smallest boxes used in box-counting method are too small, the size of them is too close to the lower cut-off scale of self-similarity (e.g. to the scale of capillaries).

Finally, it should be emphasized that the model described above cannot be used equally well for all the scale-lengths. The experimental data [16,17] indicate that for some scale-lengths the vascular tree can be notably non-self-similar: the exponent of the local fit to a power-law (referred to as the "local fractal dimension") revealed a significant dependence on space-scale. Further experimental data are needed to determine the range of applicability of the model.

4 Trees with $D_s < D$.

Most of the ordinary trees fall into this category. Typically, the fractal dimension of them is something between two and three. The trees with $D_s < 2$ are very "transparent"; the shade of such a tree (even with leaves) has significant holes. On the other hand, the trees with $D_s \geq 3$ are very thick: it is impossible to climb on these trees, because all the space of the heads of the trees is filled with branches.

Despite the fact that the ordinary trees can be easily accessed and measured, it is rather difficult to calculate the fractal dimension of them. This is caused by the three-dimensional geometry. One possible solution is to measure the length l_i and mass M_i of each branch and find the similarity dimension as the minimum of the function

$$F(D_s) = \sum_i (l_{1i}^{D_s} + l_{2i}^{D_s} - l_{3i}^{D_s})^2 / l_{3i}^{2D_s}. \qquad (4)$$

In fact, we can do the measurements even on two-dimensional photographic images, assumed that trees have lost their leaves and all the branches can be distinguished[5]. For instance, using the images of several birch trees we obtained $D \approx 2.6$.

[5]The other methods would fail here and yield $D = 2$.

5 Propagation of passive component in blood vessel system

In this section we outline a simple implementation of the model of vascular tree [18]. We consider the transport of a passive admixture through the blood vessel system. It is assumed that the admixture has been injected

into tissues and fills a certain region between the vessels. Besides, the following assumptions are made:

a) outside the vessels, the propagation of the admixture is diffusive, of molecular diffusivity D_0;

b) the admixture particles can penetrate the walls of the vessels;

c) the presence of the admixture around and inside the vessels does not affect substantially the blood flow in these vessels. However, a small change (by a factor of the order of two) in the rate of the blood flow is admitted;

d) a vessel is called to be of size L, if its length is between L and $2L$. The vessels of size L form an homogeneous network;

e) the transport is accomplished in the venous half of the blood-vessel tree. In fact the admixture is convected also by the arterial flow, but this is the convection towards the capillaries and the transport distance in the arterial tree is limited by the size of the vessel where the injection was made;

f) the blood flow in vessels is laminar (c.f. [11]).

The analysis is based on two "integrals of motion": the first one is the expression for the total volume of the whole body:

$$V = N(L)L\lambda(L)^2, \tag{5}$$

where $\lambda(L)$ denotes the average distance between the neighboring vessels of size L and $N(L)$ — the total number of vessels of size L.

The second one is the estimate of the total flux of blood through the heart:

$$Q = N(L)v(L)d(L)^2. \tag{6}$$

Here $v(L)$ denotes the characteristic velocity of the blood in a vessel of size L and $d(L)$ — the diameter of the vessel of size L. These equations are valid for any value of L. Sometimes it is more convenient to use the combined and hence a dependent "integral of motion":

$$V/Q = \frac{L\lambda(L)^2}{v(L)d(L)^2} \approx 1000s. \tag{7}$$

Here the numerical value 1000s was obtained by substituting $V = 70\text{dm}^3$ and $Q = 70\text{cm}^3$.

Let us assume that inside the tissues there is a spot of passive admixture which diffuses into the blood vessels and will be carried into the other parts of the organism by blood. The admixture can be an injection, a venom of an insect or of a snake or something else. The character of propagation depends on the seed diffusivity D_0 and on the initial size of the spot r. It can be shown that there are four qualitatively different regimes of propagation.

The admixture propagates in the form of a "sausage" around the vessel stretching out of the initial spot. The diameter of it can be assessed as $\sqrt{D_0 t}$ and the "stretching" velocity of the "sausage" as

$$v_{eff} \approx \frac{d(L)^2}{D_0 t} v(L). \tag{8}$$

If the spot is large and diffusivity low, the admixture fills the vascular system approximately during one rotational cycle of blood, $\tau \approx W/Q \approx 1\text{min}$, W being the total volume of the blood.

Otherwise the convection is slowed down by diffusion inside the tissues. It can be shown that in this case the characteristic time of invading the whole organism is given by $\tau = V/Q \approx 1000\text{s}$.

6 Conclusion

We have considered three different classes of fractal trees, with $D_s < D$, $D_s = D$ and $D_s > D$, where D_s is the similarity dimension and D — the dimension of the embedding space. Most of the physiological tree-like structures belong to the second class and most of the ordinary trees — to the first one. We have discussed the fractal model of vascular system with $D_s = 3.4$.

On the basis of this model, we have analyzed the transport of passive component by blood. Depending on the diffusivity of the passive component, the characteristic time of invading the whole vascular tree can vary from one to twenty minutes.

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