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TRANSPORT PROCESSES IN FRACTAL BIOLOGICAL NETWORKS

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Abstract. The spreading rate of infected regions in the lung is studied. It is assumed that the lung has a self-similar tree-like structure and that the infection can propagate both convectively along the airways and invasively across the walls of the alveoli. The scaling laws of the evolution of the infected spot are derived. Depending on the parameters of the model, the propagation can be explosive. Also, the transport of a passive component in a blood-vessel system is analysed. It is shown that the convection rate depends crucially on the initial size of the spot of the contaminant and on the mobility of its particles. The characteristic absorption time varies between 1 and 20 min.

Key words: fractal, transport, blood-vessels, lung.

1. INTRODUCTION

The fractal tree-like systems can be met rather often in biology [1]. The lung and the blood-vessel tree are among the most well-studied systems of this kind, due to their great importance in medicine. Several mathematical models have been proposed to describe the airway tree of a lung [2–5] and the tree of blood-vessels [5–10]. These models deal with the statistical size distribution of the constituent elements (bronchial tubes, blood-vessels) [2,7] and with the spatial structure of the respective trees [3–6,8–10]. The recently proposed model of the blood-vessel system [6] satisfies also additional requirements of homogeneous blood supply of the organism, stability with respect to slight damages of the system, and consistency with the processes governing the growth of the blood-vessel tree.

The physiological processes both in blood-vessels [7] and in bronchial tubes [11] are studied in detail. However, the processes in a fractal tree as a whole have

attracted much less attention. In this paper we show that the fractalness can have an essential influence on the physiological processes. First, we propose a possible scenario of the propagation of infection in the fractal network of airways in a lung. Also, we suggest a simple model of the transport of passive components in a blood-vessel system. This model allows us to assess the transport rate of the admixture.

2. PROPAGATION OF INFECTION IN A LUNG

In this section we exploit the fractal model of the human lung presented in paper [5]. The basic elements of the model are as follows. The lung is treated as a self-similar set of bronchial tubes. Thus, for instance, we do not distinguish the alveolar ducts from the bronchioli and call both the bronchial tubes (though, of different size). The size of a bronchial tube is characterized by the flux of air q in it. A bronchial tube of nth generation branches into two tubes of the $(n+1)$st generation. The two branches can be of different size, the ratio of the sizes $k = q_1/q_2$ being a randomly distributed quantity. However, it is assumed that the two branches are of the same order of magnitude, i.e., that the distribution function of the quantity k vanishes at small ($< 1/2$) and large (> 2) values of k.

The numerical data are taken from [11]. For a human lung there is approximately $N = 28$ generations of the bronchial tubes. The last generation, the alveoli, are of the length of $l_N \approx 0.23$ μm and of the diameter $d_N \approx 0.28\,\mu$m. Starting from the generation number of $n = 4$ there is quite a good scaling law for the length of the tubes, $l_n \propto a_n^{3/4}$. Here $a_n \propto 2^{-n/3}$ denotes the characteristic distance between the branches of the nth generation. However, for the diameter d_n and hence for the volume of the tube $V_n = \pi l_n d_n^2/4$, the law is less regular. This irregularity implies that the real bronchial tree is not strictly self-similar and sometimes it is necessary to take this circumstance into account. The volumes of the bronchial tubes are presented in Table 1 as a function of the generation number n.

According to [11], by inhalation the air flow is turbulent approximately down to the 20th generation of tubes. By expiration, the air flow is much more laminar: the switching point to the turbulence is approximately at $n = 7$. Such a behaviour of the air flow leads us to the formulation of a model of the transport of bacteria (or virus) with the following assumptions.

1. The bacteria invade diffusively a layer of air near the walls of an infected alveolus.

2. During expiration the infected air is brought to the larger bronchial tubes and mixed with the air from other alveoli.

3. This mixture is carried by the next inhalation from the bronchial tubes to all the alveoli of the lung. Note that the fraction of the infected air in an alveolus depends on the distance from the originally infected alveolus. The alveolus will also be infected if there is a bacterium in the diffusion layer near the walls of it.

Table 1. Dependence of the volume of the bronchial tubes V_n on the generation number n ($N = 28$; V_N – volume of an alveolus)

n	V_n/V_N	n	V_n/V_N
0	2600000	12	205
1	462000	13	123
2	83900	14	81.9
3	22400	15	56.5
4	15800	16	38.5
5	7890	17	26.6
6	5240	18	19.5
7	2620	19	14.8
8	1310	20	11.0
9	817	21	8.96
10	493	22	6.98
11	287	23	5.92

Such a model implies that the bacteria replicate quickly in comparison with the propagation time. Also it is assumed that the bacteria maintain their replicative capabilities while being convected.

The first observation is that in the case of *high diffusivity* of bacteria when

$$d_N^2 \lesssim D_0 T, \tag{1}$$

the diffusive layer near the walls of the alveoli fills them completely. Here T denotes the inhalation period and D_0 – the diffusivity of the bacteria. The width of the layer δ is simply the radius of the alveoli

$$\delta \approx d_N/2.$$

In the opposite case of *low diffusivity*, the bacteria fill only the captured air, i.e., that fraction of air which is close to the walls of the alveoli and is not pushed out during the expiration. The width of such a layer can be assessed as

$$\delta \approx d_N k/2,$$

where k denotes the ratio of the volumes of the lung before and after the inhalation. Suppose the saturated concentration of the bacteria at the surface of the alveoli is c_0. Then, in the case of high diffusivity, the number of bacteria pushed into the bronchial tubes from a single infected alveolus is given by

$$m_N \approx V_N(1-k)c_0, \quad V_N \approx \pi d_N^2 l_N/4. \tag{2}$$

In case of low diffusivity the gradient of the concentration can be assessed as c_0/δ, hence the flux density of bacteria is $q \approx D_0 c_0/\delta$. The number of bacteria can be estimated as $m_N \approx qS_N$, where $S_N \approx \pi d_N l_N$ denotes the area of the walls of an alveolus. So, in this case Eq. (2) should be substituted by

$$m_N \approx \pi d_N l_N c_0 D_0 T/\delta = 2\pi l_N c_0 D_0 T/k. \tag{3}$$

Suppose there is only one infected alveolus. Let us assess the probability of infecting the alveolus at a distance a during one cycle of expiration and inhalation. If there are more than one infected alveoli, the probabilities are simply added (assuming that the resulting probability is much less than one). To begin with, we calculate the fraction of infected air after an expiration in such a bronchial tube of the nth generation which is the ancestor of the infected alveolus f_n. The air in such a tube is the mixture of the air from the infected alveolus and the air from $2^{N-n}-1$ healthy alveoli. Thus we have $f_n \approx 2^{n-N}$. The average concentration of bacteria in the air from the infected alveolus is m_N/V_N. The number of bacteria in the tube under consideration is

$$m_n \approx \frac{m_N}{V_N} f_n V_n = m_N 2^{n-N} \frac{V_n}{V_N}. \tag{4}$$

Here $V_n = \pi d_n^2 l_n/4$ is the volume of the tube. The distance between two alveoli a can be associated with the generation number $n(a)$ of such a bronchial tube which is the smallest common ancestor of both alveoli:

$$a^3 \approx V_N 2^{N-n(a)}. \tag{5}$$

Here we took into account that the alveoli fill almost all the space of the lung and that the branch forms a compact structure of volume a^3. Thus the total volume of those alveoli, which are the descendants of the given ancestor tube, is also equal to a^3.

The bacteria can be carried to the distance a only by those volumes of air which are after the expiration in the bronchial tube of nth generation with $n \leq n(a)$. After the inhalation, all these bacteria will be equally distributed over all the alveoli of the same branch. The number of bacteria transported to the distance of the order of a (i.e., to the distance which is longer than a and shorter than $2a$) from the origin, can be calculated as

$$M(a) \approx \sum_{n \leq n(a)} m_n 2^{n-N} \frac{V_n}{V_N} 2^{n-n(a)}. \tag{6}$$

In the case of high diffusivity all these bacteria reach the walls of the alveoli, so that $M(a)$ gives us the estimate of the probability of infecting an alveolus at the distance a from the originally infected alveolus, i.e., of the probability we are looking for. In the case of low diffusivity, some of the bacteria will be pushed out by the subsequent

expiration, again. In that case the probability of the capture can be estimated as $p(a) \approx m(a)D_0T/d_N^2$. Using Eqs. (2)–(4) and keeping only the first term in Eq. (6), we obtain

$$p(a) \approx \begin{cases} \dfrac{\pi l_N d_N^2 c_0 (1-k) V_{n(a)} 2^{n(a)-N}}{4V_N}, & d_N^2 < D_0T, \\ \dfrac{2\pi l_N c_0 V_{n(a)} 2^{n(a)-N} (D_0T)^2}{kV_N d_N^2}, & d_N^2 > D_0T. \end{cases} \tag{7}$$

Neglecting the subsequent terms of Eq. (6) is justified by the fact that this sum converges as a geometric progression. Hence, the whole sum is of the same order of magnitude as its first term. Thus we see that the probability of infecting a specific alveolus at a distance a is

$$p(a) \propto V_{n(a)} 2^{n(a)},$$

and, according to the data in Table 1, vanishes rapidly at large values of a.

Further, let us try to understand how the size of the infected spot will behave. Suppose, at a certain moment the size of it is r. Then the number of infected alveoli is r^3/V_N and hence the size-doubling probability $P_2(r)$ is given by

$$P_2(r) \approx r^3 p(r)/V_N.$$

The characteristic size-doubling time $\tau(r)$ can be found using the equality

$$\tau(r) P_2(r) \approx 1.$$

Here the duration of the inhalation-expiration cycle is assumed to be of the unit length. According to Eq. (7), we find

$$\tau(r) \approx (\pi l_N c_0 V_{n(r)})^{-1} \begin{cases} \dfrac{4V_N}{d_N^2(1-k)}, & d_N^2 < D_0T, \\ \dfrac{kV_N d_N^2}{2(D_0T)^2}, & d_N^2 > D_0T. \end{cases} \tag{8}$$

The most important feature of this equation can be expressed by the scaling law

$$\tau(r) \propto 1/V_{n(r)}.$$

Thus we see that the size-doubling time decreases with increasing size of the spot. Besides, the sum $\tau(r) + \tau(2r) + \tau(4r) + \ldots$ converges. Thus, during a finite time, the spot will occupy the whole space. In other words, the behaviour of the spot is explosive.

We have ignored the possibility of invasive propagation of the infection through the walls of the alveoli. That mechanism would lead to a linear law for the size of

the infected spot. Within the framework of the model presented above, there are three possibilities:

1) the evolution of the spot is completely invasive and the size of it increases linearly in time;

2) the dominating process is convection and the size of the infected spot increases explosively;

3) at the first stage, by small sizes of the spot, the process is governed by invasion through the walls of the alveoli and $r(t) \propto t$; at the second stage, when the spot has become larger than the critical size, the convection will be more effective than the invasion and further the spot grows explosively.

It should be emphasized that the scenario outlined in this section is closely related to the assumptions of the model: we have neglected the time delay needed to infect an alveolus (in comparison with the propagation time $\tau(r)$); also, we have neglected the possibility that during the longer travel paths, a significant fraction of bacteria can loose the capability to infect other alveoli. These factors deserve a closer study, since they can substantially affect the infection process and the behaviour of the infected spot.

3. PROPAGATION OF A PASSIVE COMPONENT IN A BLOOD-VESSEL SYSTEM

In this section we study 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, we make the following assumptions.

1. Outside the vessels, the admixture propagation is diffusive, of molecular diffusivity D_0.

2. The admixture particles can penetrate the walls of the vessels.

3. 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 one) in the rate of the blood flow is admitted.

4. A vessel is called to be of size L if its length is between L and $2L$. In accordance with the model of the blood-vessel system [6], the vessels of size L form a quasi-homogeneous network and the distance between neighbouring vessels is much less than L.

5. 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. Thus the transport distance in the arterial tree is limited by the size of the vessel where the injection has been made.

6. The flow in vessels is laminar [12].

The 4th assumption can be restated in the following way: the distance λ between the neighbouring vessels of size L depends only on the size L and is assessed as

$\lambda = \lambda(L)$. Further, we introduce the functions $N(L)$ – the total number of vessels of size L, and $d(L)$ – the diameter of the vessel of size L.

There are two simple but still useful relations. The first one is the expression for the total volume of the whole body:

$$V = N(L)L[\lambda(L)]^2. \tag{9}$$

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

$$Q = N(L)v(L)[d(L)]^2. \tag{10}$$

Here $v(L)$ denotes the characteristic velocity of the blood in a vessel of size L.

It should be emphasized that Eqs. (9) and (10) are valid for any value of L; one can say that the combinations $NL\lambda^2$ and Nvd^2 are the "integrals of motion" of our model. Sometimes it is more convenient to use the combined and hence a dependent integral of motion:

$$\frac{V}{Q} = \frac{L[\lambda(L)]^2}{v(L)[d(L)]^2} \approx 1000\,\mathrm{s}. \tag{11}$$

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

Suppose 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 the blood. The admixture can be an injection, a venom of an insect or of a snake or something else. For the sake of brevity, further we refer to it simply as to a venom.

We show that there are four qualitatively different regimes of venom propagation, depending on the initial size of the spot r and molecular diffusivity of the venom D_0.

1. Evolution of a large spot by high values of seed diffusivity. If the amount of the injected venom is large, the region between the tissues filled by the venom has a considerable size, $r_0 > \lambda_0$, where λ_0 is the size of the smallest vessels (capillaries). So, even if the site of the injection is random, some of the vessels of size $L > \lambda_0$ will be surrounded by the venom. More precisely, the "typical", i.e., the most probable situation is that the size L of the largest vessel surrounded by the venom is given by the relationship

$$\lambda(L) = r_0. \tag{12}$$

To begin with, let the time t, passed since the injection was made, satisfy the condition

$$[d(L)]^2/D_0 < t < [\lambda(L)]^2/D_0 = r_0^2/D_0. \tag{13}$$

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

(13) means that the width of the "sausage" exceeds the diameter of the vessel, but is less than the distance between the vessels. The length of it can be found in the following way. We note that the molecules of the venom spend most of the time outside the core-vessel of the "sausage". The fraction of time spent inside the vessel can be estimated using the ergodicity hypothesis, i.e., as the ratio of the cross-sections of the vessel and of the "sausage", $[d(L)]^2/D_0t$. So the effective velocity of the venom v_{eff} is given by

$$v_{\text{eff}} \approx \frac{d(L)^2}{D_0 t} v(L). \tag{14}$$

Now we can assess the length of the "sausage" as $l(t) \approx \int v_{\text{eff}} \mathrm{d}t$. Assuming that the length l is less than the length of the vessel L, we find

$$l \approx \frac{[d(L)]^2 v(L)}{D_0} \ln \frac{tD_0}{[d(L)]^2}. \tag{15}$$

Here we took the lower integration limit equal to $t_0 = d(L)^2/D_0$. Indeed, by $t < t_0$ the venom fills only a thin layer of blood near the walls of the vessel, where the blood flow is much slower than $v(L)$ (presumed that the blood-flow is laminar [12] and that the diffusivities in the blood and in the tissues are approximately equal). The assumption $l < L$ can be rewritten using Eqs. (11),(12), and (15); neglecting the logarithmic factor it reads

$$r_0^2/D_0 \; < \; V/Q = 1000\,\text{s}. \tag{16}$$

2. Evolution of a large spot by small diffusivity. The approximation of a large spot implies that the condition (13) is satisfied. However, instead of (16) we have now the opposite inequality

$$r_0^2/D_0 \; > \; V/Q = 1000\,\text{s}. \tag{17}$$

The size of the largest vessel surrounded by the venom is given by Eq. (12). However, the flow in that vessel is now so fast that Eq. (15) would give a contradictory result: the length of the "sausage" would exceed the length of the vessel itself, $l > L$. In fact, the "sausage" occupies quickly ($t < [d(L)]^2/D_0$) the whole vessel. Further the venom is carried to the larger vessel where it is mixed with the blood from the other branch. In that vessel, the convection is even faster. The convection time is so short ($L/v(L) < [d(L)]^2/D_0$) that the admixture has no opportunity to diffuse over the tissues and in such a way to slow down the convection along the vessel. Thus, further transport is purely convective; a rough estimate for the propagation distance $l(t)$ can be found from the equation

$$l \approx v(l)t. \tag{18}$$

It follows that the time needed to reach the heart is less than the rotation time of the blood. The latter is assessed as $t_0 = W/Q \approx 1$ min, W being the total volume of the blood.

3. Short-time evolution of a small spot. In the case of small spot sizes the inequality (13) is satisfied only during a short period just after the injection and soon it becomes opposite,

$$[\lambda(L)]^2/D_0 < t. \tag{19}$$

The expression (14) can still be used, it gives us the effective velocity of the partial transport along the vessel of size L. However, now L will change in time since $\sqrt{D_0 t} > r_0$. Consequently, the spot spreads not only along the vessels, but also in the perpendicular direction. During the evolution of the spot, larger and larger vessels will be surrounded by the venom. The size L of the largest vessel, which is embedded by the spot of the venom and hence takes part in the transport process, can be assessed via $[\lambda(L)]^2 \approx D_0 t$. We rewrite this equation as

$$L = L(\sqrt{D_0 t}), \tag{20}$$

where $L(\lambda)$ designates the reverse function of $\lambda(L)$.

Neglecting the contribution of the smaller vessels in the total transport, the effective transport velocity can be estimated as

$$v_{\text{eff}} = \frac{[d(L(\lambda))]^2}{\lambda^2} v(L(\lambda))\Big|_{\lambda=\sqrt{D_0 t}}.$$

After substituting the "integral of motion" (11), we result in a simple expression for the length of the spot $l = v_{\text{eff}} t$,

$$l = L(\sqrt{D_0 t})tQ/V = L(\sqrt{D_0 t})t/1000\,\text{s}. \tag{21}$$

This equation is valid under the assumption that the length of the polluted area is less than the length of the largest vessel participating in the transport process, $l < L(\sqrt{D_0 t})$. This condition can be rewritten together with the inequality (19) as

$$\lambda^2/D_0 < t < V/Q = 1000\,\text{s}. \tag{22}$$

So, Eq. (21) describes the process in the short time limit, $t < 1000$ s.

4. Long-time evolution of a small spot. Upon achieving the moment $t = 1000$ s, propagation of the venom is accelerated since the largest size of the vessels involved into the process is no more limited by the value of L. Now, the longitudinal transport is more efficient in occupying large vessels than by the transverse diffusion. The critical length L_* of the spot, when switching to the long time limit occurs, can be estimated by $L_* \approx v_{\text{eff}}(L_*)t$. Substituting v_{eff} from Eq. (14) we obtain

$$L_* \approx v(L_*)[d(L_*)]^2/D_0. \tag{23}$$

Further, increasing the value of L, $L > L_*$, the term $v_{\text{eff}}(L)t \approx v(L)[d(L)]^2/D_0$ grows faster than L. The time needed for the spot to pass the distance between two branching points will decrease in time and the process acquires an explosive character. Hence the venom is carried over the rest of the organism within following few time intervals of duration $\tau_1 = V/Q = 1000$ s.

As a conclusion we note that the size of the spot of the injection, as well as the diffusivity of the admixture affect drastically the transport rate of the admixture. The characteristic time scale varies from $\tau_0 \approx 1$ min to $\tau_1 \approx 1000$ s. The first scale here, τ_0, is relevant to the injections into venules and to the bites of snakes, while the second scale, τ_1, describes a sting of an insect.

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ÜLEKANDEPROTSESSID FRAKTAALSETES BIOLOOGILISTES STRUKTUURIDES

Jaan KALDA

On modelleeritud infektsiooni poolt haaratud piirkonna laienemist kopsus eeldusel, et kopsul on enesesarnane puulaadne struktuur ja infektsioon võib levida nii konvektiivselt piki õhu liikumise teid kui ka invasiivselt läbi alveoolide seinte. On tuletatud skaleerumisseadused infektsiooni poolt haaratud piirkonna evolutsiooni kirjeldamiseks. Sõltuvalt parameetrite väärtustest võib piirkonna suurus kasvada plahvatuslikult.

Samuti on vaadeldud passiivse komponendi edasikandumist piki veresoonestikku ning näidatud, et konvektsiooni kiirus sõltub olulisel määral nii lisandaine laigu algsest suurusest kui ka selle osakeste liikuvusest. Karakteerne aeg, mille jooksul lisandaine hajub üle kogu organismi, on inimese puhul 1–20 minutit.