Fast heat propagation in living tissue caused by branching artery network

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We analyze the effect of blood flow through large arteries of peripheral circulation on heat transfer in living tissue. Blood flow in such arteries gives rise to fast heat propagation over large scales, which is described in terms of heat superdiffusion. The corresponding bioheat heat equation is derived. In particular, we show that under local strong heating of a small tissue domain the temperature distribution inside the surrounding tissue is affected substantially by heat superdiffusion.

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I. INTRODUCTION

There is a great variety of inhomogeneous media where transport phenomena exhibit intriguing anomalous properties, the investigation of which is certain to refine understanding the basic characteristics of complex systems widely met in nature (see, e.g., [1–6]). However, the mathematical description of these phenomena is far from being developed well and seems to remain a challenging problem for a long time.

The studying of the anomalous transport phenomena introduces new mathematical objects into physics. One of them is living tissue, which is interesting from different points of view. First, the understanding of the basic characteristics of mass and heat transfer in living tissue is important for the application of mathematical modeling in medicine. Second, the notion of living tissue as a medium with certain, maybe, nontrivial properties forms the basis of describing higher organisms at the mesoscopic level. Third, the description of mass and heat transfer in living tissue forms a problem of the fundamental physics, relevant to the advection-diffusion problem. Moreover, living tissue and transport phenomena in it can be regarded as a new individual class of active fractal media with special anomalous properties playing the essential role in the life nature [7,8].

When living tissue is heated sufficiently strongly its response will be primarily directed to smothering the temperature increase. Therefore in order to specify its response we should begin with the consideration of particular ways in which living tissue can control temperature variations. The matter is that the complex structure of the velocity field in the vascular network in contrast to turbulence ([1,2]) is partly given beforehand. Therefore the temperature distribution inside the region of heated tissue is essentially nonuniform. In particular, the temperature of blood flowing through a sufficiently large vessel of regional circulation can differ remarkably from the temperature of the surrounding cellular tissue. Moreover, if the surrounding tissue is locally heated its temperature will vary substantially along such a vessel, whereas the blood temperature in it will be practically constant. There is a question of how to average temperature distribution over a certain domain in order to get a right bioheat transfer problem. Analyzing the properties of transport phenomena in living tissue caused by its fractal structure vascular network it is possible to develop regular theory of heat transfer in living tissue [8].

In this paper by qualitative description we derive an equation for heat transfer in living tissue with blood flow through a large artery tree.

II. LIVING TISSUE AS A HETEROGENEOUS MEDIUM

Blood flowing through vessels forms paths of fast heat transport in living tissue and under typical conditions it is blood flow that governs heat propagation on scales about or greater than 1 cm (for an introduction to this problem see, e.g., [9,10]). Blood vessels make up a complex network being practically a fractal. The larger is a vessel, the faster is the blood motion in it and, so, the stronger is the effect of blood flow in the given vessel on heat transfer. Blood flow in capillaries practically does not affect heat propagation whereas blood inside large vessels moves so fast that its heat interaction with the surrounding cellular tissue is ignorable [9]. Thus there should be vessels of a certain length ℓ_v that are the smallest ones among the vessels wherein blood flow affects heat transfer remarkably. The value of ℓ_v can be estimated as [8] (see also [9,10])

$$\ell_v \sim \sqrt{\frac{D}{jfL_n}}, \tag{1}$$

where $D=\kappa/(c\rho)$ is the temperature diffusivity of the cellular tissue determined by its thermal conductivity κ, specific heat c, and density ρ, the value j is the blood perfusion rate (the volume of blood going through tissue region of unit volume per unit time), and the factor $L_n \sim \ln(l/a)$ is the logarithm of the mean ratio of the individual length to radius of blood vessels forming peripheral circulation. For the vascular networks made up of the paired artery and vein trees where all the vessels are grouped into the pairs of the closely spaced arteries and veins with opposite blood currents the coefficient $f \sim L_n^{-1/2}$ accounts for the countercurrent effect

Initially the factor f was phenomenologically introduced in the bioheat equation to take into account a certain renor-

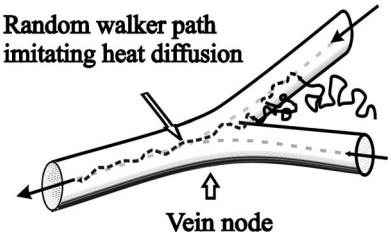

FIG. 1. Schematic illustration of the effect of blood flow through the vein tree on heat diffusion imitated by random walks. The figure shows trapping of a random walker because of getting the internal points of a large vein after passing the vein node.

malization of the blood perfusion rate caused by the countercurrent effect [11–13]. Its theoretical estimate was obtained in [14,15] as well as in [8] (announced for the first time in [16]). For the vascular networks where the artery and vein trees are arranged independently of each other the factor f should be set equal to unity, $f=1$. In particular, for the typical values of the ratio $l/a \sim 20-40$ [17], the thermal conductivity $\kappa \sim 7\times 10^{-3}$ W/cm K, the heat capacity $c \sim 3.5$ J/g K, and the density $\rho \sim 1$ g/cm^3 of the tissue as well as setting the blood perfusion rate $j \sim 0.3$ min^{-1} from Eq. (1) we get the estimates $\ell_v \sim 4$ mm and $L_n \approx 3-4$.

In the mean-field approximation the effect of blood flow on heat transfer is reduced to the renormalization of the temperature diffusivity, $D \to D_{\text{eff}}$, [14] and the appearance of the effective heat sink fj [9,8,15] in the bioheat equation:

$$\frac{\partial T}{\partial t} = \nabla(D_{\text{eff}} \nabla T) - fj(T - T_a) + q_T. \tag{2}$$

Here $T(\mathbf{r},t)$ is the tissue temperature field averaged over scales about ℓ_v, the parameter T_a is the blood temperature inside the systemic circulation arteries, and the summand $q_T(\mathbf{r},t)$ called below the temperature generation rate is specified by the heat generation rate q as $q_T = q/(c\rho)$. The renormalization of the temperature diffusivity is mainly determined by the blood vessels of lengths about ℓ_v and due to the fractal structure of vascular networks the renormalization coefficient $F = D_{\text{eff}}/D$ is practically a constant of unity order, $F \gtrsim 1$ [8]. Let us imitate the temperature evolution in terms of random walks whose concentration is $(T - T_a)$. Then the part of the vein tree made up of vessels whose lengths exceed or are about the scale ℓ_v forms the system of traps. In fact, blood streams going through the vein tree merge into greater streams at the nodes (Fig. 1). Therefore an effective random walker after reaching the boundary of one of these veins inevitably will be moved by blood flow into the internal points of large veins. Then, due to relatively fast blood motion inside these veins it will be carried away from the tissue region under consideration, which may be described in terms of the walker trapping or, what is the same, the heat sink [8]. Since the mean distance between these veins is determined mainly by the shortest ones, i.e., by the veins of length ℓ_v the mean time during which a walker wanders inside the cellular tissue before being trapped is [8]

$$\tau \sim \frac{\ell_v^2}{D} L_n. \tag{3}$$

In obtaining the given expression we have assumed the vascular network to be embedded uniformly in the cellular tissue, so the tissue volume ℓ_v^3 falls per one vein (and artery, respectively) of length ℓ_v. Whence it follows, in particular, that the rate at which the walkers are being trapped by these veins, i.e., the rate of their disappearance, is estimated as $1/\tau$, leading together with expression (1) to the heat sink of intensity fj in the bioheat equation (2). The characteristic spatial scale of walker diffusion in the cellular tissue before being trapped is $\ell_T \sim \sqrt{D\tau}$, i.e.,

$$\ell_T \sim \ell_v \sqrt{L_n} \sim \sqrt{\frac{D}{jf}} \sim 1 \text{ cm}. \tag{4}$$

The scale ℓ_T gives us also the mean penetration depth of heat penetration into the cellular tissue from a point source or, what is the same, the widening of the temperature distribution caused by heat diffusion in the cellular tissue. It is the result obtained within the mean-field approximation.

Beyond the scope of the mean-field theory we meet several phenomena. One of them is the temperature nonuniformities caused by the vessel discreteness [18] which can be described assuming the heat sink in Eq. (2) to contain a random component. In this case transport phenomena could be described by the equation [8,19]

$$\frac{\partial T}{\partial t} = \nabla(D_{\text{eff}} \nabla T) - fj(T - T_a) + q_T + g(\mathbf{r}), \tag{5}$$

where random field $g(\mathbf{r})$ satisfies the correlation conditions. In this case the correlation function $G(|\mathbf{r}-\mathbf{r}'|)$ of the temperature nonuniformities $[\langle T(\mathbf{r})\rangle = 0, \langle T(\mathbf{r}), T(\mathbf{r}')\rangle = G(|\mathbf{r}-\mathbf{r}'|)]$ depends on the temperature, blood flow rate, and $\mathbf{r}$-multiplier $\text{erf}(|\mathbf{r}-\mathbf{r}'|)/(|\mathbf{r}-\mathbf{r}'|)$ [8,19].

Another phenomenon is the fast heat transport over the scales substantially exceeding the length ℓ_T, caused by the process of blood flow through the artery tree, which occurs due to the convective heat transport in large vessels. In this case, the term $g(\mathbf{r})$ has a different essence from the one that it had at investigation of nonuniformities where correlation conditions were applied. In our case it takes into account additional heat transport caused by the branching artery network. Based on the qualitative description of transport phenomena in the vicinity of large vessels, we derive the approximate analytical form of the term $g(\mathbf{r})$. The idea of this derivation implies an estimation of the influence of the fast transport phenomena $g_l(\mathbf{r})$ on each scale of the hierarchy level l, averaging this influence over all possible realization $\langle g_l(\mathbf{r})\rangle$ and then integrating over the whole hierarchical architectonics in order to get the analytical expression for the term $g(\mathbf{r})$ presented in Eq. (5).

We emphasize that transport phenomena in the living tissue with branching artery network and large vessels possess anomalous properties and the bioheat transfer equation (2) does not apply in this case. The mentioned phenomena is the main subject of the present paper.

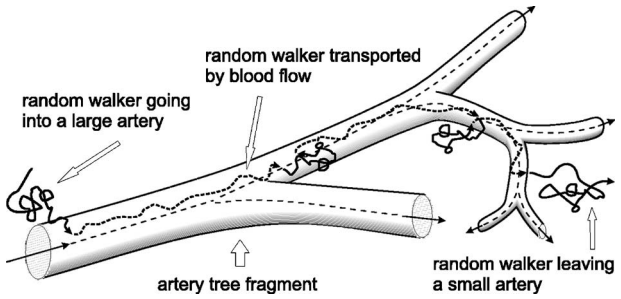

FIG. 2. Schematic illustration of the anomalously fast heat propagation caused by blood flow through a large artery tree in terms of random walks. The figure shows the effective walker motion with blood from a large artery to a small one where the walker leaves it wandering in the cellular tissue.

It should be noted that the standard method of modeling the heat transfer in the close proximity of large vessels by implementing the Navier-Stokes equation along with the model (2) is much more complicated for practical use (see, for example, [20]) because it requires simultaneous solving of three-dimensional hydrodynamic and parabolic equations. Our model consists of a modified bioheat equation and it makes it possible to get approximate temperature distribution in living tissue even without taking into account exact geometry of the artery branching network.

III. FAST HEAT TRANSPORT WITH BLOOD FLOW THROUGH LARGE ARTERY TREE

Let at a certain time a random walker wandering in the cellular tissue get a boundary of a large artery, i.e., an artery of length exceeding ℓ_v. It should be noted that such an event is of low probability and cannot be considered within the standard mean-field approximation [8] because the relative number of large arteries is small. Due to the direction of the blood motion from larger arteries to smaller ones as well as the high blood flow rate in the large arteries the walker will be transported fast to one of the arteries of length ℓ_v (Fig. 2). The blood flow rate in small vessels is not high enough to affect the walker motion essentially and it has inevitably to leave this artery and wander in the cellular tissue until being trapped by the veins of length ℓ_v. Thereby a certain not too large number of random walkers generated, for example, inside a cellular tissue neighborhood of a point $\mathbf{r}$ can be found during the time τ inside a cellular tissue neighborhood of a point $\mathbf{r}'$ at a distance much larger than ℓ_v, i.e., $|\mathbf{r}-\mathbf{r}'| \gg \ell_v$. The given effect may be regarded as anomalously fast heat diffusion in living tissue, i.e., heat superdiffusion.

Dealing with heat transfer in living tissue we may confine our consideration to the peripheral vascular networks typically embedded uniformly into the cellular tissue, at least at the first approximation [21]. The latter statement means, in particular, the fact that for a fixed peripheral vascular network the vessel collection comprising all the arteries of length l meets the condition of the volume l^3 approximately falling per each one of these arteries. Therefore as is seen in Fig. 2 a walker going into a large artery of length l at initial time during the time τ before being trapped by the veins can be found equiprobably at each point of the given artery neighborhood of size l. In other words, this walker makes a large jump of length l that exceeds substantially the mean-field diffusion length ℓ_T. In what follows we will analyze the temperature distribution averaged over all the possible realizations of the vascular network embedding. This enables us to regard a walker entering a large artery of length l as a random event whose probability is independent of the walker initial position. Thereby, the probability P_l for a walker to make a large jump over the distance l is also independent of the spatial coordinates $\mathbf{r}$. It should be noted that for a fixed realization of the vascular network embedding the probability P_l depends essentially on the spatial coordinates $\mathbf{r}$ and the heat transfer in living tissue on large scales has to exhibit substantial dependence on the specific position of the heat sources.

Now we estimate the value of P_l assuming the heat sources to be localized inside a domain $Q_{\mathcal{L}}$ of size $\mathcal{L}$. Two different factors determine the value of P_l. First, it is the process of walker trapping by an artery of length $l > \mathcal{L}$ going through the domain $Q_{\mathcal{L}}$. If $l < \mathcal{L}$ blood flow in this artery has practically no effect on heat diffusion. On the average a random walker during the time τ travels the distance ℓ_T in the cellular tissue until being trapped by the veins of length ℓ_v. So for a walker to enter this artery and, thus, to leave the domain $Q_{\mathcal{L}}$ with blood flow in it the walker, on one hand, should be located at initial time inside a cylindrical neighborhood Q_l of the given artery whose radius is about ℓ_T and the volume is $\mathcal{L}\ell_T^2$. On the other hand, it has to avoid being trapped by the veins of length ℓ_v. The probability of the latter event is about $(\ell_v/\ell_T)^2$. Indeed, a vein of length ℓ_v may be treated as a trap of cylindrical form. Thereby in qualitative analysis the walker trapping can be described in terms of two-dimensional random walks in the plane perpendicular to the artery under consideration where the trapping veins are represented by small circular regions [6,8]. Their density is about $1/\ell_v^2$ which directly leads to the latter estimate. Therefore the total number of walkers leaving the domain $Q_{\mathcal{L}}$ with blood flow through the given artery per unit time is

$$\frac{1}{\tau}\left(\frac{\ell_v}{\ell_T}\right)^2 \mathcal{L}\ell_T^2(T-T_a) = \frac{D}{L_n}\mathcal{L}(T-T_a). \tag{6}$$

In obtaining Eq. (6) we have taken into account expression (3). Since the trapped walkers spread uniformly over a region of size l the resulting density of the walker transition rate to a point $\mathbf{r}$ spaced at a distance about l from the domain $Q_{\mathcal{L}}$ is

$$g_l(\mathbf{r}) \sim \frac{D}{L_n}\frac{\mathcal{L}}{l^3}(T-T_a). \tag{7}$$

It should be noted that the transition rate $g_l(\mathbf{r})$, as it must, does not depend on the local value of blood perfusion rate.

At the second step we should average the obtained transition rate $g_l(\mathbf{r})$ over the possible realizations of the vascular network embedding [8]. We suggest the space-filling requirement for the vascular network to fill precisely the space of a fixed relative volume at each hierarchy level. This idea is quite similar to those considered in [21,22]. Although this suggestion is not true for the explanation of metabolism state

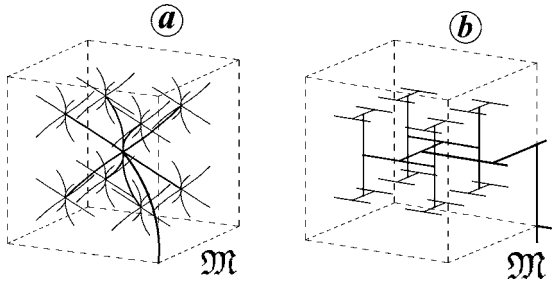

FIG. 3. Models of the peripheral artery network embedding into the cellular tissue, (a) fourfold node model used in the present analysis and (b) a more realistic dichotomic artery tree uniformly embedded into a cellular tissue domain $\mathcal{M}$. In the qualitative description of heat transfer both the models lead to the same result.

behavior [23] from the standpoint of heat transfer vascular network architectonic is of little consequence. The matter is that temperature distribution in living tissue is practically independent of specific details of vessel branching. In particular, it can depend on the mean distance between vessels of a given level or the mean number of arteries of the same length. These characteristics called the self-averaging property of heat transfer in living tissue allow one to consider a model for the vascular network chosen for convenience [8].

Let us adopt a simplified model for the vascular network shown in Fig. 3(a) where the vessel lengths l_n and l_{n+1} of the neighboring hierarchy levels n and $n+1$ are related as $l_n = 2l_{n+1}$. Figure 3(b) demonstrates a more adequate model for the peripheral artery tree which, however, within the framework of the present qualitative analysis, may be reduced to the former one by combining three sequent twofold nodes into one effective fourfold node at all the levels. In this case the cubic domain of volume l_n^3 falls per each artery of level n. Let us now consider individually three characteristic forms of the domain $Q_{\mathcal{L}}$, a ball or a cube of size $\mathcal{L}(d=3)$, an infinitely long cylinder of radius $\mathcal{L}(d=2)$, and a plane layer of thickness $\mathcal{L}(d=1)$. For the ball or the cube, i.e., a region bounded in three dimensions, the probability that an artery of level n passes through the domain $Q_{\mathcal{L}}$ is about

$$P_l^{(3e)} \sim \left(\frac{\mathcal{L}}{l_n}\right)^2.$$

For the infinitely long cylinder

$$P_l^{(2e)} \sim \left(\frac{\mathcal{L}}{l_n}\right),$$

and for the plane layer $P_l^{(1e)} \sim 1$. Multiplying $g_l(\mathbf{r})$ by the corresponding values of $P_l^{(e)}$ we get the result of averaging the walker transition rate $g_l(\mathbf{r})$ over the possible realizations of the vascular network embedding. The obtained result is written as

$$\langle g_l(\mathbf{r})\rangle \sim \frac{D}{L_n}\frac{\mathcal{L}^d}{l_n^{2+d}}(T-T_a), \tag{8}$$

where the value d actually plays the role of the dimension of the space inside which the temperature field can be considered. At the next step we should sum the terms (8) over all the levels of the large artery tree. However, due to the strong increase of the terms (8), $\langle g_l(\mathbf{r})\rangle \propto 2^{n(2+d)}$, as the level number n increases the arteries of length $l \sim r$ mainly contribute to the value of $\langle g_l(\mathbf{r})\rangle$. So the term describing the fast heat transport with blood flow through large arteries from the domain $Q_{\mathcal{L}}$ (located near the origin of the coordinate system) can be written as

$$g(\mathbf{r}) \sim \frac{D}{L_n}\int_{\mathcal{M}} d\mathbf{r}' \frac{T(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|^5}, \tag{9}$$

where $\mathcal{M}$ is the region containing the peripheral vascular network as a whole and the integration in the three-dimensional space over the domain $Q_{\mathcal{L}}$ allows for all its three considered types.

Expression (9) together with the mean-filed bioheat equation (2) enables us to write the following equation governing the anomalous heat transfer in living tissue:

$$\frac{\partial T}{\partial t} = D\nabla^2 T - fj(T-T_a) + q_T + \frac{D}{L_n}\int_{\mathcal{M}} d\mathbf{r}' \frac{T(\mathbf{r}')-T(\mathbf{r})}{|\mathbf{r}-\mathbf{r}'|^5 + \ell_v^5}, \tag{10}$$

where we have added directly the value ℓ_v in order to cut off the spatial scales smaller than the length ℓ_v and ignored the difference between the effective temperature diffusivity and the true one of the cellular tissue. Equation (10) is the desired governing equation of the anomalous fast heat diffusion in living tissue for the averaged temperature field. It should be noted that the second term on the right-hand side of Eq. (10) depends weakly on the blood perfusion rate. Therefore for the nonuniform distribution of the blood perfusion rate $j(\mathbf{r},t)$ Eq. (10) holds also.

A. Anomalous temperature distribution under local strong heating

Hyperthermia treatment as well as thermotherapy of small tumors of size about or less than 1 cm are related to local strong heating of living tissue up to temperatures of about 45 °C or higher values. In this case the tissue region heated directly, for example, by laser irradiation is also of a similar size. Due to the tissue response to such strong heating the blood perfusion rate can grow tenfold locally whereas in the neighboring regions the blood perfusion rate remains practically unchanged [24]. The feasibility of such nonuniform distribution of the blood perfusion rate may be explained applying to the cooperative mechanism of self-regulation in hierarchically organized active media [8,25]. Therefore in the region affected directly the blood perfusion rate $j_{\max}$ can exceed the blood perfusion rate j_0 in the surrounding tissue substantially. In this case the characteristic length of heat diffusion into the surrounding tissue is about

$$\ell_T^* \sim \sqrt{\frac{D}{fj_{\max}}}, \tag{11}$$

giving us also the minimal size $\mathcal{L}_{\min}$ of the region wherein the tissue temperature increase $(T_{\max}-T_a)$ is mainly local-

ized. In the neighboring tissue the blood perfusion rate keeps up a sufficiently low value j_0, which makes the heat propagation with blood flow through large arteries considerable. Indeed, let us estimate the temperature increase caused by this effect using the obtained equation (10). The temperature increase $T(r)-T_a$ at a point spaced at the distance $r>\mathcal{L}$ from the region (of size $\mathcal{L}$) is affected directly, i.e., the tail of the temperature distribution is mainly determined by the anomalous heat diffusion and, so, is estimated by the expression

$$T(r) - T_a \sim \frac{j_{\max}}{L_n j_0} \frac{(\ell_T^*)^2 \mathcal{L}^3}{r^5} (T_{\max} - T_a). \tag{12}$$

As seen from Eq. (12) for a sufficiently local and strong heating of the tissue, i.e., when $\mathcal{L} \sim \ell_T^*$ and $j_{\max} \gg j_0$, the temperature increase at not too distant points such that $r \gtrsim \mathcal{L}$ can be considerable. Otherwise the anomalous heat diffusion is ignorable.

IV. CONCLUSION

In this paper we do not claim the complete solution of the heat transfer problem for living tissue with large arteries. Based on the well-known equivalence of the diffusion type process and random walks, we have designed an equation governing the anomalous heat transfer in living tissue. By qualitative description we have shown that heat diffusion in living tissue caused by a branching artery network possesses anomalous properties. Our particular difference in relation with standard heat transfer problems [8] concerns the view of Eq. (10). The last term in this equation is nonlocal and at small distances from large arteries its influence is essential [Eq. (12)]. It means that the standard bioheat equation can not be applied for investigation temperature distribution in the vicinity of large arteries and some more complicated equations should be used. Although the present model is a simplified picture of the process it captures the main characteristic features of heat transfer in living tissue in the presence of large arteries.

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