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EFFECT OF BLOOD VESSEL DISCRETENESS ON NECROSIS FORMATION DURING LASER INDUCED THERMAL COAGULATION LIMITED BY HEAT DIFFUSION†

I. A. Lubashevsky and A. V. Priezzhev
Moscow State University, Department of Physics, Moscow 119899, Russia

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ABSTRACT

When heated, living tissue exhibits random nonuniformities in temperature that are due to the discreteness of vessel arrangement. Because of the strong temperature dependence of the thermal coagulation rate these nonuniformities should substantially affect the necrosis growth induced by local heating. In the present work we study the effect of vessel discreteness on the form of a necrosis domain when its growth is limited by heat diffusion into the surrounding tissue. Namely, we analyze the characteristics of the necrosis boundary that are due to vessel discreteness. In particular, we find the mean amplitude δ_Γ and the correlation length l_Γ of the necrosis boundary perturbations depending on the main tissue parameters. In addition, it is shown that there are universal relations between the mean size $\mathfrak{R}$ of the necrosis domain and the characteristics δ_Γ, l_Γ of the boundary perturbations, which are due to the fractal structure of the vascular network. © *1999 Society of Photo-Optical Instrumentation Engineers.* [S1083-3668(99)00702-9]

Keywords necrosis domain; thermal coagulation; vessel discreteness; random temperature nonuniformities; random interface perturbations.

1 INTRODUCTION: TEMPERATURE NONUNIFORMITIES DUE TO BLOOD VESSEL DISCRETENESS

Blood flowing through the vascular network in living tissue forms paths of fast heat transport and under typical conditions it is blood flow that governs heat propagation on scales exceeding several millimeters (for an introduction to this problem see, e.g., Refs. 1 and 2). The relative volume of the vascular network is rather small, so vessels directly controlling heat transfer are separated by distances much greater than their radii. Therefore, when heated, living tissue inevitably has to exhibit spatial nonuniformities $\delta T(\mathbf{r},t)$ in the temperature.[3] The particular details of the vessel arrangement on scales about several millimeters are practically unknown and, moreover, alter in various tissues and may be at different points of one tissue. So, on such scales it is reasonable to treat the vessel architectonics as random.[4] In this case the resulting temperature nonuniformities are also regarded as random and can be characterized by the mean amplitude σ and the correlation length λ.

Due to extremely strong dependence of the thermal coagulation rate on temperature such nonuniformities should affect substantially the necrosis growth under strong local heating induced, for example, by laser light absorption. This effect is the subject of the present paper where we analyze the corresponding random perturbations of the necrosis form. Dealing with this problem we, in fact, keep in mind the following physical model (Figure 1). Absorption of laser light delivered into a small internal region of living tissue causes the temperature to attain such high values (about 70 °C) that lead to immediate coagulation in this region. Heat diffusion into the surrounding live tissue causes its further thermal coagulation, giving rise to the growth of the necrosis domain. In this case the temperature distribution becomes substantially nonuniform and for the tissue to coagulate at peripheral points heat diffusion should cause the temperature to grow at these points (see also Ref. 5).

This problem has been briefly considered in our previous paper[6] where, however, we have used a number of simplifying assumptions such as regarding the temperature nonuniformities as fixed beforehand and ignoring the difference between the thermal conductivities of damaged and undamaged

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Dr. Lubashevsky's e-mail address is ialub@fpl.gpi.ru
Dr. Priezzhev's e-mail address is avp@lbp.phys.msu.su

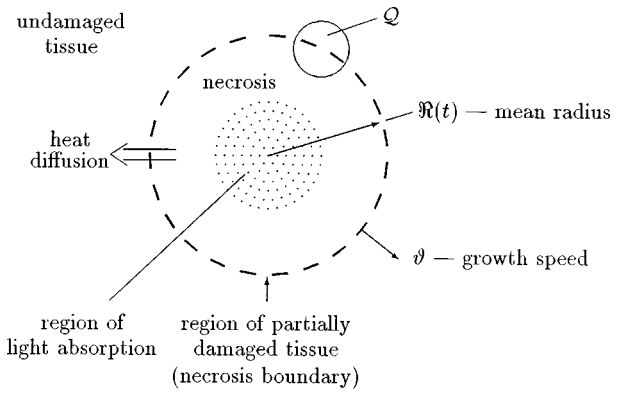

Fig. 1 The necrosis growth due to local thermal coagulation limited by heat diffusion.

tissue. In the present paper we analyze the given problem in detail, basing it on a more precise approach. In order to make its key points clearer, let us first briefly remind the main tissue characteristics governing heat transfer (the mathematical description used here is developed in Ref. 7).

1.1 BACKGROUND: CHARACTERISTICS OF HEAT TRANSFER IN LIVING TISSUE

For the typical values of the blood perfusion rate $j \sim 0.3$–$0.7\,\mathrm{min}^{-1}$ (in organs such as stomach, intestine, and spleen[8]) there is a certain minimal spatial scale (in general, varying in space)

$$l_v(\mathbf{r}) \sim \sqrt{\frac{\kappa}{c\rho f j(\mathbf{r}) L_n}} \tag{1.1}$$

on which the living tissue can be regarded as a homogeneous continuum. Here κ, c, ρ are the thermal conductivity, the heat capacity, and the density of the tissue, respectively, the factor $f<1$ accounts for the counter-current effect,[9,10] and $j(\mathbf{r})$ is the blood perfusion rate averaged over the scale $l_v(\mathbf{r})$ in the vicinity of the point $\mathbf{r}$. The factor L_n is given by the expression $L_n=\ln(l/a)$, where l/a is the mean ratio of the individual length to radius of blood vessels forming peripheral systems of blood circulation. We point out that exactly the ratio $1/L_n$ plays the role of small parameter in the theory of bioheat transfer. So the vessel discreteness should lead to visible effects because such a parameter cannot be very small in magnitude. In particular, for the typical values of the ratio $l/a \sim 40$,[11] the thermal conductivity $\kappa \sim 7\times10^{-3}\,\mathrm{W/cm\,K}$, the heat capacity $c \sim 3.5\,\mathrm{J/g\,K}$, and the density $\rho \sim 1\,\mathrm{g/cm}^3$ of the tissue. As well as setting the blood perfusion rate $j \sim 0.3\,\mathrm{min}^{-1}$ and the factor $f \sim 0.5$ we get $l_v \sim 4$ mm and $L_n \approx 4$.

The heat exchange between blood and the cellular tissue is directly controlled by vessels of length l_v. The shorter vessels can only affect the heat transfer on scales much smaller than l_v, renormalizing the thermal conductivity: $\kappa \to \kappa_{\mathrm{eff}}$. Due to the fractal structure of the vascular network the effective thermal conductivity κ_{eff} of the undamaged tissue can be regarded as a constant exceeding the true thermal conductivity κ of the cellular tissue by a factor of order unity:[7] $\kappa_{\mathrm{eff}} \approx (2\text{ to }3)\,\kappa$. The latter estimate is in reasonable agreement with the available experimental data, at least for $j \lesssim 0.1\,\mathrm{min}^{-1}$ (see, e.g., Refs. 12 and 13). The veins whose lengths are larger than l_v form a joint vessel system playing the role of the heat sink. In the given vessels heated blood flows so fast that it has practically no time to come into thermal equilibrium with the surrounding cellular tissue. This effect is conventionally described by the term $c_b\rho_b f j(\mathbf{r})[T(\mathbf{r})-T_a]$ which specifies the rate of heat dissipation through the large veins [here $T(\mathbf{r})$ and T_a are the local tissue temperature and the temperature of blood in systemic arteries, and c_b, ρ_b are the heat capacity and the density of blood] (see also Refs. 1 and 10).

In the mean field approximation the microscopic equations governing heat exchange between the cellular tissue and blood flowing through individual vessels are averaged over spatial scales of order l_v. In addition, the temperature nonuniformity in the close vicinity of the large vessels (vein and arteries) is ignored due to the small relative volume of the corresponding neighborhood. In this way we can get the following generalized bioheat equation for the tissue temperature $\bar{T}(\mathbf{r},t)$ averaged over the scale l_v[7]

$$c\rho \frac{\partial \bar{T}}{\partial t} = \nabla(\kappa_{\mathrm{eff}} \nabla \bar{T}) - f c_b \rho_b j(\bar{T} - T_a) + q, \tag{1.2}$$

where $q(\mathbf{r},t)$ is the heat generation rate and the constant[‡] $f \sim 1/\sqrt{L_n}$. It should be noted that Eq. (1.2) was first proposed in Ref. 10, where, however, the quantities κ_{eff} and f have been treated as phenomenological parameters. In particular, from Eq. (1.2) we find that the field $\bar{T}(\mathbf{r},t)$ cannot exhibit substantial variations on scales smaller than

$$l_T(\mathbf{r}) \sim \sqrt{\frac{\kappa}{c\rho j(\mathbf{r}) f}} \sim \sqrt{L_n} l_v(\mathbf{r}) \sim 10\,\mathrm{mm}. \tag{1.3}$$

The latter numerical estimate has been obtained using the given values of the main tissue parameters. Expression (1.3) contains the factor L_n formally treated in the bioheat transfer theory as a large parameter, substantiating the validity of the bioheat equation (1.2). In fact, in the mean field approximation we ignore the tissue temperature nonuniformities on scales less than l_v which should be small in comparison with the overheating $(\bar{T}-T_a)$ by virtue of the formal inequality $l_v/l_T \sim 1/\sqrt{L_n} \ll 1$. The physical meaning of the latter inequality is the fact

[‡]We note that a similar formula for the factor f has been obtained in Ref. 14 considering heat transfer in muscles.

that the tissue domain of radius about l_T contains a large number of veins of length l_v forming the system of practically singular heat sinks.

Length l_T also gives the characteristic depth of the temperature penetration into the perfused tissue due to heat diffusion as well as the mean size $\mathfrak{R}$ of the necrosis domain formed during the typical course of local thermal treatment:[15,16]

$$\mathfrak{R}\sim l_T. \tag{1.4}$$

The latter fact, in particular, justifies the application of the bioheat equation (1.2) to the description of the necrosis growth in all the regions except for the layer $\mathbb{L}_\zeta$ of partially damaged tissue where thermal coagulation is underway. Indeed, taking into account the available experimental data[17] the rate $\omega(T)$ of thermal coagulation can be approximated by the expression*

$$\omega(T)=\omega_0\exp\left(\frac{T-T_0}{\Delta}\right), \tag{1.5}$$

where $\omega_0=\omega(T_0)$ at a certain fixed temperature T_0 and $\Delta\sim 3$ to 5 °C is a constant ($\Delta\simeq 3.26$ °C for pig liver at $T_0=65$ °C). Therefore the thickness δ_ζ of the layer $\mathbb{L}_\zeta$ and the mean temperature gradient G near it are related by the expression

$$\delta_\zeta\sim\frac{\Delta}{G}\sim\frac{\Delta}{(T^*-T_a)}l_T. \tag{1.6}$$

Here the value of G has been estimated as $G\sim(T^*-T_a)/l_T$ and the mean temperature T^* in the layer $\mathbb{L}_\zeta$ has been assumed to depend slowly on time and to take values approximately equal to $T^*\approx 65$ °C, which is justified for the typical conditions of the thermal treatment.[18–20] In addition, in obtaining (1.6) we have taken into account that the temperature distribution in the vicinity of the necrosis domain is characterized by a single scale of the order of its mean size $\mathfrak{R}\sim l_T$.[15,16] So from (1.3) and (1.6) we get

$$\frac{\delta_\zeta}{l_v}\sim\frac{\Delta\sqrt{L_n}}{(T^*-T_a)}\sim 0.25, \tag{1.7}$$

whence it follows that the layer $\mathbb{L}_\zeta$ of partially damaged tissue is not thick enough for the temperature distribution in it to be described rigorously by the bioheat equation (1.2) of the mean field theory. Moreover, due to the fractal structure of the vascular network the amplitude σ of the random temperature nonuniformities caused by the vessel discreteness can be estimated as[7]

$$\sigma\sim\frac{1}{L_n}(\bar{T}-T_a). \tag{1.8}$$

Taking into account also an additional numerical factor[7] in the latter expression we find that $\sigma\approx(10\text{ to }20)\%(\bar{T}-T_a)$ and $\sigma\sim 3$ to 6°C for the typical value $\bar{T}\sim T^*\sim 65$ °C of the temperature in the layer $\mathbb{L}_\zeta$.[18–20] So, the amplitude σ of the random temperature nonuniformities turns out to be of the same order as or even greater than the parameter Δ characterizing the power of the temperature dependence of the thermal coagulation rate, $\sigma\gtrsim\Delta$. Therefore, the random temperature nonuniformities should affect substantially thermal coagulation disturbing inevitably the form of the layer $\mathbb{L}_\zeta$.

In order to describe the dynamics of thermal coagulation in the layer $\mathbb{L}_\zeta$ of partially damaged tissue and, thus, to complete the mathematical description of the necrosis growth, we are to go beyond the scope of the mean field theory. In other words, we have to take directly into account the random temperature nonuniformities in the vicinity of the layer $\mathbb{L}_\zeta$.

According to the results to be obtained below the amplitude δ_Γ of random perturbations of the layer $\mathbb{L}_\zeta$, the correlation length l_Γ of these perturbations (Figure 3), and the correlation length λ of the random temperature nonuniformities meet the formal inequalities:

$$\delta_\zeta\ll\delta_\Gamma\ll l_\Gamma\sim\lambda\sim l_v\ll l_T\sim\mathfrak{R}, \tag{1.9}$$

provided the values $1/L_n$ and $\Delta/(T^*-T_a)$ are treated as small parameters. These conditions enable us, first, to ignore the thickness of the layer $\mathbb{L}_\zeta$, i.e., to regard it as an infinitely thin interface Γ of the necrosis domain and, thus, to use the free boundary model for local thermal coagulation.[18,19] Second, we may consider the effect of the vessel discreteness for the undamaged tissue only.

In general, the vessel discreteness affects both the heat propagation through the tissue and the heat dissipation, perturbing the effective thermal conductivity κ_{eff} as well as causing the rate of temperature dissipation fj to exhibit spatial nonuniformities. On scales of order l_v the former effect, however, is responsible mainly for the particular details of the temperature distribution, whereas the latter one governs the amplitude of the temperature

*The given form of $\omega(T)$ dependence which is chosen to simplify the following mathematical manipulation practically coincides with the the standard Arrhenius approximation:

$$\omega(T)\propto\exp\left(-\frac{E}{T}\right)$$

in the neighborhood of the temperature T_0 whose thickness is much less than $\sqrt{T_0\Delta}$, where $\Delta=T_0^2/E$. This follows from the identity:

$$\frac{E}{T}=\frac{E}{T_0}-\frac{T-T_0}{\Delta}+\frac{(T-T_0)^2}{T_0\Delta}\frac{1}{1+\dfrac{T-T_0}{T_0}}.$$

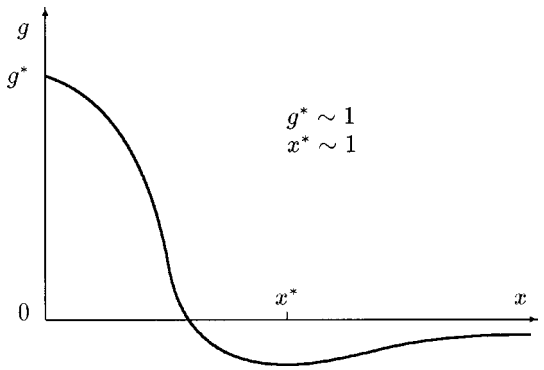

Fig. 2 Typical form of the correlation function of the blood perfusion rate nonuniformities caused by the vessel discreteness.

nonuniformities.** The greater the characteristic scale of the random temperature nonuniformities, the stronger the corresponding perturbations of the layer $\mathbb{L}_\zeta$. So we can confine our consideration to spatial scales of order l_v and describe the effect of the vessel discreteness in terms of the random spatial variations in the blood perfusion rate:

$$j(\mathbf{r},t)\rightarrow j(\mathbf{r},t)+\delta j(\mathbf{r},t), \tag{1.10}$$

where, as before, the smooth field $j(\mathbf{r},t)$ is the blood perfusion rate averaged over scales about l_v and $\delta j(\mathbf{r})$ is its random component, $\langle \delta j(\mathbf{r},t)\rangle = 0$, allowing for the vessel discreteness on these scales. The random field $\delta j(\mathbf{r},t)$ obeys the blood conservation. For uniformly heated undamaged living tissue the latter condition can be written as

$$\int d\mathbf{r}\, g^0(\mathbf{r}) = 0,$$

where $g^0(\mathbf{r})$ is the correlation function

$$\langle \delta j(\mathbf{r},t)\,\delta j(\mathbf{r}',t)\rangle = j^2 g^0(\mathbf{r}-\mathbf{r}'),$$

such that for $x = r/l_v$ we have $g(x)\sim 1$ for $x \lesssim 1$ and $g(x) \ll 1$ for $x \gg 1$. A typical form of the function $g^0(x)$ is shown in Figure 2.

Therefore in order to describe the effect of the vessel discreteness on the necrosis formation we may use the following generalized bioheat equation containing the random component of the blood perfusion rate:

$$c\rho\frac{\partial T}{\partial t} = \nabla(\kappa_{\text{eff}}\nabla T) - fc_b\rho_b(j+\delta j)(T-T_a) + q, \tag{1.11}$$

where T is the true tissue temperature. Equation (1.11) actually forms the basis for the following analysis.

The dynamics of the necrosis growth limited by heat diffusion, namely, the time dependence of the necrosis size $\mathfrak{R}(t)$, is rather insensitive to the particular details of the temperature distribution inside the layer $\mathbb{L}_\zeta$ of partially damaged tissue.[15,16,18–20] In this case the necrosis growth is actually controlled by the mean temperature T^* in the layer $\mathbb{L}_\zeta$. In particular, the validity of the mean field equation (1.2) on scales about $\mathfrak{R}$ justifies this statement. So under such conditions the vessel discreteness should affect mainly the form of the necrosis domain rather than the time dependence $\mathfrak{R}(t)$. The latter fact enables us to confine our analysis to a certain small neighborhood of the layer $\mathbb{L}_\zeta$.

2 DYNAMICS OF THERMAL COAGULATION NEAR THE NECROSIS BOUNDARY

The temperature distribution in the necrosis domain as a whole is characterized practically by a single spatial scale $\mathfrak{R}\sim l_T$ and by a single temporal scale $1/(jf)\sim(l_T^2 c\rho)/\kappa\sim\tau$ which approximately is equal to the typical duration τ of the corresponding thermal treatment and is about several minutes.[15,16] The necrosis boundary as a physical region of the transition from the coagulated to undamaged tissue is described by a number of additional spatial scales. It is the thickness δ_ζ of the layer $\mathbb{L}_\zeta$ of partially damaged tissue, the mean amplitude δ_Γ of the necrosis boundary perturbations due to the random temperature nonuniformities, and the correlation lengths $l_\Gamma\sim\lambda\sim l_v$ of these perturbations coinciding with the correlation length λ of the temperature nonuniformities. These spatial scales correspond to a number of temporal scales. In particular, it is the time $\tau_r\sim(l_v^2 c\rho)/\kappa$ describing development of the random temperature nonuniformities and the time $\tau_\Gamma\sim l_v/\vartheta$ during which the necrosis boundary passes the distance l_v at the velocity $\vartheta\sim\mathfrak{R}/\tau$, i.e., the time characterizing the dynamics of the necrosis boundary perturbations. By virtue of the inequality $l_v \ll l_T\sim\mathfrak{R}$ these temporal scales meet the condition

$$\tau_r \ll \tau_\Gamma \ll \tau. \tag{2.1}$$

Let us consider a certain neighborhood $\mathcal{Q}$ of the necrosis boundary Γ or, what is the same, of the layer $\mathbb{L}_\zeta$ of partially damaged tissue treated as an infinitely thin interface (Figure 3). The thickness $\mathcal{L}$ of the neighborhood $\mathcal{Q}$ is formally assumed to obey the condition $l_v \ll \mathcal{L} \ll l_T\sim\mathfrak{R}$. We study the dynamics of the interface Γ on temporal scales corresponding to its motion inside the neighborhood $\mathcal{Q}$ provided the latter is fixed in space. In this case inequalities

**It should be noted that blood flow through the large arteries can give rise to the fast heat transport over scales much greater than l_T. Under certain conditions it may appear that the effective thermal conductivity κ_{eff} exceeds the thermal conductivity of the cellular tissue by tenfold due to this effect. However, such a fast heat transport cannot be described in terms of the mean field theory and deserves an individual consideration.[21,22] Besides, on the average, its role is not too essential because of the sufficiently small relative volume of the large arteries. Therefore in the present analysis the given effect is ignored. The same concerns the temperature nonuniformities caused by large arteries and veins.

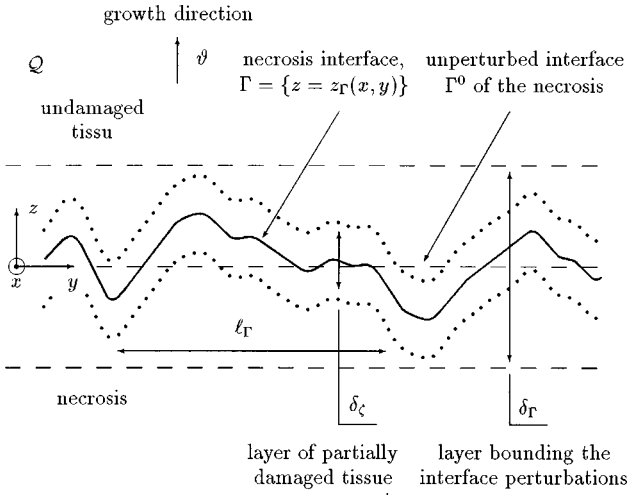

Fig. 3 Form of the necrosis boundary.

(1.9) and (2.1) allow us, first, to adopt the quasistationary approximation for the temperature distribution and, second, to use the free boundary model[18,19] for thermal coagulation. In the quasistationary approximation we ignore the transient term in Eq. (1.11). Besides, we take directly into account only the terms $\nabla(\kappa_{\text{eff}}\nabla T), fc_b\rho_b\delta j(T-T_a)$ for the undamaged tissue, and the term $\nabla(\kappa\nabla T)$ for the necrosis because the other terms of the bioheat equation are responsible for the spatial variations in the tissue temperature on scales about $l_T \gg \mathcal{L}$. In addition, since the temperature variations in the neighborhood $\mathcal{Q}$ are small in comparison with the overheating (T^*-T_a) we set $(T-T_a)\approx(T^*-T_a)$. In other words, we write for the undamaged tissue in the neighborhood $\mathcal{Q}$ and for the necrosis, respectively,

$$l_{T^*}^2\nabla^2 T = \frac{\delta j}{j^*}(T^*-T_a), \tag{2.2}$$

$$\nabla^2 T = 0, \tag{2.3}$$

where j^* is the mean rate of blood perfusion inside the neighborhood $\mathcal{Q}$ and

$$l_{T^*} = \sqrt{\frac{\kappa_{\text{eff}}}{fc_b\rho_b j^*}} \tag{2.4}$$

is actually the value of the scale l_T near the necrosis boundary. The form of the necrosis boundary Γ^0 averaged in the neighborhood $\mathcal{Q}$ on scales about $\mathcal{L}$ can be treated as a plane. So, due to heat conservation we can write for the averaged temperature gradients $\langle\nabla T\rangle$ far from the boundary Γ^0 $(|z| \gg \delta_\Gamma)$ the following relation:

$$\langle\nabla T\rangle = \begin{cases} \left(0,0,-\dfrac{1}{F}G\right) & \text{for} \quad z>0, \\ (0,0,-G) & \text{for} \quad z<0. \end{cases} \tag{2.5}$$

Here the coordinate system $\{x,y,z\}$ is chosen as shown in Figure 3, the factor $F=\kappa_{\text{eff}}/\kappa$ is treated as a constant of order unity, $F \gtrsim 1$, and the value G of the temperature gradient near the necrosis boundary in the damaged tissue is also assumed to be a constant on scales about $\mathcal{L}$ and is estimated as

$$G \sim \frac{T_{\max}-T^*}{\mathfrak{R}}, \tag{2.6}$$

where $T_{\max}$ is the temperature in the necrosis center.

The free boundary model[18,19] assumes tissue temperature T to be continuous at the interface Γ and the temperature gradient to have a jump caused by the heat conservation, i.e.,

$$T_{\Gamma-0} = T_{\Gamma+0} = T_\Gamma, \tag{2.7}$$

$$\nabla_n T|_{\Gamma-0} = F\nabla_n T|_{\Gamma+0}, \tag{2.8}$$

where the subscripts $\Gamma-0$, $\Gamma+0$ point out that the corresponding quantities are taken at the interface Γ on the necrosis and undamaged tissue sides, respectively. Besides, this model relates the normal velocity ϑ_n of the interface Γ at a certain point to the local value T_Γ of the tissue temperature by the expression

$$\vartheta_n \cong \mathfrak{I}_0\frac{\Delta}{G}\omega(T_\Gamma), \tag{2.9}$$

where $\mathfrak{I}_0$ is a constant of order unity. Whence taking into account also (1.5) we get

$$T_\Gamma = T_0 + \Delta\ln\left(\frac{\vartheta_n G}{\mathfrak{I}_0\omega_0\Delta}\right). \tag{2.10}$$

Due to inequalities (1.9) and (2.1) we deal with the developed perturbations of the necrosis boundary Γ moving practically like a solid interface and, thus, in the case under consideration spatial and temporal variations in the velocity ϑ_n as well as temporal variations in the gradient G can be ignored. Then from expression (2.10) we obtain that the temperature T_Γ at the interface Γ is actually a constant value with which we will identify the previously introduced characteristic temperature T^* in the layer $\mathbb{L}_\zeta$:§

$$T_\Gamma = T^*. \tag{2.11}$$

Equations (2.2), (2.3) and boundary conditions (2.7), (2.8), (2.11) form the desired description of the perturbed necrosis interface.

Besides, in order to complete this description we have to specify the mean properties of the random nonuniformities in the blood perfusion rate near the necrosis interface Γ. The correlation function

§As shown in Ref. 6 the same conditions can also be found formally using the distributed model.[23,24]

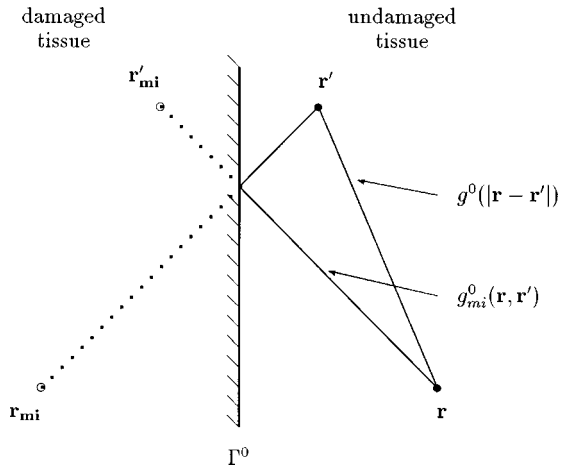

Fig. 4 The point collection specifying the correlation function $g(,')$ of the perfusion nonuniformities near the necrosis boundary (Γ^0 is its unperturbed position).

$g(\mathbf{r},\mathbf{r}')$ of these nonuniformities near the necrosis interface Γ and in the bulk of the undamaged tissue can differ in form. However, the particular details of the function $g(\mathbf{r},\mathbf{r}')$ are of little consequence, which allows us to specify it in a way simplifying the following mathematical manipulations. By virtue of inequalities (1.9), namely, due to $\delta_\Gamma \ll l_v$, let us construct the correlation function $g_\Gamma(\mathbf{r},\mathbf{r}')$ near the necrosis interface Γ as is shown in Figure 4 using the correlation function $g^0(\mathbf{r}-\mathbf{r}')$ of the living tissue bulk (i.e., far from the necrosis region) and the mirror images $\mathbf{r}_{mi}$, $\mathbf{r}'_{mi}$ of the points $\mathbf{r}$, $\mathbf{r}'$ with respect to the unperturbed position Γ^0 of the necrosis interface Γ. In other words, for the points near the interface Γ we set $\langle \delta j(\mathbf{r},t)\,\delta j(\mathbf{r}',t)\rangle \simeq (j^*)^2 g_\Gamma(\mathbf{r},\mathbf{r}')$, where

$$g_\Gamma(\mathbf{r},\mathbf{r}') = g^0(|\mathbf{r}-\mathbf{r}'|/l_v) + g^0_{mi}(\mathbf{r},\mathbf{r}'), \qquad (2.12)$$

$$g^0_{mi}(\mathbf{r},\mathbf{r}') = g^0(|\mathbf{r}-\mathbf{r}'_{mi}|/l_v) \equiv g^0(|\mathbf{r}_{mi}-\mathbf{r}'|/l_v). \qquad (2.13)$$

In the next section basing on the developed description we will analyze the particular properties of the necrosis interface.

3 FORM OF THE NECROSIS INTERFACE

As we claimed in Sec. 1 it turns out that the amplitude δ_Γ of the necrosis interface perturbations is small in comparison with their correlation length l_Γ. Therefore we may analyze the above stated system of equations treating the deviation of the interface Γ from its mean position Γ^0 [the function $z_\Gamma(x,y)$ in Figure 3] as small perturbations of the plane geometry of the interface Γ. Then using the description developed in the previous section and the standard technique of solving such equations,[25] we can show that the perturbation $z_\Gamma(x,y)$ of the necrosis interface and the random nonuniformities in the blood perfusion rate $\delta j(x,y,z)$ are related by the expression

$$z_\Gamma(x,y) = -\frac{F(T^*-T_a)}{4\pi l^2_{T^*} j_* G}\int_0^{+\infty} dz' \int^{+\infty}\!\!\int_{-\infty} dx'\,dy' \times \frac{\delta j(x',y',z')}{\sqrt{(x-x')^2+(y-y')^2+(z')^2}}. \qquad (3.1)$$

Expressions (2.12) and (3.1) give us the main results of the present analysis. In particular, after routine arithmetical manipulations we find that the mean amplitude $\delta_\Gamma \overset{\text{def}}{=} \langle z^2_\Gamma\rangle^{1/2}$ of the necrosis boundary perturbations is

$$\delta_\Gamma = \frac{F(T^*-T_a)}{\sqrt{2}L_n G}\sqrt{g^0(0)} \sim \frac{1}{L_n}\Re, \qquad (3.2)$$

where we have taken into account the estimate $G \sim (T^*-T_a)/\Re$ and $g^0(0)\sim 1$, $F\sim 1$. Besides, we see that the correlation length l_Γ of these perturbations coincides with the correlation length of the perfusion rate nonuniformities l_v, so, by virtue of (1.3), (1.4):

$$l_\Gamma = l_v \sim \frac{1}{\sqrt{L_n}}\Re. \qquad (3.3)$$

Expression (3.3) gives us also the estimate of the characteristic time τ_Γ describing the dynamics of the necrosis boundary perturbations:

$$\tau_\Gamma \sim \frac{l_v}{\vartheta} \sim \frac{l_v \tau}{\Re} \sim \frac{1}{\sqrt{L_n}}\tau \qquad (3.4)$$

because the necrosis boundary perturbations are governed mainly by the temperature nonuniformities of scales about l_v.

Concluding the present section note that at the beginning we have assumed the layer of partially damaged tissue to be sufficiently thin in comparison with the amplitude δ_Γ of the necrosis boundary perturbations. This assumption is basic in the present analysis using the free boundary model, so we now should justify it. From (1.6) and (3.2) we find

$$\frac{\delta_\zeta}{\delta_\Gamma} = \frac{\sqrt{2}}{F\sqrt{g^0(0)}}\frac{\Delta L_n}{(T^*-T_a)} \sim 0.5 \qquad (3.5)$$

for the typical values of the parameters $\Delta\sim 3$ °C, $T^*\sim 65$ °C, $T_a \approx 37$ °C, and $L_n\sim 4$. This estimate shows that in fact the ratio $\delta_\zeta/\delta_\Gamma$ can be treated as a small parameter. In other words, the random perturbations of the necrosis boundary do sufficiently exceed its physical thickness, i.e., the thickness of the layer of partially damaged tissue. Besides, by virtue of the inequality $\delta_\Gamma \ll \Re$ the fact that in the

present approximation we have obtained a specific expression for the necrosis perturbations demonstrates that the adopted free boundary model holds and gives an adequate relation between the velocity ϑ of the necrosis interface and the coagulation temperature T^*. At the first approximation this relation is not affected by the random temperature nonuniformities.

It also should be pointed out that the universal form of relations (3.2)–(3.4) is due to the vascular network being fractal in structure.[7]

In addition, to make the physical sense of the main result (3.2) more clear let us obtain this estimate in a simple qualitative way. At the first approximation we can state[18] that at the necrosis boundary Γ the temperature is a fixed constant $T^* \sim 65$ °C. In this case the form of the necrosis domain perturbed by the random temperature nonuniformities $\delta T(\mathbf{r},t)$ is specified by the condition

$$[\bar{T}(\mathbf{r},t)+\delta T(\mathbf{r},t)]|_{\mathbf{r}\in\Gamma}=T^*. \tag{3.6}$$

In a neighborhood of the necrosis boundary Γ whose size is much less than the mean necrosis radius $\Re$ the spatial variations in the averaged temperature $\bar{T}(\mathbf{r},t)$ can be approximated by a linear dependence on the spatial coordinates $\mathbf{r}$:

$$\bar{T}(\mathbf{r},t)\approx T^*-G[r-\Re] \tag{3.7}$$

provided the origin, $\mathbf{r}=0$, is placed at the necrosis center. Then taking into account (1.8) and (3.7) we find from (3.6) the mean amplitude of the necrosis boundary perturbations,

$$\delta_\Gamma\sim\frac{\sigma}{G}\sim\frac{1}{L_n}l_T\sim\frac{1}{L_n}\Re \tag{3.8}$$

or, what is the same, the thickness of the layer inside which the random perturbations of the necrosis boundary are practically located (Figure 3).

4 CONCLUSION

In the present paper we have analyzed the effect of the vascular network discreteness on the form of the necrosis domain whose growth is due to thermal coagulation limited by heat diffusion. This discreteness manifests itself in temperature nonuniformities treated as random.

In particular, we have shown that:

- The random perturbation of the necrosis boundary caused by such temperature nonuniformities exceeds remarkably in amplitude the thickness δ_ζ of the layer of partially damaged tissue where thermal coagulation is under way.
- The mean amplitude δ_Γ of these perturbations, the correlation length l_Γ, and the characteristic time τ_Γ of their dynamics are estimated as

$$\delta_\Gamma\sim\frac{1}{L_n}\Re,\quad l_\Gamma\sim\frac{1}{\sqrt{L_n}}\Re,\quad \tau_\Gamma\sim\frac{1}{\sqrt{L_n}}\tau,$$

where $\Re$ is the mean size of the necrosis domain, τ is a typical duration of the thermotherapy course, and the factor $L_n\approx\ln(l/a)$ ($l/a\sim 40$ is the characteristic ratio of the individual length to radius of blood vessels forming peripheral circulation systems).
- The practically universal form of the given expressions relating the physical parameters δ_Γ, l_Γ, τ_Γ of the random perturbations of the necrosis boundary to the mean necrosis size $\Re$ and a typical duration τ of the thermotherapy course is due to the vascular network being fractal in structure.
- Because of the inequality $\delta_\Gamma \ll \Re$ the free boundary model[18,19] gives the adequate relation between the necrosis growth velocity ϑ and the coagulation temperature T^* although it ignores the necrosis boundary perturbations caused by the vessel discreteness as well as considers the layer of partially damaged tissue infinitely thin.

Therefore, in describing local thermal coagulation with a mean field theory like the ''distributed'' model[23,24] that does not directly deal with random temperature nonuniformities, one has to regard the layer of partially damaged tissue and the layer containing the random perturbation of the necrosis boundary as a single effective layer of partially damaged tissue. The latter, however, increases the thickness $\delta_\zeta^{\text{eff}}$ of such an effective layer by several times with respect to this value predicted by a ''pure'' mean field theory. Another possible way to avoid this problem is to use the free boundary model,[18,19] treating these layers as an infinitely thin interface by virtue of $\delta_\Gamma, \delta_\zeta \ll \Re$.

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