# A Mathematical Model of Temperature Distribution in Frozen Tissue

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**Abstract.** A computer simulation for a frozen region expansion around a cryoprobe in liver tissue is presented and compared with experimental measurements in liver tissue. Both the analytical solution under simplifying assumptions and the numerical solution of the heat equation were tested. No analytical solution is possible when studying the freezing process in the time scope of minutes. The problem is that the solution needs spherical coordinate transformation, which is singular in the origin. For the frozen region, the analytical solution is not constrained, and conclusions are unrealistic. Neither does it account for the cryoprobe diameter. The numeric solution to the same problem is much more informative. It adopts the natural boundary conditions that are the constant temperatures of both the cooling medium and the bath. Comparisons between the numerical solution and experimental measurements show good approximation of the problem by the model of temperature distribution in a homogeneous medium which freezes around a cryoprobe. Differences were smaller than the apparent measurement errors. Our approach allows relevant results to be obtained within the time period available during the surgery.

**Key words:** Cryoprobe — Temperature distribution — Mathematical model

## Introduction

Cryosurgery has been successfully applied for treating primary and metastatic cancer of the liver. Often, this procedure is the only option when tumors are unresectable. Patients with primary hepatocellular cancer face low resectability rates (Rubinsky and Onik 1991). Cryosurgery uses cryoprobes inserted into the tumor. Freezing is initiated by liquid nitrogen circulating through the probe which causes the tissue around the probe to freeze. If cooling rates are high, the tumor cells are irreversibly damaged below a certain temperature.

To achieve optimum results, the placement of cryoprobes with respect to the

neoplastic tissue is critical. This concerns the duration of the treatment, minimum damage to the healthy tissue, and maximum probability to destroy the cancerous tissue. The extent to which a region of frozen tissue can be monitored accurately during surgery is limited, and fundamental understanding of the mechanisms of damage caused by cryosurgery is still lacking (Bischof et al. 1993). We have tried to model the freezing process by the heat equation to obtain reliable estimates for treatment effects at defined placements of the cryoprobe. This problem has also been partially analyzed by Weill et al. (1993). We used polar coordinates to minimize computation time.

Our aim was to provide fast and reliable estimates of the freezing effects for a defined placement of the cryoprobe. This task is difficult due to the restricted resolution power of ultrasound imaging for detecting tumor extension and monitoring ice-ball formation. Because the treatment time usually exceeds ten minutes, this longer time range is important for assessing the tolerance on the position of isotherms. With our approach and program, the time required to calculate isotherms is within the scope available during the surgery.

## Materials and Methods

Beef or pig livers were immersed in a bath of 37°C. After temperature equilibration, 1-3 cryoprobes were placed into the liver tissue. Several (8-12) thermocouples were inserted in the liver tissue between the probes and also outside the probes in equidistant positions. During 15–20 minutes of maximum cooling, temperature data were sampled from each thermocouple at 1 minute intervals. Results from experiments with perfused livers of living pigs and non-perfused livers were compared. The temperature data obtained during the second freezing phase in perfused liver were almost identical with the data obtained in isolated, non-perfused livers.

### *Mathematical Description of the Problem*

To obtain a comprehensive model, several simplifying assumptions are required. The effective part of the cryoprobe is considered as a sphere, and the origin of a spherical coordinate system is placed at the center of this sphere. The tissue is treated as a homogeneous medium, initially at a uniform temperature. The cryoprobe cools the surrounding tissue, which results in two phases within the medium, a frozen region and an unfrozen region separated by an interface termed the freezing front. The thermal properties of the frozen and unfrozen regions are assumed to be constant within each phase but different between the phases.

The Fourier law states that the heat flow through a body, $q$, per unit time is proportional to the area of the body, $A$, through which the heat is flowing, and to the temperature difference between any two points in the direction of the heat flow

$(T_1 - T_2)$, and is inversely proportional to the distance between these points, $l$,

$$q = k \cdot A \cdot (T_1 - T_2)/l$$

or

$$q = -k \cdot A \cdot \frac{\mathrm{d}T}{\mathrm{d}x} \tag{1}$$

where $k$ [W.m$^{-1}$.K$^{-1}$] is thermal conductivity.
The Fourier transient conduction equation is

$$\alpha \cdot \frac{\partial^2 T}{\partial x^2} = \frac{\partial T}{\partial t} \tag{2}$$

where

$$\alpha = \frac{k}{\rho \cdot c} \tag{3}$$

and $c$ is the specific heat at constant pressure (Bald 1987).

For a point heat sink, the temperature distribution is described by the heat equation in spherical coordinates in each phase

$$\frac{\partial^2 T}{\partial r^2} + \frac{2}{r} \cdot \left(\frac{\partial T}{\partial r}\right) = \frac{1}{\alpha} \cdot \left(\frac{\partial T}{\partial t}\right). \tag{4}$$

The uniform initial temperature condition is

$$T_l(r, t) = T_i; \quad 0 < r < \infty, \quad t = 0. \tag{5}$$

Due to the phase change occurring during the freezing process, interface conditions at the freezing front are also required. Temperature continuity at the interface requires that

$$T_s(r, t) = T_l(r, t) = T_M; \; r = s(t), \; t > 0 \tag{6}$$

and from the conservation of energy at the interface

$$k_s \cdot \frac{\partial T_s}{\partial r} - k_l \cdot \frac{\partial T_l}{\partial r} = \rho \cdot L \cdot \frac{\mathrm{d}s(t)}{\mathrm{d}t}; \; r = s(t), \; t > 0 \tag{7}$$

where $s(t)$, the freezing front, is the location of the interface separating the frozen from unfrozen regions. Indices $s$ and $l$ correspond to the solid and liquid phases respectively.

The boundary condition maintains the initial temperature at infinity

$$T_l(\infty, t) = T_i, \quad t \geq 0. \tag{8}$$

**Table 1.**

| | | | |
|---|---|---|---|
| $\alpha_s$ | $4.5 \times 10^{-7}$ | $m^2s^{-1}$ | the thermal diffusivity of the frozen tissue |
| $\alpha_{sl}$ | 3 | 1 | the ratio of thermal diffusivities in frozen and unfrozen tissue |
| $L_u$ | $333.6 \times 10^3$ | $J.kg^{-1}$ | latent heat of water |
| $\rho$ | $1.0 \times 10^3$ | $kg.m^{-3}$ | specific mass of the tissue |
| $c$ | 3000 | $J.kg^{-1}.K^{-1}$ | specific heat at constant pressure |

The essential parameters of the model are in Table 1. These parameters were selected from Bald (1987) and Duck (1990).

The obvious idea is to use the analytical solution of the heat equation, but a solution has only been found for special arrangements. The problem described by equations [4–8] can be solved analytically (Carslaw and Jaeger 1959; Crank 1964); however, properties of the heat sink need additional assumptions. In particular the heat sink is a point, and

$$\lim_{r \to 0} \left( 4\pi r^2 k_s \cdot \frac{\partial T_s}{\partial r} \right) = 2 \cdot Q \cdot (\alpha_s \cdot t)^{\frac{1}{2}}$$

where $Q$ is a constant associated with the point heat sink. To simplify expressions, dimensionless variables are used. The dimensionless temperature variables are

$$\Theta_s = \frac{T_s - T_i}{T_M - T_i} \qquad \Theta_l = \frac{T_l - T_i}{T_M - T_i},$$

and the dimensionless heat sink coefficient is

$$Q^* = \frac{Q}{2\pi \cdot k_s (T_M - T_i)}.$$

Then, the solution for the frozen region is

$$\Theta_s(\eta) = 1 - Q^* \cdot \left( \frac{\exp(-\eta^2)}{2\eta} - \frac{\exp(-\lambda^2)}{2\lambda} - \frac{\pi^{1/2}}{2 \cdot (\operatorname{erfc}(\eta) - \operatorname{erfc}(\lambda))} \right),$$

and for the unfrozen region, the temperature profile is

$$\Theta_l(\eta) = \frac{\dfrac{\exp(-\eta^2 \cdot \alpha_{sl})}{2\eta \cdot \alpha_{sl}^{\frac{1}{2}}} - \dfrac{\pi^{\frac{1}{2}}}{2 \operatorname{erfc}(\eta \cdot \alpha_{sl}^{\frac{1}{2}})}}{\dfrac{\exp(-\lambda^2 \cdot \alpha_{sl})}{2\lambda \cdot \alpha_{sl}^{\frac{1}{2}}} - \dfrac{\pi^{\frac{1}{2}}}{2 \cdot \operatorname{erfc}(\lambda \cdot \alpha_{sl}^{\frac{1}{2}})}}.$$

where the dimensionless variable $\eta$ is chosen to be

$$\eta = \frac{r}{2 \cdot (\alpha_s t)^{\frac{1}{2}}},$$

and the location of the freezing front, s(t), as a dimensionless variable is

$$\lambda = \frac{s(t)}{2 \cdot (\alpha_s t)^{\frac{1}{2}}}.$$

However, the analytical solution does not consider the actual properties of the cryoprobe. Actually, the dimension of the cryoprobe cannot be neglected. For the cryoprobe with a diameter $a$, the additional boundary condition is

$$T_s(a,t) = T_Z, \quad t \geq 0, \tag{9}$$

which says that the boundary is kept at the temperature of the cooling medium, e.g. liquid nitrogen. Therefore, the numerical solution is a choice. The implicit method according to Twitzell (1984) was used.

The parabolic partial differential equation [4–9] is solved on the finite spatial interval $0 < a \leq r \leq R$, and the boundary condition [8] changes to

$$T_l(R,t) = T_l, \quad t \geq 0. \tag{10}$$

For computation, the dimensionless temperature variables are used. The spatial interval $\langle 0, R \rangle$ is divided into $N+1$ subintervals each of width $h$, so that $(N+1) \cdot h = R$, and the independent variable $t$ is discretized in steps of length $l$. The region for which the heat equation is solved was covered by a rectangular mesh, the mesh points having coordinates $(mh, nl)$, where $m = 0, 1, \ldots, N+1$ and $n = 0, 1, 2, \ldots$ The space and time partial derivatives are approximated by the differences

$$\frac{\partial T}{\partial r} = \frac{T(r+h,t) - T(r,t)}{h} + O(h)$$

$$\frac{\partial^2 T}{\partial r^2} = \frac{T(r-h,t) - 2T(r,t) + T(r+h,t)}{h^2} + O(h^2)$$

$$\frac{\partial T}{\partial t} = \frac{T(r,t+l) - T(r,t)}{l} + O(l).$$

The solution, $T(m \cdot h, n \cdot l)$, of an approximating difference scheme is denoted by $U_m^n$. With respect to [10], $U_{N+1}^n = 0$, and the system of linear equations in the solid

phase has the form

$$(1+2p_s)\cdot U_c^{n+1} - p_s\cdot\frac{c+1}{c}\cdot U_{c+1}^{n+1} = U_c^n + p_s\cdot\frac{U_Z}{2}$$

$$\ldots$$

$$-p_s\cdot\frac{m-1}{m}\cdot U_{m-1}^{n+1} + (1+2p_s)\cdot U_m^{n+1} - p_s\cdot\frac{m+1}{m}\cdot U_{m+1}^{n+1} = U_m^n,\quad c<m<f$$

$$\ldots$$

$$-p_s\cdot\frac{f-1}{f}\cdot U_{f-1}^{n+1} + \left(1+\left(2-\frac{f+1}{f}\cdot\frac{s_n-(f+1)h}{s_n-fh}\right)p\right)\cdot U_f^{n+1} =$$

$$= U_f^n + p_s\cdot\frac{(f+1)}{f}\cdot\frac{h}{(s_n-fh)}\cdot U_M$$

where $p_s=\alpha_s\cdot l/h^2$, $c\cdot h=a$, the cryoprobe radius, and the radius of the frozen region, $s_n$. In the liquid phase $p_l=\alpha_l\cdot l/h^2$, and

$$\left(1+\left(2-\frac{f\cdot(s_n-f\cdot h)}{(f+1)(s_n-(f+1)h)}\right)\cdot p_l\right)\cdot U_{f+1}^{n+1} - p_l\cdot\frac{f+2}{f+1}\cdot U_{f+2}^{n+1} =$$

$$= U_{f+1}^n + p_l\cdot\frac{f}{(f+1)}\cdot\frac{h}{(f+1)h-s_n}\cdot U_M$$

$$\ldots$$

$$-p_l\cdot\frac{(m-1)}{m}\cdot U_{m-1}^{n+1} + (1+2p_l)\cdot U_m^{n+1} - p_l\cdot\frac{(m+1)}{m}\cdot U_{m+1}^{n+1} = U_m^n,$$
$$f+1<m<N$$

$$\ldots$$

$$-p_l\cdot\frac{N-2}{N-1}\cdot U_{N-1}^{n+1} + (1+2p_l)\cdot U_N^{n+1} = U_N^n$$

The position of the front between the frozen and unfrozen regions, $s_n$, is determined from the equation [7]

$$s_{n+1} = s_n + v_n\cdot l$$

$$v_{n+1} = \frac{1}{\rho\cdot L}\cdot\left(k_s\cdot\frac{U_M-U_f^{n+1}}{s_{n+1}-fh} - k_l\cdot\frac{U_M-U_{f+1}^{n+1}}{s_{n+1}-(f+1)h}\right)$$

To test whether cells are killed, it is important to calculate the cooling rate in the proximity of the front.

$$\frac{\partial T}{\partial t} = v_{n+1}\cdot\frac{U_M-U_{f+1}^{n+1}}{s_{n+1}-(f+1)h}$$

The computed solution of this scheme is obtained for each time step by using the decomposition of the tridiagonal matrix of the linear system and by applying the Doolittle method (Twitzell 1984).

## Results

The distribution of temperature around the cryoprobe during cryosurgery is a very important characteristic for determining the extent of tissue destruction A decrease of temperature below −50 °C is considered satisfactory for killing a cell However, an additional condition should be fulfilled For cell killing, the actual freezing rate must hold above a minimum freezing rate which is a few centigrades per minute

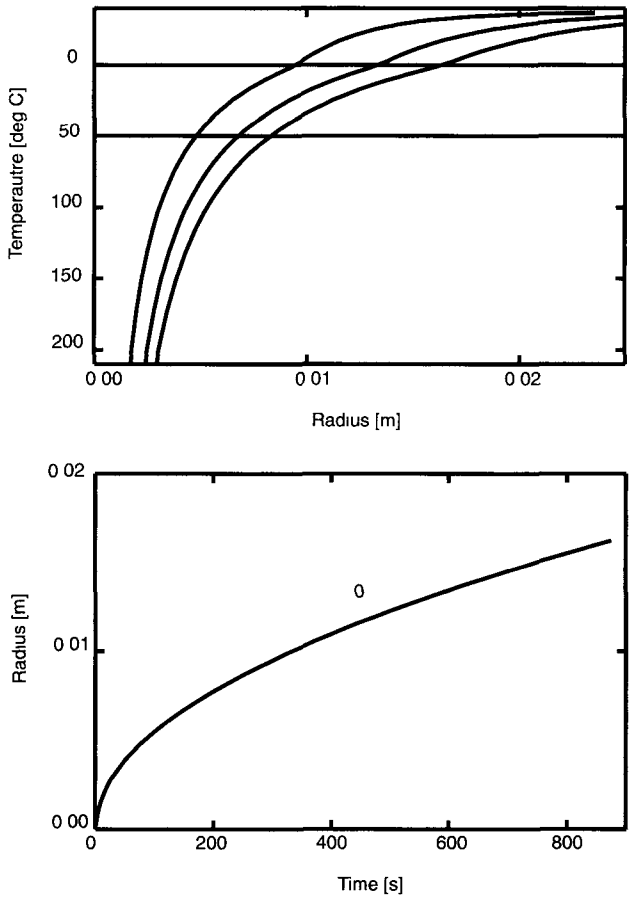


**Figure 1.** The analytical solution of the heat equation (upper panel) was determined according to Scott and Scott (personal communication) (1992) It can be seen that temperature in the frozen region is lower than −200 °C Moreover, the heat gradient is unrealistically high what influences the movement of the freezing front Parameters of the tissue are according to Duck (1990), and are listed in Table 1 It is supposed that the tissue freezes at 0 °C Temperature distribution is plotted at 0, 300, 600, and 900 s In the lower panel, movements of 0 °C isotherms are shown

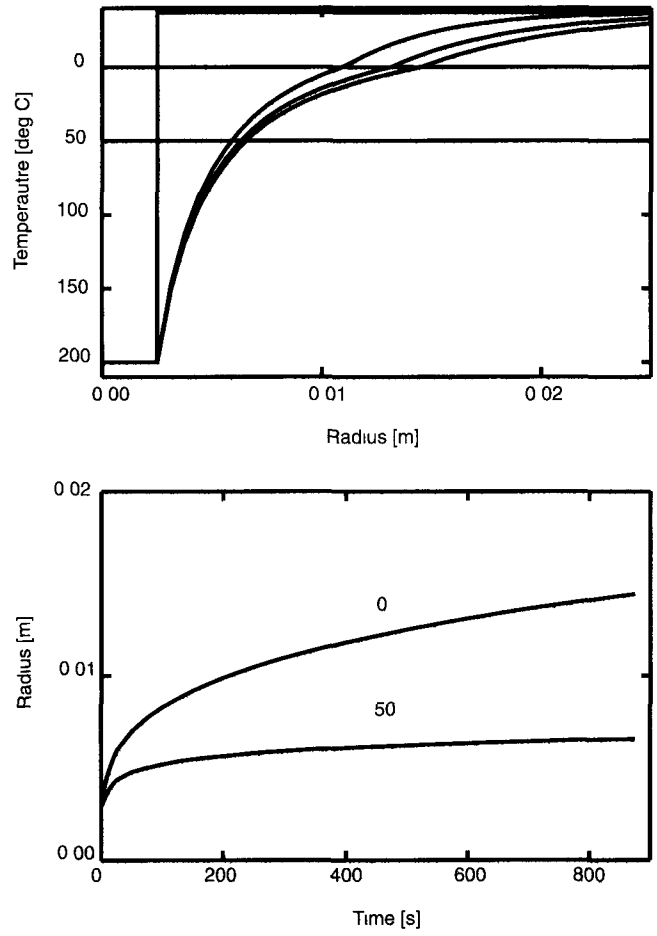


**Figure 2.** The numerical solution of the heat equation (upper panel) shows the temperature distribution in the liver tissue around a ball-shaped cryoprobe with the radius of 2 5 mm and temperature of −200 °C Compare with Fig 1, where the same tissue heat parameters are used In the lower panel, movements of 0 °C and −50 °C isotherms are shown

Therefore, we tried to determine the radius of the frozen tissue and the radius of the region with temperature below −50 °C

Primarily, we tested the applicability of the analytical solution of the partial differential equation for heat [4–8], and this solution was compared with the numerical solution on a finite spatial interval The spatial region was chosen large enough to exclude effects of the boundary

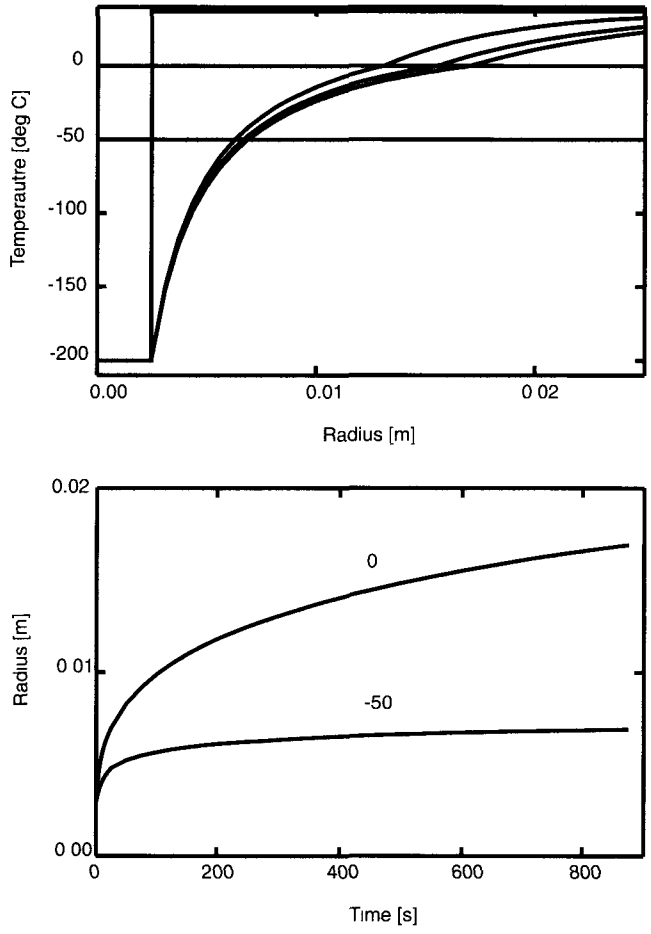


**Figure 3.** The effect of increasing thermal conductivity and diffusivity in both solid and liquid phases is shown. All the parameters were multiplied by 2. When compared with Fig. 2, the effect meets expectations. The temperature decreases faster than in Fig. 2.

For the frozen region, the analytical solution (Fig. 1) is not constrained, and conclusions about the temperature distribution in the frozen tissue are unrealistic. Therefore, it cannot be used to estimate the freezing effects, especially for long cooling periods. Also, the analytical solution does not account for the cryoprobe diameter, which is an important characteristic for the cryosurgery procedure.

The drawback of the problem formulation is the incorrect assumption of a specific temperature of tissue solidification. Due to the presence of intracellular and extracellular compartments with different ionic composition and movement

of water between these compartments during freezing, ice crystals form within a temperature range rather than at a specific temperature value. However, for test computations (Fig. 2), we chose the freezing point at 0 °C. Due to the empirical knowledge that lowering temperature down to about −50 °C kills the cell, we also drew the position of the −50 °C isotherm.

For further applications of the model, we tested the sensitivities of the individual thermal parameters. It appeared that the solution of the model is the most sensitive to thermal diffusivity, $\alpha$, and to temperature of the freezing point, $T_M$. For other parameters, changes amounting to multiples of experimentally measured values did not change the solution substantially. The effect of doubling the diffusivity parameter is shown in Fig. 3. These conclusions allowed to restrict the number of adjustable parameters of the model to an approximation of experimental measurements.

We tried to approximate experimental data by the model of temperature distribution in the liver tissue. The essential parameters of the model were selected from published data. The best fit of the system of temperature measurements is presented in Fig. 4 with the parameters listed below. Temperature measurements were performed at points 5; 8; 10; 12; 15; 17: and 20 mm from the cryoprobe surface. For distances 5 and 15 mm, there were thermocouples placed symmetrically to the cryoprobe, and two values were obtained for each distance. The probe diameter was 10 mm. Experimental measurements are represented by the solid curves. A preliminary check of the individual parameters showed that the solution of the thermal conductivity equation is mainly sensitive to two parameters, thermal diffusivity, $\alpha$, and temperature of the melting point, $T_M$. Their effects are the following. The thermal diffusivity influences proportionally the rate of tissue cooling. Its influence is demonstrated by the dotted curve corresponding to $\alpha_s = 4.0 \times 10^{-7}$ m$^2$s$^{-1}$, and the dashed curve corresponding to $\alpha_s = 4.2 \times 10^{-7}$ m$^2$s$^{-1}$. The first one gives a better fit. The value is about 20% lower than reported in literature ($\alpha_s = 4.5 \times 10^{-7}$ m$^2$s$^{-1}$). The freezing temperature, $T_M$, mainly influences the temperature distribution in the frozen region. The best fit was at $T_M = -12$ °C. This is a reasonable value, because no distinct temperature point for tissue solidification exists. This process takes place between zero degree and the eutectic point (about −21 °C).

The approximation of the experimental curves (Fig. 4) by the model is very good compared with the difference of the experimental measurements in points placed symmetrically with respect to the cryoprobe.

After the first freezing, the tissue was heated slowly to the initial temperature, and then the freezing procedure was repeated. We expected some changes to occur in temperature parameters when the tissue was frozen for the second time. However, the differences were negligible, and can be explained by changes in the thermocouple positions due to tissue volume changes.

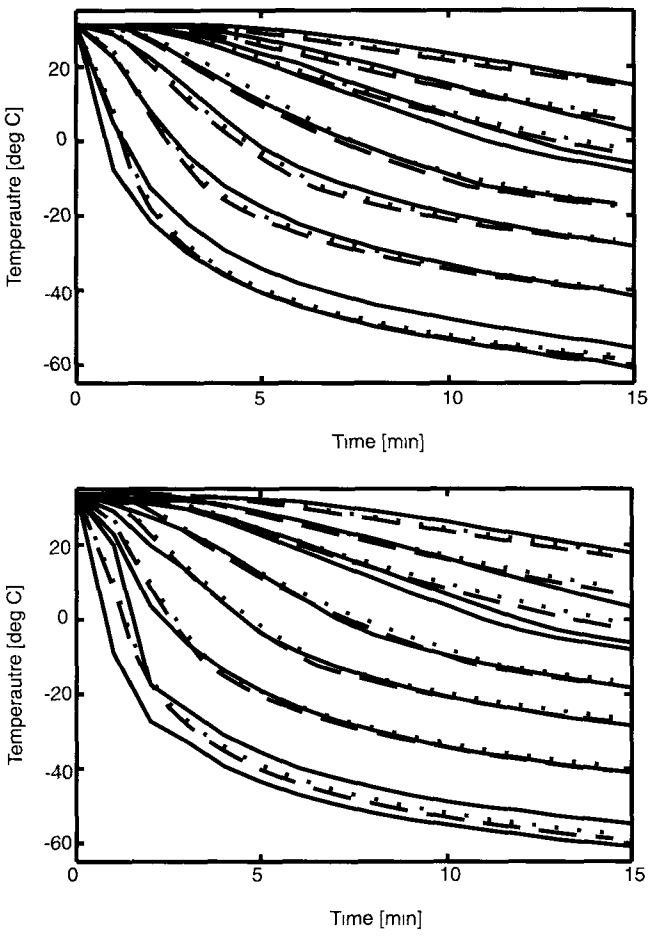


**Figure 4.** Temperature measurements were performed at points 5; 8; 10; 12; 15; 17; and 20 mm from the cryoprobe surface. From bottom to top, the curves represent increasing distances from the probe surface. The probe radius was 5 mm. The upper panel represents the first freezing beginning from 31.2 °C and lasting 15 minutes. The tissue was left to thaw, it was then heated to 33.7 °C, and the procedure was repeated (lower panel). Experimental measurements are represented by the solid curves. The model data were computed with parameters $T_M = -12\,°C$, $\alpha_s = 4.0 \times 10^{-7}\ m^2 s^{-1}$ (dotted line), or $\alpha_s = 4.2 \times 10^{-7}\ m^2 s^{-1}$ (dashed line), and the other parameters are listed in Table 1.

## Discussion

For the presented computations, data from literature were used, which took into account the different thermal properties of the frozen and unfrozen tissue. There-

fore, the simulations can be expected to be realistic. However, the data used were obtained under various experimental conditions, and they might not be fully consistent. Direct comparisons of experimental measurements with numerical simulations can be the only test. Such a test based on data from the liver tissue has shown that with the exception of thermal diffusivity, $\alpha$, other thermal parameters are applicable. The solution is most sensitive just for $\alpha$ and $T_M$. The best value determined by approximation of experimental data was $\alpha_s = 4.0 \times 10^{-7}$ $m^2s^{-1}$, which was about 10 percent lower than the value listed in Table 1. Due to a low sensitivity to the other parameters, the temperature dependence of $L$ has not been taken into account.

The physical events that occur when individual cells are cooled and eventually freeze have been described by Mazur (1984). As cooling occurs down to about $-5\,°C$, the cells and their surrounding medium remain unfrozen because of supercooling. In the interval between approx. $-5$ and $-15\,°C$, ice crystals form in the external medium either homogeneously or heterogeneously, depending on whether or not any seeding takes place. During this period the inside of the cell remains unfrozen and supercooled because presumably the plasma membrane prevents ice crystals growing into the cell interior.

The normal freezing point of water at the atmospheric pressure is $0\,°C$. The freezing point is significantly influenced, however, if solutes are added to water. During the freezing of a binary mixture the phase change occurs over a finite temperature range. Normally, for slow equilibrium freezing, the concentration of solutes would increase before complete freezing of the mixture at the eutectic point (about $-21\,°C$). Therefore, $T_M = -12\,°C$, as determined by the best approximation, is a reasonable value.

The common observation is that ice appears in the extracellular medium before it appears inside the cells; and the cells themselves remain unfrozen at temperatures as low as $-5$ to $-15\,°C$, even in the presence of extracellular ice.

Temperatures between $-5$ and $-50\,°C$ are the most critical. Within that range, the immediate lethality of freezing usually increases with the decreasing temperature. Temperatures below approx. $-50\,°C$ usually have no further killing effect (assuming that the cooling velocity remains constant) (Mazur 1963; Mazur 1984).

Since cooling and warming rates and final temperatures influence cell injury profoundly, it is important to know the distribution of temperatures and rates in that portion of the tissue that does freeze.

As far as the shape of the "iceball", is concerned, model assumptions are simplified in this case. The cryoprobe is not a sphere; rather, it is a rod with a spherical tip. Therefore, the assumption of point symmetry is only an approximation. We chose the spherical coordinate system and radial symmetry. When the cryoprobe is not very long, this system describes the experimental situation well. In the opposite case, the ice ball is pear shaped, and cylindrical coordinates are a better

choice. This situation can be further improved by using a model with more spatial variables.

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Final version accepted January 12, 1996