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CONTROL OF SURFACE TEMPERATURES TO OPTIMIZE SURVIVAL IN CRYOPRESERVATION

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ABSTRACT

The long-term preservation of living tissue for transplantation has proved to be a clinically viable technique in the last several decades. The survival of living cells after preservation has been established to be a strong function of the thermal histories of the specimen, and the cooling rate has been identified as a crucial factor in determining the ultimate survival of the cell sample. In practice, one has control over the size and shape of the freezing container and the manipulation of the environmental cooling conditions. When preserving bulk tissue or an entire organ, a maximum survival rate could be achieved by maintaining optimal values of the cooling rates locally throughout the specimen. In practice, the optimal local cooling rates are difficult to achieve because surface conditions are not propagated uniformly into the interior due to the nonuniform geometries of organs and the variation of thermal properties in the various tissue layers.

Here, we illustrate the use of an inverse design and optimization technique which was originally developed for an aerospace application. This technique has been adapted to the unsteady heat transfer equation in order to determine exterior cooling conditions which will produce maximum survival rates throughout a given tissue. It is shown that the optimal local cooling rates can be enforced by using unsteady temperature variations on the walls of a container in which the cryoprotective agent (CPA) and the bulk tissue sample or organ are located. An optimal time-space variation of the container wall temperature can be determined using an inverse formulation in conjunction with optimization.

The goal of this project is to demonstrate computationally that the inverse design technique can be very useful in controlling cryopreservation protocols. This inverse design technique is demonstrated for a canine kidney in a cylindrical container in order to prove the feasibility and applicability of the technique. These time and spatially varying thermal boundary conditions produce nearly optimal, constant local cooling rates throughout the entire kidney.

Key words: Cryopreservation, heat conduction, optimization, bioengineering.

NOTATION

c	specific heat per unit mass (Wm sec/kg)
k	thermal conductivity (W/m deg C)
L	number of triangular area elements
q	heat flux (W/m^2)

N	number of elements on the boundary
n	unit outward normal vector
r	distance from a point to a node (m)
t	time (sec)
T	temperature (deg C)
α	thermal diffusivity ($\alpha = k/\rho c$)
Γ	boundary of the domain W
φ	space interpolation function
ψ	time interpolation function
θ	internal angle at the boundary node
ρc	heat capacitance (W sec/m^2)
Ω	domain of interest

INTRODUCTION

The long-term frozen preservation of living cells and tissue has been developed as a clinically effective technique during the past several decades. The survival of living cells after frozen preservation has been clearly established to be a strong function of the temperature-time history of the specimen [19]. Numerous thermal parameters are required to fully specify a freeze-thaw protocol. These include the cooling and warming rates, nucleation and storage temperatures, and the intermediate isothermal holding periods [6]. Research has identified the cooling rate as a uniquely crucial factor in determining the ultimate fate of a frozen cell. This phenomena is illustrated effectively by a typical cell survival signature (Figure 1) where the measured post-thaw survival is expressed as a function of the cooling rate during freezing [22]. The characteristic shape of the signature includes a maximum value at an intermediate cooling rate, above and below which the survival rates decrease monotonically.

When preserving living human bulk tissues (veins, valves, ligaments, embryo, bone, spleen, semen, etc.) for the purpose of transplantation, the tissue is cooled in a cryoprotective agent (CPA) to a prescribed low temperature and held at this temperature until used. In practice, optimal survival rates can only be attained throughout a given specimen when a nearly constant localized cooling rate can be achieved and maintained throughout the specimen. Two factors are primary deterrents to achieving this idealized cooling process. First, since all real systems of interest have finite dimensions, thermal transport properties and latent heats, the surface thermal conditions are not propagated uniformly to interior locations. Secondly, it is not known how the environmental temperature should be manipulated so as to create and maintain optimal local cooling rates throughout the specimen.

During the cooling process there is an optimal cooling rate [19] for each particular type of tissue of an organ which maximizes the survivability of the living cells and reduces the problem of future rejection by the organ recipient's body. Once the optimal cooling rates for each type of tissue have been experimentally determined, they can be enforced in a number of ways. One method [4, 17, 18] that offers a practical solution is to determine the proper surface thermal conditions of the container in which the CPA and the tissue are located so that the optimal local cooling rates are achieved at each instant of time and at every point in the tissue. These container surface thermal conditions are very difficult to determine because of the irregular shape of human organs and the fact that different cell types have different optimal cooling rates.

Experiments have shown that although a whole organ does not survive freezing, cells and parts of the organ survive. At the present time, freezing protocols use a single cooling rate at every point on the outside surface of an organ [5, 11, 12]. Nevertheless, this procedure results in considerably different values of local cooling rates inside the organ [20, 21]. Previous modeling [7, 8, 9, 10] has shown that thermal boundary conditions are not propagated uniformly into the interior of a cylindrical system, resulting in a non-uniform distribution of temperature histories and cooling rates throughout the spatial domain. Thus, no single value of the cooling rate can be effectively used to control survival rates in a bulk container. In fact, at the center of the container the cooling rates may increase dramatically during phase change [8, 10, 21] so that cooling rates may differ by more than an order of magnitude [16] between the surface and deep in the interior of the organ. The ability to adjust surface thermal conditions so as to effect desired cooling rates throughout an entire organ would represent a significant advancement in the technology of organ preservation [4, 17, 18].

The purpose of this work will be to prove the feasibility of using an inverse design technique to determine numerically how one should manipulate surface thermal conditions so as to maximize cell survival throughout a bulk sample or whole organ. The idea of using optimization techniques coupled with the boundary element method to develop an inverse design procedure was originated in the aerospace industry [2, 3, 4, 13, 14, 15]. Here, this technique will be used to determine surface cooling temperatures that will effect a nearly constant cooling rate at interior locations in a canine kidney.

Initially, one guesses the surface cooling conditions. Since survival is directly related to cooling rates, one can specify local optimal cooling rates and the container surface thermal conditions are then adjusted iteratively. During each optimization iteration, a two-dimensional unsteady heat conduction equation was solved using a direct boundary element method [1, 2, 3, 4, 13, 14, 15] and a two-dimensional transient heat conduction equation [4, 17, 18]. This particular application is valid for tissue cooling and does not include phase change. However, it does prove the validity of the basic concept and applicability of the inverse design procedure since more complete mathematical models of the heat transfer process can be substituted in the future.

MATHEMATICAL MODEL

The differential equation governing two-dimensional transient heat conduction in a homogeneous material is

$$\alpha \nabla^2 T = \frac{\partial T}{\partial t} \quad \text{on } \Omega \tag{1}$$

with temperatures specified on the surface

$$T = \bar{T} \quad \text{along } \Gamma_1 \tag{2}$$

or heat fluxed specified on the surface

$$q = \frac{\partial T}{\partial n} = \bar{q} \quad \text{along } \Gamma_2 \tag{3}$$

Here, a simple model of heat conduction is used which assumes that material properties are independent of temperature and which ignores latent heat release, both of which are invalid for freezing an actual organ. However, this simple model serves to demonstrate the feasibility of controlling interior cooling rates by using inverse design techniques to determine how to manipulate container surface temperatures as a function of time.

BOUNDARY ELEMENT METHOD

At each step of the optimization procedure, a two-dimensional unsteady heat conduction equation is solved. This can be achieved by using finite elements, finite differences, or boundary element methods. Here, a direct boundary element method is used in which temperature appears as a primary variable [1]. In this simple example, the boundary element method is used because the number of unknowns is associated with the nodes on the boundary and, in general, this is much smaller than the number of nodes in the interior. However, the matrix problem associated with the boundary element method is dense. In the actual cryopreservation problem, which includes a moving phase boundary with temperature dependent thermal properties in the two phases as well as a nonlinear release of latent heat, one should consider replacing the boundary element method with the finite element method. The direct formulation of the boundary element method can be derived from the weighted residual method [1].

$$\int_{t_o}^{t_F} \int_{\Omega} \left(\nabla^2 T - \frac{1}{\alpha} \frac{\partial T}{\partial t} \right) T^* \, d\Omega \, dt = \int_{t_o}^{t_F} \int_{\Gamma_2} (q - \bar{q}) T^* \, d\Gamma \, dt - \int_{t_o}^{t_F} \int_{\Gamma_1} (T - T^*) q^* \, d\Gamma \, dt \tag{4}$$

where T* is the time dependent fundamental solution

$$T^* = \frac{1}{4\pi\alpha(t_F - t)} \exp\left(\frac{-r^2}{4\alpha(t_F - t)} \right) H(t_F - t) \, ; \qquad q^* = \frac{\partial T^*}{\partial n} \tag{5}$$

Integrating the Laplacian in (4) by parts twice, and integrating the time derivative once [1] gives

$$\int_{t_o}^{t_F}\int_{\Omega}\left(\nabla^2 T^* + \frac{1}{\alpha}\frac{\partial T^*}{\partial t}\right) T\,d\Omega dt - \frac{1}{\alpha}\left[\int_{\Omega} TT^*\,d\Omega\right]_{t_o}^{t_F} = -\int_{t_o}^{t_F}\int_{\Gamma_2} qT^*\,d\Gamma dt + \int_{t_o}^{t_F}\int_{\Gamma_1} Tq^*\,d\Gamma dt \quad (6)$$

Substituting Equation (5) into the left-hand side of Equation (6), the final form of the boundary integral equation [1] is

$$CT + \alpha\int_{t_o}^{t_F}\int Tq^*\,d\Gamma dt = \alpha\int_{t_o}^{t_F}\int_{\Gamma} qT^*\,d\Gamma dt + \int_{\Omega} T_o T^*\,d\Omega \quad (7)$$

This equation provides a functional relationship between T and q over Ω which ensures their compatibility as boundary data. Here, C is the value of the local scaled internal angle of the boundary Γ, that is,

$$C = \frac{\theta}{2\pi} \quad (8)$$

Equation (7) can be discretized into a series of N straight elements on the surface Γ with the variation of T and q assumed along each element. Using φ and ψ as the space and time interpolation functions, respectively, for both T and q, equation (7) can be written for the N elements as:

$$C_i T_i^F + \alpha\sum_{j=1}^{N}\left(\int_{\Gamma_j}\varphi^t\left(\int_{t_{F-1}}^{t_F} q^*\psi\,dt\right)d\Gamma\right)T^n = \alpha\sum_{j=1}^{N}\left(\int_{\Gamma_j}\varphi^t\left(\int_{t_{F-1}}^{t_F} T^*\psi\,dt\right)d\Gamma\right)q^n + \sum_{m=1}^{L}\int_{\Omega} T^* T_{F-1}\,d\Omega \quad (9)$$

When using constant time interpolation ($\psi = 1$), the values of T and q remain constant during each time step, thus creating a matrix of linear algebraic equations [17]

$$[A]\{T_F\} = [B]\{q_F\} + [G]\{T_{F-1}\} \quad (10)$$

where square brackets designate geometric coefficient matrices and curly brackets designate vector of unknown and known quantities.

THE OPTIMIZATION PROCEDURE

The surface temperature of the cooling container can be continuously adjusted in time and space in order to maintain the specified local prescribed cooling rates throughout the specimen. To implement this in time, the circumferential variation of temperature on the container wall was approximated with a Chebyshev polynomial in terms of the scaled circumferential angle [4, 16, 17]. The coefficients of these polynomials were adjusted iteratively in order to maintain the desired local cooling rates inside the organ. The initial values of the coefficients of the polynomials are specified and the transient temperature distribution is computed. From this, the local cooling rates are determined at a number of specified points in the organ [17]. A normalized error function can then be formed as a sum of least squares of deviations of the computed and the specified local cooling rates. The new temperature distribution on the container walls is determined by minimizing the error function at the next time step during the cooling process. The minimization procedure used in this work was the Davidson-Fletcher-Powell conjugate gradient algorithm [23]. Thus, the desired optimal local cooling rates are achieved throughout the specimen by determining the proper instantaneous values of the coefficients of the Chebyshev polynomial representing the temperature variation on the surface of the container.

NUMERICAL RESULTS

In order to verify the accuracy of the computer code, a test case with a known analytic solution was used. The objective of this test case was to determine the accuracy of the computer code when the domain is multiply connected. The domain (Figure 2) was approximated by three concentric circles with radii of $r_1 = 0.5$, $r_2 = 1.0$, and $r_3 = 1.5$, all having equal values of the

thermal diffusivity, $\alpha = 5.0$. This configuration was then subjected to time dependent boundary conditions $T = bt$ on the outside surface, $r_3 = a$. The analytical solution to this problem is given by [17, 18]

$$T = b\left(t - \frac{a^2 - r^2}{4\alpha}\right) + \frac{2b}{a\alpha}\sum_{n=1}^{\infty}\exp(-\alpha\gamma_n^2 t)\frac{J_o(r\gamma_n)}{\gamma_n^3 J_1(a\gamma_n)} \tag{11}$$

where γ_n are the positive roots of

$$J_o(a\gamma_n) = 0 \tag{12}$$

Here, J_0 and J_1 are the Bessel functions of the first kind of order zero and order one, respectively. The heat flux at the surface is found by taking the normal derivative of Equation (11) at the outer radius. This results in

$$q = -k\left.\frac{\partial T}{\partial r}\right|_{r=a} = \frac{-bk}{\alpha}\left[\frac{a}{2} - \frac{2}{a}\sum_{n=1}^{\infty}\exp(-\alpha\gamma_n^2 t)/\gamma_n^2\right] \tag{13}$$

The time variation of computed temperatures at different radii is shown in Figure 3 and the time varying surface flux is shown in Figure 4. They agreed reasonably well with the analytical solutions, confirming that the code is correctly treating the multiply connected domains. Then, to investigate the variation of the radial temperature distribution as a function of the thermal diffusivity coefficient in each region, we used α_1=10, α_2=1 and α_3=0.1 which would simulate a two material cylindrical model of a kidney in a container filled with a highly heat conductive CPA. The initial normalized temperature distribution was a constant T=1.0. The temperature on the outer surface was suddenly lowered to zero. The computed radial temperature distributions at different times are shown in Figure 5. A time step of 0.05 was used. This test was then repeated with the thermal diffusivities reversed, that is, α_1=1, α_2=0.1 and α_3=10. The configuration was subjected to identical boundary conditions, and the resulting radial temperature distributions at different times are plotted in Figure 6.

These results indicate that for the purpose of attaining nearly uniform cooling rates in an interior region it is advantageous to place a low diffusivity buffer ($\alpha_1 < \alpha_2$) between the interior region and the surface. Due to the finite thermal properties of the interior region, the boundary conditions are propagated at a nonuniform rate. The low diffusivity CPA then acts like a thermal equalizer which allows thermal boundary conditions to propagate into the interior at a rate at which they can be uniformly absorbed and transmitted. In other words, all thermal gradients should be confined as much as possible to the region filled by the CPA. This will be possible if the CPA has low thermal conductivity.

To demonstrate a practical application of the optimization design process, an actual canine kidney was approximated by three multiply connected regions shown in Figure 7 which includes the outer annulus which simulates the CPA fluid and the two inner regions which simulate the two distinct tissues of a kidney. The diffusivities used were α_1=0.00154, α_2=0.0169 and α_3=0.0255. A total of 114 boundary nodes were used to approximate the three surfaces involved and 418 triangular elements were used to discretize the three regions. Linear spatial interpolation and constant time step of Δt=30 seconds were used. The initial temperature of the entire system was 305 K and the prescribed optimal cooling rate in every triangular element forming the kidney domain was -2.5 K/min. No cooling rate was prescribed in the CPA. A sixth order Chebyshev polynomial in terms of the circumferential angle was used to represent the variable boundary temperature on the surface of the container. When the initial guess for the surface temperature (not optimized) is used, the relative average error of the cooling rate in the kidney was 11.7% after 10 minutes. In contrast, when the container wall temperatures were determined using optimization techniques, the relative error of the cooling rate in the kidney was reduced to less than 1% during the entire 20 minute cooling protocol which was simulated.

The circumferential variation of optimized container wall temperatures are shown in Figure 8. The temperature fields are not axisymmetric due to the kidney geometry and placement in the container.

A three-dimensional perspective of the temperatures in the kidney/CPA system are shown in Figure 9. This clearly illustrates that nearly uniform temperatures and cooling rates can be achieved in irregularly shaped interior regions with non-uniform thermal properties by the transient manipulation of thermal boundary conditions.

CONCLUSIONS

An inverse design procedure has been used in a very simple setting to demonstrate the determination of the appropriate surface thermal conditions to match prescribed values of cooling rates at given points in a biological container. This procedure results in very smooth, reasonable temperature profiles which satisfy the prescribed conditions. This work shows that it is feasible to use an inverse design procedure in creating a cryopreservation protocol. In practice, this procedure will have to be generalized to treat the transient, three-dimensioned mathematical models with phase change where the thermal properties change in each phase and latent heat is released in a nonlinear pattern during solidification. This preliminary study shows that this procedure has great promise in helping to design an optimal freezing protocol so as to maximize the survivability of cells during the cryopreservation procedure.

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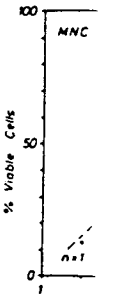

Figure 1.
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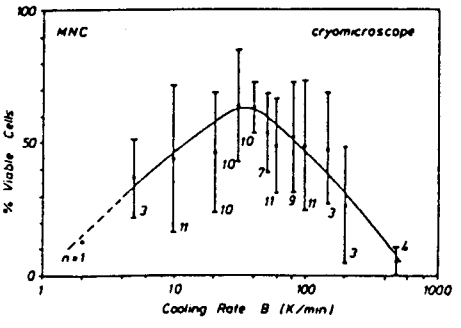


Figure 1. Survival of lymphocytes cooled at constant rates (reprinted from [3]).

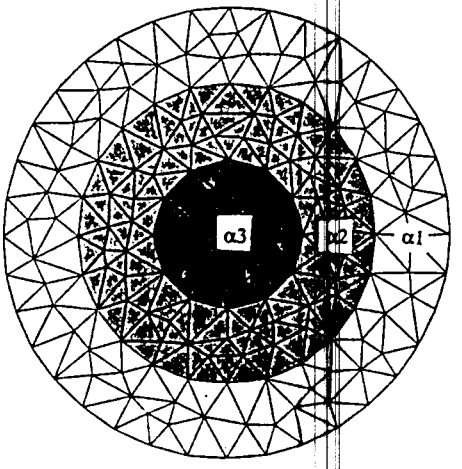


Figure 2. Computational grid for a test composite domain consisting of three concentric cylinders with $\alpha_1 = \alpha_2 = \alpha_3 = 1.0$.

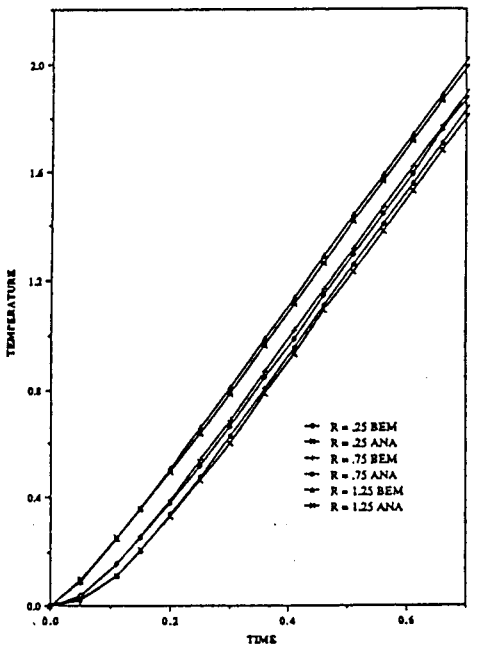


Figure 3. Temperature variation with time for a test case.

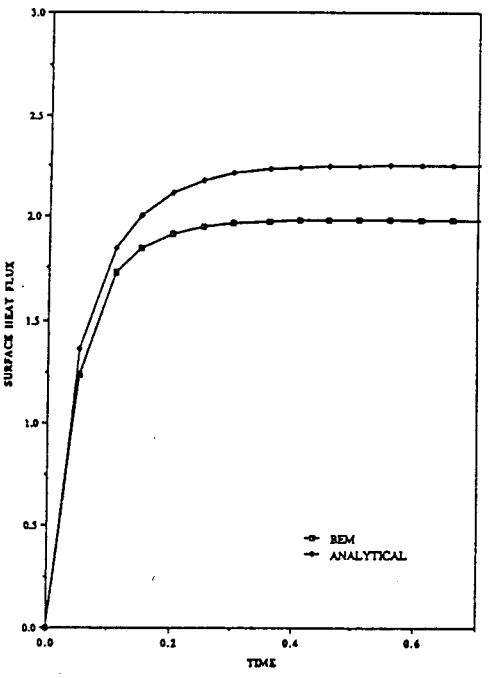


Figure 4. Surface heat flux variation for a test case.

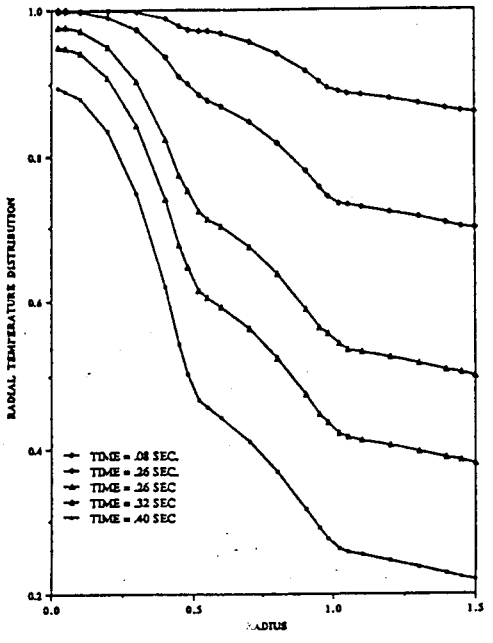


Figure 5. Radial temperature distribution for a composite circular domain, with $\alpha_1 = 10$, $\alpha_2 = 1$, and $\alpha_3 = 0.1$.

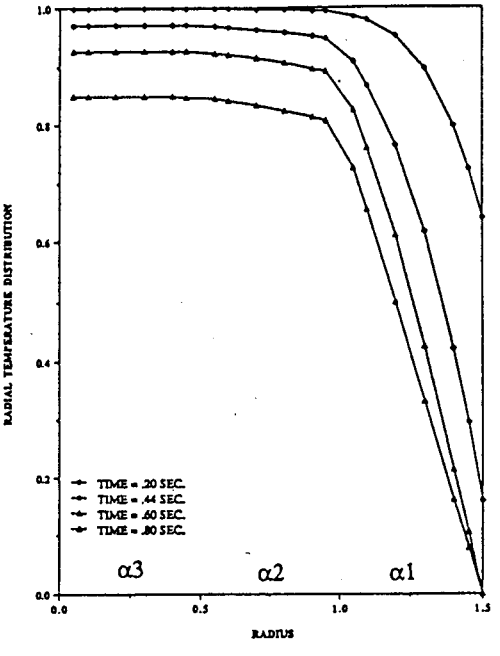
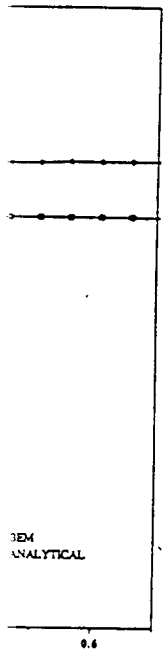


Figure 6. Radial temperature distribution for a composite circular domain, with $\alpha_1 = 0.1$, $\alpha_2 = 1$, and $\alpha_3 = 10$.



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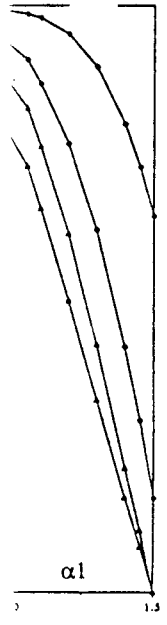

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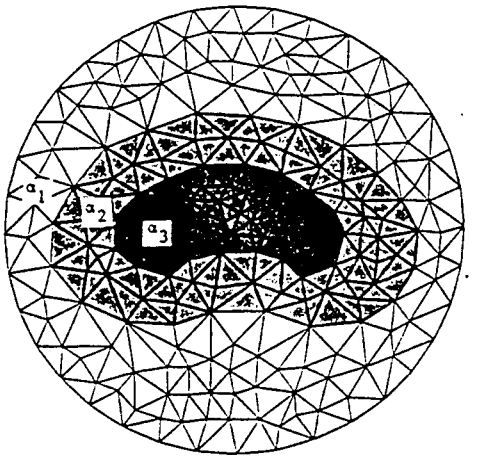


Figure 7. Computational grid for the kidney in a cylindrical container.

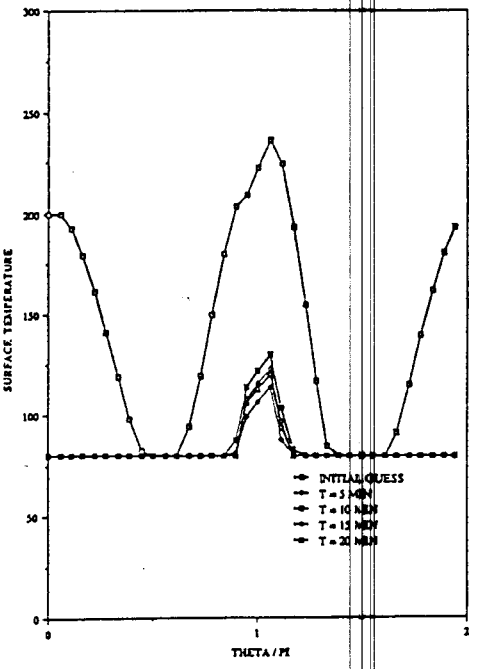
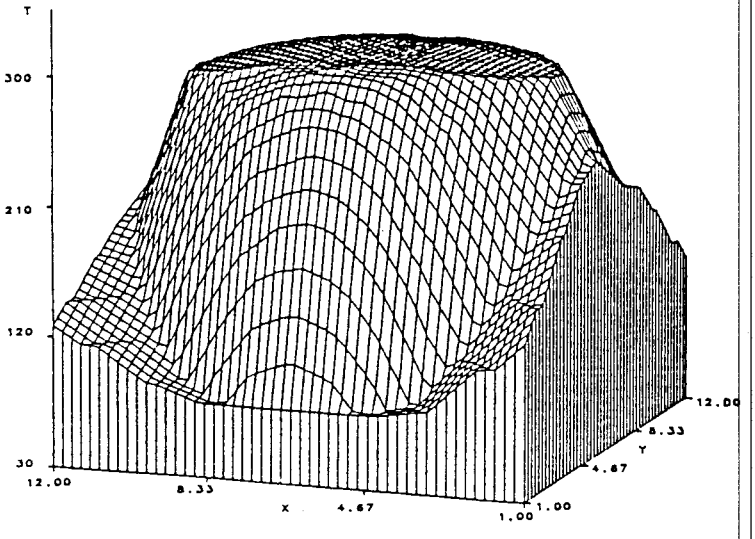
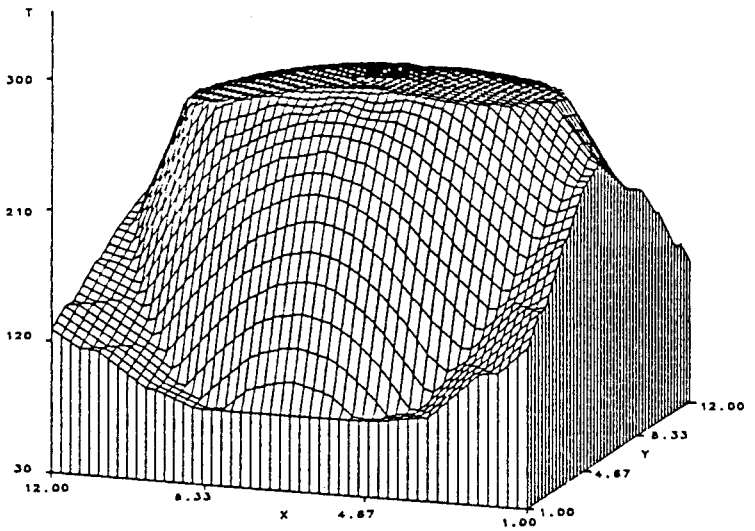
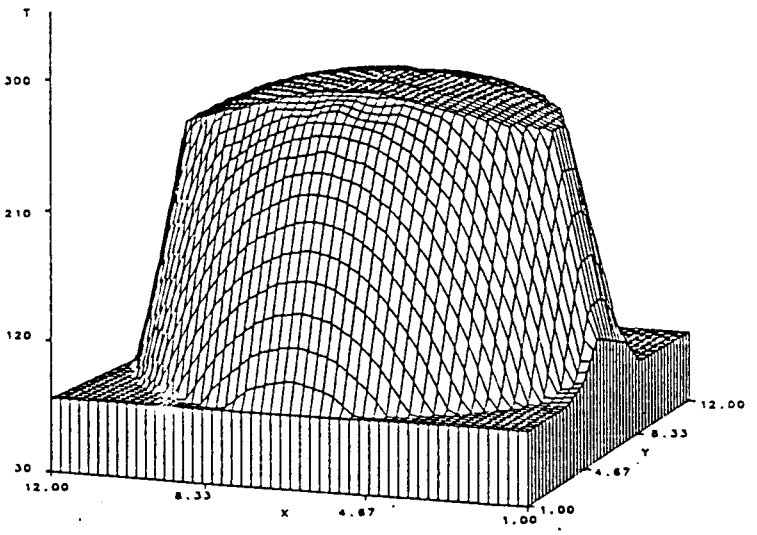
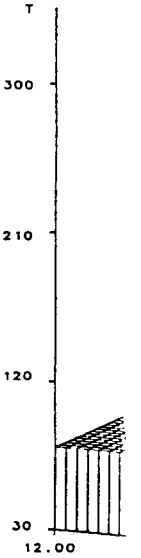


Figure 8. Circumferential distribution of optimized container wall temperatures at different times.









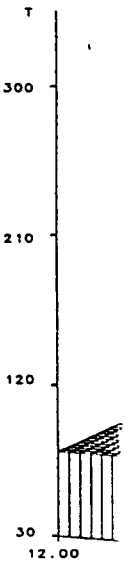


Figure 9. Persp
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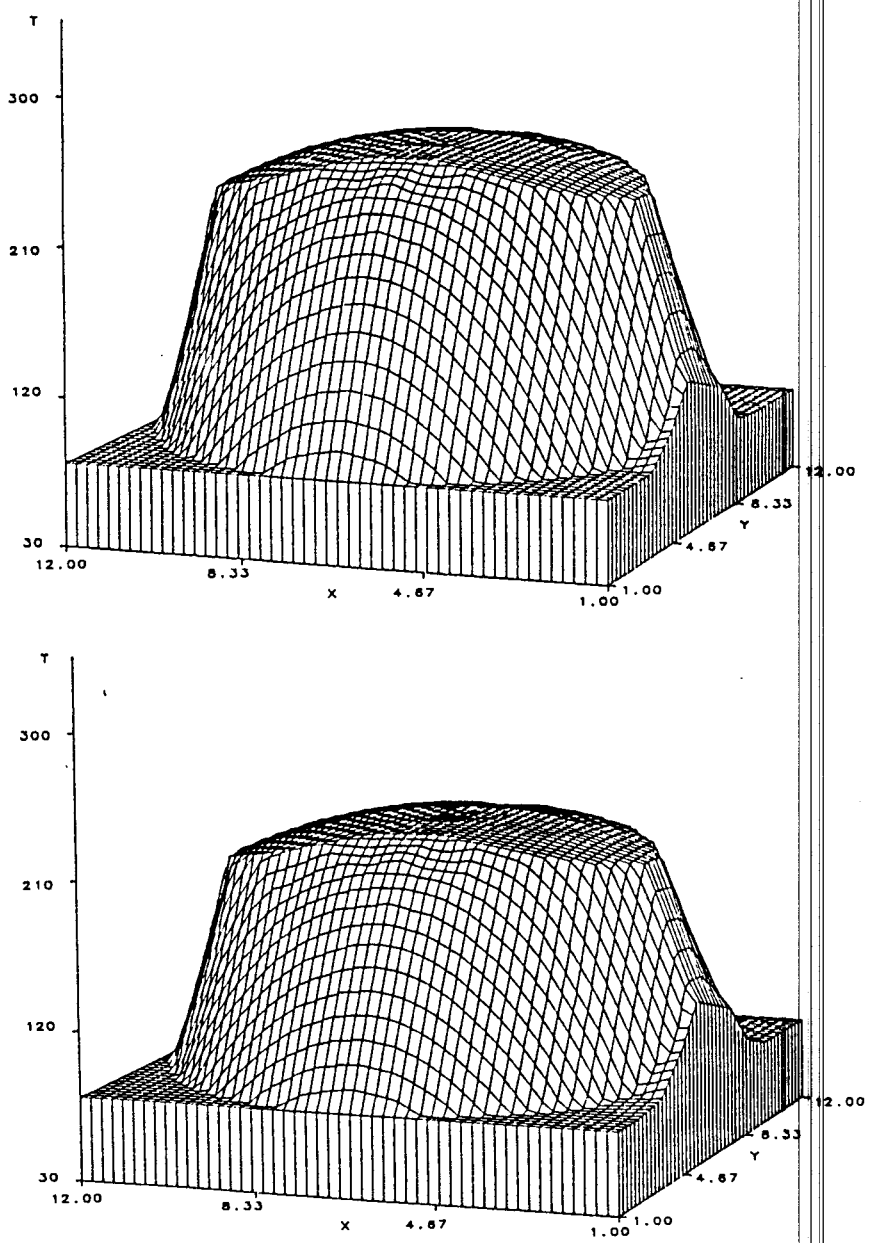

Figure 9. Perspective view of the temperature evolution field in the kidney cooling case: a) after 5 minutes; b) after 10 minutes without optimization; c) after 10 minutes and optimization; d) after 15 minutes and optimization; e) after 20 minutes and optimization.