Cryopreservation of living tissues is a necessary part of many medical procedures such as organ and tissue transplants, conservation of reproductive and stem cells, and etc. However, cells and tissues can be damaged by the cryopreservation process itself. Biological experiments show that both rapid and slow freezing rates can be injurious. Moreover, better results can be obtained, if the ambient temperature falls not monotonically in time, especially in the range were the latent heat is being released.

The paper is devoted to the statement of mathematical models describing the process of freezing and application of optimal control theory or differential games to the design of optimal cooling protocols that minimize damaging effects during the release of the latent heat.

Usually, tissue samples are being frozen using special plants e.g. of the IceCube family developed by SY-LAB, Geräte GmbH (Austria). The main part of such plants is a freezing chamber supplied by a cooling system. An ampoule with a tissue sample surrounded by a liquid is placed into the chamber. The plant is controlled by a computer that allows the user to prescribe a cooling protocol to be tracked. The main trouble in the process of freezing is the release of the latent heat resulting in an irregular behavior of the temperature, which causes the growth of damaging dendrites and extremal changes in the temperature. The aim of the control is to reduce and smooth the latent part of the process and minimize the temperature drops. Two models of freezing are considered.

1. The first model is obtained by averaging of the temperature and the enthalpy, which yields the following system of ordinary differential equations

\[
\dot{H} = -SV^{-1}h(T - T_e), \quad \dot{T}_e = u, \quad |u| \leq \mu,
\]

where \(H\) is the mean enthalpy density, \(T\) is the mean surface temperature, \(T_e\) is the chamber temperature, \(V\) and \(S\) denote the volume and the surface
area of the ampoule, respectively. The parameter \( u \) controls the rate of the chamber temperature. To close equation (1), an approximate substitutive relation \( T = T(H) \) is obtained by recovering the surface temperature \( T(t) \) of the ampoule for a given temperature profile \( T_s(t) \).

The analysis of this model with the Pontryagin maximum principle shows that the required smoothing of the process of the latent heat release is achieved by a single cooling impulse whose parameters (the start and finish times and the power) can be found by solving a proper minimization problem. Using such techniques, a computer module for smoothing the process of the latent heat release has been developed and implemented.

Another approach to the design of improved cooling protocols is based on differential game theory [1]. Since the function \( T(H) \) is recovered with some error, it should be replaced by \( T(H) + v \) where \( v (|v| \leq \nu) \) is an unpredictable control of the opposite player. Two different payoffs are considered. The first one is the time integral of the quadratic deviation from a prescribed temperature profile. The second one expresses the penalization of the mean-square deviation from a given slope. The outlined differential games are solved numerically using both the backward construction of the attainability fronts [2] and the grid method [3] for the corresponding Hamilton-Jacobi equations. The investigation shows that the optimal cooling profiles found are stable with respect to realistic measurement errors.

2. The second model of freezing is based on the so-called phase-field model described by PDEs. In [4], an optimal control problem for such a model is stated and investigated from the mathematical and algorithmic points of view. Results of [4] are adopted to the design of improved cooling protocols for freezing plants. The optimal control is computed using the gradient descent method based on adjoint equations.

References


