Abstract
The investigation concerns the application of optimal control techniques to the minimization of damaging factors in cryopreservation of living cells and tissues in order to reduce the injuring effects of freezing and thawing and improve the survival rate of frozen and subsequently thawed out cells. The objective of the study is the development of mathematical models that describe processes occurring during cryopreservation of living cells and tissues. Such models governed by ordinary and partial differential equations contain control parameters and objective functional that reflects the survival rate of tissue cells.

Analytical characterization, numerical implementation, and practical verification of optimal controls through experiments are discussed.

Some cell-damaging factors of cooling and thawing
1. Recrystallization of small ice crystals into large ones (rapid cooling but slow thawing)
2. Large pressures exerted on the cell membranes during freezing (rapid and slow cooling)
3. Further osmotic dehydration occurring during the warming phase, if the osmotic equilibrium was violated because of the rapid cooling (rapid cooling but slow thawing)
4. Phatholysis and swelling of cells when more ice melts.

I. Recrystallization

\[ \frac{\partial \phi}{\partial t} = K \Delta \phi - \frac{\partial}{\partial x} \left( \phi \frac{\partial \phi}{\partial x} \right) \]

Ice formation in the milieu

Temperature (snapshot)

\[ T(x, t) = \begin{cases} \text{inside} & \text{water} \\ \text{outside} & \text{ice} \end{cases} \]

\[ \phi(x, t) = \begin{cases} \text{liquid} & \text{water} \\ \text{solid} & \text{ice} \end{cases} \]

Cell thawing under minimization of the osmotic inflow

\[ \beta(t) = 1 - \beta(t) \]

\[ \beta(t) = \frac{\text{liquid volume fraction}}{\text{total volume fraction}} \]

Dynamic programming method

Function of optimal result

65% less water inflow with optimal control

Pressure exerted on a single cell when the ambient solute is freezing

The liquid inside the cell is still unfrozen as that outside the cell is already frozen. This results in a large pressure exerted on the cell.

Experiments with a freezer IceCube 14/15SM

(main features)

- Cooling system is based on gas nitrogen
- Chamber and sample temperature sensors
- Input of cooling protocols from a file or manually
- Chamber temperature tracks the cooling protocol

Averaged model of the process

\[ \frac{\partial}{\partial x} \left( \rho c \frac{\partial T}{\partial x} \right) = \frac{\partial}{\partial x} \left( K \frac{\partial T}{\partial x} \right) \]

Ice formation in small pores

\[ \frac{\partial \phi}{\partial t} = K \Delta \phi - \frac{\partial}{\partial x} \left( \phi \frac{\partial \phi}{\partial x} \right) \]

Constitutive law:

\[ \beta(t) = \frac{\text{liquid volume fraction}}{\text{total volume fraction}} = \frac{\text{water}}{\text{water} + \text{ice}} \]

Function \( \phi \) is recovered from data obtained in experiments with tissue samples.

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