Simulation of Cell Shrinkage Caused by Osmotic Cellular Dehydration during Freezing

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Abstract: Cryopreservation of living cells is a necessary part of many medical procedures. However, cells and tissues can be damaged by the cryopreservation process itself. One of the most injuring factors of cryopreservation is dehydration and shrinkage of cells due to the osmotic outflow of the intracellular liquid caused by the increase of the salt concentration in the extracellular solution during its freezing. The mechanism of the osmotic effect is the following. Salt comes from the frozen part of the extracellular liquid to the unfrozen one whose current volume decreases. This causes the increase in the extracellular salt concentration ($c_{\rm out}$). The intracellular osmotic pressure forces osmotic outflow to balance the intracellular ($c_{\rm in}$) and extracellular salt concentrations. Modeling of the cell shrinkage is based on free boundary problem techniques. The main relation here is the so called Stefan condition: $V_n = \chi(c_{\rm out} - c_{\rm in})$, where V_n is the normal velocity of the cell boundary, and the right-hand-side represents the osmotic flux that is proportional to the difference of the concentrations. The extracellular salt concentration $c_{\rm out}$ depends on the unfrozen extracellular water content β_ℓ defined from the following phase field model (see M. Frémond: *Non-smooth thermomechanics.* Springer-Verlag, Berlin, 2002):

$$\rho C \frac{\partial \theta}{\partial t} + \rho L \frac{\partial \beta_\ell}{\partial t} - \mathcal{K}\Delta\theta = 0, \quad \beta_\ell = \phi\left(\frac{L\theta}{T_0(T_0+\theta)}\right),$$

where θ is the Celsius temperature, T_0 the freezing point (K), L the latent heat, ρ the density, C the specific heat capacity, $\mathcal{K}$ the heat conductivity coefficient. The function ϕ is recovered from data obtained in experiments with tissue samples.

It is not hard to prove that the current region $\Sigma(t)$ occupied by the cell is the complement to the attainable set of the control problem

$$\dot{x} = \chi(c_{\rm out} - c_{\rm in}) \cdot v, \quad x \in R^3 \text{ (or } R^2), \quad \|v\| \le 1,$$

provided that the initial set is the complement to $\Sigma(0)$, x the state vector, and v the control variable. We present a very rapid numerical method for the treatment of this problem in the case of two dimensions ($x \in R^2$). Such a method has been developed for computing solvability sets in differential game theory (see e.g. V. S. Patsko and V. L. Turova: *Level sets of the value function in differential games with the homicidal chauffeur dynamics.* Int. Game Theory Review, Vol. 3, No. 1, pp. 67–112, 2001).

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