

Mechanical and Thermal Damage Accumulation and Recovery in Cell and Tissue Products

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Background:

The successful delivery of cell/tissue based products from factory to bedside is one of the key challenges for commercialisation of regenerative medicine. Cell/tissue based products will experience mechanical and thermal impacts to some extent during transportation. Although plenty of research has been carried out to identify the biological response of cell/tissue to mechanical stress and hypothermic/hyperthermic exposure, most of this research is in a physiological or pathological context.

Mechanical impact:

It is known that cells within a skeleton system sense and correspond to the mechanics they experience ¹. However, little is known about the extent of mechanical impact experienced by cell/tissue-based products and the threshold that would induce accumulative non-reversible damage during transportation. Information gathered from in vitro research on the effects of cumulative mechanical force to cells and tissues^{2,3} would be a good lead for using mathematical modelling techniques to understand the underlining biophysics.

Thermal impact:

Most of the researchers in the field of cryobiology believe that the mechanism of damage caused during freezing with low cooling rates is chemical and related to the hypertonicity of the extracellular solution. However, there is some evidence to indicate that cells may be destroyed during freezing also by compression between ice crystals. It has been demonstrated experimentally, and also by mathematical modelling, that cell viability decreases steeply when cells are compressed to 30% of their original diameter⁴.

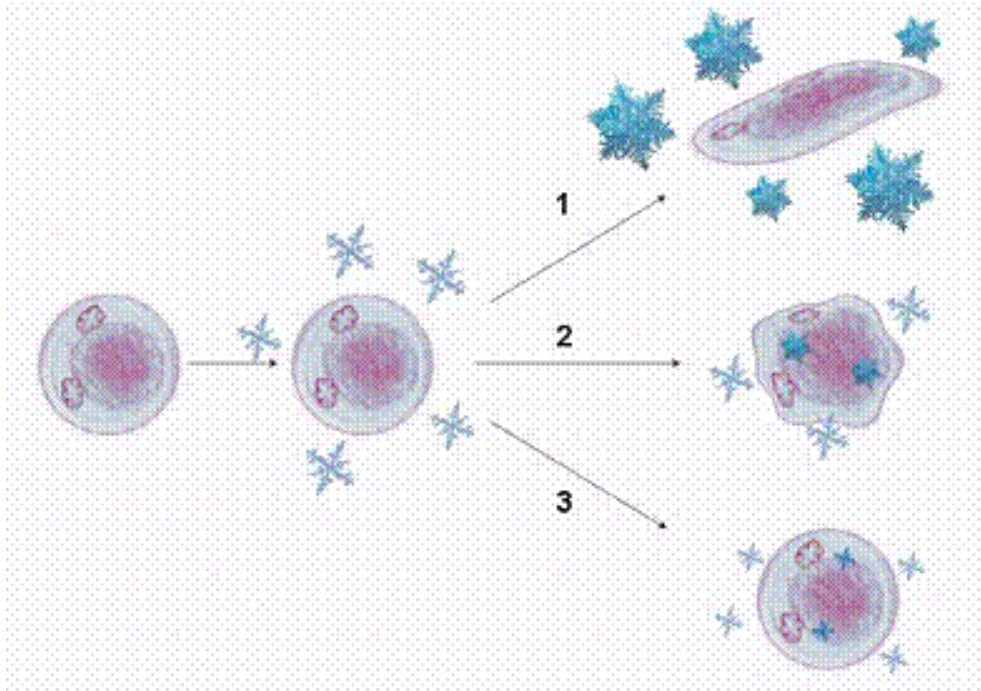
Problem statement:

Typically, there are two types of delivery state of cell/tissue based products, frozen or growing.

1. **Frozen products:** How does the rate of temperature change affect the
 - a) phase change of water,
 - b) cell size,
 - c) dehydration and re-hydration of cell body,
 - d) local electrolyse concentration
 - e) osmosis cross cell membrane

and what would be the cumulative effect of these changes?

- 2. Growing products:** What is the influence of
- air,
 - space above,
 - temperature change of shipping environment,
 - shear force,
 - gas-liquid interface
- to the growing cells or tissue containing growing cells?



Cooling rate and intracellular and extracellular crystal formation
 1. Slow cooling 2. Fast Cooling 3. Very fast Cooling

¹ Mechanical stress directly suppresses osteoclast differentiation in RAW264.7 cells, Suzuki, N; Yoshimura, Y; Deyama, Y, et al., INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE Volume: 21 Issue: 3, 291-296, 2008

² In vitro models to study compressive strain-induced muscle cell damage, Bouten, CVC; Breuls, RGM; Peeters, EAG, et al., Conference Information: Euromech Colloquium on Mechanobiology of Cells and Tissues, APR 24-26, 2001 NANCY FRANCE, BIORHEOLOGY Volume: 40 Issue: 1-3, 383-388, 2003

³ Influence of mechanical stress on cell viability, Huselstein, C; de Isla, N; Kolopp-Sarda, MN, et al., Conference Information: 4th International Symposium on Mechanobiology of Cartilage and Chondrocyte, MAY 20-22, 2006 Budapest HUNGARY, BIORHEOLOGY Volume: 43 Issue: 3-4, 371-375, 2006

⁴ Viability of deformed cells, Takamatsu H, Rubinsky B, CRYOBIOLOGY Volume: 39 Issue: 3 Pages: 243-251 Published: NOV 1999