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Reliability Evaluation for Biomedical Systems: Case Study of a Biological Cell Freezing

Arezoo Amirpourabasi, Mohammad Pourgol-Mohammad* and Hanieh Niroomand-Oscuii

Sahand University of Technology, Iran

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***Corresponding author:** Mohammad Pourgol-Mohammad, Sahand University of Technology, Iran, Email: mpourgol@gmail.com

Abstract

This research proposes reliability evaluation for performance of biomechanical stresses scenarios. This is part of broader researches done by the authors for comprehensive analysis of the biological reliability analysis [1,2]. A literature review is conducted in area of biomechanics phenomenological processes in order to classify the approaches for success criteria determination and reliability metrics calculation based on their merits and limitations. The modeling of this complex medium, in context of mechanical stresses, requires numerical solution of conservation equation and inclusion of corresponding constitution models. Determination of success criteria (first phase for reliability calculation in this research) is a challenging object, and requires consideration of several dependent figures of merits (e.g. temperature, mass and etc.). The developed success criteria matrix is based on the approaches of representation of the figures of merit. A multi-objective criteria is developed according to the phenomena occurrence in the intended study and the selected proper figure(s) of merit. The matrix determines the region of acceptance as well as the rejection area. The reliability index is proposed to estimate the probability of the success based on the calculated system performance in a non-deterministic (stochastic parameters) approach. By augmentation of developed success criteria and the system analysis calculation, a decision is made on the success and rejection of the system performance. The methodology is applied to the case of cell cryopreservation phenomenon. The process of freezing in living cells is considerably more complicated than in a solution, primarily due to the presence of cellular structure. The process is considered a transient biomechanical process which is mechanical stress on the cell structure including the thermal and mass transport. The success criteria are determined based on two figures of merit of temperature and mass and their rate of change. Numerical calculation is completed for study of thermal and mass behavior for the transient of the cell. The uncertain parameters are considered random and Monte Carlo simulation is conducted for inclusion of their variation in the calculation. The situation is specified for the observation of the success criteria and occurrence of the failure.

Introduction

Biological medium is complex in the correlated occurrence of microscopic and macroscopic phenomena. In many biological processes, so it would be important to set success criteria which establish the minimum system performance required to operate, during a specified period of time, to ensure that the critical safety functions are met within the limits of acceptance criteria. So, setting reliability index for this complex system is potentially important to evaluate its reliability.

Setting reliability index requires determining success criteria matrix which is generally a complex and subjective process. It is the case in biological medium of several dependent figures of merits. e.g. temperature, mass and correlated parameters like crystallization and shrinkage in the cells and tissues. The classic reliability method has been studied for various systems by many researchers [3].

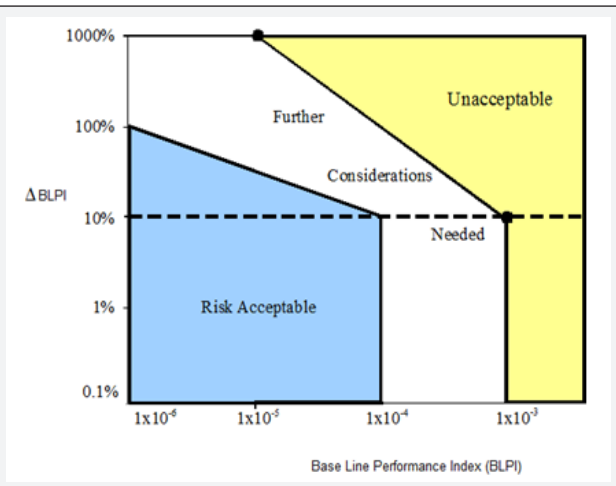

Figure 1: Acceptable risk levels based on changes in base line performance index [3].

In a general term, Modarres [3] assessed the acceptance criteria in context of risk analysis. The concept of acceptance criteria in context of risk analysis is shown in Figure 1. In context of the biological applications, body heat losses are affected by air temperature, humidity, velocity, and other factors. These factors would be considered as success criteria in thermal relaxation in human body. Albrektsson [4] attempted to propose a pioneer work on success criteria in assessment of long-term efficacy of currently used dental implants in different implant applications, which could be used to standardize the basis for comments on each type of implant. Esposito [5] evaluated biological factors contributing to failures of osseointegrated oral implants. The literature and researches are reviewed to provide the clinician with scientifically-based diagnosis criteria for monitoring the implant condition. Datta [6] set success criteria for temperature and humidity combinations for human comfort. It means if the temperature or humidity is deviated out of this region, the comfortless is compromised.

Studholme [6] discusses the cellular responses to thermal loading of a complex thermo-physical process, i.e. heat transfer process coupled with phase change, moving phase interface, mass transport. The cell damage is mainly caused by disruption of cell membranes and organelles due to the volume expansion of intracellular ice crystals. And ice crystals are correlated with heat transfer process and mass transfer process and rate of them, in this research it is aimed to set a safe region in transient thermal stress to minimize or eliminate cell damage during cryopreservation. The authors in their previous works attempted to develop the success criteria for biological systems, the presented ideas are neither mature nor comprehensive and more on solving a specific problem. Lin [7] explored qualitative and quantitative method to analyse human reliability of medical devices in his research. He determined risk factors like the occurrence, severity and detection using the opinions of different experts. He analysed and built an assessment model of human reliability of medical devices to improve the safety of medical devices. Meghdadi [8] evaluated an image-based tumour growth by taking into account uncertainty in the model parameters. This research attempts to develop context-free comprehensive success criteria.

Methodology Structure

This research proposes a general success criteria development approach and the quantitative index for reliability performance evaluation of biomechanics transient stresses scenarios. A literature review is conducted in area of biological phenomena in order to classify the approaches for success criteria determination and their merits, and evaluation of reliability in biological medium. In this research time dependent performance is used to demonstrate the system success.

The developed success criteria matrix is based on the approaches of representation of the figures of merit. A multi-objective criterion is developed according to the various phenomena occurrence in the intended application and the selected corresponding figures of merit. Figure 2 shows the demonstration of biological methodology structure. In this figure, the methodology structure is divided to 3 elements: Element 1- Requirements and Code Capabilities: it is for a specific scenario: first, it identifies the important processes that must be considered in experiments and analyses. Element 2- Assessment and ranging of parameters: it is for augmentation of the success criteria and system performance analysis. So it is needed to establish success criteria matrix and system performance analysis. In the system performance analysis model nodalizaiton and structure is developed and determined their validation and verification. At the end, computation code, experiment and expert elicitation accuracy is determined. For establishment of figure of merit, setting success criteria is required. After setting success criteria, if there is more than one, response surface analysis is performed. Element 3- In this section sensitivity calculations is performed and then, total uncertainty is done to calculate specific scenario in a specific case study is determined.

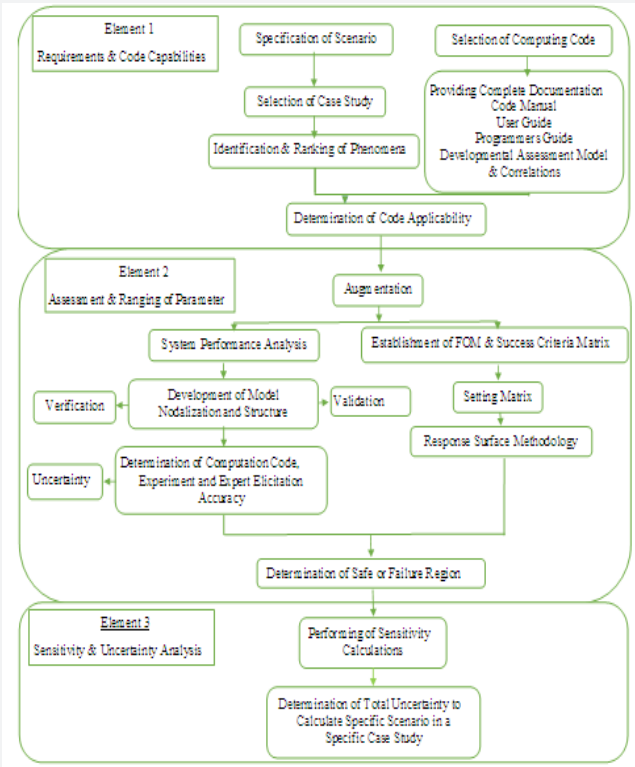

Figure 2: General biological methodology structure.

A reliability index is proposed here to evaluate the survival likelihood of the organ under given stress scenario. The threshold exceedance probability is the primary quantity of interest in reliability evaluation where the organ fails when stress trend exceeds the preset success criteria in a biological organ.

Success criteria determination methodology

The structure of the methodology of setting success criteria is shown in the flowchart in Figure 3. Success criteria

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determination starts with identification and estimation of initiating events frequency as shown in the block A of the Figure. The system performance is analysed to determine the figure of merit behaviour under transient stresses (block B). This task requires the development of the transient scenario and acquisition of the supporting data (block C and D). Failure mode and effect analysis provides a technical support for systematic identification of system failure mode/mechanism and their effect on system performance. This results in screening out the relevant figures of merits for the given problem. Since the uncertainty sources contribute to the precision of the calculation, the uncertainties and their importance are considered in the interpretation of the results and the process of the decision making (block E and F). By augmentation of developed success criteria and the system analysis calculation, a decision is made on the success and rejection of the system performance (block G)

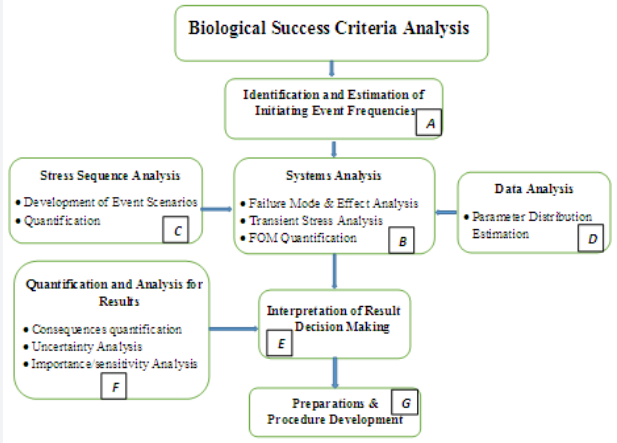

Figure 3: The methodology structure flowchart for determination of biological success criteria.

System performance analysis

Thermal and chemical behaviour of biological medium is complex in its nature. It requires accurate modelling and consideration of the complicated structure of the biological case study. Due to enormous uncertainties in the calculations, the deterministic/conservative approaches leave questions on validity and precision of the solution and providing better estimates for decision makers [9]. By conservative methods, it means that the assumptions, boundary/initial conditions and models are selected based on a pessimistic approach. The methodology of choice is best estimate solution plus uncertainty quantification. By best estimation, the most accurate model with the best chosen parameters, and realistic boundary condition and initial values. This will require companion of the uncertainty analysis along with the calculation results. The uncertainty sources include aleatory (inherent variation and irreducible) and epistemic (knowledge-based and reducible) in the parameters and forms of the models [10]. Monte Carlo simulation is the preferred approach for complex modelling with stochastic behaviour. The approach takes into account the uncertainty of the sources in the model form and parameters to propagate them through the numerical computation model to result the output uncertainty distribution.

Monte carlo simulation and sample size determination

In the probabilistic approach to uncertainty propagation, the dependent and independent variable are treated as random variables. Most of the methods to perform the uncertainty propagation are primarily based on some form of Monte Carlo analysis. There are four Monte Carlo simulation methods: Classical Monte Carlo simulation, Bayes' Monte Carlo method, Bootstrap method and Wilk's tolerance limits [3]. In this research, Wilk's tolerance limits were used. As facilities, systems and their models become more complex and costly to run, the use of tolerance limit uncertainly characterization is gaining popularity. For example, in very complex models containing several uncertain, classical Bayes' and bootstrap Monte Carlo simulation may become impractical. Often in complex computer-based models in which calculation of values requires significant amount of time and effort, the traditional Monte Carlo simulation is not possible. Wilk's tolerance limit is used in these cases. In the framework of Monte Carlo approach, there could be different algorithms for finding uncertainties of Y in $Y = f(x_1, x_2,..., x_n)$.

The general steps are illustrated for constructing the confidence limit for Y using this method. These steps are:

a) For each xi element in $Y = f(x_1, x_2,...,xn)$, estimate an interval/distribution for each x_i, i=1, ..., n. Generate the determined number of samples from each interval/distribution.

b) Calculate the corresponding classical estimate of Y in $Y = f(x_1, x_2,..., xn)$.

c) Repeat steps 1-2 for sufficiently large number of times to get a large samplie of Y.

d) Using the sample obtained in step 3, and choosing a confidence level $(1 - \alpha)$, construct the respective confidence limit for Y. Schematic of the Monte Carlo Simulation is demonstrated in Figure 4. It is clear that the samples are taken from the cumulative distribution function (CDF) rather than probability density function (PDF).

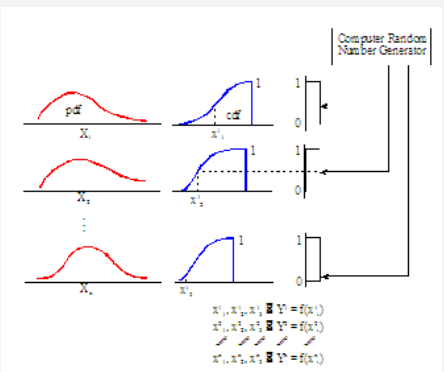

Figure 4: Schematic demonstration of monte carlo simulation [3].

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Sample size determination: The sample size is calculated based on Wilks order statistics [11,12]. The problem is to calculate a tolerance range (L, U) for a random variable X represented by the sample, $x_1,...,x_n$, and the corresponding size of the sample. Depending on the figure of merits, the tolerance limit is one-sided or two-sided (e.g., two-sided for the temperature and one-sided for the temperature rate of the change in the cell). Consider tolerance limits L and U for probability level γ of a limited sample S of size N, the probability β that at least γ proportion of the X's in another indefinitely large sample S_2 will lie between L and U as in equation 1:

$$P\left(\int_L^U f(x)dx \geq \gamma\right) = \beta \quad \text{..... (1)}$$

The sample size is calculated for the specified coverage of γ, in β confidence level for a two-sided figure of merit by using the following table. The Pearson correlation [9] is approach of choice for inclusion of the parameter dependencies. The dependencies are not discussed in this paper however; it is planned to be studies in future of this research.

Augmentation of the success criteria and system performance analysis

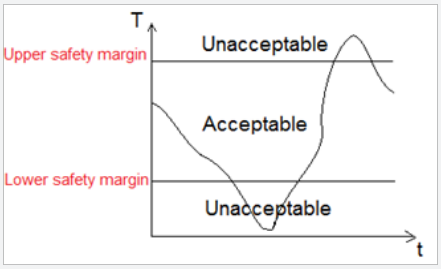

Figure 5: Schematic demonstration of the augmentation of acceptance region with the system performance.

By augmentation of developed success criteria and the system analysis calculation, a decision is made on the success and rejection of the system performance. This is shown schematically in the Figure 4. The Figure 5 shows the acceptance and rejection regions and the corresponding time segments which system performance falls on those regions. In some studies, there is a more than one success criterion, like mass transfer, heat transfer and their rate. So it is suggested to determine response surface method for determination of the success criteria based on multi-criteria [14]. Response surface methodology (RSM) explores the relationships between several explanatory variables and one or more response variables. The main idea of RSM is to use a sequence of designed experiments to obtain an optimal response (for this methodology, optimal success criteria) [13]. The next step is augmentation of the optimal success multi-criteria and system analysis performance.

Reliability index evaluation

There are several probabilistic approaches for reliability assessment including

a) The advanced second moment method, and

b) Non-parametric estimation method. The non-parametric estimation method is done here by using Monte Carlo sampling to find the success and failure trials. The advanced second moment method is parametric which means the reliability is determined based on a performance function expressed in terms of basic random variables for relevant loads and structural strength. As it is shown below, Z is performance function [14]:

$$Z = Z(X_1, X_2, ..., X_n) = R - L \quad \text{.....(2)}$$

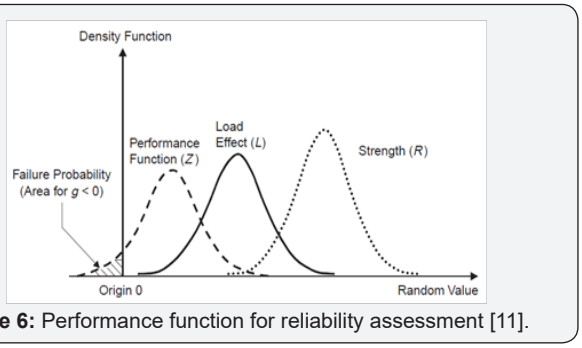

Figure 6: Performance function for reliability assessment [11].

As Figure 6 shows, R is resistance or strength and L is the load or demand. The failure surface (or the limit state function) of interest is defined as Z=0. Accordingly, when Z<0, the element is in the failure state, and, when Z>0, it is in the survival state.

Distribution function is used in the advanced second moment method. If joint probability density function for the basic random variables (X_i) is $f_{X1,X2,...,Xn}(X_1,X_2,...,X_n)$, The failure probability, P_f, of the element can be given by the integral:

$$P_f = \int...\int f_{X1,X2,...,Xn}(x_1,x_2,...,x_n)dx_1dx_2...dx_3 \quad \text{.....(3)}$$

It is possible to use the equations below for reliability index instead of using direct integration,

$$\overline{Z} \cong Z\left(\overline{x_1}, \overline{x_2}, ..., \overline{x_n}\right) \quad \text{.....(4)}$$

$$\beta = \frac{\mu_Z}{\sigma_Z} \quad \text{..... (5)}$$

Where is the mean of a random variable and is standard deviation. So, a measure of reliability can be estimated by introducing the reliability index, which is shown in above equation. Also it is possible to use the equations below too:

$$P_f = 1 - \varphi(\beta) \quad \text{..... (6)}$$

That is the cumulative distribution function of the standard normal variate. In the non-parametric method, an estimate of the mean failure probability is calculated as the following equation:

$$\overline{P_f} = \frac{N_f}{N} \quad \text{..... (7)}$$

Which Nf is the number of simulation cycles for which Z<0 in N simulation cycles. The mean failure probability can be the reliability index [14].

Case Study

A case study is performed here to investigate the effect of phenomenological variations on tissue freezing.

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Cryopreservation studies cell life in low temperature. The process preserves cells in low temperature without significantly damaging their function for normal use condition (e.g. viability, mechanical properties) [15]. Cryopreservation is a very important process utilized in many applications like fertilization, stem cell research, preservation of organs for transplantation surgery and storage and transportation of tissue engineered products [16]. It was identified as a critical enabling technology for tissue engineering, where the ability to store tissue constructs for prolonged periods of time is a requirement for the mass-production, quality-control testing, distribution, and banking of tissue engineered products [17].

The cellular response is a complex thermo physical process to thermal loading at cryogenic temperatures, i.e. heat transfer process coupled with phase change, moving phase interface, mass transport (e.g. water) owing to osmotic pressure difference and volume change on freezing. Given that the most abundant element in biological materials is water, the biophysical response of cells to cryopreservation is determined primarily by phase transformations and transport of intra and extra cellular biological water [17]. Cell failure or damage during cryopreservation is generally correlated to biophysical changes like mass and heat transfer, including cellular dehydration as well as intracellular and extracellular ice crystal formation [15].

At t =0, the tissue, initially at temperature T = 273K, is frozen by suddenly immersing it into liquid nitrogen [15]. Since the process is a transient stress in the cell structure, the success criteria is determined based on four figures of merit of temperature, mass and their rate of change. The temperature and mass rate of change affect the rate of crystallization and cell shrinkage. They have to be considered in the success criteria matrix. Since there is possibility of cell damage during cryopreservation due to excessive shrinkage. When the high concentrations of intracellular salts become toxic (at low intermediate temperatures), the cells may be shrunken beyond the limit from which they can return to their normal size [18]. This is the case for crystallization where the excessive amount damages the properties of the cell.

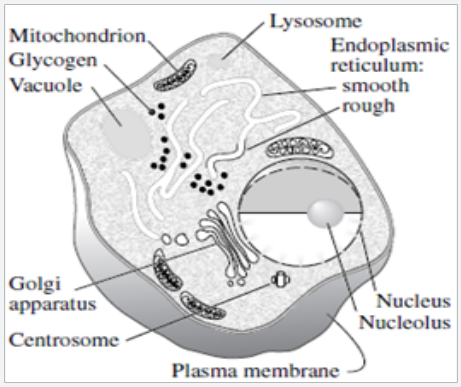

Figure 7: Particular intracellular structure [5].

Particular intracellular structure is present within each cell, depending on the cell type. As shown in Figure 7, a cell typically has compound structure. They contain organelles and cytoskeleton. Organelles enclosed nucleus, which they are causes of the complex chemical reaction. And extracellular is usually taken to be outside the plasma membranes, and occupied by fluid. The composition of the extracellular space includes mostly water, metabolites, ions, various proteins and non-protein substances (i.e. DNA, RNA, lipids, microbial products etc.) that might affect cellular function [19]. The developed simplified model is shown Figure 8 for the tissue's complex geometrical structure.

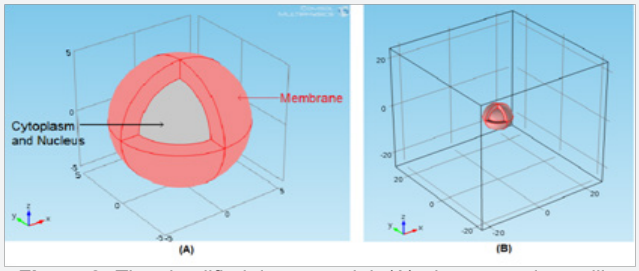

Figure 8: The simplified tissue model. (A): demonstration cell's layer, (B) demonstration cell and extracellular medium.

In this model, the compartment concept is employed where the most relevant physical dimensions are used to describe each compartment. This concept aids in the localization of the various thermal and chemical phenomena. As shown in Figure 8: The simplified tissue model. (A): demonstration cell's layer, (B) demonstration cell and extracellular medium. a spherical model is considered here to represent the real cell composed of two distinct layers; internal central volume and external membrane layer. Since the real cell has core structure of the liquid surrounded with the solid membrane type material. And as shown in Figure 8 (B), the extracellular assumed as a cube which it contains cell and mostly water mixed with saline to preserve cell. This model represents reasonably sufficient the scope of this research. Experimental data is needed to validate accuracy of the developed model. The material properties are estimated for the layers of the developed model based on their composition. The thermal conductivity of each cell is slightly lower than that of water because cell is made up of water by around 70%-80%. Excluding water, main components of cell are protein and lipid [20]. The basic material properties are adjusted for better estimation of the actual materials. Based on expert elicitation. Estimation of density and capacity for both of the layers.

Numerical analysis

In this research a system of coupled heat transfer model (conduction) with phase change (ice crystallization and/or vitrification) (equation (2)) and mass transport through cell membranes (equation (3)) was solved.The mesh size and type are determined based of the required accuracy and evaluation

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criteria. The model approximates the body tissue with a sphere in a cube and assumes that its boundary convective heat flux with h=10W/m^{2}K and external temperature 77K during the entire procedure; ρ is the tissue density (kg/m^3); C is the tissue's specific heat (J/ (kg•K)); and k is its thermal conductivity (W/ (m•K)). The COMSOL Multiphysics with MATLAB was used to solve this system (Table 1).

Table 1: The sample size calculation for the γ, β. (a): (one-sided). (b): (two-sided).

	β		
γ	0.90	0.95	0.99
0.90	22	45	239
0.95	29	59	299
0.99	44	90	459

	β			
γ	0.50	0.90	0.95	0.99
0.50	3	17	34	163
0.80	5	29	59	299
0.90	7	38	77	388
0.95	8	46	93	473
0.99	11	64	130	663

The boundary conditions for the following equations should be determined and included in the simulation.

$$\frac{\partial T}{\partial t} = \frac{k}{\rho c_p}\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial T}{\partial r}\right) + \frac{Q}{\rho c_p} \quad \text{..... (8)}$$

Q is neglected in this study.

$$\frac{dW_c}{dt} = -\frac{dI_c}{dt} + JA_m \quad \text{.....(9)}$$

Mass flux: J = - LpRT [(Cs$_1$-Cs$_2$) +σ (Cc$_1$-CC$_2$)] (10)

where

L_p membrane permeability to water

R universal gas constant

T temperature

C_s salt ion concentration

C_c CPA concentration

Wc cell solution (aqueous liquid solution and vitrified solid solution) volume fraction

I_c cell ice volume fraction

Am cell surface area

σ reflection coefficient

The membrane permeability to water, L_p is temperature dependent following the Arrhenius relationship.

$$L_p = L_{pR}\exp\left(-\frac{E_L}{R}\left(\frac{1}{T}-\frac{1}{T_R}\right)\right) \quad \text{.....(11)}$$

$L_{p,R}$ is the value at the reference temperature (T_R), and EL is called the activation energies. The model solves the above equations with the given boundary conditions to obtain the temperature and mass field as a function of time.

Monte carlo simulation

Table 2: The parameters range of variation in the cell application [20,21].

NO	Parameter	Lower Bound	Upper Bound	Median
1	k (Wm^{-1}K^{-1})	0.558	0.592	0.575
2	ρ (Kg/m^3)	1000	1060	1030
3	c (J/kg°K)	3600	4200	3900
4	Lp,R (m3/Ns)*10^{-15}	3.045	9.135	6.09
5	σ	0.4	1.2	0.8

The uncertainty of the parameters is considered in the calculations of the cell transient behaviour under thermal and mass stresses. The uncertainty sources are the model coefficient and model form. The uncertain parameters as shown in Table 2, are the cell thermal coefficient (K), density (ρ), and specific thermal capacity (C), permeability L_{pR} and reflection coefficient σ.

Carlo simulation is used to repeat simulation many times in order to obtain the distribution of an unknown stochastic entity. The supporting data are evaluated for the determination of the range/distribution of the parameters. Expert judgment is utilized for better estimations of the range/distributions. Based on the Wilk's order statistics relations, the confidence level and the tolerance are required for determination of the sample size. In this study, the confidence level of 95% with tolerance of 95% is justified a proper acceptance for biological applications. The sample size for this setting is 93 with this confidence level and tolerance. The code is first used to divide the whole time process to six parts. In each part the new temperature (T) is considered then the new k and C are calculated from the equation (6,7) [22]. The Monte Carlo simulation is done in new intervals. This process is completed for 93 iterations.

$$k = 2.24 + 0.005975(273 - T)^{1.156} \quad \text{.....(12)}$$

$$C_p = 7.16T + 138 \quad \text{..... (13)}$$

Success criteria

In this research, the most important factors are: cells recovery after freezing, stopping chemical reactions and the freezing technology. Cells can endure storage at low temperatures such as 77K (the boiling point of liquid nitrogen) to 63K (the liquid nitrogen freezing point) and there is insufficient thermal energy for chemical reactions in this temperature so it would be lower

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acceptance bound [22-25]. Ultra-rapid cooling rates (e.g. >106˚K/min) are technically difficult to achieve [26]. So 1400°K/min is determined sufficient rate for this case study. The bounds for the temperature, its rate, the water loss and the allowed rate of crystallization is given in The Table 3. Rate of crystallization was not studied in this research. The determination of the success criteria is more complex in biological media in comparison with the physical systems. The rate of temperature influences this factor significant. The success criteria consider these attributes concurrently. The Table 3 shows the bounds for the selected figure of merits. As shown in Figure 9A, 8 out of 93 iterations of temperature are located in unacceptable temperature region, 5 out of 93 iterations are located in unacceptable temperature rate region and as shown in Figure 9B, 5 out of 93 iterations are located in unacceptable water loss region.

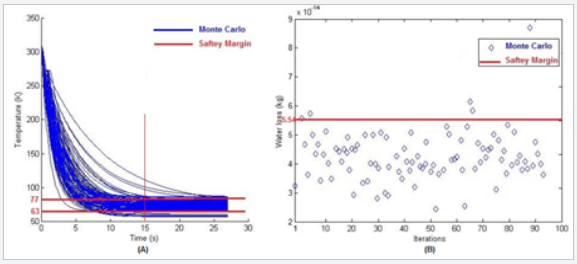

Figure 9: Success Determination for Cell Thermal and Chemical Behavior under Thermal Stresses.

Table 3: The bounds for the Figure of Merits in Thermal Stresses [23].

No.	Figure of Merit	Acceptance Bound	
		Lower	Upper
1	Temperature	77K	63K
2	Temperature Rate of Change	NA	1400˚K/min
3	Rate of Crystallization	NA	21%
4	Water Loss	NA	30%

Reliability index estimation

The Figure 9 shows demonstration of the methodology for thermal and chemical calculations. Figure 9A, demonstrates the heat transfer and its rate safe region. Figure 9B, shows the water loss safe region. The safe region for temperature is between 77K and 63K. This cell also cannot endure the temperature rate more than -1400˚K/min which means it should get to steady state in 15s.

Monte Carlo simulation (MCS) technique was used in this study. If the Monte Carlo simulation is conducted 93 times and the behaviour of the cell is observed for each set of the simulation, the probability of the cell success is determined based on the number of the success and the probability of cell failure is determined based on the number of the failure and it is not parametric. The figure shows the failure probability of the cell with these success criteria. In this study failure probability for water loss was 5.4% (5 out of 93), for temperature was 8.6% (8 out of 93) and for rate of temperature was 5.4% (5 out of 93). Equation (7) was used to calculate the failure probability.

Results and Discussion

Given that cell damage may result from excessive water loss, insufficient rate of temperature changes and extreme temperature change. In this research developed success criteria minimizes the probability of cell injury during freezing in cryopreservation process.

The augmentation of the cell thermal and chemical analysis and the developed success criteria provides the region of the acceptance and rejection. If there are tolerances in the preserving temperature of the freezing process setting, it might be possible that the cell falls out of the safe region. The freezing temperature is usually set for temperature of the 77K but if it varied in the range of 83K and 58K then these variations should be included in the system performance analysis under the freezing thermal stress. The freezing set points variation is considered in the analysis by random sampling in each of the performance analysis. The sets which fall out of the acceptance region are considered as the damaging scenario to the cell. The Figure 9 shows demonstration of the methodology for thermal and chemical calculations of a typical cell cryopreservation which cannot survive on the temperature below 63K and upper 77K. This cell also cannot endure the temperature rate change more than -1400˚K/min. If the Monte Carlo simulation is conducted 93 times and the behaviour of the cell is observed for each set of the simulation, the rate of the cell success is determined based on the number of the success. The figure shows the success rate of the cell with these success criteria. As it is shown, about 9% is failed (8 out of 93 of the simulations). So the simulation does not demonstrate that the success process is achieved. But 85 out of 93 of the simulations are in the safe margin, which means the simulation is achieved coverage 90% and confidence level 95%. Even it is possible to achieve lower confidence level with upper coverage like: coverage 95% and confidence level 90% or coverage 90% and confidence level 90% and coverage 90% and confidence level 95%.

Concluding Remarks

Limited failure mode and effect analysis should be performed for identification of the dominant failures for the corresponding figure of merits. Biological environment is complex in correlated occurrence of microscopic and macroscopic phenomena. Therefore, the modelling of this complex medium, in context of mechanical stresses, requires numerical solution of conservation equation and inclusion of corresponding constitution models. Determination of success criteria is a challenging object, and is needed for reliability calculation in future research. This requires consideration of several dependent figures of merits (e.g. temperature, mass and etc.).

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It is suggested the study continues on a tissue instead of a single cell. Other cell material properties should also be included in the research. The research is continued to extend the paper to other more complex application and more general acceptance criteria like the rate of crystallization, that would need to solve the conservation equations together. Even it is suggested to utilize the second moment method to calculate reliability index.

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