Literature Review

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Cryobiology plays an essential role in the field of medicine in developing a facilitation towards medical interventions. Although it has been less than 50 years since we had the recovery of living cells frozen to cryogenic temperatures, there has been a growth in the field which has extended its benefits to area such as agriculture, horticulture, forestry and the conservation of endangered species [4]. Researches have been conducted towards ways in preserving blood, heart valves and other tissues by Han et Al. [5] and Lloyd et Al. [11] to name but a few. To be able to preserve the organs successfully, there has been numerous limitations and one of this is the propagation of lethal intracellular ice formation but it also expands towards extreme dehydration as well as high salt concentrations producing by the formation of extracellular ice.

To improve the cryopreservation protocols, Mazur was able to derive a quantitative relation between the amount of water in a cell and its temperature. This study [9] used a differential equation involving cooling rate, surface-volume ratio, membrane permeability to water and temperature coefficient of the permeability constant to derive that quantitative relation. It was then continued by Levin [8] to develop a one-dimensional model for the diffusion transport in a liquid solution with a semipermeable boundary.

In Mazur's papers [9], the results produced by his research highlighted the optimal cooling rates to minimize the ice formation and maximize survival of the ice by preventing the internal freezing. For instance, the average cooling rates of average cells, cells with a higher permeability, large cells and human red blood cells were $1°C/\text{min}$, $500°C/\text{min}$, $10°C/\text{min}$ and about 2500 to $5000°C/\text{min}$.

To better understand the intracellular ice in a cell, agent-based model is used as a simulation technique to study complex systems [2] and topics like cyrobiology. Since the prime focus of the work is around the intracellular ice formation, a physiochemical model was proposed by Toner [10] to analyze the ice formation inside biological cells during freezing, considering both the surface-catalyzed nucleation (SCN) and volume-catalyzed nucleation (VCN) mechanisms.

After this, Karlson's three-part, coupled model of cell dehydration, nucleation and crystal growth [7] was used to study the intracellular ice formation in the cultured hepatocytes that were frozen in the presence of dimethyl sulfoxide.

Predicting intracellular ice formation in the cell-to-cell interaction became important to understand ice propagation and ice nucleation growth between the target cell and its neighbouring cell. Irimia and Karlson [6] investigated the kinetics of intracellular ice formation (IIF) in tissue constructs using a combination of theoretical modelling and experimental cryomicroscopy, to understand the mechanisms of IIF and its spatial distribution in linear tissue constructs. Their study found that the nondimensional rate of intercellular ice propagation was measured to be 10.4 ∓ 0.1. The study also developed a Markov chain that help to describe the kinetics of the IIF in an ensemble of pairs. For each IIF, ordinary differential equation (ODE) were solved for each of the IIF probability tissue outcome.

$$\frac{dP}{d\tau} = Q(a) \cdot P \tag{1}$$

Majority of the studies discussed so far have been revolving around a small dimen of the cell-based models but there has been studies utilizing the continuum models which looks into the homogenous material specifically as well [3]. Although this gives a decent bird-eye view on the ice propagation across the tissue, it does not provide a reasoning behind why a particular cell may survive and the cell may otherwise.

Basing on the foundational work performed by Amiri and Dr Benson [1], our work revolves around scaling up the model to larger tissue sizes by making use of OpenMP parallelization and threads for considering past values of τ to calculate the future ones. For instance, utilizing τ_1 to calculate the value of τ_2 while also considering the concept of cell connection breakages and how it could affect our value of τ. This is done by considering every cell as an agent in side our Physicell multicellular system which plays a role in interacting with cells in a multi-substrate 3D-microenvironments. Beyond this project, the study has a potential for future applications in ice expansion and propagation in liver tissue with different cell types, mass and heat transport, and the presence of cryoprotective agents.

References

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