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ANALYZING HEAT GENERATED FROM ELECTRO-OSMOTIC FLOW UTILIZING COMPUTATIONAL FLUID DYNAMICS

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ANALYZING HEAT GENERATED FROM ELECTRO-OSMOTIC FLOW UTILIZING COMPUTATIONAL FLUID DYNAMICS

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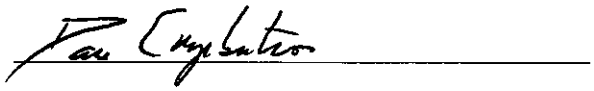

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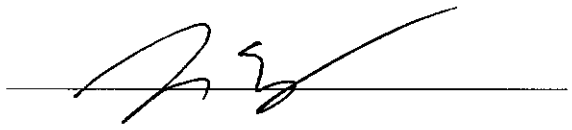

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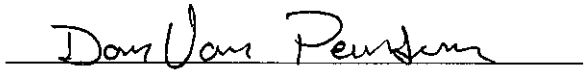

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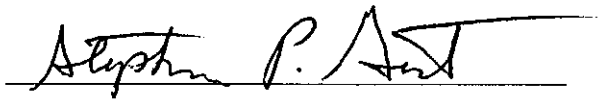

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ABSTRACT

Analyzing Heat Generated from Electro-Osmotic Flow Utilizing Computational Fluid Dynamics

Jordan Grothe

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Without extensive vascularization, the transfer of fluid and nutrients through human tissue is limited to diffusion and weak interstitial flow. Electroosmosis, or the flow of fluid driven by an electrical field, has become a promising solution. Scientists have begun applying electricity to human tissue to promote stronger interstitial flow; however, optimization of this process has proven to be a challenge due to ohmic heating. Cells function within a small range of temperatures and exposure to voltages exceeding the threshold will cause cells to degrade and die prematurely. This research seeks to better understand and quantify the range of voltage where the heat generated leads to cell degradation and death. Utilizing a computational fluid dynamics software, Sim Center Star-CCM+, a representative model of tissue mimicking a clinical application of electricity to the knee was created and used to test a variety of voltages while monitoring the temperature and time; this data was then compared to prior-established values depicting when cells undergo irreversible damage. Research has already shown that electrical stimulation can drastically increase the rate at which a wound heals; understanding the thresholds for when damage occurs will allow clinicians and scientists to optimize this process while avoiding cell damage.

Key Words: Electro-osmosis, electricity, wound healing, tissue engineering

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CHAPTER ONE

Introduction

For years, clinicians and tissue engineers alike have struggled with mass transfer in the absence of vascularization. Without pathways for interstitial fluid to flow through, the transfer of nutrients and the removal of wastes can be particularly difficult. Electro-osmotic flow, that is, the flow of fluid driven by the application of an electric field, could provide a solution to this issue because of its ability to generate mass flow without force or moving parts. This has led clinicians and scientists to pursue researching the effects of externally applying electric fields to drive interstitial flow, yet many questions remain, such as how to optimize the flow without damaging the cells. Common clinical applications utilizing electrically driven flow involve applying a cathode and anode directly to the skin surrounding a wound. Electro-osmotic flow could also be utilized in tissue engineering to help generate larger, more complex tissues. Because electricity generates heat, more research is needed to be done to better understand what range of electrical fields can be safely applied for different durations of time without damaging the surrounding tissue.

When electricity is applied to tissues, electro-osmotic flow is generated, and many layers of surrounding cells develop. An electric double layer (EDL) is made when the cells interact with the interstitial fluid [1]. Furthermore, in the presence of an electric field, cations will migrate towards the cathode, and anions will migrate toward the anode.

Because the EDL generally has more cations than anions, and the cations will migrate towards the cathode, a flow of fluid will be caused from the cathode to the anode [1]. This is the process by which electro-osmotic flow occurs.

Because of the nature of electricity, heating accompanies electro-osmosis. Whenever an electric field is generated, ohmic heating, also referred to as Joule heating, will occur. While this heat does not cause a significant change in temperature of the tissue at lower voltages, it can cause a larger number of cells to increase in temperature at higher voltages. This is problematic because human cells can only survive in variable temperatures for a specific amount of time. Just as somebody in a hot desert will get dehydrated and die faster than somebody in cooler weather, human cells are only able to live in high-temperatures for a limited amount of time. This work is concerned with the ohmic heating that occurs when electro-osmotic flow is externally generated. Furthermore, this work utilizes prior-established values to establish limits on the temperature.

Computational fluid dynamics allows researchers to study the effects of electricity on tissue without risking damage to real human tissue. This research primarily utilizes Star-CCM+, a commercially available computational fluid dynamics software. Using this, a model of tissue can be made to allow researchers to perform a variety of tests to see how real tissue would likely react. The software allows values to be assigned to the model that are consistent with that of tissue, such as density, electrical conductivity, and thermal conductivity. In this work, the tissue model was exposed to a variety of voltages, and the temperature of the tissue was monitored.

Electrical stimulation has the potential to be a viable solution in speeding up the healing of wounds. It has already been utilized in some clinical applications and shows special

promise when looking at diabetic wounds. Because of electrical stimulations unique ability to generate interstitial flow without involving pressure, it allows the nutrients to be brought to growing cells and wastes to be removed from the wound bed quicker. This leads to quicker recovery times, and a reduced risk of infection. Some products promoting wound healing by enhancing electro-osmotic flow are already in clinical use. These products have shown an increase in the rate of wound healing as well as a decrease in visits to a clinician [2]. Furthermore, dressings have been developed to be electrically conductive and, with external electrical stimulation, have succeeded in increasing the rate of wound healing [2]. Electro-osmotic flow has a promising future in medicine, so research in this area is important.

Electro-osmosis can also be useful in tissue engineering applications. One of the main problems tissue engineers face is the inability to generate flow through tissue that lacks vascularization. Vessels can be difficult to engineer due to their microscopic size. Without a way to bring nutrients to the growing cells and remove wastes, engineers are limited in how large and complex they can make tissues. Electrical stimulation could help alleviate this issue because it does not rely on vessel sizes and allows for interstitial flow between the cells. A better understanding of electro-osmosis could lead to the ability to develop larger, more complex tissues.

CHAPTER TWO

Research Goals and Hypothesis

This research seeks to quantify the upper-level of the range where the application of an electric field leads to cell death due to the joule-heating that occurs. It is currently believed that the range for safe electrical field application is somewhere between 10 mV/mm and 1000 mV/mm, but little is understood about precise range where the cells will degrade due to the ohmic heating that occurs. This research hopes to find a more precise electric field that is the upper threshold for when the electricity causes thermal damage to the cells and surrounding tissue.

We hypothesize that a threshold for the electric field will be near 1,000 mV/mm before the temperature is too high for five seconds and leads to cell degradation and death. We hypothesize this because it is the currently accepted upper threshold for the safe range of electrical field application. While other things can cause cell death, ohmic heating would be a natural limitation when applying an electrical field. We anticipate only finding the range for five second applications because most clinical settings do not apply the electric field for longer than that duration of time. Furthermore, with the longer time span, the electric field will have to be lower because as time goes on, more heat would be generated and trapped within the tissue.

CHAPTER THREE

Review of Relevant Literature

Without vascularization, the transfer of interstitial fluid is severely limited to diffusion across pores. Both tissue engineering and wound regeneration face limitations from this because all cells require nutrients to survive. However, manipulation of electro-osmotic flow would allow scientists and clinicians to overcome some of these challenges, allowing for the creation of more robust tissues and quicker recovery rates from epidermal wounds. While electroosmosis has been studied for years, the mechanisms behind it and the clinical applications remains relatively unknown [3]. External applications of electric fields to drive electroosmosis are already being used in clinical settings, but their usage is limited by the lack of full understanding in the process and its side-effects.

Electroosmosis is the process by which a flow of fluid is driven in the presence of an electrical field. The fluid is generally ionized and moves around charged or polar surfaces [1]. Multiple theories seek to explain this process, but much is still unknown. In the body, electroosmosis can allow nutrients to be delivered to cells, wastes to be removed from cells, and smaller cells to be driven to areas in the body where they are needed.

During electroosmosis, multiple layers are developed outside of the electrode. Two layers, referred to as the Stern layer and the diffusive layer, form what is called the electric double

layer (EDL) at the solid-liquid interface [4]. These layers are developed when a charged surface (such as the electrode) interacts with a liquid containing ions (such as interstitial fluid) [1]. The Stern layer is generated by the high concentration of counterions on the charged surface of the electrode [5]. The ions in this layer are tightly bound to the surface of the cell and are immobile; in contrast, ions in the diffuse layer are mobile. The diffuse layer is the region where the net charge reaches zero because the coion concentration evens out of the counterion concentration [5]. When subject to electrical flow, ions inside the diffuse layer of the EDL move, causing the surrounding interstitial fluid to also move. The electrical field will cause cations to migrate towards the cathode and anions to migrate to the anode. Because the EDL contains more cations than anions, the fluid typically flows in the direction of the cathode from the anode [1]. The movement of the ions in the EDL also causes the surrounding fluid to move with it [5, 6]. The surrounding interstitial fluid will often contain wastes expelled from the cell and be depleted of the nutrients that the cell requires to live. By cycling out this fluid, electro-osmosis can bring in a nutrient-rich flow while removing the wastes. Because this flow is driven by ions, mass transfer is possible without the application of force or moving parts.

In many cases, the interstitial flow surrounding the cells will not affect the cell because of the surrounding plasma membrane. In some cases, the electric field will also cause galvanotaxis. Galvanotaxis is defined as the migration of a cell in a particular direction and is influenced by the electroosmotic, electrophoretic, and drag forces [3]. Galvanotaxis has been induced by electric fields in the range of .1 to 10 V/cm [7]. Studies have found that the substrate the cell is grown on also can affect its growth; neurites grown on positive substrates grew towards the anode, and neurites grown on negative substances grew

towards the cathode [8]. Galvanotaxis has been observed in epidermal keratinocytes, dermal fibroblasts, and other immune cells that play a role in the wound healing process; these cells will migrate toward the cathodal end of the electrical field [2]. This provides yet another way for electro-osmosis to aide in the regeneration of wounds outside of strictly delivering nutrients and removing wastes.

One of the leading theories as to why some cells will migrate towards the poles is due to the macromolecules on the surface membrane of the cell. In the presence of an electric field, negatively charged macromolecules will migrate towards the cathode side of the cell if the macromolecule's zeta potential (the potential difference in charge between the surface of the macromolecule and the surrounding interstitial fluid) is less negative than that of the cell surface. The converse is also true; if the zeta potential of the cell surface is less negative than that of the macromolecule, the macromolecules will accumulate on the anodal side [9]. The lower threshold for application of an electric field where cells begin to migrate is 10 mV/mm, when the electrical potential difference of 10-300 uV is between the cell walls [10]. This causes the electromigration of the surface macromolecules without activating the plasma membrane voltage sensors; furthermore, the larger the extracellular domain of the cell, the greater the effect of the electro-osmotic flow [10].

Because electro-osmotic flow provides a solution to delivering nutrients in areas with low vascularization, it has already been used for wound healing and will likely be used for tissue engineering in the future. It is thought that electric fields can increase the rate at which a wound heals because they increase the movement of neutrophils and macrophages, cells that are essential to wound healing [11]. The skin naturally carries a charge, but when damaged, a current is made driving nutrients and wound regeneration cells from outside of

the wound to the center of it [11]. When damaged, the transepidermal potential (TEP) is reduced; however, once healed, the potential difference returns to its original value, where it is negative on the surface of the skin [2]. Furthermore, cell proliferation, blood perfusion, and tissue matrix production have been seen to increase with electrical stimulation [2]. A variety of products for electrical stimulation are already in clinical use, such as WoundEL. Studies following this particular product, which involves low-frequency pulses, have found improved rates of wound healing with use [2]. These preliminary products show that electro-osmotic flow has the potential to be an important medicinal approach to healing more extensive and deeper wounds that would typically require months because of their poor vascularization.

Tissue engineering has also found electro-osmosis to be potentially useful because one of the main challenges it currently faces is a difficulty in generating flow throughout the developing tissues, causing an inability to supply essential nutrients to the cells; weak electric fields have been able to generate electro-osmotic flow through small pathways, reducing cell mortality [12].

One of the main challenges that electro-osmotic flow devices face is that the heat generated from the application of an electric field can lead to cell degradation and death in extreme cases. In the application of DC electric fields, tissue damage can occur from electrolysis or heating. As stated previously, applying an electric field causes an increase in temperature from Joule (ohmic) heating. Because human cells are dependent on being in a specific range of temperatures for functioning, this heating can cause issues. Human cells typically live thrive in temperatures from 37-39°C [13]. Cell degradation and death are dependent on both the temperature and the duration of exposure. Studies have shown that damage

does not occur to cells below 44°C; once exceeded, damage nearly doubles for each additional degree [14]. In 50°C, cells will survive for 4 minutes; for 55°C, cells will only survive for 30 seconds [14]. At 60°C, cells will survive for 5 seconds. One potential solution to this would be pulsing the electric field, allowing for relaxation and cooling in between flows. Another option would be lowering the voltage of the electric field to allow for longer, continuous flow with less ohmic heating.

CHAPTER FOUR

Methods

Model Development

A prior-made model of human tissue was utilized to simulate a clinical application of electric stimulation therapy. Two concentric cylinders, as seen in Figure 1, were created in Solidworks then imported to Sim Center Star-CCM+, a commercially available Multiphysics solver. Next, a mesh was made separately for each cylinder. Both meshes had the same qualities, including polyhedral mesher, prism layer mesher, surface remesher, and automatic surface repair. The meshers were then adjusted to increase the accuracy of the model. For the outside cylinder, the base size was set to .5 mm with 4 prism layers; for the inside cylinder, the base size was set to 8.0E-5 m with two prism layers. Next, the surface area was broken down into three parts: two faces and one wall. In the inner cylinder, the face on the negative z-axis was assigned 'anode,' and the face on the positive z-axis was assigned 'cathode'. These faces were given equal, opposite electric potentials. For example, if the anode was assigned an electric potential of 25V, the cathode would be assigned -25V.

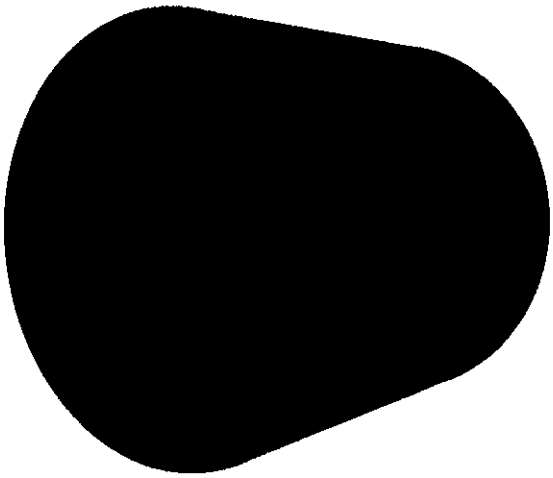

Figure 1: Image of Model Geometry

Assumptions

The model was assumed to be a uniform tissue. The model was intended to mimic a knee and was assigned values consistent with that of cartilaginous tissue. Two continua were created, identical to each-other in all aspects except for electrical conductivity. The continua were defined as three-dimensional liquids with a constant density; segregated, laminar, and implicit unsteady flow was assumed. The liquid was also subject to ohmic (Joule) heating. Electrical conductivity was set to 1.3126 S/m for the inner cylinder and 0 for the outer cylinder. For the purpose of this research, the outer cylinder did not need to conduct electricity because the monitored values were inside the center of the inner cylinder. Thermal conductivity was set to 1.3 W/m-k. The initial static temperature was set to 310.15 K, consistent with average body temperature.

Limitations

The model is limited in the scope of prediction it can do. Because the tissue is modeled to mimic a knee, it would be inappropriate to utilize this model's values to predict what would occur in the electrical application to other parts of the body, notably, those more abundant in nervous or muscular tissue because of differences in electrical conductivity. Furthermore, the model is not divided into further parts to distinguish the variety of tissues that are found within the knee, so a 'worst-case' scenario is generated, as the values were chosen on what would occur if the knee was all one type of tissue. The model also inaccurately shows 'hot-spots' where electrodes would be applied due to how the software calculates the electrical field.

Mathematical Approach

To determine the electrical field range, different voltages were tested then converted into the corresponding electric field value. The first tested voltages were based off of the current range for safe electrical field applications. The lower-end voltage was first established; next, an upper-end voltage was established. After running the model, the temperature of the center point in the inner cylinder was recorded into an Excel spreadsheet. A binary search method was primarily utilized to narrow down the range until a range of ~1 mV/mm was obtained. The upper-end voltage was adjusted to the previously tested voltage if the temperature exceeded the safe range. If the temperature stayed within the allowable range, the lower-end voltage was adjusted. The next voltage tested was in the middle of this new upper and lower ends. In instances where the desired temperature was clearly closer to one side of the range, a voltage skewed more towards that end would be tested.

The raw data was transferred from electric potentials to electric field to make it more universally applicable. Electric field was found through a series of calculations. First, the electric potential was multiplied by two because it was applied as an electric potential on both sides of the model. On the cathode side, it was applied as a positive potential; on the anode side, it was applied as a negative potential. Then, the resulting number was divided by 50 mm, or the width of the model. Finally, to convert the number from volts per millimeter to millivolts per millimeter, the resultant was multiplied by 1,000. Excel was utilized to speed up this process.

CHAPTER FIVE

Results

Our research found the different ranges of voltages that could be applied before the model's temperature was too high for an extended period of time, causing the 'cells' to die. For the first part of the research, the temperature needed to stay below 333 K for 5 seconds. For the 10 mm model at 5 seconds, an electric potential of 93.2305 V on the cathode side reached the temperature of 332.923 K, and an electric potential of 93.25 V reached a temperature of 333.005 K. Limitations in the model did not allow the range to be more precise. Table I shows the tested values and their resulting temperatures after running the model for 5 seconds.

Table I: Results of 5 second exposure. Electric potentials tested on the 10 mm model and the temperature after 5 seconds.

Electric Potential (V)	Temperature (K)
25	310.32
56	311.715
76	313.043
87	313.941
92	314.386
92.625	314.449
92.9375	314.455
93.09375	314.444
93.171875	314.479
93.2109	314.471
93.2305	314.48
93.2403	314.472
93.25	314.486
94.5	314.631
97	314.845
137	319.516
250	327.99

The second part required keeping the temperature lower than 328 K for 30 seconds. For the 10 mm model at 30 seconds, an electric potential on the cathode of 33.5 V increased the temperature to 327.979 K, and an electric potential of 33.525 V reached a temperature of 328.005 K. Like the earlier trial, the software did not allow the range to be narrowed down further. Table II shows the tested voltages and their resulting temperatures after running the model for thirty seconds.

Table II: Results of 30 second exposure. Electric potentials tested on the 10 mm model and the temperature after 30 seconds.

Electric Potential (V)	Temperature (K)
25	320.048
31.5	325.916
33.25	327.715
33.5	327.979
33.525	328.005
33.55	328.032
33.6	328.085
33.75	328.249
34	328.519
37.5	332.495
76	401.625

CHAPTER SIX

Discussion

The values that the model needed to stay below were 60 degrees Celsius in the case of the 5 second trial and 55 degrees Celsius in the case of the 30 second trial. Looking through the resulting data revealed the electric field that could be applied before the temperature of the tissue rose above the viable range. For the 5 second trial, the electric field was the range from 3729.22 mV/mm to 3730 mV/mm. For the 30 second trial, the electric field range was 1340 mV/mm to 1341 mV/mm. The lower-end of both of these ranges were decided to be the threshold for damage because they remained below the required temperature.

An electric field of 1340 mV/mm can be applied to tissue for 30 seconds before the ohmic heating causes the temperature to rise above 55 degrees Celsius. An electric field of 3729.22 mV/mm can be applied to tissue for 5 seconds before the temperature surpasses the viable range of 60 degrees Celsius.

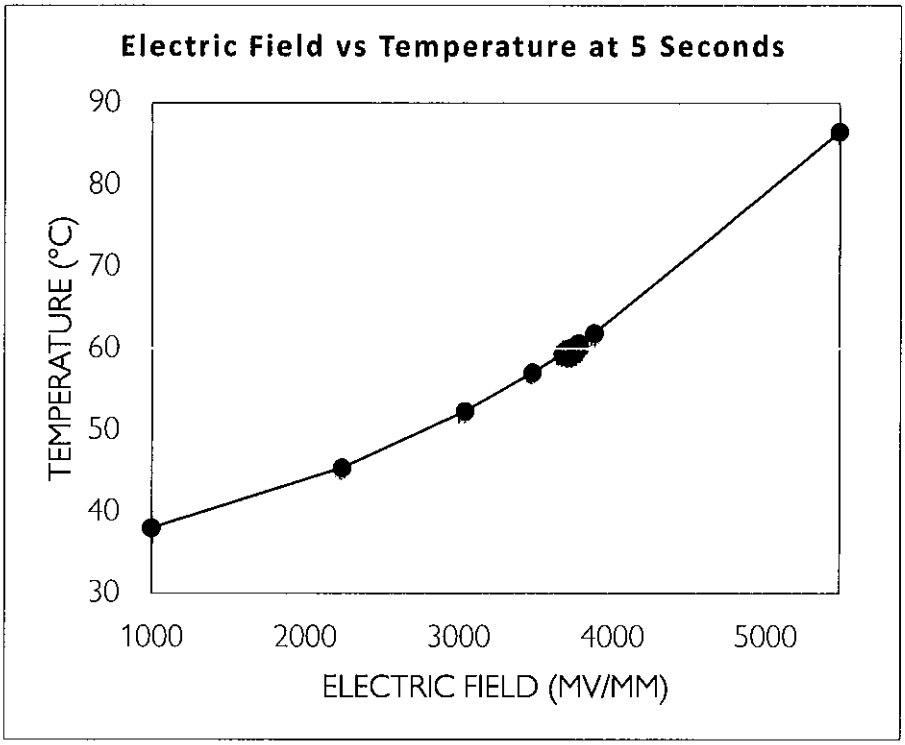

Figure 2: Electric Field vs Temperature at 5 seconds Graph. A graph of the temperature caused by the application of a given electric field after 5 seconds. The horizontal line represents the threshold for cell death.

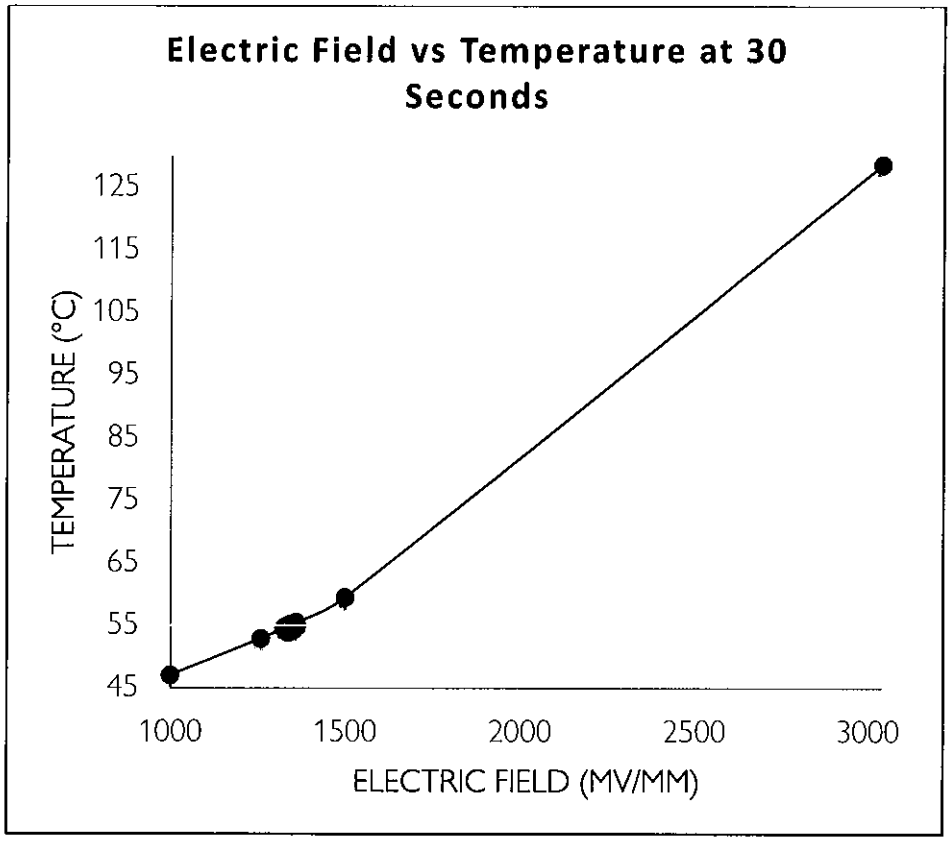

Figure 3: Electric Field vs Temperature at 30 seconds Graph. A graph of the temperature caused by the application of a given electric field after 30 seconds. The horizontal line represents the threshold for cell death.

CHAPTER SEVEN

Conclusions

This work found the upper-level of the range of electrical application that does not damage cells due to the generation of heat. An electric field of 1,340 mV/mm can be applied to cartilaginous tissue for 30 seconds before a temperature of 55 degrees Celsius is reached, and cell death may begin to occur from the temperature. For 5 seconds, an electric field of 3,729.22 can be applied before the temperature surpasses 60 degrees Celsius. Understanding this range is important because it provides clinicians and scientists with a guideline for when the electric field will begin to damage the cells from ohmic heating. Furthermore, this work demonstrates that other factors must be currently limiting the safe application of electric fields, as the current range for safe electric field application is thought to range from 10 mV/mm to 1,000 mV/mm.

CHAPTER EIGHT

Future Work

The next steps to better understanding electro-osmotic flow and its implications in both clinical and tissue engineering applications would involve finding what factor is currently limiting the range for safe application. This may be electrolysis, in which case, the model could be set up to monitor how much electric current has passed through the center of the model then compare that with the literature on how much electric current cells can withstand.

Another future step would be better refining the current model. This would involve breaking down the model into separate parts to create a more accurate picture of the different tissues involved in the knee. This could also potentially involve accounting for blood flow, and the dissipation of heat that occurs from that.

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