Abstract — Surgical resection and thermal ablation techniques have been shown to have suboptimal efficacy for the treatment of osteoid osteomas due to the high risk of complications and large ablation zones. Ablation technologies that utilize electric fields instead of thermal energy to produce nanosized pores in tumor cell membranes have been shown to be an attractive method for treating a wide variety of cancers due to the short ablation times and non-invasive nature of the procedure. We propose a nanosecond pulse electric field ablation system utilizing a pulse generator as a compact solution to ablate osteoid osteomas without harming the healthy bone, leading to reduced instances of post-operative complications.

Clinical Relevance — This establishes the efficacy of nanosecond pulse electric field ablation to ensure complete nidus ablation.

INTRODUCTION

Osteoid osteomas are small, benign bone tumors typically found in adolescents that cause pain and discomfort. The standard of care for treating osteoid osteomas has been surgical resection. Although surgical resection has been shown to have success rates of 88%-97% in removing osteoid osteomas, these procedures have a high rate of complications (20-45%) including hematoma, infection, and avascular necrosis [0, 1]. Additionally, surgically induced bone defects can increase the risk of fracture [2, 3, 4].

Minimally-invasive ablation techniques have been implemented to treat osteoid osteomas, as these techniques have been proven to cause fewer postoperative complications than conventional surgical excision [2]. Currently, radiofrequency ablation is the most common thermal ablation treatment for osteoid osteomas due to its wide availability, short postprocedural hospitalization, and ablation zone of 3-4cm [2]. Alternatively, microwave ablation has been shown to have faster ablation time and deeper tissue penetration. This is not without drawbacks. With the average nidus size of approximately 1 cm, the microwave ablation zone of 5-7 cm poses the risk of causing thermal damage to non-target tissues. This collateral damage proves to be a major drawback of microwave ablation for the treatment of osteoid osteoma [2]. In a preliminary study, Fan et al. used microwave ablation for the treatment of malignant bone tumors with a 74% success rate [5]. However, complications such as fracture, local recurrence, and infection still arose in the study, likely due to thermal damage to the surrounding healthy tissue. While radiofrequency and microwave ablation have various benefits for treating osteoid osteomas, other energy types may provide these same benefits of ablation time and tissue penetration while also limiting the ablation zone.

More recently, non-thermal ablation technologies have been investigated for tumor ablation that utilize electric fields rather than thermal energy. Irreversible electroporation (IRE) delivers low electric fields (low kV/cm) in pulses with durations of milliseconds or microseconds. The electric energy creates pores in the cell membranes of the tumor cells which disrupts ionic gradients, eventually causing the cell to die from necrosis [6]. Nanosecond pulse electric field (nsPEF) ablation uses a similar technique but with higher electric fields (tens of kV/cm) with a nanosecond duration. The advantage of nsPEF ablation over IRE is that nsPEF ablation creates pores in both the plasma membranes as well as intracellular membranes, resulting in a phenomenon known as supra-electroporation [6]. Several studies have shown how this supra-electroporation leads to the induction of apoptosis and DNA damage [6, 7, 8]. Compared to other ablation techniques, nsPEF ablation is more time-efficient as only 100 pulses are needed to effectively destroy the tumor [6, 7]. The ability of nsPEF to rapidly induce cell death non-invasively without the use of heat or chemicals makes it an attractive treatment option for a plethora of cancers.

While the literature has shown that nsPEF ablation has been successful in treating a variety of tumors, it has not been extensively researched for the ablation of osteoid osteoma. This study aims to address this gap in knowledge and proposes a nanosecond pulse generator that will be used to induce supra-electroporation in osteoid osteomas. The nanosecond pulse generator will be used in combination with a custom probe, and both of these components will comprise the entire nanosecond pulse electric field ablation system. By using a novel power generator, this solution will target osteoid osteomas with more precision, limiting collateral damage to surrounding bone or tissue.

For this preliminary study, only the pulse generator was verified as the probe design is still being perfected. Testing the new nanosecond pulse generator *in silico* using Multisim software demonstrates a pulse with a magnitude of approximately 2 V is produced. While other nanosecond pulse generators can produce pulses with a voltage greater than 1 kV, this study still offers verification that the simplified circuit used in this study produces pulses of electrical energy. This provides the confidence needed to further develop the project by building upon the current circuit design to achieve the voltages required for effective ablation. Future studies should be conducted to further verify the circuit design as well as the probe before validating the entire ablation system by assessing its feasibility *in vivo* for the removal of osteoid osteomas.

METHODS

Multisim software was used to simulate the circuit needed for the nanosecond pulse generator. In a paper published by Krishnaswamy et al., a detailed schematic is provided for an avalanche pulse generator circuit which served as the inspiration for this study [9]. Using the avalanche pulse generator circuit as a starting point, this study aimed to first simulate the findings of Krishnaswamy et al., and then alter key parameters to change the output characteristics of the circuit. The circuit model used in the Multisim simulation was assembled as seen in figure 1. The DC power supply block, which consisted of a 8-14.5 VDC power supply followed by a DC-DC converter, was simplified as a 2.5 kV voltage source in the simulation. The transformer was modeled with no leakage inductance or resistance; the core was modeled as non-ideal with a flux of 250uWb * tanh(.2*i) where “i” was the magnetizing inductance current. The Bipolar Junction Transistor (BJT) NPN transistor was used to model the avalanche transistor. This transistor provided a conservative estimate of the circuit as it lacked the quick response of the avalanche transistors. The rise time of the trigger source was specified as 0.5 nanoseconds and varying levels of voltages were applied to assess the impact of the voltage on the output waveform. Peak voltage and rise time of the waveform were analyzed using a transient analysis with a step time of 0.1 nanoseconds.

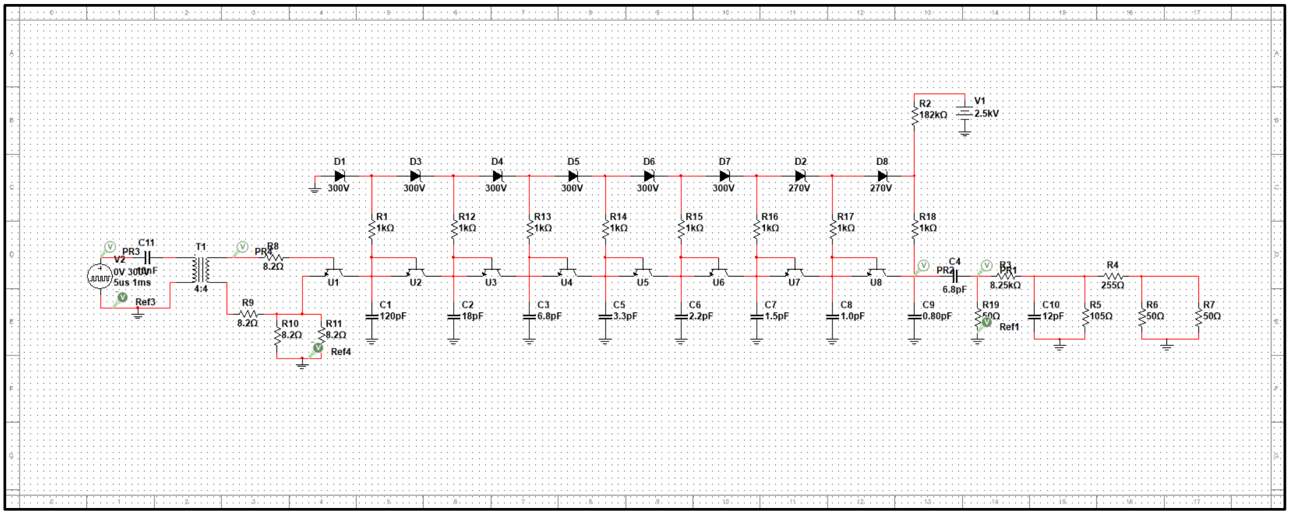

Figure 1: Circuit design (schematic of pulse generator circuit)

RESULTS

The rise times were quantified in Figure 3, and the peak voltages were quantified in Figure 4 for six different trigger source voltages of 5, 10, 15, 20, 100, and 300 volts.

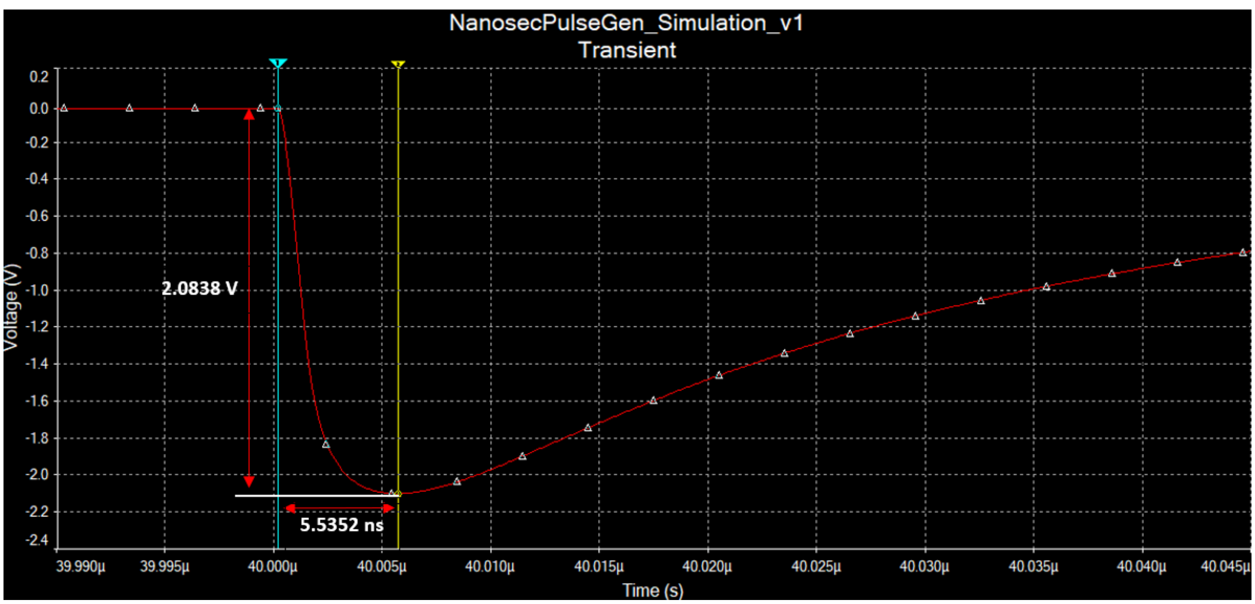

Figure 2: Simulation Results with a 5V Trigger Source. The Rise time was 5.5352 nanoseconds and the Peak Pulse Voltage was 2.0838 V.

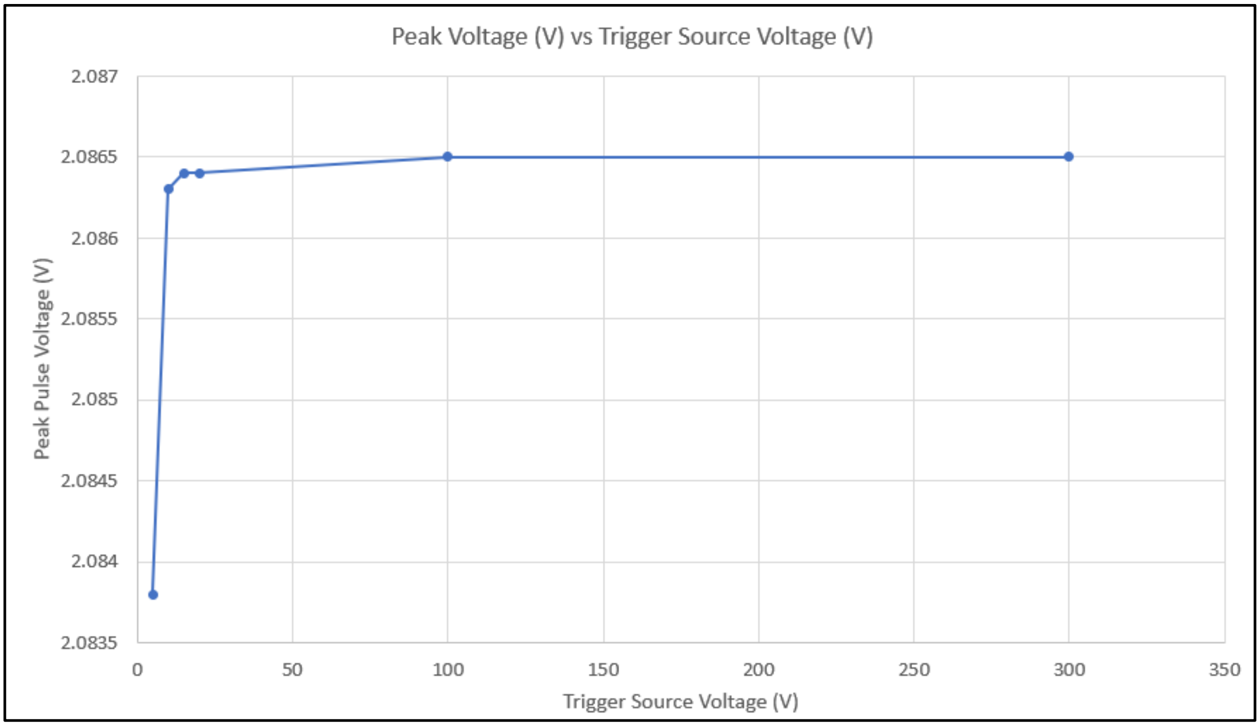

Figure 3: Simulation Results comparing Peak Pulse Voltage with changing Trigger Source Voltages.

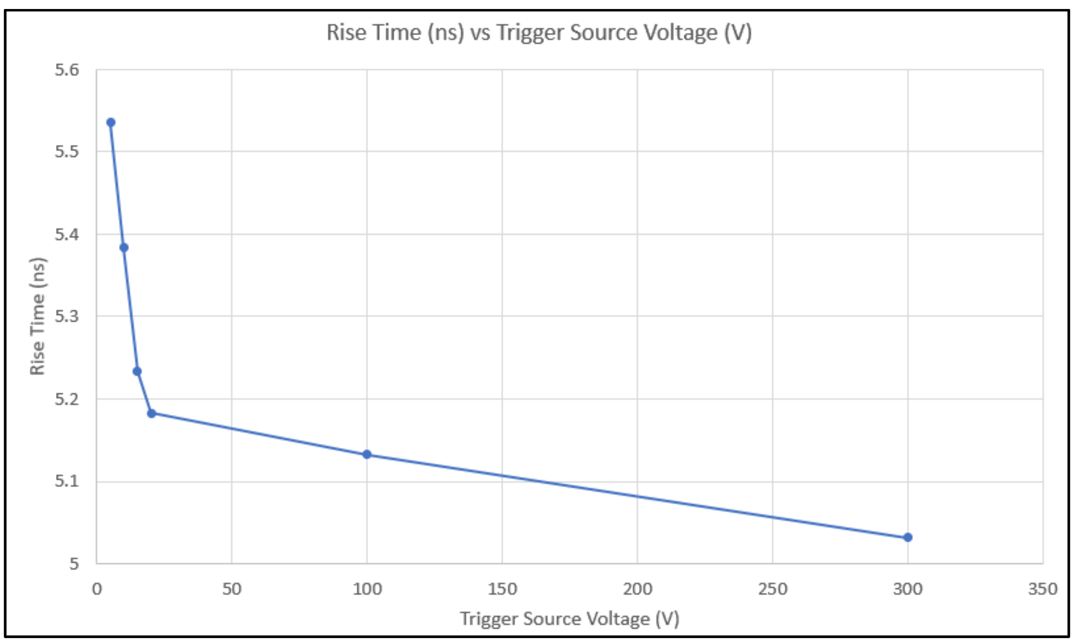

Figure 4: Simulation Results comparing Rise Time of the Pulse with changing Trigger Source Voltages.

DISCUSSION

In Figure 2, the output signal was shown in the time-domain with a single trigger source voltage of 5 volts. This output signal showed promising results in that it had the shape of a pulse that could be used in electroporation applications. However, the voltage magnitude was roughly a thousandth of the desired value [9]. This decreased magnitude would render the device useless in electroporation applications. However, further modification of the simulation could lead to a more appropriate waveform for the generator's intended use. Additionally, a prototype of the generator could be assembled and the output voltage could be assessed to compare results with the simulation. While this would have a cost associated with it, the testing may reveal limitations of the Multisim simulation software.

According to Figure 3, the peak voltage approached a horizontal asymptote at around 2 volts with an increasing trigger source voltage. These peak voltage values deviated from normal kilovolt values for the peak voltage in similar ablation technologies by orders of magnitude. On the other hand, rise times of around 5 nanoseconds (see Figure 4) were very plausible and much lower than millisecond to microsecond rise times in similar technologies. In order to improve the rise times to the subnanosecond range in future simulations, avalanche transistors could be used instead of ideal transistors.

There were a number of limitations in this study that hindered the results. First, this study was restricted to a simulated environment, which idealized many components to a form that was not indicative of their real-world state. Second, this study was limited to a short 15-week period of clinical research, needs statement identification and selection, finally followed with experimental design and performance. With additional time in the future, this study would be able to put together a real world model of the pulse generator.

Although this study found rather low peak pulse voltages, the overall nature of these pulses still offered verification for the treatment of osteoid osteomas with nanosecond pulse electric field ablation technologies. This study was able to produce pulses with short rise times, which was a key waveform characteristic when evaluating a pulse generator for its capability of treating osteoid osteomas via ablation.

CONCLUSION

This study aimed to test a new nanosecond pulse generator *in silico* with Multisim software to produce a pulse capable of powering an ablation probe utilizing a simplified circuit design. Although the resulting voltage magnitude was approximately a thousandth of the desired value, the output signal had the shape of a signal used in electroporation applications. With further modification of the schematic design of the circuit, the design shows promise in achieving a desirable waveform for the intended application. A prototype of the generator could also be fabricated and further tested to analyze the output voltage. This testing would reveal and mitigate the limitations of the *in silico* experiment. In addition to the verification of the variability in power of the circuit design, future studies could focus on the verification and validation of the efficiency of the circuit. Using Multisim or electromagnetic simulation, the circuit could be modified to operate between 915 MHz and 2450 MHz in order to have an ablation time of less than 10 minutes. The results of this study provides confidence in accurate modification of the circuit design to produce desired output signals and pulse magnitudes for use in the treatment of osteoid osteomas. Future studies should test the pulse generator with the ablation probe on an *ex vivo* tissue sample to analyze the effectiveness of the ablation technology on osteoid osteomas.

References

[0] C. Neyisci, Y. Erdem, “Safe and Effective Treatment Choice for Osteoid Osteoma: Computed Tomography-guided Percutaneous Radiofrequency Ablation,” *Cureus* vol. 11, no. 8. pp. e5526, Aug. 2019. Accessed on: Apr. 21, 2021. [Online]. Available doi: 10.7759/cureus.5526

[1] Y. Oc, B. E. Kilinc, S. Cennet, M. M. Boyacioglu, R. Ertugrul, and A. Varol, “Complications of Computer Tomography Assisted Radiofrequency Ablation in the Treatment of Osteoid Osteoma,” *BioMed Research International*, vol. 2019, pp. 1–6, May 2019, doi: 10.1155/2019/4376851.

[2] “Thermal Ablation of Osteoid Osteoma: Overview and Step-by-Step Guide,” *RadioGraphics*, vol. 29, pp. 2127-2141, Nov. 2009. Accessed on: Mar. 3, 2021. [Online]. Available doi: 10.1148/rg.297095081

[3] D. I. Rosenthal, F. J. Hornicek, M. W. Wolfe, L. C. Jennings, M. C. Gebhardt, H. J. Mankin, “Percutaneous Radiofrequency Coagulation of Osteoid Osteoma Compared with Operative Treatment,” *The Journal of Bone and Joint Surgery*, vol. 80, no. 6, pp. 815-821, June 1998. Accessed on: Mar. 7, 2021. [Online]. Available doi: 10.2106/00004623-199806000-00005

[4] Z. G. Papathanassiou, P. Megas, T. Petsas, D. J. Papachristou, J. Nilas, D. Siablis, “Osteoid Osteoma: Diagnosis and Treatment,” *Orthopedics*, vol. 11, no. 31, pp. 1118-1127, Nov. 2008. Accessed on: Mar. 7, 2021. [Online]. Available doi: 10.3928/01477447-20081101-20

[5] Q. Fan, B. Ma, Y. Zhou, M. Zhang, X. Hao, “Bone tumors of the extremities or pelvis treated by microwave-induced hyperthermia,” *Clinical orthopaedics and related research*, no. 406, 2015. Accessed on: Mar. 7, 2021. [Online]. Available doi: 10.1097/01.blo.0000037439.23683.9c

[6] S. Beebe, N. Sain, and W. Ren, “Induction of Cell Death Mechanisms and Apoptosis by Nanosecond Pulsed Electric Fields (nsPEFs),” *Cells*, vol. 2, no. 1, pp. 136–162, Mar. 2013, doi: 10.3390/cells2010136.

[7] X. Chen, J. F. Kolb, R. J. Swanson, K. H. Schoenbach, and S. J. Beebe, “Apoptosis initiation and angiogenesis inhibition: melanoma targets for nanosecond pulsed electric fields,” *Pigment Cell & Melanoma Research*, vol. 23, no. 4, pp. 554–563, Apr. 2010, doi: 10.1111/j.1755-148x.2010.00704.x.

[8] T. Koga, K. Morotomi-Yano, T. Sakugawa, H. Saitoh, and K. Yano, “Nanosecond pulsed electric fields induce extracellular release of chromosomal DNA and histone citrullination in neutrophil-differentiated HL-60 cells,” *Scientific Reports*, vol. 9, no. 1, Jun. 2019, doi: 10.1038/s41598-019-44817-9.

[9] P. Krishnaswamy, A. Kuthi, P. T. Vernier and M. A. Gundersen, "Compact Subnanosecond Pulse Generator Using Avalanche Transistors for Cell Electroperturbation Studies," *IEEE Transactions on Dielectrics and Electrical Insulation*, vol. 14, no. 4, pp. 873-877, Aug. 2007, doi: 10.1109/TDEI.2007.4286518.