Design of a Predictor Model of Temperature to Predict Ultrasound Treatment Success

Analysis of the 2016 European Union Medical Device Regulation

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

When new medical devices arise, so does medical device regulation. On May 26, 2021, the European Union (EU) implemented a new regulation on medical devices to protect the health and safety of users (Regulation (EU) 2017/745 of the European Parliament and of the Council, 2021). Any medical device currently on the market must receive re-certification under the Medical Device Regulation (MDR), but the certification process is slow (Andreae, 2023). The vague regulations and documentation require resources unavailable to small and mid-sized companies (Andreae, 2022). These regulations will result in a decrease in accepted medical devices, causing a burden on smaller companies and their users. Focused ultrasound companies are smaller and primarily impacted by these stringent regulations.

This new statute impacts my proposal to improve focused ultrasounds. Using high intensity focused ultrasound (HIFU) to treat neurological diseases is relatively new. The first instance was in 1960 (Christian et al., 2014). A target in the brain is focused on and heated up to around 58 ℃ to successfully ablate the target (Yamamoto et al., 2020). Currently, CT scans predict the likelihood of treatment success (Marquet et al., 2006). The skull density ratio (SDR) is derived from these CT scans to determine if ultrasound beams will lose heat while reaching a target in the brain (Boutet et al., 2019). This metric fails to account for skull thickness, resulting in an inaccurate prediction of treatment success. To improve this metric, my team and I aim to predict the delivered temperature. We will do so by creating a temperature prediction model.

High intensity focused ultrasounds help treat previously untreatable neurological diseases. The regulations impact the practicality of our design. Although the EU's regulation aims to improve safety, it will lead to less innovation (Van Laere et al., 2021). The relationship

between society and technology impacts the progress that technology can make. Without a connection between the two, technology no longer improves society, and improvements stagnate.

To ensure that medical innovation occurs, I must analyze medical devices' social and technical sides. I will improve high intensity focused ultrasounds by using a machine-learning algorithm that will predict the delivered temperature. To ensure that this proposed metric is implemented, I will use technological momentum to analyze the MDR. I will use this framework to better understand the timeline of technologies and how regulations and society's perceptions fit within the timeline. I will use the insight gained from this analysis to impact my design choices in my technical project.

Technical Project Proposal

Focused ultrasounds are gaining rapid technological acceptance as a non-invasive treatment method that targets brain heating and ablation (ter Haar & Coussios, 2007). Applications of focused ultrasounds are wide-ranging, spanning from neurological diseases such as Alzheimer's and Parkinson's to physical malignancies such as brain tumors (Meng et al., 2021). During treatment, multiple focused ultrasound beams are converged to a focal point on a pre-chosen target. The treatment is successful when the ultrasound ablates the target. The physicians can determine this from the peak average temperature reached in the target region during treatment and the known required ablation temperature. Treatment success is highly dependent on anatomical heterogeneity among patients, requiring an individualized treatment eligibility metric. The greatest loss of ultrasound energy occurs within material interfaces in the porous bone of the skull; therefore, the current clinical eligibility metric, the skull-density ratio (SDR), measures the ratio of the skull density between the skull's cancellous and cortical bones (Boutet et al., 2019).

The SDR is an imperfect indication of treatment success; in a Parkinson's trial, patients with a favorable SDR required more energy deposition than predicted (Sammartino et al., 2019). The SDR loses accuracy as a metric because it fails to account for key anatomical details such as skull thickness and key technological parameters such as sonication energy and duration. Should SDR continue to be used as the treatment eligibility metric for focused ultrasound clinical trials, many patients who can receive life-changing benefits from the treatment will be excluded from the trials. Patients who cannot benefit will experience frustration and sadness due to treatment failure, and the budding technology will lose credibility and sociotechnical momentum.

We hypothesize that 1) predicting temperature deposition in the target region, 2) using a multiple-regressor machine learning model, and 3) considering additional anatomical heterogeneities and transducer parameters will create a more accurate treatment eligibility metric than the SDR. Our technological project aims to output the predicted maximum average temperature reached during treatment. Initially, this will take the form of a single number within a < 5 ℃ confidence interval. Ultimately, we aim to produce a predicted thermometry data spread (the temperature map in the brain during an ultrasound treatment) for a chosen patient, given their anatomical details and the planned treatment parameters. We will visualize the thermometry data to help our understanding, as seen in Figure 1.

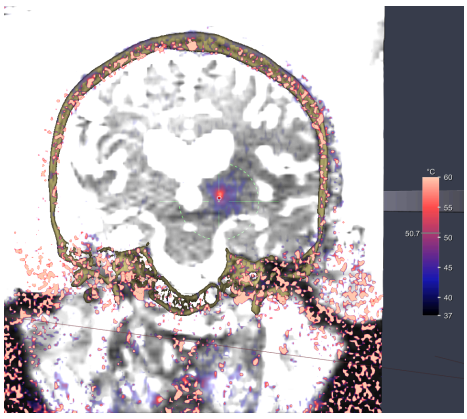

Figure 1. Ultrasound treatment data loaded into Kranion, showing thermometry data

Our advisors at the Focused Ultrasound Foundation (FUSF) have provided anonymized data from patients undergoing treatment at the UVA Focused Ultrasound Center. We will select significant variables to include in the multiple regressor model based on a literature review and perform principal component analysis (PCA) of the provided by-sonication treatment data. Kranion, an open-source focused ultrasound treatment planning software developed by FUSF, can load treatment exports as shown in Figure 1 (Sammartino et al., 2019). Kranion will help us visualize the effect of anatomical variance on HIFU treatment and the thermometry map. Although we will use Python due to its expanded machine learning capabilities, we hope to integrate the model with existing Graphical User Interface (GUI) displays in Groovy, Kranion's native language.

We will observe network model examples from scholarly articles on existing computational models for focused ultrasound target temperature prediction. These models rely on previously derived thermal dose equations, which will help us confirm our model results in the future (Revathy & Sadasivam, 2016; Sassaroli et al., 2012). Our model will be trained and tested on anonymized patient data from the UVA Focused Ultrasound Center. Over 100 datasets are available to us, and we aim to use all of them to increase statistical rigor. At a minimum, we will add 20 datasets for each independent variable added to the multiple regressor model to avoid overfitting. Since we are completing our work for the FUSF, a local nonprofit, success will also be measured in terms of project reusability, meaning we must keep detailed documentation throughout our project and publish all code as open-source.

STS Project Proposal

With an increase in software and artificial intelligence in medical devices, the United States (US) and the European Union (EU) put in place new regulatory responses to ensure and

promote safe innovation (Van Laere et al., 2021). To regulate device approvals, the EU appoints for-profit companies, called notified bodies, to determine approval (Maak & Wylie, 2016). The failure of a handful of high-profile medical devices led to these new EU regulations. For example, an elbow implant received certification in the EU but not in the US (Maak & Wylie, 2016). The Food and Drug Administration voiced concerns about fractures, and clinical evidence of these fractures led to its removal from the EU. Due to these failures, the EU revisited its previous regulations. These changes aimed to improve the safety of medical regulations, but the lack of transparency and public access to information creates a burden on smaller medical device companies (Thienpont et al., 2020). There is also no central source of information for medical devices, which means that people submitting requests through the EU regulatory system have no point of reference (Fraser et al., 2018). There is a severe lack of notified bodies and a lack of transparency among them. Although the regulation was put in place to increase safety, the lack of transparency and slow process cause an unnecessary burden on smaller medical device companies, such as focused ultrasound groups.

While the MDR causes a burden on medical device companies, the critiques fail to explain the entire picture. They fail to take into account the timeline of technology and society's impact on technology. There are a range of opinions on the MDR. On the one hand, researchers praise the MDR for its stricter regulations. Especially with medical artificial intelligence devices, similar to our technical project, the increased regulations and stricter notified bodies were a sign of a safer technological future (Niemiec, 2022). On the other hand, these regulations are criticized for being too strict. For early clinical trials and smaller companies, the barriers to getting devices to the global market are too high, creating uncertainty (Prince et al., 2022). Both of these points of view fail to take into consideration the social aspect of medical devices and the

timeline of technology. Understanding both of these is integral to understanding how regulations are put in place and how to mitigate the constraints placed by regulations in the future.

I argue that to understand the full scope of the impact of the MDR and to prevent further burdens on medical device companies, the social and technological timeline must be analyzed. Understanding how these regulations arise will allow engineers to implement more medical devices. Technological momentum accounts for the interconnected and evolving relationship between technology and society. This framework argues that initially, society influences technology, but as it gains momentum, its influence over society increases (Hughes, 2009). While technologies gain momentum, a reverse salient can hold them back. A reverse salient is a component that causes the system to fall back, reducing its technological momentum. I will use two elements of technological momentum to explain the effect of the MDR. Medical devices, and more specifically, HIFU, are at the beginning of their technological momentum. Currently, there is uncertainty around these devices, causing increased fear and regulation. I argue that the regulations are put in place without an understanding of medical devices, meaning that society is currently attempting to shape the growth of medical devices. Since the devices are at the beginning of their momentum, society's perception is formative. Following this idea, these regulations and this societal view serve as a reverse salient. To undertake this analysis, I will use evidence from MDR critiques, official regulation statutes, previous regulations and their effect on other technologies, and testimonies from smaller medical innovation companies.

Conclusion

The deliverable for the proposed technological problem will be a temperature predictor trained on existing data. Predicting the temperature will offer an innovation to HIFU, ensuring that we can predict patient treatment success. The STS research paper will connect to the

innovation success of HIFU, specifically focusing on the new EU regulation. The paper will aim to determine the future of medical device innovation and understand the impact of society and regulation on technology. Using technological momentum, I will argue that society impacts novel medical devices due to uncertainty around newer technologies. Society's perception impacts technology through regulation. These regulations, therefore, serve as a reverse salient in this technological system. From the analysis of society's impact on device regulation, I will ensure that our design is transparent and well-documented. The transparency helps with the societal view and the documentation reduces the negative weight of regulation, creating a model that has momentum.

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