DESIGN OF A NOVEL CRANIAL FIXATION DEVICE FOR FOCUSED ULTRASOUND BLOOD-BRAIN-BARRIER OPENING

A SHIFT TOWARDS DATA-DRIVEN MEDICINE: HOW ARTIFICIAL INTELLIGENCE APPLICATIONS IN MEDICAL IMAGING AFFECT HEALTHCARE SYSTEMS

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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

With over eleven million dollars invested by the commonwealth of Virginia and another 18 million funded by the public and private sectors, the Focused Ultrasound Foundation at the University of Virginia is revolutionizing the treatment of many medical disorders by developing a non-invasive, early-stage therapeutic technology (*State Invests $4 Million in UVA FUS Center*, 2016). One significant use for focused ultrasound (FUS) is the opening of the blood-brain-barrier (BBBO), which will allow for the expansion and access of the brain drug treatments and therapies. In the treatment of brain disorders, the patient's head is secured to the machine with a headframe to restrict movement during procedures (White, 2021). However, the stereotactic frames currently being used in clinical trials were originally designed for general radiosurgery, making the frames suboptimal for FUS techniques as they interfere with the treatment envelope of the device by hindering the ultrasonic beams from reaching the target area. The final technical deliverable, a novel cranial fixation device optimized for FUS BBBO procedures, will enable the full realization and implementation of FUS treatment for neurological diseases and brain tumors.

While ultrasound technology is rapidly being adapted for therapeutics, its original applications in medical imaging are also undergoing dramatic transformations along with those of other imaging techniques. Advances in both imaging and computational resources has led to the development of artificial intelligence (AI) and machine learning (ML) applications in various imaging tasks such as risk assessment, detection, diagnosis, prognosis, therapy response, and multi-omics disease discovery (Barragán-Montero et al., 2021). With a continuous rise in medical imaging rates due to their ever-increasing uses in personalized and preventative medicine, there is a significant need for these automated tools to collect, store, and process imaging data and to reduce the rising burdens on radiologists. However, these tools can create strains in the modern healthcare system due to their computationally-heavy, data-driven nature and their automated functionality in such a complex field that has no room for error. The final STS deliverable will explore and predict the sociotechnical and systemic changes that will occur with the inevitable introduction of AI in medical imaging.

Design Of A Novel Cranial Fixation Device For Focused Ultrasound Blood-Brain-Barrier Opening

Focused Ultrasound (FUS) has the potential to significantly improve the quality of health and life while reducing the cost of treatments and care. Currently, FUS technology is being developed and applied on 152 medical indications and disorders with 32 worldwide regulatory approvals and 7 approved by the FDA. Each of these applications provides a disruptive alternative or complement to surgery, radiation therapy, immunotherapy, and targeted drug delivery and activation. The technology works by using an acoustic lens to concentrate a multitude of intersecting beams of ultrasound deep in the body with extreme accuracy and precision. At the focal point, the energy created by the convergence of the multiple beams causes biological effects that can treat a variety of medical disorders (White, 2021).

At the University of Virginia (UVA Health), Dr. Jason Sheehan, MD, Ph.D, is leading a multicenter clinical trial in the application of FUS for the treatment of glioblastoma (GBM). GBM is an aggressive, malignant cancer that forms in the brain and spinal cord, which traditionally involves brain surgery followed by chemotherapy and radiation. Even with these treatments, the median survival of patients after being diagnosed with GBM is only 15-18 months. A primary reason for the treatment’s ineffectiveness is the Blood-Brain-Barrier (BBB), a layer of tightly packed cells that surrounds the brain and protects it from any toxic substances from the bloodstream and surrounding tissues (*First Glioblastoma Patient Treated in Focused*

Ultrasound Clinical Trial, 2021; InSightec, 2021). The BBB's impermeability only allows 5% of over 7000 small-molecule drugs from diffusing into the brain, hindering the treatment of many neurological disorders (Konofagou et al., 2012). By applying low-intensity beams to a region of the BBB near the tumor, FUS can temporarily and reversibly open the barrier to allow for targeted and effective delivery of the chemotherapy drug to the GBM tumor. The main goal of Phase 1 clinical trials is to test and determine the efficacy and safety of the BBBO procedures for future applications in drug delivery for cancers and other neurological disorders which have struggled to be treated effectively prior due to the BBB (*First Glioblastoma Patient Treated in Focused Ultrasound Clinical Trial*, 2021).

For the FUS-BBBO procedure, the patient's head is placed within an ultrasound transducer system while the patient lies down on an MRI bed (InSightec, 2021). The patient's head is mounted and secured to the bed in a fixed position with a cranial fixation device to restrict movement during the procedure. However, current cranial fixation devices used in FUS applications are suboptimal as they are designed and utilized for other neurosurgical applications such as stereotactic radiosurgery and functional neurosurgery. The devices interfere with the structure and functionality of the ultrasound transducer due to their bulky size and their ability to disrupt or block incoming FUS beams. These devices are a critical barrier to success as they limit the application of FUS treatment to a majority of the posterior and lateral regions of the cranium, thus limiting the overall volume in the brain that can be treated. Consequently, this limitation reduces the number of patients that are able to receive the FUS treatment, hindering the available sample size needed for the clinical trial for GBM therapy.

Given that there is a necessity to develop an improved cranial fixation device for FUS BBBO procedures, certain objectives, or *specific aims*, need to be established. The first aim of developing a better stabilization device is to ensure a near-complete restriction of head movement during the BBBO procedure. This aim will be accomplished by re-engineering existing headframes or even thermoplastic masks that are currently being used for radiosurgery applications. One of the first steps of this aim is to delve into in-depth research about headframes and thermoplastic masks, and decide which type of cranial fixation device is best suited for BBBO applications. With BBBO, there is a larger range of allowed head movement compared to radiosurgical ones since the treatment area is larger than a specific target point. The chosen stabilization device (head frame or mask) will have the capability of adapting to specified margins based on device fit within the machine, allowing the machine to accommodate for a variety of patient head sizes and shapes while also keeping the head as stable as possible.

The second aim is to minimize the interference of the fixation device with the ultrasound transdurcer during the BBBO procedure. A virtual program will be used to model the positioning of the frame within the machine, in addition to modeling the ability of the machine to access certain points within the head that require treatment. By modeling and simulating the access areas provided by the device and the efficacy of the headframe in securing the cranium while minimizing ultrasound hindrance, quantitative comparisons to previous models will be done to pinpoint where exactly the new device should be altered for optimizaiton. Along with physical compatibility, the material used to construct the frame or mask has to be radiologically compatible with the Magnetic Resonance Imaging (MRI) machine and ultrasound transducer to avoid attenuation and artifacts during the procedure.

The third aim tying into building a better cranial fixation device is ensuring that the aforementioned device is a minimally-invasive device that minimizes patient discomfort. Currently, when a patient is set up to undergo a radiosurgery procedure with a cranial fixation device, there is significant patient discomfort during the placement of the device, the procedure itself, and removal of the device. Such discomfort is usually caused by the deployment of pins underneath the patient's skin and in direct contact with the skull to ensure minimum head mobility. To combat such discomfort, the team proposes to develop and experiment with many designs which do not require the use of such pins, with the goal of creating a device that still keeps the cranium stable for the BBBO procedure. The improved headframe design will be qualitatively determined through a survey which will measure the subjects' comfort levels when they are fitted with the device in a non-operational setting. This survey will be conducted by going into the clinic and testing the device on a variety of subjects with different head shapes and sizes, along with different demographics.

The expected engineering design outcome for the technical project is the development of an improved design and prototype of a cranial fixation device for FUS-BBBO procedures. After clinical testing on patients, the best design will be determined based on patient comfort, stabilization of the cranium, and increased access to the treatment area. The development and implementation of an improved and optimized cranial fixation device by the Capstone team will assist the Focused Ultrasound center and the clinicians working within it to realize the full potential of FUS-BBBO treatments by enabling rapid and effective clinical trials, improved and more expansive health outcomes, and development of future FUS applications.

A Shift Towards Data-Driven Medicine: How Artificial Intelligence Applications In Medical Imaging Affect Healthcare Systems

Medical imaging is a vital cornerstone of medicine and healthcare, an essential factor for effective diagnosis and treatment of diseases. Over the past few decades, there has been a rapid rise in the advancements and rates of medical imaging techniques due to its application in precision and personalized medicine, which utilizes an abundance of patient data to optimize clinical decision making and significantly improve patient outcomes (Alexander et al., 2020). Due to this increase in medical imaging data and use, there is a significant shortage in the number of radiologists available to collect, analyze, and conduct decisions on this data in order to diagnose and treat patients with 90% of radiologists reporting an increased workload over the past 3 years. Additionally, the latest medical imaging techniques require processing and analysis of increasingly complex 3D images which can quickly become computationally tedious, wieldy, and time consuming to handle by the radiologists themselves (Pesapane et al., 2018).

Fortunately, artificial intelligence, which includes machine learning and deep learning, addresses these issues by automating image analyses, aiding in disease detection and localization, and facilitating informed and efficient decision-making. These machine learning algorithms process large amounts of imaging data and incorporate other medical information as well to provide an optimized and expansive understanding of the patient's medical issues (Mandal et al., 2018). However, a majority of these technologies have yet to be fully implemented in clinics and hospitals due to the computationally heavy nature of these algorithms which require a lot of data and a healthcare system to reinforce it. Machine learning and deep learning methods require enormous datasets to train their algorithms, which are hard to come by in the privacy and anonymity-focused healthcare field (Willemink et al., 2020). Additionally, the datasets have to be accurate and representative of the entire population of patients. For example, Larrazabal et al. (2020) discovered that deep neural networks trained on gender imbalanced X-ray image datasets used to diagnose thoracic diseases had worse performances for underrepresented genders (Larrazabal et al., 2020). If not solved, biases in datasets can lead to significant disparate treatment and impact of patients. Lastly, many of these methods have extremely dense and convoluted algorithms that make them hard to decipher by doctors and patients (Morris et al., 2018). While there is substantial research being conducted on developing many of these new technologies, there is a need to analyze and predict how this technology will affect healthcare systems in the future and determine the necessary changes required to improve its implementation in the industry.

Analysis of this impact will be conducted through the lens of the Actor-Network Theory (ANT) STS framework. This theory studies the associations and socio-technical connections between actors, which can either human or non-human, in the form of a complex, modularized network. ANT constructs a heterogeneous network of actors that allows one to discover intricate relationships between social and technical entities. Also, the addition of actors and connections to a network can be used to open up black boxes that were previously less understood (Cressman, 2009). However, a common criticism of this framework is that the network can become too complex and detailed such that it loses its ability to gain any insight on the system or technology. The choice of where to "cut the network", or decide which actors to include or exclude, is also difficult and often an uncertainty or arbitrary assumption of the framework (McLean & Hassard, 2004). In order to overcome these criticisims, the scope of the network will be limited to only the key consitutents which directly interact with medical imaging technologies and will be determined through extensive research on the topic.

Research Question and Methodology

Research Question: "How will the introduction of artificial intelligence applications in medical imaging affect the healthcare system and its constituents in handling and utilizing healthcare data?"

This research question will be answered by using the Network Analysis and Policy Analysis methodologies. First, the structure of the ANT network will be established without the addition of machine learning tools in medical imaging. Specifically, Network Analysis will be used to understand how the different actors of the healthcare system such as patients, `radiologists, and hospitals connect with each other based on data collection, transfer, and privacy methods. A combination of keywords such as “medical imaging”, “hospital systems”, “data-driven medicine”, “medical data”, etc. will be used to search for primary and secondary sources that express each actor’s sentiments on data-driven decision making. At the same time, the Policy Analysis methodology will be applied to understand the policies of larger organizations and institutions such as the government and hospitals regarding their medical imaging technologies and how such data is handled currently. This research will expand upon the black box model of the ANT network and add an additional layer of complexity and information that will then be investigated further. Once the ANT network is established with all relevant information, primary sources of various medical imaging tools with artificial intelligence that are already clinically implemented or commercialized will be analyzed for their effects on this ANT network. The addition of this new technological actor will create strains or strengthen connections among or within other actors in the network. Having the information organized into a network will aid significantly in discerning distinct effects of the artificial intelligence tools on each of the relevant actors, and determining the overall ability for these tools to either integrate into the current structure of society or completely alter the structure of the healthcare system itself (Cresswell et al., 2010).

Conclusion

Ultimately, the implementation of artificial intelligence in medical imaging could catalyze a shift of the entire healthcare system towards highly personalized and data-driven medicine. Predicting how healthcare institutions, patients, and radiologists will react to the initiation and growth of these advanced technologies will assist in better understanding this shift and its repercussions. Additionally, an optimized cranial fixation device will increase the available access to FUS treatment on the brain allowing for a larger variety and locations of disease states to be treated in patients, thus significantly improving patient prognosis and quality of life. By enabling and expediting clinical trials of BBBO treatments using FUS, the novel cranial fixation device will assist the Focused Ultrasound Foundation and UVA Health in reaching their development goals, and eventually tailoring and utilizing the same device for other types of FUS treatments.

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