Predicting Future Tumor Location in Patients with Brain Metastases

(Technical Paper)

Criteria for Successful Integration of Machine Learning Tools in a Medical Setting

(STS Paper)

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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

Introduction

In many ways, technology has become the backbone of modern medicine, with uses spanning from diagnostics to treatment assessment, and even intervention. Namely, scientific understanding of cardiac processes led to the development of pacemakers, which are now implemented in approximately 200,000 patients per year in the U.S. alone (Boink, Christoffels, Robinson, & Tan, 2015; "Permanent Leadless Cardiac Pacing," n.d.). Additionally, several studies describe the usefulness of incorporating extensive genomic research into the creation of personalized treatment plans (Ashley et al., 2010; Chawla & Davis, 2013; Manolio, 2010). The technical portion of this thesis utilizes a machine learning approach to predict cancer occurrence prior to tumor visibility and patient response to gamma knife radiosurgery (GKS).

Currently, tumors are located using visual inspection of medical imaging by oncologists, and diagnosed via biopsy (Stephens & Aigner, 2016). Blood and serum tests are able to indicate tumor presence, often before visual detection by oncologists (Lin et al., 2011; Zhang et al., 2016). These tests, however, are unable to determine tumor location. If successful, the technology described in the technical portion of this thesis will recognize and locate tumors before they become visible to radiation oncologists. This new method of tumor prediction will pave the way for increased emphasis on preventive medicine in oncology, which has historically improved the quality of patient care (Balas et al., 2000; Hood, Heath, Phelps, & Lin, 2004).

Once tumors are detected, prediction of tumor response to intervention is used to inform treatment plans. Existing methodologies for assessing tumor response are limited in accuracy and by the number of variables incorporated into the model (Bibault, Giraud, & Burgun, 2016; El Naqa et al., 2009; Mansouri et al., 2015). Given that the model described in the technical portion of this thesis displays increased accuracy of GKS response assessment, it will provide oncologists with useful information for the development of improved treatment plans.

The technology's promise in improving patient care is, however, directly tied to its introduction, acceptance, and integration into the medical field. To inform the process of implementation of the technology, the relationship between machine learning and society within the medical field must first be analyzed. This analysis identifies and evaluates factors that will contribute to the technology's overall success. The hope of the study is to determine specific evaluations of accuracy, modifications to the technology, and implementation strategies that will facilitate the integration of machine learning technologies into Gamma Knife Radiosurgery treatment evaluation.

A Machine Learning Approach to Gamma Knife Radiosurgery Evaluation

Brain metastasis, or the spread of a primary cancer to the brain creating a secondary tumor, is a significant consideration and complication in developing cancer treatment plans. Estimates for the percentage of cancer patients who develop brain metastasis has been reported as ranging from 20-40% depending on the type of data reviewed (Nussbaum, Djalilian, Cho, & Hall, 1996). However, this range likely understates the actual incidence rate. The majority of these estimates are based on sets of historical data in which metastasis may not have been accurately documented, especially in the case of discovery in terminally ill patients and asymptomatic metastasis (Gavrilovic & Posner, 2005). Additionally, as identification and treatment of primary cancers continue to increase patient survival time, the incidence rates for brain metastasis also increase (Fox, Cheung, Patel, Suki, & Rao, 2011). One of the main factors for brain metastasis incidence is the histology of the primary cancer. Lung cancer is the most common primary cancer to develop brain metastasis, with incidences up to 65%. Other high incidence cancers include breast cancer and melanoma (Nayak, Lee, & Wen, 2012). Brain metastases contribute unique neurological clinical manifestations that can further decrease the quality of life of cancer patients. The most common presenting symptom for brain metastases is headaches (50%), followed by focal weakness (27%) and change in mental status (31%). Seizures are a less common presenting symptom (10%) but occur in a significant amount (40%) of patients over the course of the illness (Klos & O'Neill, 2004). For some patients, neurological symptoms are so debilitating, that the brain metastases are identified by MRI before a primary cancer is discovered ("Brain metastases from an unknown primary tumour: which diagnostic procedures are indicated? | Journal of Neurology, Neurosurgery & Psychiatry," n.d.). The prognosis for brain metastases is not favorable, with a median survival of 3.4 months, and a two-year survival percentage of only 4% (Lagerwaard et al., 1999). Lagerwaard et al. do show that patient prognosis has a significant dependence on treatment method (Lagerwaard et al., 1999).

Gamma knife radiosurgery (GKS) is an effective tool for the treatment of brain metastasis (Muacevic et al., 1999; Petrovich, Yu, Giannotta, O'day, & Apuzzo, 2002). GKS is a procedure that allows for precise targeting of radiation treatment at the convergence of 192 individually focused gamma radiation sources (Lunsford, Flickinger, Lindner, & Maitz, 1989). The ability to target specific points in the brain without releasing high levels of radiation to surrounding tissue makes GKS a popular choice for treatment of brain metastasis, especially in the case of multiple recurring tumors. Currently, GKS treatment plans are developed by physicians based on an array of T2, diffusion, and perfusion MRIs. These plans are limited by an incomplete knowledge of how individual tumors will react to certain doses and the inability to predict where new tumors will arise. To this end, the team proposes to develop a machine learning application that will predict tumor response to a given GKS dosage (Aim 1). Additionally, the team will go a step further to develop a machine learning application that will predict the location of new brain metastases during initial screening (Aim 2).

Aim 1: Predict tumor response to gamma knife radiation treatment from MRI data:

A. Use programs that were developed by a prior capstone team to automate the capture of tumor volume from MRI data.
B. Determine a predictive model of correlation between treatment and change in volumetric data using existing machine learning algorithms, such as alexnet and resnet18.
C. Analyze the accuracy of the model in predicting the manner in which tumors will respond to treatment based on volumetric data.

Aim 2: Predict future tumor occurrence based on prior MRI data:

A. Utilize MRI data of patients with recurrent tumor formation to capture volumes that will become cancerous in the future.
B. Analyze MRI data of pre-cancerous volumes in comparison to that of healthy tissue using existing neural networks.
C. Determine if this model can accurately predict tumor occurrence based on MRI data taken prior to its visible diagnosis. This is made possible because medical imaging prior to visualization of the tumor is often available for many patients.

Completion of these aims provides a tool for medical professionals to predict and better understand the behavior of brain cancer metastasis in both pre and post radiation therapy. Ultimately, advancement of this work could lead to more efficient radiation treatment (a1) and the development of targeted preventive therapies (a2).

Analyzing the Relationship Between Society and Machine Learning in Medicine

Success in implementation of any technology is determined by the usefulness of the technology over the current approach, as well as the technology's ease of integration into the field. If a technology is created but the field rejects it, it has no impact, and therefore cannot be seen as useful. To combat this, technology may be adapted and adjusted in order to facilitate integration.

This paper focuses on the integration of machine learning technology into Gamma Knife Radiosurgery treatment evaluation. Prior to implementation, the societal impact of the information derived from the technology must be assessed. This assessment ensures that the technology's use provides the patient with the overall net benefit that characterizes success. Understanding the data derived from the technology and its possible implications are essential in enabling patient benefit.

The theory of technological momentum will be used in understanding the relationship between technology and society, with regards to implementation of machine learning technologies within a medical setting. Technological momentum proposes that while technology is shaped by society, society is also shaped by technology (Hughes, 1969). This is the combination of technological determinism and social constructionism (Klein & Kleinman, 2002; Smith, n.d.). This theory allows for evaluation of the complex interdependencies between technology and society, without the loss of perspective that oversimplification by either of the aforementioned theories can provide.

Factors and individuals contributing to the technology's integration will be assessed using Actor-Network Theory (ANT). ANT provides a methodology for describing complex interdependencies within a system (Cressman, 2018). At first glance, main stake-holders may be assumed to be solely patients, radiologists, and physicians. However, this disregards the interaction of hospital administrators, nurses, and individuals responsible for data collection with the technology. ANT will be used to identify unexpected stake-holders and interdependencies of the system. By looking at the integration of technology into society as a complex web, rather than a linear system, the manner in which a technology will be received and the impact it will have may be better assessed.

Additionally, the medical field's transition from reliance solely on medical professional assessment, to heavy incorporation of technology and computational analysis will be analyzed as a paradigm shift. Paradigms are defined as "universally recognized scientific achievements that, for a time, provide model problems and solutions for a community of researchers" (Kuhn, 2012). These paradigms are replaced over time, and this process is known as a paradigm shift. Exemplified by transitions such as that from a geocentric to heliocentric view of the universe, paradigm shifts change the nature of the field in which they exist ("Converging Perspectives on Conceptual Change | Mapping an Emerging Paradigm in the Learning Sciences," n.d.; Kuhn, 2012). Medical diagnosis and intervention by experts' interpretation of data, derived from existing knowledge of the field, can be considered an established paradigm. This thesis argues that a new paradigm, defined by heavy reliance of medical professionals on technology for interpretation of data, is now emerging to replace the old one. This transition is what categorizes a paradigm shift.

The aforementioned theories will provide lenses through which to analyze the interactions between machine learning and the medical environment where it is proposed to be used. The use of these theories in conjunction with one another rectifies many of the short fallings observed when using the theories individually. For example, ANT has been critiqued for lack of defined scope and differentiation between human and non-human actors (Latour, 1996; Murdoch, 1998). Through paradigm shift analysis, a scope can be more clearly defined. Additionally, by incorporating the theory of technological momentum, the importance of human factors can be emphasized. Conversely, the systematic nature of ANT provides clarity of interdependence that is not readily achieved through a technological momentum based approach. By analyzing this interaction through multiple lenses, a broader picture of the complex interaction between the two subjects in question can be observed.

Research Questions and Methods

This thesis attempts to describe the complex relationship between machine learning technology and the medical environment in which it is implemented by answering four major questions: Who is affected by the technology? What factors effect individual acceptance of the technology over the current approach? What steps can be taken to ease integration of the technology? What are unintentional consequences of data collection by the technology?

Historical case studies and discourse analysis focused on machine learning technology used within the medical field will be conducted. Historical case studies will be conducted through review of existing literature and discourse analysis will be focused on information derived from other mediums, such as movies and podcasts. Data on how machine learning technologies were received by stakeholders will be recorded to construct a better understanding of the relationship between individuals and the technology.

Research will also be conducted on how data from these studies was protected by means of policy analysis. This will give insight into what kind of policy should be established prior to release of the technology, as to avoid unintended consequences of misdistribution of data. This is of particular importance within the medical field, where lack of data protection may have serious consequences for the patient. For example, collected genomic data has been proposed as a possible resource for insurance companies to adjust rates (Nill, Laczniak, & Thistle, 2019). Additionally, the film *Gattaca* touches on the concern of use of medical data as a platform for discrimination if it is not properly protected (Niccol, 1997).

Additional information will be derived from interviews conducted with radiologists from the GKS lab in the spring semester. In this interview, participants will be asked what metrics of accuracy and types of training must be provided in order for them to deem the machine learning approach to GKS useful. This evaluation will provide information on the current degree of acceptance of the technology in the field.

Conclusion

The successful creation and implementation of machine learning technologies within the medical field shows promise in improving medical care. An improved model for tumor response to GKS provides radiologists with additional information to guide treatment plan creation, in turn improving patient care. A predictive model for tumor occurrence prior to visibility allows for increased incorporation of preventative medicine into cranial oncology. These advancements are dependent on the successfulness of the technology. For the technology to be successful, stake-holders must be willing and able to integrate machine learning into everyday practice and operation. By assessing the factors that contribute to such willingness and ability, a framework can be constructed that details how technology can be improved and adjusted in order to facilitate success.

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