Project Summary/Abstract

This year alone, more than 1.8 million new cancer cases are expected to be diagnosed in the United States. Out of these, 606,520 Americans will die [1]. The burden of cancer care is financially significant with more than $94 billion in earnings being lost in the US due to cancer death in 2015. Along with chemotherapy and surgery, radiation therapy (RT) is an effective method of cancer treatment, with more than half of all cancer patients managed by RT having higher survival rates [2]. Owing to technological advancements in RT delivery, radiation dose can now conform to a tumor's 3D shape by up to 2 mm accuracy. This allows for further dose escalation to tumors, while minimizing dose to nearby healthy organs-at-risk (OAR). This has significantly improved tumor control and normal tissue sparing on cancer patients. In most clinics today, the images used for dose treatment planning are from computed tomography (CT). However, CT lacks the soft tissues contrast in the patient's cranium necessary to guarantee precise irradiation. Magnetic resonance imaging (MRI), however, is a very effective real-time imaging modality for tracking internal tissues' motion for dose reconstruction and real-time image adaptation.

The University Medical Center at Utrecht and Viewray have working prototypes of simultaneous MR imaging and irradiation from linear accelerator RT. A drawback of these integrated MRI-LINAC systems however is that intracranial head motions can cause MR imaging artifacts during MR imaging – limiting the effectiveness of MRI as an imaging modality. The state-of-the-art mechanisms for keeping the head static in clinics are rigid Brown-Robert-Wells head frames [3] or thermoplastic face masks. However, patients find these devices inconvenient, and highly invasive. Furthermore, they cause poor patient compliance to prescribed radiation dose and they cause clinical inefficiencies [4]. Explorative active robotic head motion control devices developed by Wiersma et al are good head stabilization devices in stereotactic radiosurgery but they are not good candidates for MRI-LINAC RTs because of their metallic linear actuators and rigid components that pose risks to the patient or MR machine [5]. **Non-magnetic, radiation transparent soft robots integrated with MRI-LINACs for treating brain as well as head and neck cancers can provide the precise irradiation recommended by AAPM task group-42 in RTs or SRS treatment procedures [6–9].** In my previous investigations, I have shown the effectiveness of soft robots at head motion correction up to submillimeter accuracy in lower task-space dimensions. **My leading hypothesis is to use an MRI/LINAC-compatible soft robot system to provide 6-DoF head motion correction in precision RT procedures**. In this project, I will (i) develop a stable motion planner for safety-aware head manipulation that avoids the exposure of OARs to unwanted radiation; (ii) develop a soft robot that is non-magnetic and radiation transparent for use in MRI-LINACs; in my mentored years. (iii) And I will validate the soft robot and motion planning algorithm on healthy human volunteers; and then in real-world patient trials in my independent years.

Project Narrative

Accurate dose targeting to malignant cancers in radiation oncology requires a clear delineation of soft tissues within the target volume in order to differentiate critical structures apart from organs-at-risk. Currently, CT images are used in this segmentation task which lack the required delineation capability. MRI provides real-time imaging characteristics for tracking anatomical motion for MRI guided RT, dose reconstruction, as well as real-time image adaptation. However, intracranial head motions can cause artifacts in MRI images. This project will leverage the high-contrast that magnetic resonance scans provide with the non-magnetic and radio-transparent compliance that soft robots provide in cranial position manipulation so as to assure better clinical outcomes for head and neck (H&N) as well as brain cancer treatments in integrated MRI-LINACs radiation therapy treatment procedures.

Description of Institutional Environment

The University of Pennsylvania (UPenn) offers an ideal setting to work at the intersection of soft matter, mechanism design, robotics, control systems and applied medical physics. The University of Pennsylvania School of Medicine (PSOM) is the oldest medical school in the United States, consistently ranks as one of the top four medical schools in the country, with access to world-class medical physics and radiation therapy (RT) facilities. It hosts the most advanced proton and conventional radiation treatment modalities available in the world and is consistently pushing the envelope of research in basic and translational clinical research. It is the only RT facility and largest center in the world that offers integrated proton therapy with conventional radiation therapy – all under one roof so that patients can choose their elective care without logistics worries. The broad range of radiation treatments available at Penn Radiation Oncology include proton therapy, intensity-modulated radiation therapy (IMRT), high-dose rate (HDR) and low-dose rate brachytherapy, partial breast irradiation, stereotactic radiosurgery (SRS), and Gamma Knife radiation. These facilities will make it easy for Dr. Ogunmolu to conduct his MRI-LINAC RT research and seek counsel from faculty and medical doctors with outstanding discipline know-how.

Institution Compatibility with Candidate's Career and Proposed Research Plan.

UPenn offers a series of seminars and workshops to assist young investigators communicate with experts in different fields and develop a successful research proposal: Dr. Ogunmolu will attend several weekly seminar series including Penn xRT Research Division's Invited Speaker Seminar Series and the Radiobiology and Imaging Program at Penn Medicine's Abramson Cancer Center. Dr. Ogunmolu will present his research once a year at the Institute for Translational Medicine and Therapeutics (ITMAT) seminar series and symposium, and Penn Institute for Medicine and Engineering (IME) Seminars and Events and Penn's GRASP Lab Seminars and Events. These seminars and events exist to disseminate strong scientific/engineering findings by prominent scientists and engineers with whom Dr. Ogunmolu will have the opportunity to meet and engage both at lunch and in the laboratory. Dr. Ogunmolu has identified an outstanding mentorship team and the training environment is described in more detail under the "*Candidate Information and Goals for Career Development*" section.

In addition to internal campus collaboration, UPenn places a high value on engagement with faculty colleagues, students and other researchers at other institutes in the United States and indeed globally. These include, but are not limited to, the National Institutes of Health (NIH), National Science Foundation (NSF), John Hopkins and Harvard Universities. As a global university, UPenn attracts the best students, faculty, staff and visiting scholars from around the world to campus to conduct teaching and impactful scientific activities. Dr. Ogunmolu is very passionate about educating and helping develop the next generation of medical roboticists, especially from under-represented minority (URM) communities. At UPenn, Dr. Ogunmolu can easily take advantage of the global diversity of Penn's staff and faculty and learn best practice on how to forge a vision that rallies the intellect and resources offered by diverse talents available that he expects to recruit and train during his R00 years. The opportunity at UPenn to partner with world-class researchers at other global universities and research institutions such as Harvard University, NIH and the NSF are resources Dr. Ogunmolu can use to build a formidable academic network for his long-term career goal needs.

The research collaboration culture is very admirable at UPenn: the university actively encourages researchers across disciplines to actively collaborate. There are numerous collaborations among faculty, postdocs and students from different departments who conduct research via resource sharing and interdisciplinary communication. Indeed, Dr. Ogunmolu has actively leveraged this opportunity since he came to UPenn by forging close alliances with Engineering staff and faculty. These alliances have helped him to generate some preliminary results faster for this project, albeit he's been slowed down by the university-wide shutdown that arose from the COVID-19 spread precautions. Drs. Wiersma and Pikul already have a strong working relationship (they have written a joint proposal recently) and are in close agreement with the needed mentoring for Dr. Ogunmolu during the K99 years of this award. Drs. Pappas and Turner are world-class experts in control theory and continuum mechanics respectively and they both hold senior administrative roles within the University – both are respective Chairs of the departments of Electrical and Systems Engineering (ESE) and Mechanical and Applied Mechanics (MEAM). They will be coordinating the career development goals outlined by Dr. Ogunmolu. Dr. Pappas will invite Dr. Ogunmolu to his office and/or laboratory at least once every three months where he will allow him to observe and learn from his administrative and leadership style that has made ESE one of the best Electrical and Systems Engineering programs in the country. Dr. Turner will also schedule a sit-in with Dr. Ogunmolu at least once a month where he will guide Dr. Ogunmolu on the specifics of NSF-style grants-writing, how to direct a mechanical engineering lab and staying within operational budgets for the department. This would be valuable to Dr. Ogunmolu during his independent years as he continues to climb the ladder of academic leadership. In addition, Drs. Turner and Pikul's laboratories will be available for Dr. Ogunmolu on an as-needed basis so that he can adequately execute the mechanical build, testing and validation of the soft robot mechanism that he has proposed in this research statement. Together with Drs. Wiersma and Pappas, they will regularly coordinate the mentoring plan for Dr. Ogunmolu via joint lab monthly meetings where they will regularly discuss ideas and resource sharing.

Plans and Statements from Mentor and Co-mentors

Mentor Statement of Support, Rodney D. Wiersma, PhD, DABR

I am delighted to offer my strong support for Dr. Ogunmolu's application for the K99/R00 Pathway to Independence Award. I recently joined the University of Pennsylvania in 2019 as an Associate Professor in the Department of Radiation Oncology. In addition, I am Director of Research for the Physics Division and Associate Director of the Medical Physics Graduate Program (MPGP). Before UPenn, I was an Assistant Professor in the Department of Radiation and Cellular Oncology at the University of Chicago. I was a Postdoctoral Scholar at Stanford University under the guidance of Lei Xing, and before Stanford, I completed my PhD in physics at the Max-Planck-Institute FKF in Stuttgart, Germany under the supervision of Nobel Laureate Prof. Klaus von Klitzing. In terms of education and mentoring, I teach MPHY606, Physics of Radiation Therapy, a core course on fundamental medical physics concepts for graduate students. While at UChicago, I taught MPHYS35100, Physics of Radiation Therapy, which is a mandatory course for all incoming graduate students, and instructs them on the fundamental theory behind production and interaction of high energy radiation for therapy purposes. I also taught MPHYS34400, Practicum in Radiation Therapy, a combined lecture and hands-on experimental course, and MPHYS35900, Cancer and Radiation Biology, which provides students with an overview of the biology and biological modeling processes in cancer. In addition, I taught BIOS29326, Introduction to Medical Physics, an undergraduate course that is aimed at teaching medical physics fundamentals to mathematically inclined students. During my academic career, I have directly mentored 6 undergraduate students, 6 graduate students, 3 medical physics residents, and 4 postdoctoral scholars.

Lekan is a highly motivated and accomplished engineer with a bright future ahead of him. As a doctoral student, he started out in the lab of Dr. Gans at UT Dallas, developing a soft manipulator prototype for patient head motion correction in intensity-modulated radiation therapy (IMRT), and later transitioned into the laboratory of Dr. Steve Jiang at UT Southwestern Medical Center in the latter half of his degree where he contributed on hastening the solve time of the classical beam orientation optimization problem in IMRT. In between his academic research on the two campuses, he spent almost a year in the consumer robotics industry in Tokyo and Boston respectively where he made contributions to vision-based motion-planning algorithms for pick-and-place as well and grasp tasks. In his PhD dissertation, Lekan's research covered the related but not necessarily connected fields of robotics, control theory and machine learning and he seamlessly straddled all three fields by providing useful contributions that have earned him recognition. This is signified by journal associate editors that continually ask for him to serve as reviewer for submitted contributions to major journals and conferences in these fields. His dissertation work earned him many first-authored publications at high-impact avenues in robotics including ICRA, IROS, and WAFR among others. Since joining my laboratory, I have found him to be very dedicated to his research, collaborative and productive. The mentoring team he has assembled within the short span of time that he has been here at Penn speaks of his team-building and collaborative spirit and is indicative of his success as a potential independent investigator.

While Lekan's accomplishments alone would make him a much sought-after postdoctoral candidate, my impression of Lekan exceeds this. When he pitched his postdoctoral candidate job talk, I found him to be very knowledgeable about medical physics even though he is from a different background. He asked well-reasoned questions and it was clear that he had thoroughly investigated the field of robotics-based stereotactic radiosurgery (SRS) research and he had creative ideas for future research directions. In the little time that I have known him, I have found him to be very thoughtful, insightful and able to get things done. I am really excited about the project he has proposed, which addresses a fundamental question in the field of robot-based head motion correction in radiation therapy treatment procedures. The role that rigid robots play in active head motion control has been well-studied by my research group in recent years. Dr. Ogunmolu brings a carefully thought-through and well-organized research plan for improving the delivery of radiation dose with magnetic resonance imaging (MRI) in order to assure real-time imaging characteristics for tracking anatomical head and neck motion for MRI guided RT, dose reconstruction, as well as real-time image adaptation. This proposal covers expertise in the fields of continuum mechanics, control systems, motion planning and soft matter. It stands to reason that his highly regarded co-mentors consider him in good stead as an excellent researcher, given that they are respectively discipline experts in their own rights in these fields. I should mention that I gave high-level direction and minor edits while he developed this plan as well as 95

Supervision/Mentoring Plan: As a postdoctoral fellow in my laboratory, during his K99 years, Lekan will learn clinical setup procedures in stereotactic radiosurgery, intensity-modulated radiation therapy and linear accelerator calibration with respect to the cancer treatment in patients since he has not undergone this type of training before. In addition, together with Drs. Pappas, Pikul, and Turner, he will get mentored support in NSF-styled grants-writing and I will coordinate the NIH-styled grants-writing courses, webinars and seminars that he can attend on the Penn campus and Penn-partner Universities. This will make him well-rounded since his research straddles the fields of engineering and medicine. As his primary mentor, I will interact directly with Lekan from time to time, via scheduled weekly meetings and by continuing to run my anytime open-door policy so that he can seek the mentorship and guidance for achieving his career goals. My input will include helping Lekan plan experiments, direct the execution of his aims, help troubleshoot whenever needed, and guide him towards completing his manuscripts.

Career Development Plan: I will be responsible for approving the coursework he will be taking on the Penn campus necessary for his career growth. I will direct Lekan in giving research talks at seminars on the Penn campus at least twice a year. This will include GRASP lab seminar series, Penn Institute for Medicine and Engineering (IME) seminar series and the Penn Radiation Oncology xRT Invited Speaker Seminar Series. When it comes time to gaining independence, I commit to having him leave with all of the equipment he purchases in his K99 years. I am 100% committed to funding Lekan via my NIH R01 grant for robotic SRS for any aspect of his research that this K99 award may not cover. In addition, Lekan will attend at least one national/international meeting in radiation oncology per annum, namely the annual meeting of the American Association of Physicists in Medicine. The University of Pennsylvania has an Office of Postdoctoral Programs that organizes a number of workshops in grant-wiring, career development and responsible conduct of research that I will ensure Lekan attends as long as they are relevant to his career during the course of his training.

Transition Plan: As he matures in his project execution, I will gradually phase him towards the independent portion of this award by encouraging him to practice job talks in our research group meetings, coordinating his research activities with that of his co-mentors by having joint lab meetings at least once every three months, applying for faculty positions. I will allow him to work on a rotation basis in Drs. Turner, Pappas, and Pikul's labs for at least three days every calendar month in order for him to continue gaining excellent engineering expertise. I will ensure that he interacts with my faculty colleagues in engineering and medicine on the Penn campus, other members of my intellectually diverse research group, as well as medical doctors who work on various aspects of radiation therapy and SRS.

Lastly, I will write and provide annual evaluations of the Lekan's progress for the mentored phase as required in the annual progress report and I will do my best in transitioning him to an independent research position by guiding the him during the job search and negotiation process and by commenting on the R00 phase application.

Co-mentor Statement of support, George J. Pappas, Ph.D

I am very pleased to serve as a co-mentor for Lekan's training and research proposal with respect to developing a stably robust motion planner for head motion compensation in order to prevent motion artifacts and improve radiation precision to targets during magnetic resonance imaging.

I am the chair of Electrical and Systems Engineering and the UPS foundation professor at the University of Pennsylvania. I have made contributions to the design and control of cyber-physical systems (CPS) towards guaranteeing safety and security in autonomy. CPS systems encompass engineered systems that are developed from, and depend upon, the seamless integration of computation and physical components such as the MRI-LINAC RT system that Lekan has proposed. This project's scope falls within my purview as the potential advance of simultaneous MR imaging and precise irradiation without suffering motion blurs from intracranial patient head motions will help enable the capability, and resilience of current RT treatment procedures in clinics. I have read Lekan's biosketch, career, and research development plan and I am convinced that this project's focus and the excellent mentorship committee he has assembled is most suitable for someone of his skills, and abilities.

Throughout my career, I have sought to find ways of improving the analysis, design and control of such systems. Optimal controllers are the go-to controllers employed in motion-planning for solving most of trajectory optimization/motion planning problems because of their effectiveness. However, the efficiency of such planners is often left unresolved, given that motion planning is a PSPACE hard problem with increasing complexity as a robot's degree of freedom (DoF) increase. More often than not, such planners fail to find solutions in complex environments such as proposed in this project. Dr. Ogunmolu's proposed robot is a high-DoF robot mechanism that requires rethinking planning algorithms for head motion correction. By postulating to solve the overall problem in a hierarchy of sub-plans, and integrating a robust control Lyapunov function motion planning framework for finding collision-free paths within the robot manipulation constraints for a head motion path planning problem, I find the integration of Freeman and Kokotovic's inverse optimality via robust stabilization approach to be conceptually innovative and promising in impact. It has potentially significant advantages compared to current motion and task planners that are broadly used in the fields of robotics, car autonomy and molecular chemistry today. Since this part of Lekan's proposal (control) is my forte, I am committed to helping him successfully realize the goals he outlined in Aim II of this research plan.

In addition, since Lekan is committed to continue to apply cutting-edge control systems to robotics throughout his career plan, I will have a monthly conference meeting with him to guide him on the technical aspects of this project that relates to control as he makes progress on this project. He will also join my research group meetings which will enable him to connect with more faculty and researchers in the area. Awarding him this grant will create a rapid growth in his career path (in control systems). I am committed to providing him with the networking assistance at the flagship national and international control conferences such as the American Control Conference (ACC) and Conference on Decision and Control (CDC). Alongside Drs. Wiersma and Turner, I will help him navigate the grant-writing part of his proposed career development plan as we discuss and evaluate his training needs throughout this grant award period. Specifically, I will provide guidelines to him on NSF and AirForce/DoD CPS -type grants that will help him become a solid independent researcher in the coming independent years.

During my twenty year career in academia, I have mentored thirty doctoral and postdoctoral members of my group to successful careers in leading universities (Cornell, Oxford, Michigan, Purdue, Duke, UCSD, etc). Based on the proposed project and Lekan's outstanding background, I am very optimistic for similar levels of success.

In conclusion, I am excited to serve on Lekan's mentoring committee as well as helping him to solve this interesting problem. Awarding this grant to him will further improve the precision of aiming radiation to tumors while sparing healthy tissues in MRI-LINAC radiation therapy, and I am confident that the impact of this award will have broader applications outside of medicine given its holistic aims. As he continues to hone well-rounded medical physics and robotics research skills, he will be equipped for greater research responsibilities that have a positive impact on healthcare delivery to a wider population of patients. I am convinced that he is poised to initiate a fruitful future career in academic bioengineering research. Therefore, I recommend this proposed research project as a highly topical and important line of inquiry, and one to which he is well-suited to accomplish.

Co-mentor Statement od support, Kevin Turner, Ph.D

I am writing to confirm that I am happy to serve as a co-mentor for Dr. Ogunmolu's soft-robotic MRI-LINAC RT project, and to enthusiastically support his K99/R00 grant application. I am currently the Chair of the Department of Mechanical and Applied Mechanics (MEAM) at the University of Pennsylvania. I have advised 23 doctoral students and postdocs since I began my faculty career in 2005 and I strongly value the training of the next generation of promising young researchers, such as Dr. Ogunmolu, who are at the forefront of strong translational research efforts with potential for real-world clinical impact. My research addresses problems at the nexus of mechanics, manufacturing, and materials, with an emphasis on research questions involving small-scale systems and interfaces. Current research projects include work on novel sensors and soft robotic systems. Because of the overlap of my research with Dr. Ogunmolu's work, I believe that I am well-positioned to guide him on executing his research aims that include aspects of mechanics, materials, and sensors. Additionally, leveraging my academic administrative experience, including serving as Chair and Graduate Chair of MEAM at Penn, I am committed to mentoring Dr. Ogunmolu in his career development towards a faculty career while he is here at Penn. I have known Dr. Ogunmolu for about 6 months now since he contacted me about developing distributed sensors for the soft actuator component of this proposal. At our first meeting, it was evident that he was well-versed in the state-of-the-art for distributed sensing for soft robots as he easily articulated what other research groups have done, shortcomings of existing technologies, and how he thought that my expertise could help him on this project. Since then we have had several exchanges and I have found his approach to research to be rigorous, creative, and exciting. As his proposed research has a strong engineering component, I am committed to providing Dr. Ogunmolu with support in the form of technical guidance and facilities support during the execution of the K99 goals of this proposal. From a facilities standpoint, I will facilitate his use of equipment in my research group's lab, as well as MEAM facilities including the Rapid Prototyping and Additive Manufacturing laboratories. These laboratories have state-of-the-art equipment that are not available in the medical school such as tensile/compression testing machines, laser-cutting machines, and advanced 3D printers. To guide Dr. Ogunmolu in his transition to the independent phase of his career, I will arrange meetings with him at least once every three months where he will observe how I direct my research group's meetings, mentor graduate students and postdocs, and identify new research directions. These meetings will be in addition to interactions that I have him about his own research. I know having first-hand meetings in these group settings will be a valuable experience for him as he continues to define his career plan and research strategy. As Dr. Ogunmolu executes the aims of this project and prepares for a career as a faculty member, I commit to advising him on practice job talks, reviewing his application materials, as well as having him as a protege when I prepare NSF-styled research proposals. In addition, I will actively recommend him for seminars at Penn and elsewhere that will be beneficial for his career growth and his visibility as a researcher. Through my conversations with him and reviewing his biosketch, I am impressed by how much he was able to accomplish as a doctoral student and the breadth of his work. He comes across as someone who reads avidly and thinks deeply about his projects, which are strong indicators that he will continue to be an invaluable member of our research community. I consider Dr. Ogunmolu to be well-qualified for an academic research career from an engineering perspective because of his intellect, blend of hardware and software skills, communication skills, and creativity. The support and protected time that he will receive from this grant will aid him in becoming an independent researcher and a leading thought-leader in the area of his proposed research. I recommend Dr. Ogunmolu without reservations and look forward to serving as a co-mentor.

Co-mentor Statement od support, James H. Pikul, Ph.D

I am writing this letter to enthusiastically support Dr. Ogunmolu and his K99/R00 Pathway to Independence Award Application. Dr. Ogunmolu is a wonderful individual who combines excellence as a scholar, a passion to solve health challenges by applying engineering solutions, a bright and cheerful character, and leadership potential. I believe these qualities perfectly align Dr. Ogunmolu with the K99/R00 Pathway to Independence Award, as he will produce excellent fundamental research, realize important benefits for patients, and transition into a strong independent leader.

I have known Dr. Ogunmolu, who goes by 'Lekan', since the Fall of 2019 when he contacted me about collaborating on his project to stabilize patient heads during radiation therapy using soft robots. Since that time, I have had several conversations with Lekan and have been able to assess his competency as a researcher and vision for his proposed work, and I have been impressed. Lekan has shown a deep understanding of his field and also quickly learns new information, which makes him a great asset in cross-disciplinary research. Lekan has published work in the top robotics conferences, which shows his ability to plan and realize high quality research. I should mention that publication in these conferences, such as the IEEE International Conference on Robotics and Automation, is equivalent to publishing in a top field journal in the robotics community. This prioritization for conference publications is different than many fields, so I want to make it clear that Lekan has a strong publication record compared to other researchers at his level in the robotics community. Lekan's invited talks to Open Robotics, Stanford University, and University of Chicago show that he is being recognized for his contributions and is an emerging leader. Lekan has also mentored six students, including two master's theses. Overall, Lekan has a strong track record of research and mentoring success and a very promising trajectory that make him an excellent candidate for the K99/R00 Pathway to Independence Award.

I am the right mentor for Lekan because I can provide him with the technical advice required for his proposed research to succeed and I have recently started my own lab at the UPenn, so I have a breadth of recent and relevant experiences to share with Lekan. I am looking forward to discussing and supervising Lekan's experimental designs and professional development. As an example of my professional success as an Assistant Professor, I am mentoring seven graduate students, two post-doctoral scholars, three master's students (2 graduated), and twelve undergraduates. Fostering a creative research group with diverse experiences is important for me, which is why I have mentored seven female students and four underrepresented minority students. While growing my lab, my group and I have published 9 journal articles (One in Nature, several in 10+ IF journals), 5 refereed conference proceedings (one best paper award), and 3 patents applications. To fund this growth, I have led several successful grant proposals including three DARPA projects (one as PI, two as co-PI), an NSF Emerging Frontiers in Research and Innovation on soft robotics (PI), an NSF CAREER award (PI), and an ONR Young Investigator Program award (PI), which sum to total awards over $6,000,000. I have, additionally, contributed to my research community and University. I am leading the Formula-SAE Penn Electric Racing Team which placed 3rd in the nation last summer. I will apply my experience and accumulated knowledge as an Assistant Professor to mentor Lekan. In addition to mentoring Lekan to achieve his own version of success, I will introduce him to other faculty in my network whose work overlaps with Lekan's interest, including the four co-PIs on my NSF EFRI grant that seeks to understand fundamental problems related to the soft devices that Lekan will use.

In summary, I strongly support Lekan's application for the K99/R00 Pathway to Independence Award. He has the technical talent, experiences, and leadership to be a successful PI. This award will allow Lekan to realize his goals of applying engineering solutions and soft robotics to critical health problems, which will ultimately benefit many patients throughout his career.

Specific Aims

More than 1.8 million new cancer cases are expected to be diagnosed in the United States in 2020 out of which 606,520 Americans will die [1]. Along with chemotherapy and surgery, radiation therapy (RT) is an effective method of cancer treatment, with more than half of all cancer patients managed by RT having higher survival rates [2]. There now exists integrated magnetic resonance imaging (MRI) with linear accelerator (LINAC) RT for more precise irradiation. These offer unrivaled, online, and real-time treatment in comparison to legacy systems [10].

Given the consistency of head motion requirement for proper beam targeting in stereotactic radiosurgey (SRS) and highly conformal head-and-neck (H&N) RT, rigid head frames or thermoplastic face masks have been employed for keeping the patient static on a treatment couch. However, frames are uncomfortable and highly invasive – causing poor patient compliance and clinical inefficacy; and masks reduce dose targeting accuracy – since mask flex causes drifts which in turn affects dose targeting accuracy. Robot mechanisms [11–13] for real-time head motion correction that have been investigated are made out of linear actuators and rigid metallic components and these are incompatible with MR. I have previously demonstrated the feasibility of soft manipulators for head motion correction in RT treatment planning in lower task space dimensions. As the quality of MR scans are limited by head motion artifacts during imaging, ***my leading hypothesis is that MRI/LINAC-compatible soft robots can to provide 6-DoF head motion correction in precise tumor irradiation tasks***. Our team, comprised of material mechanics, medical physics, control systems and soft matter experts, will address these issues via the following specific aims:

K99 Aim I: A Distributively-Innervated, Non-magnetic, and Radiation-Transparent Soft Robot and Actuator.

K99 Aim I.A: Soft Actuators Fabrication: We will fabricate fiber-reinforced actuators to constrain deformation along specific Eulerian directions in order to simplify control. Made entirely out of radio-transparent and non-metallic parts, these actuators will be adaptable under MR coils and the large tubular MR magnets, and hence suitable for patient head motion compensation in emerging MRI-LINAC treatment procedures. A hierarchical sensing and control scheme is proposed: the soft actuators will deform in a manner similar to the fast activation ($\leq$2secs) of, for example, the papillae of the octopus, and will have rich surface innervation (e.g. similar to the cuttlefish skin) to aid rich system state perception; this will enable accurate feedback control of the pressurization within the actuator's air chambers. *This will demonstrate for the first time that soft actuators can excel at precise deformation schemes that are safe and compliant for real-world medical robot applications.*

K99 Aim I.B: Mechanism Synthesis: Phantom-based Control Experiments. We will develop a fully parallel soft robot capable of providing head manipulation along 6 DoFs by using the developed actuator in *K99 Aim I.A*; the soft robot will be adaptable to pre-existing LINACs. A soft robot mechanism will be constructed, able to fit under the MR coils and able to (re)position 3D printed phantoms as needed during treatment. Head motion will be measured by a 3D surface imaging sensor and feed it to the motion planner's head position feedback controller. Patient safety systems based on automated treatment beam shut off will be incorporated into the finished design.

K99 Aim II: To Develop a Multi-Modal and Robustly Stable Optimal Motion-Planner.

Our preliminary results show the need for a safety-aware head manipulation motion planner for executing optimal collision-free paths between transition modes such that manipulating the patient's head does not expose normal brain tissues to high radiation doses. We will find a robustly stable and optimal head motion trajectory for moving the head from a start location $\xi_i \in \mathbb{SE}(3)$ to a goal location $\xi_f \in \mathbb{SE}(3)$ safely. The current convention in robotics is to use layered planning whereby search is hastened by solving a planning problem at various abstraction levels. However, such planners often miss stability-guarantees in their optimal path formulations hence resulting in paths that are not stably robust. *We will address the current gap in knowledge in geometric manipulation under manifold constraints that leave out stability analysis by leveraging an asymptotically stable robust control Lyapunov function optimally stable motion-planning feedback controller that generates optimally-robust single modes that guide head motion transitions in the presence of constraints in the head-robot workspace.*

R00 Aim: To Validate the Mechanism on Phantoms and Healthy Human Subjects.

The developed motion-planner in *K99 Aim II* will be used in the real-time head motion correction in phantom and healthy human volunteer MRI-LINAC RT experiments. An end-to-end testing with 3D-printed head phantoms containing dosimetric gel will be used to evaluate 3D radiation dose accuracy for both single and multiple target SRS plans. A 20 volunteer study with a mock radiation beam will be conducted in a clinical environment to verify that head pose can be safely controlled to within ≤ 0.5mm and $\leq 0.5°$ statistical endpoint for greater than 95% of the treatment time.

After the execution of these aims, this project will demonstrate that soft robotic MRI-LINAC RT is ready for widespread clinical deployment. With its transformational clinical potential, this system will enable the availability of novel precision irradiation in combined MRI and LINAC RT for more patients, improve therapeutic outcomes, reduce patient invasiveness, reduce current setup times from hours to minutes, and will be compatible with thousands of pre-existing LINACs.

Future Plans: ***I plan to expand this project into my own independent research laboratory where I will study to design and control soft robots for broad biomedical engineering applications in human-robot interfaces.***

Candidate Information and Goals for Career Development

Doctoral Research Background

In 2014, I enrolled at the University of Texas at Dallas where I collaborated with medical physicists at the University of Texas Southwestern Medical Center in fabricating and controlling a soft robot for the real-time patient head motion correction in radiation therapy (RT). This project resulted in three first-authored publications at top robotics conferences (IROS, which has the second highest impact factor for robotics publications). In the course of time, my UT Southwestern advisor (Steve Jiang) requested that I join his lab for the rest of the duration of my PhD. There I continued to work on other medical physics problems such as building a robust database of clinical dose based on past doctor's prescriptions; this was used by our research team for RT treatment planning studies. I also developed an automated framework for solving the non-convex beam orientation optimization problem in RT; as well as assist other postdocs and graduate students in the lab. Based on my dose calculation work, up to ten top medical physics and robotics[1] journal publications have resulted from this research group. Of those, I am a first author and a co-author on two of those research papers. In addition, other publications were presented at the American Association of Physicists in Medicine's annual meetings, International Conference on Robotics and Automation (ICRA) and the Intelligent Robots and Systems (IROS) conferences -- the two top robotics conferences in the world. In the last year of my doctoral studies, my various research outputs culminated in invited talks at Stanford's Department of Energy Resources, and Open Robotics (the largest open source for robotics foundation in the world). After graduating in 2019, I joined Dr. Wiersma's laboratory as a postdoc.

Postdoctoral Research Background

Currently in my postdoctoral duties, I work on problems spanning conceptualization of new hardware and software tools for improving the treatment planning process in cancer radiation therapy. My work has made meaningful impact in disciplines within and outside medicine, with citations from government and higher learning research institutions across the globe. Since Starting my postdoc in the Wiersma group, I have been working on the motion-planning algorithm for the Wiersma Group's 6-6 Stewart-Gough platform, phasing out the buggy codebase for motion-compensation to a modular and simplified python code, as well as started building a full-fledged 6-DoF real-time soft robot motion compensator in emerging magnetic resonance imaging (MRI)-linear accelerator(LINAC) RT technologies. Since joining Dr. Wiersma's lab last Fall, my work has resulted in two first-authored research dissemination at the 2020 joint annual meeting of the AAPM and COMP -- one of these works, based on the soft robot mechanism for MRI-LINAC being proposed herein was selected for a talk at the J.R. Cameron-J.R. Cunningham symposium. Another paper was accepted and recently presented at ICRA 2020.

My next research goal is to develop a comprehensive motion planning framework for both of our lab's robot platforms for head motion correction. Leveraging preliminary work on exploring implicit spaces in constrained sampling-based motion planning, I want to develop a robust control Lyapunov function scheme in ensuring the stability and manifold-constraints' satisfaction of feasible collision-free paths during head motion correction in RT or emerging MRI-LINAC RT techniques. Afterwards, I will validate this motion planner on mine and Dr. Wiersma's robots.

Career Goals and Objectives

Training Objectives

I require at least one more year of mentored research for the following reasons. While a doctoral student, I worked on three projects and between three advisors, namely (i) the development of the soft robot mechanism with my primary doctoral thesis advisor; (ii) guaranteeing the robustness of deep reinforcement learning policies with my UT Dallas co-advisor, Dr. Tyler Summers; and (iii) improving the solve time of the non-convex classical beam orientation optimization problem in intensity modulated radiation therapy (IMRT) -- with my UT Southwestern advisor, Dr. Steve Jiang.

These projects left me stretched too thin that my contributions to science were not as impactful as I would like them to be. I produced top-scholastic papers at major high-impact conference venues but had little time to turn

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[1] My work was presented at the 13th algorithms for robotics workshop in 2018 and subsequently published in the Springer's Proceedings in Advanced Robotics book in 2019.

my work into journals. To properly put things in perspective, I have only spent two years on this soft robot project, which has not been long enough to establish research independence as well as make me competitive on the job market. I need to learn from the experts on my mentoring so I that can demonstrate further novel contributions to soft robot sensing, modeling, and control. I want to spend at least one more year at Penn because these assembled team of mentors would be invaluable and critical in further honing my intellect and in me establishing an independent career.

Mentored Phase Objectives

Firstly, I want to achieve 6-DoF control of head motion correction using the robot mechanism I propose. I will develop the motion planning algorithm that is safety-aware for executing optimal collision-free paths between head motion transition modes such that the patient's head motion path does not expose normal brain tissues to high radiation dose. Therefore, I will closely work with Dr. Pappas, meeting with him at least once a month, in developing the robust control Lyapunov function motion planning problem. As he is an expert in control systems design, I will continually seek his feedback as I develop this algorithm. Stakeholders in the field of motion planning will be regularly consulted to ensure that such the proposed hierarchical multi-planning system generates exponentially stable paths in the underlying dynamic system. I also plan on taking the motion planning course in the School of Engineering to further enhance my training in this regard. **Secondly**, I want to develop a distributively-innervated, non-magnetic, and radiation-transparent fiber-reinforced soft actuator and then use it in building the soft robot. This aim will scale previous soft actuator designs in my PhD to a full 6-DoF soft robot capable of providing head manipulation along 6 DoFs and will be compatible with pre-existing LINACs. As the mathematical model of the actuators span continuum mechanics and topics in adhesives, I have sought the mentorship of Dr. Turner who has assured me of an open-door policy whenever problems come up in this stage of the design. He will connect me with other postdocs in his research group and be freely available in order to hasten the development of the model and adhesives for this component of the project. He will also guide me in continuum mechanics courses I will be taking on the Penn campus. Dr. Pikul's expertise comes in in this regard as he directs the hardware build of the robot mechanism. He will leverage his soft matter expertise in supervising this phase of the project. **Lastly**, Penn campus offers a variety of seminars and workshops on a weekly basis that covers the aspects of this proposal that will be highly beneficial for my research. I will attend seminars as highlighted in the “project training activities” table.

Independent Phase Objectives

My goal is to transition a tenured principal investigator role preferably at an R1 research institution, within a year or two, where I can continue to solve problems in emerging medical robotics fields that have positive clinical effect on real-world patients. This proposed research will be the foundation of my future research funding. As soon as I accept a tenure-track position, I plan to apply for the NSF CAREER award, NIH New Innovator Award and Pew Biomedical Scholars Award. This will prepare me for my first R01 grant submission to the national cancer institute. In the independent years, I will recruit human volunteers and test the motion-planning algorithm and soft robot mechanism in real-time, first on phantoms and then on healthy human volunteers, in an MR machine, RT treatment machines, and stereotactic radiosurgery (SRS) protocols.

Training Activities Plan During Award Period

Below, I have outlined a training plan necessary to accomplish my aims and to gain the necessary skills required to be an effective and independent research investigator, teacher, and mentor as an assistant professor. Additional coursework, campus seminars participation in my research discipline areas, and consultation with my mentorship committee that will enhance my training experience are included as well as a mentored job search that will be critical to my future success in securing a faculty position. Detailed training activities are delineated in the “Project Training Activities” table.

Project Training Activities

ACTIVITY	Modality	Specific Activities	ACTUAL START	ACTUAL DURATION	PERIODS				
					Y1	Y2	Y3	Y4	Y5
Motion-planning synthesis for soft robot	Seminars	Penn GRASP Lab Seminar Series	2020	2Y	X	X			
Extend knowledge of manifold constraints in implicit places to motion planning in soft robotics		Penn IME Seminars and Events	2020	2Y	X	X			
Prove stability analysis of motion planner for soft robot-head system using the inverse stability from robust planning paradign	Coursework	Motion Planning	2021	0.5 Y		X			
Apply these results to K99 Aim I of Research Strategy	Training	Mentor: Weekly Meeting	2020	2Y	X	X			
		Co-Mentors: Monthly/Quaterly	2020	2Y	X	X			
Continuum-Mechanical Model and Actuators Construction	Seminars	Penn Laboratory for Research on the Structure of Matter (LRSM) Seminars and Lectures	2020	2Y	X	X			
Receive trainng in continuum mechanics and soft matter fabrication technologies		Penn XRT Invited Speaker Seminar Series	2020	2Y	X	X			
Conduct research specified in Aims II and III of K99 research strategy	Coursework	MEAM 514: Design for Manufacturability	2020	0.5 Y	X				
		MEAM 630: Advanced Continuum Mechanics		0.5 Y		X			
	Training	Mentor: Weekly Meeting	2020	2Y		X			
Apply these results to K99 Aim II and III of Research Strategy		Co-Mentors: Monthly/Quaterly	2020	2Y	X	X			
Career Development	Seminars	Penn Laboratory for Research on the Structure of Matter (LRSM) Seminars and Lectures	2020	2Y	x	X			
Effective comunication skills		Penn XRT Invited Speaker Seminar Series	2020	2Y	X	X			
Research group management	Coursework	Courses in teaching/speaking	2020	0.5 Y		X	X	X	
Faculty job search/interviews		Courses in leadership/people management		0.5 Y		X	X	X	X
	Training	Manuscripts and grants-writing	2020	2Y		X	X	X	X
		Serve as associate editor for robotics/control/medical physics journals and top conferences	2020	2Y		X	X	X	X

1 Research Strategy

1.1 Significance

Around the world, cancer is a burden to rich and poor nations alike. The International Agency for Research on Cancers estimates that the highest rates of cancer incidence over the coming decades will fall on low- and middle-income countries [14]. In 2020 alone, more than 1.8 million new cancer cases will be diagnosed in the United States. Out of these, almost 607,000 people are expected to die [1] with cancer gulping about 4.2% of overall health care spending. Radiation therapy (RT) can be an invaluable single cancer treatment modality: it is cost-effective (accounting for only 5% of the total cost of cancer care [15]), and it is more effective given its advanced mode of radiation production and delivery. By shaping the geometry of high-energy radiation it allows radiation escalation to tumor targets while simultaneously sparing organs-at-risk (OARs). The importance of RT is underscored by the fact that half of all cancer patients undergo RT treatment during the course of their illness – an estimated 40% of all curative cancer treatment modality are performed with RT [16]. In major RT treatment modalities today, computed tomography (CT) is used to plan dose delivery. However, CT images have low soft tissues contrast which in turn affects the exposure of OARs to toxicity when used for treatment planning.

Magnetic resonance imaging (MRI) of cancers of the brain, and head and neck (H&N), however, can provide exceptional soft tissues contrast and allow greater delineation of cancerous from non-cancerous tissues. There now exists integrated magnetic resonance imaging (that offers superior soft tissues visualization) with linear accelerator (LINAC) RT (that offer unrivaled, online, and real-time cancer RT treatment) [10, 17]. Some of these systems have been commercialized e.g. Elekta AB's (Sweden) 1.5T diagnostic imaging system [10], Viewray 's MRIdian system [18], or the MagnetTx's (Canada) Aurora RT system [19] among others. However, producing high quality MRI images is challenging as patient motion often occurs during image acquisition leading to artifacts and poor image quality. For combined MRI-LINAC systems [17, 20, 21], the effect of random and involuntary patient motion introduces motion artifacts which can lead to incomplete irradiation of the tumor target and exposure of healthy tissues to radiation toxicity. These artifacts in image collection lower the accuracy of online and real-time precise radiation dose delivery, which in turn affects clinical efficacy.

Therefore, to avoid intracranial patient motions, it is paramount to keep the patient accurately positioned on the treatment table, especially in applications aimed at more precise irradiation such as in head and neck cancers. The importance of accurate patient positioning is further underscored by accumulating evidence that patient displacement and collimator and gantry angle misalignment during RT showed high sensitivity to small perturbations: a 3-mm error in anterior-posterior direction caused 38% decrease in minimum target dose [22]. Thus, to automatically align patient motion during RT, state-of-the-art clinical approaches use the Brown-Robert-Wells (BRW) frame [3], a mask, or emerging robotic head motion compensators to stabilize patient head motion on the treatment couch.

1.1.1 Known roles of frames in cranial positioning compensation

In frame-based approaches, a metal ring (the Brown-Robert-Wells frame) is attached to the patient's skull using screws, and then bolted to the treatment table, Fig. 1a. Discomfort and severe pain often results from long hours of minimally invasive surgery where the skull is fixed with pins for head immobilization during stereo-tactic radiosurgery (SRS). The invasiveness and discomfort associated with the frame are a principal cause of poor patient compliance and poor clinical efficacy. For some patients, frame placement is not feasible due to extreme cranial anatomy or prior surgical bone flaps. In cases where multiple radiation therapy (RT) deliveries are needed, patients cannot be subjected to daily attachment and removal of the frame.

(a) The BRW SRS Frame [23] *(b)* Frames with MRI Coils *(c)* Wiersma SG-Robot [24]

Figure 1: Existing frame and mask (a-b), and frameless and maskless robotic systems (c).

1.1.2 Known roles of masks in cranial positioning compensation

These limitations of frames have spurred clinics to start using thermoplastic face masks. Here, a porous mask is deformed to fit the geometry of the patient's head and neck region and then fastened to the treatment table. As the mask is flexible, during the course of treatment, it loses its firmness around the patient so that the inaccuracy of dose targeting is inevitable. The flexibility of masks has been identified to cause a drift of up to 6mm. This is unacceptable given the AAPM TG-42 positioning accuracy guidelines that specify < 2 mm accuracy [25]. Changes in the mask's physical texture from repeated application and shrinking, Fig. 1b, can also lower treatment accuracy. These inconsistencies are not suitable for deep tumors located nearby critical structures such as the brain stem or for newer treatment modalities such as single isocenter multiple-target SRS, which are highly sensitive to rotational head motions. Even so, conventional LINACs used at most cancer centers are insufficient for the high geometric accuracy and precision required of SRS for isocenter localization [26].

1.1.3 Known roles of rigid robots in positioning compensation

To overcome these issues, explorative robotic patients' cranial positioning research have studied the feasibility of maintaining stable patient cranial motion consistent with treatment plans. For example, the Wiersma Lab's Stewart-Gough (SG) platform [11, 27, 28], illustrated in Fig. 1(c), achieves ≤ 0.5mm and $\leq 0.5°$ positioning accuracy 90% of the time. It is constructed as a 6-6 SG platform out of linear actuators, electric motors and rigid metallic components. While effective at head position compensation in SRS treatment procedures, it is not adaptable for new MRI-integration with LINAC RTs that offer better real-time soft tissues delineation for a precise irradiation. With the potential to better aid clinical accuracy in SRS-based systems when commissioned, these systems are not suitable for the emerging MRI-LINAC machines. This is because they utilize rigid metallic components, electric motors and linear actuators which are not suitable for the large tubular magnets of the MR machine: they interfere with the magnetic fields of the MR machine and have been known to lead to patient fatality or significantly damage the MR machine when clinicians have been careless about bringing metallic materials into the treatment room [5].

1.1.4 Hypothesis

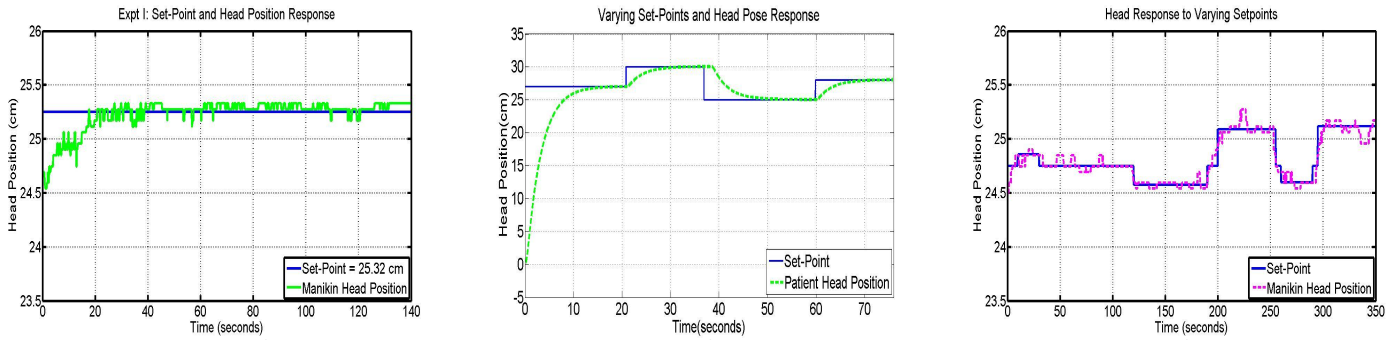
Existing immobilization devices, Fig. 1a,&c, are not suitable for this because of their electro-mechanical parts that introduce safety concerns. An asymptotically stable in the large and optimal motion-planner can find collision-free paths that satisfy head motion constraints and resolve the abnormalities inherent in current controllers used in head motion correction systems [9, 11, 12, 27]. Therefore, **we hypothesize that non-magnetic, non-radiation attenuating soft robots integrated with MRI/LINAC-coils operating under a robustly optimal and stable task and motion planner can provide the 6-DoF head motion correction necessary in precision RT treatment procedures to serve as a viable alternative to current mask-based as well as frameless and maskless robot-based cranial manipulation systems**. We will test this leading hypothesis to see if 6-DOF target motion of a patient is ≤ 0.5 mm and $\leq 0.5°$ for greater than 95% of the treatment time using MRI imaging for soft robot-based motion compensation.

1.2 Innovation.

My work was the first to demonstrate the feasibility of vision-based 3 DOF control of soft manipulators for cranial motion management in RT [6–9]. (i) The newly proposed mechanism is made entirely of no metal (hence not susceptible to magnetic fields) and is radiation-transparent so that it is compatible with MRI-LINACs RTs and SRS. It would be compatible with all 15000+ pre-existing LINACs worldwide and implemented as a standard treatment table modular accessory which avoids costly room modification or re-engineered equipment. With an inexpensive cost, it has potential to bring state-of-the-art RT methods to developing nations with older LINAC technologies. (ii) Increased clinical efficiencies: Its little patient invasiveness, and quick-connect, quick-disconnect modularity on a couch – important for patients with varying cranial anatomy – will ease the logistical setup of current immobilization and maskless robotic systems. Currently, total in-clinic treatment times can range from 6–8 hours. Soft robotic MRI-LINACs will significantly minimize setup complexities; the time required to perform SRS as a neurosurgeon is no longer required for frame placement or the construction of specialized thermoplastic masks. Instead of hours, treatment setup time will be reduced to a few minutes, as the patient lies down and the robot quickly adjusts to bring the intracranial target to the correct position. (iii) This mechanism can be adapted to confined spaces under MRI coils (see Fig. 1b) given its compactness, and light weight.

To our knowledge, **no currently-available technology exists today that can perform real-time head position stabilization *without dose attenuation* in an online, real-time fashion whilst guaranteeing patient safety similar to our proposed MRI-LINAC non-magnetic and radio-transparent soft robotic RT positioning system**. The advanced image guidance from an MRI scan will improve positioning accuracy and irradiation efficacy via a real-time $\mathbb{SE}(3)$ motion-planning control that finds the best 6D trajectory in each head motion transition mode so as to minimize exposure of healthy brain tissues to radiation and adapts to non-rigid body response between the robot and patient's head.

Upon successful completion, this soft robot will be used for active head motion stabilization within an MR machine. It will be adaptable for use in SRS, standalone MRIs, emerging MRI-LINAC technologies, and brain as well as H&N RTs. It will provide accurate RT beam targeting as well as preventing patient motion MRI imaging artifacts. This technology will improve therapeutic outcomes, and eliminate patient invasiveness.



(a) Head response to fixed setpoint. *(b)* Head trajectory follower simulation *(c)* Head trajectory follower experiment

Figure 2: Steady state head stabilization. Reprinted from [7].

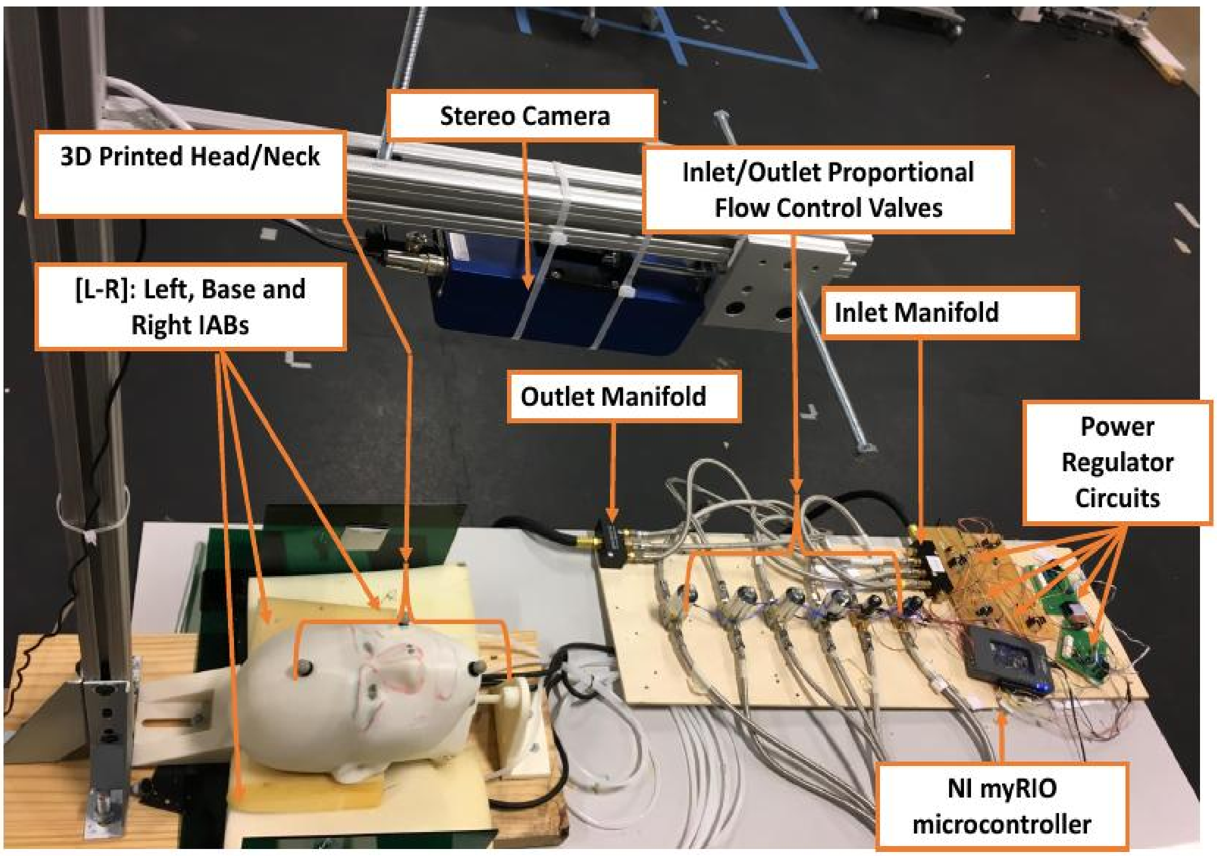
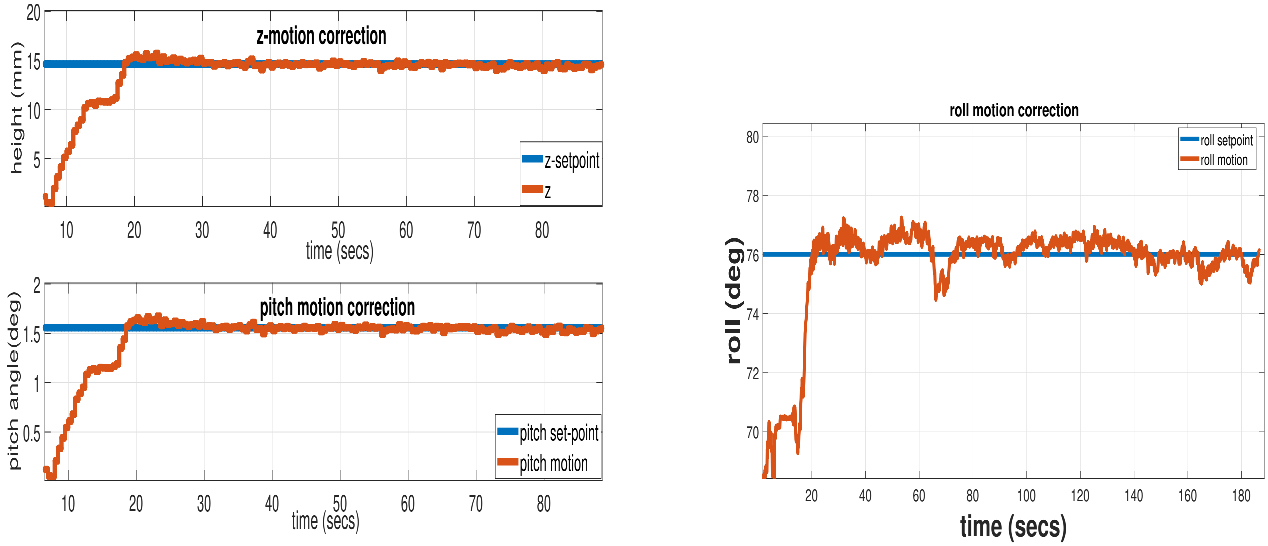


Figure 3: Three DoF Testbed. Reprinted from [9].

1.3 Approach.

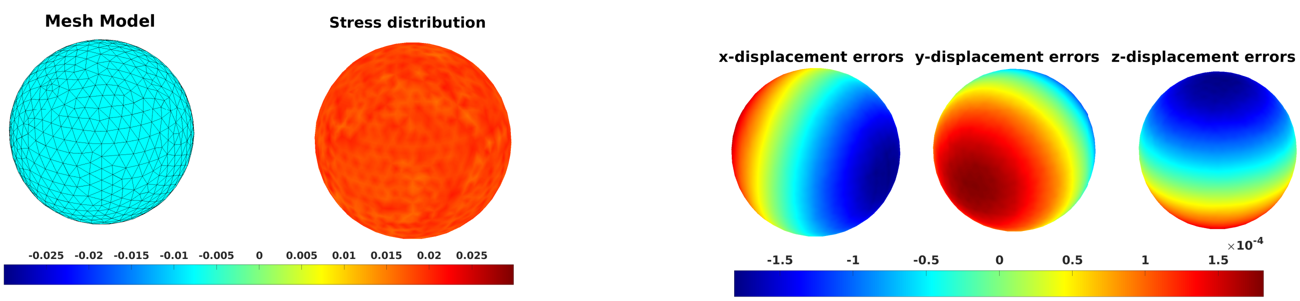
1.3.1 Preliminary Work

My preliminary work on soft manipulators for patient head motion compensation in RT shows that non-magnetic and radiation-transparent soft robots can compensate head motion within the submillimeter and subdegree accuracy requirement of AAPM-task group 42 by up to 3 DoFs [6–9]. For example, in a cascaded PID-PI controller loop, I showed head motion correction for setpoint- and trajectory-following to be accurate within ≤ 0.5mm for a task of lowering or raising the head on a treatment table [7], shown in Fig. 2. Furthermore, Fig. 3 illustrates the testbed I used in generating the 3-DoF control results of Fig. 4. The setup consists of a phantom with a neck simulator that models the ball joint in the human torso. A vision-based 3D sensor acquires the face's point cloud in real-time, which is then processed for features-extraction and the 6D coordinates of the head (here using the tip of the nose) are transmitted to a microcontroller (National Instruments®myRIO); the myRIO then regulates the flow of compressed air into a set of proportional solenoid valves. The amount of air within the set of inflatable



(a) Z and pitch motion correction. *(b)* Roll motion correction.

Figure 4: Convergence of head motion to steady state along 3 DoFs. Reprinted from [9].



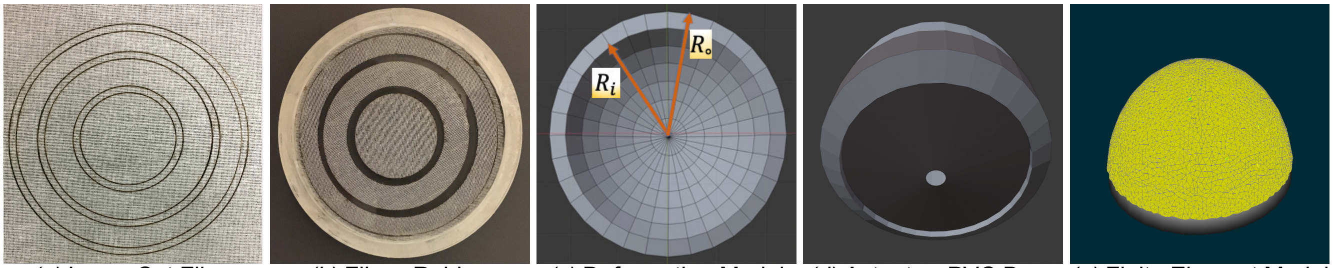
(a) **Left**: Mesh model. **Right**: Stress distribution post-defomation. *(b)* Displacement errors along x, y, z coordinates.

Inputs					Outputs		
C_1	C_2	$R_i(mm)$	$r_i(mm)$	$R_\circ(mm)$	$r_\circ(mm)$	$P(psi)$	ΔV
$1.1e4$	$2.2e4$	2.7	3	3	3.3	$.76$	$\approxeq 0$

Figure 5: Volumetric Deformation of a Soft Actuator (Expansion). Reprinted from [30].

air bladders (IABs), in turn raise, lower, or tilt the head on the mock treatment table. The dynamics of the head interaction with the IABs and air pressure supply were carried with a lumped prediction error model [29]. This model was then used in a controller that leveraged indirect model reference adaptive control with optimal state regulation in order to ensure the head follows set trajectory through steady-state [9]. Some of these results are reprinted in Fig. 2 and Fig. 4 respectively.

Now, in a new class of soft actuator designs, and contrary to stochastic system identification techniques I used previously [7–9], we can now specifically regulate volume fractions within the IABs as well as accurately control their spatial deformations based on specific nonlinear elastic deformation relationships [30]. Being continuum, compliant and configurable (C3) for manipulation tasks, we recently demonstrated in control experiments that they are well-capable of providing patient head motion compensation [24]. Contrary to remote-controlled airbags that have been used in upper mandible and head manipulation [31], our actuators deform based on their material moduli, compressed air pressurization and incompressibility constraints when given a reference trajectory. To our knowledge, ours are the first to explore C3 materials as actuation systems for cranial manipulation in robotic radiotherapy. Deforming based on a prescribed internal pressurization, their surface displacement errors are accurate to the order of $< 1.5 \times 10^{-}4$mm [30]. These results are reprinted in Fig. 5 where a spherically-textured soft actuator was prescribed to deform from an initial internal radius, $R_i = 2.7$mm from the reference configuration to $r_i = 3.3$mm in the current configuration. Our derived constitutive relation between the applied pressure and the radius of the actuator suggests a pressure of 0.76 psi was required to realize this deformation. The charts



(a) Laser-Cut Fiber *(b)* Fiber+Rubber *(c)* Deformation Model *(d)* Actuator+PVC Base *(e)* Finite Element Model

Figure 6: Soft actuator fabrication procedure.

of Fig. 5 illustrates the response of the actuator based on a prescribed pressure, where C_1 and C_2 are appropriate material moduli. Notice a displacement error of 1.5×10^{-4} along the rectangular Cartesian coordinates and a near-zero volumetric change$i.e.$ $\Delta V \approxeq= 0$. This shows that with *highly accurate pressure sensors*, and equipped with properly calibrated proportional solenoid valves, we can regulate the air within a soft actuator's chamber so that specific and highly precise deformation behaviors are realizable for consumer soft actuators.

1.3.2 K_{99} Aim I: A Distributively-Innervated, Non-magnetic, and Radiation-Transparent Soft Robot and Actuator.

Rationale: While the design of Fig. 3 is relevant to head motion control on an RT treatment table, it is not a complete motion correction system owing to its underactuated characteristics: it is only able to correct motion for up to three DoFs. Motion of the head occurs along six DoFs and they are not independent.

Aim I.A: Soft Actuators Fabrication: Iterating further on my previous designs [6, 8, 9], we now propose a new class of C3 soft actuators [30, 32, 33] as the composition of a non-magnetic and radiation-transparent soft robot for use in MRI-LINACs to further aid dose delivery precision. The component soft actuators are planar and circular in their reference configuration. Upon compressed air actuation, they deform along their radial direction (see computer model in Fig. 6) based on the physical constraints baked into the elastomer-fabric matrix. This actuation design is inspired by the behavior of the skin papillae of certain Cephalopods (octopus, cuttlefish, bivalves and mollusks) which can transform their physical texture from 2D to 3D in less than 2 seconds [34, 35]. The actuators exhibit a radially symmetric deformation and are constrained along their circumferential axis under pneumatic actuation based on their novel design. There exists no electrical wirings or embedded electronics to assure that the actuators reach a desired configuration.

Procedure.

I. Soft Actuator Design: Here we describe our preliminary work on the actuator fabrication as illustrated in Fig. 6. A thin-layered fabric is laser cut into circular patterns (Fig. 6a), the cut meshes are removed and laid onto uncured silicone (Fig. 6b) which has been poured into a mold. We further add a silicone topcoat layer to the fabric before we allow it to cure at room temperature. Upon low pneumatic pressurization, the cured rubber deforms, obeying a Circumferentially-COnstrained And Radially Stretched fiber-Elastomer (CCOARSE) property [36] (Fig. 6c). The soft robot, after cure, is laid onto an impact-resistant, low-temperature rigid PVC insulation foam sheet, encased in a carbon fiber material. This aids radiation transparency (Fig. 6d). The finite elastic deformation mesh model of the soft robot for simulation purposes is shown in (Fig. 6e). This proposed fabrication method allows us to rapidly iterate different designs using compressed low air pressure (1-15 psi) that is (i) cheaply available, (ii) environmentally-friendly, (iii) avoids electrical wirings, (iv) is lightweight, and (v) inviscid which will make the soft robot adaptable for MRI-LINAC systems – creating a clean and safe human-robot workspace.

II. Pneumatic System Design: We now describe ongoing work on the integration of the soft actuator design proposed above with the rest of the pneumatic actuation system. This system is illustrated in Fig. 7. A compressed air canister supplies air at a fixed pressure (e.g. 15 psi) through a firm polyurethane air tubing into a 4-20mA output-M12 pressure transducer plug connection. The outlet of this pressure transmitter conveys the airflow into a proportional solenoid valve which then leads to the inlet air connector of the soft actuator mechanism. The electronic regulating circuit of Fig. 7 is a standard current source circuit that varies the air flow rate within the proportional valve by adjusting the current flowing through its shunt resistor. In addition, a venturi pump proportionaly removes air to regulate volume within the actuator so that the pressure differential maintains head along a setpoint or follow a varying trajectory.

III. Preliminary Actuation Experiments: We now describe preliminary experiments that reproduces deformation behavior similar to the spikes observed in the skin papillae of the Octopus. We cast silicone from Smooth-On Inc's dragon skin (475 psi tensile strength and 10A shore hardness) and reinforce the elastomer with fabric material, thus imposing the CCOARSE property by constraining the circumferential expansion of the elastomer and exerting a radially symmetric stretch as shown in the bottom row of Fig. 8. This considerably simplifies the deformation's dynamical model [33]. Two different designs are shown in Fig. 8. The two leftmost images indicate the behavior of the elastomer-only actuator upon pressurization while the

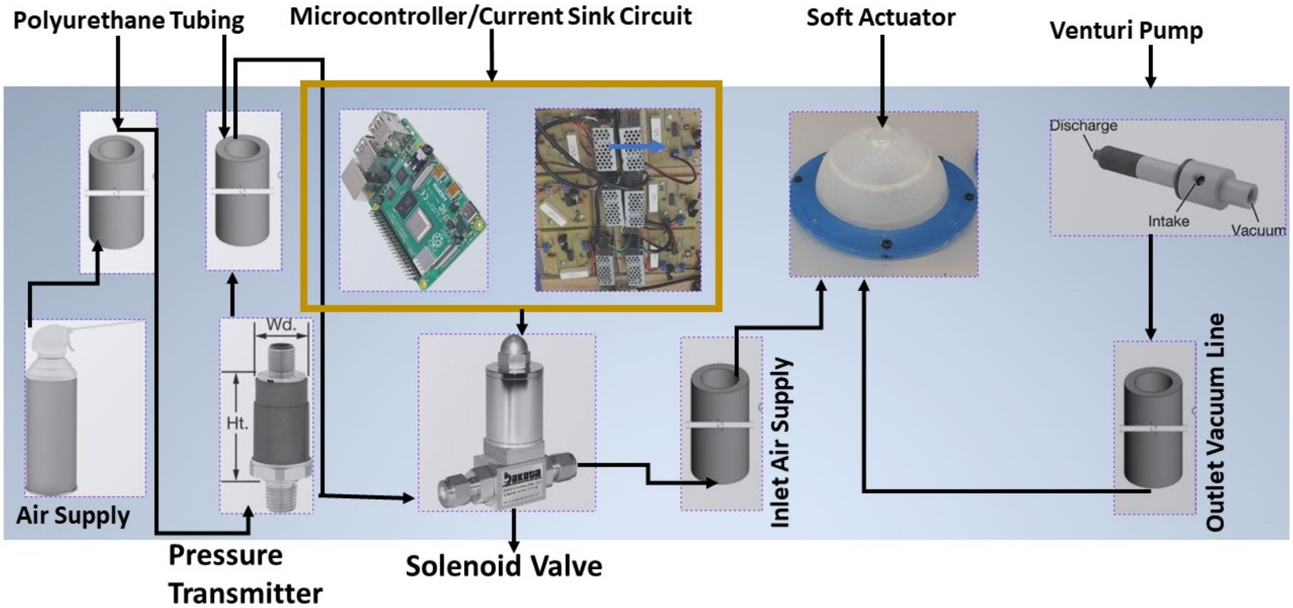


Figure 7: Actuator deformation control scheme.

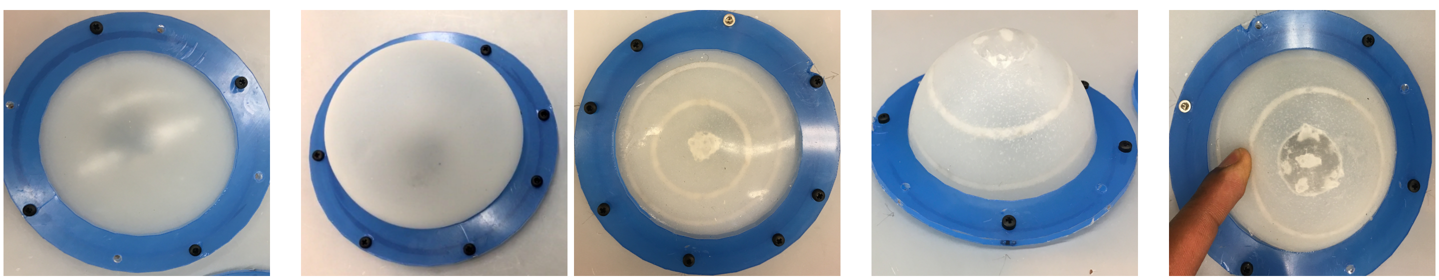


Figure 8: Deformation of elastomer-only and elastomeric-fiber actuators.

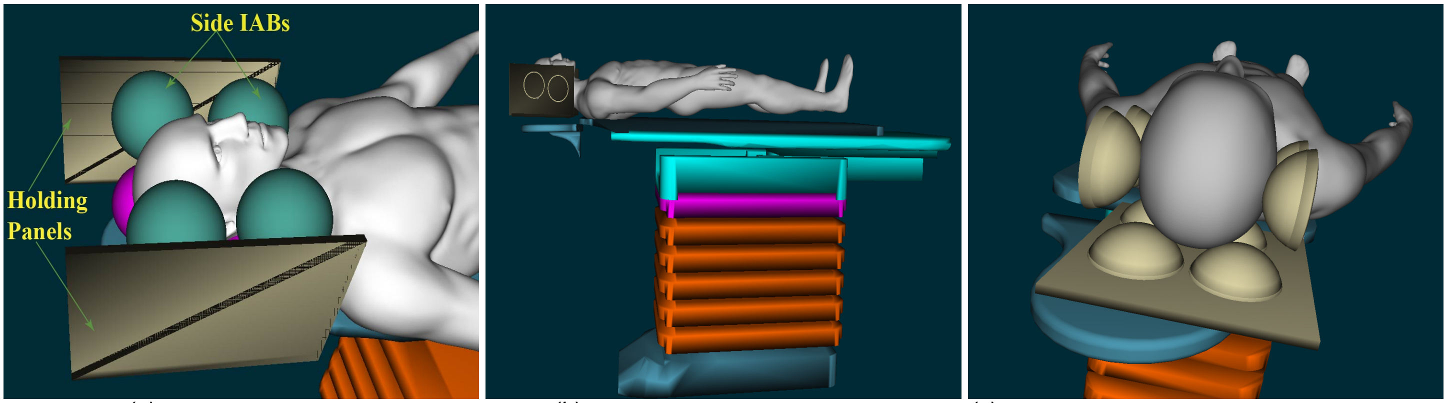
remaining images signify the elastic behavior of the fiber-reinforced actuator. As seen, the elastomer-only material exhibits a circumferential as well as radial bulge while the fiber-reinforced ones only deform along the axial direction. We can generate a full *Gaussian deformation* and return to the reference planar configuration in 2 seconds (see more images and videos in scriptedonachip.com/soro) similar to the spikes produced by the skin papillae of the Octopus. These quick Gaussian spikes will be useful for rapid head motion correction in MRI-LINACs. The soft compliance and tensile strength of this silicone material make it well-suited for treatment procedures where non-magnetic and radiation-transparent components can boost stereotactic precision as well as improve tumor control in MRI-LINACs.

IV. Flexible Piezoresistive Distributed Sensor Integration: In a recent formulation [30], we mapped the relationship between the applied pressure to the deformed radius of a soft actuator using the standard Mooney-Rivlin formulation [37,38]. Suppose that C_1 and C_2 are appropriate material moduli for the soft actuator, then the applied pressure in the internal walls of the actuator is given by the relation

$$P(r) = \int_{r_i}^{r_\circ} \left[2C_1 \left(\frac{r}{R^2} - \frac{R^4}{r^5} \right) + 2C_2 \left(\frac{r^3}{R^4} - \frac{R^2}{r^3} \right) \right] dr \tag{1}$$

where r_i and $r_\circ$ are respectively the internal and external radius of the actuator walls in the current configuration, and they have corresponding forms R_i and $R_\circ$ in the reference configuration.

Owing to our precise manipulation requirement, a richly innervated means of sensing actuator deformation at high strains (owing to large reactive head forces) is necessary for effective closed-loop feedback control of head motion. Specifically, **we will laser-cut electrical grade Kapton sheets, weave them in twisting formations with fiberglass materials to mimic**



(a) Setup close-up view. *(b)* Patient, IABs holders and couch. *(c)* SRS configurability setup with IAB Half-domes.

Figure 9: Proposed MRI-compatible LINAC patient motion compensation system.

the bending of beams that enable accurate sensing [39]. The sensors will then be neatly covalently bonded (without adhesives) to the soft actuators' surface by plasma treatment [40]. The proprioception of the soft actuators will be captured by an LSTM deep-learning network such as used in my previous works [41–43]: this will predict the configuration of each soft actuator in prescribed actuation sequences, even with feedback from non-monotonic, hysteretic, soft piezoresistive sensors. This fabrication approach is attractive because (i) it allows the separation of the fabrication of the soft actuator design from the piezo-resistive sensors; and (ii) we can separately characterize the deformation sensing properties of the piezoresistive fiberglass-polyimide sensors for QA purposes before respective integration onto the component actuators.

Aim I.B. Mechanism Synthesis: Phantom Control Experiments.

Rationale: Case for a parallel soft manipulator. Open-loop kinematic chains have a low transportable load and poor accuracy since the weight of the segments that follow each link and the load of the structure contributes to the large flexure of torques; their links magnify errors from shoulder out to the end-effector, consequently hampering their use for sophisticated control strategies that may minimize or eliminate load-dependent error. Parallel configurations, in spite of their higher number of actuated joints, distribute the weight of the load around the links of the robot, improve manipulation accuracy, have a desirable lightness property, and minimize the flexure torques that are otherwise common with open-loop kinematic chains. Given the non-cummulativeness of actuator errors in parallel configurations, greater precision is possible with minimal control complication [44].

Procedure.

A. Head Motion Correction in $\mathbb{SE}(3)$: We will systematically synthesize and analyze parallel soft robot manipulators for head and neck motion correction in MRI-LINAC systems. The configuration that shall be investigated shall consist of soft actuators so arranged that their independent or coupled actuation can produce the needed head motion correction along the left-right (LR), the anterior-posterior (AP) , and/or the superior-inferior (SI) axes. We will analyze the manipulation map, kinematics and kinetics of the respective closed-loop chains, and analyze the contact equations between the IAB system and head.

Fig. 9b shows an example standalone motion correction setup (MRI coils, and LINAC not shown). By the modular design illustrated in Fig. 9c, the coils of an MRI can be easily overlaid on the side shields shown in Fig. 9b. In a parallel kinematic manner, the soft domes are positioned around the patient's cranial region while the patient lies supine on a typical MRI/RT treatment couch (Fig. 9c) and will be held in place around the head by impact-resistant low-temperature rigid PVC foam insulation sheet within carbon fiber. Velcro stickers (not shown) will be affixed to the planar soft dome holders to accommodate different patient cranial geometry – thus providing a modularization that ensures re-usability. The side actuators will correct head motion along the LR axis of the head anatomy $i.e.$ (yaw and roll motions), while the bottom ones will correct head motion along the AP direction. The SI motion will be adjusted by the two lower actuators on the bottom of the neck. The domes underneath the forehead would control pure z translation and pitch rotary motions.

In preliminary work [33], I have synthesized differential kinematics [45], continuum mechanics [46, 47] and multi-bodied kinematics. Equation (**??**) yields the cranial manipulation constraint between the soft actuators and the head so that we can find the respective translational and rotational head velocity components, v_h, ω_h respectively in world frames. We can easily find the pseudo inverse of the manipulation map, G in (**??**), so as to determine head velocity on the treatment couch. The derivation of this equation is detailed in [32].This mechanism shall be validated under the standalone MRI treatment facility at Penn Radiation Oncology (xRT) to ensure that the designed mechanism does not interfere with the magnets of the MR machine.

B. Potential Pitfalls and Alternative Approaches. CCOARSE Gaussian-textured actuators may prove unneeded in the final analysis as other configurations may be found more suitable such as our previous cuboidal-textured actuators [9]. If this is the case, other geometries may be imbibed into the robot mechanism to ascertain which actuator and linkage connection for a 6-DoF real-time cranial motion compensation is best for MRI motion-artifacts elimination.

1.3.3 K_{99} **Aim II: To Develop a Multi-Modal and Robustly Stable Optimal Motion-Planner.**

Rationale: Current RT and SRS robot-based head motion compensation techniques are pre-programmed and heavily calibrated within their environment in order to find the optimal and safest path required in moving a patient's cranial structure from one location to another in the robot workspace [7, 9, 11, 12, 24, 27, 28, 48, 49]. While these schemes work for specific automation tasks, they require extensive calibration and parameters adjustment to get them to work for every new head motion control task. It is not enough for us to find a valid path c that is free of collisions. We also want the head motion to follow constraints that are functions of the robot's geometry, avoids radiation hitting critical structures, follows a path that does not increase proneness to claustrophobia [50], and lowers the problem's dimensionality. Similar to [51], we define these *manifold constraints* to capture loop closure constraints, end-effector constraints etc.

Procedure: For preliminaries, we refer reviewers to [33, 51–56]. A forward kinematic map from the configuration of the i^{th} IAB, $\boldsymbol{\chi}_{iab_i}$, maps from respective IAB configurations to head position and orientation $i.e.\ K_{iab_i} : \boldsymbol{\chi}_{iab_i} \rightarrow \mathbb{SE}(3)$. The head velocity with respect to a fixed base frame in terms of IAB velocities can be written in terms of the forward kinematics Jacobian: $\begin{pmatrix} v_{iab_i} & \omega_{iab_i} \end{pmatrix}^T = \frac{\partial K_{iab_i}}{\partial \mathbf{r}_i} \frac{d\mathbf{r}}{dt} K_{iab_i}^{-1} = \boldsymbol{J}_i(\mathbf{r}_i)\dot{\mathbf{r}}_i$ where $\mathbf{r}_i$ is the spatial position of IAB i in generalized coordinates, and $(v_{iab_i}^T, \omega_{iab_i}^T) \in \mathbb{R}^6$ represents the linear and angular velocity of the i^{th} IAB about its screw basis. In essence, $\mathbf{r}_i \in \mathbb{R}^3$ with its rows are mapped to scalars by an appropriate choice of norm[1]. For $\mathcal{C}^2$-smooth k-constraint functions $G_1, \ldots, G_k$ $(1 \leq k \leq n)$, a constraint is fulfilled when $g_i(\xi) = 0$ and we write out the composite constraint function $G : \mathbb{R}^n \rightarrow \mathbb{R}^k$ with respect to the contact Jacobians as $G_i^T(\xi_h, \xi_{iab_i})\xi_h = B_i^T(\xi_h, \xi_{iab_i})\boldsymbol{J}_{c_i}(\xi_h, \mathbf{r}_{r_i})\dot{\xi}_{iab_i}$ for an IAB's selection matrix $B_i^T(\xi_h, \xi_{iab_i}) \in \mathbb{R}_i^m$, where m_i is the range of all the forces and moments for the chosen contact primitive (or union of contact primitives), and $\boldsymbol{J}_{c_i}$ is the contact between the head and the respective IABs. Therefore, for k actuators in the soft robot, we have the following manipulation constraint $\begin{bmatrix} G_1^T & \cdots & G_k^T \end{bmatrix}^T \begin{pmatrix} v_h & w_h \end{pmatrix}^T = \textbf{diag} \begin{pmatrix} B_1^T \boldsymbol{J}_{c_1} & \cdots & B_k^T \boldsymbol{J}_{c_k} \end{pmatrix}^T \begin{pmatrix} \dot{\mathbf{r}}_{iab_1} & \ldots & \dot{\mathbf{r}}_{iab_k} \end{pmatrix}$. The details of this derivation are presented in my unpublished work [33]. We call $\mathcal{M}_{free}$ the free constraint manifold of the overall manifold, $\mathcal{M}$, which is defined as $\mathcal{M}_{free} = \mathcal{M} \cap \mathcal{Q}_{free}$.

Constrained RCLF Motion Planning: Find an RCLF collision-free path $\sigma^\star : [0, 1] \rightarrow \mathcal{M}_{free}$ given a path planning problem $(\mathcal{Q}_{free}, \xi_i, \mathcal{Q}_{goal})$, manipulation constraint, G, and cost function V such that $V(\sigma^\star) = \min_{\sigma \in \Sigma_{\mathcal{M}_{free}}} V(\sigma)$ if one exists.

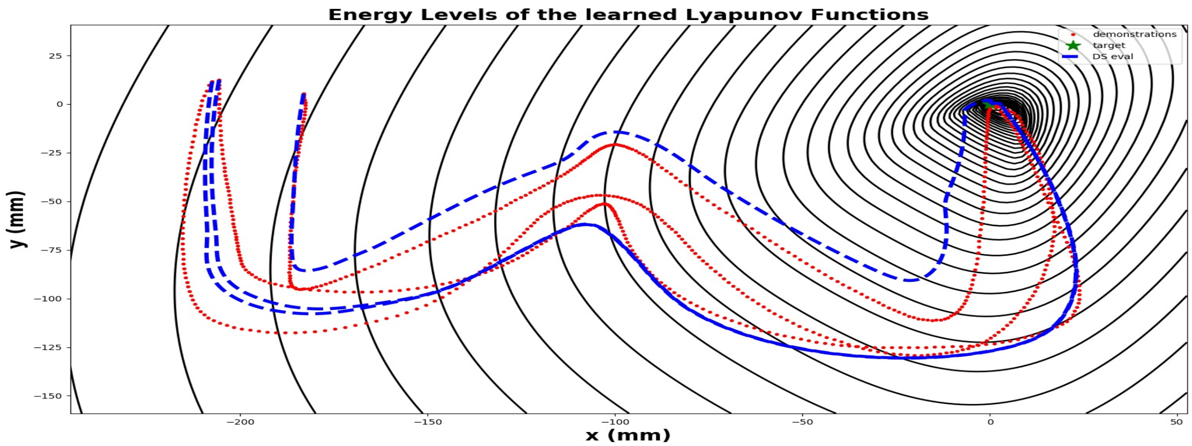
We have conducted initial feasibility tests for the stabilizing command for items 1 and 2 in subsection B above by solving a constrained optimization problem to choose the collision-free stabilizing command among the possible solutions. My implementation takes a greedy approach using the L-BFGS optimization algorithm with box constraints, in contrast to the quadratic nonlinear constrained optimization used by [57], to find the minimal value of the control law u at each time step such that u it is stable. Results of this implementation on toy robot nonlinear control from example demonstrations in 2D task space, implemented in python (see [58]), are reprinted in Fig. 10.

Potential Problems and Alternate Approaches: If for some computational reason, the hierarchical planner takes too long to find a robustly stable and optimal solution for the constrained head motion-planning problem, we will either resort to a straightforward controller, without the layered planning approach or use standard interpolation methods.

1.3.4 R_{00} **Aim: To Validate the Mechanism on Phantoms and Healthy Human Subjects.**

Phantom based dose accuracy verification: To verify accuracy in terms of delivered dose, a complete end-to-end evaluation of the robotic MRI-LINAC system will be carried out using anthropomorphic phantom studies. From our preliminary data, we have seen the ability of task-specific controllers to correct head motion to steady state. The method of [28] were, however, found to be inadequate for comprehensive 3D dose analysis given the setup and calibration logistics due to a 5mm spacing between Gafchromic films along the superior-inferior direction. Such spacing will not resolve small targets as commonly seen in brain metastasis where mets have been reported to be as small as 5mm in diameter [59]. To overcome this limitation, we propose to use 3D printing technology for our in-house anthropomorphic head phantoms [60, 61]. A 3D printer is available to the PI. Prior patient MRI scans will be used to extract geometric features of the head. The outside skin of the inner skull bone defining the brain cavity will be segmented and imported into the 3D printer. Filaments with tissue equivalent electron densities and stopping powers will be purchased. To simulate soft tissues (skin, muscle, fat, etc.), a filament with a water equivalent density ($1g/cm^3$) will be used (abs, polysterine, polylactic acid, etc.) to simulate bony structure (skull), a higher density between $1.3 - 1.5g/cm^3$ will be used (nylon, pett, polycarbonate, etc.). To measure 3D dose distribution at high spatial resolutions, the cranial cavity will be filled with a dosimetric gelatin [62, 63]. Polymer gel dosimetry (PGD) is a branch of 3D dosimetry where a carefully tuned recipe of radio-sensitive chemicals dissolved in gelatin form a 3D dosimeter that will respond to radiation in a predictable way. Irradiation of the PGD causes polymerization, changing the linear attenuation coefficient $\approx 1mg/cm^3$ per $1Gy$ of absorbed dose [64]. Post-irradiation, the gel can be read using a MRI

[1] I used the $l2$-norm im my implementation.



(a) Reproducing a nonlinear W-shaped motion

Figure 10: A CLF motion executor (red curves) that shows convergence to local attractors (green asterisks) and follows 3 different set trajectories (blue curves) for 2D nonlinear motion-trajectory problems on the WAM robot. Reproduced from [58].

to acquire 3D dosimetric information. We will follow the procedure in [65] in order to create the gel.

We will use treatment planning software (iPlan, BrainLab, Germany) to create several SRS plans that simulate both single and multiple target SRS treatment cases. The reference 3D facial surface template will be extracted from the MR scan and imported into AlignRT vision software for real-time tracking purposes. As described above, the outside surface to the inner skull region of the head will be extracted from the MRI scan and used to make an anthropomorphic phantom by 3D printing methods. The phantom skull will be filled with dosimetric gel and placed within the soft robot at the LINAC's isocenter. The robot prototype will be used to move the phantom based on previously recorded 6D head motion data from volunteers. The following cases will be simulated: no motion (reference), uncorrected 6D head motion, and robot-stabilized 6D head motion. Accurate reproduction of this motion will be confirmed by real-time 6D tracking of the target by the AlignRT system. At the end of each LINAC delivery, an MRI scan of the phantom will be made, and the 3D dose information read out. Standard gamma 27 analysis procedures using a 1% dose-to-agreement and 1mm distance-to-agreement criteria will be used. Both the uncorrected and robot-stabilized case will be compared against the no motion reference. Pass criteria will be a $>$95% pass rate at all target sites.

Human volunteer studies: An IRB trial has been established (IRB14-0535) for recruitment of 20 healthy volunteers for testing on Dr. Wiersma's robotic SRS system. In all cases no treatment beams will be used; therefore, no exposure of volunteers to radiation will occur. To simulate actual MRI-LINAC RT clinical conditions: (1) The volunteer will enter the MRI simulation room and lay in a relaxed supine position on the MRI couch; (2) Using the MRI software, a virtual brain target point will be rigidly attached to this reference surface; (3) The volunteer will enter the LINAC room and lay in a relaxed supine position on the LINAC table with their head supported by the sot robot mechanism; (4) The robot will determine the dextrous workspace and then move the head to the center of this workspace; (5) Using the 3D reference surface captured in step 1, the MRI software will track the virtual intracranial target as defined in step 2, and the treatment table will be coarsely adjusted by hand until the target is <2 mm from LINAC isocenter; (6) Robotic target motion stabilization to the isocenter will be monitored for the length of a typical SRS treatment (≈ 15 min); (7) A virtual integrated SRS treatment will be performed without use of the treatment beam and will include all LINAC gantry and treatment table angles. (8) The previous step will be repeated, but without the use of robotic target motion stabilization. After each session, the recorded 6D target motion data will be analyzed using similar metrics used in previous studies to evaluate the effectiveness of the system [66, 67], namely calculation of positional deviation histograms and the total percent of time that the target remained under a 0.5mm and $0.5°$ threshold.

Potential pitfalls and alternative strategies: It may occur that certain patients suffer from head motions that are affected by frequent muscle twitches, spasms, or other conditions that may result in ineffective intracranial target motion stabilization using the proposed device. If this is the case, a patient suitability test will be conducted before the initial MR plan simulation where the MR imaging system will monitor the patient's head motions for 2-5 minutes in order to verify motion stability. If a patient does not meet the necessary criteria for safe and effective intracranial target stabilization they will not be considered for this MRI-LINAC RT intervention and will instead undergo conventional therapy.

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Training in the Responsible Conduct of Research

To instruct postdoctoral researchers in responsible conduct of research, the University of Pennsylvania Biomedical Postdoc Program mandates postdoctoral training in responsible conduct of research. This training consists of both online and in-person components.

Format

First year postdocs are required to complete two introductory online courses designed by the Collaborative Institutional Training Initiative (CITI) at the University of Miami (citiprogram.org). Online courses are intended as a framework for further discussion and development through monthly 90-minute in-person courses in specific topics relating to responsible conduct of research led by faculty members and staff of the university.

Subject Matter

Introductory online courses cover:

- Research misconduct;
- Data management;
- Mentoring;
- Conflicts of interest;
- Publication practices;
- Ethical issues in research; and
- The use of human and animal subjects.

Monthly in-person seminar topics planned for 2020 include (i) collaboration with industry; (ii) ethical issues in genome research; (iii) ethical issues in peer review; (iv) data collection and management; (v) handling conflicts of interest; (vi) responsible laboratory procedures; (vii) University of Pennsylvania policies concerning research integrity and misconduct reporting; (viii) ethical issues in human and animal research; (ix) the mentor/mentee relationship, and more.

Faculty Participation

The RCR seminars are directed by the Biomedical Postdoctoral Program and is led by faculty and staff including professors in the medical and graduate schools, members of the Institutional Animal Care and Use Committee (IACUC), the Institutional Review Board (IRB), as well as staff such as members of the legal department and senior administrators engaged in research compliance efforts. My mentor, Dr. Rodney Wiersma, conducts an annual laboratory-specific RCR session for all lab members. One-on-one training and discussion will also be provided by Dr. Wiersma through supervision of research activities, sharing experience and insight and reviewing scientific issues and ethical challenges associated with my project and related work in the lab.

Duration of Instruction

The University of Pennsylvania's RCR seminars are 90 minutes long, consisting of $\sim$60 minutes of lecture and $\sim$30 minutes of faculty/staff led discussion or small group case-study exercises.

Frequency of Instruction

Postdocs must attend at least 8 sessions (12 hours) of these in-person trainings during their tenure at the university.

Facilities and Other Resources

Clinical

The Department of Radiation Oncology is in an 80,000 square foot space on the concourse level of the new Perelman Center for Advanced Medicine. The clinical Department includes the most advanced conventional radiation treatment modalities available, including proton radiotherapy.

Laboratory/Office

The Wiersma Lab is located in the John Morgan Building and consits of approximately 1500 square feet of research space. Dr. Wiersma's office is located next to the lab and consits of approximately 200 square feet of space. Within the lab there is dedicated desks and seating for 6 students or postdocs.

In addition, the Research Division of the Department of Radiation Oncology consists of approximately 11,630 square feet of research space in the new 523,000 SF state-of- the-art Smilow Center for Translational Research (SCTR). Additionally, a dedicated research gantry with adjacent laboratory space for cell culture and small animal work is available in the Roberts Proton Facility. Our new facilities in SCTR include 6,800 square feet of lab space, including benches and dedicated rooms; 1,085 square feet of equipment space; and 1,650 square feet of office space. Administration and common areas comprise another 2,100 square feet.

Computer Resources

The University of Pennsylvania Health System (UPHS) maintains the Department of Radiation Oncology's computer network throughout its clinical and research space. The network is currently utilized by over 150 users connected via optical fiber lines. The Radiation Biology Division has multiple computers for word processing and scientific applications. Each PI has multiple PCs in their office and laboratories. Additionally, many pieces of laboratory equipment have dedicated computers with custom software packages. A dedicated computer resources staff is available to rapidly respond to problems within the system. There are numerous computer resources within the University system that are available to researchers and students. Software licenses for Matlab®, COMSOL® are available to perform finite-element and numerical calculations for light transport

Other Resources

Radiation Oncology Imaging Service Centers

Our department is home to two imaging service centers. On the clinical side, a service center (Director, Lillie Lin, MD). is available for radiologic evaluation of patients for the purpose of research studies. Equipment available through this service center includes CT (2 Siemens large bore "Sensation" CT scanners (CT Simulation)), PET/CT (1 Phillips "Brilliance" large bore PET/CT scanner in PET/CT Simulation), and MRI (Siemens "Espree" 1.5 Tesla MRI simulation scanner (MRI Simulation).

A second Imaging Service Center within the Research Division of our Department (Director, Cameron Koch, PhD) provides resources for microscopy-based imaging of cells or tissue sections, as well as those for CT imaging and subsequent irradiation of small animals. Microscopy-based imaging is prioritized for the assessment of tissue oxygenation via analysis of hypoxia marker binding. The core provides access to the hypoxia markers EF5 or EF3 and fluorochrome-labeled antibodies suitable for their detection. Equipment includes cryostats and Nikon Eclipse fluorescence microscopes with computer-controlled stages and low-noise cooled CCD cameras. Numerous methods have been developed to quantify use of this instrument specifically for the detection of hypoxia, but the equipment can be used for any type of fluorescence measurement.

Small animal imaging/irradiation is carried out using the Small Animal Radiation Research Platform (SARRP; Director, Costas Koumenis; Technical Manager, Cameron Koch). The SARRP encompasses an X-ray machine whose highly collimated beam can be directed precisely, even for fields coming from multiple directions, using the information derived from an on-board Cone-Beam-CT (CBCT). The 3-D research space is defined by a robotic stage with multiple degrees of movement and by a rotatable gantry for the X-ray tube. Notably, the x-ray tube of the CBCT and of X-ray delivery are the same since the X-ray source for both uses is the same (a dual-function X-ray tube). Standard beam sizes range from 0.5 mm to 5 mm, and additional rectangular and square shapes (e.g. 3mm x 9mm). We have also custom fabricated several other shapes for specific purposes (e.g. 'D' shaped collimators for half-tumor irradiation). One of the most difficult targeting applications has involved the irradiation of mouse thymus, and the success of this procedure has been documented using gammaH2AX formation in the thymus gland. The capabilities of this instrument go a long way to satisfying the critical need for animal radiotherapy to be done in a manner comparable to that used in humans - that is the possibility of combining multiple collimated fields in order to protect normal tissue.

Core Facilities

In addition to our research laboratories and department-based services centers, we have access to many core facilities. These include:

- Microscopy core – Andrea Stout/Jon Epstein

- Radioimmunoassay and Biomarkers Core – Heather Collins/Steve Master
- Translational Core Laboratories – Ted Mifflin/Steve Master
- Animal Imaging – Steve Pickup/Mitch Schnall
- Behavioral Testing Core – Ted Abel/Amita Sehgal
- Human Immunology Core – Jean Boyer/Eline Luning Prak
- Molecular Cardiology Research Center Mouse Transgenic and Knockout
- Core Facility – Ed Morrisey
- Flow Cytometry and Cell Sorting Core – Hank Pletcher/Jonni Moore
- Histology and Gene Expression Core – Min Min Lu/Mike Parmacek
- Mouse Cardiovascular Physiology & Microsurgery Core – Tao Wang/Mark Kahn
- Functional Genomics Core – Jonathan Schug/Klaus Kaestner
- Islet Cell Biology Core - Nicolai Doliba/ Franz Matschinsky
- Research Instrumentation Shop- William Pennie/Mark Lennon

Additional information on the cores that we most commonly utilize is as follows:

The **Research Instrumentation Shop** provides resources for the custom design and construction of research instrumentation and apparatus, including but not limited to novel devices for animal restraint and shielding, tissue culture chambers providing environmental control, and specialized microscopy stages. The instrument design specialists of this core also have experience in the construction of optical devices that is utilized by researchers who need customized fiberoptic probes.

Institute for Translational Medicine and Therapeutics

The Department of Radiation Oncology maintains a clinical research core of research nurses and data managers who assist with the regulatory, nursing, sample collection, and data management aspects of a clinical trial. The Institute for Translational Medicine and Therapeutics (ITMAT) at Penn supports research at the interface of basic and clinical research, with a particular focus on the development of new and safer therapeutic entities. ITMAT includes its own faculty and basic research space, the Clinical and Translational Research Center (CTRC) with a repertoire of cores, programs, and centers designed to support research endeavors between proof of concept in cellular and animal model systems across the translational divide into proof of concept and dose selection in humans. ITMAT has expanded to include investigators focused on clinical and translational research in all schools at Penn, the Children's Hospital of Philadelphia, the Wistar Institute, and the University of Sciences in Philadelphia. These partner institutions competed successfully for the Clinical and Translational Science Award (CTSA) funded under the NIH Roadmap, designating ITMAT as the academic home for the program. This campus-wide membership represents a resource for a PI seeking internal or external collaborations

Abramson Cancer Center

The University of Pennsylvania Abramson Cancer Center was founded in 1973. The National Cancer Institute designated it as a Comprehensive Cancer Center in 1991. The Cancer Center received accolades in its competing renewal in 1999 with a 63

School of Medicine

The School of Medicine at the University of Pennsylvania has several common resources that benefit our research. The biomedical library is located at the juncture of the Hospital and the School of Medicine, contains over 161,000 total volumes and nearly 3,000 journal subscriptions. In addition to the printed materials, the Library provides access to over 500 full-text electronic journals, over 100 bibliographic databases and numerous other web-based resources. It aids faculty investigators and research trainees through such services such as interlibrary loans, reference assistance, and hands-on computer instruction provided by highly trained medical librarians. In addition to the Biomedical Library, we have access to additional health sciences libraries on or near campus, including those at the Veterinary and Dental Schools and Children's Hospital, as well as all the other Penn Libraries.

Equipment

The equipment needed to carry out the mentored phase of this research is available in Drs. Wiersma, Turner and MEAM laboratories. The Wiersma Lab and the MEAM department are separated apart by only 800 yards on campus. Dr. Turner's lab is located within the MEAM department.

Laboratory Equipment.

Major equipment housed within the Wiersma Lab includes:

- FDM 3D Printer;
- Accessories such as batteries and chargers, crimping tool, and power tool accessories;
- Soldering station including soldering iron, solder, flux, and suction-based solder removal;
- Microscope;
- Pneumatic air outlets;
- NDI Polaris 6DoF infrared marker tracking camera;
- 6DoF hexapod motion phantom;
- 3DoF translational motion phantom;
- Motor motion controllers;
- NI PCI-7358 8 axis stepper/servo controller;
- NI PCI-7344 4 axis stepper/servo controller;
- Slushengine 7 axis stepper controller;
- NI MID-7604 stepper power drives;
- National Instruments NuDrive-4SX-411;
- Amptek x-ray spectrum detector with CdTe diode detector;
- Amptek multi-channel analyzer;
- Oscilloscopes;
- Tektronix DPO 3014 4 channel;
- Tektronix 2465 DVS 4 channel;
- EG&G 7260 lock-in amplifier.

Software:

- Mathworks MATLAB;
- National Instruments LabVeiw;
- Solidworks

Common Equipment located in the Perelman Center for Advanced Medcine (PCAM).
Dr. Wiersma has unrestricted access to clinical equipment in the Perelman Center for Advanced Medcine (PCAM) that can be used off hours. He will grant Dr. Ogunmolu access to use these facilities as needed in an unrestricted fashion. Major equipment includes:

- Proton MLC G4 with 5 treatment rooms;
- Linear Accelerators
  - 3 Varian TrueBeam
  - 2 Varian Halcyon
- CT Scanner
  - Philips Brilliance Big Bore
- Treatment planning simulation software
  - Varian Eclipse
  - BrainLab iPlan
- Ionization chambers and associated electrometers;
- Harshaw Q5 5500 automated TLD reader;
- Phantoms: RANDO anthropomorphic phantom, CIRS STEEV SRS phantom, QUASAR respiratory motion phantom, Delta4 IMRT/VMAT dose phantom;
- 3D printer, Axiom 20, Airwolf3D;
- Machine Shop
- A 2000 ft^2 machine shop is in the basement of the John Morgan Building. This shop is available for use by project personnel. Major equipment includes:
  - Precision lathes
  - Milling machines
  - Drill presses