# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: James H. Pikul

eRA COMMONS USER NAME (credential, e.g., agency login): PIKULJ
POSITION TITLE: Assistant Professor, Mechanical Engineering and Applied Mechanics, The University of Pennsylvania

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Illinois at Urbana-Champaign | PhD | 2015 | Mechanical Engineering |
| University of Illinois at Urbana-Champaign | MS | 2011 | Mechanical Engineering |
| University of Illinois at Urbana-Champaign | BS | 2009 | Mechanical Engineering |

## A. Personal Statement

I have the expertise, leadership, training, and motivation necessary to successfully mentor Olalekan Ogunmolu for his K99 fellowship. I am a mechanical engineer with expertise in materials engineering, micro and nanoscale fabrication, soft robotics, and electrochemistry. My group combines these expertise to enable new robotic capabilities. This is demonstrated by my recent publication in *Science*[1], which presents a new physical approach for controlling the shape transformation of stretchable material surfaces, in an engineered system that provides reversible actuation, fast response, large forces, geometric and sequential control, and ease of fabrication. I also have expertise in electrochemistry, which I have used to improve the mobility of robots[2], to make the world's most power dense batteries[3], and realize the first room-temperature healing of metal[4]. I have also led many projects, including several $1,000,000 plus projects sponsored by NSF and DARPA. I will use this expertise to mentor Olalekan in science, leadership, and management throughout his project.

1. James H. Pikul, Shuo Li, Hedan Bai, Roger T. Hanlon, Itai Cohen, Robert F. Shepherd, "Stretchable surfaces with programmable 3-D texture morphing for synthetic camouflaging skins", *Science*, vol. 358, pp. 210-214, October 18, 2017.

2. Cameron A. Aubin, Snehashis Choudhury, Rhiannon Jerch, Lynden A. Archer, James H. Pikul, Robert F. Shepherd, "Electrolytic Vascular Systems for Energy Dense Robots", *Nature*, 1, June, 2019.

3. James H. Pikul, Huigang Zhang, Jiung Cho, Paul V. Braun, and William P. King, "High power lithium ion micro batteries from interdigitated three-dimensional bicontinuous nanoporous electrodes", *Nature Communications*, vol. 4, pp. 1732, 2013

4. Zakaria Hsain, James H. Pikul, "Low-energy Room-temperature Healing of Cellular Metals", *Advanced Functional Materials*, pp. 1905631, August 2019.

**B. Positions and Honors**

**Positions**

| | | |
|---|---|---|
| 2017 – Present | Assistant Professor | University of Pennsylvania |
| 2015 – 2017 | Postdoctoral associate | Cornell University |

**Honors**

2020 Moore Inventor Fellow through the Gordon and Betty Moore Foundation
2019 Best Paper Award at The 19th International Conference on Micro and Nanotechnology for Power Generation and Energy Conversion Applications (PowerMEMS), Krakow, 2019
2019 NSF CAREER award in ECCS - CCSS
2019 Scialog Fellow through the Research Corporation for Science Advancement - Advanced Energy Storage
2019 Office of Naval Research Young Investigator Award
2013 Materials Research Society Gold Award

**C. Contributions to Science**

**1. Control and mobility of soft robotics**

Technologies using soft, stretchable materials are increasingly important, yet we are unable to control how they stretch with much more sophistication than inflating balloons. Nature, however, demonstrates remarkable control of stretchable surfaces: for example, cephalopods can project hierarchical structures from their skin in milliseconds for a wide range of textural camouflage, run across the ocean floor, change color, and hydrojet at high speeds through the ocean. Inspired by nature, I have developed theoretical and experimental techniques that enable the design, fabrication, and control of soft robotics. I have pioneered shape control of soft, stretchable materials by prescribing strain in inflated and expanded 2-D surfaces. My combined theoretical and experimental work has led to state-of-the-art capabilities for controlling the shape of soft surfaces that deform into complex shapes. I have also demonstrated the use of flow battery chemistries to increase the energy density of machines, vehicles, and robots by adding energy storage functionality into existing fluidic actuators. This improves the energy density of the robot by more than 4X. I have received an NSF CAREER award for this work.

A. James H. Pikul, Shuo Li, Hedan Bai, Roger T. Hanlon, Itai Cohen, Robert F. Shepherd, “Stretchable surfaces with programmable 3-D texture morphing for synthetic camouflaging skins”, *Science*, vol. 358, pp. 210-214, October 18, 2017.

B. Steven Ceron, Itai Cohen, Robert F. Shepherd, James H. Pikul, Cindy Harnett, “Fiber Embroidery of Self-Sensing Soft Actuators”, *Biomimetics*, vol. 3, September 2018.

C. Cameron A. Aubin, Snehashis Choudhury, Rhiannon Jerch, Lynden A. Archer, James H. Pikul, Robert F. Shepherd, “Electrolytic Vascular Systems for Energy Dense Robots”, *Nature*, 1, June, 2019.

D. T.J. Wallin, J.H. Pikul, S. Bodkhe, B.N. Peele, B.C. Mac Murray, D. Therriault, B.W. McEnerney, R.P. Dillon, E.P. Giannelis, R.F. Shepherd, “Click chemistry stereolithography for soft robots that self-heal”, *Journal of Materials Chemistry B*, vol. 5, pp. 6249-6255, 2017.

**2. Energy storage with increased energy and power**

In my research group, we seek to realize new battery architectures that enhanced battery performance or enable entirely new functionality. Metal-air batteries offer higher energy densities that lithium ion batteries. We have recently expanded the architectural advantage of metal-air batteries by demonstrating the ability to electrochemically extract energy from external metal surfaces using a metal-air scavenger (MAS) composed of a hydrogel electrolyte connected to a cathode current collector. This new approach can power microelectronics and cm scale robotic devices that operate on or near metal surfaces. The effective energy density of the metal-air scavenger was 2.3 times greater than prior metal-air batteries and 12.7 times greater than commercial lithium-ion batteries. This work is being funded through an ONR-YIP. There is also increasing need for higher performance microbatteries due to the increased growth of internet-connected devices (125 billion by 2030) and micro-robotics. I have been a global leader in developing high performance microbatteries for the last 8 years, and my group is continuing to make significant strides in this area. My prior work showed that we could make microbatteries with the power density of supercapacitors, 1,000 times higher than the power density of commercial batteries. Current work in my lab is focused on three funded DARPA SHort-Range Independent Microrobotic Platforms projects. I am the PI on one and co-PI on the other two. The goal of these projects is to realize novel energy storage technologies for microrobots.

A. Min Wang, Unnati Joshi, James H. Pikul, “Powering electronics by scavenging energy from external metals” *ACS Energy Letters*, 2020

B. James H. Pikul, Paul V. Braun, William P. King, “Performance modeling and design of ultra-high power microbatteries”, *Journal of the Electrochemical Society*, vol. 164.11, pp. E3122-E3131, 2017.

C. Hailong Ning, James H. Pikul, Runyu Zhang, Xuejiao Li, Sheng Xu, Junjie Wang, John A. Rogers, William Paul King, and Paul V. Braun, " Holographic Patterning of High Performance on-chip 3D Lithium-ion Microbatteries”, *Proceeding of the National Academy of Sciences*, vol. 112, no. 21, pp. 6573-6578, 2015.

D. James H. Pikul, Huigang Zhang, Jiung Cho, Paul V. Braun, and William P. King, “High power lithium ion micro batteries from interdigitated three-dimensional bicontinuous nanoporous electrodes”, *Nature Communications*, vol. 4, pp. 1732, 2013

### 3. <u>Multifunctional Materials</u>

My lab’s work on multifunctional materials is inspired by the complex functionalities in natural materials (like self-healing fractures in bone) and the incredible benefit similar functionalities would offer to engineered systems. We use modern engineering and design principles to realize new synthetic materials with mechanical and chemical properties not available in natural or man-made materials. In one project, we have combined new models of nanoscale self-assembly with electrochemical deposition to realize high-strength and light-weight metals. I recently published work showing that these materials (with 200-500 nm pore sizes) could achieve the strength of titanium and the density of water. My group has also demonstrated rapid, effective, low-energy, and room-temperature healing of metallic materials by using electrochemistry and polymer-coated cellular nickel to mimic the transport-mediated healing of bone. This is the first room temperature healing of metals since humans have first used metals 6,000 years ago.

A. James H. Pikul**,** Sezer Özerinç, Burigede Liu, Runyu Zhang, Paul V. Braun, Vikram S. Deshpande, William P. King, " High strength metallic wood from nanostructured nickel inverse opal materials", *Scientific Reports*, 9.1, 2019.

B. James H. Pikul, Paul V. Braun, and William P. King, “Micromechanical devices with controllable stiffness fabricated from regular 3D porous materials”, *Journal of Micromechanics and Microengineering*, vol. 24, 105006, 2014

C. Zakaria Hsain, James H. Pikul, “Low-energy Room-temperature Healing of Cellular Metals”, *Advanced Functional Materials*, pp. 1905631, August 2019.

**D. Additional Information: Research Support and/or Scholastic Performance**

**<u>Ongoing Research Support</u>**

DARPA: PI

“Electrochemical deposition of thick and continuous electrodes for high voltage and energy density lithium metal microbatteries”

- Co-PI are Paul Braun (University of Illinois at Urbana-Champaign) and John Cook (Xerion Advanced Battery Corp.)
- 03-01-2019 to 02-28-2022

Office of Naval Research Young Investigator Program: PI

“Understanding electrochemically induced surface evolution and transport at metal-hydrogel interfaces for metal-air scavenger power sources”

- 04-15-2019 to 04-14-2022

NSF: PI

“EFRI C3 SoRo: 3-D surface control for object manipulation with stretchable Materials”

- Co-PIs are Michael Posa, Mark Yim, Chris Santangelo (U. Mass – Amherst), Ryan Hayward (U. Mass – Amherst)
- 01-01-2020 to 12-31-2023

NSF: PI

“MRSEC: Surface Evolution of Dealloyed Mesoporous Metals for Oxygen Metals for Oxygen Reduction Catalysts in Metal-Air Battery and Fuel Cell Electrodes”

- Co-PI are Eric Detsi (MSE) and Eric Stach (MSE)
- 09-01-2018 to 08-31-2020

NSF CAREER: PI

“CAREER: Power and information transmission kinetics in multifunctional electrolytic vascular systems”

- 02-01-2020 to 01-31-2025

DARPA: co-PI

“Integrated High Voltage Battery and Magnetic Conversion Micropower Systems for Efficient Power Delivery to Microbiotic Actuators”

- PI is Mark Allen, Co-PI is Sue Bidstrup-Allen
- 03-01-2019 to 02-28-2022

**<u>Completed Research Support</u>**

None

# BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Turner, Kevin T.

eRA COMMONS USER NAME (credential, e.g., agency login): KEVINTTURNER

POSITION TITLE: Professor and Chair, Mechanical Engineering and Applied Mechanics, The University of Pennsylvania

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Johns Hopkins University | B.S | 05/1999 | Mechanical Engineering |
| Massachusetts Institute of Technology | M.S | 05/2001 | Mechanical Engineering |
| Massachusetts Institute of Technology | Ph.D | 05/2004 | Mechanical Engineering |
| Massachusetts Institute of Technology | Postdoctoral | 08/2005 | Materials Science and Engineering |

## A. Personal Statement

My research addresses fundamental and applied problems at the intersection of the fields of surface and interface mechanics and micro- and nanosystems. Surface and interface mechanics, which encompasses fracture, contact, and adhesion mechanics, plays a crucial role in determining the behavior of many micro- and nano-scale systems and manufacturing processes. My research group uses a combination of experimental measurements, analytical modeling, and numerical simulations to improve and realize innovative micro- and nanomanufacturing processes as well as to develop new approaches to measure the mechanical properties of interfaces at small scales. My current work includes projects in nanocomposites, materials with tunable adhesive properties, and flexible electronics.

The proposed project includes development of soft mechanical sensors. I will leverage my expertise in sensors, mechanics of materials, and flexible electronics in my mentoring role on the proposed project.

## B. Positions and Honors

**<u>Position and Employment</u>**

| | |
|---|---|
| 1999-2004 | Research Assistant, Massachusetts Institute of Technology, Cambridge, MA |
| 2004-2005 | Postdoctoral Associate and Lecturer, Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA |
| 2005-2011 | Assistant Professor of Mechanical Engineering, University of Wisconsin, Madison, WI |
| 2006-2011 | Faculty Affiliate, Materials Science Program, University of Wisconsin, Madison, WI |
| 2007-2011 | Faculty Affiliate, Biomedical Engineering, University of Wisconsin, Madison, WI |
| 2011-2011 | Associate Professor of Mechanical Engineering, University of Wisconsin, Madison, WI |
| 2011-present | co-Founder, systeMECH, Inc, Madison, WI |
| 2011-2016 | Associate Professor of Mechanical Engineering and Applied Mechanics (primary) and Materials Science and Engineering (secondary) University of Pennsylvania, Philadelphia, PA |
| 2012-2017 | Director, Quattrone (Wolf) Nanofabrication Facility, University of Pennsylvania |
| 2016-2019 | Graduate Group Chair, Mechanical Engineering & Applied Mechanics, University of Pennsylvania |
| 2019-present | Chair, Mechanical Engineering & Applied Mechanics, University of Pennsylvania |

**Memberships**

1998-present Member, American Society of Mechanical Engineering
2000-present Member, Materials Research Society
2008-present Member, Adhesion Society

**Honors**

| | |
|---|---|
| 2008 | ASEE Ferdinand P. Beer and E. Russell Johnston, Jr. Outstanding New Mechanics Educator |
| 2009 | National Science Foundation CAREER Award |
| 2009 | 3M Non-tenured Faculty Award |
| 2009 | R&D 100 Award for UNCD AFM probes |
| 2011 | Young Adhesion Scientist Award, the Adhesion Society |
| 2011 | Outstanding Young Manufacturing Engineer Award, the Society of Manufacturing Engineers |
| 2012 | NAE Frontiers of Engineering Symposium, invited participant |
| 2014 | ASME Sia Nemat-Nasser Early Career Award |

## C. Contribution to Science

1. Microelectronic and microelectromechanical devices need to have robust and stable performance over long service lives. The performance of these devices hinge critically on the mechanical properties of the materials and interfaces formed during the fabrication process. Thus, characterization of the mechanical properties of devices and materials after fabrication is critical. Turner has developed and implemented numerous small-scale mechanical testing to interrogate mechanical properties in fabricated devices. Because of the size of the devices and features, innovative mechanical testing and modeling techniques are often required. Examples of such work are included in the following publications.

    a. Grierson DS, Liu J, Carpick RW, and **Turner KT** (2013) Adhesion of nanoscale asperities with power-law profiles, *Journal of Mechanics and Physics of Solids*, 61: 597-610.
    b. Wald MJ, Considine JM, and **Turner KT** (2013) Determining the Elastic Modulus of Compliant Thin Films Supported on Substrates from Flat Punch Indentation Measurements," *Experimental Mechanics,* 53: 931-41.
    c. Cavallo F, Grierson DS, **Turner KT**, and Lagally MG (2011) "Soft Si": Effective stiffness of supported crystalline nanomembranes, *ACS Nano*, 5: 5400-7.
    d. Tadepalli R and **Turner KT** (2008) A chevron specimen for the measurement of mixed-mode interface toughness of wafer bonds, *Engineering Fracture Mechanics*, 75: 1310-19.

2. Wear of materials is a ubiquitous problem that limits the performance of many systems, ranging from bearings to microscale devices to biomechanical joints. Wear is a significant issue that limits the lifetime of atomic force microscope probes in nanometrology and nanofabrication processes. Turner, in collaboration with others, has investigated the wear of atomic force microscope probes at the nanoscale and developed new understanding of the mechanisms of wear. Specifically, the papers below show and atom-by-atom attrition process with a rate that increases with applied stress.

    a. Vahdat V, Ryan KE, Keating PL, Jiang Y, Adiga SP, Schall JD, **Turner KT**, Harrison JA, and Carpick RW (2014) Atomic-scale wear of amorphous hydrogenated carbon during intermittent contact: a combined study using experiment, simulation, and theory, *ACS Nano*, 8: 7027-40.
    b. Vahdat V, Grierson DS, **Turner KT**, and Carpick RW (2013) Mechanics of interaction and atomic-scale wear of amplitude modulation atomic force microscopy probes, *ACS Nano*, 7: 3221-35.
    c. Liu J, Grierson DS, Moldovan N, Notbohm J, Li S, Jaroenapibal P, O'Connor SD, Sumant AV, Neelakantan N, Carlisle JA, **Turner KT**, Carpick RW (2010) Preventing nanoscale wear of atomic force microscopy tips through the use of monolithic ultrananocrystalline diamond probes, *Small*, 6: 1140-49.
    d. Liu J, Notbohm J, Carpick RW, and **Turner KT** (2010) Method for characterizing nanoscale wear of atomic force microscope tips, *ACS Nano*, 4: 3763-72.

**Complete List of Published Work in MyBibliography:**

http://turner.seas.upenn.edu/publications.htm

**D. Research Support**

**Current Research Projects**

NSF 1542153 (PI: M. Allen) 09/01/15-08/31/20
NNCI: Mid-Atlantic Nanotechnology Hub (MANTH) for Research, Education, & Innovation
The goal of this award is to make nanotechnology infrastructure at the University of Pennsylvania broadly available to academic and industrial users in the mid-Atlantic region.
Role: co-Principal Investigator

NIH/NIAMS R01 AR071718 (PI: X. Liu) 04/01/17-03/31/22
Effects of reproduction and lactation on postmenopausal bone health
The major goals of this project are to identify the critical phenotypic bone structure, material properties, and mechano-sensitivity resulting from reproduction and lactation that protect the maternal skeleton from future postmenopausal bone loss.
Role: Senior personnel

NSF 1663037 (PI: K. Turner) 04/01/17-03/31/21
Collaborative Research: Exploiting tunable stiffness for dynamic adhesion control at the macro- and micro-scale
The major goal of this project is to exploit materials with tunable stiffness to realize surfaces with dynamic and switchable adhesion properties.
Role: Principal Investigator

U.S. Endowment for Forestry & Communities, Inc (PI: K. Turner) 05/01/17 – 09/30/20
3D Printing of Cellulose Nanofibril Materials
The major goal of this proposal is to investigate the fabrication of bulk nanocellulose parts via additive manufacturing (i.e. 3D printing) techniques.
Role: Principal Investigator

NSF 1662695 (PI: D. Lee) 06/01/17-03/31/21
Nanostructured Composite Coatings to Harden and Toughen Polymer Surfaces
The major goal of this project is to investigate the processing, structure, property relationships of nanoparticle composite films synthesized through capillary rise infiltration.
Role: co-Principal Investigator

USDA/NIFA 2016-08810 (PI: K. Turner) 07/01/17-06/30/20
Engineering Cellulose Nanomaterials with High Toughness
The major goal of this project is to investigate the toughness and crack growth resistance of materials based cellulose nanomaterials.
Role: Principal Investigator

NSF 1720530 (PI: A. Yodh) 09/01/17-08/31/23
Materials Research Science and Engineering Center (MRSEC)
The major goal of Turner's work in this center is to examine the mechanics and fracture of disorded solids, including molecular glasses and nanoparticle films.
Role: Senior Personnel

NSF 1761726 (PI: J. Bassani) 04/01/18-03/31/21
Tailoring interface geometry to realize controlled and directionally-dependent adhesion
The major goal of this project is to investigate strategies to tailor the interface toughness (fracture resistance) through micro- and nano-patterning.

Role: co-Principal Investigator

NSF 1830475 (PI: K. Turner) 09/01/18 – 08/31/21
NRI:INT:COLLAB: Soft Active Contact Pads with Tunable Stiffness and Adhesion for Customizable Robotic Grasping
The major goal of this project is to develop robotic gripping strategies based on materials with tunable stiffness.
Role: Principal Investigator

**<u>Past Research Projects (<3 years old)</u>**

NSF 1435745 (PI: Turner) 09/01/2014-08/31/2018
Structured Composite Materials with Variable Adhesion Properties
This grant supports the design, fabrication, and characterization of novel micro- and nano-structured surfaces with tunable adhesion.
Role: Principle Investigator

University of Pennsylvania

Penn Engineering

School of Engineering and Applied Science
Department of Mechanical Engineering
and Applied Mechanics
272 Towne Building
220 South 33rd Street
Philadelphia, PA 19104-6315

Dr. James Pikul
*Assistant Professor*

Tel: 215.573.2786
Fax: 215.573.6334
pikul@seas.upenn.edu

May 21, 2020

Dear Selection Committee Members,

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.

Sincerely,

James H. Pikul

## 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 [22]. **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 [23–26].** 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 characteristic 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.

# Institutional Environment

## *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) consistently ranks as one of the top four medical schools in the United States, with access to world-class medical physics and radiation therapy 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. Molu to conduct his MRI-LINAC RT research and seek counsel from faculty and medical doctors with outstanding discipline know-how.

The research collaboration culture is very admirable at UPenn: the university actively encourages researchers across disparate disciplines and departments to actively collaborate and to follow wherever science leads them. There are numerous collaborations among faculty, postdocs and students from different departments who conduct research via resource sharing and interdisciplinary communication. Indeed, Dr. Molu has actively leveraged this opportunity since he came to UPenn by forging close alliances with Engineering staff in the Rapid Prototyping Lab, Additive Manufacturing Lab and Penn Medicine Instrumentation shop. These alliances have helped him to generate some preliminary results faster for this project, albeit he's been slowed down by the university 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. Molu 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. Molu. Dr. Pappas will invite Dr. Molu to his office and/or laboratory at least once a month 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. Molu at least once a month where he will guide Dr. Molu 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. Molu 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. Molu 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. Molu via joint lab monthly meetings where they will regularly discuss ideas and resource sharing.

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

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. Molu is very passionate about educating and helping develop the next generation of medical roboticists, especially from under-represented minority (URM) communities. At UPenn, Dr. Molu 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. Molu can use to build a formidable academic network for his long-term career goal needs.

With respect to this research plan, Dr. Molu has already assembled a diverse and well-qualified mentoring team that are recognized as world-class experts in the disciplines of control theory, robotics and medical physics – all of them based at UPenn – and no farther than a 1000 yard distance from Dr. Molu's primary office location on campus. Dr. Molu will leverage this world-class faculties in executing the aims prescribed in this project. For example, the motion planning algorithm has a strong control systems component to it. Dr. Pappas will be providing the needed guidance and mentorship to ensure that all tasks during the execution of this aim proceed smoothly. The soft robots fabrication will be closely supervised by Dr. Pikul, who has invaluable experience building soft actuators that respond accurately to prescribed pressure. When it comes to adhesives and models of soft matter, no researcher is better on the UPenn Campus than Dr. Turner. He will be responsible for the direction and supervision of the validation of the modeling of the proposed fiber reinforced soft actuator in this project. Finally, Dr. Wiersma will coordinate this project on all the required medical physics parts of this work including MRI and LINAC tests.

Aside from spending the majority of his time in the Dr. Wiersma's lab, Dr. Molu will have access to major research facilities at Penn Medicine as needed to conduct his research. Dr. Molu will have access to a wide variety of investigators including his co-mentors, Drs. Pappas, Pikul, and Turner. Penn faculty are renowned for being highly interactive and generous with their time, and all of these investigators from the various excellent research communities that intersect with this project's aims will be available to Dr. Molu. In addition, 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. Molu 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. Molu 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. Molu will have the opportunity to meet and engage both at lunch and in the laboratory. Dr. Molu 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.

## *Institutional Commitment to Training*

The University of Pennsylvania was the first institution in the country to recognize the need for formal postdoctoral training and created the Biomedical Postdoctoral Program (BPP). The school of medicine has the largest cohort of postdocs anywhere in the United States (1200+ postdocs). BPP supports training programs in laboratory management, scientific and grant writing, scientific presentation skills and responsible conduct of research. In addition, BPP partners with the Penn Career Services office to offer one-on-one career counseling and resume critiques as well as seminars in networking, negotiation skills, navigating the academic job search process and the "Faculty Conversations" seminar series which explores aspects of the early academic career stage. Access to these grant writing workshops, career services and other services are freely available to every postdoc in PSOM and Dr. Molu will endeavor to take advantage of every one of them in the course of his mentored phase at UPenn.

In addition, the school of engineering (Penngineering) has the rapid prototyping lab (RPL), additive manufacturing labs and world class mechanical manufacturing machines such as lathes that are available to all university researchers who are working on innovative technologies. In addition, the University of Pennsylvania is one of the few institutions of higher learning in the United States with an entity that links the intellectual and entrepreneurial initiatives necessary for advancing knowledge and generating economic development $i.e.$ Pennovation Works. As Dr. Molu's research has a translational clinical potential, he will leverage the resources available at Pennovation, BPP, and Penngineering while executing the mentored phase of this research to assure full development as a world-class researcher. Lastly, he will participate in the annual departmental professional courses and workshops including *Clinical Trails in Oncology* and the department of Radiation Oncology's *Annual Course on Proton Therapy*.

## *Access to material resources for training*

My sponsor's lab is located in the John Morgan Building. In addition to a designated space for my work, the lab houses an FDM 3D printer, auxiliary electronics and soft matter fabrication supplies. The instrumentation and machining workshop is equipped with classic lathe machines, drilling machines and other associated equipment available for researchers' use. My mentor will provide me with the medical physics training needed fulfill the radiation oncological clinical trials proposed in this project. Working closely with my co-mentors in the school of Engineering, I will have access to the tension testing, laser-cutting and lathe machines I would need in the hardware fabrication. Many additional instrumentation and training resources are available from core facilities located on campus; while none of these are required for my proposed project, they may be necessary for alternative approaches and offer opportunities for further training in follow-up studies to my proposal.

# Candidate Information and Goals for Career Development

## *Candidate's Background*

***Predoctoral Research***

My first major scientific project was my undergraduate thesis when I worked on the single fractional parentage coefficients in the sd-shell nuclei. This project exposed me to the art of peer review, learning existing knowledge from scholastic literature, finding inconsistencies between existing claims and observed results, and finding a new problem and solving it with new tools. As calculating the single-particle and many-particle angular momentum of wavefunctions for s- and d-configurations in the sd-shell proved tedious, I automated my calculations by writing codes in C++ and Matlab. After three months of consultations with my advisor, and my continual probing for answers, I solved for sd-shell coefficients of fractional parentage using the Clebsch-Gordon coefficients for the $d^2$, $d^3$ and $d^4$ configurations. I learned the importance of consistency, hardwork and curiosity.

I would go on to study for a masters degree in Control systems at the University of Sheffield where I specialized in robotics under the mentorship of Dr. Tony Dodd. I fiddled with mobile robots, designed vision-based algorithms for quadcopter flights, and participated in unmanned aerial vehicle navigation student competitions. I was part of the Engineers without Borders society where we built low-cost wind-turbine for Heeley farm in Sheffield, as well as designed a robotic prosthetic arm for a child suffering from epilepsy – these two projects made us earn the society of the year award from the University.

***Doctoral Research***

I later enrolled at the University of Texas at Dallas where I would collaborate 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 major avenues for disseminating robotics and automation research. In the course of time, my UT Southwestern advisor (Steve Jiang) requested for me to come join his lab for the rest 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 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***

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 highered 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 planing framework for both of our lab's robot platforms for head motion correction. Leveraging preliminary work from the Kavraki lab on exploring implicit spaces in constrained sampling-based motion planning, I want to leverage 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 incorporate this motion planner on the physical build of my soft robot mechanism as well as Dr. Wiersma's Stewart-Gough robot.

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

## *Career Goals and Objectives*

Along with the excellent researchers that I collaborate with at Penn Medicine and Penn Engineering, I am working on the next stages of deploying robots on real-world cancer patients to help doctors, medical physicists, dosimetrists and lab clinicians better manage cancer treatments. My ultimate goal is in making the application of my control and robotics technologies pervasive in consumer robotics and the internet of things (IoT) industry as my research career progresses.

*Training Objectives*

In order to accomplish my long-term career and research goals I require at least one more year of mentored research for the following reasons. While a doctoral student, I worked between three projects, 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, while exciting in their own rights, left me stretched too thin that my contributions to science was not as impactful as I would like it to be. I produced top-scholastic papers at major high-impact conference venues but had little time to turn 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 discipline experts such as Drs. Pikul, Turner and Pappas (they are on my co-mentoring team) so I 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 for further honing my intellectual curiosity and in me establishing an independent career.

*Mentored Phase Objectives*

**Firstly**, I want to scale the erstwhile developed soft robot and its control algorithm up to six degrees of freedom for complete head-motion compensation. In the mentored phase of this award, I will work on the motion planing 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 doses $i.e.$ the patient's head motion in the robot's complete workspace must be *collision-free* and must satisfy manipulation mode constraints. Realizing smooth head transitions in space requires going from one state space mode to another so that the planner must find a sequence of single-mode motions and valid transitions between modes that realize this multi-modal motion manipulation. For geometric manipulation problems under manifold constraints such as the one proposed here, the general approach in robotics is to use trajectory optimization or sampling-based planning schemes. I will use an hierarchical multi-planning system that takes cues from a discrete "lead" for biasing search into robustly stable and optimal mode transitions. Stability will be assured by generating exponentially stable paths in the underlying dynamic system. Leveraging online search protocols, we will bias search for robustly optimal and feasible paths to a sequence of modes that yield a smooth representation of head motion. This would fulfill my Aim II in the K99 years. **Secondly**, to fulfill my K99 Aim I, I will develop a distributively-innervated, non-magnetic, and radiation-transparent soft actuator. This aim will scale previous soft actuator designs to a full 6-DoF soft robot capable of providing head manipulation along 6 DoFs and will be compatible with pre-existing LINACs. The actuators will be fiber-reinforced to constrain deformation along specific Eulerian directions in order to simplify control. Made entirely out of radio-transparent and non-metallic parts, this Gen 2.0 design 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. **Lastly**, I will synthesize the actuators and motion planning algorithm, so that it is adaptable under MR coils and in RT treatment protocols (as outlined in my K99 Aim III).

*Independent Phase Objectives*

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 in order to ascertain its effectiveness at real-time head motion compensation. When the veracity of this mechanism is proven, I will conduct a clinical trial on 20 whole brain patients where validation of this system will be determined by a statistical endpoint. Success will be that a 6D intracranial target is $\leq$ 0.5mm and $\leq$0.5° for greater than 95% of the treatment time.

**My goal** is ***to transition to an independent investigator role***, $i.e.$ 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.

As I am currently a non-tenured faculty at Brandeis University graduate school of professional education where I teach and mentor masters students in robot autonomy, robot kinematics and dynamics, I have found this role to be fulfilling and stimulating in my career path as it enables me in rediscovering established concepts and imparting my knowledge to the next generation of bio-roboticists.

### *Training Activities Plan During Award Period*

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 in the table below. Additional coursework, campus seminars participation in my research discipline areas, and consultation with my mentorship committee will enhance my training experience. A mentored job search is also a part of my training plan, which will be critical to my future success in securing a faculty position.

As Aim I of my K99 plan concerns a developing a state-of-the-art motion planner for soft robots, I thought it necessary to go through a formal motion planning coursework in my K99 year(s). The School of Engineering at the University of Pennsylvania offers world-class robotics courses that I plan to participate in. In my K99 year(s), I will consult extensively with motion-planning experts in the School of Engineering in order to broaden my horizon and improve my edge when I am developing this algorithm. Professor George Pappas in the engineering school is a world-class expert in the fields of control theory and machine learning and his expertise will provide a very meaningful discipline supervision of the robust control Lyapunov function model that is articulated as part of the motion-planner algorithm. As I travel around the country and internationally to attend robotics conferences, I will study to meet and learn from world-class motion planning experts such as Lydia Kavraki and Steven LaValle, which will hopefully open up avenues for future collaboration on these subjects in my independent years. For Aim II of the K99 years, I will closely work with Professor Kevin Turner, in developing a high-fidelity continuum elastic model for the soft actuators. While he is not on my mentoring committee, I have been in talks with Professor Ponte Castaneda on ways of further robustifying my existing continuum model for the soft actuators. He has been very welcoming and is willing to continue to help as I grow in my career.

In my independent years, the strong relationships I would have nurtured at Penn Engineering and Medicine would be invaluable as I navigate my career path as an independent scientific investigator. Obtaining this award will be a great opportunity for me to learn and develop cutting-edge medical robotics tools and frameworks in applied medical physics. I believe the award will give me an opportunity to learn from excellent robotics and medical physicists. As I participate in the rich exchange of ideas at national and international meetings, it will widen my horizon. Gaining in-depth insight, I will be equipped with greater discipline knowledge as I continue to hone well-rounded robotics, control and medical physics research skills for a future independent scientific investigator career; this will stimulate rapid growth in my career path, helping me assume bigger research responsibilities.

# 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 | | | |

| ACTIVITY | Modality | Specific Activities | ACTUAL START | ACTUAL DURATION | PERIODS | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Y1 | Y2 | Y3 | Y4 | Y5 |
| 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 |

## *Candidate's Plan to Provide Mentoring*

I have carefully chosen my mentor and co-mentors to reflect the needs of the aims articulated in this proposal. Taken together, the respective expertise described in this proposal span (i) robust adaptive optimal control; (ii) motion planning; (iii) mechanics of materials; (iv) continuum mechanics/elasticity theory; (v) soft robots fabrication; and (vi) medical physics. No team is better able to mentor me on these subjects than Professors George Pappas, Kevin Turner, James Pikul and Rodney Wiersma.

*Professor George Pappas*

Professor Pappas is the UPS foundation Professor at the University of Pennsylvania. He holds a principal appointment in the Electrical and Systems Engineering Department and has cross-appointments in the Computer and Information Science (CIS), as well as Mechanical Engineering and Applied Mechanics (MEAM) departments. He has made pioneering contributions to the analysis, design, and control of cyber-physical systems with applications to safe and secure autonomy. Dr. Pappas developed an award-winning theory of hierarchical model approximation across continuous-time control models, discrete-event software models, and hybrid systems (cyberphysical models) which resulted in a paradigm of approximate symbolic abstractions for continuous and hybrid control systems, bridging together semantically continuous-time and discrete-event systems. He subsequently leveraged his approximation theory in order to develop the first rigorous theory of robustness for temporal logic safety specifications and analysis for continuous control systems. These foundational and influential achievements enabled the development of numerous safety analysis and synthesis tools by the cyberphysical systems community. The emerging field of semantic SLAMs was invented by him. I will be relying on his deep control theory expertise, and project management prowess in successfully executing $K_{99}$ *Aims II and III* described in this proposal. He has graciously accepted to continue to provide mentorship and supervision of my career development during the independent phase of this award. As we are physically located on the same campus, I will ensure that I meet with him at least twice a month to discuss my progress on this project as well as continually seek his mentorship on navigating the junior academic hurdles that I may encounter as my career develops.

*Professor Kevin Turner*

Professor Turner is the Professor and Chair of the Mechanical Engineering and Applied Mechanics (MEAM) at The University of Pennsylvania. His research addresses fundamental and applied problems at the intersection of surface/interface mechanics and micro/nano-systems. His research group uses a combination of experimental measurements, analytical modeling, and numerical simulations to improve and realize innovative micro- and nano-manufacturing processes as well as to develop new approaches to measure the mechanical properties of interfaces at small scales. I will be using some of the instrumentation available in MEAM and Professor Turner's lab in executing $K_{99}$ Aims I and III during the mentored phase of this project. MEAM houses Penn's Rapid Prototyping Laboratory (RPL), ADDitive Manufacturing Laboratory (ADDLab) as well as Dr. Turner's laboratory. These laboratories offer state-of-the-art additive manufacturing capabilities such as soft lithography 3D printers as well as general-purpose mechanical engineering instrumentation such as moduli testing machines. In addition, Dr. Turner will provide supervision and guidance in the continuum mechanical model and adhesives development at the interface of the robot and human head during the construction of the proposed robot. Given his excellent administrative expertise, Dr. Turner will coach me on job talks, laboratory management and I will meet with him and his research group at least twice a month.

*Professor James Pikul*

Professor Pikul is an Assistant Professor at Penn's MEAM. Professor Pikul is a mechanical engineer by training with expertise in materials engineering, micro and nanoscale fabrication, soft robotics, and electrochemistry. His group combines these expertise to enable new robotic capabilities. He recent patent and publication in Science demonstrates a new physical approach for controlling the shape transformation of stretchable material surfaces, in an engineered system that provides reversible actuation, fast response, large forces, geometric and sequential control, as well as ease of fabrication. Specifically, Dr. Pikul will be responsible for the supervision of hardware fabrication of the soft robots and guide with mentoring support in NSF-style grants writing.

*Professor Rodney Wiersma*

Professor Wiersma is an Associate Professor at Penn's Department of Radiation Oncology as well as the Director of Physics Research in the department. Dr. Wiersma has been at the forefront of robot-based radiation therapy since he was Assistant Professor at the University of Chicago. His research group was the first to demonstrate the capability of a rigid 6-6 Stewart-Gough platform to correct patient head motion in real-time on human volunteers in stereotactic radiosurgery. Dr. Wiersma is my current postdoc advisor. In the mentored phase of this award, he will oversee the execution of this project. While I will be responsible for project execution, Dr. Wiersma will actively help with the coordination with other co-mentors in terms of joint lab meetings, mentoring, laboratory management, and grants writing.

## 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 [5].

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 erstwhile 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 [6–8] for real-time head motion correction on the couch that have been investigated are made out of linear actuators and rigid metallic components and these are incompatible with MR. During my PhD, I used 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 to use an MRI/LINAC-compatible soft robot system to provide 6-DoF head motion correction in precision RT procedures***. 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: To Develop 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, this design 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: Soft Robot Development:* 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 the patient 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 $\xi_i \in SE(3)$ to a goal location $\xi_f \in SE(3)$ 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 for assuring safety in the execution of planned paths. *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 in order to safely generate optimally-robust single modes that guide transitions that precisely move the head in the presence of medical constraints in the head-robot workspace.*

**R00 Aim I: To Validate the Mechanism on Healthy Human Subjects.**

The developed motion-planner in my *K99 Aim II* will be used in the real-time head motion correction in mock MRI-LINAC RT phantom and healthy human volunteer 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 linear and angular head position control and patient safety systems.

**R00 Aim II: To Validate Mechanism on Oncological Human Subjects.**

A clinical trial on 20 whole brain patients will be performed where validation of this system will be determined by a statistical endpoint. Success will be that a 6D intracranial target is $\leq$ 0.5mm and $\leq$0.5$^\circ$ for greater than 95% of the treatment time. Upon successful completion and novel use in in maskless MRI-LINAC systems, this project will demonstrate that soft robotic SRS is ready for widespread clinical deployment. With its transformational clinical potential, our soft robot head motion compensation in MRI-LINAC RT will enable the availability of novel radiation dose delivery to a larger population of patients, improve therapeutic outcomes, reduce patient invasiveness, improve clinical efficiencies by reducing 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.***

# Research Strategy

## Significance

Integrating magnetic resonance imaging (MRI) functionality with radiation therapy (RT) linear accelerator (LINAC) can better render the visualization of the soft tissues of lesions and surrounding healthy organs-at-risks (OARs) during cancer RT treatment planning and procedures. This is because MR scans, in contrast to the prevalent computed tomography (CT) scans used in clinics today, provide a richly contrasted image of internal body tissues. More importantly, MRI-LINAC integration can be done in an unrivaled, online, and real-time fashion to aid a more precise radiation dose delivery in RT [5]. There are now MRI-LINAC systems such as Raaymakers et al's [5, 9], which was later commercialized by Elekta AB (Sweden) [5].The MRIdian system is another one of such technologies, essentially an MRI-based image-guided RT [10], developed by Viewray (USA). There is also the Aurora RT system from MagnetTx (Canada) [11], or the non-commissioned Australian MRI-Linac project [12]. While MRI-LINAC integration has been widely researched [5, 9, 13, 14], the effect of random and involuntary patient motion causes motion artifacts which lowers the quality of MR imaging scans for use in brain and head and neck (H&N) RT. These artifacts in image collection lower the accuracy of online and real-time precise radiation dose delivery, which in turn affects clinical efficacy.

During RT, 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 [15].Thus, to automatically align patient motion during RT, state-of-the-art clinical approaches use either a frame or a mask to stabilize patient motion on the treatment couch.

#### Known roles of frames in 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.

#### Known roles of masks in 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 [18]. 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


*(a)* The BRW SRS Frame [16] *(b)* Frames with MRI Coils *(c)* Wiersma SG-Robot [17] *(d)* Ostyn's Stewart platform [8]

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

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 [19].

### Known roles of rigid robots in positioning compensation

To overcome these issues, explorative robotic positioning research studies have demonstrated the feasibility of maintaining stable patient cranial motion consistent with treatment plans. For example, the Wiersma Lab's Stewart-Gough (SG) platform [6, 20, 21], illustrated in Fig. 1(c), achieves $\leq 0.5$mm 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. The Ostyn et al research group sought to alleviate this rigid structure by 3D printing the mechanical components of the Stewart-Gough platform [8]. It is worth noting, however, that this platform uses stepper motors as well (see Fig. 1(d)) to actuate the legs of the robot. This by nature leads to radiation attenuation. With the potential to aid better 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 [22].

Published work from the Wiersma lab shows that a rigid parallel robot can provide the online, real-time patient motion compensation in mock SRS and RT treatments (see Fig. 2). Here, using an LBFGS-based trajectory optimization formulation for patient head motion compensation, the algorithm was able to maintain a $\leq 0.5$mm and $\leq 0.5°$ clinical tolerance objective for 100% of the treatment time [21]. But observe that not all constraints are adhered to: for example, observe the overshoot along $Z$ for the tumor in the LINAC frame and the wriggly trajectories along the rotational axis of the tumor before it reaches steady state. Furthermore, while this robot does work well for SRS treatment procedures, it does not translate to integrating MRI functionality with LINACs owing to its structural mechanical characteristics.

### Known roles of soft robots in RT

My preliminary work on soft manipulators for patient head motion compensation in RT shows that novel soft robot manipulators can compensate head motion within the submillimeter and subdegree accuracy of the AAPM-TG42 stipulation for up to 3 DoFs [23–26]. In a cascaded PID-PI controller loop, I initially showed head motion correction for head setpoint- and trajectory-following to be accurate to within $\leq 1.5$mm for a task of lowering or raising the head along on a treatment table [23]. These results are duplicated in Fig. 3. Furthermore, Fig. 4 illustrates the testbed I used in generating the 3-DoF control results of Fig. 5. Here, 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 sent 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 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 [27]. 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 [24]. Some of these results are reprinted in Fig. 3 and Fig. 5 respectively.

Now, in a new class of soft actuator designs, and contrary to stochastic system identification techniques I used in my previous models [23, 24, 26], 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 [28]. 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 [17]. Contrary to remote-controlled airbags that have been used in upper mandible and head manipulation [29], 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 prescribed internal pressurization, their surface displacement errors are accurate to the order of $< 1.5 \times 10^{-}4$mm [28]. These results are reiterated in Fig. 6 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. Based on my derived constitutive relation between the applied pressure and the radius of the actuator, a pressure of $0.76$ psi was found to be suitable to realize this deformation. The charts of Fig. 6 illustrates the response of the actuator based on a prescribed pressure, where $C_1$ and $C_2$ are appropriate material moduli. With the standard local volume preservation principle, we notice a displacement error of

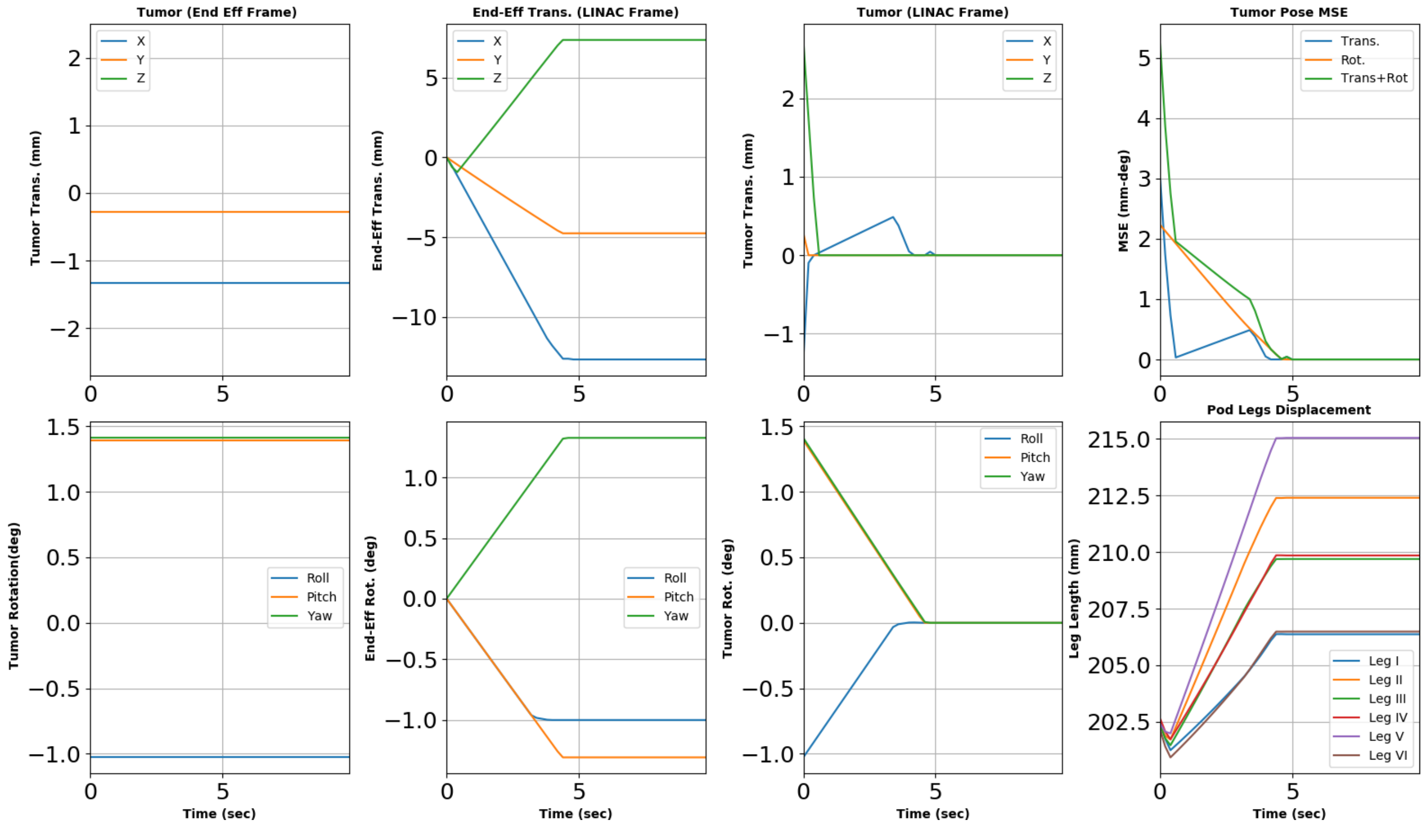
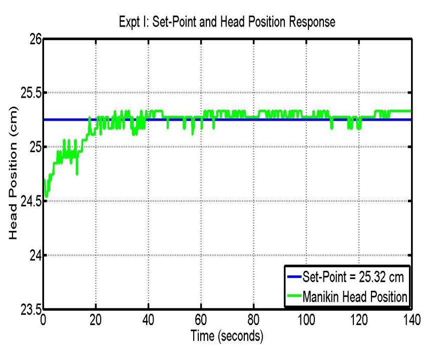
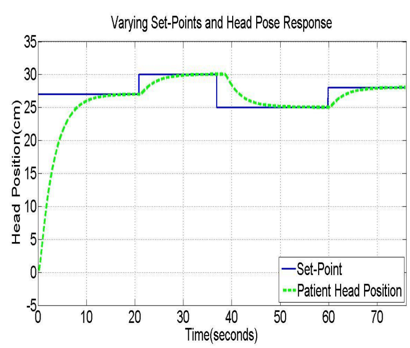


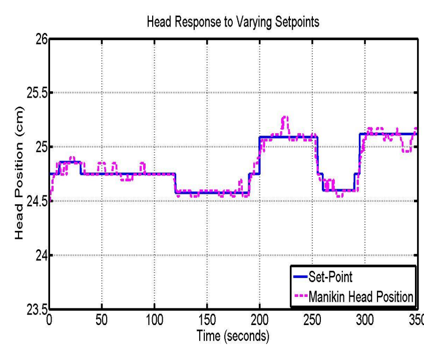

Figure 2: Isocenter Head Stabilization Results Using the Wiersma Rigid Stewart-Gough Platform. Reprinted with permission from [21].




*(a)* Head response to fixed setpoint.




*(b)* Head trajectory follower simulation




*(c)* Head trajectory follower experiment

Figure 3: 1-DoF Online, Real-Time Head Motion Correction. Reprinted from [23].

$1.5 \times 10^{-4}$ along the rectangular Cartesian coordinates and a 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.

### Hypothesis

My **leading hypothesis** is to use MRI/LINAC-compatible soft robot system that can provide 6-DoF head motion correction in precision RT procedures to serve as a viable alternative to current mask-based as well as frameless and maskless robot-based cranial manipulation systems. In this sentiment, ***I hypothesize*** *that time-resolved MRI-LINAC techniques, which provide superior soft tissue scans, in conjunction with non-magnetic and radiation transparent soft robots can provide superior brain or H&N radiation dose targets for precise MRI-LINAC RT treatment procedures*. Existing frame-based immobilization

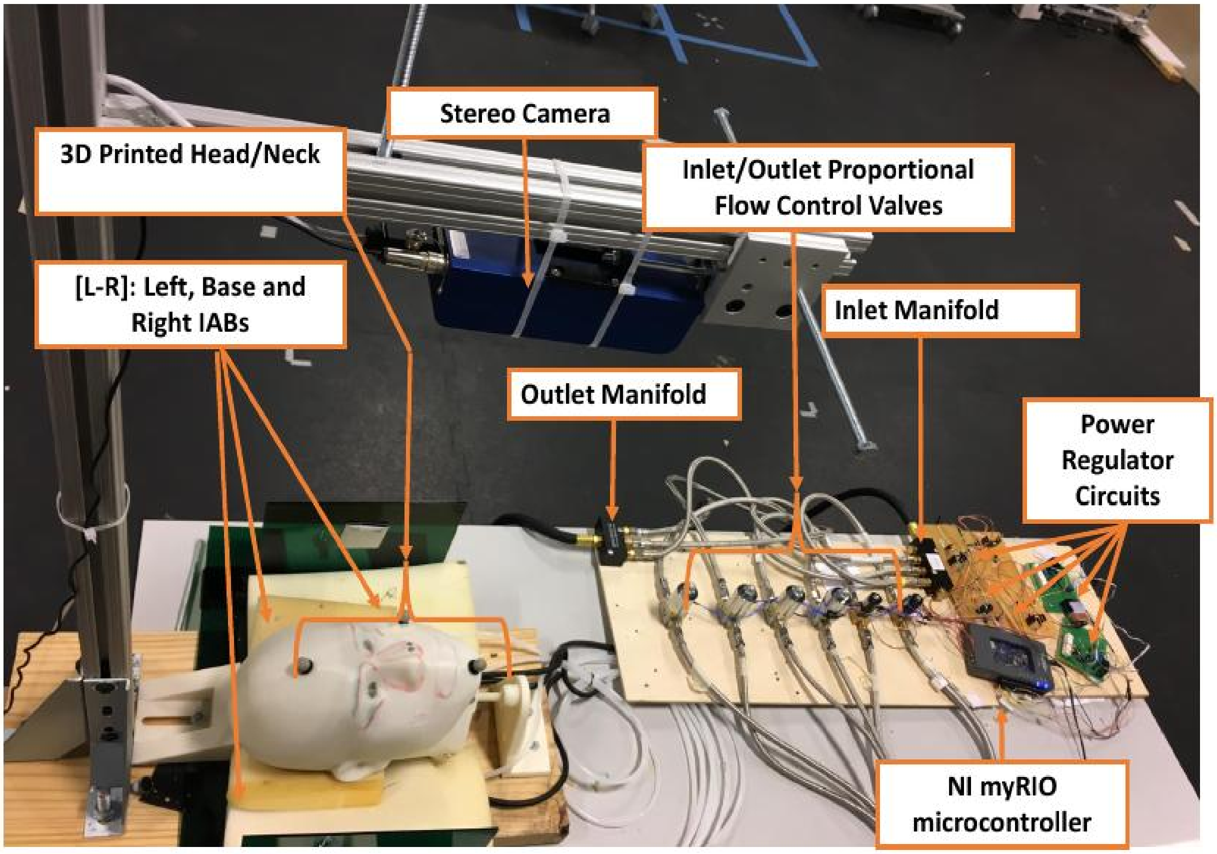
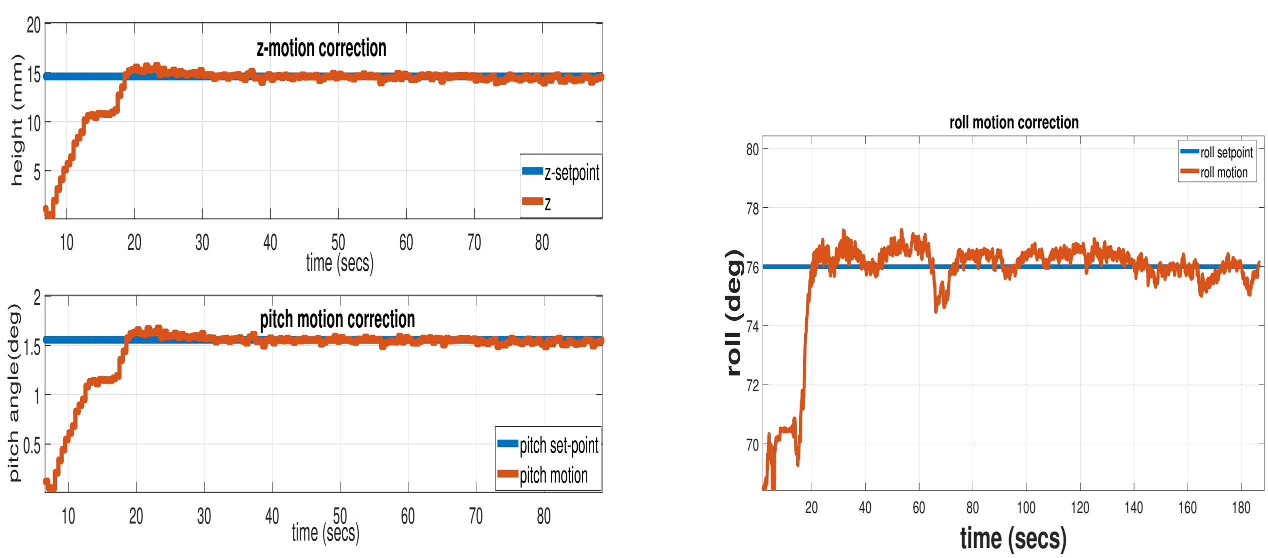


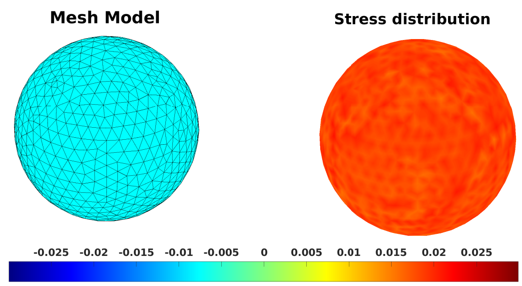

Figure 4: Three DoF Testbed. Reprinted from [24].



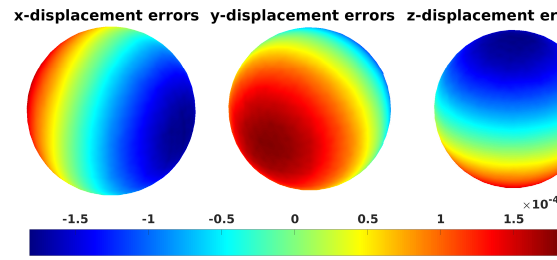

*(a)* $Z$ and pitch motion correction. *(b)* Roll motion correction.

Figure 5: 3-DoF Online, Real-Time Head Motion Correction. Reprinted from [24].

devices, Fig. 1a, and frameless and maskless rigid robotic motion correction mechanisms, Fig. 1c&d, are not suitable for this because of their electro-mechanical parts that introduce serious safety concerns. Furthermore, ***I hypothesize*** *that an asymptotically stable in the large and optimal motion-planner can find collision-free paths that satisfy head motion constraints can resolve the abnormalities inherent in current controllers used in head motion correction systems [6, 7, 20, 24], This will*




*(a)* **Left**: Mesh model. **Right**: Stress distribution post-defomation.




*(b)* Displacement errors along $x, y, z$ coordinates.

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

Figure 6: Volumetric Deformation of a Soft Actuator (Expansion). Reprinted from [28].

*alleviate the overshoots experienced during head motion correction as illustrated in* Fig. 2. I will test this leading hypothesis to see if 6-DOF target motion of a patient is $\leq 0.5$ mm and $\leq 0.5°$ for greater than 95% of the treatment time using MRI imaging for soft robot-based motion compensation.

Along with other experiments where I verified that vision-based control of soft robots can geometrically correct patient motion precisely fast-enough in real-time up to three DOFs [23–26], and existing hybrid MRI-compatible RT systems [9, 13, 14], we will test these hypotheses that soft robots can provide position accuracy that is consistent for use in standalone MRIs, MRI-LINAC RT systems or SRS-alone treatment procedures in order to (i) negate the deleterious effects of *interfractional* setup variation on patients; (ii) correct the complex *intrafractional geometric uncertainties* such as posture changes, and body deformation with minimal invasiveness; (iii) eliminate radiation attenuation associated with the metallic components of frames and rigid robotic patient motion compensation systems; and (iv) correct the flex associated with thermoplastic face masks; (v) reduction of radionecrosis. Typically, a radiation oncologist typically adds a 1-3mm volume margin around the tumor to ensure adequate radiation dose coverage in the event of head motion. This exposes more brain tissue to radiation and greatly increases the risk of radionecrosis. The mechanism has the potential to significantly reduce these margins and therefore improve therapeutic outcomes. while *not interfering with the MR machine's magnetic field*.

## Innovation.

*Conceptual 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 [23–26]; we are extending this to 6-DOF control with my novel advanced mechanism

- 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. This would include conventional L-arm (Elekta, Varian), robotic arm (Cyberknife), and ring-type (Tomotherapy) LINACs. It would be implemented as a standard treatment table accessory that can be easily attached and de-attached from the end of the table and would not require costly room modification or other dedicated equipment. Since it is likely to be inexpensive, it has potential to bring state-of-the-art RT methods to developing nations with older LINAC technologies.

- This mechanism can be adapted to confined spaces under MRI coils (see Fig. 1b) given its compactness, and light weight.

- Increased clinical efficiencies. It possesses little invasiveness to the patient, and exhibits a quick-connect, quick-disconnect modularity on a couch – important for patients with varying cranial anatomy – thus easing the logistical setup workload of current immobilization and maskless robotic systems. As current SRS setup procedures are highly complex, expensive, and can require support from highly trained medical staff such as neurosurgeons. Total in-clinic treatment times can range from 6–8 hours. Soft robotic MRI-LINACs in RT and SRS will significantly cut down on the setup complexities and 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.

- Less invasion to patients than current frame or frameless SRS systems. The soft robotic SRS will not require a frame or mask around the patient's head. The only requirement is for the patient to lie down on a soft foam headrest. Advanced optical guidance systems will then detect positional deviations and the robot will make automated head corrections.

*Technical/Healthcare Innovation*

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 robot RT positioning system**. The superior image guidance from an MRI scan will improve positioning accuracy and irradiation efficacy via a real-time 6D 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. These soft robotic automatic patient motion compensation systems have broad applications in medical imaging and cancerous tumor management: standalone MRIs, emerging MRI-LINAC technologies, brain RTs and H&N RTs. Throughout the rest of this document, these applications will be broadly referred to as MRI LINACs. As photon-based cancer treatment accounts for $> 50\%$ of all cancer treatments [30], these exploratory experiments are relevant to public health and have transformational clinical potential because they may provide (i) proof-of-concept evidence that soft robots are compatible with standalone MRI imaging modalities; (ii) evidence of precise and automatic motion management with non-magnetic and radiation-transparent soft robots in emerging hybrid MRI-accelerator RT; (iii) an emergence of a better brain and H&N cancer management technology that can be adapted to confined spaces under MRI coils (see Fig. 1b). Upon successful completion, this soft robot will be used for active head motion stabilization within an MR machine. It will be adaptable for 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.

## Approach.

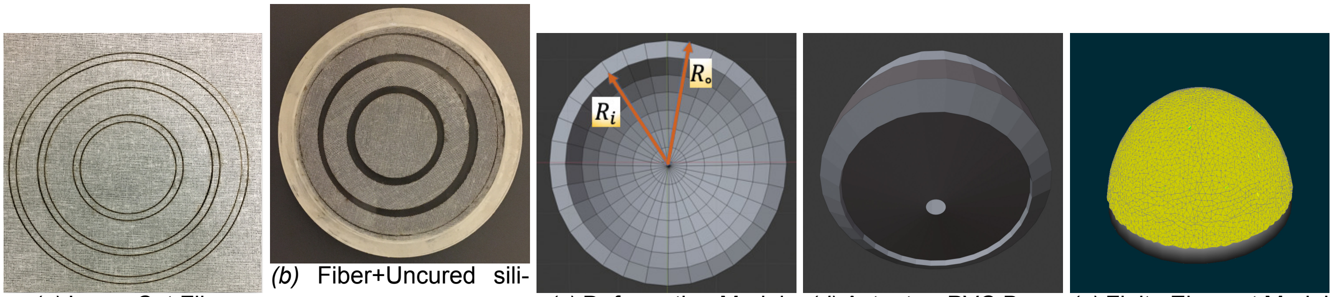
### $K_{99}$ Aim I: To Develop a Distributively-Innervated, Non-magnetic, and Radiation-Transparent Soft Actuator.

**Rationale:** For though the design of Fig. 4 is relevant to head motion control on an RT treatment table, it is not a complete motion correction system owing to its underactuated mechanism: 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. Therefore, to realize a full patient motion compensation, more actuators are needed in the mechanism. To this end, and iterating further on my previous designs [24–26], I now propose a new class of continuum, compliant and configurable (C3) light, and agile soft actuators [28, 31, 32] which are 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 the radial direction (see computer model in Fig. 7) 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 [33, 34]. 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.

**Hypothesis:** Based on previous success of air actuated elastomeric chambers for manipulating patient head motion correction in real-time, I hypothesize that a fully-compliant and parallel soft robot can effectively correct patient head motion (given a robustly stable and optimal controller) such that the motion artifacts that are prone in MR imaging can be eliminated. This will assure an improved RT treatment outcomes in modern MRI-LINAC RTs.

**Procedure.**

**A. Soft Actuator Design**: The soft actuator fabrication methodology is illustrated in Fig. 7. A thin-layered fabric is laser cut into circular patterns (Fig. 7a), the cut meshes are removed and laid onto uncured silicone (Fig. 7b) 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 [35] (Fig. 7c). This unique deformation pattern is similar to the way a balloon would stretch along its axial direction if a rope were tied around its circumference. 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. 7d). The finite elastic deformation mesh model of the soft robot for simulation purposes is shown in (Fig. 7e). This proposed fabrication method allows us to rapidly iterate different designs using compressed low air pressure (1-15 psi) that




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

Figure 7: Soft actuator fabrication procedure.

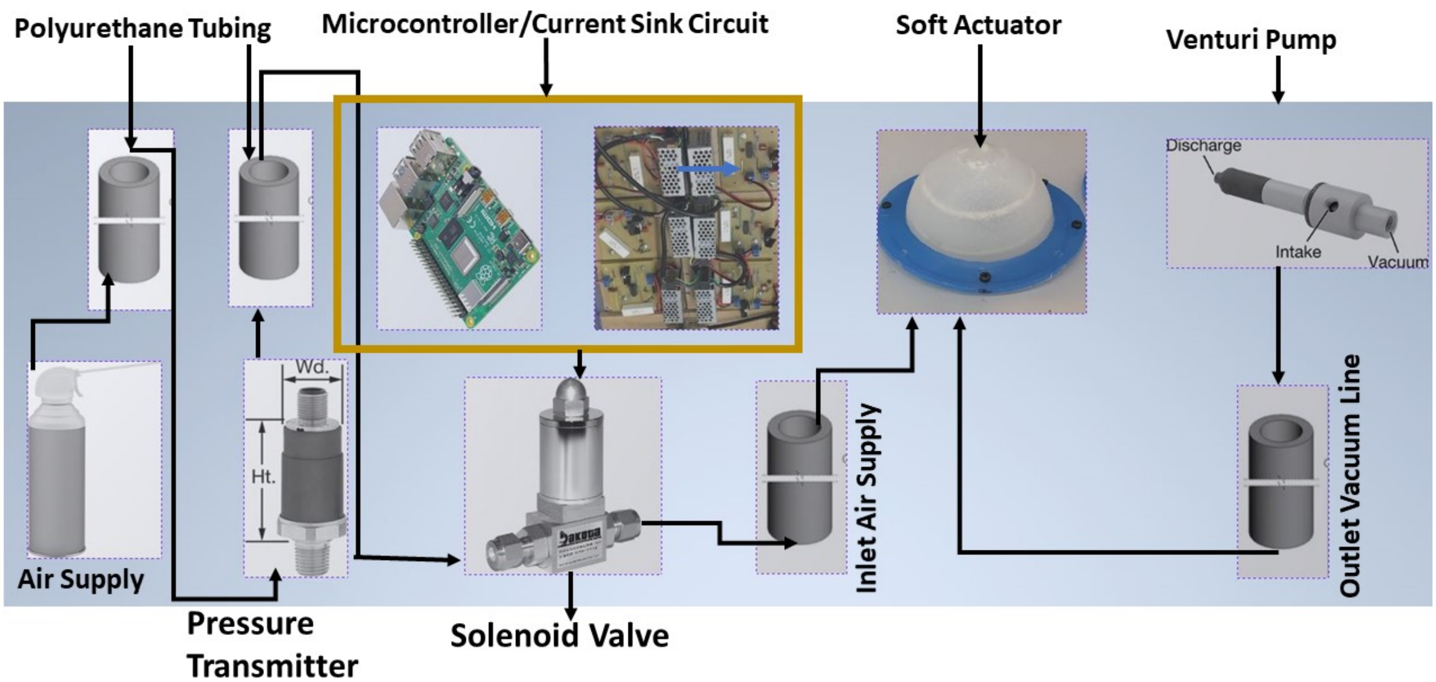



Figure 8: Pneumatic System showing proportional solenoid valve, electronic pressure regulators and raspberry pi microcontroller.

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. As the air inflow into the chambers of the elastomers need to be carefully regulated, we will build current source electronic regulator circuits that proportionally vary the amount of airflow though connecting hoses that lead into the proportional solenoid valves used in earlier experiments [24].

**B. Pneumatic System Design**: We now describe the integration of the soft actuator design proposed above with the rest of the pneumatic actuation system. This system is illustrated in Fig. 8. A self-contained 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 choice of pressure transmitter is important owing to the accuracy requirement for air volume within the chamber of the soft actuator. In our experience, the G2 series of pressure transducers from Ashcroft®are an excellent choice for such application as this: it offers a $\pm 1.00\%$ total error band accuracy; being highly configurable, it offers a pressure range that meets our actuation needs and it can be easily integrated into our overall mechanism. The outlet of this pressure transmitter conveys the airflow into a proportional solenoid valve. We use proportioning valves to control the amount of airflow into the actuator's air chamber because of the air flow precision requirement needed to correctly manipulate the

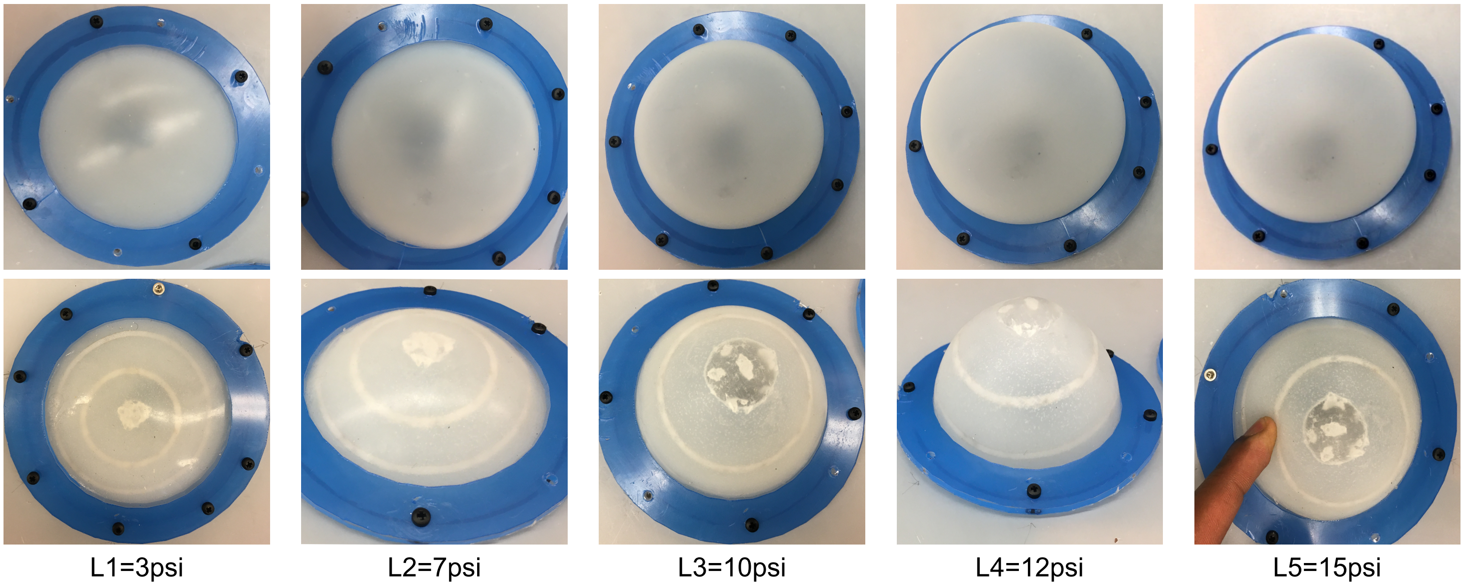


Figure 9: Deformation Levels of elastomer (top) and Elastomeric-Fiber Matrix (bottom) under Low Air Pressurization (3-15psi).

head. The outlet of this solenoid valve then leads to the inlet air connector of the soft actuator. The electronic regulating circuit shown in Fig. 8 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 removes air at a proportional pressure compared to the inlet supply pressure. This pressure differential helps maintain head along a setpoint or follow a varying trajectory.

**C. Preliminary Actuation Experiments:** We have initial experiments that reproduces deformation behavior similar to the spike observed in the skin papillae of the Octopus. This is described in what follows. We cast silicone from Smooth-On Inc's dragon skin ($475$ psi tensile strength and $10$A shore hardness), whose material properties exhibit enough softness for patient comfort and enough firmness that withstands extremely nonlinear deformation from the wrench produced by the typical human head (55-65 kg [36–38]. The ingrained fabric membrane within the elastomer imposes the CCOARSE property, constraining the circumferential expansion of the rubber and exerting a radially symmetric stretch as shown in the bottom row of Fig. 9. This considerably simplifies the dynamics model that governs the deformation [32]. Two different designs are shown in the top and bottom rows of Fig. 9. The rubber material is screwed onto a bottom PVC foam sheet using a laser-cut acrylic planar ring. We use **nylon** Phillips screws. The behavior at different levels of pressurization are indicated in each column of the figure. The top row shows the cured silicone without fabric while the bottom row shows the silicone with the entrenched fiber matrix within the elastomer. As can be seen, the material in the top row exhibits a circumferential bulge as well as radial bulge while the ones in the bottom row only extend along the axial direction. As can be seen in the bottom row, 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.

**D. Flexible Piezoresistive Distributed Sensor Integration**: In a recent formulation [28], we mapped the relationship between the applied pressure to the deformed radius of a soft actuator using the standard Mooney-Rivlin formulation [39, 40]. 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. Taking cues from the precise control schemes of rigid robot manipulators made possible by presence of joint encoders and harmonic drives that enable precise control of the joint angles between robot links, a means of sensing the "measure of deformation" based on the amount of pressure in the actuator's air chamber is necessary for a successful control.

There have been various measures proposed in literature over the past few years about sensing volumetric deformation of a soft actuator. For example, embedded optically-laced fiber sensors based on the principle of frustrated total internal reflection, and distributed throughout a 3D printed elastomer, were used to generate a cointegrated body, sensing, and communication network for a soft robot's state sensing [41]. They have also found applications in innervated soft finger prosthetic hand designs [42], where a very lossy optical waveguide was used in an open-loop control setting to detect shape and texture. While in softness grasp dexterity, they appear promising, they are not yet suitable for human-level texture-based sensitivity (nanometers) despite their complex design. Stretchable sensors with rheological properties have been erstwhile embedded within an elastomer using 3D printing techniques [43]; and though they have been shown to be mechanically receptive, and scalable up to e.g. $\sim$400% strain, their electrical resistance gives at strains $> 400$% owing to the percolation of the networked components [43]. Pneumatic actuator networks patterned within an elastomeric robot body via a multi-material, embedded 3D printing technique have been tried [44]. Dielectric elastomers (DE) making use of the static charge properties of passive electronic components have been shown capable of measuring strain by up to 1692% under the Maxwell pressure law [45]. This DE actuators generally rely on electrostatic voltage discharge to sense deformation [46].

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. Borrowing cues from the observational and short/long-term learning skills arising from the afferent neural networks on the exteroceptive skins of Cephalopods [34, Ch. 2], we will integrate volumetric tactile mechano-receptors on the soft actuators' skins. As we aim to avoid rigid electro-mechanical sources hat can hamper radiation delivery within the design, we will shun DEAs. Optical waveguides would be attractive but they are expensive to integrate for volumetric sensing. Instead, I propose tactile stretchable kirigami sensors made out of polyimides (Kapton sheets) and fiberglass membranes. Meso-scale stretchable Kirigami layer-by-layer manufacture of soft robots have recently been shown to be relevant for fast and precise deployment of robots [47, 48] with high sensing accuracy . Even so, the 3D perception of the environment of these piezoresistive innervated soft robot skins can be perceived using deep learning [49]. In this sentiment, I will laser-cut electrical grade Kapton sheets, weave them in twisting formations with fiberglass materials to mimic the bending of beams that enable accurate sensing [47]. The sensors will then be neatly covalently bonded (without adhesives) to the soft actuators' surface by plasma treatment [50]. The proprioception of the soft actuators will be captured by an LSTM deep-learning network such as I used in my previous works [51–53]: this will predict the configuration of each soft actuator during both prescribed and random 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; (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; and (iii) it offers a modular and cheap fabrication design methodology that eases troubleshooting during the construction phase.

**E. Expected results**: I expect to see individual soft actuators obeying the prescribed pressure law given in (1) so that the deformation radius of the actuators exactly follows an applied pressure similar to the presented simulation results of Fig. 6, further elaborated in [28]. In addition, as I am skilled and well-versed in inference using deep-learning methods (see representative publications [51, 52, 54, 55]), I expect that the stretchable Kirigami sensor layers embedded within the elastomeric actuator membranes will produce rich innervated data that can be processed with deep learning based methods [49] for onward control processing.

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

**Rationale:** Current SRS-based immobilization and 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 [7,17,20,56,57]. Techniques used range from PID control schemes [6,23], reduced-order observer feedback control design [26], optimal and robustly stable indirect model reference adaptive control design [24], to local trajectory optimization schemes [21]. While these schemes work manually for specific automation task, they require extensive calibration and adjustment of parameters so as to get them to work in each new environment and for every new head motion control task. For these robots to execute tasks autonomously, a motion planning system capable of generating feasible motion from high-level requirements is needed. In addition, this motion planning system must respect the constraints on a task in order achieve success, such as turning the translating the head about its cranial-caudal axis, or rotating the head about its neck fulcrum. *I will reformulate these control tasks into a manifold-constrained geometric motion planning problem, concerned with finding a feasible optimal and collision-free path for a patient's head motion.*

In order to optimally move the patient's head in an optimally safe and collision-free path that avoids the exposure of normal tissues to high radiation dose, and is not task-dependent, it is important to develop a motion-planner that (i) executes head motion in the robot's workspace by first finding a collision-free path; (ii) improves the plan into a better plan if the original plan is not efficient or does not satisfy C-space constraints; this may involve multiple iterations; (iii) considers how to move the head along a path that is stable and robust for execution in spite of modeling errors and uncertainties, while maintaining various speeds that satisfy various momentum considerations; and lastly (iv) the found plan must be included in a hierarchical planning framework so that the original plan reaches termination, in order to allow larger plans in the hierarchy to roll out as needed. This planing approach is consistent with motion planning algorithms used in robotics [58].

**Hypotheses**: The requirements produced by this problem and in many other safety-critical problem domains (e.g., household caretaking, IMRT, assistive robots in epileptic patients, and disaster recovery) motivate the study of safety-aware motion planners with constraints. Therefore, **I hypothesize that a layered planning algorithm will find a hierarchical multi-planning sequences of motion that biases search into *optimal mode* transitions**. This layered composition of plans will first compute collision-free paths $\mathcal{C}_{free}$ for moving the head between the start and goal poses. A higher hierarchical planning layer will then leverage encoded manipulation constraints within the robot-head interface to ensure that sensitive H&N structures are not damaged by radiation while the lower collision-free path in the hierarchy is to be executed. This layer of the planning algorithm might need to be repeatedly carried out in a fast computational loop to ensure all $\mathcal{C}$-space constraints are satisfied. Then a higher level plan takes the actions from the two previous lower level plans and generates a robustly stable controller in the sense of Lyapunov such that it can move the head along the $\mathcal{C}_{free}$ paths even in the presence of parametric errors, or uncertainty in model dynamics [24,59,60]. **I further hypothesize that the overall hierarchical plan be sequentially structured so that head motion transitions between *planning modes* ($i.e.$ from an initial location $\xi_i \in$ *SE*$(3)$ to a goal reqgion $\mathcal{Q}_{goal}$) are executed by leveraging online search protocols, which bias search for optimal and feasible paths to a sequence of modes that yield a smooth representation of head motion.** By these hypotheses, *I will address the current gap in geometric manipulation problems under manifold constraints that leave out stability analysis in the feedback control mode of the motion planner. I will achieve this by leveraging a Lyapunov-based stable estimator of the underlying dynamic system in safely generating optimally-robust single modes that guide transitions that precisely move the head.*

**Procedure:** I will formulate a stable geometrical representation of the underlying dynamical system and bias search toward optimally stable and robust short-task plans by providing an optimality-based method for choosing a control law once an robust control Lyapnov function (RCLF) [61] is known. I will develop an optimally stable and probabilistically-complete multi-modal planner that has broad applications to general multi-modal planning tasks in safety-critical problems in medical robotics.

**A. Preliminaries:** Let the set of all possible configurations of the head-robot system be $\mathcal{Q}$ in the C-space $\mathcal{C}$ [62]. Suppose that after a number synthesis of the proposed mechanism [63], the dimension of the robot is $n$. A particular configuration of the robot is defined by $\xi \in \mathcal{Q}$. We assume that the $\mathcal{C}$ is a closed and bounded metric space, and that $\mathcal{Q}$ is a measurable space $(\mathcal{Q}, \mathcal{B}_{\mathcal{Q}})$ for a $\mathcal{B}_{\mathcal{Q}}$ Borel $\sigma$-algebra on $\mathcal{C}$, generated from the metric [64]. The set of obstacles to be avoided are a closed set $\mathcal{Q}_{obs}$, which defines the free configuration space $\mathcal{Q}_{free}$, such that $\mathcal{Q}_{free} = cl(\mathcal{Q} \backslash \mathcal{Q}_{obs})$[2]. Our goal is to find a path from $\xi_i$ to some region of interest $\mathcal{Q}_{goal} \subset \mathcal{Q}$, $i.e.$ a continuous injective map $\sigma : [0,1] \to \mathcal{Q}_{free}$ such that $\sigma(0) = \xi_i$, and $\sigma(1) \in cl(\mathcal{Q}_{goal})$. In addition, a smooth positive definite and radially unbounded function $V(\xi)$ is a control Lyapunov function (CLF) for the head-robot control affine system $\dot{\xi} = f(\xi) + g(\xi, u)$ if

$$\frac{\partial V}{\partial \xi}(\xi) f(\xi) + \frac{\partial V}{\partial \xi}(\xi) g(\xi) q(\xi) \leq -P(\xi) \; \forall \; \xi \neq 0 \tag{2}$$

where $P(\xi)$ is some positive definite function, $u \in \mathbb{R}^6$ is a control input, and $f(0,0) = 0$.

**B. An asymptotically stable in the large and optimal motion-planner:** Our goal is to find an optimal collision-free path, $c$, with respect to a CLF $V(\xi) : \mathbb{R}^n \to \mathbb{R}^d$ such that

- $V(\xi)$ is positive for all $\xi \in \mathbb{R}^d \backslash \mathcal{Q}_{goal}$; and $V(\xi)$ exhibits a unique global minimum in the target region $\mathcal{Q}_{goal}$, where $V(\mathcal{Q}_{goal}) = 0$;
- as the head moves along any of the trajectories, we must have $V(\xi^{t,n}) > V(\xi^{t+1,n})$, and $V(\xi^{T^n,n}) = 0$; $i.e.$ $V(\xi)$ decreases as time increases and $V(\cdot)$ vanishes when the actuators reach steady state after deformation;
- in addition, we require $V(\cdot)$ to satisfy the CLF requirement in (2)
- robust head motion during motion execution shall be guaranteed by devising *robust stabilizability via continuous state feedback* [61], provided that there exists an RCLF on the control-affine system.

We want to choose a control input $u = q(\xi)$ for some function $q(\xi)$ with $q(0) = 0$ so that equilibrium $\xi_e = 0$ of the closed-loop system

$$\dot{\xi} = f(\xi, q(\xi)) \tag{3}$$

[2] $cl(X)$ is the closure of a set, $X$.

is asymptotically stable in the large [65]. The first condition ensures the cost function is a valid Lyapunov function while the second option maintains the stability property in the sense of Lyapunov ($i.e.$ $\dot{V}$ being negative semi-definite for all $\xi \in \mathbb{R}^d \backslash \mathcal{Q}_{goal}$. To avoid wasting control energy and missing optimality during motion execution, as is common with the cancellation or domination of nonlinear terms in feedback linearization, the third option will leverage the *inverse optimal stabilization* in a differential game setting based on the pointwise min-norm control law of [61]. This is attractive because rather than solve a Hamilton-Jacobi-Isaacs (HJI) equation for a control law that yields the path $c$, the pointwise min-norm control law yields a robustly stabilizable and optimal synthesis of the head motion correction problem.

**C. Manifold Constraints:** 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 [66], and lower the problem's dimensionality. Similar to [64], we define these *manifold constraints* to capture loop closure constraints, end-effector constraints etc. 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 $i.e.$ $K_{iab_i} : \boldsymbol{\chi}_{iab_i} \to SE(3)$. 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:

$$\begin{pmatrix} v_{iab_i} \\ \omega_{iab_i} \end{pmatrix} = \frac{\partial K_{iab_i}}{\partial \mathbf{r}_i} \frac{d\mathbf{r}}{dt} K_{iab_i}^{-1} = \boldsymbol{J}_i(\mathbf{r}_i)\dot{\mathbf{r}}_i \tag{4}$$

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[3]. The contact between the head and the IABs is mapped by the Jacobian

$$\boldsymbol{J}_{c_i}(\xi_h, \xi_{iab_i}) = \begin{bmatrix} \mathbf{I} & \hat{\boldsymbol{w}}(r_{c_i}) \\ \mathbf{0} & \mathbf{I} \end{bmatrix} J_{r_i}, \tag{5}$$

where $\boldsymbol{J}_{c_i} : \dot{\xi}_{r_i} \to \begin{bmatrix} v_{c_i}^T, & w_{c_i}^T \end{bmatrix}^T$, $r_{c_i} \in \mathbb{R}^3$ is a vector between the head reference point (e.g. the center of mass) and the contact with the $i^{th}$ IAB, $\xi_h$ is the position and relative orientation of the head, $\xi_{iab_i}$ is the position and relative orientation of the $i^{th}$ soft robot in world coordinates, $\hat{\boldsymbol{w}}(r_{c_i})$ is an anti-symmetric matrix for the vector $r_{c_i}$, and $\xi_r = (\xi_{r_1}, \xi_{r_2}, \cdots, \xi_{r_k}), (1 \le k \le n)$ are the positions and orientations for each of the IABs. For $\mathcal{C}^2$-smooth $k$-constraint functions $G_1, \ldots, G_k$ $(1 \le k \le n)$, a constraint is fulfilled when $g_i(\xi) = 0$ and we write out the composite constraint function $G : \mathbb{R}^n \to \mathbb{R}^k$ with respect to the contact Jacobians as

$$G_i^T(\xi_h, \xi_{iab_i})\xi_h = B_i^T(\xi_h, \xi_{iab_i})\boldsymbol{J}_{c_i}(\xi_h, \mathbf{r}_{r_i})\dot{\xi}_{iab_i} \tag{6}$$

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). Therefore, for $k$ actuators in the soft robot, we have the following manipulation constraint

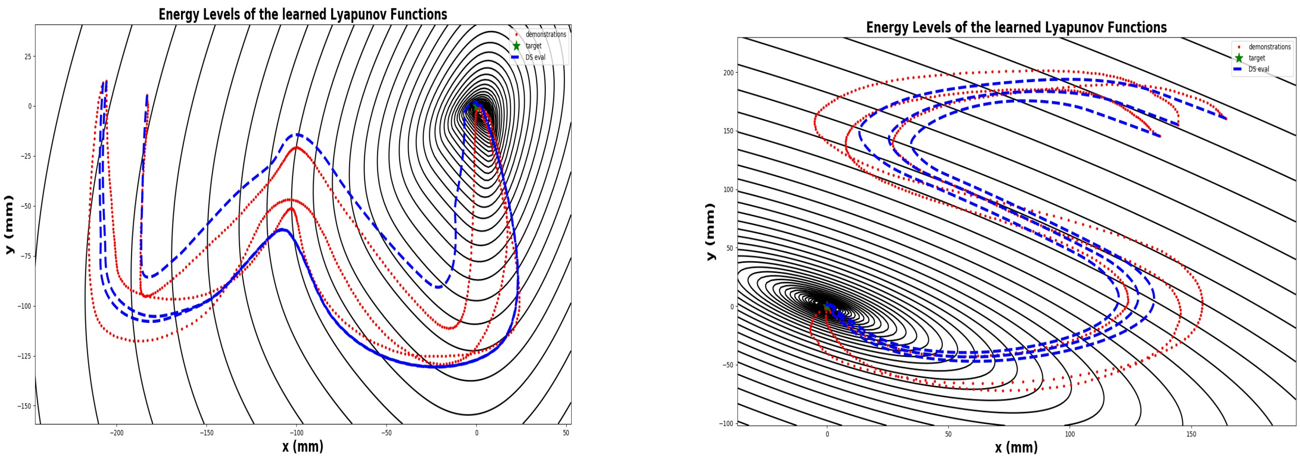
$$\begin{bmatrix} G_1^T \\ \vdots \\ G_k^T \end{bmatrix} \begin{pmatrix} v_h \\ w_h \end{pmatrix} = \textbf{diag} \begin{pmatrix} B_1^T \boldsymbol{J}_{c_1} \\ \vdots \\ B_k^T \boldsymbol{J}_{c_k} \end{pmatrix} \begin{pmatrix} \dot{\mathbf{r}}_{iab_1} \\ \vdots \\ \dot{\mathbf{r}}_{iab_k} \end{pmatrix}. \tag{7}$$

The details of this derivation are presented in my unpublished work [32]. We call $\mathcal{M}_{free}$ the free constraint manifold of the overall manifold, $\mathcal{M}$, which is defined as $\mathcal{M}_{free} = \mathcal{M} \cap \mathcal{Q}_{free}$.

**Problem 1** (Constrained RCLF Motion Planning)**.** *Find an RCLF collision-free path $\sigma^\star : [0, 1] \to \mathcal{M}_{free}$ 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.*

**Expected results:** Previously, the stabilizing command for items 1 and 2 in subsection B above was computed 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 [67], 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 [68]), are reprinted in Fig. 10. When the problem identified in Prob. 1 is solved, I should expect my results to provide better trajectory tracking than the non-RCLF implementation I implemented in [68] owing to the account for all possible manifold constraints in the problem formulation.

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




*(a)* Reproducing a nonlinear W-shape motion

*(b)* Reproducing a nonlinear S-shape 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.

### $K_{99}$ Aim III: Mechanism Assembly. Phantom and Healthy Volunteer 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. Thus, most serially-joined manipulators are stiffened during the manufacturing process – thus, inherently exhibiting a high load-to-weight ratio and a complicated actuation system. Moreover, their passive bending stiffness overwhelms the degree of deformation. 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 (albeit at the expense of a reduced workspace), 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 [69].

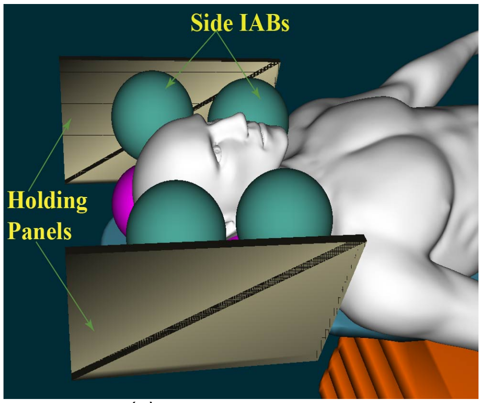
**Hypothesis.**

Owing to the success of parallel robot mechanisms at precise manipulation tasks [6,24,70–72], **I hypothesize that a parallel soft-manipulator mechanism will yield the desired submillimeter and subdegree accuracy necessary for online, real-time head motion control in MRI-LINAC RT.**

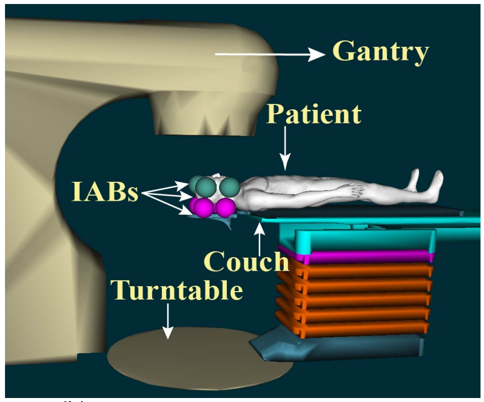
**Procedure.**

**A. Head Motion Correction in $\mathbb{SE}(3)$:** I will systematically synthesize and analyze parallel soft robot manipulators for head and neck motion correction in MRI-LINAC systems. I will then leverage the kinematics and kinetics of soft manipulators which I proposed in [32] to construct the hierarchical motion planner in Aim II. Synthesizing multi-DOF parallel soft robots is challenging given the inter-dependency of the parameters that characterize the deformation, the individual robot constraints' relative three dimensional orientation, permitted motion orientations, the three dimensional relation between constraints and allowed motions, and the possibility of multiple assembly modes that may result in the same end-effector pose [70]. 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 ssuperior-inferior (SI) axes. I 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.

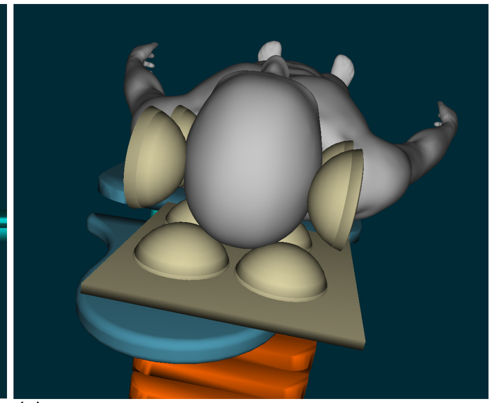
Fig. 11b shows an example standalone motion correction prototype for an IMRT system while Fig. 11c shows the proposed mechanism for MRI-LINAC systems (without MRI coils). Owing to the modular design, the coils of an MRI can be easily integrated onto this mechanism. In a parallel kinematic manner, the soft domes are positioned around the patient's cranial region while the patient lies supine on a typical MRI/RT treatment couch (Fig. 11b). The soft domes will be held in place around the head by impact-resistant low-temperature rigid PVC foam insulation sheet that is encased in 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 for different patients. The side actuators will correct head motion



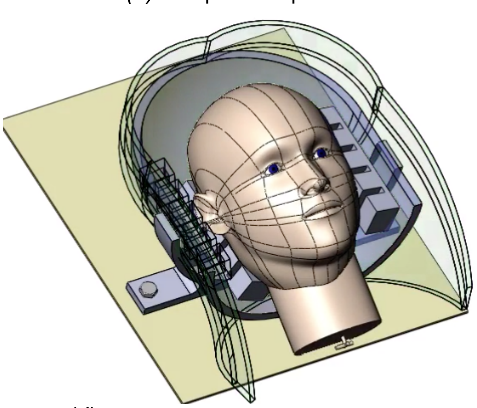

*(a)* Setup close-up view.



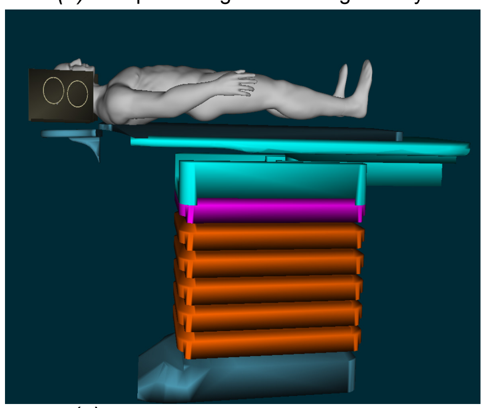

*(b)* Setup showing IMRT configurability.



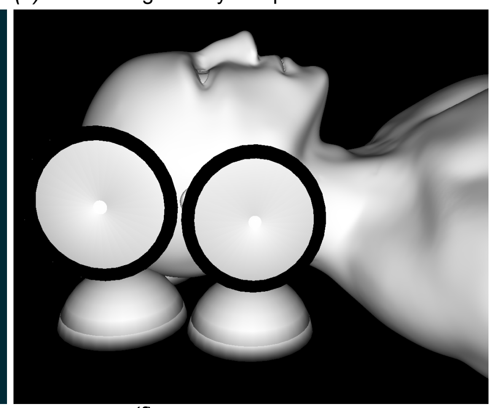
*(c)* SRS configurability setup with IAB Half-domes.



*(d)* Wearable setup under MRI Coils.

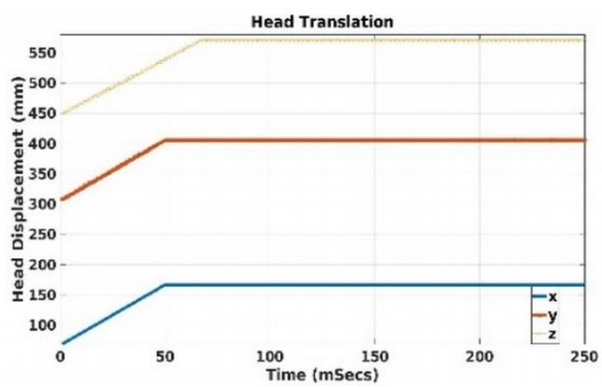


*(e)* Patient, IABs holders and couch.

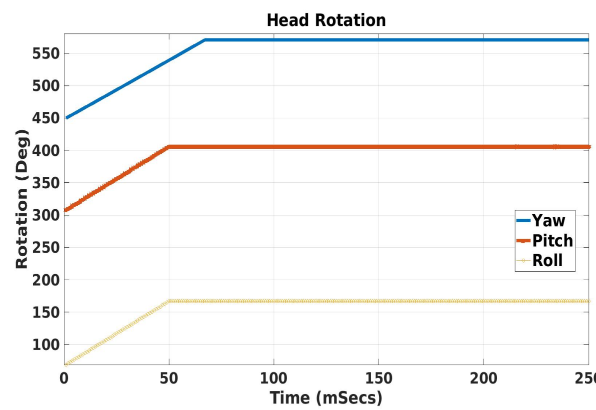


*(f)* Patient-Robot System.

Figure 11: Proposed MRI-compatible LINAC patient motion compensation system.




*(a)* Translational motion.




*(b)* Rotational motion.

Figure 12: Open-loop setpoint-following for patient's head motion in $\mathbb{SE}(3)$. Reprinted from [17].

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. These will conform deformation in a non-Gaussian fashion through an appropriate configuration of fiber-reinforcing (see videos). The domes underneath the forehead would control pure $z$ translation and pitch rotasry motions.

In preliminary work [32], I have synthesized differential kinematics [73], continuum mechanics [74, 75] and multi-bodied kinematics. Equation (7) 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, $v_h, \omega_h$ respectively in world frames. We can easily find the pseudo inverse of the manipulation map, $G$ in (7), so as to determine head velocity on the treatment couch. The derivation of this equation is detailed in [31].

**B. Expected Results:** I would expect that my results will follow the open-loop head motion control simulation results in the

SOFA [76] framework as presented in my recently accepted publication [17] using the proposed setup of Fig. 11f: raising or rotating the head in $\mathbb{SE}(3)$ resulted in steady-state reference trajectory tracking along all 6-DoFs of head motion as shown in Fig. 12.

$R_{00}$ **Aim: Patient oncological clinical trials.**

To verify accuracy of delivered dose, a complete end-to-end evaluation of the robotic MRI-compatible RT system will be conducted using anthropomorphic phantom studies. From the preliminary data (Fig. 3, 5, 12), whereupon excellent agreement was found between head motion and given target trajectory using the adaptive controller proposed in [24]. Once we ascertain the efficacy of this, we will move to healthy human volunteer trials.

**Statistical Plan:** Phantom-based and healthy human volunteer trials will be conducted after we finish the design and build of the proposed system. A complete 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 MRI-compatible RT plans. A 20 volunteer study with a mock radiation beam will be conducted in a clinical environment to verify 6DOF head control and patient safety systems. A clinical study on 20 whole brain patients will be performed where validation of method will be determined by a statistical endpoint defining success as to whether or not the 6D intracranial target is $\leq 0.5$mm and $\leq 0.5°$ for greater than 95% of the treatment time.

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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

**Laboratory.** The research described within this application will be carried out in the John Morgan Building (JMB), which is located in the School of Medicine (SOM). The 209,167 square feet building houses the Johnson Pavilion (which contains the biomedical library with ad-hoc 3D printers freely available to students and researchers), Richards Laboratories, Anatomy Chemistry Building and through them to the rest of the Medical Complex. The department of radiation oncology is located less than a mile away in the Smilow center for translational research which houses all biological-related research fellows and faculties as well as staff.

The laboratory is in room 183 in JMB and it is equipped with two fume hoods, three compressed air supply outlets, three vacuum outlets, three gas supply outlets, two double workbenches, two double wall cabinets, and space for up to six researchers. Standard equipment in the lab include drilling machines, general-purpose mechanical cabinets (pliers, drill bits, and such), microscopes, two hand-wash sinks, and a first-aid kit. The lab is also equipped with an FDM 3D printer. The lab includes four double benches and workspace for ten researchers.

**Office.** As of the writing of this grant, I am the only research staff hat uses the lab. The applicant's mentor has an office which is directly connected to lab work-area. In addition, two similar rooms are connected to the common lab area that are not currently being actively used.

**Roberts Proton Therapy Center.**

The radiation therapy facilities in the medical school, as well as the faculties, students, postdocs and staff at Penn Medicine and Penn Engineering make the University of Pennsylvania an ideal institution to carry out this cutting-edge research in autonomous robots, computer vision, mechanobiology, and the physics of cancer. Its excellent faculties in the areas of expertise needed to successfully complete this research present an opportunity to learn from the best minds in the field and create a product that has a transformational clinical potential. Since we are part of the department of radiation oncology, the applicant and his mentor have full access to the Roberts Proton Therapy Center, which is located less than a mile away from JMB in the Smilow Center for Translational Research. The Roberts Proton Therapy Center combines the unmatched expertise of world-renowned radiation specialists with the latest technology and compassionate care. With five treatment rooms and a dedicated research room, the Roberts proton therapy center is the world's largest center that integrates proton with conventional radiation therapy. As this research proposal is multifaceted with components consisting testing the soft robot under standalone MR machines, RT machines or integrated MRI-LINAC RTs, no other location offers a better support for carrying out the research described in this work. In addition, in my independent years, I can leverage the connection with the Children Hospital of Philadelphia in evaluating the effectiveness of this robot on children going through radiation therapy.

**Scientific Environment.** Penn provides an outstanding intellectual and scientific environment for the proposed studies. The University offers a unique environment for research in the biomedical science, which significantly impacts on the research enterprise of Penn SOM. The Penn SOM was the first medical school in the United States, has a rich history as a research-intensive institution and continues to be an international leader in the generation of new knowledge and treatment modalities to improve cancer care. The multidisciplinary research at Penn's 12 schools is supported by numerous core facilities, has university wide standard trainings and services. The proximity of the buildings and schools allow for enhanced collaborations between faculty and across schools.

# Equipment

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

**Laboratory Equipment.**

- FDM 3D Printer;
- Instron testing machine;
- Hand tools set including pliers, cutters and snips hammer, spanners, hex keys, nut drivers, screw drivers, wrenches and wrench sets;
- Accessories such as batteries and chargers, crimping tool, and power tool accessories;
- Soldering station including soldering iron, solder, flux, and suction-based solder removal;
- Passive and active electronic components including carbon-film resistors, capacitors, transistors, integrated circuits and electronic prototyping boards;
- Microscope;
- Pneumatic air outlets.

## List of Referees

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