Review of Thesis Proposal – 1 st draft

Reviewer Name: Arushri Swarup
Investigator Name: Kevin Luo
Peer Review Committee #: 9
Project Title: Groove cutting topology selection to eliminate the snapping problem in concentric tube manipulators

Brief description of project (to be completed by reviewer):

This project will be modeling, fabricating and testing cut patterns on tubes in order to optimize concentric tubes to improve the stiffness ratio and range of motion of the concentric tube robot. Modeling using FEM software will determine the optimal topologies to be fabricated and then tested. Stiffness will be optimized so that the tubes do not snap while being used.

In addition to your detailed comments and corrections within the document, please answer the following questions and provide explanations/suggestions where appropriate.
1. Are the objectives/research questions clear? Yes
2. Is the literature review appropriate and complete? Yes – describe why nitinol is good and what the limitations of minimally invasive surgery are and how concentric tube robots will address these limitations
3. Is the rationale for the study coherent and complete? yes
4. Is the research innovative? yes
5. Are the methods (design, measurement, analysis) appropriate to achieve the objectives? Yes, as explained
6. Are the expected study outcomes compelling and complete? Is there a dissemination plan and timeline? yes
7. Is the study feasible? yes
8. Is the organization of ideas clear and easy to follow? yes
9. Was the document easy to read and understand? Yes – good flow and easy for a person who is unfamiliar to the research to read and understand
10. What is your overall assessment of the project? Interesting project! Seems like it’s feasible and requires both design and validation.
11. Please identify major issues and specific recommendations. See comments in the proposal. Well done!

Lastly, based on your review, please complete the evaluation form on the following page and identify areas where improvements are needed.

Institute of Biomaterials & Biomedical Engineering
UNIVERSITY OF TORONTO

Groove cutting topology selection to eliminate the snapping problem in concentric tube manipulators

M.A.Sc Thesis Proposal

Kevin Ai Xin Jue Luo

30.10.2016

Supervisor: Dr. James Drake

Institute of Biomaterials and Biomedical Engineering
Theme: IBBME Theme: Engineering in a Clinical Setting & Clinical Engineering

CIGITI Centre for Image Guided Innovation & Therapeutic Intervention

SickKids

Abstract:

Background: Recently, there has been intensive research in the use of concentric tube robots for minimally invasive surgery. A concentric tube manipulator consists of one or more pre-curved tubes inserted within another tube that is fixed. Relative rotational and translational motion between the tubes will result in movement of the distal tip of the manipulator. One major issue associated with concentric tube manipulators is the occurrence of the undesirable snapping phenomenon. **Aim and Methodology:** This proposed research aims to evaluate methods of eliminating the snapping problem by laser cutting topologies, (i.e. grooves/slots) in order to reduce the ratio between bending stiffness and torsional stiffness of the tube. The effect of these groove topologies will be first simulated using FEM software. The different topologies will be evaluated based on the decrease in stiffness ratio as well as increase in maximum local stress. The best performing topologies will be manufactured and tested to see if snapping is eliminated and if the strength of the new tube holds up. **Expected Results:** We expect to see that while most of the chosen topologies improve stiffness ratio, there are 2 to 3 topologies that perform better than others. **Significance:** This research could potentially make the choice of concentric tube cutting topologies easier in the future, so that the snapping problem is avoided.

Keywords: *concentric tube, laser cutting, snapping, surgical robot, topology, groove, stiffness ratio*

Introduction:

In recent years, there has been extensive innovative research on the uses of concentric-tube telescopic robots in minimally invasive surgery. A concentric-tube system is a set of two or more metal tubes in which one tube is inserted into the next tube. In a set of two tubes, at least one of the tubes is pre-curved at the distal end. The translational and rotational degrees of freedom of the pre-curved tube are individually actuated at the tube's proximal end. If a system consists of more than one pre-curved tube, then each pre-curved tube would typically be actuated to separately rotate and translate in their length-wise direction with respect to one another [1]. As each tube moves with respect to another, their differing curvatures and orientations would cause the tubes to conform to one orientation for the portion of their lengths that are overlapping. Thus, by actuating the rotation and translation of each tube at the proximal end, we can steer a very small distal end of the innermost tube (on the scale of a few millimetres in diameter) in a confined space. The ability to not only precisely steer the end effector but also the shape of the entire length of the concentric tubes makes this method especially suitable for minimally invasive surgery [1]–[4].

One mechanical limitation that exists with the use of pre-curved concentric tube robots is the occurrence of the "snapping problem" [5], [6]. As pre-curved tubes move with respect to one another, they build up stored elastic energy due to both bending and torsion. The stable orientation and shape of the concentric tubes is where the stored energy is at a minimum. However, there can at times be more than one minima [5]–[7]. When this occurs, the shape can suddenly change, exhibiting an undesired snapping motion.

Background and Literature Research:

Review of the snapping problem:

When a set of two tubes are chosen such that there are more than one local minima in the energy landscape, snapping can occur, and this is known as bifurcation. This is highly unwanted for surgical applications because having such instabilities make it extremely difficult for an operator to work with. The critical point at which bifurcation occurs has been analyzed by DuPont et al. [8], and it can be avoided if the inequality (1) is satisfied.

$$L\sqrt{\kappa_1\kappa_2\frac{\frac{E_2I_2}{G_2J_2}+\frac{E_2I_2}{E_1I_1}\frac{E_1I_1}{G_1J_1}}{1+\frac{E_2I_2}{E_1I_1}}} < \frac{\pi}{2} \qquad (1)$$

Here, the parameter L represents the length of overlap between tubes 1 and 2. K1 and K2 are expressions of the curvatures of each of the tubes. E and G are the elastic and shear moduli respectively, and I and J are the area moment and polar moment of inertia respectively. (1) Shows that one approach to avoiding bifurcation is by minimising the extent of curvature of one or both of the tubes. However, one drawback to this is that a tube with less pre-curvature would result in a smaller workspace. This would limit the range of the range of motion of the robot and detriments the capabilities of a concentric tube system [6].

Previous Efforts:

An alternative approach would be trying to minimize the ratio EJ/GJ, which represents the quotient of bending stiffness over torsion stiffness. It has been shown in the past that it is possible to reduce this ratio by cutting groove topologies (patterns) on the tube in order to decrease area moment of inertia, and thus reducing the stiffness ratio [6], [7].

This method has been shown to be viable by Azimian et al. [ref] and Kim et al. [ref]. In the aforementioned research, both experimental results and FEM simulations show that the EI/GJ ratio is reduced by cutting groove topologies similar to that shown in figures (1) and (2). Research by Azimian et al. [7] and Kim et al. [6] has also shown through experiments that cutting grooves/slots on the tubes was capable of eliminating the snapping problem that existed without the grooves.

The majority of research on the mechanical properties of concentric tube systems has been performed with a super elastic nickel-titanium alloy named nitinol as the tube material [7], [9]–[12] . Nitinol is a super-elastic alloy that can be re-shaped easily by heating a specimen to above its transition temperature, and has high yield strains compared to most other metals such as steel and aluminum.

While previous research has identified that groove cutting is a viable method to avoid the snapping problem, effects of factors such as reduced yield strength has not been extensively explored. Furthermore, no attempt has been made in experimentally testing a sufficiently wide variety of groove topologies in order to identify which patterns are superior when the above two factors are considered. These factors are relevant because if one of the concentric tubes becomes plastic during an operation, its movement will be extremely difficult to predict and control [6]–[9].

Project Aims, Research Questions, Hypotheses and Methodology:

Aim 1: Use FEM simulation to characterize and rate a series 20 well-differed groove topologies based on their effect on the reduction of 1. bending to torsion stiffness ratio, and 2. bending strength.

Research Question: How will the choice of groove topologies aimed at reducing the bending to torsion stiffness ratio affect limiting factors such as decreased bending strength?

Hypothesis: Through simulation, it will be shown that while certain groove topologies have greater effect in reducing stiffness ratio, they may also prove to be more detrimental to the strength of the tube. This will lead to an identification of 5 to 10 groove topologies that have relatively better performance (when all aforementioned factors are considered).

Methods:

20 different cut topologies will be chosen and created using 3D modeling software. These cut patterns should all be designed to remove more material in the lateral direction than in the longitudinal direction. This is so that the decrease in the area moment of inertia in the Y-X plane is more than the polar moment of inertia decrease in the Y direction (refer to figure 3). These

models will then be put in to ANSYS FEM software and simulated separately under torsional load and bending load. The displacements under torsional and bending stress will be used to obtain torsional stiffness GJ using equation (1) and bending stiffness EI using equation (2) respectively.

$$\theta = L\ T\ /\ (J\ G) \quad (1)$$

$$\delta_{max} = \frac{Pl^3}{3EI} \quad (2)$$

Here, L represents the overall length of the tube, P represents the downward force creating the bending load, and T represents applied torque. Both loading conditions will consist of a single torsion or bending load at the distal end of the tube. The stiffness values from these results will be compared to the results of a simulation performed with an unmodified tube of the same thickness, diameter, and length.

As part of the simulation, the element under highest stress will be examined, and the stress will be compared to the maximum stress exhibited on a tube without cut patterns. The hypothesis implies that the maximum stress in cut tubes will be higher. 5 to 10 different groove topologies based on their ability to decrease the stiffness ratio while also minimising the increase in maximum stress.

Aim 2: Use test equipment to test the selected grooved tubes in order to verify simulation results of decrease stiffness ratio, while also testing to see if the grooved tubes exhibit yielding.

Research Question: Do the results of experimental testing of groove topologies comply with theoretical implications derived from FEM simulation? Specifically, is the snapping problem eliminated as predicted, and do the tubes yield during movement?

Hypothesis: The grooved tubes will not exhibit snapping under test conditions that are identical to conditions and parameters prescribed in the FEM simulation. However, some tubes will show signs of local yielding, which will help us point to two or three optimal tube cut patterns that do not yield.

Methods: After choosing 5 to 10 groove topologies, these topologies are then cut out from identical tubes using a laser tube cutting machine. This type of pattern cutting has been shown to be accurate enough to suit the needs of this experiment. Laser cutting has been used in manufacturing nitinol tube structures in the past [6], [7], [12]. These tubes will then be tested in a torsion testing setup built for this specific purpose, this will tell us the torsional stiffness. The bending stiffness will then be tested using an Instrom tensile testing system. The bending to torsional stiffness ratios of each tube will then be compared to that of the unmodified tube with the same length, diameter and wall thickness.

Next, the tubes will be set into an aluminum mold that defines the pre-curvature of the tube, and then heated to above nitinol's transformation temperature. This pre-curvature will be selected so that an unmodified tube will exhibit snapping when reaching the extents of its workspace. The unmodified tube will undergo this process as well. Each tube will then be placed within a larger tube of the same curvature in an experimental setup. The larger tube will be fixed while the smaller tube is actuated and turned. The unmodified tube will be tested first to confirm that snapping does occur at some point in its workspace. The cut tubes will then be tested to see if snapping occurs in them. This process will be done using video tracking, with a camera placed so that it sits in front of the testing setup, facing the distal end of the concentric tubes. To determine if plastic yielding is occurs, a cycle of movement will be repeated for 20 times to see if the path of the distal end remains consistent every time. This is because once nitinol reaches its yield stress, it loses elasticity and does not return to its original shape when load is taken away.

Expected Results:

We expect to see through FEM simulation that the majority of the 20 selected tube topologies will have a lower bending to torsional stiffness ratio EI/GJ than the unmodified tube. The relatively large variety of topologies chosen will give us a better idea of which kind of patterns and pattern parameters will yield better results. We also expect to see that the bending and torsional stiffness ratio is shown to be lower in cut tubes through experimental testing. We expect to eliminate the snapping problem in the two-tube experimental setup, while also seeing that some of the tubes show yielding.

Timeline:

The general proposed timeline for this research is presented in form of a Gantt chart (see Appendix Table 1). The start date is considered to be September 2016, and the end date is targeted to be September 2016.

Dissemination Plan:

The results of this research could potentially yield one peer-reviewed publication.

1. Groove cutting topology selection to eliminate the snapping problem in concentric tube manipulators.

This can be potentially published in the journals:

1. IEEE Transactions in Robotics

2. Mechanism and Machine Theory

Conclusions and Significance:

This study will point out which topologies of groove cutting perform better in concentric tube robots through both simulation and experiments. This makes future choices of tubes and tube cutting topologies much easier and provides rationale. This study provides multiple solutions to eliminating the snapping problem whenever it poses a problem to designing for a specific surgical operation.

Appendix A: References

[1] Dupont P Dupont P Gosline A Vasilyev N Lock J et. al., “Concentric Tube Robots for Minimally Invasive Surgery,” *Hamlyn Symp. Med. Robot. 2012*, 2012.

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[4] C. Bedell, J. Lock, A. Gosline, and P. E. Dupont, “Design optimization of concentric tube robots based on task and anatomical constraints,” in *2011 IEEE International Conference on Robotics and Automation*, 2011, pp. 398–403.

[5] W. I. R. Gilbert H, Hendrick R, “Elastic Stability of Concentric Tube Robots: A Stability Measure and Design Test,” *IEEE Trans. Robot.*, vol. 32, no. 1, pp. 20–35, 2016.

[6] J.-S. Kim, D.-Y. Lee, K. Kim, S. Kang, and K.-J. Cho, “Toward a solution to the snapping problem in a concentric-tube continuum robot: Grooved tubes with anisotropy,” in *2014 IEEE International Conference on Robotics and Automation (ICRA)*, 2014, pp. 5871–5876.

[7] D. J. Azimian H, Francis P, Looi T, “Structurally-redesigned concentric-tube manipulators with improved stability,” *2014 IEEE/RSJ Int. Conf. Intell. Robot. Syst.*, pp. 2030–2035, 2014.

[8] B. E. Dupont P, Lock J, Itkowitz B, “Design and Control of Concentric-Tube Robots,” *IEEE Trans. Robot.*, vol. 26, no. 2, pp. 209–225, 2010.

[9] R. J. Webster, J. M. Romano, and N. J. Cowan, “Mechanics of Precurved-Tube Continuum Robots,” *IEEE Trans. Robot.*, vol. 25, no. 1, pp. 67–78, Feb. 2009.

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[11] M. T. Chikhaoui, K. Rabenorosoa, and N. Andreff, “Kinematics and performance analysis of a novel concentric tube robotic structure with embedded soft micro-actuation,” *Mech. Mach. Theory*, vol. 104, pp. 234–254, Oct. 2016.

[12] A. T. Tung, B.-H. Park, Gü. Niemeyer, and D. H. Liang, “Laser-Machined Shape Memory Alloy Actuators for Active Catheters,” *IEEE/ASME Trans. Mechatronics*, vol. 12, no. 4, pp. 439–446, Aug. 2007.

Appendix B: Figures and Tables

Figure 1: 3-D model of modified tube topology used by Azimian et al. [7]

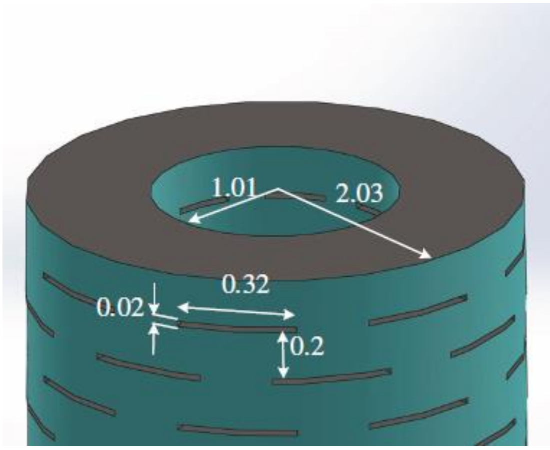

Figure 2: Modified tube topology used by Kim et al. [6]

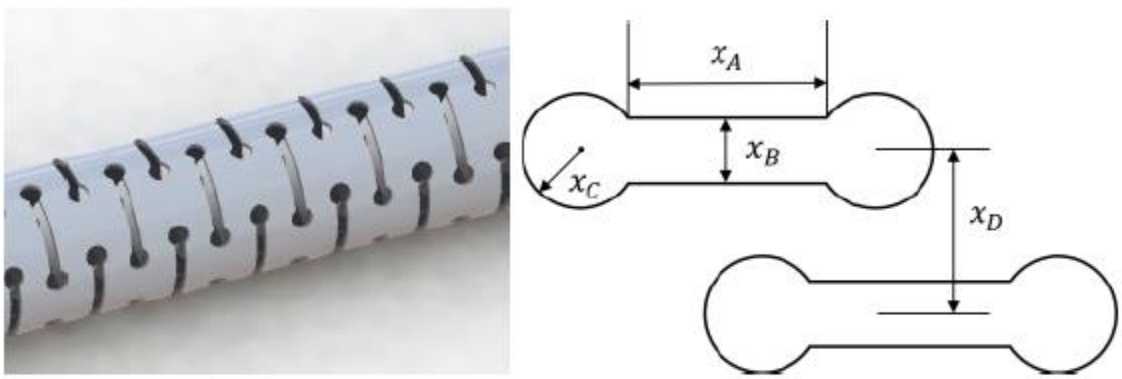

Figure 3: (left) view of tube in the XY plane, (right) view of tube in the Y axis cross section

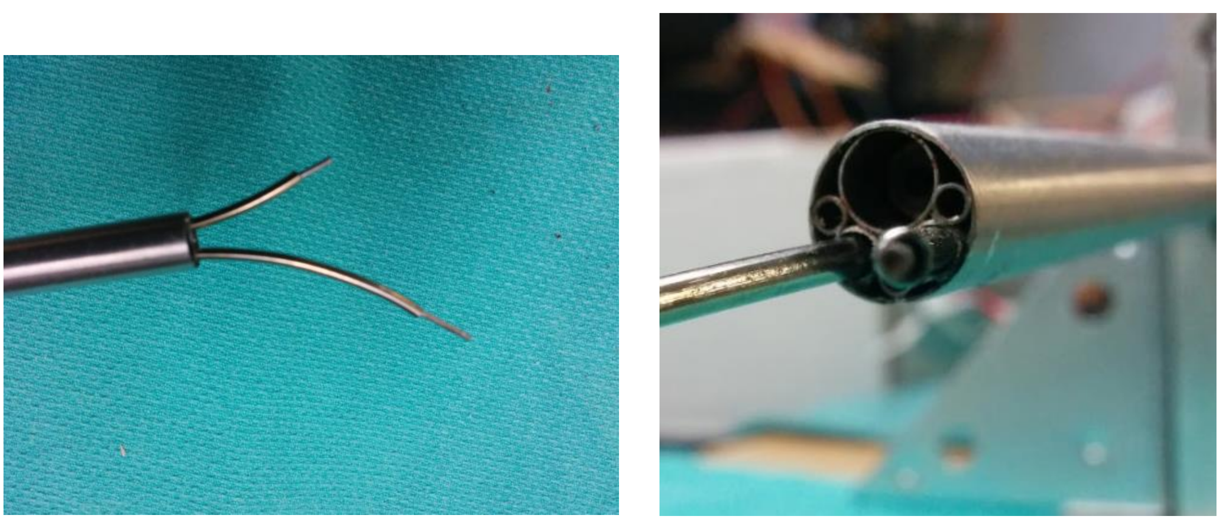

Table 1: Gantt Chart Timeline of Research Activities over 24 months

Activity	Time (Months)											
	2	4	6	8	10	12	14	16	18	20	22	24
Literature review												
Thesis proposal formulation												
Preparation for first Committee meeting												
Building of tension testing setup												
Procurement and testing laser cutting machine												
Creating 3-D models of 20 groove patterns												
Running FEM Simulations of 20 tubes												
Analysis of FEM simulation results and comparison												
Cutting selected groove patterns												
Torsion and bending testing of tubes												
Testing of tube to see if snapping exists												
Analysis of results from experiments												
Writing: Publications												
Writing: Thesis												
Thesis Defense												

Kevin Luo

Components	Description	Mark	Areas for Improvement
Abstract	Short (<400 words); Presents a concise summary of what's to come including: background/rationale, objectives/questions, methods, expected results/significance	10 /10	good, concise, clear
Rationale/Motivating Problem	Describes the clinical or practical problem; Convincing rationale noting the social implications and/or need	8 /10	good - explaining why C.T.'s are required for MIS.
Background/Literature Review	Provides the reader with the knowledge needed to understand the proposed research; synthesizes previous research and knowledge in the field	9 /10	yes - explain why nitinol is good.
Objectives/Research question & hypotheses	Specific and focused; Quantitative and precise	10 /10	yes - good - clear, thorough
Methods	Sufficient detail to convey what and how you plan to address your objectives/questions; descriptions of special equipment, design, & protocols; description of planned data analyses	15 /15	veery good - detailed, organized, thorough, clear
Expected Results/Outcomes	Preliminary results (if applicable); Expected results; Timeline; Dissemination plan	10 /10	
Significance/Conclusions	Description of the contributions your proposed research will make; What are the implications of your research?	8 /10	elaborate on the implications clinically
Citations/References	Appropriate formatting; key papers referenced; appropriate number to support proposal; mixture of types (e.g. journals and conference papers)	5 /5	
Itemized response to peer reviews	Provides complete and thoughtful responses to peer review feedback; justifies choices and/or makes revisions as appropriate	5 /5	
Overall			
Organization	Use of sub-headings; logical flow	5 /5	
Presentation	Use of graphs, charts and figures; formatting	5 /5	well explained.
Readability/grammar	Language, spelling, grammar	5 /5	good flow - easy to read & follow
	Total	95 **/100**	**/100**

Real-time Motion Tracking of Abdominal Targets based on MRI

by

Tianyu Zhou

A thesis proposal submitted for BME1450 Bioengineering Science
IBBME Theme: Engineering in a Clinical Setting & Clinical Engineering

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November 4, 2016

Abstract

Neuroblastoma is the most common extracranial solid tumour in children 0-14 years of age. The proximity of sites of neuroblastoma to the renal artery poses challenges for conventional surgery. High-intensity focused ultrasound (HIFU) is a non-ionizing, non-invasive therapeutic technology that is particularly suited to thermally lesion internal abdominal targets, and is thus a promising alternative in treating neuroblastoma. Magnetic resonance (MR) thermometry provides real-time thermal mapping and dose calculations for monitoring the HIFU procedure. However, smaller targets of pediatric patients demand accurate HIFU monitoring to ensure the safety of healthy tissues in close proximity. Abdominal targets undergo a range of motions as well as non-rigid deformations, which give rise to artifacts in MR thermometry, and also demand for precise tracking of the HIFU focal point with the target. A hybrid method (Principal Component Analysis and Projection onto Dipole Fields, or PCA-PDF) has been shown to be feasible to correct for MR thermometry in real-time. However, more *in vivo* experiments are in need to validate this method. In addition, a method is needed to quantify the motions and deformations of the targets, and this method needs to be validated in *in vivo* HIFU treatments for clinical translation. This research will first validate the PCA-PDF motion compensation method. Then the traditional optical flow tracking technique will be adapted to current framework as the gold standard. Next, the learning-based fusion method will be implemented and optimized as the proposed solution. Both methods will be tested in *in vivo* experiments and their performances in accuracy, precision and speed will be compared. It is expected that all methods investigated will consistently meet the performance requirement of a real-time MRg-HIFU intervention, and that the learning-based fusion method will outperform the gold standard optical flow tracking method, in terms of accuracy, precision, and speed. The research will demonstrate the feasibility and safety of MRg-HIFU for non-invasive treatment of neuroblastoma. Results from this project will support the safe application of MRgHIFU in the abdomen and will lead to novel clinical studies using MRgHIFU for neuroblastoma in children.

Keywords: real-time MR-guidance, motion analysis, high intensity focused ultrasound

1. Introduction

Neuroblastoma is the most common extracranial solid tumour in children 0-14 years of age [1], forming most often in the adrenal gland or kidneys. Its proximity to the renal artery poses challenges for conventional surgery. High-intensity focused ultrasound (HIFU) is a non-ionizing, non-invasive therapeutic technology that is particularly suited for creating localized thermal ablation in diseased internal organs such as the kidneys, liver, pancreas, and spleen. HIFU is advantageous in treating pediatric neuroblastoma over conventional surgery, due to the following: ~~to the facts that~~

1) The smaller-sized anatomy of pediatric patients posess ~~more~~ greater risk~~s~~ for conventional surgery, compared to larger adult-sized anatomy.
2) The HIFU beam is able to penetrate deeper into the tissue to reach the target anatomy in ~~a~~ smaller ~~anatomy~~patients.

~~However, with the advantage~~However, there are also ~~come~~ challenges with this technique. Smaller anatomical targets of pediatric patients demand accurate HIFU monitoring to ensure the safety of healthy tissues in close proximity.

Magnetic resonance (MR) thermometry provides real-time thermal mapping and dose calculations for monitoring the HIFU procedure, as well as signaling for the end point of the therapy. However, throughout the procedure, abdominal targets undergo a range of motions including respiratory motion, long-term motion (e.g. peristalsis), spontaneous motion (e.g. coughing, twitching) [2] as well as non-rigid deformations. These motions are responsible for artifacts in MR thermometry (data?). Moreover, the movements and deformations of the targets also make sustained sonication challenging, since dynamic repositioning of the HIFU focal point is required. Sustained sonication is preferred for highly perfused abdominal organs in order to achieve a sufficiently high temperature elevation to induce necrosis [3].

Comment [AS1]: Is the patient conscious during HIFU treatment? If so, I would mention that before this sentence

Comment [AS2]: Please define sonication

To correct for MR thermometry, a hybrid method has been designed and implemented that ~~was~~ is able to achieve a temperature stability and precision of 0.85 °C and 1.00 °C, respectively, in *in vivo* porcine and human kidneys [4]. However, more *in vivo* experiments are needed to validate and ~~to~~ streamline this method.

To facilitate dynamic refocusing of the HIFU beam in tracking the targeted organ, an automated method is needed to continuously quantify the organ motions and deformations. Previous studies have separately presented techniques for tracking of respiratory motion [2] and long-term motion [5], and method to bypass the scarce spontaneous motion [2]. However not all of the methods have been validated *in vivo*. Therefore, to address this knowledge gap, ~~To the best of the author's knowledge, there still yet exists~~ a~~a~~ solution ~~that~~ to quantify~~ies for~~ organ elastic deformations in HIFU procedure will be developed. All of the motions and deformations need to be accounted for in one integrated solution ~~package~~ platform to best estimate the overall target displacement. Furthermore, ~~the method as a package~~this platform ~~needs~~ will~~to~~ be validated through~~in~~ *in vivo* HIFU treatments for clinical translation.

2. Research Question and Hypothesis

Research Question: Can movement and deformation of abdominal targets be quantified in real time to facilitate focusing of the HIFU beam to track a target?

Hypothesis: Quantifying movement and deformation of abdominal targets in real time will enable the dynamic refocusing of the HIFU beam during *in vivo* treatments.

3. Objectives

The overall goal is to design, implement, refine, and evaluate a motion tracking algorithm to quantify abdominal organ movements and deformations during *in vivo* MR guided high-intensity focused ultrasound (MRg-HIFU) treatments.

Objective 1: Develop an integrated algorithm to quantify abdominal organ movements and deformations

Objective 2: Optimize the algorithm to achieve acceptable accuracy, precision and speed
Objective 3: Validate the algorithm ~~with~~ through *in vivo* (MRg-HIFU) treatments.

4. Literature Review

Jeremy Tan completed his Master's thesis entitled “*Motion Compensation using Principal Component Analysis and Projection onto Dipole Fields for Abdominal Magnetic Resonance Thermometry*” in 2016. His research focused on eliminating motion and susceptibility artifacts in MR thermometry that are caused by respiration (periodic) and peristalsis (aperiodic). In his study, a hybrid method was designed and implemented that combined principal component analysis (PCA) and projection onto dipole fields (PDF), both of which work on MR phase images without resorting to any external interaction or supplementary tracking tools. The method was shown to achieve a temperature stability and precision of 0.85 °C and 1.00 °C, respectively, in *in vivo* porcine and human kidneys [4].

Comment [AS3]: Tie each paragraph back to your objectives or hypothesis – how will each piece of literature that you have been talking about help you to achieve your objectives?

Formatted: Font: Italic

Comment [AS4]: I would split this sentence into two

In a recent study by Zachiu *et al*, an optical flow tracking technique that tracks respiratory motion was proposed. The proposed method improved upon the existing one based on the algorithm proposed by Horn and Schunck ~~(H and S),~~ which assumes that pixels conserve their intensity along their trajectory, to which a spatial regularity constraint of the estimated motion is added. It was tested in the livers and kidneys of two healthy volunteers under free-breathing conditions. Results showed that:~~,~~ the new method demonstrated greater robustness to local grey-level intensity variations introduced by arterial pulsations and~~; also showed was~~ compatibility with real-time MR-guided beam interventions, including MRg-HIFU. A limiting factor of this study is that it will not be validated ~~the lack of validation of the proposed method~~ under realistic beam therapy scenarios [2].

Comment [AS5]: Instead, write the year when the study was published

Comment [AS6]: How come? Is it too expensive? Does it take too much time? How does this statement relate to the study by Zachiu et al? Need a linking sentence here

Another recent study carried out by Zachiu *et al* exploited the episodic workflow of HIFU therapy to implement a motion correction strategy for long-term motion of the target area over the entire duration of the intervention. The authors proposed the integration of 3D MR scans in the therapy workflow during the inactivity intervals. Displacements were estimated using an optical flow algorithm applied on the 3D acquired images. A preliminary study was conducted on ten healthy volunteers and proved that slow physiological motion can exceed acceptable therapeutic margins. An *in vivo* experiment was conducted on a porcine liver, which validated the compatibility of the proposed motion correction strategy with the workflow of a MR-guided HIFU therapy under clinical conditions [5].

Comment [AS7]: date

Comment [AS8]: Will your experiments build upon this preliminary study? If so, please state that to clarify for the reader

In a book chapter ~~authored~~ by Wang *et al*, a probabilistic framework was presented that relies on anatomically indexed component-based object models which integrate several sources of information to determine the temporal trajectory of the deformable target. Large annotated imaging databases are exploited to encode the domain knowledge in shape models and motion models and to learn discriminative image classifiers for the target appearance. The chapter demonstrates various medical image analysis applications with focus on cardiology such as 2D auto left heart, catheter detection and tracking, 3D cardiac chambers surface tracking, and 4D complex cardiac structure tracking, in multiple modalities including Ultrasound (US), cardiac Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and X-ray fluoroscopy. Comparison studies were carried out in a 3D ultrasound and a 4D CT motion tracking cases that demonstrate better performance of the learning-based fusion method over the traditional optical flow method in accuracy [6].

Comment [AS9]: include book's name

Comment [AS10]: how does this chapter help your experiments/objectives? Need a concluding sentence that explains why this chapter is useful to your work

5. Methods

This research will first validate the PCA-PDF motion compensation method. Then the optical flow tracking technique will be adapted to current framework, available in the lab, as the gold standard. Next, the learning-based fusion method will be implemented and optimized as the proposed solution. Both methods will be tested in *in vivo* experiments and their performances in accuracy, precision and speed will be compared. The phases of the research are detailed as follows:

Comment [AS11]: gold standard means traditional method right? I would clarify here why it's the gold standard

5.1. Phase 1 – Validation of PCA-PDF motion compensation method for abdominal magnetic resonance thermometry

At least nine MRg-HIFU sonication experiments of abdominal targets in a healthy pig model are being conducted. Imaging is performed on Philips 3T Achieva scanner using 4mm regular cell. Datasets are collected during ventilated breathing and arrested breathing. Motion compensation software that

Comment [AS12]: why 9? Is it due to statistical reasoning, cost or time? Or a combination?

implements the PCA-PDF algorithm will be run both online and offline. Datasets will be processed to evaluate the accuracy and precision of this particular algorithm, and its processing time will be calculated to determine its feasibility in real-time MRg-HIFU interventions.

Comment [AS13]: What do you mean by this?

Specifically, the aim of the algorithm is to achieve: ~~it is aimed that the algorithm to achieve~~
a) An accuracy of ± 1 °C within the targeted cell and to ± 3 °C in the periphery~~, and~~
b) A processing time, for a single dynamic, less than the dynamic scan time of the MR sequence of 573 ms [4].

Comment [AS14]: Reference?

5.2. Phase 2 – Adaptation of optical flow tracking technique for tracking of respiratory motion and long-term motion (gold standard)

An improved optical flow tracking technique, as proposed by <insert author’s name here>~~in [2],~~ will be adapted to the in-house Python framework [2]. The algorithm can be mathematically expressed with the following function~~al~~ [2]:

$$E_{L2L1}(u,v) = \int\int_{\Omega} \left|I_x u + I_y v + I_t\right| + \beta^2(\|\nabla u\|_2^2 + \|\nabla v\|_2^2)\,\mathrm{d}x\mathrm{d}y$$

Comment [AS15]: I would describe each term more simplistically, so that someone who has never heard about this technology would be able to understand exactly what everything means

where Ω is the image domain, u and v are the components of the 2D displacement vectors and β is a user-defined weighting factor designed to link the data fidelity term (first term of the integral in equation) and the regularity of the estimated motion field (second term of the integral in equation). The minimization with respect to u and v will be done via the primal-dual algorithm [7]. Configuration parameters of the numerical scheme need to be tuned in order to ensure a fast convergence of the algorithm under various conditions in terms of noise/observed organ displacement amplitudes [2].

Comment [AS16]: Define what each parameter means and link it to your experiment

5.3. Phase 3 – Implementation and optimization of learning-based fusion method

Comment [AS17]: Clearly define and/or label the inputs and outputs of each algorithm shown and the significance to this phase

A promising learning-based fusion method will be implemented in Python as the proposed solution. To obtain shape models, discriminative image classifiers for target appearance are trained in this framework, using marginal space learning (MSL) [8] and the probabilistic boosting-tree (PBT) [9], as illustrated in Fig.1.

Comment [AS18]: Explain what each block in the diagram represents and its function

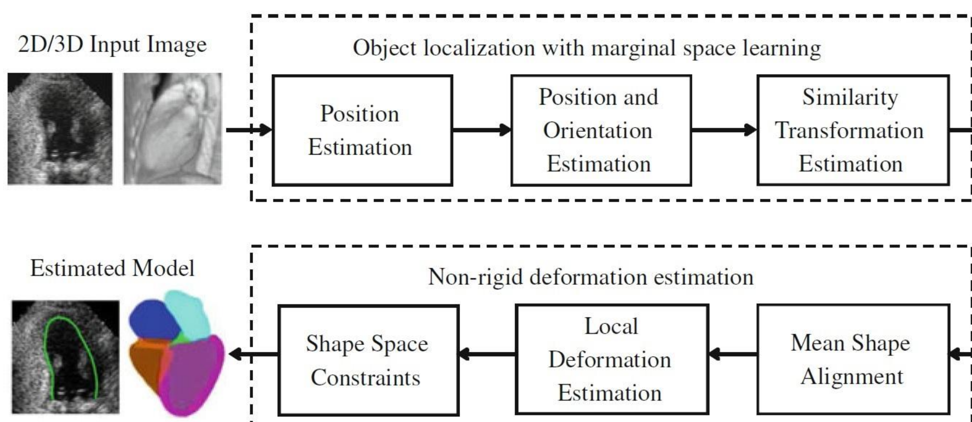

Fig. 1: Diagram for learning-based object detection and non-rigid deformation estimation [6]

To obtain motion models, manifold learning is then used to extract a compact form of the dynamic information [10].

Fused together, these lead to a nonparametric representation of the probability density function that characterizes the object appearance. Inspired by [11], tracking is performed by obtaining ~~independently~~

~~from each model~~ an independent motion estimate, from each model, and its uncertainty through a single probabilistic framework as follows:~~,~~

$$\arg\max_{\mathbf{X}_t} p(\mathbf{X}_t|\mathbf{Z}_{0:t}) = \arg\max_{\mathbf{X}_t} p(\mathbf{Z}_t|\mathbf{X}_t)\,p(\mathbf{X}_t|\mathbf{Z}_{0:t-1})$$

where $\mathbf{Z}0{:}t = \mathbf{Z}0, \ldots, \mathbf{Z}t$ are the image observations from the input image sequence $I0{:}t = I0, \ldots, It$. In this framework, an anatomy-indexed mesh model is built to represent the object of interest. The block diagram of Fig. 2 summarizes the workflow.

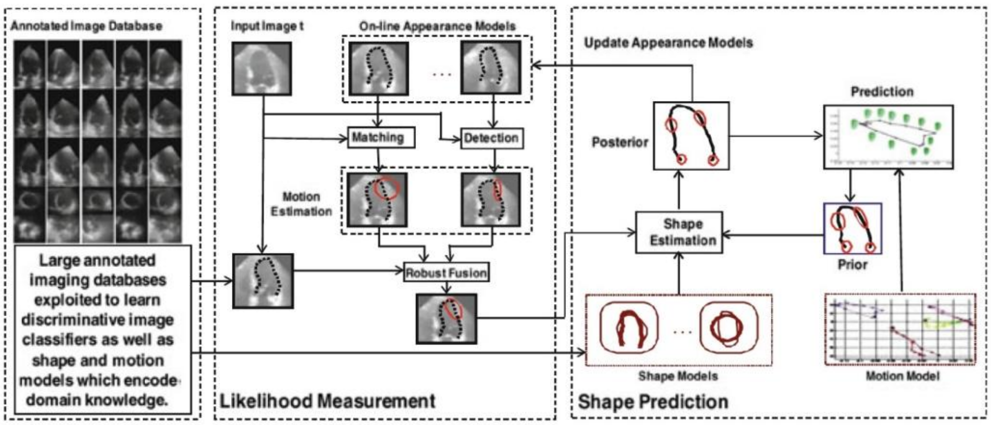

Fig. 2: A block diagram of the probabilistic motion estimation framework including the likelihood measurement and shape prediction processes [6]

Comment [AS19]: Explain what each part of the diagram means and what the outputs mean (ie. Shape prediction – is this the shape of the target? Link this back to the objectives)

After implementation, parameter tuning and optimization of the code will be carried out for accuracy, precision and speed.

5.4. Phase 4 – Validation of learning-based fusion method with *in vivo* experiments

The dataset obtained in Phase 1 will be used to test the learning-based fusion method. Accuracy and precision of the algorithm will be evaluated, and processing time will be calculated to determine its feasibility in real-time MRg-HIFU interventions. The algorithm aims to achieve, by voxel-wise estimation of displacement vectors, a consistent sub-voxel accuracy within 2.5×2.5×7 mm^3 voxel size [2]. Also it is aimed to have a processing time, for a single dynamic, well under the dynamic scan time of the MR sequence of 573 ms [4].

Comment [AS20]: Explain voxels

Comment [AS21]: Is this a good voxel size? Why is this a good or bad voxel accuracy? Maybe provide a threshold or reference voxel size that you can compare this one with. Please provide context.

6. Expected Results and Outcomes

It is expected that~~,~~ all methods investigated will consistently meet the performance requirement of a real-time MRg-HIFU intervention. Specifically, the motion compensation method will achieve an accuracy of ± 1 °C within the targeted cell and to ± 3 °C in the periphery. Both of the motion tracking methods, optical flow tracking and learning-based fusion method, will achieve, by voxel-wise estimation of displacement vectors, a consistent sub-voxel accuracy within 2.5×2.5×7 mm^3 voxel size [2]. All of the motion compensation method and the motion tracking methods will have a processing time, for a single dynamic, well under the dynamic scan time of the MR sequence of 573 ms.

In addition, it is expected that the learning-based fusion method will outperform the gold standard optical flow tracking method, in terms of accuracy, precision, and speed.

6.1. Progress and Timeline

The timeline for this thesis is depicted in Appendix A. Progress to date includes conducting a literature review to gather background information and creating a preliminary thesis proposal.

6.2. Dissemination Plan

This project could potential yield two peer-reviewed publications or one large publication.

1. Validation of Motion Compensation using Principal Component Analysis and Projection onto Dipole Fields for Abdominal Magnetic Resonance Thermometry
2. Real-time Motion Tracking of Abdominal Targets based on MRI using a learning-based fusion method

These papers could potentially be published in the following journals:

- Journal of Magnetic Resonance Imaging
- Computerized Medical Imaging and Graphics
- Magnetic Resonance in Medicine

7. Conclusions/Significance

These experiments will help design and develop treatment protocols, including MR pulse sequences, and the sonication parameters for the MRgHIFU system. The research will demonstrate the feasibility and safety of MRg-HIFU for non-invasive treatment of neuroblastoma. The long-term goal of the project is to use focused ultrasound to noninvasively treat neuroblastoma clinically. Results from this project will support the safe application of MRgHIFU in the abdomen and will lead to novel clinical studies using MRgHIFU for neuroblastoma in children.

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Appendix A – Timeline

	2016				2017												2018							
	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A
Literature review	■	■	■	■	■	■	■	■	■	■														
Write thesis proposal			■																					
HIFU experiments on pigs			■	■																				
Validate PCA-PDF method			■	■																				
Adapt optical flow technique					■	■																		
Implement LBF method							■	■	■	■														
Optimize LBF method											■	■												
Committee meeting #1													■											
Validate LBF method on pig dataset													■	■	■									
Validate LBF method on human dataset																■	■	■						
Write peer-reviewed publications																			■	■	■	■	■	
Write thesis																			■	■	■	■	■	
Presentation																				■				
Thesis defense																								■

Review of Thesis Proposal – 1 st draft

Reviewer Name: Arushri Swarup
Investigator Name: Tianyu Zhou
Peer Review Committee #: 9
Project Title: Real-Time Motion Tracking of Abdominal Targets based on MRI
Brief description of project (to be completed by reviewer):

This project will be developing an algorithm to quantify targets *in vivo* to focus a HIFU beam on a moving abdominal target. Using current technologies, PCA and PDF, an *in vivo* model will be validated after the algorithm is developed. As well, a learning based fusion method will be validated *in vivo* and will be compared to the optical flow tracking technique, which is the current framework.

In addition to your detailed comments and corrections within the document, please answer the following questions and provide explanations/suggestions where appropriate.

1. Are the objectives/research questions clear? Yes
2. Is the literature review appropriate and complete? Yes, but to clarify each piece of literature, explain its significance to objectives or hypothesis
3. Is the rationale for the study coherent and complete? Yes
4. Is the research innovative? Yes (as described by the knowledge gap)
5. Are the methods (design, measurement, analysis) appropriate to achieve the objectives? Yes - as seen in the plan and explanations
6. Are the expected study outcomes compelling and complete? Is there a dissemination plan and timeline? yes
7. Is the study feasible? yes
8. Is the organization of ideas clear and easy to follow? yes
9. Was the document easy to read and understand? Please use simpler language and simpler terms. Please write it as though explaining this to someone who is unfamiliar with the technology. I found some parts a little bit hard to understand because I am unfamiliar with the technology. Please see comments within the documents on how to clarify for the reader.
10. What is your overall assessment of the project? Well done and seems feasible to achieve for a Master's
11. Please identify major issues and specific recommendations. See above comments. Overall it is a good idea and project, just needs to be written for someone unfamiliar with the subject.

Tianyu Zhou

Components	Description	Mark	Areas for Improvement
Abstract	Short (<400 words); Presents a concise summary of what's to come including: background/rationale, objectives/questions, methods, expected results/significance	9 /10	clear & thorough good overview.
Rationale/Motivating Problem	Describes the clinical or practical problem; Convincing rationale noting the social implications and/or need	8/10	yes - good motivation - maybe include cost of neuroblastoma and how common it is (give a number)
Background/Literature Review	Provides the reader with the knowledge needed to understand the proposed research; synthesizes previous research and knowledge in the field	6/10	good overview of lit. seems thorough as it has a good flow leading to the proposed problem - doesn't leave reader with unanswered questions. but ensure that you link them back to your objectives to clarify why each piece is relevant.
Objectives/Research question & hypotheses	Specific and focused; Quantitative and precise	10 /10	good - clear, concise!
Methods	Sufficient detail to convey what and how you plan to address your objectives/questions; descriptions of special equipment, design, & protocols; description of planned data analyses	10/15	+ good orgalization - try to use simpler language so someone who is unfamiliar to this research would understand.
Expected Results/Outcomes	Preliminary results (if applicable); Expected results; Timeline; Dissemination plan	7 /10	explain voxels and why the 2.5x2.5x7 size is good or bad.
Significance/Conclusions	Description of the contributions your proposed research will make; What are the implications of your research?	7 /10	elaborate on significance - is this significant on other diseases as well? or if only for N.B., re-iterate how common it is and what the cost-saving would be or increased improved therapeutic effect.
Citations/References	Appropriate formatting; key papers referenced; appropriate number to support proposal; mixture of types (e.g. journals and conference papers)	5 /5	used books, thesis, and papers ✓
Itemized response to peer reviews	Provides complete and thoughtful responses to peer review feedback; justifies choices and/or makes revisions as appropriate	5 /5	
Overall			
Organization	Use of sub-headings; logical flow	5 /5	
Presentation	Use of graphs, charts and figures; formatting	3 /5	need ~~[illegible]~~ clearer explanation of figures ~~and sentence~~
Readability/grammar	Language, spelling, grammar	4/5	minor style edits (see doc. w/ notes)
	Total	79/100	/100