Control Interface For Autonomous Robotic Brain Surgery Using Magnetically Stimulated Particles

Team Name: Team Nson

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1. Executive Summary:

This document provides an introduction and proposed methodology for our team's senior design project in collaboration with George Mason University (GMU) and Weinberg Medical Physics LLC (WMP). The expected working timeframe is from Fall 2018 - Spring 2019.

Our project is the design and implementation of a software control interface for operating an electropermanent magnetic control system (MCS). This MCS is constructed by WMP to transport and activate magnetic particles loaded with therapeutic payloads inside the human body. Our project will operate the MCS to autonomously deliver these particles along a user-defined path.

The control interface will consist of 4 overarching modules coded in C++:

1) **Graphic User Interface (GUI)**
2) **Image Segmentation Module**
3) **Control Module**
4) **Physics Module**

Technical aspects for this project include, but are not limited to, a thorough understanding of magnetic fields and gradients, therapy carriers, MCS operational specifications, GUI design and functionality, software engineering, and C++ programming.

Contents of this proposal include:

- Proposed system design with justification against considered alternatives
- Detailed technical approach of the major system components
- Administrative aspects revolving around team organization and obligations
- Terms and conditions regarding safety, equipment, and handling of restricted data

2. Project Overview:

A. Preliminary Literature Review

Studies have shown that manipulating particles via magnetic stimulation is a promising method for noninvasive delivery of therapeutic payloads [1]. Over two decades since the first human trials, research in magnetic particle transport has greatly advanced and expanded. For example, Yu et al. conducted a magnetic particle imaging (MPI) study that used particles as a safe, high contrast imaging modality to highlight tumors inside rats [2]. Jahari et al. were able to induce a drilling motion on magnetic nanoparticles using Helmholtz coil pairs to result in more efficient deposition of the particles into the deep brain of mice [3]. However, achieving deep particle targeting faces major challenges such as magnetic field strength attenuation with distance into the body, lack of real-time imaging, and the complexity of control algorithms [1].

Research in robotic surgical systems are contributing to improve the safety and effectiveness of minimally invasive surgeries, by reducing surgeon hand tremors and margin errors [4]. For example, Opfermann et al.'s smart tissue autonomous robot (STAR) system was tested and found to be capable of tumor resection with greater accuracy than that of expert surgeons [4]. The system used imagine algorithms with Near Infrared (NIR) markers to execute precise cut trajectories [4].

There has been growing interest in brain drug delivery through the olfactory region. The blood brain barrier (BBB) is a system of capillaries that supplies nutrients to the brain and spinal cord which limits permeability brain and can be avoided through the olfactory system [5]. Bypassing the BBB allows for direct access to the brain and leads to adequate absorption and uptake of drugs. Despite this advantage, the structural complexity of the human nose makes it difficult to access the olfactory. The olfactory is located above the superior meatus and only allows a few particles of an inhaled substance to enter unassisted [6]. We propose the use of magnetic field gradients to actively direct particles for intranasal delivery, increasing the total deposition of particles to the target region.

B. Impact on Society

Many technologies have been implemented for the use of brain surgery and drug delivery. Limitations to some of these technologies, include their invasiveness and complexity. For example although robotic surgical systems reduce surgeon errors and are considered a minimally invasive alternative to surgeon led operations, they require the brain to be exposed outside the cranium, leading to aesthetic scarring post-operation. Another limitation includes the non-autonomous nature of the robotic surgical systems. These systems require constant surgeon involvement, who need extensive training to be able to operate them.

Our software aims to significantly reduce the amount of surgeon training and involvement required by enabling autonomous operation of a novel magnetic array-based robotic surgical system. This system is completely non-invasive and only requires an initial surgeon input to carry out the surgery. Successful project completion will make advancements in automated surgery, reduction in procedure times, and reduction in invasive injuries such as aesthetic scarring.

C. Problem Statement

Despite advancements in research, major limitations are holding back clinical implementation of nose-to-brain magnetic particle delivery. These include physiological obstructions to particle transport, magnetic field strength attenuation as particles travel to deeper targets, and impracticality of manually operating magnet arrays in real-time. Weinberg Medical Physics is constructing an electropermanent magnetic control system to address many of these issues. To supplement their device's operation, we will design and implement a control interface allowing for the system to autonomously deliver magnetic particles from the nose to user-defined locations in the deep brain. Depending on the type of particle, various therapies could be delivered to these locations, for example drugs, genes, or heat.

D. Project Objectives and Requirements

Objectives

1. Design software control modules for MCS operation
2. Design an interactive GUI for surgeon usage

Requirements

Control Modules (non-GUI)

- Must track and segment magnetic resonance (MR) images to determine particle locations
- Must guide particles along user-defined path via image feedback
- Must be able to perform particle manipulations including: Translation, Rotation, Aggregation, Dispersion, and Activation
- Must include safety measures between every interaction between the modules.
- Must be coded in C++

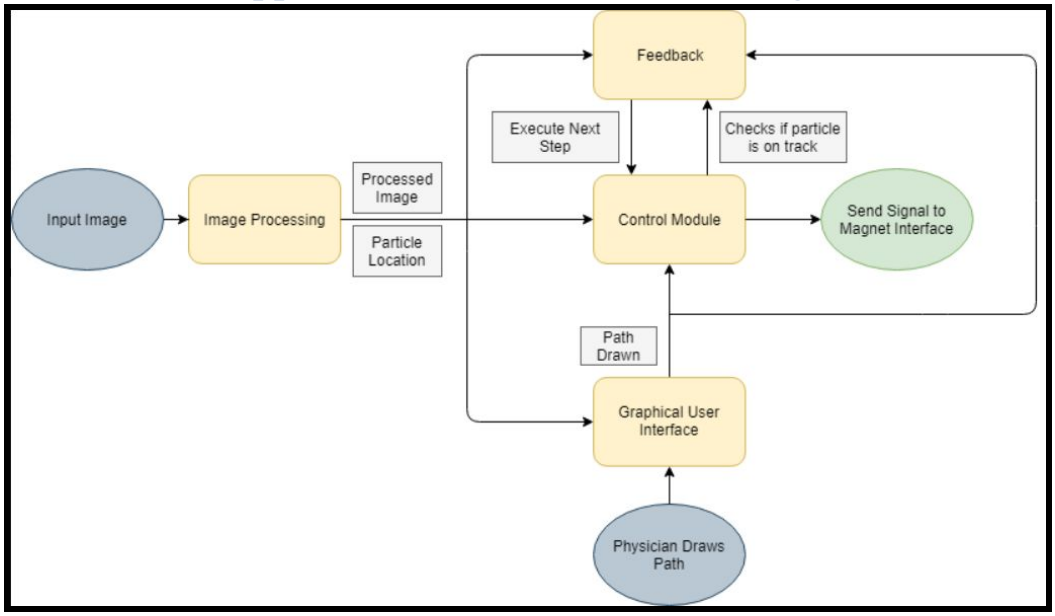
GUI

- Must be able to receive and process a 3D path input from the user
- Must discretize user-specified path into a 3D point array
- Must be able to collect live feed of MR images and display them on GUI
- Must be coded in C++ via QT integrated development environment (The Qt Company, Espoo, Finland)

3. System Design and Technical Approach

A. Proposed System Approaches

Approach #1: Control-Centric Design



This system is control-centric due to the multiple major responsibilities fulfilled by the Control Module. The control module acts as the only connection between the software and the magnetic hardware system.

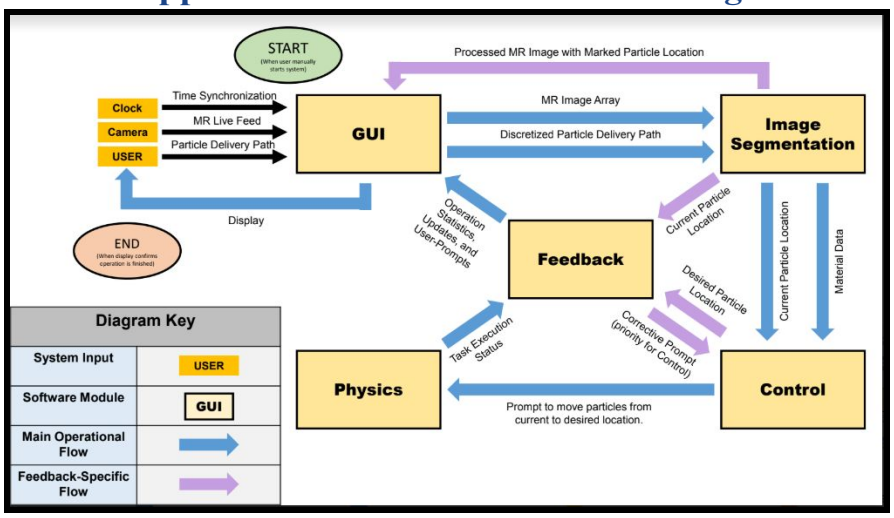
General System Operation:

1. An input image array is segmented by the **Image Processing** module to obtain particle(s) location and create a 3D representation of their current location. The locations are then sent to the **Graphical User Interface (GUI)** for the user to see. The second input is a 3D path drawn by the physician using the GUI. The GUI discretizes the input, then sends it to the next module.

2. The **Control** module receives the discretized path and the current particle(s) location. The module computes the required magnetic field gradient and current to move the particle(s) along the user-defined path. This information is sent to the microcontroller for execution.

3. The **Feedback** module ensures that the particle(s) are on the user-defined path. If the particle(s) deviate from the path, the module computes the necessary microcontroller command to return particle(s) on track. The computed command is sent back to the control module for execution. When the particles reach the target destination, the control module confirms that system operation is complete.

Approach #2: Feedback-Centric Design



This system is feedback-centric due to interactions and dependence of the other modules with the Feedback module. The Feedback module is at the "center" of the system operation.

General System Operation:

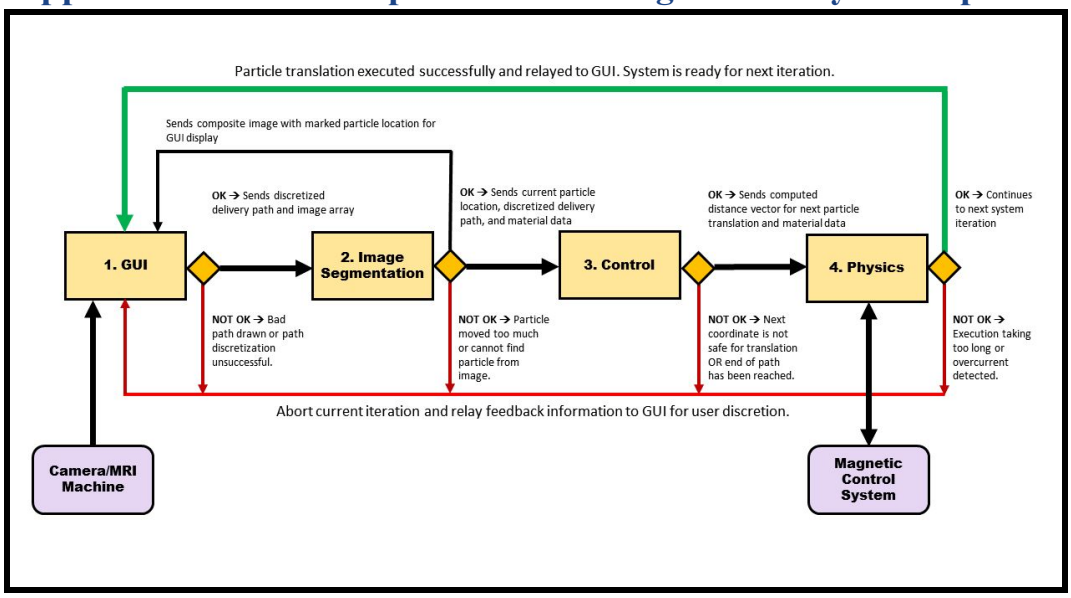
1. The **Graphical User Interface (GUI)** discretizes a 3D path inputted by the user. This is sent to the **Image Segmentation** module along with an MR image array. The images are segmented to obtain particle(s) location and material data. A composite image is created with marked particle(s) location to be relayed back to the GUI for the user visualization.

2. The **Control** module receives the current particle(s) location and material data. It sends the **Feedback** module the desired particle location (result of current translation). Control then sends a prompt to **Physics** module to move the particle(s) to the desired location. After Physics executes the translation, the execution status is sent to Feedback.

3. Feedback obtains the new current particle(s) location from Image Segmentation and compares it to the previously obtained desired particle location. If the locations do not match within reason, a special corrective prompt is sent to Control (takes priority) to pass onto Physics. Regardless of corrective prompt, statistics and other updates are relayed to the GUI for user discretion.

4. When Control determines that the end of the path has been reached, an update is sent to Feedback, which stops system operation. A final notification of operation completion is relayed back to the GUI.

Approach #3: Linear Operation with Regular Safety Checkpoints



This system operates in a linear fashion. The modules execute in sequential order. A module cannot interact with the next module unless the attached safety checkpoint is cleared. If checkpoint is not cleared, the system aborts the operation.

General System Operation:

1. The **Graphical User Interface (GUI)** is fed MR images from the MRI machine. The user draws a 3D path using the images displayed on the GUI. The GUI discretizes the path into a set of coordinates. The drawn path is then processed through the safety checkpoint. The checkpoint evaluates the validity of the discretized path.

2. The **Image Segmentation** module receives an array of MR images and the discretized path from the GUI. The images are segmented to obtain the particle(s) location and determine the material data (i.e. bone or tissue). The particle location is checked by the safety checkpoint. The checkpoint confirms it is successfully located. A composite image with marked particle(s) location is sent back to the GUI for user visualization.

3. The **Control** module receives the particle(s) location, discretized path, and material data from the Image Segmentation module. The control module uses the received inputs to compute a distance vector for particle translation. Before particle is moved the safety checkpoint confirms that the translation is safe.

4. The **Physics** module receives the computed distance vector and material data from the control module. It then instructs WMP's magnetic control system (MCS) to execute the particle translation. Once the translation has been executed, the physics module relays this back to the physics module. The occurrence of a possible error is checked by the safety checkpoint. If the checkpoint confirms that no error has occurred, the translation is successful. This status is relayed to the GUI, and the system's begins the next iteration.

Pros and Cons of All Approaches

Control-Centric Design

Pros	Cons
• Feedback and Control modules continuously interact to ensure system safety.	• Timing of module actions and information flow is ambiguous. • Confusion due to instances of several inputs from a module to multiple modules

Feedback-Centric Design

Pros	Cons
• Provides safety checks for all modules.	• Feedback module is overloaded with too many tasks; very dangerous for operation. • Timing of module actions and information flow is ambiguous, especially with regards to corrective prompts from Feedback module. • System structure is too complex.

Linear Operation with Regular Safety Checkpoints

Pros	Cons
• Linear system operation is clear. Information flow is better defined. • Safety checkpoints attached to each module greatly strengthens system safety. Any system malfunctions are prevented from intensifying.	• Linear system operation and regular safety checkpoints may noticeably slow down system execution time. • System is very sensitive to errors. System operation can be aborted even when minor errors are detected.

Selected Approach:

Our selected approach is **Linear Operation with Regular Safety Checkpoints** due to the benefits of greatly increased safety and simplified design. Also, loss of some operational efficiency is a much more manageable downside than some of the downsides of the other approaches.

B. System Components Description for Selected Approach

> **Note:**
> ← indicates the module sending the input.
> → indicates the module receiving the output.

Graphical User Interface (GUI):

Input: User-Drawn Path Input (**← User**), MR Image Array (**← Camera/MRI Machine**), Clock (**← System**), Processed Image with Marked Particles (**← Image Segmentation**)
Output: Discretized Particle Delivery Path (**→ Image Segmentation**), GUI Execution Status (**→ GUI**)

- The GUI is used to obtain the path drawn by the physician.
- Displays the processed images, particle location, particle statistics, and operational status to update the physician on the progress of the magnetic particles.
- Prompts the user to draw a new path if necessary.
- Allows the user to terminate operation.

Image Segmentation Module:

Input: Image Array, Discretized Particle Delivery Path (**← GUI**)
Output: Current Particle(s) Location, Material Data, Image Segmentation Execution Status (**→ GUI**), Processed Image with Marked Particles (**→ GUI**)

- This module is used to determine the location of the magnetic particles.
- Creates a 3D model from 2D image array input.
- Uses a Kalman filter and other image processing techniques to locate the magnetic particles in three dimensions.
- Determines material composition of local particle environment.

Control Module

Input: Current Particle(s) Location, Image Segmentation Execution Status (**← Image Segmentation**), User-Drawn Path(**← GUI**)
Output: Computed Force Vector (**→ Physics**), Control Execution Status (**→ GUI**)

- Used to determine if the particles are still on the user-created path.
    - If particle(s) are not on track, computes vector to return particle(s) on track.
    - If particle(s) are on track, computes vector to move particle(s) to next coordinate along user-defined path.
- Ensures computed vector lies within the MCS's technical capabilities.
- Passes vector onto Physics module.

Physics Module:

Input: Computer Force Vector (← **Control**)
Output: Electrical Current Specifications For Next Particle Translation (→ **WMP MCS**), Physics Execution Status (→ **GUI**)

- Interfaces with hardware system to instantiate a magnetic field gradient to move particles in the direction of a vector supplied by the Control module
- Sends operational status to GUI. This includes if there are any issues moving the particle(s) and if the path needs to be redrawn by user.
- This module will be implemented by WMP

C. Applicable Formulae and/or Algorithms

Below are engineering formulae that we expect to implement in our project. Note that this list is not rigid. We expect to utilize many more formulae and algorithms as our project develops further and our strategy matures.

Formulae

- **Biot-Savart Law** - The magnetic field *B* at a position *r* generated by a current *I* in 3D-space over a can be computed using the Biot-Savart Law:

$$B(r) = \frac{\mu_0}{4\pi}\int_C \frac{Idl \times r'}{|r'|^3}$$

- **Solenoid Magnetic Field** - The magnetic field *B* for a solenoid with *n* turns and current *I* can be derived from Biot-Savart Law:

$$B = \mu_0 nI$$

- **Gauss's Law for Magnetism** - The magnetic field *B* out of a closed surface S can be calculated using Gauss's Law for Magnetism:

$$\oiint_S B \cdot dA = 0$$

Algorithms

- **K-means clustering algorithm** - This machine learning algorithm can be used to detect clusters of particles. Cluster location can help compute the best vector to maneuver multiple groups of particles along the desired trajectory, as well as correct deviating particle groups. The goal of k-means is to essentially minimize the objective function, which will signify that computed centroids are truly at the center of determined clusters.

$$J = \sum_{j=1}^{k} \sum_{i=1}^{n} \left\| x_i^j - c_j \right\|^2$$

k = number of clusters	c_j *= centroid for cluster j*	*J = objective function*
n = number of cases	x_i^j *= case i in cluster j*	$x_i^j - c_j$ *= distance equation*

D. House of Quality Chart

Legend		
Icon	Description	Score
⊖	Strong Relationship	9
O	Moderate Relationship	3
▲	Weak Relationship	1

Row #	Max Relationship Value in Row	Relative Weight	Weight / Importance	Demanded Quality (a.k.a. "Customer Requirements" or "Whats")	Graphical User Interface (GUI)	Image Segmentation Module	Control Module	Physics Module
Column #					1	2	3	4
				Direction of Improvement: Minimize (▼), Maximize (▲), or Target (x)	▲	▲	▲	▲
1	9	8.0	7.0	Provide feedback to physicians	⊖		▲	
2	9	10.2	9.0	Receive 3D physician particle delivery path input	⊖			
3	9	11.4	10.0	Discretize 3D path input	⊖			
4	9	8.0	7.0	Examine MR Images	O	⊖		
5	9	11.4	10.0	Verify completion of particle delivery	▲		⊖	
6	9	11.4	10.0	Terminate/alter path	⊖		⊖	
7	9	11.4	10.0	Determine Particle Locations	O	⊖		
8	9	9.1	8.0	Interact with microcontrollers	▲			⊖
9	9	8.0	7.0	Obtain materal data		⊖		
10	9	11.4	10.0	Perform particle translation along discretized path			O	⊖
				Difficulty (0=Easy to Accomplish, 10=Extremely Difficult)	8	9	5	8
				Max Relationship Value in Column	9	9	9	9
				Weight / Importance	446.6	245.5	246.6	184.1
				Relative Weight	39.8	21.9	22.0	16.4

E. Applicable Standards and Codes

The following standards are issued by the Food and Drug Administration (FDA) as industry guidelines for documenting the development, clinical safety, and verification and validation of medical software devices intended for market submission. Note that the FDA standards define "medical software device" as any device that contains one or more software components, parts, or accessories to carry out or supplement medical procedures. A medical software device may take the form of firmware, stand-alone software, software accessories to medical devices, etc.

Because our software device is intended for therapeutic applications, we will adhere to these standards. We will produce and expand upon the recommended documentation alongside the development of our software.

Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (2005) [7]

This standard provides information regarding the FDA-recommended documentation for industry to provide in their pre-market submissions of medical device software. Recommended documentation covers software requirements and implementation, hazard analysis, verification and validation, development history, and other areas. Criteria for injury classification and the medical software level of concern are also clearly defined.

Key Areas

- **Level of Concern:** Criteria for establishing the appropriate level of concern (major, moderate, minor) to a medical software device. It is based upon device function and associated risk of injury.
- **Software Description:** Comprehensive overview of device features controlled by the software. Describes software operation and intended operational environment.
- **Device Hazard Analysis:** Analysis of hardware and software hazards associated with the device's intended use. Includes corrective measures taken during hazards.
- **Software Requirements Specification (SRS):** Provides software requirements including areas such as functional, performance, interface, design, etc.. Essentially describes what the software device is supposed to do.
- **Architecture Design Chart:** Flowchart depicting relationships among major functional units in the software. Hardware interactions and data flow are typically included.
- **Software Design Specification (SDS):** Software requirements implementation. References other documents such as detailed software specifications.
- **Traceability Analysis:** Link between product design requirements, design specifications, and testing requirements. Hazards are coupled with mitigation testing.

- **Software Development Environment Description:** Software development life cycle plan. This may include a list or description of software coding standards, configuration management, and maintenance.

- **Verification and Validation Documentation:** Testing documentation used for vindicating that the medical software device performs as expected and meets stakeholder requirements.

- **Revision Level History:** Documentation that records and lists software device version changes.

Software as a Medical Device (SaMD): Clinical Evaluation Guidance for Industry and Food and Drug Administration Staff (2017) [8]

This standard discusses the International Medical Device Regulators Forum (IMDRF) process used to clinically evaluate medical device software. The FDA considers IMDRF as a significant forum to discuss future directions in medical device regulatory harmonization. The 4 main components of the evaluation process include 1) Clinical Evaluation, 2) Valid Clinical Association, 3) Analytical Validation, and 4) Clinical Validation.

Key Areas

- **Clinical Evaluation**: A comprehensive list of activities conducted in the assessment and analysis of a SaMD's clinical safety following the document's tenets will be upkept.

- **Clinical Association**: Statement regarding the extent to which the SaMD's output is clinically accepted or well-founded and corresponds accurately in the real world to the healthcare situation and condition will be established along with a valid association between the SaMD output and the SaMD's targeted clinical condition as recommended by the literature.

- **Analytical Validation**: Objective evidence demonstrating that the software was constructed properly will be provided following the document's template along with extensive documentation proving that all software specifications were met.

- **Clinical Validation**: Software functionality will be tested against existing data from studies conducted for the same intended use or for a different intended use following the guidelines listed in the documentation.

General Principles of Software Validation; Final Guidance for Industry and FDA Staff Document issued (2002) [9]

This standard outlines general validation principles offered by the FDA to be used in the design, development, or manufacturing of medical device software. Suggested guidelines include System and Software Requirements, Data Throughput, Risk Assessment, and Error Management.

Key Areas

- **Software Requirement Specifications**: A comprehensive summary of software requirements including performance, I/O, functionality, and user interaction among other critical specifications.

- **Design Review**: Proposed system designs will be systematically examined to evaluate the capability of the design to meet system requirements.

- **Testing**: An exhausted list of test cases will be created using the predefined tenets for software testing. Verification and validation procedures will be taken into consideration as noted in the document.

- **Maintenance and Software Changes**: Sufficient regression analysis will follow any perfective, corrective, or adaptive software maintenance performed as suggested by the literature.

F. Supportive Drawings

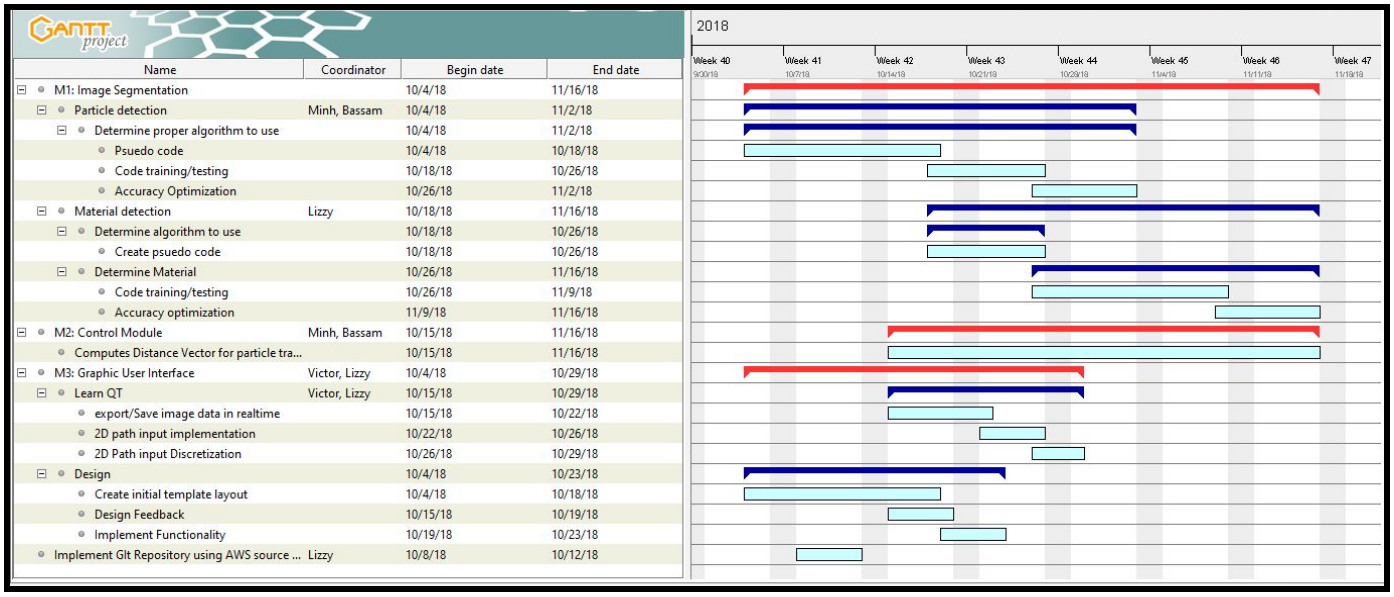
System design diagrams are provided in the previous Proposed System Designs subsection (pp. 6 - 8).

3. Administration and Team Planning

A. Budget

As of 10/04/2018, it is still not clear if we will require a budget as our project will primarily be built using open-source software. The need for a budget will be discussed in future meetings with our sponsors and advisors. In the case that hardware will need be built for system validation beyond computer simulations, we estimate a rough budget of $1000.

B. Progress-to-Date



Name	Coordinator	Begin date	End date
M1: Image Segmentation		10/4/18	11/16/18
Particle detection	Minh, Bassam	10/4/18	11/2/18
Determine proper algorithm to use		10/4/18	11/2/18
Psuedo code		10/4/18	10/18/18
Code training/testing		10/18/18	10/26/18
Accuracy Optimization		10/26/18	11/2/18
Material detection	Lizzy	10/18/18	11/16/18
Determine algorithm to use		10/18/18	10/26/18
Create psuedo code		10/18/18	10/26/18
Determine Material		10/26/18	11/16/18
Code training/testing		10/26/18	11/9/18
Accuracy optimization		11/9/18	11/16/18
M2: Control Module	Minh, Bassam	10/15/18	11/16/18
Computes Distance Vector for particle tra...		10/15/18	11/16/18
M3: Graphic User Interface	Victor, Lizzy	10/4/18	10/29/18
Learn QT	Victor, Lizzy	10/15/18	10/29/18
export/Save image data in realtime		10/15/18	10/22/18
2D path input implementation		10/22/18	10/26/18
2D Path input Discretization		10/26/18	10/29/18
Design		10/4/18	10/23/18
Create initial template layout		10/4/18	10/18/18
Design Feedback		10/15/18	10/19/18
Implement Functionality		10/19/18	10/23/18
Implement Git Repository using AWS source ...	Lizzy	10/8/18	10/12/18

C. Updated Team Organizational Structure

Roles and Responsibilities:

Role	Name	Responsibility
Project Manager	Victor Huynh (lead)	● Ensures quality of project deliverables ● Set appointments and meeting with sponsors and stakeholders ● Ensures completion of administrative tasks ● Manages team budget ● Oversees team coordination and communication
Front-End Design	Victor Huynh (lead) Elizabeth Ankrah Bassam Mutawak	● GUI design ● GUI functionality
Back-End Design	Bassam Mutawak (lead) Elizabeth Ankrah Victor Huynh Minh Quan Do	● Image segmentation module development ● Control module development ● System Safety Checkpoints
System Design	Minh Quan Do (lead) Bassam Mutawak Victor Huynh	● Overall system design ● Ensure module integration
Testing & Evaluation	All members	● Verification and Validation ● GUI testing ● Module testing

References

[1] B. Shapiro, S. Kulkarni, A. Nacev, S. Muro, P. Y. Stepanov, and I. N. Weinberg, "Open Challenges in Magnetic Drug Targeting," *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, vol. 7, no. 3, pp. 446–457, May 2015.

[2] E. Y. Yu *et al.*, "Magnetic Particle Imaging: A Novel in Vivo Imaging Platform for Cancer Detection," *Nano Lett.*, vol. 17, no. 3, pp. 1648–1654, Mar. 2017.

[3] S. Jafari *et al.*, "Magnetic drilling enhances intra-nasal transport of particles into rodent brain," *Journal of Magnetism and Magnetic Materials*, vol. 469, pp. 302–305, Jan. 2019.

[4] J. D. Opfermann *et al.*, "Semi-autonomous electrosurgery for tumor resection using a multi-degree of freedom electrosurgical tool and visual servoing," in *2017 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS)*, 2017, pp. 3653–3660.

[5] J. Dong, Y. Shang, K. Inthavong, H.-K. Chan, and J. Tu, "Numerical Comparison of Nasal Aerosol Administration Systems for Efficient Nose-to-Brain Drug Delivery," *Pharm Res*, vol. 35, no. 1, p. 5, Dec. 2017.

[6] X. A. Si and J. Xi, "Modeling and Simulations of Olfactory Drug Delivery with Passive and Active Controls of Nasally Inhaled Pharmaceutical Aerosols," *J Vis Exp*, no. 111, May 2016.

[7] U.S. Department Of Health and Human Services, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," May 2005.

[8] U.S Department Of Health and Human Services, "Software as a Medical Device (SAMD): Clinical Evaluation - Guidance for Industry and Food and Drug Administration Staff," June 2017.

[9] U.S. Department Of Health and Human Services, "General Principles of Software Validation; Final Guidance for Industry and FDA Staff," January 2002.