Jacob A. Pomerantz April 1, 2024

Antiretroviral Implant Automation

Abstract:

This grant proposal requests funding to support research this summer on antiretroviral bio-implant automation. Long-acting antiretroviral (LARV) therapy is a promising new HIV treatment in which polymer or bio-erodible casings are filled with ARV medications and inserted subdermally, commonly in the upper arm. While LARV treatment is largely still in the clinical testing and research phases, the FDA has recently approved a few antiretroviral subcutaneous drug delivery implant designs. As the potential benefits of LARV are increasingly recognized - LARV eliminates the risk of forgetting to take a daily medication, can dispense medication for up to six months, and offers the possibility of combining multiple medications - the scalable manufacture of the treatment remains in question.

The goal of this research is to design and manufacture an autonomous machine that will be able to mass-produce this medication. Working with Professor Kornel Ehmann, this research will address the increasing need for manufacturing capabilities of LARV implants, by creating them without human assistance. The research will include use of 3D modeling software to design parts that will work together in a functioning assembly; manufacture the parts in-house or via third parties; and physically assemble the different components once they have been manufactured. This research will also include coding of pneumatics and stepper motors required to make the assembled machine function autonomously. The end result will reduce production costs for these subcutaneous implants, enhance consistency of the product, and increase accessibility to this life-saving treatment.

Section 1:

This work will occur in Evanston, IL, this summer. As this work requires extensive hands-on work, the Ford Engineering and Design Center will be utilized to manufacture and test newly designed components.

Currently, the general steps in making LARV implants include: drug and polymer selection, formulation development, manufacturing, sterilization, and quality control. To date, researchers and developers have selected drugs and polymers suitable in this treatment. It is important that a biocompatible polymer that can safely degrade or remain inert is chosen. For this project, medical grade thermoplastic polyurethane (TPU) in the form of cannula tubes will be used to house the medication, in the form of pellets, because of its suitable mechanical properties. Developing the formulation requires precision as it must be designed to release the drug at the desired rate. The primary focus of this research is to develop a process that packages the pellets within the cannula tubing.

Thus far, subcutaneous implants are made through extrusion, injection molding, or compression molding. This research aims to simplify the manufacturing process using a continuous or intermittent automated assembly system. This research will produce new knowledge as it will establish new methods for automating the assembly of drug delivery devices. These methods will be more efficient, precise, and scalable for mass-production. Furthermore, our project could set a precedent for the use of automated assembly systems in the pharmaceutical industry. As there are many regulations with pharmaceuticals, we hope this machine can pioneer the use of automated manufacturing in created medicine.

Section 2:

The automated assembly process involves four steps which already exist in manufacturing processes, however, they are not yet combined into one continuous process with this intended outcome. These steps are: cutting the TPU cannula to length, sealing one end of the implant, inserting the TPU with the antiretroviral pellets, and sealing the second end. The process must be capable of repeating these steps for multiple units.

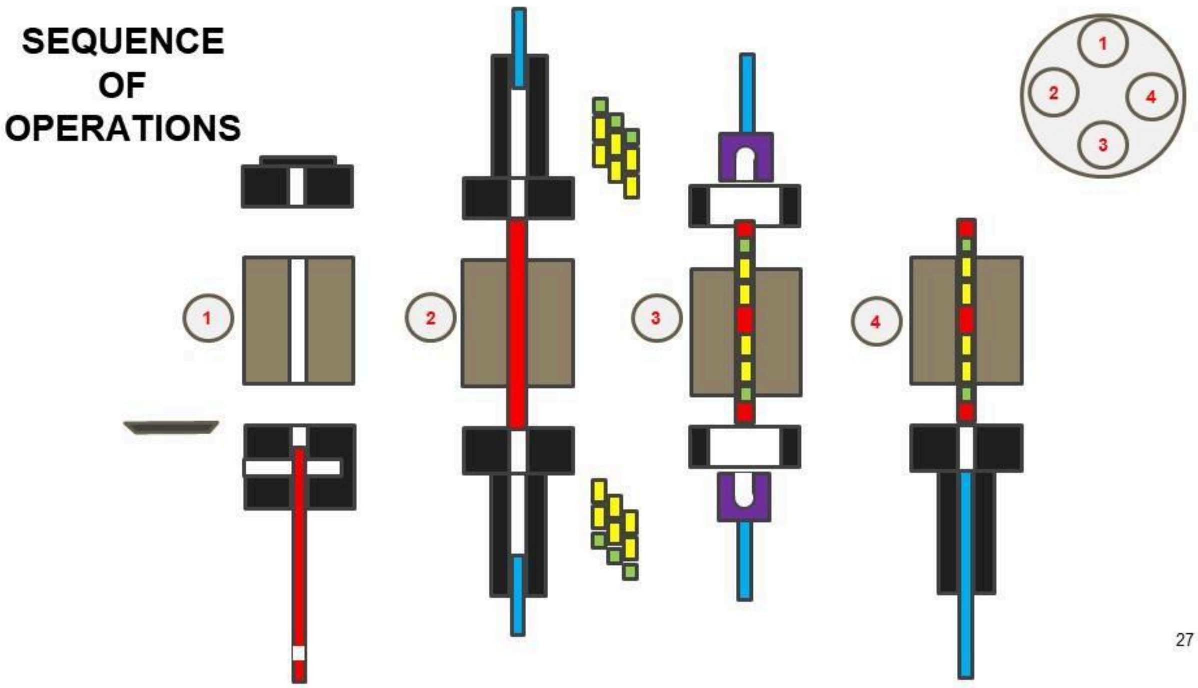

Figure 1: Ordered Assembly Steps in Implant Manufacturing Process

The primary components of this machine will function using a stepper motor and pneumatic actuators. As seen in the figure 2 below, the machine has two "arms" and a center "tombstone" with a rotating centerpiece. A thin ball bearing is press-fit onto the rotating centerpiece which sits on the tombstone. A large gear is attached to the end of the centerpiece and a small gear is precisely located in the top corner of the tombstone. The stepper motor rotates the small gear which interacts with the larger gear and thus rotates the centerpiece. The actuators and stepper motor need to be coded so that they work in unison.

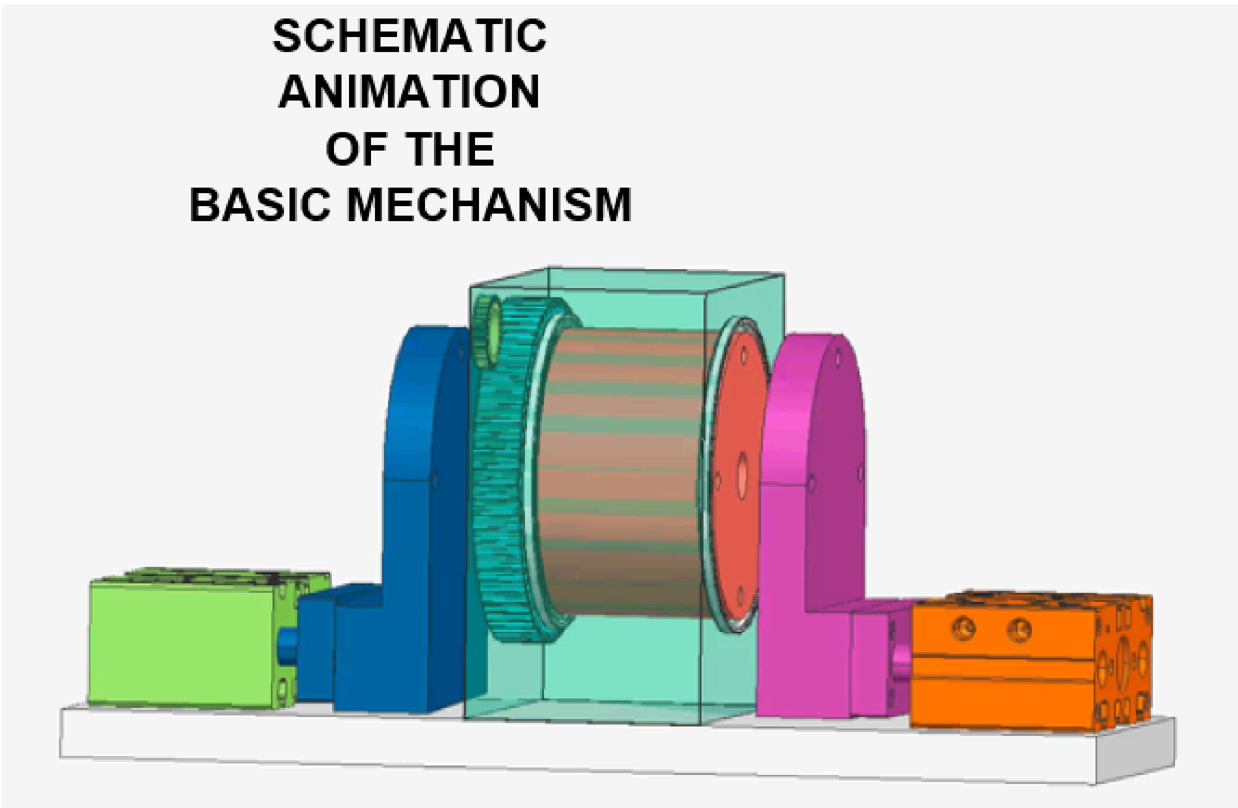

Figure 2: Simplified Representation of Machine Function

The centerpiece and the 2 arms have 4 through holes, each corresponding to a different step in the implant creation process. During each step, the 2 arms extend in, and the centerpiece rotates 90 degrees. In the first step, the cannula is fed through one of the holes and follows along a groove on the inside of the tombstone. Once the cannula reaches the end of the groove, a spring loaded mechanism is triggered which causes an actuator to extend downwards with the blade and cut the TPU.

In the second step, a pneumatic actuator inserts the sized cannula tubing into a Vante Saffire catheter tip forming machine. The cannula is inserted into a cavity mold that uses induction heating to melt and seal the end of the cannula tube. In the third step, a pneumatic actuator inserts the pellet medication into the sized and sealed cannula tube before the other end of the tube is sealed and removed from the assembly process.

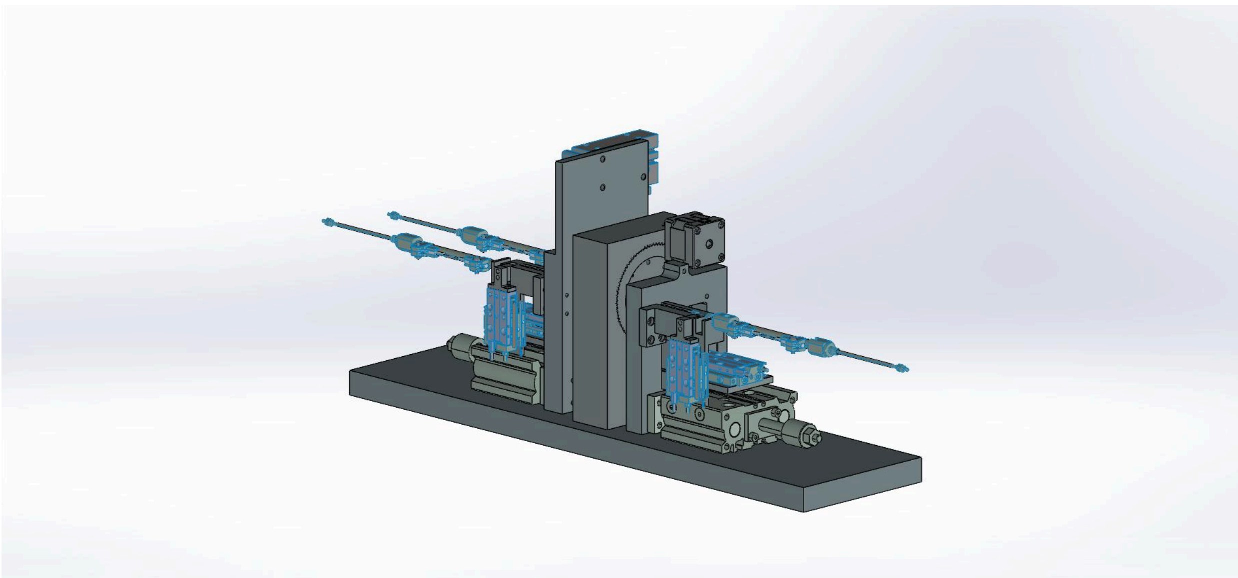

Figure 3: CAD Model of the Machine

Our first immediate task is to finalize the design of and manufacture the tombstone. The tombstone must mount to the baseplate and have two precisely located and machined bores. The first bore is for the centerpiece. This centerpiece must press fit into the tombstone and its holes must align perfectly with the corresponding holes on the arms. Furthermore, this bore has internal features for 2 retaining rings to secure the bearings. The second bore is to house the small gear which will rotate the centerpiece. This bore must be located with precision so that the pitch diameters align and the gear is not exposed. It must also align with the stepper motor.

The second task is to manufacture the loaders that *load* the pellets into the cannula. These pieces must have precisely located holes to align with the arms. This is so the pneumatics can extend and insert the medication into the cannula. Lastly, mounts for the sealer and other pneumatics must be manufactured. We will do this in-house using conventional and CNC milling machines.

This summer, the loaders and the tombstone will be finalized and manufactured. The design work will include detailed measurement of the pre-existing components to evaluate the relationship of the critical features to one another. Once these measurements are taken, 3D modeling software will be utilized to redesign the loaders and tombstone to meet these specifications. Engineering drawings of the tombstone and loaders will be made for any outsourced manufacturing. CAM software will be utilized to create G-Code that can be run on the CNC milling machines to create some of the mounts. After the components have been made, is assembling and coding. The coding will be done in C++ to ensure that the stepper motor and pneumatics operate in conjunction. It is important that this is done right for long term machine use and implant consistency.

Section 3:

I believe that this machine has the potential to change people's lives. The work that needs to be done on this machine needs to be done on site which is why it is imperative that I am able to be close to Evanston this summer. This grant will provide me with a much needed accessibility to resources I would not have elsewhere, and the opportunity to continue working with Professor Ehmann to witness the successful completion of this project. Thus, as I will be living nearby, this grant will provide me with the funds for provisions, transportation to campus, and supplies and equipment to do my research. Furthermore, being awarded a grant is a mark of recognition and prestige within the academic and professional community. As I very much want to receive my PHD and work towards researching and developing technologies that will benefit the future, receiving this grant is a good first step towards my goal.

References:

Weld, Ethel D, and Charles Flexner. "Long-Acting Implants to Treat and Prevent HIV Infection." *Current Opinion in HIV and AIDS*, U.S. National Library of Medicine, Jan. 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7050620/.

Edwards, Gabriel G, et al. "Long-Acting Injectable Therapy for People with HIV: Looking Ahead with Lessons from Psychiatry and Addiction Medicine." *AIDS and Behavior*, U.S. National Library of Medicine, Jan. 2023, www.ncbi.nlm.nih.gov/pmc/articles/PMC9443641/.

Khoshick Ganesh, Shihhsien Yang, Sofia Schillace, Valeria Vita, Yaoke Wang, Kornel F. Ehmann, Ping Guo, "A review of manufacturing techniques for subcutaneous drug delivery implants," Procedia CIRP, Volume 110, 2022, Pages 329-334, ISSN 2212-8271, https://doi.org/10.1016/j.procir.2022.06.059.

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Education

Northwestern University, Evanston, Illinois; GPA: **3.5**
Bachelor of Science in ***Mechanical Engineering,*** *Manufacturing Concentration, Segal Design Certificate*

Relevant Experience

Northwestern Formula Society of Automotive Engineers: Powertrain Sub-team 10/22 - Present

- Active member (8-10 hours per week) of team responsible for maximizing power output of electric car for competition, while optimizing cost and weight.
- Team lead designing accumulator container and mounts for NFR 24. Apply CAD, FEA, and CAM software to design, test, and manufacture battery container and mounts.
- Manufacturing responsibilities include operation of waterjet and other CNCs to produce an array of car components, and assisting chief engineer with welding car chassis.

Ford Engineering Design Center: Shop Trainer 09/23 - Present

- Employed by Northwestern University in the Ford Design and Manufacturing Shop ~ 8 hours per week to train and assist undergraduate and graduate students in use of machinery and equipment.
- Complete modules on manufacturing methods and applications to broaden personal skills.

Research Assistant: McCormick School of Engineering 09/23 - Present

- Collaborate with Professors Kornel Ehmann and Ping Guo to manufacture automated implant device for delivery of HIV medication.
- Manufacture and assemble machine with 4 integrated processes: cutting TPU plastic to deliver medication, implanting HIV tablets, sealing ends of implant, and removing formed medication from machine.
- Work has required extensive redesign of prior prototype, identification and ordering of appropriate parts, manufacturing of new and old components, and testing of new design's operational function.

Skills

Computer: Proficient in SolidWorks, Python, MatLab, HTML 5, CSS 3, FeatureCAM
Language: Hebrew

Additional Projects

X-ray Positioning Device: Designed and manufactured imaging prototype for use with immobile patients
Electric Skateboard: Designed electric vehicle; built battery in 12s3p configuration; installed ESC, BMS, and motors