

A precise handheld injection device for cardiac interventions

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Abstract

Stem cell research is an emerging field at the center of much heated debate and controversy. Since this is such a developing technique, stem cell research is currently being studied on animal subjects. One technique that is currently being researched is the injection of stem cells to restore function to cardiac muscle after myocardial infarction, otherwise known as a heart attack, in which the blood supply to the heart is interrupted causing the cells to die. The current protocol calls for the manual injection of stem cells through a syringe and catheter system. Manual injection methods are inaccurate due to human variability. This leads to changes in pressure during the injection, which compromises the viability of the cells due to the excess shear stress from the pulsated pressure. Our team of highly experienced Biomedical Engineers has chosen to design and build an automated, handheld injection device that will inject the cells at a constant pressure to increase testing repeatability and ensure cell viability.

Background

Cell-based therapies have emerged as a potential revolutionary therapy for heart disease (1). Clinical trials using bone marrow derived stem cells administered to pigs gave positive results in the area of cardiomyoplasty. In this study, cells were injected via a percutaneous-injection catheter (2). Other studies have used cellular therapy to reverse myocardial dysfunction. Echocardiographic studies showed an improvement in global and regional left ventricular function in cell-treated sheep (3). Another study involving rats determined implanted skeletal myoblasts formed viable grafts in infarcted myocardium, echoing the results of the previous studies (4).

Motivation

Although these studies and others show promising results, our client, Dr. Amish Raval, is concerned about the consistency of the data due to the injection process. The current protocol calls for a manual injection of 100-200 μL of stem cells over a period of 15 to 30 seconds. To accomplish this task, Dr. Raval uses a stopwatch to record the injection time while pushing the syringe and trying to maintain a relatively constant injection pressure. This variability causes changes in injection pressure, which causes unnecessary shear stress on the cells.

A device is needed to make this process more automatic and accurate so reproducible results can be obtained within his lab as well as other labs around the country. Dr. Raval has asked our team to come up with a design that will bring about more consistent study results by being able to consider the injection pressure as an experimental control variable.

Problem Statement

Our client, Dr. Amish Raval, of the University of Wisconsin School of Medicine and Public Health, researches the effect of stem cells on rebuilding muscle tissue. Currently, Dr. Raval uses a minimally invasive procedure in which he manually injects stem cells through a catheter to muscle tissues over a designated period of time. In order to eliminate the variable pressure from manual injection, an automated method is desired. Current syringe pumps are large, expensive, and only provide constant flow rates. The goal of this project is to create a low cost and handheld syringe pump that ensures cell viability by maintaining a constant injection pressure.

Client Requirements

Our client has given us a number of requirements that our design has to meet. For starters, the device needs to be small enough to be able to be handheld. It will be used during a minimally invasive surgery, and when it is not in use it will be set on a small equipment tray placed on the patient. Next, due to its use in a sterile environment, the device must be disposable. This increases the safety for the patient from the risk of infection. Our client has characterized the device as disposable if it can be manufactured between \$30 and \$50. The intent is for it to be able to be sold in a disposable kit with the syringe and catheter system for each trial. Another requirement is that the device must be simple to operate. The more complicated the device is, the greater the risk of misuse by operators and undesired results. One button operation is preferred and is the safest design. The device must be portable and cordless so as not to add to surgical room clutter. Most importantly the device has to be able to inject at a constant pressure. This is important because as pressure increases, stress on the cells increases and adversely puts cell viability at risk. Having a constant pressure is more important than having a constant rate because even if the rate is constant, due to resistance in the system and muscle, the pressure could become too high and cause unnecessary damage to the cells. Due to the fact that the point of this device is to deliver the cells safely and in a repeatable fashion, a difference in cell environment over multiple tests is very undesirable. Lastly, an alarm should be incorporated if possible in order to alert the surgeons if a certain threshold pressure has been exceeded. This will allow it to be known that the cells may have been in an undesirable environment that could, again, skew results. The researcher could then omit the data from such a test.

Existing Devices

The problem of injecting a volume of fluid into the body at a constant rate is not a unique problem. A number of different styles of infusion bags, infusion pumps, and syringe pumps have been used to provide control over the injection process. Although these devices have a similar function to the prototype we are designing, they do not meet our client's needs specifically. The following products are the closest examples of what our client is looking for, but none of them are viable options for this specific application.

The first device is called the SpringFusor, and is a spring-driven syringe infusion pump that costs \$45-65 from Allied Medical (Figure 1). While this device is fairly inexpensive and falls within our client's budget, it has a few design flaws. First of all, the SpringFusor is designed to inject fluids over a period of hours, and could not be used to inject stem cells through a very thin catheter over periods as short as 15 seconds. Even if a spring with a larger spring constant was used, the use of a compression spring inside the tube exerts a non-constant force on the plunger creating a change in pressure and flow rate (Figure 2). The high pressure and flow rate at the start of injection could cause shear stress on the stem cells, compromising their viability. The SpringFusor also controls the flow rate of the injection by using different diameter microbore tubing (larger diameter, faster flow rate). Our client could not use this feature because he must inject the cells through a catheter of fixed diameter due to regulations and biocompatibility, which have already been met by this protocol. Finally, our client is using 1 to 3mL syringes to inject very small volumes (100-200 μ L), and the SpringFusor can only accommodate specific syringe sizes, the smallest of which is 10mL.



Figure 1 – SpringFusor, a spring-driven infusion pump. <http://www.alliedmedical.com.au/springfusor/?cID=3>

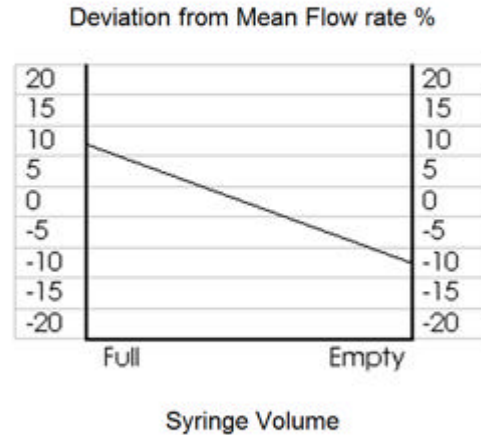


Figure 2 – Shows problem with design of SpringFusor: flow rate is higher when syringe is full, adding unwanted shear stresses to stem cells. Figure taken from http://www.gomedical.com.au/products/springfusor_data_sheet.htm

While there are other spring-driven devices similar to the SpringFusor such as the Medifuse

by 3M Healthcare, Patent No. 5,954,695 (Sims) and 4,632,669 (Phipps), they all show similar design flaws and could not be used for our client’s specific application.

There are also a multitude of programmable infusion devices driven by electric motors that could provide a similar function to our client’s needs, but are not ideal because of their high cost, large size and complexity. The least expensive version on the market is the NE-300 "Just Infusion" Syringe Pump, which costs \$275 (Figure 3). Our client has made it clear that the device should either be disposable (and thus low-cost) or easy to sterilize between uses, which the “Just Infusion” pump would not be. These electrical devices also have a very large footprint and are heavy (the “Just Infusion” pump weighs 1.63kg). Also, the “Just Infusion” pump is not approved for use in humans, making it more expensive if it were to become approved. Because our client is working in an already cramped operating room, these larger devices are not ideal. Finally, these motor-driven infusion pumps inject fluids at a constant rate, not a constant pressure like our client would like. Patent No. 5,295,967 nearly overcomes this problem by measuring

the force exerted on the syringe plunger and displaying the corresponding pressure on a screen, but this still does not control the pressure within the syringe with any kind of feedback mechanism (Figure 4). The client could constantly monitor the pressure and adjust the rate accordingly, but this system is not fully automated, and still provides room for user error and variations between injections.



Figure 3 – NE-300 "Just Infusion" Syringe Pump. Costs \$275 from New Era Pump Systems Inc. <<http://www.syringepump.com/NE-300.htm>>

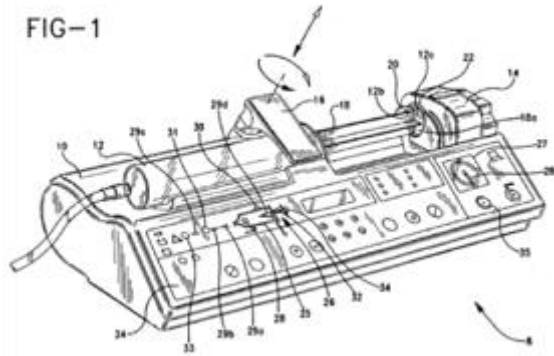


Figure 4 – Syringe pump having continuous pressure monitoring and display. Patent #5,295,967. <<http://www.freepatentsonline.com/5295967.pdf>>

Ethics

Research using human embryonic stem cells is a very promising field that shows great potential to be used in the regeneration of diseased or injured tissue. However, because the embryo must be destroyed when stem cells are harvested, the use of stem cells in research has been a topic of heated debate. While we are not directly participating in this research, we must maintain a professional attitude about the design of this injection device because it will contribute to this field.

Ergonomics

This injection device will be used in a small operating space, and should be as compact as possible. The procedure for catheter placement, loading the syringe, and injection of stem cells is complex and meticulous as it stands and the addition of another device will only complicate this procedure more.

The most extensive user-device interaction will occur during the loading of the device. Before loading the syringe the device will be present to the appropriate dimensions for proper injection. The procedure to lock the device in this position should be as simple as possible while still allowing for an accurate amount of fluid to be injected each time. The placement of the syringe in the prototype should be obvious and intuitive for the user, and include a fastening mechanism that holds the syringe securely in place. The release of this stored energy onto the syringe plunger should take one fluid motion by the user, whether it is pressing a button, turning a valve, or releasing a screw. No action should be required of the user during a fully automated injection process. Finally, after the device has completed the injection, the syringe should be simple to remove.

Design Proposal 1: Pneumatic Design

The most accurate method of pressure application is through the use of a pneumatic system. This is due to the air in the actuator always being at a constant pressure as long as the regulator is working properly. The constant pressure creates a constant force, which is the desirable result. The design will incorporate readily available parts from online suppliers. This makes for very simple fabrication and assembly. Connections could be threaded or press fit, depending on the final design. Components

will consist of a pressurized vessel (most likely a CO2 cartridge), on-off/release valve, regulator, actuator and tubing. The vessel is the energy source for the entire system and the on-off/release valve controls when the energy is released. The on-off valve has an integrated release valve for the output side so that when the system has been pressurized, it can be depressurized in order to use it again. If the air in the system was not releasable, the actuator would only be used once before it was stuck in the fully open position. The regulator is in place to reduce the pressure input into the actuator, as well as make the output pressure adjustable. The actuator is the component that does the physical work; as air enters, the arm is extended, exerting a force. The pneumatic system does have its drawbacks though; it would most

likely be the heaviest and largest of all the designs. Also, any inherent problems of high-pressure systems will also apply such as gas leaking from the system. If these drawbacks can

be minimized, this design could be very competitive.

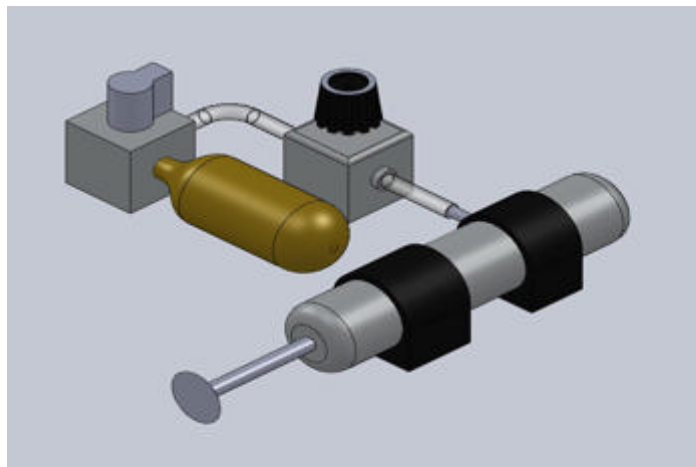


Figure 5: Pneumatic design proposal

Design Proposal 2: Electrical Design

The second design proposal is an electrical system that consists of a motor driven gear system that will inject the syringe at a constant pressure. This design consists of a battery powered motor, a gear and a gear track, a pressure sensor, and a software system

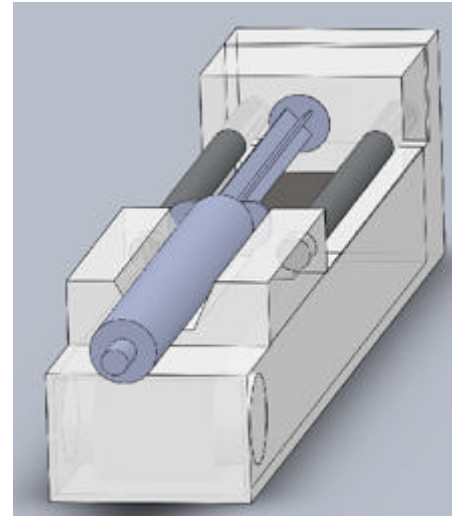
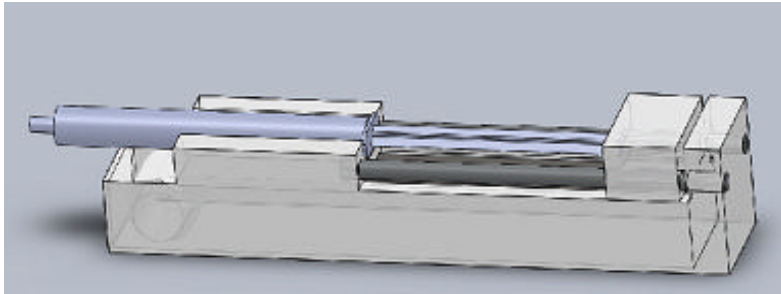
to provide feedback that will control the speed of the motor. This design is advantageous for our client because it will have a pressure sensor that will read out the pressure of the injection. This pressure sensor will also be attached to the motor and it will have a program set up such that it will be able to control the speed at which the motor turns. This way if the pressure deviates at all from the set pressure, the system will be able to adjust itself so that it always injects at a constant pressure. This system is a very precise design and will be the best design to ensure cell viability because of the regulated pressure system. It is also very easy and convenient for the client to use because it is an automated system that only requires it to be activated by turning the on switch. However, there are a few disadvantages to this design. With the motor included in the system it will be a heavier and bulkier system. Also since it will be battery operated and have the electrical components of the feedback system this design will not be disposable, which is one of our main requirements from our client. This design also contains a lot more parts that will be more complicated to assemble and manufacture and our client is looking for a very simple design so all the extra components are not necessary to include in our final product.



Figure 6: Electrical design proposal

Design Proposal 3: Mechanical Design

The third design is a mechanical system that consists of a preset spring loaded into the system. The injection of the syringe in this design is controlled by the energy that is released from the spring. There is a switch on the side of the design that will activate the release of the loaded spring. Once the spring is released it will push a block that will push the plunger of the syringe to inject the stem cells into the catheter. This is a much more simple design than the other proposals. The favorable qualities of this design is that it is a very small, lightweight, and compact design. It is a handheld device that will be very easy for the client to operate and will not take up a lot of space for the equipment in the operating room. Because of its very simplistic nature, this design will be very inexpensive to assemble and manufacture and thus it will be able to be produced as a disposable product. One of the challenges that come with this design will be finding a suitable spring that can be used to inject the syringe at a constant pressure. We have found that the pressure a spring exerts over time decreases linearly with time. However, we will need to adjust the system so the spring exerts pressure at a nearly constant rate over time. To do this we are going to find a spring that operates over a much longer time period than the 30 seconds. We will then set the spring so that it only operates over a portion of its compression to exert a nearly constant pressure over the injection time frame.



Design Evaluation

After taking into account all three design ideas, a design matrix was created to help evaluate each design based on initial design criteria. The three different design choices were assessed using the following design characteristics; ease of use, cost, precision, size, and manufacturability (Figure 8). Each category has an individual point allowance combining for a total possible score of 100 points for each design. Precision had the highest point allowance because it is most important for the client to achieve a desired, repeatable pressure with each cell injection. Size and cost also had high point allowances because these aspects are also important to the client because the device must be small, handheld, and disposable. Ease of use and manufacturability also were used to evaluate each design because it must be simple to operate and easy to construct to avoid large costs respectively.

Design Matrix

Design Characteristics	Pneumatic	Mechanical	Electrical
Ease of Use (15)	10	12	15
Cost (20)	13	20	10
Precision (30)	30	23	29
Size (25)	19	25	21
Manufacturability (10)	7	10	3
TOTAL (100)	79	90	78

Figure 8: The design matrix.

The mechanical device scored high in nearly every category and was decided to be the best design overall. Electrical was designated the easiest to use because it would only require on/off switch activation. Mechanical and pneumatic were not far behind but may be trickier when dealing with springs and compressed air respectively. The mechanical device achieved maximum points in the manufacturability, size, and cost categories because the design is simple to make, and has fewer and simpler parts. Electrical and pneumatic parts are often larger and more expensive making these designs less desirable. Mechanical scored the least of the three in precision however, because of spring capabilities. A suitable spring needs to be found with has an effective operation range where the change in force vs. displacement is minimal. If the correct spring can be

found, the mechanical option will have much better precision and similar to the other designs.

Future Work

The mechanical design was chosen to be the best design based on the design matrix and client requirements. After picking this design, many things need to be done so that a prototype can be presented at the end of the semester. The first task on hand is to find a suitable spring for the mechanical operation. As mentioned above, this spring needs to have an effective operation range that minimizes the change in the force due to spring displacement. Other mechanical syringe pump designs were ordered to investigate their functions so their basic principles can be applied to this design project. After establishing a final design and finding a suitable spring, all other materials need to be purchased and construction needs to take place. After building the design, extensive testing will be performed to assess the accuracy and precision of the device and investigate whether the device is suitable for stem cell injection.

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APPENDIX A

A precise handheld injection device for cardiac interventions Product Design Specification Report

Team Members

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Problem Statement

Our client, Dr. Amish Raval, of the University of Wisconsin School of Medicine and Public Health, researches the effect of stem cells on rebuilding muscle tissue. Currently, Dr. Raval uses a minimally invasive procedure in which he manually injects stem cells through a catheter to muscle tissue over a period of time. In order to eliminate the variable pressure from manual injection, an automated method is desired. Current syringe pumps are large, expensive, and only provide constant flow rates. The goal of this project is to create a low cost and handheld syringe pump that ensures cell viability by maintaining a constant injection pressure.

Client Requirements

- Small, handheld device
- Disposable after each use – must be able to be mass produced at a relatively low cost
- Must be non-motorized – no cords or plugs required; however, it can be battery operated
- Must inject at a constant infusion pressure
- Have a feedback system that will turn off if the pressure exceeds a certain threshold

Design Requirements

Physical and Operational Requirements

- a) *Performance Requirements* – The device is designed to be disposable and thus is required to deliver the pressure at a constant rate for one injection. It should be small enough so that the operator is able to hold it in his hand while operating it independently. It needs to be able to handle up to a 3mL syringe.
- b) *Safety* – The device should have an absence of sharp edges and abrasive surfaces. It must be light enough so that the operator is able to operate with one hand and is able to place it on the patient during surgery without any adverse consequences.
- c) *Accuracy and Reliability* – This device is required to inject the stem cells at a continuous constant rate of delivery. There must be a pressure sensor with a feedback loop to maintain an accurate pressure input of the injection.
- d) *Life in Service* – This is a disposable device and is needed only for a one-time use.

- e) *Shelf Life* – It will need to be designed so it can be mass produced and be suitable for an enclosed shelf life for unlimited time before use.
- f) *Operating Environment* – This device will be used in a sterile operating room. Each device needs to be sterilized and pre-packaged individually for use.
- g) *Ergonomics* – This device needs to be operated by the user individually during a surgical procedure. It must not put any undue stress or strain on either the user or his environment during the operation.
- h) *Size* – The model should be handheld and no larger than a 40 in² footprint
- i) *Weight* – The model should weigh no more than 5lbs
- j) *Materials* – All of the materials used in this device must be sterile, non-flammable non-radioactive, and non-corrosive
- k) *Aesthetics* – The aesthetics of this design and not important. It just needs to be clean and sterile.

Product Characteristics

- a) *Quantity* – One product that would be able to be mass produced in the future
- b) *Target Product Cost* – The product must be able to be manufactured for under \$50 per item.

Miscellaneous

- a) *Standards and Specifications* – The syringe and catheter system is already approved and passes all regulations. Since our product will not come in contact with any component inside of this system it will not need any to undergo regulation approval
- b) *Customer* – Our client wants a simple device that is easy to use and injects the stem cells at a constant pressure over a given time period with a feedback mechanism that prevents it from exceeding a certain threshold of pressure.
- c) *Patient-related concerns* – The product needs to be sterile because it will be used during an injection operation in the operating room.
- d) *Competition* – There are certain products on that market that contain a few components that will be incorporated into our final product; however there is no current design that accommodates all of our design specifications.