

Rapid Micro-Injector for Stiffness Measurements in Mice Hearts

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BME 402**

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Abstract

Diastolic dysfunction is a condition where the stiffening of cardiac tissue causes increased end-diastolic pressure and, ultimately decreased stroke volume from the left ventricle [2]. This can lead to many complications. Interest to researchers rests on the fact that diastolic dysfunction is implicated in more than 70% of heart failure patients aged 80 or more [3]. This makes the measurement of the cardiac tissue stiffness quite significant. Stiffness is defined as change in pressure over change in volume. Since a mouse heart catheter to measure pressure already exists, a device is needed to create changes in volume. As for significant specifications, 3 μ l of saline must be delivered to the catheter in less than 5 ms. This paper evaluates four proposed microinjection designs to develop a flow rate of 3 μ l in 5 ms. Evaluating each proposal led us to pursue a design that includes a piezoelectric actuator used to mechanically displace a syringe plunger and thus dispense saline into the catheter. The main benefit of this design is that it has a sub millisecond response and it has the ability to retract the saline. Preliminary testing shows promising results for this device, although future work includes circuitry design or the purchase of a new power supply to drive the piezo stack.

1. Background

1.1 Problem Statement

We are interested in designing a device that rapidly increases the catheter volume by $3 \mu\text{l}$ to measure stiffness during specific intervals of the cardiac cycle in mice. The compliance of the heart is defined as change in pressure divided by change in volume (dP/dV). A catheter and pressure transducer that fits in mouse hearts is already in use for stiffness measurements, so we are only focused on changing the volume of fluid in the catheter tip. Since a mouse heart beats 240 times every minute, the injection needs to be complete within 5 ms to accurately study conditions at specific intervals of the cardiac cycle. Figure 1 illustrates the project overview and outlines our role in creating a stiffness measurement device. Again, the catheter and balloon along with the pressure sensor are already in place. Our goal is to design the rapid injection device to create volume change very rapidly.

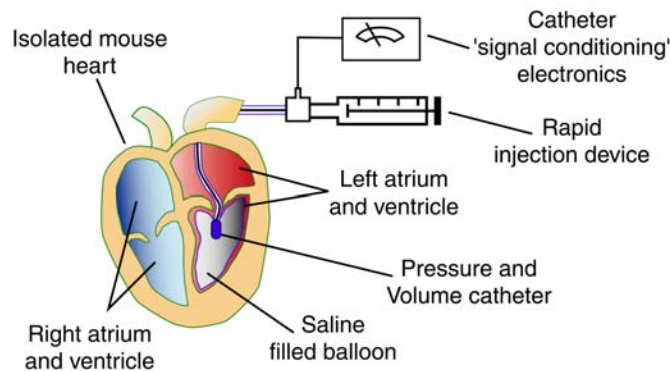


Figure 1: Project Overview [3]

1.2 Motivation

Diastolic dysfunction is a medical condition that adversely affects the diastolic phase of the cardiac cycle. During the diastolic phase, the left and right ventricles of the heart are in a relaxation state and fill with blood. With diastolic dysfunction, the left ventricle does not fill with an optimal amount of blood before contraction causing a decrease in stroke volume. The stroke volume is defined as the amount of blood that leaves the LV and is distributed to the rest of the body each contraction [2,3].

The major cause of diastolic dysfunction and the reason for the lacking stroke volume is the stiffening of the cardiac tissue in the walls of the LV. The end diastolic volume in the LV is dependent on the compliance of the cardiac muscle tissue itself and will continue to decrease with increasing ventricular hypertrophy [3]. As the LV wall becomes increasingly stiff, end diastolic pressure will be reached sooner as the chamber fills with blood. An LV pressure volume loop shows the relationship between pressure and volume in that specific chamber. Figure 2 displays the theoretical LV pressure volume loop in a healthy heart.

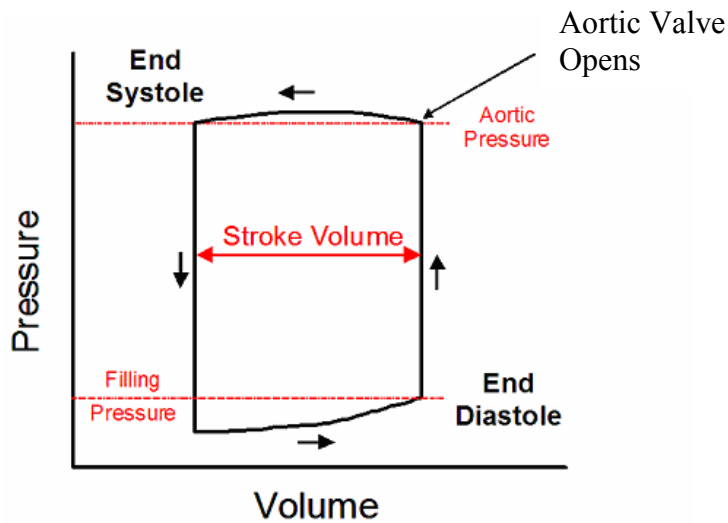


Figure 2: LV pressure/volume loop in a healthy heart [3]

As the loop is traced from left to right beginning in the lower left hand corner, pressure in the LV will increase with LV volume until a certain pressure is reached. Once the pressure in the LV exceeds that of the aorta, the aortic valve will open and blood will be ejected from the chamber. In this case an optimal stroke volume is observed.

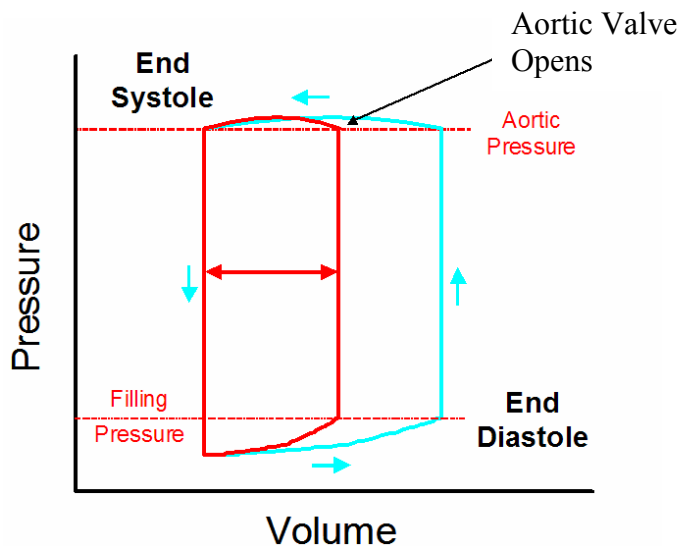


Figure 3: LV pressure/volume loop in a heart with diastolic dysfunction [3]

Figure 3 displays a pressure volume loop in a heart affected by diastolic dysfunction. LV hypertrophy or the stiffening of cardiac tissue causes LV pressure to increase at a greater rate vs. volume. In this case, LV pressure will exceed aortic pressure sooner ejecting blood into the aorta prematurely. Blood is ejected before an optimal volume or stroke volume is in the LV [2,3].

Diastolic dysfunction causes a variety of conditions relative to the heart and is implicated in more than 70% of heart failure patients that are aged 80 or more [3]. Origins of cardiac tissue stiffness are not well understood, yet the condition generally affects older patients. One of the major complications of LV stiffness is the increase in left atrial and pulmonary venous pressures. Because there is a lack of blood entering the LV, the blood will begin to back up and increase pressure in vasculature preceding the LV. This can lead to pulmonary congestive heart failure and pulmonary edema [2].

With the wide ranging problems associated with diastolic dysfunction, researchers have high interests in determining cardiac muscle stiffness in patients. Researchers are also interested in determining stiffness at different stages in the cardiac cycle. Stiffness (dP/dV) is a dynamic measurement and continuously changes as pressure and volume changes in the LV. The Problem with developing a method to dynamically measure stiffness in a live beating heart is making the measurement fast enough. For example, a live mouse heart beats 260 times every minute. Therefore, to achieve a measurement at a certain instance in the cardiac cycle would need an extremely high response time for measurement accuracy and precision.

1.3 Competitive Products

Micro Injection System

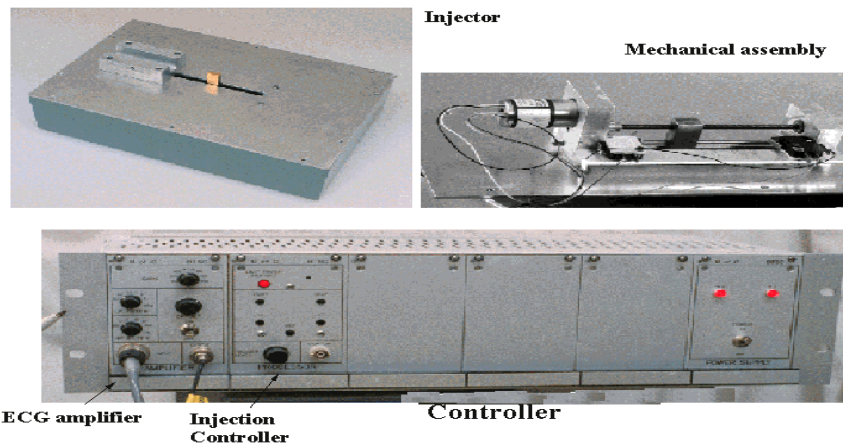


Figure 4: Micro Injection System [6]

An existing device that is the most similar to a device that the mouse heart team is designing is the Micro Injection System. This product was developed by the Biomedical Technical Support Center (BTSC) at the University of Calgary, Canada. This device can inject minute volumes of fluid into small animal's heart during scientific experiments. Also, there is an option to set the system such that it is synchronized with the animal's heart beat. The Injection drive consists of a special syringe holder, a stepping motor and a mechanical gear assembly and can be operated from either a 220V/50Hz or a 120V/60Hz outlet [6]. The web site for this device contains no information about the price of the device. We were unable to contact the BTSC people to obtain further information about the device.

1.4 Product Design Specifications

Our goal is to design a device that injects a small amount of saline into a balloon that is situated in the left ventricle of a mouse heart. This balloon will already be filled with an initial volume of fluid. We will add a small amount of fluid to attain a change in volume in the left ventricular balloon. At the instant volume is changed, a change in pressure will also be calculated via a pressure transducer which is also inside the LV balloon. Subsequently, a pressure measurement can be obtained at the instant the volume is changed by taking (dP/dV).

In order to be effective, the bolus of saline injected into the LV balloon must be precisely the same every time. The difficulty involved here is in the relative size of a mouse heart. It is so small, that the volume injected must be on the order of micro-liters. Furthermore, the mouse heart beats extremely fast compared to a human heart—about 8 times faster. Therefore the bolus must be injected instantaneously to account for changes in the cardiac cycle. One of the main goals of the device is the ability correlate stiffness measurements with different phases in the cardiac rhythm. Whether the cardiac chambers are in relaxation mode or contraction mode will make a difference in the measurement results. Figure 7 depicts the sort of curves that stiffness data will be plotted against. This figure shows only the phases in a human heart, which in completion takes about 0.8 seconds. A mouse heart beat cycle will only last a tenth of a second.

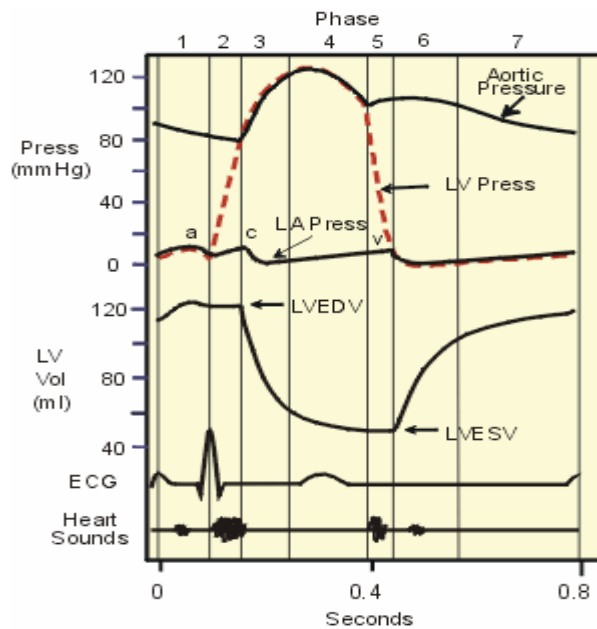


Figure 7: Phases of the cardiac cycle in a human heart [2]

Following is a list of some important specifications that our client wants this device to have. This device should:

- Inject a fixed quantity (3-5 μl) of saline through a catheter into a left ventricular balloon
- Operate in less than 5 ms
- Attach to a catheter with 200 μm diameter opening
- Must operate with an electrical logic pulse
- Length of catheter from fluid injector to end of tube is at least 2-3 cm

By injecting a small amount of saline solution inside the catheter, we obtain the change in volume inside the catheter that can be used to figure out the stiffness of the heart muscles. We need this device to have an ejection interval of 5 milliseconds because our client wants to make very precise measurements at very precise intervals of a cardiac cycle.

2. Preliminary Designs

The mouse heart team brainstormed several ideas in order to design a micro injector device that would accomplish all the required specifications. Intense online research was done to help come up with ideas for the design. Through this research, the mouse heart team came up with three good designs. Following is a discussion about those designs.

2.1 Design 1: Solenoid Armature

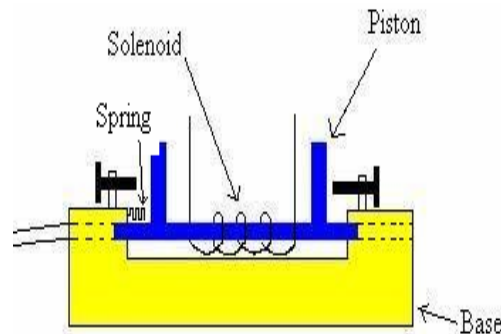


Figure 8: Solenoid Armature Design

The first design that the Mouse Heart team came up with is a ‘Solenoid Armature’ design. This design is composed of a solenoid electromagnet with a movable armature in between the coiled loops. A solenoid is a specially designed electromagnet. It usually consists of a coil and a movable iron core called the armature. When current flows through a wire, a magnetic field is set up around the wire. If a coil of many turns of wire is used, this magnetic field becomes many times stronger, flowing around the coil and through its center in a doughnut shape as shown in Figure 9.

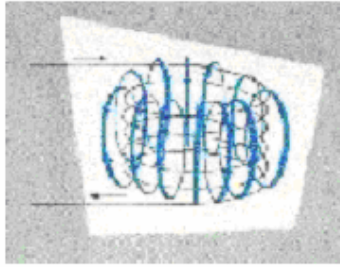


Figure 9: Magnetic Field Around a Coiled Wire [9]

When the coil of the solenoid design is energized with current, the magnetic field causes the armature to move in one direction. When the armature moves, it can be used to push a small amount of saline solution. The movable core is spring-loaded to allow the core to retract when the current is switched off. The force generated is approximately proportional to the current.

Few of the advantages of this design are that it is inexpensive and involves simple circuitry. However, we were not able to find a solenoid that could accelerate the armature fast enough so as to provide an ejection interval of 5 milliseconds. Another problem with this design is that it is hard to get it to inject precise amounts of such minute volumes as 3-5 μL .

2.2 Design 2: Hydraulic Electronic Unit Injector (HEUI)

With help from professor Fronzack and John Ha from the UW-Madison department of Mechanical Engineering, we decided to look into modifying a new high velocity fuel injection system. The hydraulic electronic unit injector (HEUI) is a relatively new fuel injection system originally developed by Caterpillar Inc. for use in their diesel fuel engines (Figure 10). The device was selected based on its high force generation and high injection speed. If implemented in our design, the device would attach to a compatible chamber that would attach to the end of the injector nozzle and would then lead into the catheter of the device.

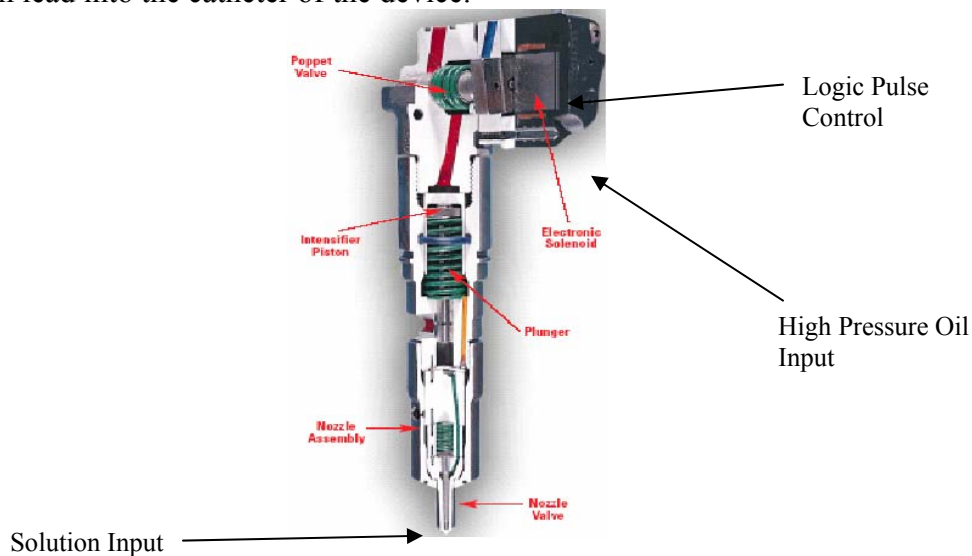


Figure 10: HEUI by Caterpillar Inc.

HEUI works off of an external high pressure oil pump that supplies high pressure oil into the fuel injector. Control of the device originates from an electrically controlled solenoid that attenuates a valve when signaled. As the poppet valve opens, high pressure oil will rush into the injector and act to force the intensifier piston downward. This action intern drives fuel, inputted externally, out of the nozzle and either into a piston chamber or the catheter of our device. Output pressure intensification is accomplished by area ratios between two components—the intensifier piston and plunger. These ratios can be changed to develop desired output pressures. Pressures can be increased to seven times that of the input pressure [5]. If used in our device, we would have to change the fuel input to a saline solution if the device were attached directly to the catheter. Because of the internal structure of the HEUI, output pressures can exceed seven times that of the input pressure. However, pressure control does depend on the pressure inputted into the system from the external oil input [4].

Many advantageous exist with the use of the device, but none more important than excellent electronic control, which is extremely rapid and precise. Other advantages include high force and pressure generation, and high output flow rates. Both the force and rapid flow rate specification would easily be met with this device, but unfortunately would probably be over met and exceeded. In addition, we would have to purchase and attach a rather expensive high pressure oil pump to the HEUI.

2.3 Design 3: Solenoid Valve

In the interest of time and uncertainty about the funding available for a piezoelectric stack, an alternative design was pursued last semester. The final prototype used a high-pressure source, along with a rapid-response micro-solenoid valve to deliver the saline. The prototype delivered saline at rates close to 3 μL with a 5 ms TTL pulse.

This design used a linear actuator as a pressure source to move the syringe. The moving syringe pushed the saline against the closed walls of the micro-solenoid valve (Figure 11) and created high pressure. A TTL pulse-generator was used to provide 5V to control the time for which the valve needed to be opened. A dual power-supply was used to run a spike and hold circuit, which opened the solenoid valve at 24V, and after the specified time, held it at 4.5V.

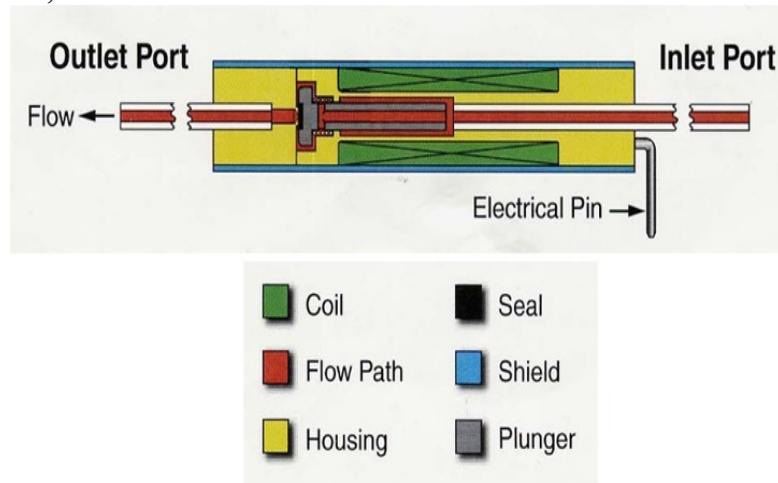


Figure 11: Schematics of Microfluidic Solenoid Valve [10]

The solenoid valve used for this design was the Lee company’s VHS-V-Chrome core (reference no. INKD059550). The prototype was sufficient to show the capabilities of the solenoid valve, but did not provide a means of bleeding the injected volume out of the catheter. Another problem seen with this design was accurately dispensing the required volume. Both of these problems are important design specifications, and therefore the initial piezoelectric stack design was chosen for this semester. For detailed information about the previous design refer to Appendix II.

2.4 Preliminary Design Decision Matrix

Evaluating the three proposals according to the most important design characteristics was accomplished with a decision matrix (Table 1). Listed in decreasing importance, speed, maintenance, compatibility, accuracy, and cost were weighted by their value to the final design. Assigning each category a value of 1, 2 or 3 for the proposed designs, and multiplying by the corresponding characteristic’s weight gives an unbiased comparison of the proposed designs.

Table 1: Decision matrix used to evaluate proposed designs.

	Solenoid Armature	HEUI	Solenoid Valve	Piezo Stack
Speed (5)	1	3	3	3
Retraction (5)	3	1	1	3
Maintenance (4)	2	2	3	3
Compatibility (3)	1	2	2	2
Accuracy (2)	3	2	2	3
Cost (1)	3	1	3	1
Total	40	39	45	57

The piezoelectric stack is the chosen design, since it excels in every category except cost. A small margin separates the solenoid valve and stack, but accuracy and retraction give the stack advantages. Compatibility is an issue with all designs, because of the catheter dimensions and injection speed.

3. Final Design

The final design uses a piezoelectric stack to drive a piston. Piezoelectric stacks consist of many layers of piezoelectric discs with thin electrodes separating each layer. When a voltage is applied to the system the electrodes become charged, causing individual layers to expand across the entire system. Maximum theoretical displacement is contingent on the number of disks in the stack and stiffness of the material. Theoretical and actual displacements vary by a factor of the force opposing motion. Stress in the

system causes an electrical charge to be produced. If the charge isn't removed rapidly the piezoelectric material creates a force opposing the motion. These systems are accurate to the nanometer, and change in length occurs within a millisecond, fulfilling two of the main specifications discussed earlier [1].

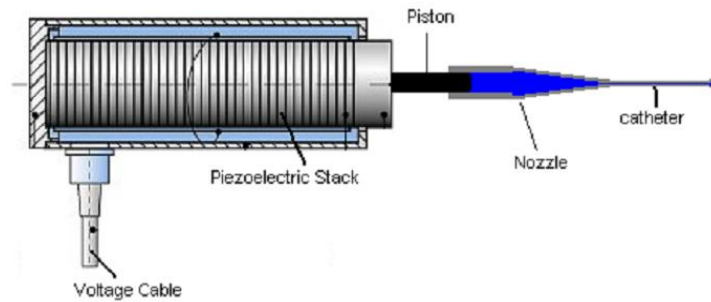


Figure 12: Piezoelectric stack design schematic [1].

The design consists of a piezoelectric stack with a syringe attached that acts as a piston to drive the saline into the catheter tube. When voltage is applied to the stack, the syringe plunger forces the fluid into the catheter tip (Figure 12). A compartment to hold the stack and catheter securely in place is needed so the system is entirely static with the exception of the desired driving force is essential. Piston diameter will depend on an analysis of the fluidic forces opposing motion and stack chosen.

This design has many advantages, most importantly an extremely rapid injection rate and very precise control over the amount of fluid injected. Additionally, the expansion of the stack can be controlled by the voltage input, so a single device could be designed to inject a variety of volumes. As with other designs, working with the catheter dimensions will require very precise machining and manufacturing.

3.1 Flow Analysis

The velocity of saline moving in the tubing can be calculated by using the continuity principal for the steady flow. The continuity equation is simply a mathematical expression of the principle of conservation of mass. For a control volume that has a single inlet and a single outlet, the principle of conservation of mass states that, for steady-state flow, the mass flow rate into the volume must equal the mass flow rate out [12].

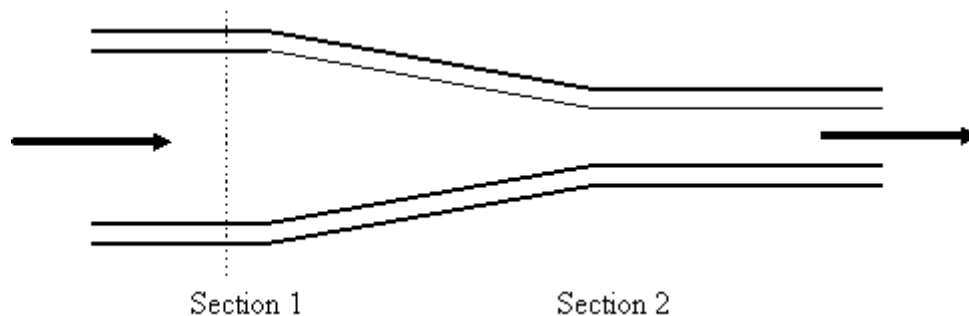


Figure 13: Fluid Flow in a tube with different cross-sectional areas

Since there is a single inlet and a single outlet, by the continuity principle, the *mass flow rate* must be the same at each section i.e. the mass going into the pipe is equal to the mass going out of the pipe. Assuming that the density of the fluid does not change as it flows, this can be expressed as:

$$A_1v_1 = A_2v_2$$

where A_1 and A_2 represent the area in Section 1 and Section 2 and v_1 and v_2 represent the velocity of the fluid flowing in Section 1 and 2 (Figure 13).

In our experimental set-up, Section 1 corresponds to the syringe and Section 2 corresponds to the tubing through which the saline solution flows. The syringe is attached to the piezo stack and moves with the same velocity as that of the stack. Knowing the resonant frequency of the piezo stack, the velocity of the stack was found to be 0.36m/s. Also, the cross-sectional area of the syringe was measured to be 2.83m². The cross-sectional area of the tubing was measured to be 5.67x10⁻³ m². Thus, the velocity of the saline in the tubing was calculated to be 17.9 m/s*.

Bernoulli's equation for steady flow was utilized to find the pressure difference across the tubing. Bernoulli's principle states that in fluid flow, an increase in velocity happens simultaneously with decrease in pressure. Mathematically, it can be represented as:

$$g \cdot h_1 + \frac{p_1}{\rho} + \frac{V_1^2}{2} = g \cdot h_2 + \frac{p_2}{\rho} + \frac{V_2^2}{2}$$

where subscripts 1 and 2 represent the two tube sections as shown above in Figure 13, V is the flow speed, p is the pressure, ρ is the density of the fluid, g is the acceleration due to gravity, and h is the height above the ground level. Assuming a steady, fully-developed, horizontal flow with no radial velocity and swirl for our set-up, the change in pressure can be represented as:

$$\Delta P = 8 \mu Q L / \pi R^4$$

where μ is the viscosity of the fluid, Q is the flow rate, L is the distance through which the fluid flows through, and R is the radius of the tube. Using the above equation, the change in pressure was calculated to be 11,825 N/m²s*.

* Refer to Appendix III for calculations.

3.1 Piezo Actuator

The piezo stack was purchased from Physik Instrumente based on its specifications and displacement capabilities (Part P239.90). The P239.90 model is equipped with thin piezo ceramic layers that provide has a maximum displacement of 180 μm at -1000 V operating voltage. To maximize the lifetime of the stack, voltages exceeding -750 V should be applied for only short durations. The piezo ceramics are encased by a stainless steel case with an internal spring preload. The translator tip emerges from a tapped hole in the steel casing and is threaded with a 6.0 mm hole for connection. Due to the large forces required in this design, the translator must be mounted by its base [11].

3.2 Syringe

A glass syringe was chosen so that the material of the syringe would not absorb any of the pressure or displacement produced by the piezo stack. The part purchased was a Hamilton Teflon Fluorocarbon Resin Luer Lock Syringe with a total volume of 2.5 mL (Hamilton No. 81420, Catalog No. 13-684-95). The syringe plunger has a 4/36" hole in its center for connection and the tip at the end of the syringe has a Luer Lock connection. The end of the syringe connects to a three-way Luer Lock valve; one valve connects to the syringe, one is for filling the chamber with saline, and the other connects to the catheter.

3.3 System Manifold

To ensure no movement of the individual components of this design, a continuous aluminum manifold was machined to keep them static. The piezo actuator rests in a groove machined in the bottom of the aluminum and its base is supported by the back of the manifold. The piezo stack and syringe physically connect with a double threaded screw to prevent movement at the connection (6 mm diameter to connect to the actuator and the opposite-end diameter of 4/36" to connect to the syringe plunger). A block at the end of the manifold has a 9.0 mm hole to support the weight of the syringe (Figure 14).

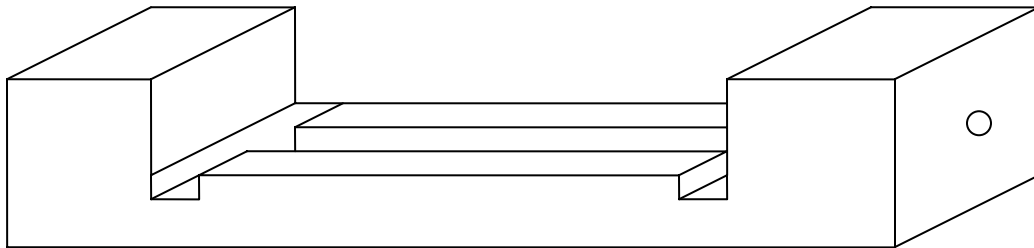


Figure 14: System Support Manifold

3.4 Electronics

Our client loaned us a Kepco BOP 1000M amplifier (Figure 15) with a 5V TTL input modification from previous physiology experiments. A function generator capable of single wave output was also obtained from the client to simulate the TTL pulses that would be used to trigger the stack during experiments.



Figure 15: Kepco BOP 1000M Amplifier

Initially, the function generator was connected to the high voltage amplifier and both waves were observed on a two channel oscilloscope. Measuring both waves simultaneously allows the rise time to be measured. At -800V , the maximum of the available oscilloscope, a rise time of less than 0.3 ms was observed.

The LEMO connector was modified for initial testing to be compatible with the BNC outlets available on the amplifier. This was accomplished by taking the cap apart, soldering a wire to the pin and wrapping the ground around the outside of the LEMO. This should be adequate for use with low voltages, and was a temporary solution while waiting for the LEMO to BNC connector from Physik Instrumente.

3.5 Testing

Initial tests were conducted with a 1 Hz TTL signal and -10V coming from the amplifier. When the leads were connected, a high pitched buzzing sound was heard and high frequency oscillations off the screen of the oscilloscope were observed. The voltage on the amplifier was then turned down to zero and the same effects were observed. During both tests movement could be felt on the tip of the stack, but could not be controlled and is thought to be damaging to the piezoelectric material.

To check if the stack was functioning properly a 12 V DC power supply was set to -10V . When the leads were connected, a ticking sound could be heard and movement could be felt on the tip of the stack. If the leads were immediately connected again, nothing was observed and it is suspected the stack was discharging.

The next step involved testing the amplifier under various conditions to determine where the problem was originating. Under the supervision and guidance of Burke O'Neal, a $0.46\text{ }\mu\text{F}$ capacitor was connected to the system and the same high frequency oscillations were observed. According to Burke, older amplifiers can't handle capacitive loads and a different electrical setup is needed, since that stack is essentially a $2\text{ }\mu\text{F}$ capacitor.

4. Future

The only current problem is obtaining an electrical supply that is capable of firing the stack. Other problems may arise once the electrical problems are fixed, but can only be determined with a fully functioning stack. Two possible electrical solutions have been designed that would accept capacitive loads.

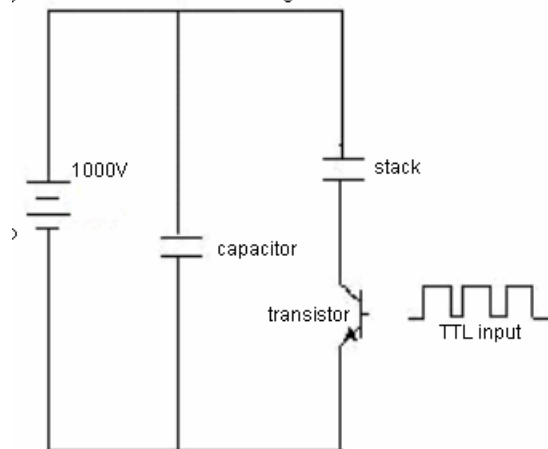


Figure 16: Electrical design using charge on large capacitor to drive stack.

The first design uses the same -1000 V power supply to charge a much larger capacitor. With the large capacitor charged it will now act as the voltage source for the smaller capacitor, piezoelectric stack. An insulated gate bipolar transistor (IGBT) is used to close the electrical circuit and fire the stack with a TTL input (Figure 16).



Figure 17: Physik Instrumente Part E-507 [1]

The second electrical solution uses the amplifier recommended by Physik Instrumente, E-507 (Figure 17). This amplifier was initially suggested by the sales representative at PI, but disregarded because of the high price, \$2870. This amplifier has a LEMO output to the stack and has been designed for use with piezoelectric stacks. This model amplifies 0-11V control input by 100, producing a maximum of +/-1100V. For maximum expansion of the stack, 180 μm , the TTL signal would be amplified to 10V.

Using either the amplifier described above or finding an amplifier that can handle capacitive loads is the best option for firing the stack. If the option of charging the large capacitor is chosen, electrical safety is the greatest concern. The capacitor should always be handled with extreme caution and discharged before leaving it unattended. One of the options mentioned should be sufficient to test the manifold and syringe system that has been assembled.

5. References

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Appendix I

Product Design Specifications

Project Title: Mouse Heart

Team Mouse Heart Members: Hannah Kirking, Ankur Sharma, Steve Trier

Date: May 2004

Function

We are interested in making a device to measure the stiffness of intact mice hearts at different phases of the cardiac cycle. Our idea is to place a pressure transducer inside a small balloon inside the mouse heart and inject small quantities (perhaps 5 μl) of saline into the balloon. The stiffness of the heart will be defined as the change in pressure divided by the change in volume. The difficult bit of the project is that we need to attain rapid measurements to precisely determine when the data was recorded (ideally within a few ms). More specifically, the main goal of the project is to design a micro-fluid injecting device that dispenses between 3-5 μl of saline into a 0.65mm ID catheter.

Client Requirements

- Inject a fixed quantity (3-5 μl) of saline through a catheter into a left ventricular balloon
- The injector must attach to a catheter with 200 μm diameter opening
- Length of catheter from fluid injector to end of tube is 2 cm
- Must do this in less than 3 ms
- Must operate with an electrical logic pulse (ex. TTL)
- Record how much fluid was injected

1. Physical and Operational Characteristics

- Performance requirements:* Inject 3-5 μl of saline solution into a balloon in less than 3 ms, against left ventricular pressure, and remove the injected volume (not time critical). The balloon needs to be filled to a desired volume prior to fluid injection, which is to be initiated by an electric logic pulse (TTL trigger). The fluid will flow through 2 cm of flexible tubing with outer diameter 200 μm , before reaching the balloon.
- Safety:* All electrical components must be enclosed to prevent harm to the researcher and mouse.
- Accuracy and reliability:* The injected portion should be consistent and measurable. Accuracy to within 1 μl of the desired volume dispensed.
- Life in Service:* Duration of experiments.

- e. *Shelf life*: approximately 5 years.
- f. *Operating conditions*: Physiology laboratory environment.
- g. *Ergonomics*: The device must easily attach to a small catheter--on the order of 100 um in diameter. The device should be hand held and easy to activate with a single hand. The injector should fire at the push of a button, key stroke, or switch through the use of an electrical pulse.
- h. *Size*: The size of the device will depend. If a digital interface is adapted to control the device, the entire device will rest on a table in the shape of a small box. A tube with an attachment for the catheter and intake apparatus will protrude from the box. The pump would rest inside of the box. The device may also be adapted into a hand held device and would be no larger than the size of a pen along with the attachment for the power source and catheter.
- i. *Weight*: A weight limit may be applicable if the device is adapted into a hand held device. If that is the case, it should be easy to lift and operate with one hand.
- k. *Materials*: No material used can be harmful to the operator. The tubing involved should sterilizable and easy to clean. The injector pump should come apart and should also be easy to clean.
- l. *Aesthetics, Appearance, and Finish*: No restrictions

2. Production Characteristics

- a. *Quantity*: 1
- b. *Target Product Cost*:
 - i. Expected cost of the first unit by the client: \$10,000
 - ii. Expected cost of the consecutive units: \$500

3. Miscellaneous

- a. *Standards and Specifications*: This product is mainly going to be used for the experimental procedures in medical research. There are no international or national standards that this product needs to follow.
- b. *Customer*: Client is interested in the mechanical properties of muscles. Through this machine he wants to measure passive pressure in intact heart in a mouse.
- c. *Patient-related concerns*: For the purpose of this project, the product is to be used on isolated mice hearts. Therefore, there is no use for this device to be sterilized, unless the heart is going to be used for some other

purposes like extracting DNA etc. However, in future this device can be developed to measure pressure in an intact heart.

- d. *Competition*: There isn't anything similar to this product out in the market. However, people at University of Calgary in CA have invented something similar to this project.

Appendix II

Solenoid Valve Design Details

Ideally, the final design uses a linear actuator assembly to provide and hold the precise values of pressure in the tubing. The actuator is used to push the plunger of a 10ml syringe filled with saline solution. The syringe is then connected to a luer-lock needle. PolyTetraFluoroEthylene (PTFE) tubing with an inner diameter of 0.85 mm is fitted on the needle. The tubing used for this project can handle pressures up to 375 psi. The tubing is chemically inert, non toxic, non porous, translucent, crack and stress resistant, autoclavable, and has a low coefficient of friction, which reduces the resistance in the flow. The other end of this tubing is attached to one of the ports of a 3-way valve. A second port is fastened to the same PTFE tubing, which goes on the inlet port of the solenoid valve. The third port of the 3-way valve is attached to a Saline-Input and Retraction mechanism that pulls back the dispensed saline, and refills the syringe with more saline. The outlet end of the solenoid is then fabricated to fit on the catheter. A TTL pulse-generator is used to provide 5V to control the time for which the valve needs to be opened. A dual power-supply is used to run a spike and hold circuit, which opens the solenoid valve at 24V, and after the specified time, holds it at 4.5V. Figure 18 lays out the flow diagram for the final design.

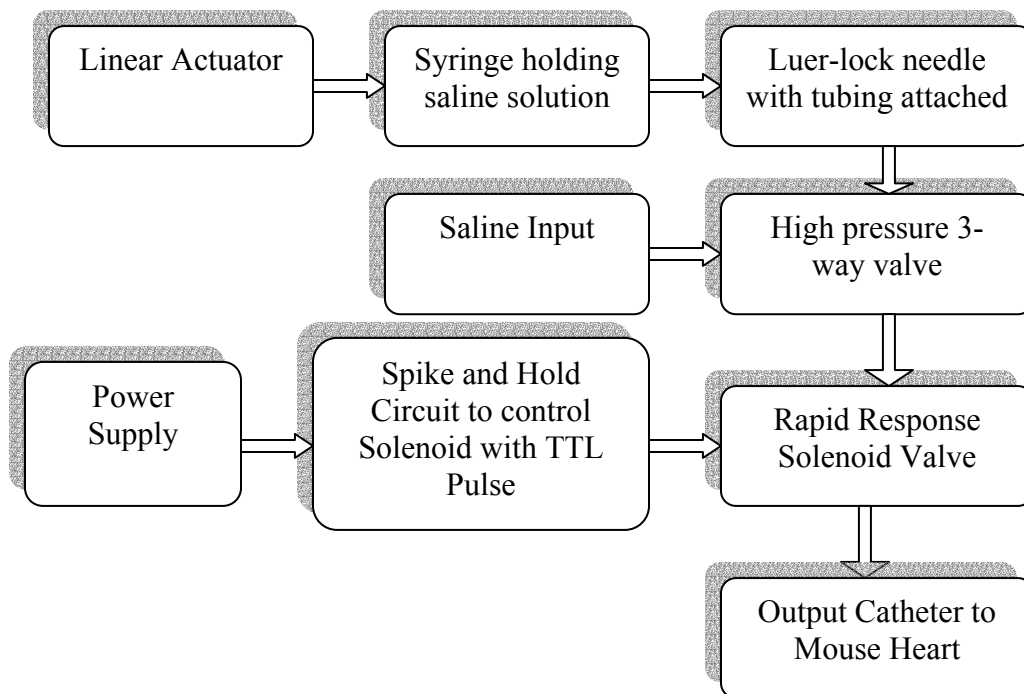


Figure 18: Final Design Flow Chart

However, the mouse heart team was not able to accommodate a 3-way valve and a Saline-Retraction mechanism in the final prototype built. In the final prototype, the linear actuator pushes on the plunger of the syringe filled with saline, maintaining a specific pressure, and forces the saline out of the syringe when the valve is open. It was

made sure that the attachment of the tubing to the syringe needle was tight enough to hold a high pressure from the actuator. The 3-way valve was bypassed and the tubing was directly connected to the solenoid inlet. The outlet of the solenoid valve was connected to a capillary through the same tubing. The diameter of the capillary was known and thus the volume of saline dispensed in the capillary could be calculated by knowing the length through which the saline moved in the capillary. This became extremely helpful during testing.

Solenoid Valve

The solenoid used for the final design is a VHS Standard Port micro-dispense valve made by the Lee Company (Figure 19). This solenoid is much smaller than all other solenoid found during the research. Its response time is between 0 and 5 ms. It uses a high speed drive circuit to attain such high speeds.

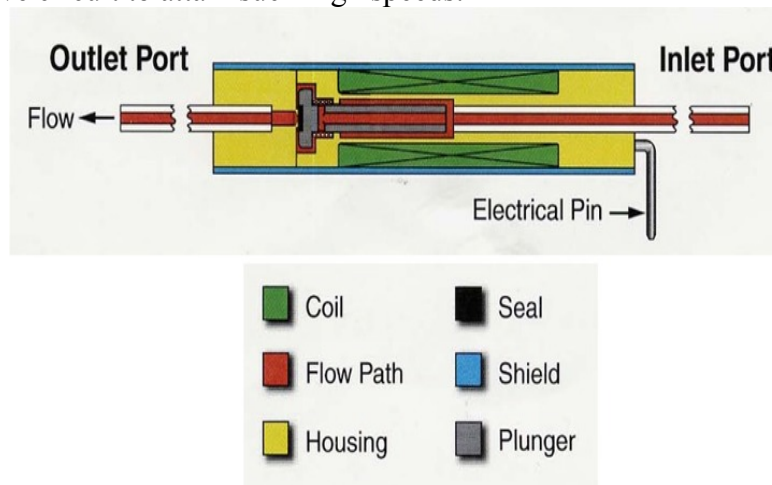


Figure 19: Schematics of Microfluidic Solenoid Valve [10]

A dual power supply is needed to run this solenoid valve. It requires 24V strike voltage to open the valve and 4.5V to hold it in the open position. A TTL pulse is needed to regulate the time for which the valve stays open. When the valve is energized, the plunger opens the flow path for a specified time. For the purpose of this project, a solenoid with Chrome-core plunger is used to resist corrosion. When the signal is removed springs inside the valve closes the valve. The dispense rate proportional to the pressure applied and the duration of the TTL signal.

Controlling the solenoid valve

A significant design specification for the injection device is the ability to easily control the timing of each injection. And not only the time interval of each injection, but also precisely when each injection is fired. One simple way to implement this is to use a TTL pulse as a signal to initiate and terminate each injection. Transistor to Transistor Logic (TTL) pulses generally act as an ON/OFF switch—an all or none response. A five volt threshold voltage is the standard voltage, which is the amount of voltage needed to turn the switch on. Any voltage applied lower than five volts will not activate the switch.

When the five volt threshold is reached, the switch is on. The signal can last in the on position depending on the frequency of the TTL wave. The frequency is the time that each pulse remains at a constant five volts. At the end of the period, the voltage will drop to zero thus turning the switch off. The frequency of the trigger signal can be varied, and thus gives us the ability to control how long the switch is triggered on a ms scale.

We decided to use a TTL pulse to control the actions of our device. A problem is that a simple TTL pulse will not activate and actuate the solenoid valve. The valve needs a larger voltage to initially open, but can stay open once activated at lower voltages. So in order to actuate the solenoid valve, we need to first provide the effective signal and control that signals timing with the TTL pulse (Figure 20). But this problem was easily solved because the Lee Company, which manufactured the solenoid valve, also develops circuitry that demonstrates the effective attenuation that we needed to trigger the valve.

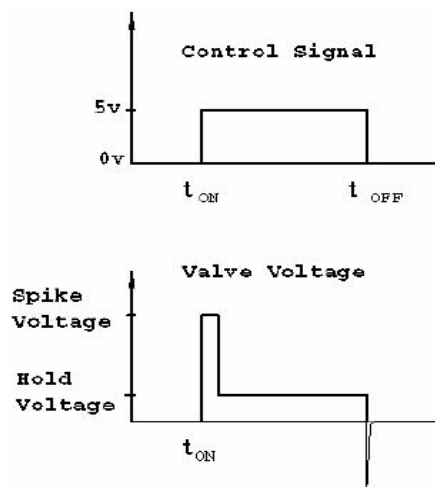


Figure 20: Control signal (TTL pulse) and corresponding drive signal (voltage across valve) [10]

The circuitry requires three voltage inputs. Two are spike and hold voltage sources that will initially actuate and hold the valve open. The two important voltages are 24 V DC and 4.5 V DC respectively. The third input is the TTL control signal.

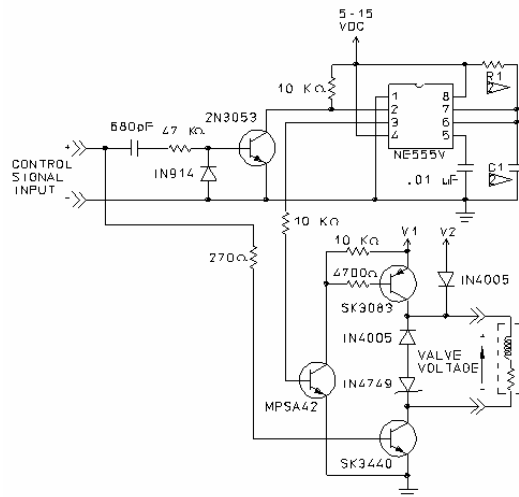


Figure 21: Spike and hold drive circuit [10]

This is a relatively simple circuit (Figure 21) that uses a TTL wave to control how long the output voltage (to the solenoid) is applied. The length of time (frequency of signal) that the threshold voltages are applied to the solenoid relates to the length of time that the valve is open. We only intend to apply a single pulse or a trigger signal to activate the valve. The TTL input is applied at the +/- control signal input terminals. The spike voltage is applied at V1 and the corresponding hold voltage is applied at V2 in the circuit diagram. The inductor and resistor shown in series inside of the dashed box represents where the solenoid valve would be inserted into the circuit [10].

Setup and Testing

Testing of the device was performed in the BME electronics lab using a dual power source (33120A) to open the valve, single wave function generator for controlling the valve. The remaining parts used include the valve, spike and hold driver, 10 cc syringe with male luer, 22 Guage needle with female luer, tygon tubing, and a 0.85 mm ID plastic capillary.

Circuit

Circuit terminals 3 and 4 are connected to channels in the dual power source set at 5 and 24.5 VDC, respectively. Grounds from both channels, along with the function generator are connected to terminal 1. Monitoring output on an oscilloscope, a square wave of 5 V and 5 ms (200 Hz) is set on the function generator. The square wave provides the TTL trigger necessary in terminal 3, which is normally off. The last two terminals are each connected to a pin on the valve. Wires in each circuit terminal are tightened securely.

Filling and Connecting

The syringe is filled with water that has been passed through a 0.2 μm filter, to maintain accuracy in the valve. The syringe is then connected to the needle-tubing attachment. The loose end of the tubing is attached to the inlet valve. The valve is triggered many times until a meniscus of water can be seen in the outlet tubing. At this point the valve is filled with water, and any output can be measured.

The syringe is unconnected and filled to 8cc with filtered water and 10cc of air. The linear actuator is then tilted up, while sliding the syringe in the machined block and connecting the luer needle. Now for testing, the back of the linear actuator is elevated to assure no air will leak into the tubing.

Testing Frequency

Measuring the syringe reveals that 1 cc is equal to 1 cm. Thus, 1 cm of compression in the above mentioned system doubles air pressure inside the syringe, according to Boyle's law, $P_1V_1=P_2V_2$. With a negligible fraction of the air being

dissolved in water, air pressure in the syringe is equal to water pressure, twice atmospheric.

Using a plastic capillary of ID = 0.85 mm, the injected volume is measured after each pulse. A change in 5.28 mm in the capillary equals the required 3 μL of fluid. Frequency of the square wave is inversely proportional the time the valve remains open, and is set at frequencies ranging from 50 to 1000 Hz for testing. The TTL wave is triggered once at 1000 Hz and output measured with a ruler. This test is performed twice at each frequency, testing a variety of frequencies down to 50 Hz. If the meniscus reaches the end of the capillary the tubing is removed from the valve and water removed by capillary forces. To resume testing the valve is triggered until the meniscus reaches the capillary.

The syringe was refilled with 8 cc water and 2 cc air, and the previous procedure reproduced three times. After each test the difference in water and air levels were unnoticeable to the human eye. Results from the three trials, 6 tests for each frequency, were averaged and graphed (Figure 22). The results obtained show a linear relationship between frequency and volume injected for about 15 psi. It is expected that an increase in pressure shifts the relationship to the left, while a decrease in pressure shifts to the right.

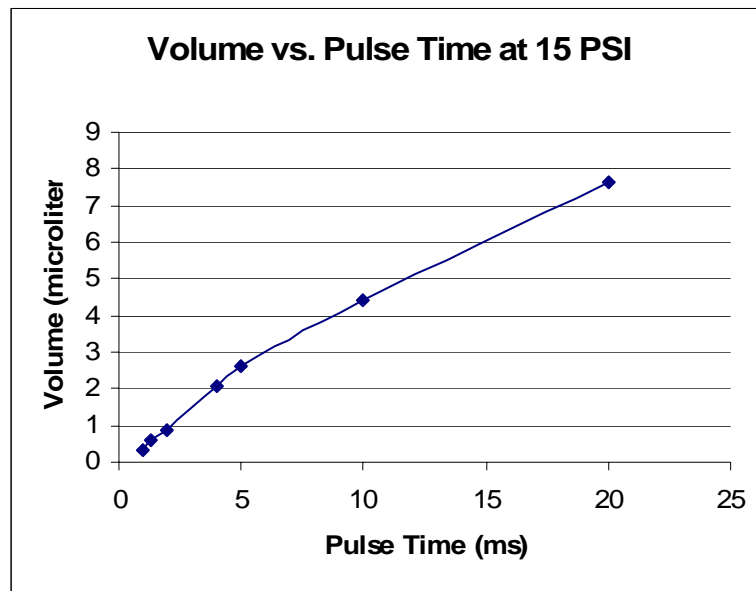


Figure 22: Volume vs pulse time—to show the effective frequency

One trial attempted to measure the effect of an increase pressure on the injection volume, but water began to leak from the needle tubing interface at about 50 psi. At this point the linear actuator was retracted until the leak disappeared, estimated at 40 psi. Tests performed at this pressure caused turbulent flow in the outlet, making it hard to properly measure the volume.

Possible Future Considerations

Since pressure determines flow rate, an accurate means of controlling and measuring pressure will be needed to produce reliable and accurate dispense volumes. Three methods for measuring and controlling pressure have been proposed. Using Bernoulli's law of continuous flow, gravity could be used to accurately control the supply pressure. Another solution places a force transducer on the plunger which could be correlated to the supply pressure. The final alternative uses a syringe pump from clinical procedures. The device has a pressure gauge in place, but would need to be modified for higher accuracy.

Increasing the pressure significantly caused the current system to leak and caused turbulent flow when injected. Although it may not be significant at the pressures we need, specifically designed fittings are available from the Lee Company. Various 062 fittings can be placed together providing a leak proof system, including fittings with tubing attachments. These would improve the accuracy and reliability of the system, but require specially ordered valves since a chrome core plunger is recommended for saline applications.

Although all the client requirements haven't been fulfilled by the current design, there are solutions to the current problems available. One major obstacle is dispensing a reliable and accurate sample, followed by removal of the precise amount injected. These volumes will be dependent on pressure differences, which will need to be controlled very accurately.

Appendix III

Flow Analysis

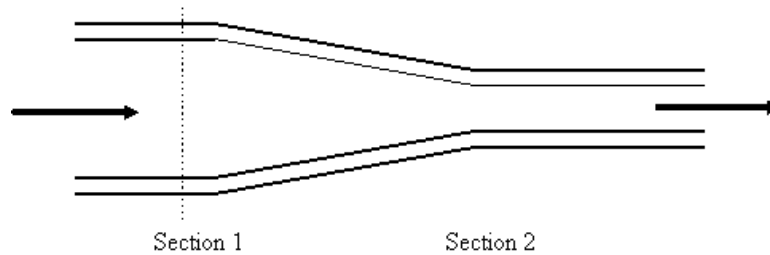


Figure 23: Theoretical Flow Model

Flow Properties:

Saline flows from section 1 to section 2 (left to right).

Area 1 > Area 2

The flow is steady, unidirectional and fully developed with no radial velocity and swirl.

1. Velocity of saline in the tubing

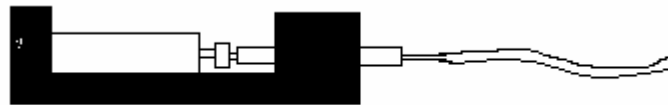


Figure 24: Device Schematic

As shown in Figure 24, the stack is attached to the plunger of the syringe and thus the syringe moves with the same speed as that of the stack.

The resonant frequency of the stack = 2000Hz

Therefore, the time per stroke for the stack = $1/\text{frequency} = 1/2000\text{Hz} = 5 \times 10^{-4} \text{ s}$

Distance moved by the stack in one cycle = $180 \mu\text{m}$

Therefore, the velocity of the stack = $\text{distance} / \text{time} = (180 \times 10^{-6} \text{ m}) / (5 \times 10^{-4} \text{ s})$
 $= 0.36 \text{ m/s}$

Therefore, the speed of the syringe plunger = 0.36 m/s

Inner cross-sectional area of the syringe = $\pi r(s)^2 = \pi (3 \times 10^{-3})^2 = 2.827 \times 10^{-5} \text{ m}^2$

Inner cross-sectional area of the tubing = $\pi r(t)^2 = \pi (0.425 \times 10^{-3})^2 = 5.67 \times 10^{-7} \text{ m}^2$

Now since

$$A_1 v_1 = A_2 v_2$$

$$(2.827 \times 10^{-5} \text{ m}^2) (0.36 \text{ m/s}) = (5.67 \times 10^{-7} \text{ m}^2) (v_2)$$

$$v_2 = 17.94 \text{ m/s}$$

therefore, the velocity of the saline flowing in the tubing was found to be **17.94m/s**.

2. Pressure difference across the tube.

ρ : density μ : viscosity

Navier Stokes Eq: $\rho \left(\frac{\partial v_x}{\partial t} + v_r \frac{\partial v_x}{\partial r} + v_\theta \frac{\partial v_x}{\partial \theta} + v_x \frac{\partial v_x}{\partial x} \right) = \rho g_z - \frac{\partial P}{\partial z} + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_x}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 v_x}{\partial \theta^2} + \frac{\partial^2 v_x}{\partial x^2} \right)$

Assumptions: long tube, fully developed flow, no radial velocity, no swirl, horizontal flow

Under these assumption for our set up, Navier Stokes Eq reduces down to:

$$\frac{\partial P}{\partial x} = \mu \left[\frac{1}{r} \left(\frac{\partial}{\partial r} \left(r \frac{\partial v_x}{\partial r} \right) \right) \right]$$

~~integrating once~~ ^{rearranging terms}, we get $\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial v_x}{\partial r} \right) = \frac{1}{\mu} \frac{\partial P}{\partial x}$

integrating once, we get $\frac{\partial v_x}{\partial r} = \frac{1}{\mu} \frac{\partial P}{\partial x} \left(\frac{r}{2} + \frac{C_1}{r} \right)$

integrating again we get $v_x = \frac{1}{\mu} \left(\frac{\partial P}{\partial x} \right) \left(\frac{1}{4} r^2 + C_1 \ln r + C_2 \right)$

Applying no slip boundary conditions we get,

$$v_x = \frac{R^2}{4\mu} (\rho g + \frac{\partial P}{\partial x}) (1 - \frac{r^2}{R^2})$$

Flow rate $Q = \int v_x dA = \frac{1}{2} \pi R^2 \left(-\frac{dP}{dx} \right) \frac{R^2}{4}$

substituting $\Delta P/L = dP/dx$

$$Q = \frac{1}{\mu} \cdot \pi R^4 \left(\frac{\Delta P}{L} \right) \Leftrightarrow \Delta P = \frac{8 Q \mu L}{\pi R^4} \quad \text{--- ①}$$

μ for saline = $1.01 \times 10^{-3} \text{ N/m}^2$

flow rate $Q = \frac{3 \text{ ml}}{5 \text{ ms}} = 6 \times 10^{-9} \text{ m}^3/\text{s}$

Using equation ① pressure gradient across the tubing was calculated as follows

$\mu = 1.01 \times 10^{-3} \text{ N/m}^2$ $L = 5 \text{ cm}$ $Q = 6 \times 10^{-9} \text{ m}^3/\text{s}$ $r = 0.425 \text{ mm}$

$$\Delta P = \frac{(8)(1.01 \times 10^{-3})(3 \times 10^{-9})(5) \text{ N ml } \cdot \text{cm}^3 \text{ cm}}{\pi (1)(.425)^4 \text{ mm}^4 \cdot \frac{\text{m}^3}{\text{mm}^3} (10^{-12}) \text{ m}^2 \cdot 5 \text{ ms} \cdot \frac{1 \text{ s}}{1000 \text{ ms}}}$$

$$= 11824.88 \frac{\text{N}}{\text{m}^2} \cdot \text{s}$$