Subject: Report for Cardiac Patch Using Tissue-Engineered Cardiac Patch

1 Executive summary

Myocardial infraction is a disease that may cause series trouble to patients. Now there is no product that can efficiently retain the functionality of injured cells from myocardial infraction. I designed a cardiac patch that uses cardiomyocytes that are induced from stem cells to retain the functionality of those damaged cells. There are blood vessels in the patch to deliver oxygen to those cells, and there is a place to hold a monitoring and stimulating circuit. From the simulation result, the blood vessels work as expected, as blood flow through those vessels, and oxygen is delivered to those space where oxygen is needed. This report will contain introduction, proposed design, simulation result of liquid flow, solute transport and diffuse, and compression, and conclusion.

2 Introduction

Heart attack, or myocardial infraction, is caused by atherosclerosis, where clot forms in the coronary artery and blocks the blood flowing into later parts. Since oxygen and nutrient cannot be efficiently delivered to those part, heart muscle would be damaged or injured. Severe heart attack may very likely cause patient to die, since heart may not be able to pump blood. After the myocardial infraction, those damaged muscle's functionality would decrease, and for the whole heart, it would want to retain its functionality, so the other side's heart muscle would grow thick, which would decrease the volume of blood that every time the heart can pump to the whole body.

There are several existing solutions to myocardial infraction. They include angioplasty, stent, drug-eluting stent, coronary artery bypass graft, heart transplant, and so on. But there are problems with all these methods. Angioplasty may not be able to retain the geometry for a long time, and the similar problem exists for stent and drug eluting stent. Coronary artery bypass graft may not last for a very long time. More seriously, these method cannot retain the functionality of those injured muscle. Heart transplant can solve the problem, but the long waiting list leads to very little hope for getting a heart. To address these problems, I designed a cardiac patch.

According to the American Heart Association's data of 2010, there is about 15.4 million people that suffer from cardiovascular disease, and there are about 7.6 million people that suffer from myocardial infraction (AMA p115). Also the estimated direct and indirect cost of cardiovascular disease for 2010 is $315.4 billion according to American Heart Association (AMA p120). From these two data, we can see that there is a broad market for devices that can treat myocardial infraction.

There are several aspects that I need to consider when designing my patch, and they include

patients, physicians, and payers. For patients, they can get a better method for treating their myocardial infraction, and it is almost the best one among all the existing solutions. Also the patch and their hearts working condition can be monitored, which would be a great thing for patient to stay alert for their heart's health conditions. So patient may likely accept this product as long as it is safe and effective. For physicians, they can better monitor patients heart after the surgery, and the patch may outperform those existing solutions. For health insurance companies, i.e. payers, the patch may last longer than existing solutions, which means they may need to pay less than existing solutions in the long run, and it may be good for them.

There are several existing cardiac patch production companies after searching on the internet. iRhythms cardiac patch mainly focuses on monitoring patients condition. Vascutek Procine Pericardial Patches mainly focus on tissue repair, especially soft tissue deficiency repair. Gore Acuseal cardiovascular patch looks like trying to repair scars on the heart. There are several kinds of cardiac patches right now, but according to the search result, there is no patchs that have the functionalities of the one that I have designed. But as for intellectual properties, those companies may possess some patents for cardiac patch, and iRhythm may have some cardiac patch monitoring patents. Another part of the intellectual property would be the method of stimulating stem cells to get cardiomyocytes. There are researches right now that conducts research on developing those methods, so there may need to be some collaborations or even need to buy intellectual properties from those research labs.

3 Proposed design

3.1 Lower part single element design

For cardiomyocytes, enough blood, or actually oxygen, is expected to be delivered to them so that they can work as expected. Blood vessels need to be carefully designed so that every cell can be offered oxygen. So for the contracting part, I want to design some blood vessel network that can efficiently transport blood throughout the networks to the entire patch.

Figure 1 is the simplified blood vessel that I want to build for my network. The upper vessel is the place where the blood would enter the vessel network. Later, the blood would flow down to the other vessel through the two ends' round vessel. In this way, theoretically, the blood would flow down from both directions and through the entire blood vessel that I have designed. Also, if the distance in between the blood vessel is carefully designed, oxygen should be able to transport to the entire patch through diffusion.

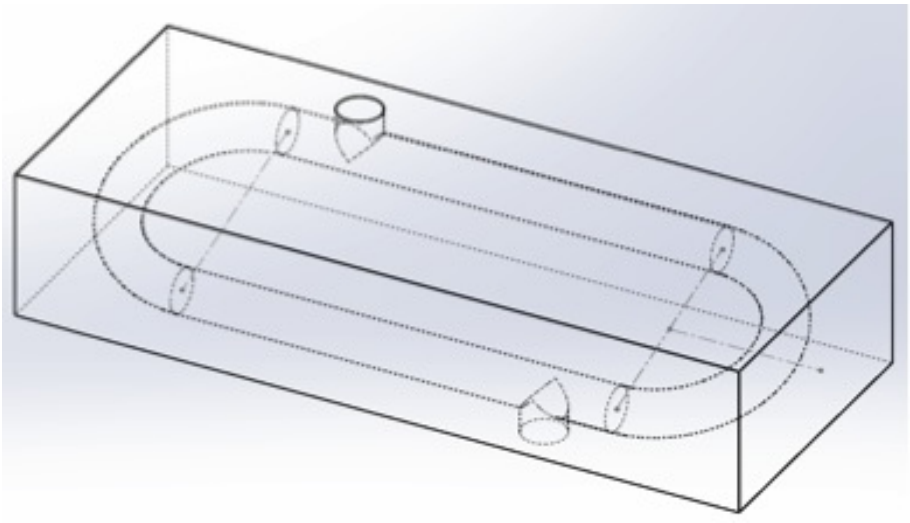

Figure 1. Single element Solidworks drawing

3.2 Two layers design

Previous patch was designed to be about 5mm or 6mm in diameter (round shape) from Miller and Fujimoto. So the design in Figure 1 may just offer one directions blood vessel. Although the blood vessel may be able to offer oxygen to the entire patch, it may not be wide enough in the horizontal direction. So there would need to be some horizontal directions' blood vessels that can deliver the blood horizontally and help the patch to grow horizontally.

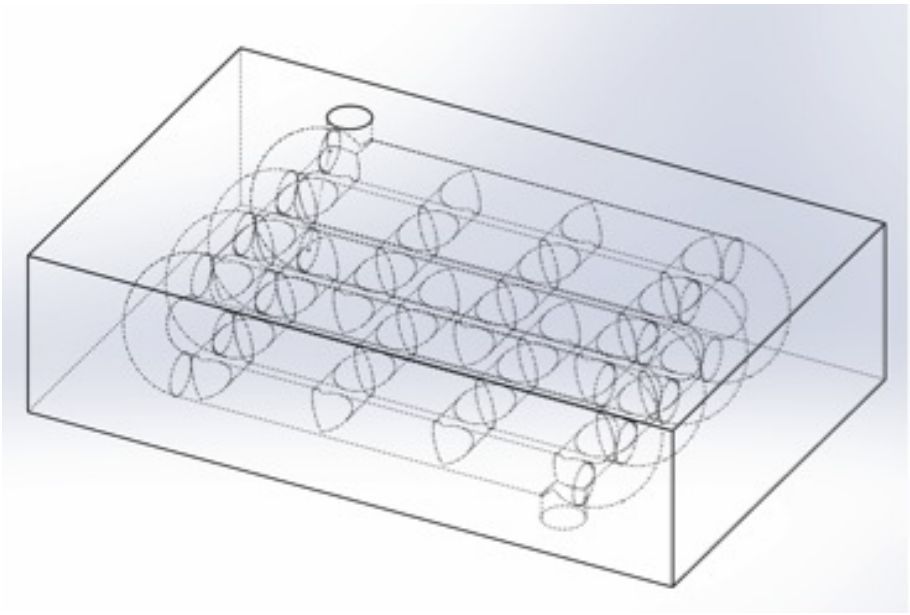

Figure 2. Two layers design Solidworks drawing

Figure 2 offered horizontal blood vessels that can deliver the blood horizontally. In this way, blood can flow both in longitude and horizontal directions. Besides, oxygen can now diffuse out from both directions vessels, which can help to increase the distance between longitude direction's blood vessels.

3.3 Lower Blood vessel design

Just two layers of the blood vessel is too thin for a cardiac patch, as those cardiomyocytes may not be able to offer enough contraction force compared with other parts of the heart. Also it may be too thin to be integrated with other parts of the heart. So the patch would need to be able to grow thicker while the oxygen can still diffuse through the entire patch.

Figure 3's colored part is where the inner blood vessels are. The outer box is where the edges of the patch are. From the colored part, the blood would come down from the cylinder and flow through this layer's blood vessels towards the upper right direction, flow down through those round blood vessels to enter the lower part, and then flow through towards the lower left direction, flow down, and repeat these procedure one more time. In this way, blood and oxygen may efficiently be sent through the entire blood vessel network.

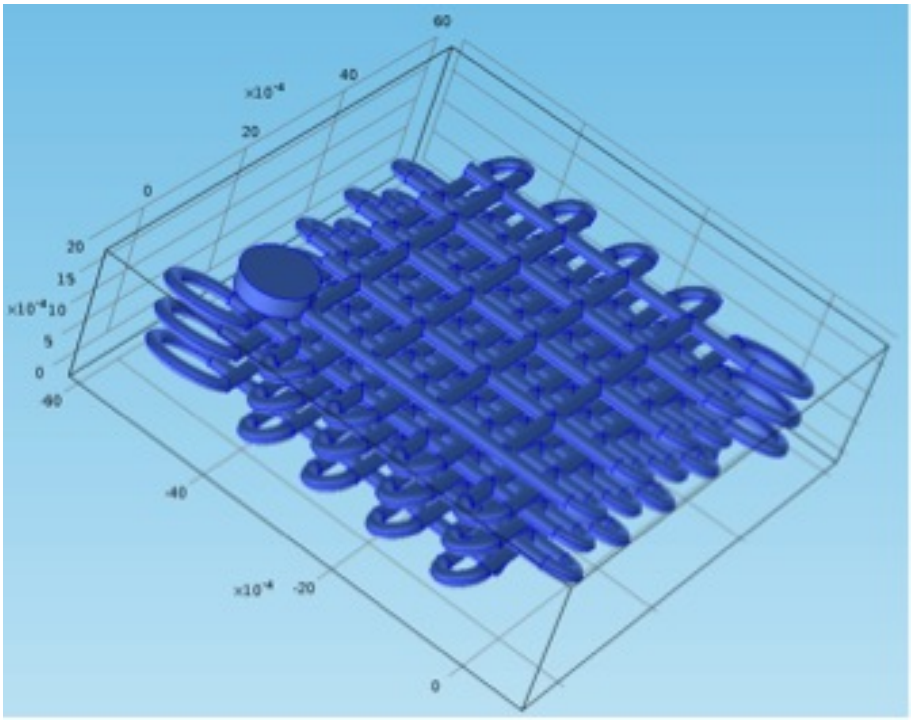

Figure 3. Lower blood vessel design

3.4 Entire final design for the structure

Right now we have the blood vessels for the lower part, but blood would need to be carried down from the coronary artery, and the remaining blood would need to go through the patch. Also from the anatomy of heart, sometimes there would be coronary vein that is very close to the coronary artery. Through the blood pressure difference between the artery and vein generated by hearts contraction, we may let the blood to be pumped through the whole blood vessel network.

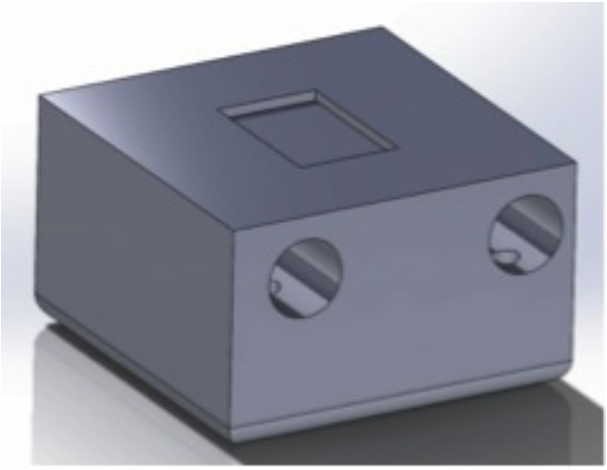

Figure 4. Outer view of the patch

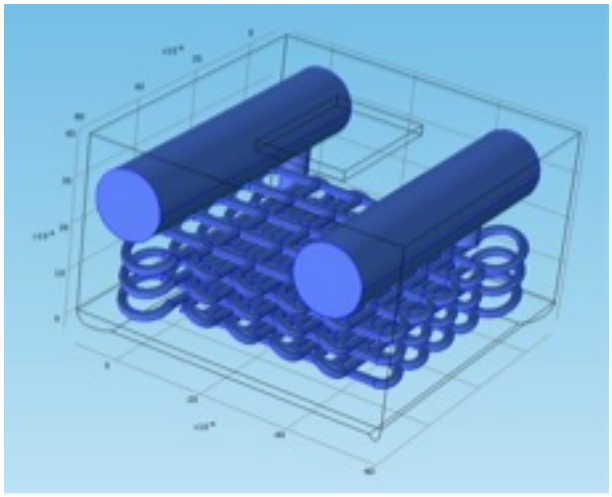

Figure 5. Inner view of the patch

The left round vessel on figure 4 is where the coronary artery is expected to be connected to the patch, and the right vessel is where the coronary vein would be. The top empty box is where the circuit is expected to be. The farthest corner of the figure 5 is where the blood is expected to flow to the coronary vein from the lower blood vessels. The size of the patch is chose according to the previous designed patch from the paper of Fujimoto and Miller.

Length	Width	Lower region thickness
7mm	7mm	2.3mm
Diameter of vessels	Diameter of vessel transporting blood down	Diameter of coronary artery and vein
0.2mm	0.6mm	1.5mm

Table 1. Dimensions used for the patch

To manufacture the patch, first we may use the method offered in Miller's paper to construct the blood vessel network using sugar. Later the blood vessel framework may be put into some kind of a carefully designed mould, where there are enough stem cells taken from the patient and incubated in the mould for a while. In this way, those stem cells may attach to the framework, and be induced to cardiomyocytes using electrical signals or even some chemical compound. Also some chemical compound that can stimulate vascularization may also be used so as to generate some capillaries between those designed blood vessels.

3.5 Circuit functionality

Figure 6 is the circuit's working principle flow chart. The circuit is expected to monitor both the heart and the patch's working condition. Through the flow chart, a digital circuit can easily be produced according to the principle of a finite state machine. The circuit would sense the heart and the patch's condition through some sensors like the accelerometer or electrode. After it has got the heart's contraction signal, it would be compared to the patch cells' working condition. If they work synchronically, the signal would be recorded. But if not, the circuit would generate some stimulate signal to the patch's cells. Later the recorded signal or the record that it has generated some stimulate signal can be sent to external

device like a cell phone through low power Bluetooth to be further analyzed. If the signal is irregular, the device may warn the patient and her physician to make some further steps. Also the circuit may even generate some stimulate signal to stabilize the heart when heart attack happens.

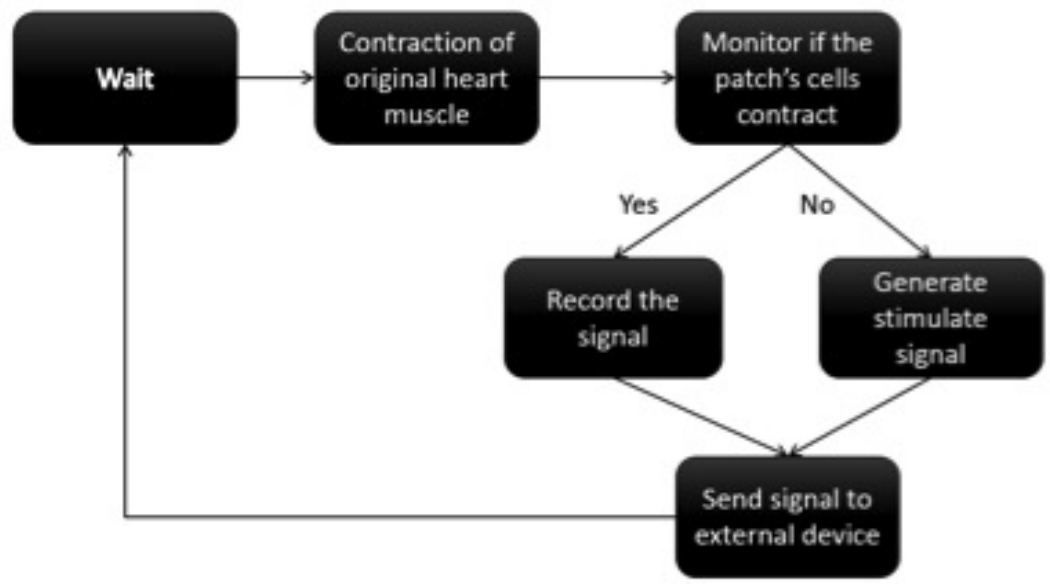

Figure 6. Circuit working principle flow chart

4 Simulation findings and Results

Simulations that were carried out in this part is done by COMSOL Multiphysics 4.3b.

4.1 Laminar flow simulation

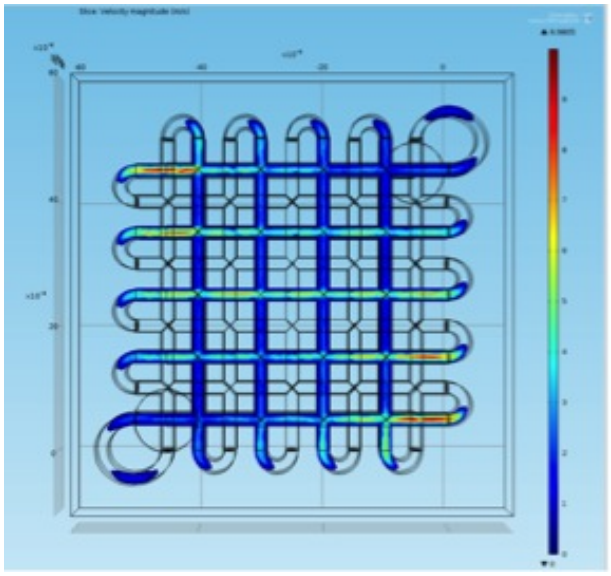

Figure 7. Top view of the velocity field in one layer's blood vessel

For the patch that I have designed, the most important thing would be that blood should be able to flow though those blood vessels. Laminar flow simulation that is incorporated in COMSOL is a good way to see if blood can flow through those networks. But for this part's simulation, COMSOL did not do well in matching different sizes, so the only simulation that I can do would be to just simulate on the lower region where the blood vessels are.

From figure 7, we can see that there are liquid flow in every blood vessels that I have designed. Through this way, blood can be transported throughout the patch. One problem is that the flow velocity is not uniform in both directions. But the design reflected in the simulation result is actually the best one, since the blood can flow through the patch. If the ends of blood inflow and outflow are changed, most of the blood would only flow through blood vessels at the end, and there would not be a lot of blood that can flow through the center part of the patch.

4.2 Mass transport simulation

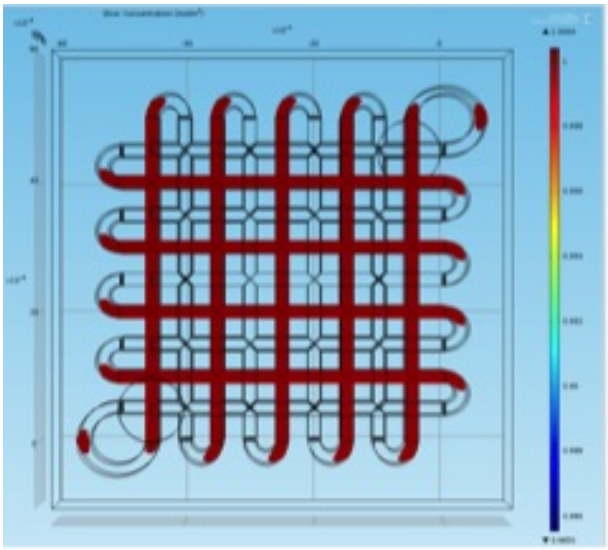

Figure 8. Top view of concentration profile in one layer

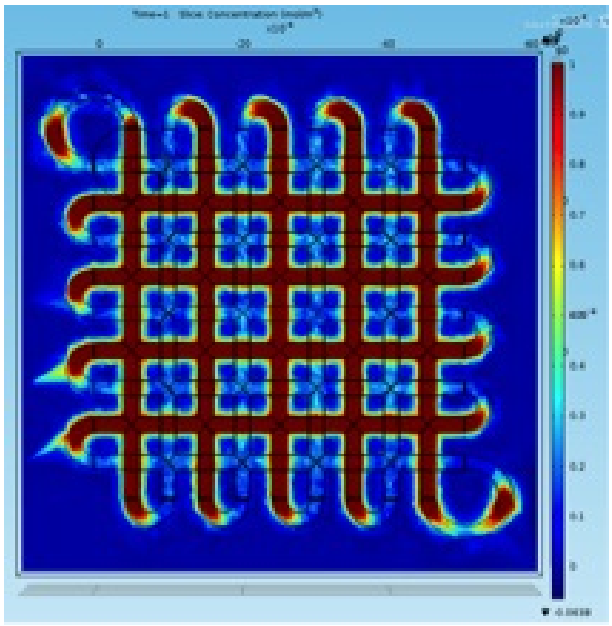

Figure 9. Top view of solute diffuse out

The concentration profile inside the patch would also be important for us in understanding the patchs functionality. Through COMSOL, it would be hard to incorporate both liquid flow within vessels, and diffusion from those vessels. So the first parts simulation just contains the concentration profile inside those vessels at steady state.

Figure 8 showed us that the concentration inside the vessels is uniform. The result is expected, because this simulation just simulated the kind of behavior when there is no solute outflow at the wall. When there is no solute outflow, the concentration would be uniform. But at least we can see from the simulation result that blood (or oxygen) is delivered to every part of the blood vessels.

Figure 9 is the simulation where the inside of the blood vessels' concentration is set to be 1 mol/L, and then the solute diffuse out from the vessels walls with the diffusion coefficient of $2.12 * 10^{-5}\ m^2/sec$ (Macdougall), and at the time point of t=10 sec. As we can see from figure 9, solute reached most of the intervascular space. The problem is that the center of those rectangles between blood vessels may have a relatively low concentration. But there are actually some capillaries expected to form between the constructed blood vessels, which can help to solve the problem. Also, by applying the principle of my design, the blood vessel density within the patch can be increased by making them denser. The design mentioned above can be regarded as some kind of a simplified design of the actual working patch. The design decreased the complexity in drawing blood vessel network while making it possible to simulate in COMSOL.

4.3 Mechanical property simulation

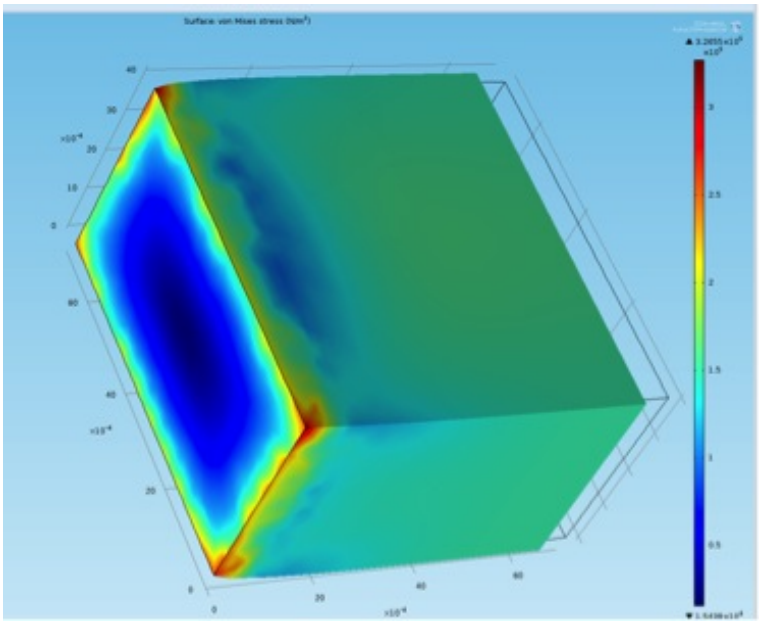

Figure 10. Compression test of the simplified design

When doing the simulation for compression, after play around with COMSOL, I thought maybe COMSOL do not allow the inside of a solid object to be hollow, so the simulation I did here is just the compression on a solid box with the dimension of my patch. The left side is fixed while the right side has some prescribed displacement.

According to figure 10, the four end points at the left surface had the highest stress. So when manufacturing the device, those four regions need to be reinforced by some other material or methods. But after all, since this is just a rough simulation, the result may not be trustworthy, since hollow region would change the stress distribution within the box, so further analysis would still be needed. The material properties used here is chosen from three papers by Vinnakota, Chen, and Mathur, where they measured the heart muscle's Young's

modulus, poisson's ration and Density. For my patch, I want to use cardiomyocytes to build my patch, so the assumption of using the heart muscle's data would be reasonable.

Young's modulus	Poisson's ratio	Density
100.3kPa	0.47	1.4g/ml

Table 2. Material Properties used for compression simulation

5 Conclusion

The design mentioned above, especially the blood vessels, worked as expected from the simulation result. The blood can flow through the blood vessels designed, and those blood vessels can offer oxygen to the intervascular space. If cells can contract as expected, the patch would work as expected.

From Miller's paper, it is possible to first build some vessel network using sugars, and then attach cells to the network. Later the sugar can be absorbed by those cells, and the blood vessel would be able to work as expected. For cells that are expected to be used to build this patch, ideally they would be cardiomyocytes that are induced from stem cells. But the problem here is that it is right now very difficult to control the differentiation of those cells. Another problem is that the coronary artery and the coronary vein would need to be connected to the patch, while leakage may happen at the connecting region. Still the power source for the monitoring circuit would be a huge problem, but as right now there exist some wireless charging technologies, this may not be a very big problem when the patch is approved on market. Also as for the regulatory pathway, the patch may very likely need to go through the whole clinical trial process, since it may be treated as level III.

Now it is hard to estimate the cost of the patch, since the materials that will be used for this patch is not the kind of material that can be purchased from the market right now. The cost for building the circuit can be estimated, but since the main part of the patch is the cell part, estimating the cost of the circuit may not be persuasive enough.

6 Reference

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