Force-Controlled Cartilage Bioreactor Project Proposal

FC Bioreactor
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Executive Summary

In this report, we look to design a bioreactor which can be used to examine the underlying causes of osteoarthritis, or the general degradation of articular cartilage. To design this system, we first look to understand the motivation, or underlying phenomena, inducing the mentioned condition. Following this, we address those most impacted by our work - that is, our stakeholders - and delve into the prior work motivating our plan for this project. After a review of prior literature, we then provide an outline for our objectives and design plans, illustrate a preliminary schedule for the semester's work, and overall detail a concrete plan for achieving the aims of this project.

Introduction

An estimated half billion individuals worldwide live with osteoarthritis (OA), causing significant detriment to quality of life and over $100 billion in annual direct & indirect costs [1]. While its expression varies, OA is often simplified as a general degradation of articular cartilage, although is more properly understood as a biochemical alteration in synovial joint tissue. While symptom-based treatment for the disease is commonplace, treatment for the condition itself, due to its inherent complexity, is far beyond the current scientific horizon. That mentioned complexity arises from the variety of signaling pathways involved in OA progression - here, we will focus on cartilage metabolism, or redox balance, as a specific agent in OA [2].

Literature has identified cartilage redox balance, synonymous in the context/scope of this work with metabolism, as a potential cause for OA. Metabolic dysregulation - or imbalance in the reliance on energy-producing cellular pathways (i.e., glycolysis & oxidative phosphorylation) - is common in many disease types. Nonetheless, the causative agent of this imbalance in redox state within the context of OA remains unknown. Recent work has postulated mechanical loading as this causative agent, with loading inducing metabolic dysfunction and OA-esque damage - further, via metabolic imaging techniques involving mechanical loading, this dysfunction has been demonstrated as a time-dependent phenomena. These imaging techniques, however, are limited to small timescales (i.e., less than one hour), thereby clearly necessitating a method by which to apply these mechanical insults over greater periods of time (i.e., several days to several weeks) [3]. Herein lies the focus of this project - that is, in order to capture the full picture of cartilage metabolic dysfunction and its relation to OA, greater timescales must be examined. Here, we outline a method by which to apply this loading, examine prior work in the field, and discuss a working plan to accomplish this aim.

Problem Statement

The Henak Lab investigates the relationship between cartilage redox balance (metabolism) and disease state. Research conducted by the Henak Lab has demonstrated that cartilage redox balance can influence cartilage disease state. Because cartilage redox balance and properties are rate-dependent, the Henak Lab requires a bioreactor to apply a controlled cyclic uniaxial compressive force to articular cartilage samples over long time scales to accurately mimic the in vivo environment. There are no commercially available force-controlled bioreactors that exactly meet the criteria set by Dr. Henak. There exist force-controlled bioreactors in literature, but none meet the specific specifications set by Dr. Henak as required for her research. The team is tasked with designing and fabricating a force-controlled 12-well cartilage bioreactor to apply the physiologically relevant mechanical stimuli articular cartilage experiences in vivo. This will ensure that Dr. Henak and the Henak Lab are able to perform the most impactful and comprehensive research possible.

Client and Stakeholders

The client, Dr. Corinne Henak, is an Assistant Professor in the Department of Mechanical Engineering and runs the Henak Lab at the University of Wisconsin-Madison. Currently, her team is focused on creating diagnostic and treatment tools for early-stage osteoarthritis by deepening their comprehension of cartilage-related illnesses. The team's primary stakeholder will be one of Dr. Henak's lab members, Jingyi Wang, a Ph.D. candidate who specializes in the relationship between oxidation and reduction (redox) balance and osteoarthritis in articular cartilage. She will be the one using a force-controlled bioreactor for her research. The team's secondary stakeholders encompass medical professionals, who play a pivotal role in the healthcare ecosystem and patients grappling with the challenges posed by osteoarthritis, a condition that affects millions of individuals. The research efforts are focused on exploring the complex dynamics of cartilage and redox balance, with a specific focus on how they respond to mechanical loading introduced by the bioreactor. This thorough investigation has the potential to change and improve our current knowledge of redox biology and disease state in articular cartilage.

Background

Currently, there is no commercially available force-controlled bioreactor. Most parties that concern themselves with these bioreactors are labs, in which it is more cost efficient for them to fabricate their own bioreactor than creating a patent to make a bioreactor commercially available. Given that this is the case, the team used several literatures as a starting point to design a force-controlled bioreactor specifically catered for the Henak lab.

Lujan's Bioreactor

The first bioreactor designed by Lujan utilizes an electromagnetic actuator. This creates a force control though a voice coil motor. The actuator that Lujan uses is capable of generating a stroke of 15mm, a peak force of 18N, a continuous force of 10N, and oscillates at a velocity up to 1.5m/s. The force generated would be an upward push motion from the bottom of the tray. Thus, the sample will be pushed upwards into the post to generate a compressive force. The component responsible for this is the plunger as seen in Figure 1, section D. The force can be controlled and programmed through LabView. In addition, this bioreactor can be operated via an open loop control.

In terms of the sample environment itself, when the lid is attached to the six well tray, it creates an enclosed environment. This contained environment is sterile and suitable for medium exchange. In terms of sterilization, the six-well tray, culture dish, and lid are all autoclavable while the machine itself is not. However, this was tackled as the former components are easily detachable from the bioreactor itself [4].

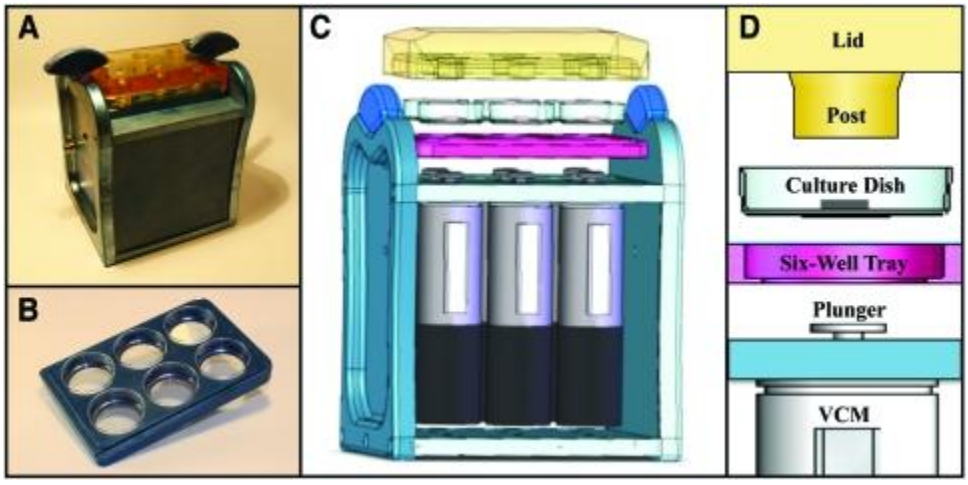

Figure 1: Breakdown schematic of Lujan's bioreactor.
A. The bioreactor. **B.** The six-well- tray.
C. The components of the bioreactor. **D.** Specific part names of each component. [4]

Meinert's Bioreactor

The second bioreactor designed by Meinert utilizes a linear force actuator. It is capable of generating a continuous force of 50N, and has a motion velocity ranging from 0.00022mm/s to 8.0mm/s. This design is different compared to Lujan's bioreactor as the force generated would be a downward motion. Thus, a PTFE piston controlled by a load cell will be driving the compressive force. Meinert's bioreactor is also capable of creating both a uniaxial and biaxial force, as well as both a shear and compressive force. The shear force can be achieved by moving the sliding platform left and right. The force, like Lujan's, can also be controlled and programmed through LabView. However, Meinert's bioreactor does not allow for an open loop control [5].

On the other hand, Meinert's bioreactor is also comparatively larger as it can house up to a 48-sample well-tray. The culture chamber of the bioreactor is enclosed, creating a sterile environment while also having a tube to control the oxygen and carbon dioxide levels within the chamber. Apart from this, the culture chamber and interior components are autoclavable, making it easy to clean and maintain [5].

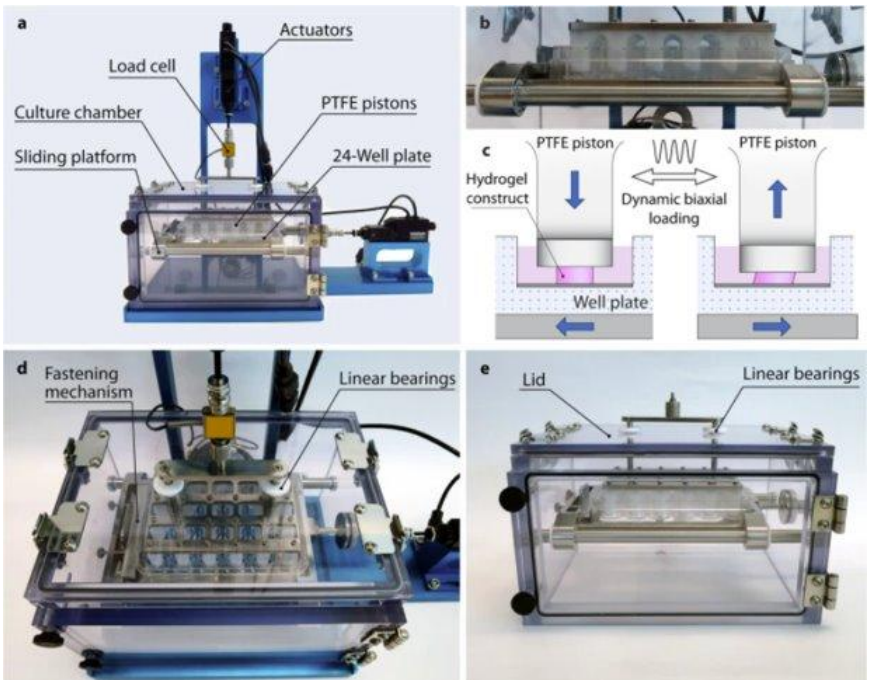

Figure 2: Breakdown of Meinert's bioreactor.
a. Front view of the bioreactor. **b**. PTFE piston plunged into the sample plate.
c. Cartoon demonstration of compressive and shear force exerted. **d.** Top view of bioreactor.
e. Angled front view of bioreactor without load cell and actuators [5].

While both bioreactors are well designed to their needs, the team will need to consider the type of actuator to use by considering the cost and ease of fabrication. Overall, the team can use both concepts from these designs to build on a design that fits the bill for the Henak lab.

Objectives

In order to provide the Henak lab with a functioning force-controlled bioreactor for their important work, the team has identified product specifications that are to be a direct quantification of the success of the prototype. The primary objective of the bioreactor is to induce 20% strain in cartilage samples that are 6mm in diameter and 2mm tall via a uniaxial compressive stress. By approximating cartilage as linear and elastic with a Young's Modulus of 1MPa, it can be calculated that this strain translates to 5.65N of force applied to the samples.

$$\sigma = E\epsilon = \frac{F_{applied}}{A} \quad \Rightarrow \quad F_{applied} = E\epsilon A$$
$$E = 1MPa,\ \epsilon = 0.2,\ A = \pi(\frac{0.006m}{2})^2 = 0.00002827m^2$$
$$F_{applied} = 5.6549N$$

Equation 1: Calculation of applied force to induce 20% strain in cartilage samples.

The interface between the sample and compressive pillars must be as frictionless as possible. This will ensure that uniaxial compressive stress is the only force applied to the samples as friction with even the slightest horizontal translation would create an undesired shearing force. It will also be pertinent that the actuator selected for the design is capable of displacing high enough to allow for easy access to the sample by Henak lab personnel. This will expedite the sample examination and imaging processes that are vital to the continued success of the Henak lab's work.

Interface with Incubator Environment

The bioreactor is to be used in the Henak Lab's incubator (seen in Figure 2), which is capable of modulating temperature and concentrations of gasses such as oxygen and nitrogen. As such, all materials and electronics used must be able to withstand this simulated in-vivo environment. Cartilage cultures must remain free from contamination throughout their growth and observation periods, so the bioreactor must not introduce any source of contamination. This necessitates that sterilization is possible for all parts of the device that are exposed to the same environment as the samples. In practice, this will likely look like an electronics box which can be wiped down with ethanol and a compressive pillar plate that can be more rigorously sanitized via autoclave.

Figure 3: The Henak lab's incubator, inside which the bioreactor will be housed.

As this incubator will require electronics, it will be necessary to access power sources from inside the incubator. There are several ports in the incubator that allow this, but care must be taken to ensure that all cables may fit through the limited space. It will also be crucial that the entire bioreactor fits inside the incubator, which has internal dimensions of 21x20x25 in.

Additional Modifications

If time permits, there are several other modifications that the team would like to make to the bioreactor. It should be noted that these would be a lower priority than all specifications mentioned prior. They will not be attempted until the team has fully fabricated a device that can induce 20% strain on cartilage samples of the desired size.

For future Henak lab research, it may be useful to modulate the interface with the sample. If the compressive pillars were able to be easily switched out to ones with, for example, a small point, indentation testing could be performed. Data obtained from indentation testing is different from uniaxial compression data, and could help further the lab's research endeavors. Furthermore, if the base on which the compressive pillars were attached could be switched to one that could accommodate more or fewer samples, cartilage well plates with 6, 12, or 24 wells could be used with the machine. This would allow for more utility of the device in different research circumstances.

Feasibility and Impact

The approximate budget provided by the Henak lab for this project is $5,000. The main obstacle to keeping under budget will likely be the actuator. The team is looking into buying an actuator to save the time and unnecessary complexity of manufacturing one that is bespoke. Preliminary research into actuator prices has suggested that something fit for this application could cost anywhere from a few hundred to $1450 [6] [7]. With careful budgeting and enough research, the actuator price should not prohibit the team from completing the project under budget.

Given the five members of the team, there should be little concern about the ability to meet deadlines for this project. Plenty of hands means that if delegation of tasks is properly done, a working and validated product by the end of the year is a very feasible goal.

Successful creation of a force-controlled bioreactor for the Henak lab will help her and her team conduct their important research on cartilage's response to stress and fatigue. Understanding cartilage in a distressed state, specifically the metabolism of cartilage in distressing conditions, will lead to a deeper understanding of diseases such as osteoarthritis. Contributing this knowledge to the field of orthopedics will help make surgeries more successful and inspire more advanced treatments for the millions of people who are impacted by OA every day.

Plan of Action

To design and fabricate a functional force-controlled bioreactor, understanding the key stakeholders as well as their desires and needs is critical for this specific application. To define the problem, open, clear communication needs to occur regularly between the team and Dr. Corinne Henak, the client. To this end, the team has established a regular weekly meeting time with Dr. Henak to discuss the design status of the bioreactor, exchange any relevant updates, and ask clarifying questions. Through these meetings, the team has defined a concrete set of deliverables and design specifications for the bioreactor, appropriate to the timeline of the project. The timeline this plan of action spans is the semester. Major deliverables for this semester include a design specification document listing all verifiable functionalities and requirements for the bioreactor as defined by Dr. Henak, a project proposal document defining the problem in detail and design requirements, full prototype CAD model of the bioreactor, and physical prototype of the bioreactor or the actuation mechanism, able to be tested and verified against the design specifications.

The team initially planned to base the design plan around linear actuators using closed-loop PID control; however, discussions with primary stakeholders revealed the complex challenges to overcome and time necessary for this approach to be successful. To design a bioreactor fulfilling the requirements set by the design specification with consideration to the available resources and timeline, the team has decided to design a bioreactor using magnetic voice coil actuators with open-loop control. The next steps include selecting an appropriate voice coil actuator, determining how to accurately control force application via current modulation, designing a CAD model around the selected actuator, and fabricating and assembling all components to achieve a functional, physical prototype of the bioreactor. The physical prototype may be a full bioreactor or an actuation mechanism, depending on the timeline, and it must be testable and verifiable against the design specifications. The team has created a Gantt chart (Table 1) to track all major project deliverables and their completion statuses. As consistent with the Gantt chart, it is likely that there will be no

significant research conducted on applicable standards, as the force-controlled bioreactor will serve exclusively as a tool enabling the investigation of the relationship between cartilage disease state and long-term cyclic mechanical stimuli in the Henak Lab.

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Sep				Oct				Nov				Dec		
Task	8	15	22	29	6	13	20	27	3	10	17	24	1	8	15
Team Object			X												
Decide on Object			X												
CAD Model			X												
BOM			X												
Writeup			X												
Project Proposal					O										
Research Previous Solutions			X												
Determine Applicable Standards															
Design Specification				X											
Report and Presentation					X										
Proof of Concept										O					
SolidWorks Model of Design, Potential 3D-Printed Model			X												
Presentation															
Midyear Review															O
Physical Prototype															
Report and Presentation															
X = Completed Tasks, O = Milestone Deadlines															

Table 1: Gantt chart highlighting major project deliverables and their completion statuses as of Week 5

Additional Arguments

Osteoarthritis is a chronic joint condition characterized by the gradual deterioration of the protective cartilage that acts as a cushion between bones to absorb compressive force and friction that occurs during the movement. This gradual breakdown in cartilage leads to discomfort and pain due to the friction created in the interface of the bones during everyday movements. Importantly, this condition is widespread, affecting more than 500 million individuals across the globe, and it tends to be more common in people over the age of 40, often significantly impacting their quality of life.

The knee joint, which typically experiences the greatest range of motion, is particularly susceptible to the effects of osteoarthritis. Despite its prevalence, there is currently no definitive cure for osteoarthritis. Instead, management options primarily revolve around the use of medications, assistive devices, and therapeutic interventions aimed at mitigating pain and improving function. Considering the complexity of this condition and the incomplete understanding of its underlying causes, it is apparent that sustained and multifaceted research efforts are deemed essential.

Conclusions

To effectively study the relationship between cartilage metabolic state, cartilage disease state, and mechanical stimuli on cartilage, Dr. Corinne Henak and the Henak Lab require a force-controlled cartilage bioreactor to apply long-term cyclic mechanical loading on cartilage samples. To this end, the team has identified concrete deliverables and design specifications, conducted extensive research on existing bioreactors with similar functionalities in literature, produced a conceptual CAD model utilizing a linear actuator, and outlined a clear plan of action moving forward with magnetic voice coil actuators. The team also understands the importance of empathy for all stakeholders. The team has developed a concrete empathy plan to which they will adhere throughout the design process. In short summary, the empathy plan entails a plan to ask questions to connect the technical requirements of the project to the underlying emotional and personal aspects of the problem and to communicate face-to-face with stakeholders whenever possible. To design and fabricate a functional force-controlled cartilage bioreactor, the team has identified major concrete deliverables and outlined a plan of action to achieve those deliverables.

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