Design of a Robotic Hindlimb of a Rat Focused on the Foot and Ankle

Innovative Impact of Regulatory Challenges Faced When Transitioning from Animal Testing to Human Clinical Trials

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

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November 8, 2024

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

My capstone project this year addresses the issue of corrective walking that is commonly diagnosed for patients with Volumetric Muscle Loss (VML), which is very common in severe battlefield wounds. VML refers to the irreversible damage to a significant portion of muscle tissue, usually resulting from serious battlefield injuries or trauma, with over 75% of cases occurring secondary to an explosion (Grogan et al., 2011). Unlike smaller-scale muscle injuries, VML surpasses the body's physiological capability to heal, leaving patients with substantial structural and functional damage including loss of strength, range of motion, and overall endurance. Current therapies primarily include muscle grafts where muscle tissue from another portion of the body (autograft) or a donor (allograft) is transplanted to reconstruct the injured region. The intense nature of these procedures, however, leads to significant limitations in their efficacy such as donor site morbidity, immune rejection, and failure to restore fully integrated muscle tissue that recovers functionality. Recent research around regenerative medicine, such as delivery of stem cell therapy, growth factors, and biomaterial scaffolds, has focused on addressing these shortcomings (Abdulghani & Mitchell, 2019) (Grogan et al., 2011) (Carnes & Pins, 2020).

Building on these advances, our capstone project aims to design an actuated robotic model to bridge the gap between computational studies and live animal testing to treat VML. The model will accelerate injury simulation and reduce the cost associated with animal testing while maintaining the complexities of VML injuries including muscular compensation tendencies.

This is where technology intersects societal acceptance. Using animal testing to prove human efficacy has been an ongoing debate (Vashishat et al., 2024) (Ritskes-Hoitinga, 2022) (MD, 2021). Rightfully so, the government has implemented numerous regulations around

animal testing and human clinical trials, the bureaucratic process involved in making this translation, and the influence of animal testing on development and approval timelines for medical technologies. While it is critical to support clinical trials with successful animal testing, to what extent is that satisfied, and how regulated should the transition be? This leads to the research question of the prospectus: “What are the regulatory challenges faced by medical researchers when transitioning from animal testing to human trials, and how do these challenges impact the speed of medical innovation?”

Technical Description

Our first, and most important objective is to develop an actuated (or some combination of both actuated and passive) robotic model of the lower portion of a Lewis Rat hindlimb. Using anatomical data and 3D bone scans of a Lewis Rat, we will create a CAD model of the hindlimb, including representative structures of bones, joints, mounting areas for the actuators, and muscle attachment points. We will utilize 3D printing to manufacture components with complex geometries such as joint intersections or small bone/ligaments and computer numerical control machining to produce more durable, simple parts such as the lower leg and foot (Young et al., 2018). To simulate tendons and muscle attachments, we will use flexible materials that best represent the structural and functional properties of those parts. Once the model is constructed, we will build an electrical control system to interface with the actuators, which will include microcontrollers (e.g., Arduino or Raspberry Pi) for fine motor control. Force sensors at the foot and joint angle sensors will be implemented to measure ground reaction forces and to monitor the position of each joint in real-time, ensuring the model properly mimics biological motion.

After building a functional model, the model will then be validated to ensure the actuated 3D model mimics the anatomical motion of the Lewis Rat hindlimb. First, a structure that can

hold the position of the knee joint in place must be created to effectively isolate the ankle and foot for motion analysis purposes while we work on the ankle and foot. Motion trackers will be placed on the robotic model at the same anatomical locations as the Lewis Rat as done in previous studies to ensure the joints are translating correctly. Analyzing the data to compare previous Lewis Rat data will be performed to measure the similarity (which drove the development of the initial simulations). Using the force readings from the sensors installed, the appropriate scaled force will be validated. Another method to validate properly replicated motion is the muscle length, velocity, and tension over time as the robot walks (Deng et al., 2020). This can be compared to live rat muscle activation to prove a statistical similarity in motion. While this would require advanced biomechanical and robotic design, it is something worth exploring to create a more accurate model.

Once a functioning model is developed and tested, the next stage of our research explores injury simulation. The main goal is to adjust the model's functionality to replicate how VML affects humans. Enabling the selective deactivation of actuators to simulate muscle "injuries" allows for customizable injury scenarios that can be induced easily and repeatedly to better understand how to treat VML. Common VML conditions and subsequent injuries seen in clinical cases will be replicated to validate the functionality of our control system by comparing the movement before and after the simulated injury.

Finally, the constructed physical model will be compared against the computational simulation to identify discrepancies due to real-world factors. By testing the robotic model on different surfaces and with varying conditions (e.g., vibrations, uneven ground, grade) the model

can be compared to computational simulations under ideal conditions to assess the influence of environmental factors that are not included in the simulations (Brooks, 1989).

The development of an actuated physical model of the rat hindlimb will offer an innovative experimental platform to simulate various VML injuries and assess the efficacy of emerging regenerative treatments. The model will offer a more precise evaluation of new biomaterials, therapies, and rehabilitation techniques with the ability to refine these strategies and work toward functional muscle recovery for VML patients. But before all of this is possible, the device must pass rigorous tests that prove its efficacy and safety before it can be tried on humans.

STS Topic Section

Since 1938, the FDA has mandated through the Federal Food, Drug, and Cosmetic Act that every new drug developed be tested on animals for proof of efficacy. In 2019, the pharmaceutical industry spent $83 billion on R&D, which, adjusted for inflation is about 10 times the amount spent in the 1980s (Research and Development in the Pharmaceutical Industry | Congressional Budget Office, 2021). In the last century, research capabilities have increased exponentially, bringing a growing number of drugs to clinical trials that require animal testing as the first validation checkpoint.

In 1959, Dr. William Russell and Rex Burch explained the 3Rs of animal testing in their book “The Principles of Humane Experimental Technique” to minimize pain, distress, and suffering for research animals while maintaining scientific integrity (Animal Use Alternatives (3Rs) | National Agricultural Library, n.d.). The 3Rs stand for Replacement, Reduction, and Refinement. *Replacement* refers to utilizing various forms of technology that could take the place

of animals in validating a drug. In today's age especially, researchers are developing numerous technologies and avenues for clinical trials that will replace animal testing. *Reduction* describes a more efficient use of research animals, lowering the amount used through strategies such as experimental design, correct statistical evaluation, and sharing resources/animals. Finally, *Refinement* emphasizes experimental modifications that eliminate or significantly reduce the animals' pain and improve welfare. This can be done using anesthetics and analgesics, humane animal handling, or environmental enrichment. Further research can be done into whether these values have remained steady or been developed over the years to better understand how animal testing safety has evolved.

In 1966, the Animal Welfare Act (AWA) was passed, requiring minimum standards of care and treatment for animals bred for research intentions. However, over 110 million animals are sacrificed annually in the US alone (Diaz et al., 2024). Here, activists and journalists argue that nearly 95% of animals are not protected by the AWA and that it should be far more inclusive. In this example, further research into which animals are protected, and to what extent, can provide insight into whether the AWA is sufficient. Further, some authors claim that the AWA, in addition to inefficiently protecting various species, lacks proper enforcement and is often overlooked (Shook 2022). Thus, the government's involvement must be further analyzed, including recent revisions to the FDA Modernization Act in 2023, which was originally passed in 2021. However, activists and researchers alike criticize more than just rules and regulations.

Not only is animal testing argued to be ethically and morally wrong, but the efficacy and cost of these tests are also challenged. Of drugs that make it through animal testing, over 90% fail when translated to human trials (Vashishat et al., 2024). In some cases, such as Alzheimer's

research, animal-tested drug trials reach a failure rate as high as 99% after undergoing clinical human trials (Hutchinson et al., 2022). Understanding why these percentages are so high and what causes these failure rates will motivate subsequent research.

Statistics like these raise questions about why such a high volume of animal-approved drugs fail human clinical trials and whether there might be more effective ways to test their efficacy. A 2018 study found that non-animal methods were more accurate than mouse models when predicting skin sensitization (Ritskes-Hoitinga, 2022). While this study only addresses one application of medical research, it exposes the growing limitations of animal testing and suggests that other avenues be re-examined. Known as New Approach Methods (NAMs), these strategies were developed to develop drugs with a higher success rate, prevent human sickness or injury resulting from unsuccessful clinical trials, and increase the speed of medical innovation approved by the FDA. Currently, the overwhelming reliance on animal testing slows drug development, with an average of 10-15 years for development and up to $6 billion per drug in extreme cases (MD, 2021). New advanced technology such as bioprinted organ models, organ-on-a-chip designs, and artificial intelligence can improve the pharmaceutical industry significantly by expediting the drug development process, reducing costs, and improving efficacy. Thus, more research must be done to explore the accuracy of these options and better understand how they can be effectively utilized.

To perform this research on effectiveness, ethical considerations, and evolving methodologies surrounding animal testing, data on historical and contemporary animal testing practices will be collected, including more detailed statistics on drug failure rates, costs, and timeframes for development. Evidence will also include case studies of drugs tested through

traditional animal models versus NAMs previously mentioned. Discussions surrounding how developed these new methods are and whether they can yet be trusted must be investigated. Cross-examining the predictive accuracy and cost efficiency of NAMs with their barriers to adoption and technical limitations will provide valuable insight into the validity of the claims previously highlighted. Another key discussion will address the 3Rs framework and how that might be improved with these new research and validation methods. Furthermore, the efficacy and ethical impact of regulatory statutes such as the AWA, FDA Modernization Act, and other relevant legislations that affect this area will be assessed. Through these investigations, this research aims to identify the most viable strategies for advancing pharmaceutical innovation in an ethical, efficient, and scientifically robust manner.

Conclusion (150-250 words)

This project bridges engineering innovation with biomedical necessity, creating a highly controlled, actuated robotic model to better understand VML injuries and accelerate the development of effective treatments. Currently, VML treatments require invasive procedures that have been validated after years of animal testing. Similarly, any new form of biomedical treatment for VML must pass various animal and clinical trials required by the FDA. The proposed model will require animal testing on rats, which will greatly inhibit the speed at which it can be produced and put into practice. By reducing dependency on live animal testing, the model enhances both ethical standards and experimental precision. Additionally, the project emphasizes the critical balance between scientific rigor and regulatory adherence in medical research. Through the thoughtful integration of technology, anatomical accuracy, and regulatory considerations, this work has the potential to advance regenerative medicine, ultimately aiming to provide VML patients with viable, effective recovery options that improve their quality of life.

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