Soft Robotics Applied to the Development of a Diaphragm Assist System

by

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B.S., University of California, Berkeley (2016)

Submitted to the Harvard-MIT Program in Health Sciences & Technology
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Medical Engineering & Medical Physics

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Abstract

Severe diaphragm dysfunction can lead to respiratory failure, requiring permanent mechanical ventilation. Permanent tethering to a mechanical ventilator via a patient’s mouth or tracheostomy can interfere with a patient’s autonomy by hindering activities like speech and swallowing. This thesis works towards a soft robotic alternative that aims to intervene internally at the diaphragm as opposed to the mouth. For medical problems that are mechanical in nature, soft robotics offer a promising solution by coupling advanced robotic control with soft elements that can interact nondestructively with biological systems. In this work, we present the findings from the development a soft robotic diaphragm assist system, from exploration to proof-of-concept.

In order to understand how soft robotic technologies interact with the respiratory system, simulators of respiratory motion and biomechanics were built with different soft actuator mechanisms. We find that pneumatic artificial muscles are capable of driving the diaphragm function in a respiratory simulator and replicating the work of breathing. Taking inspiration from this biomimetic system, pneumatic artificial muscles are designed and optimized for use in the diaphragm assist system. By implanting contractile, soft robotic actuators above the diaphragm to push down on the diaphragm during inspiration, this diaphragm assist system functions as an implantable ventilator. We demonstrate the proof-of-concept feasibility of this system to augment physiological metrics of ventilation in an in vivo porcine model of varied respiratory insufficiency. This system synchronizes with native respiratory effort to augment respiratory function.

This diaphragm assist system lays the foundational work for a new therapeutic ventilation option that aims to restore respiratory performance without sacrificing quality of life.

Thesis Supervisor: Ellen T. Roche, PhD
Title: Associate Professor, Department of Mechanical Engineering and Institute for Medical Engineering & Sciences
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Chapter 1

Introduction

1.1 Overall Motivation

The diaphragm is the major muscle responsible for inspiration, and contributes to up to 70% of the inspiratory tidal volume in a healthy individual [1, 2]. Diaphragm dysfunction can result from a variety of etiologies including phrenic nerve trauma and neuromuscular disease [3, 4, 5]. Owing to the degenerative nature of many of these etiologies, mechanical respiratory failure exists as a continuous spectrum of loss of function. Severe diaphragm dysfunction or paralysis can lead to chronic respiratory failure. When disease progresses beyond the treatment capacity of noninvasive treatment, patients must make the difficult decision to opt for permanent invasive ventilation via a tracheostomy or to pursue palliative care with an understanding of the terminal nature of their disease. Invasive ventilation can interfere with many aspects of a patient’s quality of life, such as hindering speech, requiring full-time care, and possibly necessitating the patient move into a care facility. There is an urgent need for new therapeutic ventilation options that restore respiratory performance without sacrificing quality of life, especially for those with the most severe cases of diaphragm dysfunction.

The use of soft matter and materials in medical robotics has opened up new robotic abilities in which soft, nondestructive components can interact with patients and improve function in biological tissues [6]. Previously, soft actuators have shown the
ability to augment heart function[7, 8] and other biological applications[6, 9]. Due to
the mechanical nature of respiratory failure, especially in the context of conditions
like muscular dystrophy, implanted soft robotic actuators applied to diaphragm have
the potential to mechanically support and augment the function of the diaphragm.

1.2 Background

1.2.1 Diaphragm Anatomy and Physiology

The diaphragm is the major inspiratory muscle and is responsible for up to 70% of the
tidal volume during inspiration[1, 10], contributing the majority of the pump function
within the respiratory system[11]. The diaphragm also plays a key role in speech and
cough generation[12]. It is a dome-shaped muscle; the top of the dome consists of a
flexible but inextensible central tendon. The dome is made of two hemidiaphragms—
the left and right sides—in which they are semi-independent. Tension on one side is
not well transmitted to the other[13]. The muscle fibers attach to the central tendon
and radiate outwards to their attachment points along the bottom of the rib cage and
a portion of the spine, seen in Fig. 1-1 and 1-2[13].

Figure 1-1: Anatomical sketch of the diaphragm and its skeletal attachments. From
[14]

Upon muscular contraction, the diaphragm flattens as muscle fibers shorten and
stiffen. The shortening of the muscle fibers pulls the central tendon downwards
(caudally) generating volume increase of the thoracic cavity in the vertical direction
Figure 1-2: Biomechanics of the diaphragm. (a) Diagram of directions of lines of tension from the part of the central tendon at the center of the hemidiaphragm domes. (b) Arrows depict vectors of tension exerted by the diaphragm on the lower margin of the ribcage, with the zone of apposition shaded. From [15]

in a piston-like fashion[13]. This lowers pleural pressure allowing for inflation of the lungs. This caudal movement of the diaphragm also increases intraabdominal pressure. Because much of the abdominal contents resides within the lower thoracic cage at end expiration, pressurization of the abdominal compartment leads to an outward force on the lower ribcage in the zone of apposition, generating volume increase of the thoracic cavity in the medial direction[11, 15]. These mechanics are illustrated in Fig. 1-2 and 1-3. There is redundancy in the respiratory system from intercostal, accessory, and even abdominal muscles, and small losses of diaphragm dysfunction are usually asymptomatic as these other muscles increase activity to compensate.

Figure 1-3: Normal mechanics of the diaphragm acting on the ribcage in which 1. the lower ribcage expands due to direct insertions, 2. the downwards motion uses the abdominal contents as a fulcrum pushing the zone of apposition outwards, and 3. the forces are countered by the elastic recoil of the lung and negative pleural pressure. From [13]
1.2.2 Diaphragm Dysfunction and Pathology

Diaphragm dysfunction can originate from a variety of etiologies, but the focus in this thesis will be on two categories of irreversible loss of pump function: phrenic nerve injury and degenerative neuromuscular disease.

In the case of phrenic nerve injury, we further narrow the focus to irreversible, bilateral diaphragm paralysis, often the result of trauma or surgical error. Although relatively infrequent, bilateral diaphragm paralysis offers insight into a zero-function model of disease. In cases of isolated diaphragm paralysis—with the other respiratory muscles intact—inspiration is achieved via compensatory actions[13]. This can lead to the paradoxical motion of the inactive diaphragm. Diaphragm paralysis often results in atrophy and thinning of the diaphragm muscle[16].

In the case of irreversible diaphragm dysfunction due to neuromuscular disease, the diaphragm—and often adjacent respiratory muscles—undergo progressive loss of function. Moderate diaphragm dysfunction is sometimes associated with normal global respiratory muscle strength due to compensation via other respiratory muscles[17]. Unfortunately, the progressive nature of degenerative neuromuscular disease indicates that this dysfunction will continue to worsen. Patients with neuromuscular disease often experience the full spectrum of decline from moderate-function often down to zero-function of the respiratory muscles. Respiratory failure is a major source of a poor quality of life and end-stage cause of death[18, 19].

1.2.3 Standard of Care

To address respiratory insufficiency, noninvasive methods of providing ventilation support are preferred, however, they are only sufficient for moderate respiratory failure. Noninvasive methods range from nocturnal or diurnal use of bilevel positive airway pressure device (BPAP)[20, 21] to noninvasive pressure support ventilation (NIPSV) via a standard mechanical ventilator[22]. If respiratory insufficiency is mild enough to be adequately supported with nocturnal use, noninvasive methods are only applied during sleep to maximize quality of life, with the consideration that these
methods can hinder motion, speech, and eating. Noninvasive methods of ventilation are not tolerated well by some patients who report claustrophobia and discomfort from asynchrony with natural breathing. Severe respiratory insufficiency necessitates invasive ventilation to support respiration.

In irreversible, bilateral diaphragm paralysis, methods of noninvasive ventilation are generally recommended[21, 23], but severe cases require invasive ventilation towards the end of life[16]. Surgical diaphragm plication—a process that creates and sutures folds into the diaphragm to stiffen and reduce the resting dimensions of the muscle—is a treatment option, but long-term outcomes of the procedure are controversial[16]. Diaphragmatic pacing via phrenic nerve stimulation has been utilized in diaphragm paralysis, but this requires an intact phrenic nerve[24]. Diaphragmatic pacing is usually not an option in bilateral paralysis[16].

For those with degenerative neuromuscular disease, noninvasive ventilation is the standard of care for initial treatment for chronic ventilator insufficiency[22]. While used, noninvasive positive pressure ventilation (NPPV) raises lung volumes, recruits atelectatic lung, and has been shown to be a key life-extending therapy[25]. However, the progressive nature of disease often causes many to worsen to the point that noninvasive ventilation is no longer adequate. When the NPPV option fails, patients can opt for invasive ventilation in the form of a tracheostomy or palliative care.

Invasive ventilation can increase the risk of potentially fatal respiratory infections, as the airway is unprotected and respiratory muscle weakness leads to an inability to clear potential pathogens[26]. Phrenic nerve pacing has minimal utility in these patients[27]. Beyond the medical considerations of addressing respiratory insufficiency, treatment decisions for these patients must also heavily consider the quality of life factors involved. A tracheostomy may decrease the ability of a patient to communicate effectively. A tracheostomy and full-time mechanical ventilation sometimes results in patients permanently living in a skilled nursing facility or they may go home with a home mechanical ventilator and near full-time nursing care, which are both costly medical options and can be financially devastating[28, 29]. When the disease progresses beyond the treatment capacity of noninvasive treatment, patients must
make an extremely difficult decision regarding their own care. They may opt for permanent invasive ventilation via a tracheostomy which can involve sacrifices to a range of aspects of quality of life or they may opt to pursue palliative care with an understanding of the terminal nature of their disease.

1.2.4 Clinical Metrics of Ventilatory Function

Clinically, respiratory distress during sleep is often one of the earliest signs of respiratory muscle decline. During sleep, respiratory muscle activity, drive, and load are attenuated, creating a significant stress test to the respiratory system, especially in the setting of decreased respiratory muscle capacity[30]. At the beginning of respiratory muscle decline, compensatory mechanisms reveal still normal daytime blood $O_2$ and $CO_2$ values. As respiratory muscle function decreases, patients present with nocturnal hypercapnic hypoventilation during sleep. Severe respiratory failure presents with continuous chronic daytime and nighttime hypercapnic hypoventilation[12, 30].

In order to determine appropriate care for each patient, there exists a large body of work in developing appropriate metrics for respiratory function[31, 32, 33, 34], characterizations of clinical manifestations of declining respiratory function[30, 35, 36], and guidelines for care decision making[1, 12, 22, 37]. To evaluate diaphragm function, there are two main methods utilized: pulmonary function tests (PFTs) and transdiaphragmatic pressure measurement. PFTs are standardized noninvasive spirometry maneuvers performed to evaluate overall respiratory function. PFTs require voluntary directed maneuvers, which are difficult to achieve in a preclinical setting. Another less commonly utilized metric is transdiaphragmatic pressure ($P_{di}$). Nonvolitional transdiaphragmatic pressure is a more direct measure of diaphragm strength and has well-established reference values for volunteers and patients with different respiratory diseases[10].

In terms of assessing acute respiratory status, monitoring arterial oxygen and carbon dioxide levels are essential. Arterial blood gases (ABGs) offer a direct measurement of oxygen ($P_aO_2$) and carbon dioxide ($P_aCO_2$) in the blood. However, ABGs only provide discrete, intermittent measurements of the respiratory status. Continuous
monitoring methods include pulse oximetry for $O_2$ saturation and capnography for $CO_2$ saturation. For monitoring ventilatory status, $CO_2$ is a far more sensitive indicator. Capnography—which measures end-tidal $CO_2$ ($EtCO_2$)—offers a noninvasive continuous measurement of carbon dioxide status. However, there exists a difference between $P_aO_2$ and $EtCO_2$ that will vary with changes in the ratio of dead space to tidal volume ($\frac{vd}{vt}$). $EtCO_2$ can be used for relative changes within a similar set of tidal volumes, but the absolute $EtCO_2$ from data sets with large changes in tidal volume will not hold as a valid reflection of $P_aO_2$ and acute respiratory status.

1.2.5 Soft Robotic Actuators

The field of soft robotics and its deformable components offers the promise of bringing the benefits of controlled robotics to systems that interface with humans. The soft, deformable actuators, made of materials including compliant polymers and silicone rubbers, can interact nondestructively with human tissue while minimizing damage[38, 6]. Mixing deformable elements with flexible but inextensible elements, application of different types of energetic activation, such as pneumatic, hydraulic, or electrical stimulation, can create controlled deformation. Compared to traditional robotics made of rigid elements, deformation is nonlinear and modelling of this deformation is nontrivial. Although there are many types of soft robotic actuators, this work will focus on the broad class of actuators powered by controlled pneumatics.

1.2.6 Medical Soft Robotics

In terms of medical soft robotics the heart has been at the center of soft robotics research efforts due to its simple mechanical function of pumping and its soft but dynamic compliance [6]. Artificial supporting devices can be used to restore the mechanical function of the heart. Previous work in our group was developed into a compressive heart sleeve to act as mechanical circulatory support by augmenting cardiac output via external compression. Soft robotics are capable of generating biomimetic motion and aiding native mechanical function[7]. One of few attempts to
use soft robotics to develop a ventilation option based on artificial diaphragm motion is described in Bashkin et al. They propose an artificial diaphragm that would require excising the native diaphragm and replacing it with an electroactive polymer[9, 39]. To our knowledge, there are no examples in the literature of attempts to provide mechanical assistance with soft robotic techniques while leaving the native diaphragm intact.

1.3 Specific Aims

There are 3 specific aims presented in this thesis:

1. Employ soft robotics to simulate the motion of the diaphragm and biomechanics of respiration through the development of a respiratory simulator.

2. Design soft robotic actuators optimized to augment downwards contractile motion of the diaphragm to generate inspiratory diaphragm function.

3. Evaluate the ability of a soft robotic diaphragm assist system to generate adequate ventilation support in an in vivo porcine model of respiratory insufficiency.

1.4 Thesis Organization

Towards these three aims, this thesis is organized into three parts: (I) Soft Robotics Applied to Respiratory Simulation comprised of Chapters 2 and 3, (II) Actuator Design for the Support of Diaphragm Function comprised of Chapter 4, and (III) A Diaphragm Assist System Demonstrated in vivo comprised of Chapters 5 and 6.

In Chapter 2, we employ the principle of biomimicry to begin our exploration of the interactions of soft robotics and diaphragm motion. We report on a necessary technological update to an existing algorithm for designing soft actuators that follow a specific complex trajectory with a single pressure source. We develop pre-curved fiber reinforced actuators that are programmed to mimic the motion trajectory of the diaphragm derived from clinical imaging data. These actuators are best poised to
model active expiration, a function that is more directly linked to accessory muscles in
the abdomen as opposed to the inspiratory function of the diaphragm. We find that
the high fidelity motion replication presented in this chapter provides a technological
advance for soft robotics, but does not fully address the challenge of replicating
diaphragm biomechanics.

We present our subsequent work in developing a soft robotic respiratory simulator
in Chapter 3. Learning from Chapter 2, we investigate contractile soft actuator
options based on their force generation and contractile properties. We show that a
specific type of high force generation pneumatic artificial muscles (PAMs) is capable
of driving a passive diaphragm in a bench top respiratory simulator, replicating a
physiological range of pressures, volumes, flows, and work of breathing. From the
exercise of developing a respiratory simulator, we have both a greater understanding
of the interactions of the different components of the respiratory simulator, and also a
platform that can enable future device optimization.

In Chapter 4, we investigate the use of the same PAMs used to drive the respiratory
simulator applied to the task of diaphragm assistance. We present the process of
tuning and investigating different actuator design parameters. Cadaver testing of
preliminary actuator designs reveals the importance of maximizing the flexural bending
force of the actuator while minimizing the tensile force of the actuator. Through
further in vitro mechanical testing, we identify a first generation actuator design for
the diaphragm assist system.

In Chapter 5, we present the considerations surrounding the development of an in
vivo experiment to test a diaphragm assist system. We discuss the instrumentation
decisions made to enable the collection of clinically and physiologically relevant data.
Then we discuss the creation of a clinical model that can demonstrate different levels
of respiratory insufficiency within each animal.

All of this work culminates in Chapter 6, where we demonstrate the performance
of the diaphragm assist system in vivo. We show how the system can augment
respiratory pressures, flows, and volumes. Through this development process, we find
that synchronization with the native respiratory effort to be a critical feature of the
system. Furthermore, we investigate the effect of the timing of the synchronization. Overall, we demonstrate the proof-of-concept of the diaphragm assist device and generate a set of recommendations for future study.

The findings of this thesis and future outlook are ultimately summarized in Chapter 7.
Part I

Soft Robotics Applied to Respiratory Simulation
Chapter 2

Simulating High Fidelity Diaphragm Motion

Due to their soft nature, soft robotics provide opportunities to create robots well suited for intimate interactions with humans and biological tissues[7, 40]. Soft robotics have often looked to biorobotics and biomimicry for inspiration. Biomimicry is a common approach to solving problems in soft robotics. By identifying capabilities in biology that we aim to introduce into robotics, we can quickly gain new insights about how to do this by studying the biological system itself [40].

We begin this work towards the ultimate goal of diaphragm assist by investigating biomimicry. Exploring the task of high-fidelity motion replication provides an initial picture of the respiratory system drawn with a soft robotics lens. The work in this chapter is reported in Hu, L. et al [41].

Due to the nonlinear behavior of "soft" materials, high fidelity motion replication is a key challenge in soft robotics. A previous key advancement towards this goal was the development of a optimization algorithm that allowed complex motions to be "programmed" into a single actuator based on precisely applied fiber-reinforcements[42].

Fiber-reinforced actuators belong to a class of soft robotic actuators called fluidic elastomer actuators. The actuators consist of a soft elastomeric body with an embedded fluid cavity; they are actuated via pressurization of the fluidic cavity. To create tunable deformation of this elastomeric body, inextensible fibers are wrapped around cylindrical
actuators to generate controlled anisotropy\textsuperscript{[43]}. The previous work characterized the tunability of cylindrical fiber-reinforced actuators and categorized them into their principal motions: extending, twisting, and bending\textsuperscript{[42, 43]}. Extending actuators lengthen or contract, depending on the fiber angle. Twisting actuators generate a rotation about the longitudinal axis along the center of the actuator. Bending actuators exist as two-material elastomer segments in which one elastomer is stiffer than the other. The less stiff material preferentially deforms causing a bending moment to generate a bend angle, $\psi$.

Because the diaphragm is a dome-shaped muscle, the complex bending motions generated by Connolly et al.\textsuperscript{[42]} provide an appropriate place to begin the challenge of motion replication. Due to the domed geometry of the diaphragm, we enhance these actuators and the actuator design algorithm by introducing another variable, $\psi(0)$, the resting bend angle—defined in reference to the starting bend angle inscribed by the initially concave side of the actuator. The introduction of $\psi(0)$ creates actuators that are pre-curved in nature, and results in an additional level of complexity in the mechanical modeling. Here, we present the theoretical update and experimental validation of this technology advancement.

\section{2.1 Overview of Pre-Curved Actuators}

The introduction of $\psi(0)$ requires an update to the definition of bending segment types. Depending on the orientation of the stiffer and less stiff elastomers, we subcategorize bending segments into flexing and counter-flexing actuators based on their pressure response ($\frac{d\psi}{dP}$), seen in Fig. 2-1, which is distinct from their time response. Flexing actuators are defined by their positive bend angle pressure response ($\frac{d\psi}{dP} > 0$) for positive pressures resulting in an initially “closing” motion ($\frac{d\psi}{dt} > 0$). Contrastingly, counter-flexing actuators are defined by their negative bend-angle-pressure response ($\left(\frac{d\psi}{dP} < 0\right)$), as they undergo an initially “opening” motion for positive pressures ($\frac{d\psi}{dt} < 0$). Note that counter-flexing actuators initially begin in an “opening” motion, however when the bend angle passes $\psi = 0$ into the negative bend angles, the actuator...
will engage in what appears to be a “closing” motion as the bend angle magnitude increases although it is deforming in the negative direction. These actuator segments cannot be simply categorized as closing or opening due to this edge case.

![Diagram of types of bending actuators](image)

**Figure 2-1:** Schematic of types of bending actuators. Fiber-reinforced actuators consist of an elastomer body with a fluid filled cavity that is wrapped in inextensible fibers (depicted in yellow). Extending and twisting segments consist of a single elastomer (white) body, whereas bending segments consist of a dual elastomer body (blue depicts the stiffer elastomer). Pre-curved bending actuators can be subcategorized into flexing and counter-flexing actuators. From [41].

The introduction of pre-curved actuator segments also complicates the geometrical considerations of the specified fiber angles. In the cylindrical actuator segments, the fibers take the three-dimensional form of a straight coil with a constant coil pitch. In order to define the fiber trajectory in pre-curved segments, we rely on referencing the circumferential angle, \( \varphi \), which is the radial angle within the cross-sectional plane orthogonal to the longitudinal axis of the actuator. The seams that join the two different elastomers for bending actuator segments exist at \( \varphi = 90^\circ \) and \( \varphi = 270^\circ \). The deformation of these elastomeric actuators is governed by the axial stress \( \sigma_{zz} \) in the material, see Fig. 2-2.

A given fiber of fiber angle \( \alpha \) for a pre-curved segment is defined by a point-wise creation of a helical trajectory with respect to the circumferential coordinate, \( \varphi \), and the subsequent rotation around the center of curvature where for every infinitesimal circumferential cross-section, the local tangential fiber angle is asserted to be \( \alpha \) (see Fig. 2-3). With the introduction of the initial curvature, the pitch varies along...
the circumferential angle, with the smallest pitch distance at \( \varphi = 0^\circ \), the innermost material line on the initially concave side, and the largest pitch distance at \( \varphi = 180^\circ \), the outermost material line on the initially convex side.

Figure 2-2: Schematic of material stress parallel to the body of the actuator (\( \sigma_{zz} \)), defined in the cross-sectional plane. From [41].

Figure 2-3: Schematic of fiber angle (\( \alpha \)) in relation to circumferential cross-sections of the actuator. From [41].

With the addition of pre-curved actuator segments, the computational optimization workflow is modified to include the new pre-curved segment types—flexion and counterflexion—in addition to the new variable \( \psi^{(0)} \), as seen in the workflow schematic in Fig. 2-4. The computational optimization takes the desired bioinspired trajectory as an input, and couples the updated analytical model with a nonlinear least-squares optimization algorithm in MATLAB (\texttt{lsqnonlin}) to minimize the objective function which is the sum of errors for all configurations \( n_{config} \) and all associated actuator segment types \( n_{type} \) where \( type = [\text{twist, link, flex, counterflex}] \) between the desired parameters (twist (\( \theta \)), link length (\( l \)) and bend angle (\( \psi \))) and the resultant parameters for a given pressure:
\[ f(\mathbf{x}) = w_{\text{twist}} \sum_{j=1}^{n_{\text{config}}} \sum_{i=1}^{n_{\text{twist}}} |\hat{\theta}_i^j(\mathbf{x}) - \hat{\theta}_i^j|^2 \]
\[ + w_{\text{flex}} \sum_{j=1}^{n_{\text{config}}} \sum_{i=1}^{n_{\text{link}}} |\hat{l}_{\text{link},i}^j(\mathbf{x}) - \hat{l}_{\text{link},i}^j|^2 \]
\[ + w_{\text{counterflex}} \sum_{j=1}^{n_{\text{config}}} \sum_{i=1}^{n_{\text{counterflex}}} |\hat{\psi}_{\text{counterflex},i}^j(\mathbf{x}) - \hat{\psi}_{\text{counterflex},i}^j|^2 \] (2.1)

Figure 2-4: Schematic of the updated optimization workflow with the inclusion of the initial curvature, \( \psi^{(0)} \), for pre-curved actuators. From [41].

The optimization will output the multi-segment actuator design parameters, in vector \( \mathbf{x} \), necessary for the fabrication and the actuation pressures to replicate the desired motion trajectory. The optimization algorithm relies on an input-dependent deviate-based weighting function. Further details about the optimization algorithm and weighting scheme can be found in the Supplementary Materials and Fig. S1. Given these parameters, we can follow a fabrication process, shown in Fig. 2-5, to cast a silicone actuator with these given specifications.

### 2.2 Materials and Methods

**Study design** The overall objective of this work was to update the design optimization of fiber-reinforced actuators to allow for pre-curved actuators. Cross-validation between the analytical model, FEA, and two experimental methods provided the
confidence to proceed with the analytical model. To generalize the effects of including non-zero $\psi^{(0)}$ into the optimization, we simulated large data sets of randomized trajectories (n=28 for each case: opening and closing trajectories) and ran them through the optimization. Initially straight actuators were given the constraint of $\psi^{(0)} = 0^\circ$, while pre-curved actuators were given the constraint $\psi^{(0)} = 0^\circ \in (0^\circ, 180^\circ]$. We measure the accuracy of the optimization via percent error between the desired input trajectory and the optimized output trajectory, and pneumatic efficiency via pressure range utilization and pneumatic surplus. Due to the long and manually intensive fabrication time, we opt to only fabricate the actuator of our test case, respiration. We use the optimization to replicate clinically derived diaphragm motion.

**Optimization algorithm** The design optimization algorithm consists of an objective function which is minimized using a trust-region method which is carried out with the MATLAB function lsqnonlin (MathWorks, Natick, MA, USA). For the objective function to be optimized, the analytical equations for extending, twisting, flexing and counter-flexing actuators have to be solved for a given input trajectory, which is discretized in its link lengths $l_{\text{link}}$, bend angles $\psi$ and twist angles $\theta$ for a finite number of configurations.

For every extending and twisting segment, the inflation-extension-torsion problem [44, 45] is solved for the axial stretch and the angle of twist, respectively and is solved
for the bend angle for every flexing and counter-flexing segment. The axial stretch of every segment is converted into discrete link lengths which, together with the derived twist and bend angles, depicts the achieved trajectory. Now, the objective function in Eq. 1 computes the weighted quadratic errors of the achieved solution compared to corresponding desired quantities of the target trajectory until the error is minimized for a given set of design parameters condensed in a vector $\mathbf{x}$. The design parameter vector $\mathbf{x}$ here comprises the actuation pressures for every configuration, the fiber angle and the length for every actuator segment and the initial bend angle for flexing and counter-flexing segments.

In contrast to the original optimization algorithm\cite{42}, the weights are not prescribed by user preference. Here, the weights are evaluated following a deviate-based weighting scheme, that is, the weights are determined according to the deviation in the input variables (see Supplementary Materials). Further, an inequality constraint was applied, so that each design parameter is restricted by an individual permitted range which incorporates the manufacturability of the whole actuator.

**Finite element modeling of actuators** In order to calibrate crucial analytical model parameters, we conducted finite element simulations of single pre-curved flexing and counter-flexing actuators with a constant length of $l = 160\text{mm}$ using the commercial FEA software Abaqus (SIMULIA, Providence, RI, USA). In all cases, the actuator was fixed at one end and a pressure was applied on its fluidic cavity linearly increasing up to a predefined value within a duration of 1s.

We performed one simulation to determine the neutral axis for flexing and counter-flexing, respectively. Both models yielded fiber angles of $\alpha = \pm 5^\circ$ and initial bend angles of $\psi(0) = 180^\circ$. In order to draw conclusions on the location of the neutral axis in the circumference, sets of nodes on the outer surface along the actuator axis were defined at $\phi = \{0, 25, 35, 45, 90, 180\}^\circ$ and $\phi = \{0, 90, 130, 150, 160, 180\}^\circ$ for flexing and counter-flexing respectively and their corresponding strain in the deformed state was computed. As already stated by Connolly, et al.\cite{42}, our extension of the analytical flexing model is defined under the assumption of thin cylindrical walls and therefore
behaves stiffer than the FEA counterpart for experimentally derived model parameters. This way, we fit effective model parameters on the basis of a set of simulations of single pre-curved flexing and counter-flexing actuators with fixed initial bend angles of $\psi^{(0)} = 180^\circ$.

The calibration procedure was evaluated by a nonlinear least-squares algorithm which minimized the error between deformed bend angles derived by FEA and the corresponding analytical solution. Subsequently, the optimized parameter set was validated on additional numerical models which yielded constant fiber angles of $\alpha = \pm 5^\circ$ but varied in their initial bend angles of $\psi^{(0)} = \{0, 60, 120, 180\}^\circ$ and $\psi^{(0)} = \{180, 210, 240, 270\}^\circ$ for flexing and counter-flexing actuators, respectively.

**Actuator fabrication**  After the actuator design parameters are output from the optimization, a computer aided design software (SolidWorks, Dassault Systèmes SE) was used to model the prescribed actuator and the molds that are 3D-printed in order to fabricate the actuator. When the model of the actuator was generated, the fibers were modeled as swept grooves into the body of actuator, so that the fabricated elastomer body contained precise guides to control the fiber orientation and placement. The fibers along pre-curved segments were initiated at the $\phi = 0^\circ$ point at one end of the segment. Molds were printed on an Objet30 Prime 3D printer (Stratasys, Ltd., Prairie, MN, USA), preferentially in VeroClear (Stratasys, Ltd., Prairie, MN, USA). They were lubricated with Ease Release 200 (Smooth-On, Inc, Macungie, PA, USA).

Multi-material actuators were cast in a multi-step process. For our actuators, the less stiff material was DragonSkin 10 Medium (Smooth-On, Inc, Macungie, PA, USA) and the stiffer material was Smooth-Sil 950 (Smooth-On, Inc, Macungie, PA, USA). Silicone was mixed in a planetary centrifugal mixer (THINKY MIXER, ARE-310, THINKY, Corp., Japan) for 30s at 2000rpm and then 30s at 2200rpm. The dominant material for an actuator, most often the less stiff one, was cast first. Further information on the silicone casting can be found in the Supplementary Materials, see Fig S4. After the first portion was cured (according to manufacturer’s cure time at room temperature), excess silicone at the joining surface was removed via a sharp knife,
revealing a fresh silicone edge. Shortly afterwards, the second material, often the stiffer material, was poured into the appropriate portions of the mold. After the actuator was fully cured, the elastomer body plus inner core were demolded. A stiff wire was run between the inner core of the mold to separate the elastomer body from the inner core, but the inner core is not yet removed. Isopropyl alcohol, (Sigma-Aldrich, Inc, St. Louis, MO, USA) was used to lubricate the demolding process.

With the inner core still inside the elastomer body, Kevlar fibers (McMaster-Carr, Elmhurst IL, USA) were hand-wound along the guiding marks around the elastomer body. The inner core was released and the ends were capped and sealed with Sil-Poxy (Smooth-On, Inc, Macungie, PA, USA). A vented screw was installed in the cured Sil-Poxy cap end at which the actuator will be pressurized from.

**Actuation validation experiments** The experimental platform consisted of a frame with adjustable elements coupling together a camera mount, a custom actuator mount, and a black sheet for the background. The actuators were fixed horizontally on the specific mount, so that the plane of bending is parallel to the ground in order to decrease effects of gravity on the bend angle. The actuators were pneumatically actuated via an electropneumatic custom control box. The videos were analyzed via a MATLAB script (MathWorks, Natick, MA, USA) to extract the enclosed bend angle, allowing comparison of the experimental results with the expected results from the optimization.

To obtain a richer level of data regarding the actuator deformation, a digital image correlation (DIC) process was also devised. DIC is an extremely versatile method of achieving non-contact full field strain maps on deformation bodies, and utilizes a speckle pattern and speckle tracking software. When a stereoscopic approach is employed utilizing two cameras, a three-dimensional strain evaluation is possible, revealing not only the strain field, but also rigid body displacement and out-of-plane displacement. The actuators were patterned first with a solid white base coat, followed by a random black speckle. High-speed videos of deformation were recorded. The strain and displacement output from discrete data points were then extracted to
positionally match the output from the corresponding FE simulation.

Further details on the instrumentation used for actuator validation experiments are available in the Appendix.

**Simulated trajectory testing** For each case (opening and closing trajectories), we generated 28-sets of random trajectory input parameters. The random trajectories adhere to the following constraints:

1. The first configuration parameters were generated using the uniform random generator function (**rand**) in MATLAB within the following bounds: \( \psi^{(1)} \in [0, \pi], l_{\text{link},1}^{1}, l_{\text{link},2}^{1} \in [32.8 \text{mm}, 100 \text{mm}] \)

2. Within one trajectory set of parameters, the bend angle may only undergo increases \((\psi_1 \leq \psi_2 \leq \psi_3 \leq \psi_4)\) or decreases \((\psi_1 \geq \psi_2 \geq \psi_3 \geq \psi_4)\), and the link length segments may only increase \((l_1 \leq l_2 \leq l_3 \leq l_4)\). Because the trajectories were constrained to only allow for motions that can be accomplished via initially straight actuators, no trajectories were allowed to cross \(\psi = 0\).

3. The final configuration parameters are generated using the uniform random generator function (**rand**) in MATLAB within the following bounds: \( \psi^{(4)} \in \{ \psi^{(4)} : \psi^{(4)} > 0 \cap [\psi^{(1)} - 79.7^\circ, \psi^{(1)} + 79.7^\circ] \}, l_{\text{link},1}^{(4)}, l_{\text{link},2}^{(4)} \in [l_{\text{link},1}^{(1)}, 1.289 \times l_{\text{link},1}^{(1)}] \). The 79.7° change in \(\psi\) is derived for the maximum change in psi for an initially straight flexing segment with a length of 20mm. The 28.9% length increase is chosen via calculating the maximum extending deformation at 100kPa for an actuator with \(\alpha = \pm 5^\circ\).

4. The two intermediate configurations are randomly spaced (**rand**) between the selected \(l_{\text{link},1}^{(1)}\) and \(l_{\text{link},1}^{(4)}\), \(l_{\text{link},2}^{(1)}\) and \(l_{\text{link},1}^{(4)}\), \(\psi^{(1)}\) and \(\psi^{(4)}\).

We calculated input-output errors for each link length and bend angle of each configuration of each trajectory-set. We combined the data sets of the closing and opening trajectories \((n=56)\) and use the prescribed output pressures from these trajectories, to calculate pressure range utilization values and pneumatic surplus values. Data
sets were not normally distributed according to a Kolmogorov-Smirnov test. The non-parametric Wilcoxon signed-rank test was used as the most appropriate paired difference test.

Sourcing clinical data  In order to demonstrate the application of the updated algorithm, we utilized published clinical data as example input trajectories into the optimization. Clinical data from Mankodi et al.[31] was used as the source for the diaphragm motion trajectory. Data for their study was registered on clinicaltrials.gov (NCT01451281) and was in compliance with the NIH Privacy Act and approved by an NIH Institutional Review Board.

2.3 Mathematical, Computational, and Experimental Model Validation

Inclusion of pre-curved segments into the optimization algorithm requires updates to the analytical solution. In order to validate that the derived analytical solution will accurately correspond with the physical actuator behavior, we first consider the case of a pre-curved actuator consisting only of a single bending segment with a uniform $\psi^{(0)}$. The kinematics are derived by evaluating the equilibrium of moments around the neutral bending axis on the capped, unfixed end of the actuator, as previously described[42].

The balance of moments is expressed as the comparison of the resulting force due to the internal pressure acting on the cap and the material response of the semi-cylindrical layers made of the two types of elastomers. We approximate the deformation at the capped end based on the well-known kinematics of the inflation-extension-torsion problem of anisotropic tubes[44, 45] and further assume there is no radial expansion $r/R = 1$ and causing the radial stress component to vanish, $\sigma_{rr} = 0$. 
2.3.1 Analytical Model

We design these actuators with an axially symmetric set of fiber wrappings so the actuator should experience no twisting, $\tau = 0$. Consequently, the deformation gradient and the left Cauchy-Green deformation tensor reads as follows:

$$
\mathbf{F} = \begin{bmatrix}
\lambda_z^{-1} & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & \lambda_z
\end{bmatrix}
$$

(2.2)

$$
\mathbf{b} = \begin{bmatrix}
\lambda_z^{-2} & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & \lambda_z^2
\end{bmatrix}
$$

(2.3)

This displays the dependence solely in axial stretch, $\lambda_z$, due to bending. In this model, the curvature in the bent configuration is constant across the whole actuator segment and the cross-sections are assumed to remain perpendicular along the actuator axis. In contrast to initially-straight bending actuators, material lines parallel to the actuator axis along the whole body of pre-curved actuators are not uniform in length with varying $\phi$. In this way, a flexing or counter-flexing actuator is, in addition to the initial bend angle $\psi(0)$, characterized by its length measured on the outermost material line along circumferential angle $\phi = 180^\circ$ within the cross-section. Using this information, we formulate a generalized axial stretch of a cylinder due to bending (in flexion or counter-flexion) of an arbitrary point in the cross-sectional plane:

$$
\lambda_z = \frac{l - \psi(0) R_0 (1 + \cos \bar{\phi}) + \psi (R_0 \cos \bar{\phi} - R \cos \varphi)}{l - \psi(0) (R_0 + R \cos \varphi)}
$$

(2.4)

Here, $\psi(0)$ and $\psi$ are the undeformed and deformed bend angles; $\varphi$ and $R$ are the circumferential coordinate and the radius within the constraints $0^\circ \leq \varphi \leq 180^\circ$ and $R_i \leq R \leq R_0$ respectively; $l$ is the actuator segment length; and $\bar{\phi}$ is the location of the neutral axis (dependent on subcategorization into flexion vs counter-flexion as seen in Fig. 2-1). The neutral axis is derived from FEA; it exists at $\varphi = 35^\circ$ for flexing and at $\varphi = 35^\circ$ for counter-flexing actuators, see Supplementary Materials for additional
information. Using this expression for axial stretch together with the assumption of an isotropic, incompressible Neo-Hookean strain energy density for the elastomer layers and a linear elastic material behavior for the fiber reinforcements as in [45], we can derive the moment around the neutral axis that originates from the material response acting against the internal pressurization as follows:

\[ M_{\text{mat}}(\psi) = 2 \int_0^\pi \int_{R_i}^{R_0} \sigma_{zz} \lambda^{-1} R (R_0 \cos \tilde{\psi} - R \cos \psi) dR d\psi \]  

(2.5)

The opposing moment around the neutral axis as a consequence of the applied pressure is given by:

\[ M_{\text{cap}}(P) = 2PR_i^2 \int_0^\pi \sin(\tilde{\varphi})^2 (R_0 \cos \tilde{\varphi} - R_i \cos \varphi) d\varphi \]  

(2.6)

Finally, our objective function evaluates the equilibrium of moments about the neutral axis to solve for the required pressure to achieve a desired bend angle via:

\[ f_{\text{EoM}}(\psi, P) = M_{\text{mat}}(\psi) - M_{\text{cap}}(P) = 0 \]  

(2.7)

For further details of this derivation see Appendix.

Derived from first principles, the analytical model is used as a mathematical tool that is potentially subject to error from simplifying assumptions. Although finite element analysis (FEA) generally provides more accurate predictions than an analytical bending model, it is far more computationally expensive. Thus, by creating an optimization algorithm that depends on a robust analytical model instead of FEA, the optimization process improves the actuator design workflow.

### 2.3.2 Computational Validation of the Analytical Model

In order to increase the general validity of the model, we analogously performed FEA simulations for flexing and counter-flexing actuators which exhibit a constant length of \( l = 160\text{mm} \) and constant fiber angle \( \alpha = \pm 5^\circ \), but vary in their initial bend angles of \( \psi(0) \). (Validation of accuracy for other parameters included in Supplementary
We ran FEA on select cases in order to validate our analytical solution, enabling us to proceed with the preferable, less computationally expensive option while also maintaining confidence in the accuracy of the analytical predictions. The analytical model demonstrates generally low relative error values. The analytical model shows relative deviations from the FEA results in the range of $2.72 \pm 0.77\%$ (Fig. 2-6) for the flexing actuators and $5.27 \pm 8.6\%$ (Fig. 2-6) for the counter-flexing actuators. The FEA predicted conformation at 27.6kPa is shown for the flexing (Fig. 2-6) and counter-flexing (Fig. 2-6) actuators. In summary, the parameter optimization offers comparable results to FEA predictions and therefore generalizes the computational validity of the analytical model for varying model parameters.

### 2.3.3 Experimental Validation of the Analytical Model

Subsequently, the analytical and finite element models were further validated with experimental data collected from physical prototypes, seen in Fig. 2-7. Physical actuator performance was evaluated on three prototypes for flexing actuators and two counter-flexing actuators with length $l = 160\text{mm}$, fiber angles $\alpha = \pm5^\circ$ and initial bend of $\psi(0) = 180^\circ$ via two methods; optical tracking of the bend angle and DIC to track the displacement of points along the actuator.

In order to compare the bend angle to the analytical predictions, flexing actuators were pneumatically activated by iteratively increasing pressures of up to 27.6kPa in 3.4kPa (0.5 psi) steps. The maximum pressure was constrained based on FEA predictions depicting a $360^\circ$ bend angle at 37kPa, in which the actuator would bend into a full circle and thus the free end would collide into the fixed end of the actuator. Counter-flexing actuators were tested in 6.9kPa (1 psi) steps until a maximum pressure of 48.3kPa (7 psi). Upon every pressure step, the valve was closed after the corresponding nominal pressure was reached and opened after the actuator occupied its steady state response. The video data was analyzed using a representative frame for each pressure step, from which the steady-state deformed bend angle was extracted.
Figure 2-6: Validating the analytical model via finite element analysis. The predicted bend angle pressure response for the analytical model and finite-element model for varying $\psi^{(0)}$ is compared for the (a) flexion and (b) counter-flexion case. The FEA deformation and strain results for specific actuators of outer length of 160mm and fiber angle of $\alpha=\pm 5^\circ$ pressurized to 27.6kPa (4psi) is shown for the (c) flexion and (d) counter-flexion case. From [41]
The comparison of the analytical model with the experimental results from the optical tracking is shown in Fig. 2-7A for a flexing actuator and in Fig. 2-7B for a counter-flexing actuator. The representative video frame at 27.6kPa is shown in Fig. 2-7C for a flexing actuator and in Fig. 2-7D for a counter-flexing actuator. One limitation of this comparison is that fabrication errors can be seen in the deviation from the prescribed ideal initial bend angle for the unpressurized configuration and the inter-actuator variability at equivalent pressures. For flexing actuators, the analytical model predicted larger changes in bend angles than the physical prototypes.

This is concordant with the previous results of the optimization work\[^{42}\], in which Connolly et al. observed this phenomenon for their initially straight bending actuators yielding low fiber angles. We assume that gravitational effects decrease the change in curvature for physical actuators and therefore, the analytical model might be seen as an idealization of the real system, since it neglects body forces and effects of inertia. Another potential source of error is gravity’s effects on the consistency and accuracy of the testing method. The bending curvature of an actuator could be out of plane, so that it appears slightly twisted around its curved axis and subsequently yields lower than expected changes in its bend angles for flexing and counter-flexing. Body forces such as gravity highly depend on the volume it affects. Shorter segments of actuators decrease these negative effects on actuator performance and, simultaneously, increase the accuracy of the analytical prediction; aiming for shorter segments is beneficial for the optimization of segmented actuator design presented in the rest of this chapter.

We conducted an additional experimental method to validate the FEA model via DIC to quantify the net in-plane displacement of various points along the physical actuator. By measuring displacement of the actuator, we reduce the influence of the manufacturing error in which the initial bend angle has slight variations from the exact prescribed initial bend angle. We compare the FEA predicted displacement of four select points along the $\varphi = 90^\circ$ material line of the actuator to the DIC derived displacement for the flexing (Fig. 2-7E) and counter-flexing (Fig. 2-7F) actuators with an initial bend angle of $\psi^{(0)} = 180^\circ$. The flexing actuator does continue to show the trend of being stiffer than predicted. We generally observe good matching of
Figure 2-7: Validating the analytical model and finite element analysis with experimental results. The experimental bend angle pressure response determined via optical tracking is compared to the analytical model for varying $\psi^{(0)}$ for the (a) flexion and (b) counter-flexion case. A representative image from the optical tracking image of bend angle for specific actuators of outer length of 160mm and fiber angle of ($\alpha=\pm 5^\circ$) pressurized to 27.6kPa (4psi) is shown for the (c) flexion and (d) counter-flexion case. The best fit arc is overlaid in red. The finite-element analysis predicted displacement is compared with the experimentally determined DIC displacement of four-discrete points for the (e) flexion and (f) counter-flexion case. The DIC image of displacement for specific actuators of outer length of 160mm and fiber angle of ($\alpha=\pm 5^\circ$) pressurized to 27.6kPa (4psi) is shown for the (g) flexion and (h) counter-flexion case. From [41]
the displacement between the DIC and FEA data, and we specifically see excellent matching for the case of the counter-flexing actuators. The displacement heat map derived from DIC showing the flexing (Fig. 2-7G) and counter-flexing (Fig. 2-7H) actuator pressurized to 27.6kPa can also be visually compared to the FEA frame in Fig. 2-6C and D, respectively.

One limitation of the DIC is that due to the curvature of the actuator, the software has trouble analyzing the edges and cannot capture data for these curved sides. With that said, we see robust qualitative matching between the heat maps plotted with the same heat scale of 2-6C,D and 2-7G,H, even without the capture of the edge effects. By cross-validating between the analytical model, the FEA, and experimental methods, we can confidently proceed with our analytical model.

2.4 Increased Fidelity of Improved Optimization

The introduction of a new decision variable, $\psi^{(0)}$, allows for the optimization to achieve more accurate outputs that have higher fidelity to the input trajectories. In order to investigate the increase in accuracy conferred by the inclusion of pre-curved segments, we tested the optimization software with sets of randomly generated input trajectories. For our simulated trajectory testing, we assume the case of a two-link input trajectory, in which each motion trajectory is composed of 4 discrete configurations ($j=4$). This assumed trajectory format is consistent with the format of the biological diaphragm motion data we use later.

It is assumed that the configurations are temporally ordered, but the pressure to achieve the first configuration $P_1$ is not necessarily the lowest nor highest pressure. Two cases of trajectory data were tested, the case of an opening angle trajectory ($\frac{d\psi}{dt} < 0$) and the case of a closing angle trajectory ($\frac{d\psi}{dt} > 0$). For each case, we generated 28 sets of random input trajectory data with four configurations per trajectory. The trajectory inputs were constrained to only cases that an initially straight actuator could generate—therefore trajectories that crossed $\psi = 0$ were excluded (see Materials and Methods for more information). Each set of input data was run through the
optimization algorithm both with the pre-curved segment capability ($\psi^{(0)} \in [0, \pi]$) and with initially straight actuators ($\psi^{(0)} = 0$).

The output trajectories were calculated based on the optimized parameters, and the output link lengths and bend angles were compared to the corresponding input link lengths and bend angles. The percent errors are shown in Fig. 2-8. Due to the high prevalence of extreme values such as the 800% error point seen in Fig. 2-8B, the data is not normally distributed and a non-parametric test is used to compare them.

Figure 2-8: Accuracy of the optimization with the inclusion of an initial bend angle, $\psi^{(0)}$. The optimization software was tested with randomly generated input trajectories, in which we compare the resulting percent-error of the optimized output trajectory compared to the desired input trajectories. (a) Closing trajectory bend angle errors ($p=0.02$). (b) Opening trajectory bend angle errors ($p=8\times10^{-14}$). (c) Closing trajectory link length errors ($p=8\times10^{-38}$). (d) Closing trajectory link length errors ($p=3\times10^{-37}$). The cases of closing and opening trajectories are tested with 28 trajectory sets each. The bend angle data sets have $n=112$. The link length data sets have $n=224$. Boxplots show the interquartile range in blue and the median value in red. Data is compared with a Wilcoxon signed-rank test. *$p<0.05$, **$p<0.01$, ***$p<0.001$ From [41]

In Fig. 2-8A, for an opening angle trajectory, the median percent error of the output bend angles derived from the parameters specified by the algorithm is 0.83% for initially straight actuators and 0.61% for pre-curved actuators. We find more substantial accuracy savings in Fig. 2-8B when we consider opening angle trajectories;
the median percent error is 4.0% for initially straight actuators and is 0.77% for pre-curved actuators. The accuracy savings are greater in link lengths than in the bend angles, which is largely influenced by how the weighting scheme in the optimization function distributes errors for the cases of initially straight actuators. For link length errors for closing trajectories, the median percent error is 14% for initially straight actuators and 0.89% for pre-curved actuators, see Fig. 2-8C. Similarly, for link length errors of closing trajectories, the median percent error is 15% for initially straight actuators and 0.66% for pre-curved actuators, see Fig. 2-8D. Manual adjustment of the weights for the initially straight actuators could lead to a more even distribution of error. Overall, we find that the deviate-based weighting provides for sufficiently small errors between the desired input trajectory and the optimized expected output trajectory.

The median percent-error for the pre-curved actuators is under 1% in all four avenues of data. The uniformity of the distribution of error in the case of pre-curved actuators indicates that the weighting scheme is appropriate for the optimization. It is notable that the initially straight actuators also have more extreme outliers in the data, indicating that the optimization with the pre-curved segment capability allows for a more robust handling of various input trajectories.

2.5 Replication of Clinically Derived Diaphragm Motion

The inclusion of pre-curved segments into our optimization algorithm enables us to mimic the initially curved states of complex biological systems. We replicate the domed motion of the diaphragm[46, 31]. Specifically, we look at replicating the coronal and sagittal plane motion of the right hemisphere. The input trajectory data was sourced from existing literature[31]. For the diaphragm especially, the introduction of pre-curved actuators is critical, because an initially straight resting configuration is unrealistic for the muscle fibers of the diaphragm.
The workflow of taking input clinical data and converting it to an actuator is seen in Fig. 2-4. First, we extract the relevant trajectory points that we aim to mimic. For the case of the diaphragm, the input data is derived from cine magnetic resonance images (MRI) from pre-existing respiratory imaging studies[31]. This MRI data is available for the coronal plane imaged at the plane through the tracheal bifurcation and the sagittal plane imaged through the right midclavicular line. We aim to replicate the motion of the diaphragm muscle found in these planes of imaging. We opt to focus on the data for the motion of the right hemisphere because the beating of the heart distorts motion tracking efforts for the left hemisphere; we make a simplification that assumes left-sided symmetry to the right sided diaphragm motion to best represent the intrinsic motion of the diaphragm muscle. As the native muscle fibers in the diaphragm anchor to the central tendon,[47, 15] we opt to track a trajectory that follows the lateral side of the diaphragm to the peak of the diaphragm curvature, assuming that this is where the fibers anchor to the central tendon. We assume no contractile motion within the central tendon.

From this, we extract the input trajectory shown in Fig. 2-9 from video frames at four time points along a single exhalation cycle. Notably, pre-curved actuators can be programmed to simulate both inspiration or expiration. However, diaphragm motion involves very high degrees of contraction in the zone of apposition[48]. Because the maximum degree of contraction is much more unstable than the maximum degree of extension, this high degree of contraction is better modeled in fiber-reinforced actuators as extension. As a result, the actuators are more accurate or exhalation than inhalation.

These trajectories are input into the optimization software, which subsequently outputs the fabrication and actuation parameters to best match these four configurations pulled from the biological data. The optimization predicts the actuator conformations shown in Fig. 2-10A. The optimization aims to match the outer edge of the actuator (the material line along \( \varphi = 180^\circ \)) to the input trajectory (the curvature of the diaphragm). Although there is some discrepancy, we see that the qualitative error largely derives from differences in the desired link length, especially link length
1. If greater link length fidelity is desired, the weights can be manually adjusted.

![Configuration 1, Configuration 2, Configuration 3, Configuration 4](image)

Figure 2-9: The diaphragm muscle motion trajectory of the right hemidiaphragm from a coronal plane is extracted and discretized from the cine MRI of a healthy subject in maximal breathing, data modified from Mankodi et al[31]. Four frames across one exhalation motion are selected. From [41].

Given the output parameters, we fabricate the actuators according to the workflow described in Fig. 2-5. The actuators are mounted onto an acrylic stand via the actuator base and pneumatically actuated using a control system that relies on electropneumatic regulators. Using a video tracking script (MATLAB), we select representative frames of the actuator in a steady state when pressurized to each of the specified pressures and compare the conformation to the expected analytical solution, see Fig. 2-10B. In order to actuate the system to replicate the dynamic motion that the input trajectories derive from, the specified pressures are plotted with the time point of their respective video frames. The conformations between the time points will be generated via a linear interpolation between the specified pressures ($P_1, P_2, P_3,$ and $P_4$), as seen in the pneumatic control scheme in Fig. 2-11.

The link lengths yield larger error values than bend angles (maximum deviation of 0.13%). The error in link lengths depict an asymmetrical distribution with a corresponding median of 0.79%, as seen in Fig. 2-12. Since this value is sufficiently small and the associated maximum error of 4.1% is still below a 5% threshold and we see good qualitative matching in Fig. 2-10A, we declare the analytical model with the underlying set of optimized design parameters as a good approximation with respect to the desired, discrete input trajectory. In Fig. 2-10B, the fabricated actuators demonstrate very good fidelity to their analytically predicted conformations;
Figure 2-10: Pre-curved actuators designed to follow diaphragmatic motion in exhalation. (a) The expected configuration of the actuator at the prescribed pressures overlaid with a close up of the selected MRI frames. (b) The deformation of the fabricated actuator is compared to the analytically predicted trajectory from the optimization. From [41].

Figure 2-11: Pre-curved actuators designed to follow diaphragmatic motion in exhalation. The pneumatic control scheme uses a linear interpolation between the specified pressures. From [41].
in fact, they show better fidelity than what is seen in the single-segment actuators investigated in Fig. 2-7. This is largely due to the shorter segment lengths of the pre-curved actuators, here they are on the order of 40-70mm compared to 160mm in the example actuator investigated earlier. The analytical solution represented by the predicted actuator outline depicts excellent agreement with the corresponding outline of the physical actuator throughout all configurations and consequently highlights the accuracy of the calibrated analytical model for reproducing the physical actuator behavior upon pressurization.

Figure 2-12: Error of the diaphragm motion FRAs. The error between the input trajectory parameters is compared with the analytically predicted link lengths and bend angles that result from the optimized actuator. Median shown in red. These actuators are dynamically compared to the input data in Movie S1. From [41]

### 2.6 Pneumatic Efficiency Enabled by Pre-Curved Actuators

By fabricating the actuators with a pre-curved configuration, the unused range of motion—indicative of an inefficient system—required to reach the first configuration from a straight cylinder is eliminated. The inclusion of pre-curved actuator segments in the optimization algorithm allows for more pneumatically efficient and more accurate replication of complex bending motion. Fluidic soft actuator systems often rely on pneumatic regulators to provide accurate and precise control. When soft actuator systems demand high operating pressures and high precision regulators, the costs of
the control system rapidly increase due to the precision engineering required to create such instrumentation. The creation of pneumatically efficient actuators relieves the requirements of a pneumatic system, allowing for the use of lower-cost control systems.

Pneumatic efficiency can be quantified via two metrics: pressure range utilization (PRU) and the pneumatic surplus value (PSV). PRU is quantified as the pneumatic range normalized to the maximum prescribed pressure via:

\[
PRU = \frac{\text{range}(P^{(1)}, ..., P^{(j)})}{\max(P^{(1)}, ..., P^{(j)})}
\]

(2.8)

In which a PRU value of one indicates a fully utilized system, and a PRU value close to zero indicates a poorly utilized system where the prescribed pressures to achieve the input configurations cluster at the maximum end of the pressure range. A poorly utilized system reflects the amount of “wasted” pneumatic work in order to achieve the conformation that exists at the lowest pressure. PRU yields a metric that can capture the unused pressure range.

Pneumatic surplus is quantified as the minimum prescribed step size in between any two configurations normalized to the minimum step size of a given pneumatic regulator via:

\[
PSV = \frac{\min(\text{abs}(P^{(j)} - P^{(j-1)}, ..., P^{(2)} - P^{(1)}))}{\text{minimum regulator step size}}
\]

(2.9)

A pneumatic surplus value (PSV) less than one indicates that the given pneumatic regulator is insufficient in its precision and is unable to achieve differentiable configurations for a given actuator. For our testing, we utilize SMC ITV1000 series electropneumatic regulators (SMC Corporation, Chiyoda, Tokyo, Japan) which have a minimum output unit of 0.7kPa (0.1psi). A PSV much greater than one indicates the surplus capacity of the pneumatic system, indicating the degree to which the actuator can suffice with a less precise, and thus less costly, pneumatic regulator.

Using the randomly generated trajectory data from earlier, we can extract the PRU and pneumatic surplus from a pool of 56 sets of trajectory data comparing the initially straight actuators with the pre-curved actuators, seen in Fig. 2-13. The pre-curved
actuators have a median value of 1 compared to the initially straight actuators with a median PRU of 0.26, indicating that the initially straight actuators have a tendency to waste three-fourths of their pressure range to achieve the lowest pressure conformation. The pre-curved actuators have a median PSV of 13 compared to the initially straight actuators median PSV of 3.2. The average pre-curved actuator can suffice with a pneumatic regulator that is 4-fold less precise to achieve the same resolution as the initially straight actuators.

![Graph showing pressure range utilization and pneumatic surplus](image)

Figure 2-13: Pre-curved segments enable pneumatic efficiency and accuracy. Using a pool of n=56 sets of randomly generated input trajectory data, we examine the effect of using pre-curved actuators on two metrics: pressure range utilization (p=9×10^{-25}) and pneumatic surplus (p=3×10^{-11}). From [41]

To investigate the effect of the inclusion of pre-curved actuator segments in the setting of replicating biologically derived motion, three sets of input trajectories were studied for the case of diaphragm motion. From the clinical MRI data in the coronal and sagittal planes, the muscle fiber trajectory of the diaphragm—which anchors from the ribcage to the central tendon [46, 31, 15]—is extracted from the right hemidiaphragm over an exhalation cycle, as seen in Fig. 2-14. The muscle fiber trajectory from the sagittal plane is broken into two trajectories, an anterior and posterior segment. The three input trajectories—derived from the motion in the coronal plane, the anterior half of the sagittal plane, and the posterior half of the sagittal plane—were input into the optimization algorithm with the imposed boundary conditions of $\psi(0) = 0$ or $\psi(0) \in [0, \pi]$, an initially straight actuator or pre-curved actuator respectively. The resulting pneumatic control scheme for these three cases
are plotted in Fig. 2-15, in which each specified pressure \((P^{(1)}, P^{(2)}, P^{(3)}, \text{ and } P^{(4)})\) is plotted, with the color directionality indicating the direction of the ordered progression from \(P^{(1)}\) to \(P^{(4)}\).

Figure 2-14: To investigate the effects on pneumatic efficiency in the case of the diaphragm, the input trajectory data is taken from the curvature of the right hemisphere of the diaphragm in a coronal plane and sagittal plane MRI data, sourced from Mankodi, et al [31]. From [41]

Figure 2-15: The pneumatic actuation parameters output from the optimization and their functional ranges are plotted for the three input trajectories. From [41]

For all three input trajectories, the pre-curved actuators consistently have lower maximum pressures, wider pressure ranges between \(P^{(1)}\) to \(P^{(4)}\), and wider step sizes
between pressures. The greatest change in required maximum pressure is seen for the input trajectory derived from the anterior half of the sagittal plane, in which the initially straight actuator demands a maximum pressure of 74.7 kPa whereas the pre-curved actuator demands a maximum pressure of 33.3 kPa—a 55% reduction. The greatest change in utilization of the pneumatic range occurs for the input data that is extracted from the posterior half of the sagittal plane, in which the pneumatic range shifts from 59.9-69.5kPa with a PRU of 0.14 for the initially straight actuator to 0-65.0 kPa with a PRU of 1 for the pre-curved actuator. The pneumatic range widened by 570%.

The smallest pressure step sizes are required by the initially straight actuators for the sagittal posterior input motion and coronal plane input motion—the smallest required step sizes are 0.01 kPa (0.01) and 0.24kPa (PSV of 0.4) respectively for the pressure difference between P3 and P4 (step sizes are not visible on the chart). The PSVs of less than one indicate that these step sizes are actually below the resolution of the minimum 0.7kPa step size of the SMC ITV1000 series electropneumatic regulators which we have used for previous work[7]. For these same input trajectories, the pre-curved actuators have a smallest required step size of 4.6kPa (PSV of 6.6) and 1.5kPa (PSV of 2.1), respectively. The initially straight set of actuators prescribed by the optimization algorithm requires a more precise pneumatic regulator with higher pressure capacity in order to generate the expected conformations.

As discussed earlier, there is a degree of inherent error when we must reconcile different actuator segment behavior that is generated by one shared fluidic cavity and uniform pressure in all segments. The optimized solution thus represents the parameters that generate a minimum overall error. When the link lengths and bend angles of expected conformation from the analytical solution are compared with the input trajectory, see Fig. 2-16, pre-curved actuators not only utilize a more pneumatically efficient actuation control scheme, but also, have more accurate conformations with respect to the desired input trajectory. The pre-curved actuators for our biological examples are all an order of magnitude more accurate in terms of percent error than the initially straight actuators (Fig. 2-16), which is consistent with
our generalized findings from Fig. 2-8.

As link length is a better representative of the diaphragm muscle function, the more accurate link length of the pre-curved actuators are better mimics of the biological diaphragm function than the initially straight actuators. These errors can be qualitatively seen in the visualization of the actuators generated for a coronal plane input trajectory in Fig. 2-17, in which the outer edge (the material line along $\varphi = 180^\circ$) intends to follow the curvature of the diaphragm. The high link length error for the initially straight actuators results in a fiber-reinforced actuator that sits fully beyond the diaphragm in the red highlighted lung region; this effect is especially apparent in the configuration 1 state. Overall, pre-curved actuators enable more pneumatically efficient and more accurate generation of biomimetic fiber-reinforced actuators compared to their initially straight counterparts.

Figure 2-16: The percent error from the optimization is calculated for the input vs. output link lengths and bend angles for the three fields of diaphragm motion. For each trajectory, link length error (coronal motion, p=0.008; SA motion, p=0.008; SP motion, p=0.02) is calculated for 2 links at four configurations (n=8) and 1 bend angle error is calculated for each configuration (n=4). From [41]
Figure 2-17: Qualitatively, the higher accuracy of the optimization with pre-curved actuators is evident in the optimization results from input derived from the coronal plane. Boxplots show the interquartile range in blue. The median is shown in red. A Wilcoxon signed rank test is used. *p<0.05, **p<0.01, ***p<0.001 From [41]

2.7 Summary and Conclusions

Pre-curved actuators provide a beneficial technology update to high fidelity fiber-reinforced actuators. When we compare the optimization results for a set of input trajectories that can be achieved by both pre-curved and initially straight actuators, we find that the optimization is both more accurate and more robust in replicating biological input data with pre-curved actuators. Pre-curved actuators also enable the creation of actuator motions that are previously unachievable. By enabling a pre-curved fabrication, we can introduce the capability of capturing “opening” angles via material orientation to utilize counter-flexing actuator segments. For some complex biological geometries such as the diaphragm, an initially straight configuration is entirely unrealistic, and thus the introduction of pre-curved actuators is a foundational improvement to create a biomimetic system of the diaphragm. We demonstrate the
robustness of application of this technology via application to expiratory motion of the human diaphragm.

For the field of soft robotics, pre-curved actuators enable the concept of pneumatic efficiency, which facilitates the usage of less powerful and/or less precise pneumatic controls, and thus less expensive instrumentation. This is necessary for the translation of biomimetic actuators into widely used technology. For pneumatic regulator equipment, economic cost scales with higher power and higher precision. Pneumatically efficient actuators decrease the final instrumentation costs of the control system required to operate these soft robotic systems. Decreasing the hardware costs and complexity is a key step in translating these soft robotic actuators to full utilization.

This work is limited by the fabrication complexity, as this technology update trades ease of fabrication for accurate bending motion replication and pneumatic efficiency, the approach would be greatly aided by innovations in multi-material manufacturing methods. A key limitation is that the current mode of fabrication is costly in both manual time and curing time, leading to long start-to-finish manufacturing time (on the order of days). A high-throughput automated but customizable manufacturing method for these multi-moduli actuators would greatly aid the application and utilization of these actuators. We also noticed age-related changes in the actuators, with actuators fabricated approximately a year ago behaving much stiffer than more recently fabricated actuators. The analytical model can easily change out the material model, so one could easily run the optimization with aged silicone parameters. Measures could also be taken to slow aging effects, such as cryogenic storage. With that said, age effects are an inherent material-based problem that would benefit from thorough characterization or advancements in materials science.

Pre-curved actuators can capture motions that initially straight actuators cannot, and are also more accurate, robust, and efficient for the motions that can be generated with initially straight actuators. They are better suited to capture the geometric complexity of biological actuators and systems. Pre-curved actuators function as an enabling technology for the creation of bioinspired robotic systems, such as an artificial diaphragm driving respiration or artificial trunk that rotates about the spine. This
work provides a robust and versatile platform to precisely translate complex in vivo motion into biomimetic soft robotic actuators.

However, we find that motion replication is not a full picture of the respiratory system itself. The high fidelity motion replication described here relies on high precision, but low density fiber reinforcements. This low density is due to the difficult manufacturing process for these actuators. As a result of the low density, the actuators are ultimately majority elastomer as opposed to inextensible Kevlar. Force coupling methods to a majority soft elastomer actuator are difficult; the pressurized elastomeric body can accomplish pushing, but cannot effectively accomplish a tensile pulling. Although our original intentions are to model inspiration, these actuators can only be applied in a pushing manner. If we opt to drive a synthetic diaphragm with these actuators, we can only model active expiration. These actuators have the potential to be coupled with the respiratory simulator described in Chapter 3 to provide active expiration, in a similar manner to patient’s contracting abdominal muscles to drive maneuvers like coughing. In order to drive diaphragm motion in way that replicates diaphragm function, tensile contracting actuators are necessary.

Ultimately, pre-curved fiber reinforced actuators serve as a beneficial technology update for high fidelity soft robotic motion replication, but lack the tensile function to replicated diaphragm biomechanics.
Chapter 3

Simulating Respiratory Biomechanics

In order to understand the interaction of soft robotic elements and the biomechanics of the respiratory system, we developed an organosynthetic soft robotic simulator, where organic components are used to capture their complex material properties—such as lung tissue—and actuation is provided by contractile soft robotic components.

Due to the large number of variables surrounding respiration—including fluctuating volumes, pressures, flow rates, and compliances—mastery of respiratory biomechanics is a complex task. Key to the physiology of the respiratory system is the compliance of the different elements. Compliance is defined as the change in volume of a space due to a change in pressure, \( \frac{dV}{dP} \). Our system allows for the tuning of compliance of different elements, such as the lungs or the abdominal cavity, via different soft material mechanisms. Respiratory pathologies often deal with compliance changes, so the tunability of compliance allows for the educational opportunity in examining the effects of isolated change. Furthermore, intricate interventional strategies such as mechanical ventilation can be difficult for students to comprehend. However, as students progress into clinical training, robust biomechanical intuition is key for guiding accurate and decisive action from the clinical care team in the environment of critical care.

Medical simulators are key educational and training tools that can enhance under-
standing and intuition of complex biological systems, presenting a hands-on learning opportunity while causing no harm to a potential patient or a living animal. Simulating the mechanics of the respiratory system in a tunable model could therefore provide an active, experiential learning tool to aid in the development of an accurate workable mental model for clinicians in training.[49] Although there exist a variety of simulators for medical training, none capture the extent of biomechanical and biophysical phenomena that govern the physiology of the respiratory system.

More specifically, medical simulators exist for a wide variety of applications, ranging from preclinical education to experiential training to medical technology testing and research.[49, 50, 51, 52, 53] Perhaps the most commonly used educational respiratory simulator is the extremely simplified bell jar model of a balloon (representing the lungs) in a jar (representing the thoracic cavity) with an elastic membrane at the base of the jar (representing the diaphragm).[51, 54] When one manually pulls on the membrane, the negative pressure generated in the jar “inflates” the lungs. This is an inexpensive and accessible model; however, it fails to teach any of the more complex concepts involved in respiratory physiology. In clinical training, medical schools will often invest in complex mannequin-based simulators that rely on computational models of the relationship between clinical respiratory indicators.[49, 50] In using computational models to display the interactions of such indicators, these simulators compartmentalize the biomechanics into a “black box” model.[49, 52] These are effective in teaching clinical responsiveness and physical exam skills, however they are extremely expensive (on the order of $150,000)[49] and often a limited resource for institutions. In research and testing, respiratory simulators are largely created for the purpose of acting as dynamic radiological imaging phantoms.[55, 56] Their focus on replicating dynamic motion of internal tissues (often focused on tumor motion with respiration for either the lung or liver).[55, 56, 57] In these systems, the motion is driven by servos and motors, with no utilization of pressure to drive air flow.

The most advanced respiratory simulator that replicates some mechanical principles of respiration in the preexisting literature is now commercially available as the ArtiChest which is marketed for use in endoscopic procedural training.[58] The
ArtiChest does drive respiration via inducing negative pressure in the thoracic cavity, utilizes fresh animal lungs (porcine or ovine), and drives a “diaphragm” balloon via pressurizing the “abdominal cavity”. However, by utilizing a passive diaphragm in which upwards motion is driven by increases in abdominal pressure it inverts the normal relationship between abdominal and thoracic pressures. In patients, increasing abdominal pressures can impede respiration. The ArtiChest does not track any pressure waveforms or display the effects of tuning the compliance of different elements in the system. Ultimately, the ArtiChest’s focus as a procedural simulator limits its utility as a preclinical educational tool.

Each of these existing simulators have a narrow application focus. None have been developed to fully explore the mechanics that drive respiration. For the most part, they focus exclusively on the thoracic cavity, neglecting the interdependence of the thoracic and abdominal cavity which are coupled by the active but flexible muscle of the diaphragm. Considering the diaphragm normally drives up to 70% of inspiratory efforts,[1] this simplification ignores key interactions that help explain the biomechanics of respiration. The few existing in silico models of diaphragmatic motion, and resultant pressures are computationally intensive and insufficient for rapid prototyping. Currently, no in vitro models exist that can replicate breathing pressures based on the movement of the diaphragm alone. Therefore, we aim to develop a simulator that is not application based but instead focused on replicating the biomechanics of this system. As such, this simulator has utility in medical education as well as in research and testing. This system is currently configured to serve as a versatile platform technology that can be adapted for intended use. Due to the modular nature of the system, specific elements can be adjusted to focus on the exact needs of different applications, such as creating an active diaphragm insert to study diaphragm dysfunction or the integration of cardiovascular flow loops to create a cardiopulmonary simulator. Currently, there are no existing simulators which are set up to be able to capture the intricate interplay of all of these systems. Robust in vitro simulators can enable rapid prototyping in the medical device design process without the use of living creatures.
As soft robotics are effective in replicating controlled muscle motion, we sought to introduce mechanically-programmable soft robotics into a dynamically pressurized system replicating diaphragm displacement, and in doing so, ventilate lungs in the thoracic cavity.

3.1 Soft Robotic Actuator Options to Drive a Diaphragm Mimic

There are many different types of soft robotic actuators that can be used as artificial muscles to drive contraction. Artificial muscles can be classified by their actuation mechanism, such as an electric field, electric power, fluid driven, and thermal actuation [59]. This thesis is focused on fluid-driven actuators, due to their simplicity, low cost, high energy efficiency, and potential for large actuation stresses [60, 61]. Fluid driven actuators can be simplified into pressure-actuated or vacuum-actuated structures [62].

**Pressure-Based Actuation** Pneumatically driven actuators often rely on a highly deformable bladder coupled with a flexible but inextensible material to control the deformation. Both fiber-reinforced actuators and McKibben actuators rely on this principle of function. Because they are both fiber and tube based actuators, they are both governed by the principle that the tube will maximize its volume (Fig. 3-1), and the maximum volume of a fiber wrapped around the tube will be reached at a critical angle of 54.4° [63, 64, 65, 66].

As described in Chapter 2, fiber-reinforced actuators are a type of pressure-actuated structure. They rely on positively-pressurized fluid to provide the energy that drives deformation. Fiber-reinforced actuators represent a hyper-precise method of motion replication via a single positive pressure. This hyper-precision also leads to fabrication difficulty.

One of the consequences of this ease of fabrication trade-off is the braid or fiber density. Fiber reinforced actuators have a low fiber density because increased fiber density can exponentially increase the fabrication time. Pre-made commercially
available expandable mesh sleeves used for McKibben actuators have a high fiber density because they are made with industrial braiding machines that do not give the end user tunable precision\[67, 68\].

For the high precision task of motion replication in Chapter 2, we accepted the high fabrication difficulty cost of fiber-reinforced actuators. However, for the task of generating contractile work against a pressure gradient, the high fiber density of McKibben actuators can generate a greater force and degree of contraction. These benefits coupled with the ease of fabrication make McKibben actuators a preferable pneumatic option for driving the diaphragm in a respiratory simulator.

**Vacuum-Based Actuation**  Depending on the application, vacuum-based actuators can be considered safer, due to the lack of high positive pressures. They are also more compact and are not limited by the mechanics of fiber angles; some vacuum-based actuators, such as fluid-driven origami-inspired artificial muscles (FOAMs), have been
shown to generate up to 90% contraction[69]. Due to their accessibility and high contraction ratio, we focus this section on these FOAM actuators.

FOAM actuators are made up of a foldable skeleton made of a rigid material surrounded by a flexible fluid-tight skin and a pneumatic connection. The skeleton’s geometry influences the deformation of the actuator [69]. Vacuum actuation drives compression of the skeleton along preset folding axes (Fig. 3-2). The maximum force generation of these FOAM actuators is determined by the material properties.

![Figure 3-2: The basic working principle that governs fluid-driven origami-inspired artificial muscles (FOAMs). From [62]](image)

Comparison of Options  McKibben and FOAM actuators (Fig. 3-3), due to their high contraction capacities, both present as promising candidates for use to drive the diaphragm in a respiratory simulator. Because we are interested in not just motion but also force, we characterize the actuators via Instron testing[62].

A few factors affect the force performance of McKibben actuators; one key factor explored in the context of the respiratory simulator is the effect of the mesh choice. Specifically, the expandable mesh of the actuator determines the maximum cross-sectional area of the actuator, which is proportional to the contractile force generated [70]. For the McKibben actuator, we examine two different expandable meshes. Their
nominal dimensions are $0.25\,\text{in}$ and $0.5\,\text{in}$, but their actual minimum diameter to maximum diameters are from a minimum of $0.125\,\text{in}$ to a maximum of $0.5\,\text{in}$ and from a minimum of $0.4375\,\text{in}$ to a maximum of $1.375\,\text{in}$ respectively.

In an isometric tensile test, we find that a pressurization of a $0.25\,\text{in}$ McKibben actuator to 20psig will generate up to $41.4\,\text{N} \pm 3.4\,\text{N}$ of tensile force (Fig. 3-4), whereas the pressurization of a $0.5\,\text{in}$ McKibben actuator to 20psi will generate up to $190.6\,\text{N} \pm 7.6\,\text{N}$ (Fig. 3-5).

In comparison, a FOAM actuator fabricated with an acrylic skeleton and a thermoplastic polyurethane (TPU) skin generates up to $28.6\,\text{N} \pm 6.8\,\text{N}$ with a vacuum force of $-5.9\text{psig}$, as seen in Fig. 3-6.
Figure 3-5: Force-contraction curve of 0.5\textit{in} McKibben Actuators characterized on the Instron. From [62]

Figure 3-6: Force-contraction curve of FOAM Actuators characterized on the Instron. From [62]
From this work, we find the fabricated FOAM actuators generate forces in the same order of magnitude as the 0.25\textit{in} McKibben actuators, whereas the 0.5\textit{in} McKibben actuators generate forces an order of magnitude higher. Although the FOAM and 0.25\textit{in} McKibben actuators generate similar forces, we find that FOAM actuators are much harder to control via vacuum regulation. The standard deviation for the FOAM actuators is 24\% of the mean force, whereas for the McKibben actuators, it is 8\% and 4\% for the 0.25\textit{in} and 0.5\textit{in} McKibben actuators, respectively. This is attributed both to reproducibility in the fabrication process and a lack of a high resolution vacuum regulator as compared to that of a pneumatic regulator[62]. The force results are heavily influenced by the dimensions and behavior of the skin of the actuator, and a lack of reproducibility in the fabrication process to fix the skin in relation to the skeleton leads to a large variation. The forces generated by McKibben actuators are less influenced by slight variations in actuator manufacturing length, and are more dependent on inherent mesh properties, which are highly controlled in their commercial manufacturing process. FOAMs rely on manually fabricated pouches and skeletons which lack this level of manufacturing control.

For the respiratory simulator, each actuator used to drive the diaphragm has a nontrivial installation process. In order to reduce the total number of actuators used, the highest force actuators, the 0.5\textit{in} McKibben actuators, are used.

3.2 An Organosynthetic Respiratory Simulator

Using these high tensile force pneumatic artificial muscles, we are able to drive diaphragm motion within our respiratory simulator. This work is reported in Horvath MA, Hu L, et al.[71]. The modular nature of the system we developed allows customization of different features that are important for various application specific uses. For example, in cases in which replicating parenchymal tissue properties of the lungs is important, organic lungs can be integrated thus combining the advantage of biologically accurate tissue mechanical properties with the controllability of the robotic system. In addition, we are able to track the pressures in both the thoracic and abdominal
cavity and the use of various silicone elastomers and soft robotic elements—i.e. the pneumatic artificial muscles (PAMS) that are used to pull the diaphragm, seen in Fig. 3-7—allows us to tune the compliance of multiple components of the system in order to replicate physiologic pressures and volumes, and therefore actively replicate the expected biomechanics of respiration. Soft robotic approaches include materials with moduli comparable with those of soft biological materials. Moduli of silicone and rubbers traditionally range between $10^4$ and $10^8$ which corresponds with the range of moduli for biologic materials from fat ($10^4$ Pa) to cartilage ($10^6$ Pa), and skin ($10^7$ - $10^8$ Pa)[38]. Silicone materials have been used previously to tune the compliance of mock blood vessels in circulatory simulators of the pulmonary system[72]. To our knowledge, there is no previously reported work utilizing tunable elastomeric materials to modulate compliance elements in the context of respiratory simulators.

![Diagram of biohybrid simulator](image)

**Figure 3-7:** A computational rendering of our biohybrid simulator focused on replicating respiratory mechanics. By tracking pressures and flows via included pressure sensors, the simulator may be utilized for a variety of education and training purposes. From [71].
3.2.1 Respiratory Mechanics

This simulator focuses on replicating physiological pressures and volumes by recreating the mechanical interactions of the lungs, diaphragm, pleural space, and abdomen.

The diaphragm is the major muscle responsible for inspiration, contributing the majority of the pump function within the respiratory system.[11] In normal tidal breathing, downwards motion of the diaphragm increases the volume of the thoracic cavity, decreasing pleural pressure \(P_{pl}\)—baseline -3 to -5 \(cmH_2O\), with quiet breathing efforts generating pleural pressures down to -9 \(cmH_2O\)[73]—and alveolar pressure \(P_{alv}\) to below the pressure at the airway opening and thus driving airflow into the lungs.

The diaphragm also couples the thoracic and abdominal cavities together, as it’s downwards motion simultaneously decreases the volume of the abdominal cavity increasing abdominal pressure \(P_{ab}\). Clinically, the most relevant pressure outputs are the pleural pressure and the abdominal pressures, see Fig. 3-8. The pleural cavity is the potential space between the tissue lining the exterior surface of the lung and the interior surface of the thoracic cavity. In our system this corresponds to intrathoracic pressure. We aim to match the physiologic pressure waveforms for the pleural and abdominal pressures to clinical data for normal breathing.

3.2.2 Replication of Respiratory Waveforms

We realize this simulator as an in vitro benchtop setup equipped with pressure and flow sensors and tunable mechanical properties. We constructed the chassis of the simulator out of optically clear plastics which act as the torso (Fig. 3-7). The chassis encloses the thoracic and abdominal cavities, separated by a diaphragm. This simulator is designed to be modular, therefore we included rapid-access ports on the sides of the acrylic boxes. The top and bottom sides of the chassis include modular tubing ports to allow for pressure controls and measurements. Our simulator assumes a rigid rib cage. The rib cage is broken into two zones: the upper 3D-printed ribs which act as a boundary between the lungs from the outer thoracic cavity space,
Figure 3-8: Schematic of how diaphragm displacement affects the pressures in the respiratory system driving airflow generating changes in the volume of the lungs, providing for the gas exchange of inspiration and expiration. From [71].

and the lower plastic shell which aims to mimic the zone of apposition (a vertical area of the diaphragm that begins at the insertion point on the inside of the lower ribs and extends to the top of the domes). Because the abdominal cavity is a much more compliant enclosure compared to the rib cage, the abdominal cavity contains a modular compliance window—a critical feature that allows us to tune the relationship between the thoracic and abdominal cavity pressure waveforms.

To generate respiration, we drive the motion of the diaphragm. The native diaphragm is a flexible but active muscle that generates up to 70% of the inspiratory tidal respiration[1] via volume change of the thoracic cavity. As a membrane, it couples the pressures of the thoracic and abdominal cavity together. In our simulator, we represent diaphragm motion via a flexible, passive silicone membrane that is moved via active pulling soft robotic elements located in the abdominal cavity. The diaphragm displacement is driven by six high tensile force pneumatic artificial muscles (PAMs).
pulling on the silicone diaphragm, shown in Fig. 3-9.

![Figure 3-9: Rendering and physical realization of the biohybrid respiratory simulator. Driven by pneumatic artificial muscles pulling on the diaphragm mimic. From [71].](image)

The PAMs are actuated via a custom electro-pneumatic control box that allows us to program specific actuation schemes, seen in Fig. 3-10A. By varying the actuation schemes and thus the actuator contraction, we can drive diaphragm motion and mimic shallow and deep breaths. In order to replicate the mechanical properties of lung parenchyma, this simulator can be coupled with organic lungs enabling the measurement of respiratory flows and volumes. Organic lungs also allow for the visualization of inflation and deflation, seen in Fig. 3-11.

Varying the degree of diaphragm effort generates a range of physiological pressures, flows, and tidal volumes, as seen in Fig 3-10 and Fig. 3-12. We achieve a range of physiological breathing pressures, generating pleural pressure between -20 and -6 cmH₂O, seen in Figure 3-10B. The contraction of the diaphragm drives the pleural pressure to be more negative and the abdominal pressure to be more positive. This difference is referred to as the transdiaphragmatic pressure and is a metric for diaphragm effort and function.

Our flow waveforms are rather tortuous; these spiking waveforms are an artifact of the highly sensitive internal control system of the electropneumatic regulators that
Figure 3-10: (A) Pneumatic artificial muscles pressurized with different input pressure waveforms generate different degrees of diaphragm displacement. (B) Measured outputs of abdominal and pleural pressure in response to varying actuator pressures. From [71].

Figure 3-11: Inclusion of organic lungs to visualize respiration and measure airflow. To visualize lung motion, the rib cage was removed. When the artificial muscles are not contracted, the diaphragm is in its resting state. With downward displacement of the diaphragm, inspiration and lung expansion are observed. From [71].

Figure 3-12: By driving the diaphragm with PAMs to inflate organic lungs, the spirometric readings replicate physiologic waveforms for flow (b), volume (c), and pleural pressure (d). P1 through P5 are defined in Fig. 3-10. From [71].
our system utilizes. Due to the signal-to-noise ratio of the pressure control at low pressure actuation—evidenced by the grey line in Fig. 3-12—the oscillatory effects of the control system are more pronounced. However, because the more relevant clinical metric is volume, the time integral is smooth enough to closely match the physiologic waveforms.

### 3.2.3 Tunable Compliances in the Respiratory Simulator

The pressures of the respiratory system interact through various organ and tissue systems, each with unique mechanical properties. The ability to vary compliance of different components in this respiratory simulator allows us to tune the performance of the simulator to match both physiologically normal conditions and also to examine the mechanical effect that pathologic changes to these compliances have on respiration.

Specifically, we can individually vary the effective compliance of the lungs, pleural space, and abdominal cavity and subsequently measure the effects of respiratory volumes and pressures.

We use organic porcine lungs to represent the compliance of “normal lung tissue”. This compliance can be decreased by wrapping the lungs in externally restrictive materials: C2 is created with a semi-distensible film around the lung and C3 is created with a non-distensible film around the lung, see Fig. 3-13. The decreased compliance mimics a net stiffening of the lungs in a restrictive lung disease.

![Variation in lung compliance](image)

**Figure 3-13:** Varying lung compliance via wrapping the lung in different film materials. From [71].
The compliance of the abdominal cavity ultimately affects the relationship between the pleural and abdominal pressure, thus a silicone window with a variable non-distensible covering allows the creation of various compliances, see Fig. 3-14. The variable compliance window of the abdominal cavity consists of a highly compliant silicone sheet that can be partially blocked by a stiff, polyurethane window covering to decrease the compliance: C1 is created with the window completely open, C2 is created with the window 33% open, C3 is created with the window 67% open, and C4 is created with the window completely closed. This can be finely tuned to mimic the effect of higher abdominal muscle tone. We can thereby control intra-abdominal pressure and mimic pathophysiological conditions like abdominal compartment syndrome. Additionally, selective actuation of the pneumatic elements contracting the diaphragm model downwards can serve as a model for unilateral diaphragm paralysis.

![Figure 3-14: (a)Schematic of a variable compliance window. (b) Effect of varying abdominal compliance via a variable compliance window. (c) Effect of variable abdominal cavity compliance on abdominal and pleural pressures during 1 cycle of respiration. From [71].](image)

Although we assume a rigid ribcage, we represent changes in thoracic cavity compliance by modulating the volume of gas between the lungs and chest walls. Because there are no defined pleural cavities and the pressure is equal throughout the space, we modulate the space external to the 3D-printed rib cage even though it is different than the native anatomy. By filling the space with an incompressible fluid, we replace the compressible air from the pleural space: C1 is created as the air fills the volume around the lungs, C2 is created with partially-filled sacs surrounding the lungs, see Fig. 3-15. This decreases the overall compliance of the volume surrounding
the lungs.

Figure 3-15: Varying chest wall compliance via reducing the amount of compressible air in the thoracic cavity by placing liquid filled bags in the chest cavity. (b) Effect of variable abdominal cavity compliance on abdominal and pleural pressures during 1 cycle of respiration. From [71].

The ability to independently control the compliance of different elements enables selective adjustment of compartment pressures in the thorax and abdomen and isolation of different mechanical phenomena for educational purposes. By examining the effects of each of these variables independently and then combined together, this simulator allows students to generate robust biomechanical mental models of the respiratory system.

3.2.4 Replication of Pathological Conditions

The compliant elements of the simulator are first tuned to generate physiologically normal biomechanics. Once the typical values are established, the modular nature of the simulator allows for the appropriate variables to be adjusted to replicate the biomechanics of pathologic conditions. We opt to simulate a key concept in early preclinical medical education: restrictive and obstructive lung disease. Intrinsic restrictive lung disease, such as pulmonary fibrosis, often occurs due to stiffened compliance changes to the lungs that prevent the necessary expansion of the lungs. We demonstrate the ability to create stiffened lung tissue in Fig. 3-16A-B; our simulator can output decreased pressures and flows resulting from the compliance change we induced to the lung tissue as shown in Fig. 3-13. In Fig. 3-16A and B, we examine the flow and volume waveforms of the simulator, and we show that given the same
diaphragm effort, increased lung stiffness decreases the ventilation capacities of the system. This can give insight into the pathophysiology of restrictive lung disease.

Obstructive lung disease is due to an increase in flow resistance in the respiratory system, such as the narrowing of the bronchioles in asthma or COPD. We can mimic the effect of increased flow resistance by adding a flow resistor in series with the airway, seen in Fig. 3-16. Increased resistance of the system leads to an increase in...
the emptying time of the lungs. If the respiratory rate increases such that there is an insufficient amount of emptying time between breaths, subsequent breaths introduce additional volume and additive pressure leading to dynamic hyperinflation. Fig 3-16C shows the decrease in tidal volume with the introduction of an obstruction, the subsequent decrease in tidal volume and introduction of dynamic hyperinflation with the addition of an increase in respiratory rate, and the worsened dynamic hyperinflation with the addition of an increase in diaphragm effort. Fig 3-16D shows the decay curve during expiration that occurs due to the added resistance, effectively increasing the RC time constant of the system. The increase in respiratory rate introduces the dynamic hyperinflation which results in the buildup of pressure, increases the minimum possible pressure generation, which ultimately requires increased diaphragm effort in order to generate the extremely negative pressures to compensate for the low tidal volume. These graphs elucidate the complexities of the respiratory mechanics that occur during obstructive lung disease.

Another pathology we can replicate is the case of a pneumothorax, when air improperly enters the pleural space, disrupting the pleural pressure, seen in Fig. 3-17A. There are broadly three types of pneumothorax—closed, open, and tension pneumothorax—which are determined by the degree of disturbance to pleural pressure. A closed pneumothorax occurs when air inappropriately enters the pleural space, but the pleural pressure remains negative. When the pleural space has equalized in pressure to the atmosphere, this is described as an open pneumothorax. And a tension pneumothorax occurs in which a valve like opening in the chest wall leads to trapping of air in the pleural space to the point where the pleural pressure is positive. This disruption can lead to a collapsed lung, which requires a chest tube to restore the negative pressure of the pleural space. To simulate the varying degrees of a pneumothorax, we set the baseline pleural pressure to different levels while keeping diaphragmatic efforts constant. Fig. 3-17B-D shows the nonlinear sensitivity of the respiratory system to the degrees of a pneumothorax. Case 1 and 2 reveal minimal change in the respiratory mechanics, displaying the general robustness of the respiratory system in which minor changes in initial pleural pressure do not affect
the ventilation. We find that Case 3 and beyond start to generate noticeable effects, delineating the inflection point at which a pneumothorax begins to have severe effects on function, demonstrating the difference in severities of the different categories of a pneumothorax. We find that in Case 4, those simulating a tension pneumothorax, we see extremely diminished lung filling capacity, as the lung struggles to expand against the pressurized pleural space. At a baseline pleural pressure of +5.5 cm H₂O, we find that the diaphragm displacement is unable to generate airflow or changes in lung volume and pleural pressure without increased breathing efforts.

![Diagram of pneumothorax categories](image)

Figure 3-17: Simulating the mechanical effects of a pneumothorax. (a) Schematic depicting the different categories of pneumothorax. (b) The ventilatory airflow measured for varying degrees of a pneumothorax. (c) The tidal volume generated for the varying degrees of a pneumothorax. (d) The measured pleural pressure in the varying degrees of a pneumothorax. From [71].

### 3.2.5 Coupling with Mechanical Ventilation

A core component of training for both medical students and resident physicians in critical care work is understanding how to operate and set positive pressure mechanical
ventilation. Mechanical ventilation is a key life-saving technology, but its many settings require proper understanding in order to provide adequate therapy. Improper ventilator settings can cause discomfort or even additional harm, such as pulmonary barotrauma. Our respiratory simulator can integrate with any existing mechanical ventilator to provide a risk-free and tailored learning environment. The goal of the simulator is not exact recapitulation of idealized waveforms, but instead demonstrating that the simulator can integrate well with existing clinical hardware for training purposes, seen in Fig. 3-18.

By operating the simulator without the active diaphragm displacement, we can demonstrate the effect of ventilator-only respiration, seen in Fig. 3-18B. Driving respiration only with the mechanical ventilator, we validate of our flow sensor outputs compared with the ventilator’s sensor outputs for both volume-controlled and pressure-controlled ventilation. Our respiratory simulator gives the additional insight of the effect of positive pressure ventilation on the pleural cavity pressure. This can provide clarity as to the distinctions in between different ventilator-modes, such as volume-controlled vs pressure-controlled ventilation. The simulator can also be operated with synchronized controlled mandatory ventilation as seen in Fig. 3-18C-D. This is an example for ventilator modes that sense inspiratory efforts by the patient and support them by delivering a volume controlled tidal volume. The respiratory simulator can be operated independent of the ventilator with a low level of breath which would not suffice for a full physiologic tidal volume. The different driving mechanisms of ventilation can be seen in the baseline waveforms of the ventilator and simulator operating independently and uncoupled, are seen in Fig. 3-18C. When connected, the same low volume breath can trigger the ventilator under the synchronized controlled mandatory ventilation mode. Inspiratory efforts of the simulated patient trigger the delivery of a pre-defined tidal volume by the ventilator, creating an additive effect of the simulator effort and ventilator effort seen in the pressure of the pleural cavity in Fig. 3-18D. The respiratory simulator can be synchronized with the ventilator and trigger breath delivery as a patient would. Additionally, our simulator reveals a measurement that is not gathered during regular operation of a mechanical ventilator—the pleural
Figure 3-18: Integration of the respiratory simulator with a mechanical ventilator. (a) Image of our experimental setup combining the simulator with an existing mechanical ventilator. (b) Flow and pressure measurements in which respiration is driven only by the mechanical ventilator. (c) Flow and pressure measurements when the ventilator is disconnected, and the simulator is driving a low tidal volume breath. (d) Flow and pressure measurements when the simulator drives a low tidal volume breath that triggers a breath on the coupled ventilator. From [71].
pressure. The value of measuring the pleural pressure, which is possible in our simulator, but difficult clinically, is in the ability to deduce the transpulmonary pressure (the difference between airway pressure and pleural pressure) rather than assume the transpulmonary pressure is well approximated by the airway opening pressure. The increased intrathoracic pressure can induce cardiovascular insufficiency in patients with hypovolemia due to the decreased venous return\[^{[74]}\]. The decrease in cardiac output is often a dramatic sudden decrease in function but can normally be reversed by fluid resuscitation. Notably, the airway waveform is less relevant to the hemodynamics than the effect of intrathoracic pressure. Therefore, our simulator provides the more relevant mechanical variable that is not directly measurable in the clinical setting. This provides an opportunity to offer a clarifying explanation to a challenging concept. The modular nature of the system allows us to adjust what outputs are visible, and so after the concept is clarified, the intrathoracic pressure reading can be removed to simulate operation with only the variables available in a clinical context. With this visualization, the simulator can expand a trainee’s mental model of the system. This model enables rapid understanding of the mechanics that allows clinicians to make smooth and decisive interventions, such as fluid resuscitation, prior to crisis\[^{[74]}\]. Our simulator, therefore, offers a key window into this complex biomechanical system by enabling accurate measurement of pressures that are not routinely measured clinically.

### 3.2.6 Simulated Work of Breathing

A graphical technique used to measure work of breathing (WOB) is the Campbell diagram, referencing pleural pressure with lung volume (Fig. 3-19). The WOB can be further decomposed into the elastic and resistive components. The green area represents the elastic WOB and the blue area represents the resistive WOB \[^{[75]}\]. Using the pressure and volume data from running the simulator connected and disconnected to the ventilator, we generate the pressure-volume (PV) loops of a Campbell diagram (Fig. 3-20).

Work of breathing is calculated from this PV loop as the internal area between
Figure 3-19: Idealized Campbell diagram. The green area represents elastic WOB and the blue area represents the resistive WOB. Reproduced from Hess, D.R. (2014)[75].

Figure 3-20: Through a Campbell diagram of our respiratory simulator, we can evaluate the capacity of the simulator to do respiratory work. The work of breathing is calculated as the shaded area of the inspiratory curve (outer edge) of the simulator drive PV loops to the passive compliance of the chest wall, derived from mechanical ventilation.
the inspiratory edge of the loop and the passive chest wall compliance derived from the mechanical ventilation PV data. By using the passive ventilation data under the volume control mode from Fig. 3-18, we estimate the compliance of the chest wall to be 80 mL/cmH\textsubscript{2}O (as seen in the solid black line in Fig. 3-20). This is stiffer than the expected range in patients—although it is more compliant than seen in 3-15. Chest wall compliance for people with chronic respiratory weakness has a wide range (117-258 mL/cmH\textsubscript{2}O) that is slightly stiffer than that of healthy patients (163-366 mL/cmH\textsubscript{2}O) [76].

The simulator-driven PV loops for respiration driven via 20 psi PAMs and 40 psi PAMs is shown in 3-20. Using six 20 psi PAMs, the simulator generated a work of breathing of 0.35 J/L. Using six 40 psi PAMs, the simulator generated a work of breathing of 0.94 J/L. Normal WOB is 0.35-0.7 J/L [77, 75, 78]. Although using 20psi PAMs generates the low end of the range of a normal work of breathing, the shape of the PV loops deviate slightly from the norm. The tortuosity of the flow and pressure waveforms seen in Fig. 3-12 for P1 (20 psi) is also seen in this PV loop. There is an isobaric tail at the top of both PV loops when the respiration is driven internally by the PAMs. This may be due to an unrealistically long plateau in the input pressure profiles leading to a static compliance phase at the end of the breath.

### 3.3 Summary and Conclusion

We demonstrate a respiratory simulator that replicates the biomechanics of ventilation that functions as an educational, training, and research tool. Our simulator drives diaphragm displacement with soft robotic actuators. By varying the contraction of these actuators, we can vary diaphragm effort to generate a spectrum of physiological pressure waveforms for the pleural and abdominal cavity. By integrating organic lungs, we can replicate ventilatory flow and tidal volumes in this bio hybrid simulator. We can independently vary the compliance of different components of the respiratory system to be finely tuned to match the physiological mechanics.

As an educational tool, this simulator replicates the mechanical physiology of the
system—showing the interdependence of pressure, volume, compliance, and flow—and grounds clinical concepts in biomechanics, providing a robust mental model for students. The modular nature of our simulator allows for not only the replication of normal physiologic motion, but also allows us to simulate a host of pathologies, sourced back to their mechanical dysfunction. The compliances can be further adjusted to simulate pathologies that derive from a change in compliance, such as restrictive lung diseases. We can adjust the resistance of the airway tree and model the effects of obstructive lung disease, such as dynamic hyperinflation. By modulating the baseline pressure in the pleural cavity, we can model the effects of different degrees of a pneumothorax on respiration. As such, this simulator has utility in preclinical education, but also in more advanced clinical training. For training of more advanced concepts, we can integrate the simulator with existing mechanical ventilators. When coupled with a mechanical ventilator, this simulator also acts as a platform to investigate the effect of different ventilator settings, providing a physical intuition between the different modes and functions and the mechanics of the respiratory system. The simulator can integrate seamlessly with different modes of mechanical ventilation including patient initiated assisted ventilation. The PAM-driven respiration of the simulator can generate a range of normal WOB.

Our simulator has limitations due to some of the simplifying assumptions made. We can couple the simulator with either silicone or ex vivo lungs, depending on the importance of replicating parenchymal properties. If the focus of a simulator exercise is examining diaphragm mechanics, silicone lungs can be used as a simplification of the system for ease of use. In the case of using ex vivo, freshly sourced, organic lung tissue to replicate the parenchymal properties, the simulator is subject to the natural inter-organism variabilities of the lung tissue. Additionally, these lungs lack pleural membranes and exist within a shared pressurized space; the simulator cannot generate different pressurized environments for the two lungs, and thus it cannot replicate conditions such as a unilateral pneumothorax. Our simulator successfully replicates physiologic tidal volume however it is not capable of generating the extremes of breath volumes. This is due to both the rigid ribcage and the simplified mechanism
of diaphragm motion. As expected by the modeling of the thorax with a rigid acrylic box where the only source of chest wall compliance in the simulator is the diaphragm, the chest wall compliances generated are a overall too stiff. Our simulator assumes rigid geometries of the rib cage; although the diaphragm is responsible for the majority of motion, the lack of accessory muscle and rib cage motion does not replicate the expiratory effort of rib cage collapse and limits the maximum volume inspired. Furthermore, the non-active diaphragm membrane of the diaphragm is not capable of generating the extremes of breath volumes. Because the diaphragm is pulled down via McKibben actuators in this simulator, it also does not accurately capture diaphragm contractile motion. Our flow and pressure waveforms show oscillating artifacts especially in the lower pressure ranges resulting from the electropneumatic regulator unit. This can be attributed to the pressure difference between the regulator input and output, as well as the compliance and resistance of the pneumatic circuit connected to the output. In our current applications, the volume of the output circuit is much greater than that of the pressure regulator, forcing the regulator to draw more pressure from the pressure source, with high wall pressures of 414 kPa. Our exact pressure output to the PAMs is dependent on the internal proprietary control scheme of the regulator unit which has an inherent rise time of 100 ms, which is slow enough to allow for overshoot and ensuing counteraction. This behavior has a minor impact on our overall flow, simulated lung respiratory volumes and pleural and abdominal pressures. Approaches to mitigate these characteristics include (i) introducing a greater capacitive component to the output circuit, (ii) minimizing necessary volume of the output circuit, (iii) using a more precise pressure regulator with a smaller range of output pressures to increase the set point pressure resolution, and (iv) using a pressure source that is closer to the maximum required output pressure.

The simulator enables the testing of devices that interact directly with the negative intrathoracic pressure and filling of the lungs, which are difficult to examine in animal cadaver studies. The simulator also enables the collection of metrics to evaluate the technology that are both more quantitative and more sensitive than the existing metrics. In the future, this platform can be modified to enable rapid prototyping of
different actuators in the context of a diaphragm assist system. Although we initially considered testing diaphragm assist actuators on this platform prior to in vivo studies, it was uncertain whether optimizing actuators on this platform would translate to improvements in vivo or if it would simply highlight limitations of the respiratory simulator. Now, with the in vivo data presented in Parts II and III of this thesis, an appropriate future next step is to tune and adapt the respiratory simulator to match our in vivo findings.

Ultimately, we have developed a respiratory simulator that is ready to be tuned to match in vivo data, and we find that McKibben actuators are capable of generating the work of breathing in our respiratory simulator by pulling on the passive diaphragm. In the same way that McKibben actuators can be used to drive the simulator’s diaphragm function from below, we explore the use of orienting McKibben actuators in a biomimetic fashion—along the dome of the diaphragm—and aim to use McKibben actuators to drive diaphragm function in vivo in Parts II and III of this thesis.
Part II

Actuator Design for the Support of Diaphragm Function
Chapter 4

Actuator Selection for a Diaphragm Assist System

4.1 Design Strategy

Respiration is a fundamentally mechanical system. The diaphragm is a dome-shaped muscle that drives up to 70% of respiration[1, 10]. As depicted in the schematic in Fig. 4-1A, when the diaphragm contracts, the arclength of the diaphragm shortens and the entire sheet of the diaphragm moves downwards, acting as a pump. The thoracic cavity volume increases and pressure decreases, ultimately driving respiration.

Our strategy aims to harness the contractile function of pneumatic artificial muscles (PAMs) to mimic and augment the native contraction of the diaphragm. Conceptually, the PAMs are placed superior to the native diaphragm so that the relaxed PAM conforms to the native curvature of the diaphragm (Fig. 4-1b). Mimicking the native diaphragm, we anchor the ends of the PAMs to the ribs (see Methods). With pressurization, the length of the PAM shortens, the arclength shortens, and the PAM mechanically pushes the diaphragm downwards.
Figure 4-1: Soft robotic strategy for diaphragm assist. (a), Schematic depicting the sagittal cross-sectional of the native diaphragm anchored to the ribs in a relaxed (left) and contracted (right) state. (b), Sagittal cross-sectional schematic of the strategy to augment diaphragm motion by placing PAMs superior to the diaphragm. The PAM conforms to the relaxed diaphragm in its unpressurized (left) state and pushes the diaphragm caudally in its pressurized (right) state.

4.2 Design Considerations

McKibben actuators are well-studied, easy-to-fabricate, high-force actuators. At their simplest, they are composed of a balloon bladder placed inside a closed, expandable mesh and connected to a fluidic source (Fig. 4-2). In this section, we consider the parameters of actuator design that will influence our design decisions.

**Actuator Length**  When referencing length of the actuator, there are three lengths to consider: the mesh length \( l_{\text{mesh}} \), the actuator length \( l_{\text{act}} \) and the contractile length \( l_c \) (Fig. 4-2,4-3).

The mesh length \( l_{\text{mesh}} \) refers to the length of the relaxed mesh used for fabrication, such as the mesh seen in Fig. 4-2.

The actuator length \( l_{\text{act}} \) refers to the total length of the fabricated actuator (Fig. 4-3). If the actuator is fabricated such that the relaxed state of the actuator has a similar profile to that of the relaxed state of the mesh, then \( l_{\text{mesh}} \) and \( l_{\text{act}} \) are nearly identical. As a result, they are often interchangeable, and \( l_{\text{mesh}} \) is used as the nominal
length of the actuator because it guides fabrication.

The contractile length \( l_c \) refers to the closed length of the relaxed mesh where the balloon sits (Fig. 4-3). This dictates the actual length of the actuator that undergoes contraction and delineates the active portion of the actuator.

The total length of the actuator and the contractile length are both important design parameters for the device. Mesh outside of the contractile length is passive mesh that provides an ideal suturing location on the device. By tuning \( l_{mesh} \) and \( l_c \) together, we can adjust the length and contraction to best fit the animal. Appropriate actuator length sized to fit the animal will be discussed in section 4.3.
**Balloon Design** McKibben actuators are favored for their ease of fabrication. Commercially available thermoplastic sheets are chosen as the balloon material to enable heat-sealing for ease of fabrication. A simple heat sealing process is conducted with a 3D printed mold to enable for rapid, customized fabrication of the internal balloon.

Beyond fabrication considerations, the key effect of the balloon design is influencing the pressure that the actuator can withstand, which will ultimately influence the forces that the actuator can generate. The material choice and geometry of the balloon and the geometry of the reinforcing mesh, as described below, determine the maximum wall stress and maximum pressure that a balloon can withstand. Our material choice was limited to low-cost, commercially-available, thermoplastic thin sheets. As an easily accessible option, the research group uses a thermoplastic elastomeric material (Stretchlon 200, FibreGlast Developments Corp.) with a tensile strength $> 8000\text{psi}$.

Beyond the material choice, the balloon dimensions will also influence the maximum pressures the actuator can withstand. The mechanics of the pressurized balloon can be understood via the mechanics of a thin-walled pressure vessel. Macroscopically, the balloon is a cylinder with spherical caps.

For this idealized shape, the hoop stress along the cylindrical walls will be:

$$\sigma = \frac{pr}{t}$$  \hspace{1cm} (4.1)

For a sphere, the wall stress is:

$$\sigma = \frac{pr}{2t}$$  \hspace{1cm} (4.2)

where $\sigma$ is the wall stress, $p$ is the internal pressure, $r$ is the radius of curvature, and $t$ is the wall thickness.

In order to achieve actuators that can withstand high actuator pressures, we find that the balloons must be oversized to the volume of the mesh determined by the contractile length. The balloon is oversized circumferentially and longitudinally.

In the case of an oversized balloon, the tight weave of the commercial mesh
reinforces the wall of the balloon and limits material stress on the balloon.

When the actuator is oversized, the wall of the balloon presses against the tight mesh, creating small uniform bulges. This is true along the cylindrical portion of the actuator if the balloon is circumferentially oversized and this is true in the spherical caps if the balloon is longitudinally oversized.

When these small bulges reinforced by the fiber are approximated as hemispheres, the stress of this sphere, \( \sigma = \frac{p r^2}{2t} \), is very small because \( r \) is very small (approximately 0.05mm, Fig. 4-4A). When the actuator is undersized longitudinally and oversized circumferentially, the cylindrical length of the balloon presses against the mesh like the case of the oversized actuator, but the cap is exposed and is not reinforced by the mesh. The stress in the cap of the undersized balloon is dictated by a much larger \( r \) (approximately 6mm Fig. 4-4B), resulting in a > 100 fold higher wall stress and a lower maximum pressure before bursting. Similar logic holds for the case of an actuator oversized longitudinally and undersized circumferentially. The balloon needs to be oversized in both dimensions; this ensures minimal strain in the material itself, allowing the balloon to function simply via filling and emptying the volume constrained by the mesh.

![Figure 4-4: Schematic depicting the mechanics of the balloon as a thin walled pressure vessel. The grey arrow, \( r \), represents the radius of the grey circle used to indicate the spherical pressure cap. The black indicates the mesh fibers, and the yellow indicates the Kevlar fixation point.](image)

Additionally, increased wall thickness \( t \) can also decrease the wall stress. However, increasing wall thickness will increase the passive volume of the balloon, displacing potential volume for pressurized air and decreasing the passive length of the actuator (where \( l_{act} < l_{mesh} \)). Unlike oversizing the balloon which yielded a 100x benefit, increasing wall thickness will only yield a linear reduction in wall stress. Ultimately,
this is a limited way to increase the pressure tolerance.

**Tubing Parameters**  The tubing couples the actuator to a pressurized fluidic system. There are two important parameters of the tubing choice, the material and the sizing.

It is critical that the tubing can be coupled to the balloon material with a hermetic seal. Commercially available polyurethane tubing can be bonded to the balloon material via a urethane adhesive (Ure-Bond II, Smooth-On, Inc.).

Tubing sizing will determine both the dimensions of the final driveline connecting the external control system to the internal implanted system and the fluidic resistance. Reducing the size of the driveline ultimately benefits later device translation by reducing footprint of the opening and the risk of infection. The fluidic resistance will determine the speed and time of filling and emptying the actuators. Because the respiratory system operates on a low frequency cycle ($> 0.5 \text{Hz}$) compared to other biological signals and we are using pressurized air, high fluidic resistance that can increase cycle time is not a priority concern. However, if the system moves to use pressurized fluid (which has a much higher viscosity than air), filling and emptying time may become of concern.

**Fixation Points**  Fixation points on a McKibben actuator determine the active contractile portion of the actuator. Fabrication techniques vary [64, 79, 62].

For rapid prototyping, zipties were used in early iterations of actuator development. Although easy to use, zipties ultimately had key limitations that required an alternative solution. First, when tightened down, the ziptie size profile (seen in Fig. 3-3) is large in relation the the dimensions of the actuator. Second, the edges of the ziptie when cut are sharp, removing a key benefit of using soft actuators. And lastly, the zipties are prone to slipping with repeated actuation. The zipties are only held in place via friction, and repeated expansion of the balloon can push the ziptie along the length of the actuator, ultimately changing the contractile length.

A key update to the manufacturing process is to sew the mesh together at the desired fixation points using Kevlar string. This is a superior method to the use of
zipties due to the very small size footprint of the final fixation, the soft nature of the material, and the immovable location, ensuring that the contractile length of the actuator is truly fixed.

**Mesh Characteristics**  The mesh of the McKibben actuator is a critical component that determines many of the functional characteristics of the final actuator. A variety of mechanical models have been used to understand how different parameters affect McKibben actuator performance[66, 63]. As previously established in Chapter 3, McKibben actuators follow the same set of mechanics that govern fiber-reinforced actuators. The fiber angle of the mesh will determine the contracting or extending behavior. The initial fiber angle of the mesh will also determine the maximum amount of contraction of the actuator. For ideal systems, the maximum contraction is independent of internal pressure[80]. The static tensile force is both a function of the internal pressure but also globally proportional to the actuator’s cross sectional area [70] as seen in section 3.1.

Commercially available braided mesh sleeves are used for consistency and ease of fabrication. For the initial actuator development, the same two meshes described in section 3.1 are compared: the 0.25\(in\) and 0.5\(in\) PET mesh.

<table>
<thead>
<tr>
<th>Design Parameter</th>
<th>0.25(in) PET mesh</th>
<th>0.25(in) PET mesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal Size</td>
<td>0.25(in)</td>
<td>0.5(in)</td>
</tr>
<tr>
<td>Minimum Cross-Sectional Diameter</td>
<td>3(mm)</td>
<td>13(mm)</td>
</tr>
<tr>
<td>Maximum Cross-Sectional Diameter</td>
<td>11(mm)</td>
<td>35(mm)</td>
</tr>
<tr>
<td>Contraction Ratio</td>
<td>0.81</td>
<td>0.69</td>
</tr>
<tr>
<td>PET Monofilament Diameter</td>
<td>0.010(in)</td>
<td>0.010(in)</td>
</tr>
</tbody>
</table>

Table 4.1: Table of mesh characteristics for two commercially available braided meshes.

**External Sleeves**  Basic parameters of McKibben actuators are presented above, but additional elements can be integrated for specific functionalities. McKibben actuators can be embedded into an elastomeric matrix for advanced 3D spatial coupling [81],
encased in medical meshes and adhesives for mechanical coupling [82], and wrapped in elastic elements to provide an elastic recoil function [8].

An external elastic sleeve can release stored elastic energy—beyond the amount stored in the actuator mesh structure—when the actuator is being depressurized. For applications such as the cardiac cycle, an external elastic element can improve actuator emptying[8]. Applied to the respiratory cycle, elastic elements have the potential to store energy from pressurization during inspiration and aid expiration. In our initial testing, we explored the effect of the inclusion of a simple latex balloon sleeve on the actuator, seen in Fig. 4-5.

![Figure 4-5: Images of a standard McKibben actuator (top) and a McKibben actuator with an optional black, matte elastic recoil sleeve (bottom).](image)

Optional external sleeves can be selected for desired functionalities. Looking towards chronic implantation, future designs may be interested in integrating smart external surfaces that can provide anti-inflammatory or anti-biofouling properties. Although not explored in this work, previous work has shown the ability to couple a smart hydrogel layer with medical soft robotics[7] that reduces inflammation without changing device function.

**Varied Actuator Design**  In terms of actuator design parameters to vary, we investigate considerations around actuator length, mesh characteristics, and the presence of the elastic sleeve for the application of augmenting diaphragm function.

Initial cadaver testing compared the two actuators shown in Fig. 4-6. The dimensions are controlled for the same total contraction length. Due to the different contraction ratios, the \( l_c \) of the 0.5in mesh is much shorter than the \( l_c \) of the 0.25in mesh. To ensure that the actuators can both anchor to the same arclength dimension, a passive inextensible tail is added to the 0.5in actuator. Two actuators with different
cross-sectional areas were used for cadaver testing, dimensions listed in Table 4.2 and shown in Fig. 4-6.

![Image](image1.png)

(a) 0.25\textit{in} diameter

![Image](image2.png)

(b) 0.5\textit{in} diameter

Figure 4-6: Images of two standard McKibben actuators made with two different mesh dimensions. Both have an optional black elastic sleeve to aid with recoil and emptying. Blue circles depict the actual size of their unpressurized (inner) and pressurized (outer) cross-sectional area. Instead of Kevlar fixation points, these actuators used nylon zipties for fixation points.

Although the two actuators are controlled for total contraction, the greater expansion dimensions of the 0.5\textit{in} mesh has a 3 fold greater pressurized volume than the 0.25\textit{in} mesh actuator. Because the target placement of the actuators is superior to the diaphragm in the thoracic cavity, the pressurized volume of the actuators has the potential to displace lung volume and counteract the mechanical assistance provided by the actuators. This is trade off that must be negotiated with the device design.
4.3 Cadaver Testing

Cadaver testing provides critical information that \textit{in vitro} testing cannot, such as information about spatial constraints, tissue properties, and adjacent physiological systems. Cadaver testing reveals key insights that are necessary to investigate prior to \textit{in vivo} testing.

\textbf{Surgical Procedure} \quad With the aid of our surgical collaborators at Boston Children’s Hospital, cadaver testing enabled the development of a surgical implantation procedure.

We accessed the chest cavity through a midline sternotomy. Next, we opened both plural cavities and placed one soft actuator along the diaphragm curvature on each cavity. To attach the device, we passed each actuator posteriorly at lowest intercostal space to outside the chest cavity and fixed it to the skin using sutures. Then, we fixed the other end to the sternum using sutures and we passed the actuation lines through a separate opening through the skin. Because the swine diaphragm’s posterior attachment extended much further caudally than the human diaphragm, the depth of the posterior attachment proved to be challenging.

After euthanizing, two Yorkshire Swine were used for cadaver testing. The swine were different weights: 40 kg and 60 kg. In the 60 kg animal, surgical implantation was significantly more difficult due to the depth of the attachment of the posterior diaphragm. The surgical procedure proved to be much easier in the 40kg animal, so we concluded that 30-40kg animals are most suitable for \textit{in vivo} testing.
Porcine Anatomy and Actuator Fit  The thoracic cavity of the pig is more oval in the anterior-posterior direction than the laterally oval human thoracic cavity [83]. As a result, the anterior-posterior arc length of the diaphragm is longer, and the posterior attachment of the diaphragm is much deeper caudally in pigs than in humans.

In these preliminary studies, a 25cm actuator can snugly fit the arc length of the diaphragm from the sternum to an anterior attachment. The additional mesh material outside of the contractile length can be used as a buffer for suturing an actuator to fit snugly on the diaphragm. For the 25cm actuator seen in Fig. 4-6A, the attachment sutures were placed in the passive mesh at the ends. For the shorter 0.5in mesh actuator seen in Fig. 4-6B, attachment sutures were placed in the passive mesh at the anterior attachment to the sternum and in the passive, inextensible, nylon tail for the posterior attachment to the rib cage.

Via the sternotomy opening with the anterior side at the bottom of the image and the posterior side at the top of the image, the diaphragm displacement from the actuator was visualized in situ in Fig. 4-7 and 4-8. Visually, we see that the 0.25in actuator generates a greater amount of displacement in the posterior diaphragm (Fig. 4-7B) compared to the 0.5in actuator (Fig. 4-8B). Although the total contractile amount of the two actuators is the same, the contractile length is more evenly distributed for the 0.25in actuator. This greater diaphragm displacement visually reveals a volume of the thoracic cavity that the lungs could fill.

Tensile Force  Another key finding from cadaver testing revealed a key consideration about the mechanics of the rib cage. Actuation of the 0.5in McKibben actuators generated such a large tensile force that from the exterior of the animal, a chest compression like effect was seen as the actuator pulled the sternum and dorsal ribcage together.

This effect can be seen internally when looking at the anterior attachment point of the actuator for the 0.5in actuator (4-8B) compared to the 0.25in actuator (4-7B). In Fig. 4-8B, a portion of the sternum is pulled into the field of view of the camera. This indicates that the tensile force of the McKibben actuator become a key consideration.
The 0.5\textit{in} McKibben Actuators generate a tensile force of up to 200N at full length when pressurized with 20psi (Fig. 3-5), and the 0.25\textit{in} McKibben Actuators generate a tensile force of up to 40N at full length when pressurized with 20psi (Fig. 3-4).

Cadaver testing indicates that 200N of tensile force is far beyond the acceptable bounds for this application, and that tensile force is a parameter that should be
minimized when possible.

**Summary** Overall, cadaver testing guided key design requirements guiding the necessary animal size and appropriate dimensions of the actuator and indicated a need to distribute the contractile length and minimize the tensile force generated. Cadaver testing revealed that the 0.25in actuator design was a more suitable candidate for driving diaphragm displacement. The 0.25in actuator displaces less volume in the thoracic cavity, was more appropriately sized to the arclength of the diaphragm, generated a greater visual volume of diaphragm displacement, and applied less tensile force to the ribcage.

### 4.4 Mechanical Characterization

Instron testing was used to investigate the mechanics surrounding fit, tension, and the addition of the elastic sleeve.

Four different types of actuators were fabricated. We varied the $l_c$: 19cm and 20cm, and we varied the presence of the elastic sleeve. Three actuators of each set of fabrication parameters were tested.

First, using a standard Instron tensile test setup, we investigated the effect of the preload on the tensile force of different actuator. Varying the tensile preload mimics the degree of fit or snugness of the actuator on the diaphragm. The actuators were set to 4 different preload conditions: a "floppy" condition, a 0.1 N condition, 1.5 N and 5 N (Fig. 4-9, left to right). The 0.1N condition was used as a 'zero preload' condition. The floppy condition was generated by first adjusting to the 0.1 N placement, and then decreasing the displacement distance by 1 mm. An electropneumatic control system was used to cycle through square waves set to 5, 10, 15, 20, 25 psi. The actual peak pressure achieved is slightly higher due to the control system.

We find that with increasing preload, all four actuator types behave in a similar manner. This is consistent with the idea that block force generated is independent of length in idealized conditions [63]. We do find that at lower preload, the actuators
with the elastic sleeve generate lower tensile forces. This is attributed to the elastic sleeve reducing the net contraction at any given pressure. At higher preload, the mesh begins to generate a similar effect, reducing the net contraction that can be achieved. This explains why these curves tend to collapse together with increasing preload.

Although tensile force is largely what McKibben actuators are used for, our application for the diaphragm is interested in the force generated in a different direction. As the arclength of the diaphragm contracts, we are interested in the flexural force generated by the muscle. In order to investigate this more application relevant force, we created a modified flexural Instron test setup (Fig. 4-10). One component is from a standard 3-point bend test, and the other is a 3D-printed holder intended to replicate the arclike setup of the diaphragm.

On our custom flexural test setup, varying preload is also investigated. The actuators were set to 4 different preload conditions: a 'floppy' condition, a 0.1 N condition, 0.5 N and 1 N (Fig. 4-11, left to right). The 0.1N condition was used as a 'zero preload' condition. The floppy condition was generated by first adjusting to the 0.1 N placement, and then increasing the displacement distance by 2 mm. The same electropneumatic control system was used to cycle through square waves set to 5, 10,
Figure 4-10: Image of our modified flexural Instron test setup to investigate the flexural force that is generated via pressurization.

15, 20, 25 psi.

Figure 4-11: The effect of increasing the flexure preload with different actuators. To investigate the interaction of the flexural preload and actuator characteristics (contractile length and the elastic sleeve), we investigate the flexural force the actuator can generate via our modified flexure setup shown in Fig. 4-10.

We find the flexural force is independent of length and increases slightly with preload. The actuators with the elastic sleeve also end up generating lower flexural forces. This is attributed to the same effect of the elastic sleeve reducing the net contraction at any given pressure.
The intent of mechanical testing is to determine parameters to optimize for increased flexural force and decreased tensile force, but the presence of the sleeve decreases both flexural and tensile forces for any given pressure. In order to make design decisions to optimize for both increased flexural force and decreased tensile force, we look at the ratio between the flexural force and tensile force for any given pressure (seen in the slope in Fig. 4-12).

Figure 4-12: The flexural force is plotted against the tensile force generated for the same corresponding pressurization.

There is negligible effect of the contractile length, although the slight discrepancy is most likely due to the method of controlling for the preload.

For any given tensile force, we find that the flexural force is maximized without the presence of the balloon sleeve. The elastic sleeve causes an upshift of the pressures required to achieve any given flexural force, ultimately results in a higher tensile force. This informs us that a sleeve that has a high durometer and stores a high amount of elastic energy, like the latex balloon used here, is nonideal. If we aim to integrate in external sleeves for other purposes, such as device-tissue coupling, it is best to seek low-durometer materials.
4.5 First Generation Design

Through a combination of cadaver and benchtop testing, we refined a set of fabrication parameters for the actuators used for in vivo testing, seen in Table 4.3.

From the actuator manufacturing stage, the fabrication protocol is updated to utilize an oversized internal balloon and kevlar fixation points. Cadaver testing reveals appropriate dimensions for the actuator, the benefit of a high $l_c$ distributed along the arclength of the diaphragm, and that the 0.25in mesh is more appropriate applied to the diaphragm. From mechanical testing shows that contractile length is independent of forced generated as long as the actuator fit is controlled and suggests the omission of the elastic sleeve.

Some of the final parameters are minorly adjusted from the tested actuators due to considerations surrounding manufacturing. The fabrication process to seal off the ends by melting the mesh reduces the total length slightly. To ensure a final actuator length that is at least 25cm, the stated mesh length for fabrication is 26cm. The contractile length was set at slightly lower than the tested 19cm to be able to accommodate the animal range of 30-40kg and to leave enough passive mesh for suturing the attachments on both sides.

Ultimately, this set of parameters for a McKibben pneumatic artificial muscle will serve as the actuator design we will use as the first generation of a soft robotic diaphragm assist system.

<table>
<thead>
<tr>
<th>Design Parameter</th>
<th>Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesh Length</td>
<td>26cm</td>
</tr>
<tr>
<td>Contractile Length</td>
<td>18cm</td>
</tr>
<tr>
<td>Balloon Length</td>
<td>20cm</td>
</tr>
<tr>
<td>Air Tubing</td>
<td>1/8” OD TPU tubing</td>
</tr>
<tr>
<td>Expandable Mesh</td>
<td>PET Overexpanded 1/4” mesh</td>
</tr>
</tbody>
</table>

Table 4.3: Table of final actuator parameters
Part III

A Diaphragm Assist System
Demonstrated in vivo
Chapter 5

\textit{in vivo} Model and Study Design

For our \textit{in vivo} testing, we aim to demonstrate the performance of the diaphragm assist system in terms of physiologically meaningful metrics in the setting of varied degrees of mechanical respiratory insufficiency.

The first challenge is instrumenting the system to capture the interconnected aspects of respiratory physiology. As established in Chapter 3, the biomechanics of the respiratory system are governed by a variety of pressures, flows, compliances, and motions. Although many instrumentation systems are available for individual components, a key challenge is integrating the sensing of different parameters into one data acquisition platform. Integrating measurements onto a single computational clock enables the investigation of the interplay between signals, such as studying pressure-volume loops. Prior investigations into soft robotics applied to respiration, such as [39], demonstrate their results through few parameters—such as motion alone—missing out on the interplay of other physiological parameters.

Deploying the instrumentation is integrated into our overall setup and surgical protocol. The cadaver testing reported in Chapter 4 provides a starting point for the development of a surgical protocol. The transition from cadaver testing to \textit{in vivo} testing reveals other additional experimental considerations, such as the animal positioning.

Because our therapeutic strategy is mechanical, the concept of a diaphragm assist system is not specific to any one etiology. As a result, we developed an animal model
designed to simulate three different levels of mechanical respiratory insufficiency within one animal. In this chapter, we present the key methods and considerations used instrument and develop an animal model of varied respiratory insufficiency to allow us to test a soft robotic diaphragm assist system.

5.1 Data Collection and Instrumentation

For the instrumentation, we aimed to understand the biomechanical effect of the device while collecting clinically meaningful physiological data. So, we aimed to instrument the system to record detailed biomechanical respiratory signals, while also taking frequent ABGs to give a clinical picture of the respiratory status. This mix of discrete, continuous, and imaging data is shown in Fig. 5-1.

Figure 5-1: Overview of the in vivo instrumentation.

To capture a whole physiological picture of the animal in our in vivo studies, it
was critical that the continuous data be collected in a uniform and synchronized system on a single clock. We used an 8- or 16- channel PowerLab (PL3508 or PL3516, ADInstruments, Dunedin, New Zealand) for a high performance data acquisition system. We instrumented all of our continuous signals to input into the PowerLab as analog signals; they were all collected at a 1000Hz sampling rate.

5.1.1 Vital Signs

Standard vital sign data were collected based off of the animal facility’s standard equipment. To collect these measurements, the animal was instrumented with a transesophageal catheter (EKG), pulse oxymeter (oxy saturation), carotid arterial sheath (arterial blood pressure), and a capnograph (end-tidal CO₂). This data was read into the animal facility’s veterinary vital signs monitor (SurgiVet, Smiths Medical, Smiths Group PLC). Through the monitor’s Data-Logger port, these four signals were read into the PowerLab system as analog inputs.

5.1.2 Spirometry

Although spirometry is collected on the animal facility’s mechanical ventilator (Dräger, Drägerwerk AG, Lübeck, Germany), there was no clear way to pull the data as a live analog output. As a result, we instrumented the setup with a mass-flow spirometer with an analog output (ESRF-ESF-100NL-02-01-03-N, ES Systems, Psychico, Greece) in line with the endotracheal tube and the Y-tubing connected to the ventilator. Using the manufacturer’s settings, the mass flow rate was converted to a volumetric flow rate in PowerLab, assuming the temperature of the humidified breath was 38°C and at a baseline pressure of 1018 mbar.

This flow rate was integrated with respect to time to yield volume waveforms. A calibration test was conducted with both ends of the spirometer sealed with parafilm to ensure zero flow, revealing that the integration of the noise over time had a positive bias. This linear drift was removed in post-processing in MATLAB by subtracting out a linear regression over time.
5.1.3 Respiratory Pressures

To collect respiratory pressures, latex esophageal balloon catheters (CooperSurgical, Trumbull, CT, USA) were fed into the stomach and the esophagus. The balloons were inflated with 3-6 mL of air. They were connected to a wheatstone-bridge-based pressure transducer (PRESS-S-000, PendoTech, Princeton, NJ, USA) powered by a 9V battery. Prior to each experiment, the precise battery voltage was measured and the sensor was recalibrated.

Because the balloon in the thoracic cavity is placed in the esophagus, it is highly sensitive to cardiac motion and artifacts. In the post-processing of the data, the heartrate for any given segment of data is calculated using either the arterial pressure or pulse oximetry waveform and a low-pass butterworth filter is applied in MATLAB (butter, filtfilt) with a cutoff frequency set to 0.1 Hz lower than the calculated heart rate.

These pressure waveforms give relative pressure data, so the absolute value of these waveforms is not of concern. For any given segment of data, the breath bounds are found via the breath volume waveform, and the average pressure at the breath bounds is set to zero. This allows a clear visualization in the change of the respiratory pressures over the course of each breath.

5.1.4 Control System

Our group has built a custom electropneumatic control system utilizing electropneumatic pressure regulators and valves (SMC Pneumatics, SMC Corp, Tokyo, Japan) controlled by a custom software (Fig. 5-2). The actuation can be set on an automatic cyclic pattern but can also be triggered off an external cyclic signal. The software is designed to allow custom pressure waveforms to be input. The control system can specify a desired waveform via an analog input to the electropneumatic regulators but the regulators are also wired to output an analog signal of the actual pressure waveform produced. This analog signal is connected to the PowerLab system.
Figure 5-2: Schematic of the simulator control system. The desired pressure waveform is generated on a laptop. A microcontroller is used to control the pressure regulator and solenoid valve to deliver the pressure waveforms to the pneumatic artificial muscles actuating the organosynthetic respiratory simulator. From [71].

5.1.5 Fluoroscopy

For a global visualization of the diaphragm motion, fluoroscopy is taken of both the coronal and sagittal planes of motion. Because fluoroscopy is used only for a qualitative overview, it is not synchronized with the rest of the physiological data.

5.1.6 Arterial Blood Gases

Arterial blood gases (ABGs) are a widely used clinical laboratory test to give a snapshot of a patient’s respiratory status. They have great clinical utility, but they are only discrete measurements. Using the animal facility’s blood gas analyzer, blood gases were taken at various timepoints during the experiments. In order to synchronize the time of the ABG with the PowerLab data, we relied on the arterial pressure waveform which indicates when an ABG is taken because the luer-lok coupling to the pressure sensor is briefly disconnected when the ABG is pulled. The time recorded per the ABG machine was used to match each ABG set with the closest time point in the arterial pressure waveform.

Although we hoped the ABGs would give insight on acute respiratory status in a way that directly correlates with the minute ventilation provided by the device, we
found poor correlation and high variation in some of the readings, specifically for the $P_aCO_2$.

We attribute this variation to a few factors.

First, there exists baseline variation within the ABG output analyzer. To examine this, we serially drew 5 ABG samples within a 15 second time period, and then serially analyzed them. In these 5 ABG samples, the $P_aCO_2$ was not consistent across samples and ranged by 2 mmHg. Greater variance was observed in the $P_aO_2$. This inconsistency inherent to the measurement system is one factor that leads to variation in the measurements.

Additionally, the minute ventilation metric we are using is the total volume of ventilated air, whereas the physiological metric that should correlated with $P_aCO_2$ is the alveolar ventilation. Although in most cases, minute ventilation and alveolar ventilation are interchangeable because the effect of dead space is minimal, the low tidal volumes due to the respiratory insufficiency (shown in Chapter 6) lead to a much larger effect of deadspace leading to a larger proportional difference between minute ventilation and alveolar ventilation. Deadspace is also a dynamic value that is composed of a constant anatomical deadspace but also a dynamic physiological deadspace that is itself a function of tidal volume. This factor could be reconciled using data from the $P_aCO_2$, $EtCO_2$, and tidal volumes. Due to the proof of concept nature of this work and the need for further subsequent improvements to the system, this exercise is left as an analysis for future work.

Nevertheless, ABGs served well as an experimental tool to affirm that an animal had appropriately recovered from the prior experimental challenge, and we still recommend the collection and further troubleshooting of this data for future studies.

### 5.2 Clinical Model

Because the diaphragm assist system aims to provide a mechanical solution to respiratory failure, it is not specific to any one disease biology. Instead, this system needs to function for a spectrum of disease. Specifically in the case of neuromuscular
disorders, progressively degenerative disease requires that a solution be functional across a spectrum of disease states. Through this in vivo study, we developed a surgical deployment setup and procedure and a method to simulate a spectrum of respiratory insufficiency within each animal.

Procedures were carried out at Boston Children’s Hospital in accordance with BCH IACUC under protocol #19-05-3907 and MIT IACUC under protocol #0118-006-21. Protocol reviews were conducted in accordance with the standards outlined in the National Research Council’s Guide for the Care and Use of Laboratory Animals and BCH’s Animal Welfare Assurance. The Boston Children’s Hospital PHS Animal Welfare Assurance Number was A3303-01. The USDA Registration Number was 14-R-0020. The AAALAC International Unit Number was 000789.

5.2.1 Overall Surgical Method

We used a total of nine 30-40 kg female Yorkshire swine. Each animal was anesthetized using isoflurane. After the induction of anesthesia, the animal was intubated and placed on mechanical ventilation. A transesophageal EKG was placed to monitor the heart rate. A carotid arterial sheath and jugular venous line were placed using cut-down technique for animal systemic and central venous pressures monitoring respectively. Two balloon catheters were placed, one in the esophagus and one in the stomach, for pressure monitoring. A Foley catheter was placed for urine output monitoring.

Following the setup, the chest cavity is accessed through midsternotomy. Next, both plural cavities are opened and one soft actuator is placed along the diaphragm curvature on each cavity. Each actuator is passed posteriorly at lowest intercostal space to outside chest cavity and fix it to the skin using sutures. Then, the anterior end is fixed to the sternum using sutures and we pass the actuation lines through separate opening through the skin. Next, the sternum is approximated using sternal wires and subcutaneous tissue and skin are closed in layers using sutures. Approximate actuator placement is visualized in a 3D rendering (Fig. 5-3). After data collection and completion of the study, we euthanized the animal using Fatal-Plus Solution
(Vortech Pharmaceuticals, Dearborn, Michigan) at a dose of 110 mg/kg/body weight.

Figure 5-3: Visualization of the placement of pneumatic artificial muscles (PAMs) (in black) superior to the diaphragm in a live pig model.

5.2.2 Animal Positioning

As discussed previously, the pig diaphragm descends further caudally on the posterior side than in humans. Prone positioning results in greater ventilation of the posterior caudal lung regions [84]. Anatomically, the weight of the liver sits on the posterior side of the diaphragm in the supine position, acting as an additional force that the diaphragm must work against. For our study, the supine position of the animal is required due to the sternotomy. To reduce this gravitational load slightly, the animal’s head and thorax was propped up slightly via surgical towels placed underneath a plexiglass board that the animal is on (Fig 5-4). Image analysis of pictures of the elevated setup found that the animals were elevated by $9^\circ\pm1^\circ$.

During one trial, the elevation of the animal’s head was performed during a respiratory challenge. The effect of elevating the animal was seen directly in the volume waveform (Fig. 5-5), raising the average volume from 113 mL to 138 mL. Considering that patient bed heights in the clinic are often maintained at a 30° or higher elevation to prevent aspiration, it is reasonable to simulate a higher degree of elevation as long as the procedure can reasonably facilitate this.
Figure 5-4: Image of elevating the animal using surgical towels to reduce the gravitational effect of the liver. The surgical towels are placed under the head and neck of the animal beneath the plexiglass board seen in the image.

Figure 5-5: Actuation pressure, flow, and volume waveforms. In the time span between 460 and 480 seconds, the animal’s head and chest are elevated from a fully supine to 9° elevation.

5.2.3 Respiratory Challenges

Each study begins with the animal in a stable respiratory state supported by mechanical ventilation. Within each animal, we run a series of respiratory challenges, each separated by a recovery period of at least 20 minute of mechanical ventilation with an ABG to confirm the animal’s return to a stable respiratory state. Respiratory challenges under different clinical models of respiratory insufficiency (discussed in Section 5.2.4) are grouped together and then conducted in order of decreasing respiratory function—respiratory challenges under the baseline isoflurane are conducted first, then the phrenic nerve is severed, and then the paralytic is administered. Within this clinical model grouping, the challenges are conducted in a random order. Each respiratory
challenge lasts between 5 and 20 minutes. Respiratory challenges allow a greater temporal view of the data with an opportunity to see if a steady state is achieved.

There are broadly two types of respiratory challenges that we used: a model of continued support where the animal was switched directly from mechanical ventilation to the diaphragm assist system and a model of interrupted support where the animal underwent a 2 minute period of unsupported ventilation, a generalized schematic shown in Fig. 5-6.

![Figure 5-6: Schematic of two different types of respiratory challenge, a continued support and interrupted support model](image)

**Continued Support**  The continued support model allows the investigation of the device’s ability to maintain a stable respiratory state. Because the compliance of the lung is volume-dependent, switching direction from mechanical ventilation to device assisted ventilation aims to minimize the change in compliance of the lung due to volume change.

**Interrupted Support**  The interrupted support model allows the investigation of the device’s ability to recover from a period of unsupported respiratory insufficiency. This model also allows us a view of the underlying respiratory effort at the beginning
of the trial. This data provides an acute baseline for the data at the beginning of the device assisted ventilation. In conducting these studies, we have seen large variability of the underlying respiratory effort during the unsupported period. Some trials show nearly 2 minutes of apnea, whereas some trials show a small but clear respiratory effort. This variability leads to a range in the amount of recovery time that a given respiratory challenge requires.

5.2.4 Modelling Respiratory Insufficiency

Because our device intervenes at the diaphragm, we aim to more precisely understand the effect of the device both in the context of global respiratory insufficiency and in a state with specifically no diaphragm function. Ultimately, we model three different levels of respiratory insufficiency within each animal: generalized respiratory depression secondary to isoflurane, diaphragm paralysis secondary to injury to the phrenic nerve, and respiratory system paralysis via a systemically administered paralytic (Fig. 5-7).

(a) Respiratory depression via isoflurane  (b) Diaphragm paralysis via severed phrenic nerves  (c) Respiratory system paralysis via a neuromuscular paralytic.

Figure 5-7: Different methods of modelling respiratory insufficiency within one animal. The respiratory depressive effects of isoflurane lead to overall attenuated function of the respiratory system. To model diaphragm paralysis, the phrenic nerve is severed, but accessory muscle function is still preserved. To model full neuromuscular paralysis and no residual respiratory function, cistracurium is administered. Gray shading indicates the period of time where the system is off and respiration is unassisted.
**Isoflurane** The respiratory depressive effects of isoflurane are used as our baseline model of respiratory insufficiency. Isoflurane produces a dose-dependent respiratory depression with an increase in respiratory rate and decrease in tidal volumes that ultimately drive an increase in arterial CO2 pressure [85]. In dogs and rats, isoflurane has been shown to cause a dose-dependent decrease diaphragm activity, as measured by transdiaphragmatic pressure \( P_{di} \) [86, 87].

The increased respiratory rate and decreased tidal volume can be seen in Fig. 5-7A. Within one animal, the dose-dependent nature of isoflurane can be observed (Fig. 5-8). There is a minor change in the animals native respiratory drive between anesthesia at 2.00% versus 2.25%, but there is a much larger drop from 2.25% to 2.50% in this animal. The degree that the device augments volume increases with the decreased respiratory baseline of isoflurane at 2.50%.

![Figure 5-8: The effect of the level of isoflurane on the native respiratory effort. This shows the waveforms immediately before and after turning the diaphragm assist system off, as indicated by the actuator pressure waveform. Actuator pressure, flow, and volume waveforms taken from the same animal at the end of different respiratory challenges. Gray shading indicates the period of time where the system is off and respiration is unassisted.](image)

In our studies, isoflurane was set to 2.00% but titrated up if the anesthesia was too shallow. Because of the interanimal variability in the response to isoflurane, 2.00% does not equate an equivalent level of respiratory depression between animals. As seen here and later in Chapter 6, variance in the underlying respiratory drive is a key variable in the *in vivo* studies that is difficult to control and influences the total
amount of augmentation.

**Severed Phrenic Nerve**  The phrenic nerve is the main nerve that innervates the diaphragm. In order to model diaphragm paralysis, the phrenic nerve was severed during the latter portion of each animal study, if enough time was remaining. This provides a more specific model of diaphragm dysfunction than the global effects of isoflurane. Because the case of the severed phrenic nerve is still conducted under the setting of isoflurane, the model of diaphragm paralysis reveals greater respiratory insufficiency than that of just the isoflurane alone, as seen in Fig. 5-7.

**Neuromuscular Paralytic**  Clinically, neuromuscular paralytics like cisatracurium are sometimes administered to prevent patient-ventilator asynchrony, but are used conservatively due to their potential adverse effects. A zero-function disease state of full respiratory system paralysis is modeled through the administration of cisatracurium. Although this is an unlikely disease state, it is a useful setting to understand the augmentation capacity of the diaphragm assist system.

The administration of a paralytic effectively zeroes out any residual respiratory function. The slight fluctuation in flow seen in 5-7C has the same frequency as the heart rate and is likely a cardiac artifact.

### 5.3 Conclusion

We developed and instrumented an *in vivo* large animal model of varied respiratory insufficiency. Our data collection system integrates key continuous physiological signals—including respiratory flows, volumes, and pressures—in addition to the operation of the actuator control system into a single data acquisition system. There are a few other types of clinically significant data, including qualitative fluoroscopic imaging data and discrete ABG data, that are also collected.

With the aid of our surgical collaborators at Boston Children’s Hospital, we establish an overall surgical protocol for the animal study. We find that animal positioning is a key parameter that can influence the results. Future work must control
for this parameter in the study design, and may find it beneficial to increase the angle beyond the $9^\circ$ reported in this work.

We aim to characterize and demonstrate the performance of the diaphragm assist system in the setting of different degrees of respiratory insufficiency. To this end, we establish three animal models using isoflurane, a severed phrenic nerve, and a neuromuscular blocker, cisatracurium. Due to the interanimal variability in response to isoflurane, future work would benefit from a protocol to control for the level of depression beyond simply the administered dose. Overall, we present the key methods and considerations used to develop and run our *in vivo* experiments to demonstrate the performance of a soft robotic diaphragm assist system in terms of physiological metrics.
Chapter 6

_in vivo_ Demonstration of Diaphragm Assist

Diaphragm dysfunction is a form of mechanical respiratory failure with few treatment options. Severe diaphragm dysfunction necessitates permanent tethering to a mechanical ventilator, which often involves key sacrifices to aspects of patient autonomy and quality of life. There is an urgent need for new therapeutic ventilation options that restore respiratory performance without sacrificing quality of life, especially for those with the most severe cases of diaphragm dysfunction.

Due to the mechanical nature of respiratory failure, implanted soft robotic actuators applied to diaphragm have the potential to mechanically support and augment the function of the diaphragm, as a portable respiratory analog to a left ventricular assist device (LVAD). There is minimal prior work investigating soft robotics applied to the augmentation of respiration; one of the few examples reports a dielectric elastomer sheet used to completely replace an excised diaphragm and generate motion [9, 39]. Contrastingly, the work presented here leaves the native diaphragm intact while demonstrating function in terms of clinically-relevant physiological metrics (ventilation flows, volumes, and pressures) in an _in vivo_ porcine model as opposed to demonstrating diaphragm motion alone.

Here, we demonstrate a diaphragm assist system that functions as an implantable ventilator by using contractile pneumatic artificial muscles (PAMs) to mechanically
augment diaphragm function during inhalation, increasing inspiration. By intervening internally at the diaphragm as opposed to at the mouth or via a tracheostomy, this strategy preserves access to key abilities relating to patient autonomy, like speech and swallowing. As a proof-of-concept, we simulate a range of mechanical respiratory insufficiency within each animal and we demonstrate the ability of the assist system to augment respiratory flows, volumes, and pressures. We also investigate specific metrics of inspiratory function including peak inspiratory flow and transdiaphragmatic pressure[77]. We show that in order to achieve effective diaphragm assistance *in vivo*, the actuation of the assist system must be synchronized to the animal’s underlying respiratory effort. To achieve this, we have built a control system in which actuation is triggered by the beginning of inspiration. Through an analysis of the respiratory waveforms, we investigate the optimal alignment of actuation with the subject’s native respiratory effort. By augmenting diaphragm function in a biomimetic fashion, we demonstrate the replication and augmentation of the native biomechanics of respiration in which a negative pleural and alveolar pressure drives airflow, as opposed to the positive pressure ventilation of standard mechanical ventilation.

### 6.1 Assist Strategy

As described in Chapter 4, our strategy aims to harness the contractile function of pneumatic artificial muscles (PAMs) to mimic and augment the native contraction of the diaphragm.

In contrast to the dielectric artificial diaphragm described by Bashkin, et al.[9, 39], our diaphragm assist system uses a set of two PAMs, leaves the native diaphragm intact, and has a low profile presence (deflated: 5 mL volume, inflated: 17 mL volume). To test this concept in a live porcine model, we surgically implanted a pair of McKibben actuators in an anterior-to-posterior direction lateral to the heart (see Methods). The actuator placement is visualized in a 3D rendering in Fig. 5-3. Fluoroscopy of the diaphragm was taken throughout the experiments. The sagittal cross-sectional view from the fluoroscopy shows the realization of our soft robotic strategy in an in vivo
pig model (Fig. 6-1c).

Figure 6-1: Soft robotic strategy for diaphragm assist. (a) Schematic depicting the sagittal cross-sectional of the native diaphragm anchored to the ribs in a relaxed (left) and contracted (right) state. (b), Sagittal cross-sectional schematic of the strategy to augment diaphragm motion by placing PAMs superior to the diaphragm. The PAM conforms to the relaxed diaphragm in its unpressurized (left) state and pushes the diaphragm caudally in its pressurized (right) state. (c) Sagittal fluoroscopy view of the in vivo porcine diaphragm with pneumatic artificial muscles in an unpressurized and pressurized state. The air-filled balloon of the actuator is outlined with a dashed line and indicated with an arrow. A and P indicate the anterior and posterior direction of the animal.

6.2 Augmenting Ventilation

To evaluate the ability of our diaphragm assist system to augment respiratory function, the subjects were instrumented to collect physiological data, including respiratory flows, volumes, and pressures within the respiratory system. The pressurization of the
soft robotic actuators was controlled via a custom-built control system; the actuation pressure data was input into the same high-resolution data acquisition system as the physiological data.

Ventilation is key to driving CO₂ exchange, so we first examine the flow and volume waveforms as metrics of ventilatory function. Flow is measured by a spirometer. Peak inspiratory flow can be used as a clinical metric of inspiratory function[77], which yields a direct measurement of the effect of the diaphragm assist system. Integrating the flow with respect to time yields a volume waveform over time. The volume of each breath (tidal volume) and its rate (minute ventilation) are the most relevant parameters of directly measuring ventilation. Pressures within the respiratory system, such as pleural and abdominal pressures, reveal information about the respiratory biomechanics that physically drive ventilation and are discussed later in this paper.

To start each study, the animal was anesthetized appropriately with isoflurane and placed on mechanical ventilation. Isoflurane induces a respiratory depression with decreased tidal volumes and increased respiratory rate that ultimately combine to a reduced minute ventilation[85]. The respiratory depression secondary to the isoflurane is used as our baseline animal model of respiratory insufficiency due to hypoventilation. Each subject has a reduced but nonzero respiratory drive and response to CO₂. Mechanical ventilation is used to support the animal throughout the implantation surgery. Within each subject, we introduce a series of respiratory challenges, collecting data during periods of unassisted ventilation (in which any spontaneous respiration is due to the native respiratory drive) and during periods of actuator assisted ventilation. Mechanical ventilation is used to restore and maintain a state of normoventilation after and between respiratory challenges, as described in Chapter 5. To investigate the effect of the diaphragm assist system, a representative respiratory challenge was chosen per subject.

In a vignette from the best responding subject (Fig. 6-2), we show that the assist system has the direct capacity to augment the peak inspiratory flow from 0.18 L/s to 0.59 L/s and the tidal volume from 55 mL to 161 mL. When the assist is resumed after a short period of unassisted respiration, the augmentation effect of the actuation
on the flow and volume waveforms returns rapidly over the course of 2 breaths.

Figure 6-2: A representative, continuous segment of actuation pressure, flow, and tidal volume waveforms from the respiratory challenge with the largest augmentation. Gray shading indicates the period of time where the diaphragm assist system is off and the subject’s respiration is unsupported.

The respiratory drive is a slow but dynamic factor underlying all of the respiratory physiology data. As seen in the first 200s of Fig. 6-3, the respiratory drive visibly increases as the low minute ventilation leads to CO$_2$ buildup. This response to CO$_2$ is dynamic and varies between subjects based on responsiveness to isoflurane. By examining the breaths immediately before and after these transition points (off-to-on and on-to-off), we can examine the direct effect of the diaphragm assist system in terms of augmenting volume and peak inspiratory flow while minimizing the influence of the changing baseline.

This analysis was conducted for one representative respiratory challenge per subject. We see a spectrum of responsiveness to the diaphragm assist system across 5 subjects (Fig. 6-4,6-5). The subjects are ordered from largest change in tidal volume at the start of the challenge to the smallest (best responder to worst responder according to Fig. 6-4b). We find the diaphragm assist system generates much larger respiratory augmentations at the beginning of a trial—when mechanical ventilation support has just been removed, minute ventilation drops suddenly, and the animal’s CO$_2$ state rises rapidly—than at the end of the respiratory challenge when the respiratory baseline is
Figure 6-3: A representative set of actuation pressure, flow, and tidal volume waveforms for one full respiratory challenge. Gray shading indicates the period of time where the system is off and respiration is unassisted.

relatively more stabilized (Fig. 6-4,6-5).

Figure 6-4: Comparison of the average (a) peak inspiratory flow and (b) tidal volume immediately before and after the point where the assist is turned on at the beginning (left two bars per subject) and off at end (right two bars per subject) of the respiratory challenge (indicated by arrows in b) across 5 subjects.

Subject A was much more responsive to the assist system than any other subject. In terms of tidal volume, 4 of the 5 subjects show an augmentation of >30 mL per breath at the beginning, whereas only 1 of the subjects shows substantial augmentation.
Figure 6-5: Body weight normalized minute ventilation achieved during the period immediately before and after the assist is turned on at the beginning and off at the end of the respiratory challenge. The range of normal minute ventilation, as reported by Hannon et al.[15], is indicated by the light green shading; the solid line indicates the mean; the dashed lines indicate the standard deviation.

to the tidal volume at the end. Of the 4 less responsive subjects (B,C,D,E), 3 of them show a mild response at the end while in the worst responder (E), the actuation overall decreased the ventilation metrics (Fig. 6-4,6-5). The worst responding subject demonstrates that poor responsiveness to the assist system may lead to a minimal or even deleterious effect on ventilation metrics.

Body weight normalized minute ventilation is used to compare these results to normal physiology. Minute ventilation is a metric of the ventilation rate, taking into account both tidal volume and the respiratory rate. In a normal, conscious pig, the expected body weight normalized minute ventilation is 198 mL/min/kg ± 41 mL/min/kg with a range of 104 mL/min/kg to 262 mL/min/kg[88]. Actuator assisted ventilation allowed all 5 subjects to reach the lower range of normal physiology, and 2 of the subjects even achieved a minute ventilation corresponding to one standard deviation below the normal mean (Fig. 6-5). However, we note that this minute ventilation is achieved with low tidal volumes and high respiratory rates, which results in a lower alveolar ventilation than the same minute ventilation achieved with high tidal volumes and low respiratory rates.

The assist system applied to subject A displayed augmentation up to 100 mL to reach a maximally achieved tidal volume of 186 mL (normalized tidal volume of 5.8 mL/kg); to reach the mean normal tidal volume reported in the literature would
require augmentation to 326 mL (normalized tidal volume of 10.1 mL/kg)[88].

6.3 Synchronized Actuation

Like with standard mechanical ventilation[89, 90] patient-ventilator synchrony in our system is critical to the ability to augment respiration. Asynchronous ventilation can destructively interfere with the underlying respiratory effort, leading to worse ventilation with assistance than without.

In order to synchronize the actuation of our assist system with the subject’s underlying respiratory effort, we built a control system (Fig 6-7) that can actuate based on the respiratory flow rate. The system uses the spirometry flow sensor as the source data. The flow data is read into our data acquisition system. The associated data analysis software allows a user-set threshold voltage; this threshold voltage was manually titrated (between a range equivalent to 0.01L/s to 0.07 L/s, with a hysteresis between 2-5%) during every respiratory trial to achieve qualitatively good synchronization, as visually recognized by the homogeneity of the real-time flow and volume waveforms. When the flow rate passes this set threshold, a digital pulse is triggered and sent to the microcontroller in our control box. The microcontroller triggers a pre-set actuation pressure waveform of one cycle of pressurization and
depressurization in the electropneumatic regulator, filling and emptying the PAMs with pressurized air (as described in Chapter 5).

Figure 6-7: Schematic of the control system. The spirometry flow sensor data is fed into the data acquisition system; when the flow sensor crosses a set threshold a trigger pulse is sent to the control box which triggers a set pressure actuation curve in the electropneumatic regulator, modulating the pressure inside the pneumatic artificial muscles. A set of idealized waveforms (indicated by the green background) show the mechanism of synchronization.

Our control system can implement both a set, rhythmic control scheme independent of the native respiratory effort or a dynamic control scheme synchronized with the underlying respiratory effort. Due to the phase and frequency mismatch between the independent actuation and the underlying respiratory effort, the mixed interference of the actuator and the underlying respiratory effort can be seen in both the flow and volume waveform (Fig. 6-8,left). Contrastingly, the well synchronized actuation reveals much more homogenous flow and volume waveforms. (Fig. 6-8,right).

Within each subject, we compare the the tidal volumes and peak inspiratory flows in one representative challenge of independent actuation with one representative challenge of synchronized actuation (details in methods). We find that synchronized actuation consistently produces much less variance in the tidal volumes (Fig 6-9). Although in some subjects—such as subject A—independent actuation achieved a few higher maximum tidal volumes, the independent actuation also achieves lower minimum tidal volumes across all subjects due to the misalignment of actuations with the underlying respiratory effort leading to destructive interference or due to actuation
6.4 Alignment of Synchronization with Underlying Respiratory Effort

As seen by the mixed interference in Fig. 6-8, the alignment of the actuation with the underlying respiratory effort will critically determine the constructive versus destructive nature of the interference. In respiratory challenges that had an independent actuation scheme or a poorly synchronized actuation scheme, we found the datasets that provide a natural variation in the timing of the actuation in relationship to the underlying...
respiratory effort.

Because mechanical respiratory failure exists as a continuous spectrum of loss of function, we looked at the implications of synchronization in different levels of baseline respiratory effort. As seen in Fig. 6-4 and 6-5, there is variance in the underlying respiratory function between subjects. To simulate a controlled change in the underlying respiratory function within the same subject, we severed the phrenic nerve in some subjects, simulating diaphragm paralysis in combination with the respiratory depression due to the isoflurane (see Methods).

This section describes the analysis of aligning the actuator synchronization to the underlying respiratory effort for two respiratory challenges within subject B: (1) the subject with preserved diaphragm function (Fig. 6-11) and (2) the subject with a severed phrenic nerve (6-12).

To optimize for maximum inspiratory augmentation, we investigate the relationship of the timing of different waveform features to the resulting tidal volume and peak inspiratory flow of each breath. The high frequency sampling of our data acquisition system (1000 Hz) allows for millisecond temporal resolution. Custom software was written to analyze the actuation pressure, flow, and volume data. Waveform features analyzed include the start of an actuation waveform \( P_0 \), peak inspiratory flow \( F_{pk} \), the start of inspiration \( V_0 \), and the start of expiration \( V_{pk} \) (Fig. 6-10).

We identified the breath bounds as determined by the local minima in the volume waveform (the locations of \( V_0 \)), and then found the time distance between the waveform features for each individual breath (further details in Methods). The distances between different features acted as different metrics of alignment and elucidated what factors are important to consider in optimizing synchronization. Many features were identified from actuation pressure, flow, and volume, but Fig. 6-11,6-12 only depicts the relationship of the actuation pressure curvature to \( V_0 \) and \( V_{pk} \). Although synchronized actuation was dynamic, it used a set pressure profile, in which \( P_0 \) and the peak pressure were a fixed distance in time apart. The relationships seen in Fig. 6-11,6-12 relative to \( P_0 \) also exist when applied to the location of peak pressure (additional analyses can be found in Appendix A). \( P_0 \) and peak pressure are just offset metrics from each other.
Figure 6-10: Representative actuation pressure, flow, and volume waveforms for a single breath. Circles mark features that can be identified from the waveforms. Features include the start of actuation ($P_0$), the start of the pressure drop ($P_{\text{drop}}$), peak inspiratory flow ($F_{pk}$), start of the breath ($V_0$), and peak tidal volume ($V_{pk}$). The dashed lines indicate the time point of each feature. Differences between different time points are labeled at the top of the diagram.

and can both broadly be used to describe the positioning of the actuation curve.

We examine the influence of these time metrics on tidal volume and peak inspiratory flow. We find the most important predictor variables are the set of time metrics related to the start of expiration ($V_{pk}$) as opposed to ($V_0$) as seen in Fig 6-11B-C and Fig 6-12B-C. With diaphragm function preserved, there is a weak linear relationship between $V_{pk} - P_0$ and the peak inspiratory flow ($R^2 = 0.31$, $p<0.001$) (Fig. 6-11B), and no significant relationship to the tidal volume ($R^2=0.04$, $p=0.001$) (Fig. 6-11C). However, when the diaphragm function is removed by severing the phrenic nerve, a clear linear relationship emerges between $V_{pk} - P_0$ and tidal volume ($R^2 = 0.84$, $p<0.001$) (Fig. 6-12B) and a weaker relationship with peak inspiratory pressure ($R^2 = 0.30$, $p<0.001$) (Fig. 6-12C).
Figure 6-11: Representative actuation pressure, flow, and volume waveforms for a single breath from one respiratory challenge with an intact phrenic nerve (b,c) and one with a severed phrenic nerve (d,e). Circles mark features that can be identified from the waveforms including the start of actuation ($P_0$), peak inspiratory flow, start of the breath ($V_0$), and peak tidal volume ($V_{pk}$), and the dashed lines indicate the time point of each feature.

Figure 6-12: Scatter plots of tidal volume and peak inspiratory flow as they relate to the time between $V_{pk}$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (b,c). Scatter plots of tidal volume as they relate to the time between $V_0$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (d,e). All data are taken from the same subject.
Notably, we do not find these relationships when using the timing between the start of actuation and the start of inspiration \((P_0 - V_0)\) as a metric. Positive values of \(P_0 - V_0\) indicate the actuation begins after the breath is initiated by the subject; negative values indicate pre-emptive triggering of \(P_0\) (often the result of setting the flow threshold too low). Within the different clusters in Fig 6-11D-E, no linear relationship emerges. When there is still preserved diaphragm function (Fig. 6-11D-E), we see that negative values of \(P_0 - V_0\) (preemptive triggering) behaves similarly to independent actuation and positive values of \(P_0 - V_0\) behave similarly to synchronized actuation as seen in Fig. 6-9.

The relationships depicted in Fig. 6-12 are replicated in separate respiratory challenges within the same subject (see Appendix A).

### 6.5 Augmenting Biomechanics

To compare the respiratory biomechanics of different modes of respiration and ventilation, pleural pressure \((P_{pl})\), abdominal pressure \((P_{ab})\), and transdiaphragmatic pressure \((P_{di})\)—in which \(P_{di} = P_{ab} - P_{pl}\)—the pressure waveforms are analyzed. Transdiaphragmatic pressure is a metric of diaphragm function[10, 91, 92]. Pleural pressure and abdominal pressure are approximated by a balloon catheter placed in the esophagus and stomach, respectively. Because these balloons are only approximations of \(P_{pl}\) and \(P_{ab}\), the measurements are interpreted as relative measurements and not absolute measurements. When analyzing relative pressure waveforms, the most informative metric is the maximum change in pressure per each breath. Respiratory pressure data was normalized in the MATLAB post-processing. For any given segment of interest, the average of the pressure reading at the breath bounds was set to zero, to allow the analysis to show the change in pressure over the course of one breath.

In Fig. 6-13, we show that across subjects (subject C was not instrumented for pressure measurements, and is therefore not shown), actuator assisted ventilation more closely matches the respiratory biomechanics of spontaneous respiration than in mechanical ventilation. Mechanical ventilation pushes air into the lungs, increasing
pleural pressure with inspiration, whereas both actuator assisted ventilation and spontaneous respiration generate a negative pleural pressure to drive airflow. As the diaphragm is passive in mechanical ventilation, we see negligible change in the abdominal pressure, whereas the caudal movement of the diaphragm in both actuator assisted ventilation and spontaneous respiration increases abdominal pressure.

Figure 6-13: Average change in pleural pressure ($P_{pl}$), abdominal pressure ($P_{ab}$), and transdiaphragmatic pressure ($P_{di}$) per breath under mechanical ventilation (MV), actuator assisted ventilation (AAV), and spontaneous respiration (SR) taken from one respiratory challenge per subject.

In the representative waveforms from subject A (Fig. 6-14)—the most responsive subject—the actuator assisted ventilation not only more closely resembles that of spontaneous respiration, but also augments all of the pressure waveforms ($P_{pl}$, $P_{ab}$, and $P_{di}$). Actuator assisted ventilation generates more negative changes in pleural pressure, greater increases in abdominal pressure, and ultimately greater increases in transdiaphragmatic pressure per breath.

As established in section 3.2.6, the Campbell diaphragm is a graphical technique used to measure work of breathing (WOB) that references pleural pressure with lung volume. Using the pressure and volume data from subject A, we generate the pressure-volume (PV) loops of a Campbell diagram (Fig. 6-15). Work of breathing is calculated from this PV loop as the internal area between the inspiratory edge of the loop and the passive chest wall compliance derived from the mechanical ventilation PV data (as described in section 3.2.6). Normal WOB is 0.35-0.7 J/L[77, 75, 78].

By using the mechanical ventilation data, we estimate the compliance of the chest
Figure 6-14: Representative $P_{pl}$, $P_{ab}$, $P_{di}$, and flow waveforms for mechanical ventilation (left), device assisted ventilation (center), and unassisted spontaneous respiration (right) from one respiratory challenge from subject A. The alternating grey and white background indicates the bounds of each breath.

Wall to be 230 mL/cmH₂O (as seen in the solid black line in Fig. 6-15). This is within the the expected range for both patients with chronic respiratory weakness (117-258 mL/cmH₂O) and healthy patients (163-366 mL/cmH₂O) [76]. As expected, this is much more compliant than the measured compliance of the respiratory simulator (80 mL/cmH₂O) reported in Chapter 3.

During attenuated spontaneous breathing, the subject’s WOB is 0.10 J/L. During actuator assisted ventilation, the assist system shares the WOB and increases the total average WOB to 0.17 J/L, a 66% increase. The shape of the PV loop during actuator assisted ventilation augments the baseline shape of spontaneous breathing.

### 6.6 Actuator-Tissue Interaction

A potential area of concern of the diaphragm assist system is potential damage or unexpected biological responses of the tissue. Because we rely on relatively high pressures and forces, there is the potential for mechanical tissue damage. Visually, after >3000 actuations over the course of a 6 hour animal experiment, there was some
Figure 6-15: Respiratory Campbell diagram plotting the pleural pressure-volume loops for representative breaths from mechanical ventilation (MV), actuator assisted ventilation (AAV), and spontaneous respiration (SR). The direction of inspiration is indicated by the arrow. The compliance of the passive chest wall derived from the MV is indicated via the long-dashed line. Shaded regions outlined by dashed lines indicate the area representative of the work of breathing (WOB).

Macroscopic redness on the diaphragm tissue underneath where the actuator sat (Fig. 6-16).

For further investigation, a sample of the diaphragm muscle tissue was taken from directly below each actuator and also from tissue lateral to the actuators with no actuator contact. Due to the acute nature of these trials, only signs of the beginning an acute inflammatory response can be detected on the hematoxylin and eosin (H&E) staining. Lung and pleural tissue was not taken for histology because it was difficult to isolate which portion of the lung was in contact with the actuator after the deflation after sacrifice. A future study should isolate an appropriate lung and pleural tissue sample prior to deflation.

For the tissue sample taken from directly below the actuator, there is some appreciable difference in inflammation between the histology of the superior surface of the diaphragm (Fig. 6-17, Fig. 6-18A,C) as compared to the inferior surface of the diaphragm. On the surface of the diaphragm in contact with the device, neutrophillic infiltrate penetrates to approximately half the depth of the connective tissue layer on the surface of the muscle. The muscle tissue is normal. When comparing the tissue samples which were in direct contact with the actuators to the tissue lateral to these samples, there is some appreciable difference in inflammation; neutrophillic infiltrate,
Figure 6-16: Image of the redness of the diaphragm tissue in contact with the actuator after >3000 cycles of actuation. The actuator is moved to the side to reveal the redness of the underlying tissue. The medial margin of the redness is highlighted with the two white arrows.

vasodilation, and hemorrhage is noted. (Fig. 6-17, Fig. 6-18A,B).

Overall, the histology reveals signs of acute inflammation in the tissue directly in contact with the actuator. Notably, these studies are sacrificial, non sterile studies, in which a portion of the inflammation is due to the 6 hour response to bacterial contamination alone. When future sterile studies are conducted, this histological analysis should also be conducted again to separate out the tissue response due to mechanical irritation or damage from the bacterial contamination. Due to the acute timeline of the experiment, we cannot draw conclusions on what the long term tissue response to the implanted actuators would be from this data alone.

Looking towards chronic implantation, we predict that the presence of the plain McKibben actuator presented here would cause an effect similar to that of a pleurodesis, an established medical procedure where a chemical or mechanical irritant
Figure 6-17: Hematoxylin and eosin (H&E) histology of the diaphragm at 1x magnification. Samples of tissue are taken from the region of the diaphragm in contact with the actuator for the duration of the study and from a region of the diaphragm lateral to the actuator. The black arrows indicate the surface of the diaphragm in contact with the actuator where one can observe signs of acute inflammation.

is intentionally applied to the pleural space to induce adhesion to reduce pleural effusions[93, 94]. Given this, we have reason to believe that the presence of the actuator in the thoracic cavity can be compatible with long term implantation. One concern that arises is the emergence of a constricting fibrous capsule that would reduce device function.

Previous work from our research group suggests that external surface treatments and smart hydrogel layers can be coupled soft robotic actuators to reduce friction and control the host response[95, 7, 96, 82, 97]. A potential future solution is creating a compressible smart hydrogel layer that controls the size of the fibrous capsule, ensuring the space is still large enough for actuator expansion. This layer could be designed in an axially asymmetric fashion in which a bio-adhesive ensures coupling of the bottom of the actuator to the diaphragm[98].

6.7 Summary and Conclusions

In this work, we use pneumatic soft robotic actuators to support and augment physiological metrics of respiration, demonstrating proof-of-concept. A set of two McKibben-style PAMs surgically implanted superior to the diaphragm are capable of providing mechanical support to the diaphragm in a large animal model of respiratory insufficiency.
Figure 6-18: Hematoxylin and eosin (H&E) histology of the superior and inferior edges of the diaphragm at 10x magnification. Samples of tissue are taken from the region of the diaphragm in contact with the actuator for the duration of the study and from a region of the diaphragm lateral to the actuator.
We report varied responsiveness to our soft robotic system between subjects, with one subject (A) showing a strong and substantive response in the peak inspiratory flow (a direct metric of inspiratory function), and tidal volume and minute ventilation (metrics of ventilation). Subject A had the highest change in peak inspiratory pressure, tidal volume, and minute ventilation; the corresponding large augmentation in peak inspiratory pressure indicates that the volume and minute ventilation augmentation are specifically due to the soft robotic actuators augmenting the diaphragm’s inspiratory function.

Future work aims to further understand what factors in system design and implantation can replicate such high responsiveness. Factors such as precise actuator placement, actuator fit, and anatomical variations are all potential directions to explore.

Our system could generate the low end of acceptable minute ventilations, but relied on high respiratory rates to do so. Due to the ventilation of dead space, this results in less alveolar ventilation than if the same minute ventilation achieved with higher tidal volumes and a lower respiratory rate. A core goal of the next generation system is to further improve the tidal volume augmentation. As the field of soft robotics advances, a more sophisticated actuator type may allow for further increases in tidal volumes in future work. Other factors in actuator design, such as the number, layout, and positioning of actuators, will also be critical.

We show that synchronization with the native respiratory effort is a critical design element in our system. Like standard mechanical ventilation, off cycle actuation of the actuators can lead to a destructive interference with the underlying respiratory effort. Synchronous actuation is key to consistent, low-variance respiratory waveforms and tidal volumes. When we actuate the system independent of the baseline respiratory effort, we see a range of mixed interference due to the phase mismatch.

The control system used in this study was a simple but effective first-generation system with many directions for improvement. In order to achieve consistent assistance from breath to breath, the synchronization must be optimized for the alignment that maximizes constructive interference. The system relied on a manually titrated threshold.
set for the flow sensor data. It is designed to be triggered at start of an inspiratory flow effort, which is related to $V_0$. However, the manual nature of the system meant that if the threshold was set too low, noise in the flow signal could cause pre-emptive or false triggering (as evidenced by the negative values for $P_0 - V_0$). Flow is an easily instrumented signal for triggering in this study, but it is a very downstream signal of the respiratory system. Using a more upstream signal (such as neuromuscular signals) would allow for a more robust control system.

An ideal smart control system should be automated, to remove the error that can result from manual titration. Our alignment analysis reveals two important considerations for improvements towards this goal.

The first consideration is that the influence of alignment changes with the degree of preserved respiratory function, as seen with the difference in results between the intact and severed the phrenic nerve. When the phrenic nerve is severed, all diaphragm motion is governed by the actuators, and misaligned actuation with the remaining native respiratory effort—expansion of the ribcage—results in more consequential destructive interference. Whereas when the phrenic nerve is intact, the net diaphragm motion results from a combination of native diaphragm function and the effect of the actuators, because the actuators only operate along 2 discrete lines on the diaphragm. The contraction of the rest of the native diaphragm motion is still synchronized with the ribcage motion, so the effects of misalignment are less apparent. This implies that optimal alignment parameters may be different for different disease states and the control system will need to be dynamic and adaptive to changes in respiratory function, even within the same patient.

The second consideration is that the actuation curve’s relationship to the beginning of expiration ($V_{pk}$) is more influential than the relationship to the beginning of inspiration ($V_0$). This implies that an updated system should trigger off of a signal related to expiration as opposed to the beginning of inspiration.

Future work lies in building a next generation control system; this includes triggering off of a more upstream signal, creating a system that is cognizant of $V_{pk}$ as opposed to $V_0$, and further investigation of dynamic actuation curves.
Ultimately, we show that the strategy to augment the native function of the diaphragm with soft robotics acts as a form of negative pressure ventilation by driving ventilation through the generation of a negative pressure in the thoracic cavity. Our diaphragm assist system is biomechanically similar to that of spontaneous breathing, sharing a substantial portion of the work of breathing in our best responding subject. By functioning as an assist device—as opposed to completely overtaking breathing—our system has the potential to be compatible with voluntary use of the diaphragm. Maneuvers such as voluntary deep breaths or drinking through a straw—abilities related to patient autonomy and quality of life—can be preserved with this implantable ventilator strategy.

Additionally, in contrast to current modes of mechanical ventilation, recapitulation of native biomechanics, as shown with this system, can avoid the deleterious effects that arise secondary to the use of positive pressure ventilation, such as barotrauma[99, 100] or hemodynamic changes in patients with concurrent cardiac pathologies[101, 102].

Although this technology requires further advancements in the net tidal volumes it can generate before it can fully match the ventilation capacity of a current mechanical ventilator, it is the first study to report the ability to rescue ventilation with an implantable ventilator. Motivated by the encouraging results of this study, we believe this technology, with optimized design, has the potential to provide a radically different ventilation technology that preserves key metrics of quality of life for people with end-stage mechanical respiratory failure.
Chapter 7

Conclusions and Future Outlook

In this thesis, we present the work done towards building the foundation of a diaphragm assist project, from the exploration through to the proof-of-concept stage. The journey has been nonlinear, as much of engineering is. Our efforts in exploring the interface of soft robotics and the respiratory system reveal insights not only for this project, but also for other projects in the research group. The physiological nature of the data and results from this work distinguishes our work from previous investigations into soft robotics and respiration.

7.1 Summary and Contributions

In Part I (Chapters 2 and 3), we explored the abilities of different types of soft robotic actuators to simulate diaphragm motion and diaphragm biomechanics. From this investigation into biomimicry, we found that McKibben pneumatic artificial muscles serve as accessible, easy-to-fabricate, contractile actuators that can drive work of breathing in a respiratory simulator. In Part II (Chapter 4), we explored the alternative application of these actuators towards diaphragm assistance. Through a combination of cadaver and in vitro characterization, we settled on a final actuator design to use for in vivo testing. In Part III (Chapters 5 and 6), we presented the experimental design of an in vivo experiment establishing the proof-of-concept of a diaphragm assist system.
In Chapter 2, we presented a technology update to fiber reinforced actuators that arose out of our pursuit of biomimicry. By introducing a new boundary condition, $\psi^{(0)}$, to the optimization algorithm to ‘mechanically program’ fiber reinforced actuators, we opened up the use of this technology to a wide range of initially bent trajectories, such as the dome of the diaphragm. Within this work, we updated the theoretical framework and provided experimental validation for this model. We established that this update improves both the accuracy of the optimization and the pneumatic efficiency of these actuators. As a whole, this is a significant contribution to the field of soft robotics and the mechanics of predicting the motion of these nonlinear bodies. In the process of this development, we found that these actuators were more suitable for replicating active expiration rather than inspiration due to their low fiber density and their greater stability in extension rather than contraction. Ultimately, we found that this high fidelity motion replication was not sufficient for simulating the contractile function of the diaphragm that drives respiration.

In Chapter 3, we presented our work in creating an organosynthetic respiratory simulator that drives respiration via soft robotic contractile elements. First, we compared two accessible pneumatically driven contractile actuators, FOAMs and McKibben PAMs. We choose the positive-pressure-driven PAMs over the vacuum-driven FOAMs for their force generation, ease and consistency of fabrication, and the increased availability of pneumatic regulators over vacuum regulators. These high force McKibben PAMs are used to drive the diaphragm in our tunable respiratory simulator. They were capable of generating a normal range of respiratory pressures, flows, and work of breathing. The tunable nature of the simulator allowed us to explore the interconnectedness of the different elements of the respiratory system—such as the compliance of the chest wall, lungs, and abdominal cavity—and their effects on respiratory pressures, flows, and volumes. From a review of the literature, we believe no other respiratory simulator has previously replicated biomechanics to this fidelity. This simulator established functionality as an educational tool and has the potential to be used as a biomechanical research test bed.

After exploring the development of respiratory simulators with different actuator
types, we chose McKibben PAMs as a promising actuator type to apply towards diaphragm assist. Chapter 4 was dedicated to the investigation of different McKibben actuator design parameters. We updated the McKibben fabrication process with a better fixation methodology with Kevlar and appropriate balloon sizing to increase the overall force generation and maximum pressure. In the cadaver testing, we found that actuators that are contractile along their entire length with low inflated volume and low tensile force are ideal for this application. We mechanically characterized variations of actuator designs and find that the omission of an external elastic sleeve optimizes the ratio of the desired flexural force to the undesired tensile force. From this analysis, we settled on a first generation actuator design for the diaphragm assist system.

In Chapter 5, we presented the work behind instrumenting and developing an appropriate animal model for \textit{in vivo} testing. We described the instrumentation of key physiological metrics, like respiratory flows, volumes, and pressures, so they could be recorded into the same data acquisition system as the actuation pressure from the electropneumatic controls and the vital signs from the animal facility instrumentation. We also discussed the collection of arterial blood gases (ABGs) and the limitations of their use in our study. In order to study the performance of the assist system in a spectrum of respiratory insufficiency, we presented the design of the animal trials and the different methods of simulating respiratory insufficiency. By using the respiratory depression secondary to isoflurane, diaphragm paralysis due to the severed phrenic nerve, and respiratory paralysis induced with cisatracurium, we generated three distinct levels of respiratory insufficiency within a single animal experiment. This provides the foundational experimental guidelines of how to setup future \textit{in vivo} studies.

In Chapter 6, we present the proof-of-concept of a soft robotic diaphragm assist \textit{in vivo}. We demonstrated the ability of the actuators to synchronize with the native respiratory effort and augment respiratory flows and volumes. In a model of respiratory insufficiency, the system managed to support the animal’s ventilation by generating the low range of normal minute ventilations, but did so using tidal volumes below the
range of normal. We found that the timing of the actuation of the system in relation to the start of expiration was more important in relation to the start of inspiration. Timing had a greater effect in the animal model with less diaphragm function. The diaphragm assist system replicated a more biomechanically similar pressure profile than that of mechanical ventilation, showing the ability to double and share the work of breathing with the native respiration effort. To our knowledge, this is the first work that demonstrates the application of soft robotics to diaphragm support via augmentation of physiological metrics like flows and pressure.

### 7.2 Suggestions for Further Research

In the development of this proof-of-concept system, we have established an initial starting point for future research projects. In Chapter 6, we show the system’s key limitation in managing the subject’s ventilatory status is the limited tidal volume augmentation. To achieve a system that can manage and control hypercapnia, the system will need to be able to generate a much larger degree of tidal volume augmentation. Below, we provide a list of additional research directions to move the development of this system forward.

**Next generation respiratory simulator** Although we have established a biomechanically robust respiratory simulator in terms of variable compliance, there still exist application-specific limitations that have prevented the use of the respiratory simulator for rapid prototyping of actuators for the diaphragm assist system. There are practical limitations to the current simulator, such as the time it takes to take apart the model to make changes to the diaphragm (on the order of an hour), or the lack of realistic attachment points such as artificial ribs that reflect the tensile force considerations shown in Chapter 4. Additionally, a benchtop model is only useful for prototyping if changes in device design will reflect similarly between the simulator and *in vivo*. Otherwise, optimizing device design on the model may simply reflect limitations of the model itself. Given the shear mass of data collected from *in vivo*
studies in Part III, we suggest the creation of a next generation respiratory simulator that installs practical user interface updates—like a new access system and mock ribs with realistic mechanical properties—and subsequent validation of the simulator by tuning the setup to replicate in vivo data. This would enable rapid prototyping of actuator designs and parameters towards increasing the tidal volume augmentation.

**Actuator optimization** Due to their well-studied mechanics and accessible fabrication, McKibben actuators proved to perform well as a proof-of-concept design choice. Further investigation should go towards both understanding what parameters would increase the performance of McKibben actuators and exploring other soft actuator types that may provide better suited for this task. Parameters that may affect the performance of McKibbens include the positioning, quantity, material choice, and dimensions of the actuators and the preload or "snugness" of the actuators upon implantation and deployment. Other potential actuator types that may be worth exploring are flat PAMs or cable based soft actuators. Flat PAMs—that only expand in 2D rather than the 3D expansion of McKibbens—could provide greater diaphragm coverage while minimizing volume that displaces potential lung expansion. Cable-based soft robotics remove the entire problem of the expanding volume of PAMs that displaces potential lung expansion. With so many potential design directions for actuator improvement, a high fidelity rapid prototyping bench top simulator will be critical for this next step.

**Control system optimization** Triggering the actuation off of the flow waveform proved an effective method to generate synchronized actuation. However, flow is a noisy downstream signal, which builds in an inherent delay in the control system. A more robust triggering mechanism would rely on a more upstream signal, such as intent to breathe, as measured via the neural activity to the respiratory muscles. This could be integrated into the system via a surface electrode (measuring intercostal EMG) or implantable electrodes (measuring phrenic nerve activity or accessory muscle EMGs). Additionally, our timing alignment analysis in Chapter 6 established that
timing relative to the start of inspiration had a greater effect than the timing relative to the start of expiration. This could be integrated via a more complex closed loop control system that varied actuation timing and patterns relative to the input neural activity. Because the respiratory system is semi-voluntary, a more advanced control system will be necessary for the integration of more complex maneuvers, such as speaking, deep breathing, or coughing. Investigations into more advanced control systems will not only improve the diaphragm assist device but may also reveal insights into the general field of synchronizing artificial ventilation with native respiratory efforts.

7.3 Final Conclusion

This project has opened the door to many new research questions including those described above. In this work, I have explored the first few branches of the path towards an alternative ventilator. Through an investigation of the interplay between soft robotics and respiratory physiology, we begin to uncover the mechanisms at play as we demonstrate the potential of this technology to be used as an alternative treatment modality for patients in need of ventilatory support. This thesis ultimately represents the foundational work towards developing a first-of-its-kind implantable ventilator.
Appendix A

Replicated Synchronization Alignment Data

As stated in section 6.4, the timing relationships depicted in Fig. 6-12 hold true beyond just the case depicted.

A.1 Using Pressure Features as Alignment Metrics

As previously discussed, there are many different features from the waveform data that can be used as markers in our timing analysis. Within the actuation pressure waveform, we can identify two different features: \( P_0 \) and \( P_{\text{drop}} \), as defined in Fig. A-1.

Figure A-1: Schematic of the actuation pressure waveform with two identified features. \( P_0 \) represents the beginning of the rise of the actuation pressure waveform and \( P_{\text{drop}} \) represents the beginning of the drop of the actuation pressure waveform.

Because of how our control system was designed, \( P_0 \) and the point of the initial
pressure drop ($P_{drop}$) were a fixed distance in time apart. They represent a constant time shift from one to the other. The relationships seen in Fig. 6-12 (reproduced below as Fig. A-2) relative to $P_0$ also exist when applied to the location of $P_{drop}$ as seen in Fig. A-3.

![Figure A-2: Replicated Fig. 6-12. Scatter plots of tidal volume and peak inspiratory flow as they relate to the time between $V_{pk}$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (b,c). Scatter plots of tidal volume as they relate to the time between $V_0$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (d,e). All data are taken from the same subject.](image)

All breaths within a respiratory challenge relied on the same set pressure actuation curve with the same timing. $P_0$ and peak pressure are just offset metrics from each other and can both broadly be used to describe the positioning of the actuation curve. Between Fig. A-2 and Fig. A-3, we see a consistent 600ms shift in the data. Although there is some variation in the data between these two plots, the overall pattern remains the same. If the system were updated to utilize a dynamic actuation control in which the actuation curves within a respiratory challenge were dynamic, these relationships would not hold as directly $P_0$ and $P_{drop}$ as seen here.
Figure A-3: Scatter plots of tidal volume and peak inspiratory flow as they relate to the time between (b,c) $V_{pk}$ and $P_{drop}$ for the same respiratory challenge as A-2 with a severed phrenic nerve. Scatter plots of tidal volume as they relate to the time between (d,e) $V_0$ and $P_0$ for the same respiratory challenge. All data are taken from the same subject.

A.2 Replicated Data Between Respiratory Challenges

Additionally, the patterns shown in A-2 are replicated not only when viewing a different timing metric, but also replicated in a duplicate respiratory challenge within the same subject. Here, we present the replicated findings of the relationships between alignment and peak flow and tidal volume in the case of the severed phrenic nerve for two different respiratory challenges within the same subject: Fig. A-2 and A-4.

Although Fig. A-4c,d contain two outliers, overall this respiratory challenge reproduces the main finding of Fig. A-2: the importance of $V_{pk}$, especially in the case of the severed phrenic nerve. The replication of this data within a separate respiratory challenge within the same subject reinforces this finding.
Figure A-4: Scatter plots of tidal volume and peak inspiratory flow as they relate to the time between $V_{pk}$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (b,c). Scatter plots of tidal volume as they relate to the time between $V_0$ and $P_0$ for one respiratory challenge with a severed phrenic nerve (d,e). All data are taken from the same subject as Fig.
Bibliography


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