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High Efficiency Asymmetric Membranes for Extracorporeal Membrane
Oxygenation

by

Torin Yeager

DISSERTATION

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of the

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a life support technology capable of providing full replacement of respiratory and, if necessary, cardiac function. ECMO allows a patient to remain hemodynamically and metabolically stable while recovering from acute respiratory distress or surgical intervention, or while awaiting a lung transplant. In essence, ECMO provides time to heal.

In its simplest form, an ECMO circuit withdraws blood with low oxygen content and high carbon dioxide content from the body and passes it over a gas exchange membrane. A continuously flowing gas supply, or sweep gas, flows on the opposite side of the membrane from the blood. The gas concentration gradients existing between the blood and sweep gas enables diffusive transport of oxygen into the blood (oxygenation), while carbon dioxide diffuses out of the blood (ventilation). The oxygenated and ventilated blood is returned to the patient's systemic circulation, where it can satisfy the metabolic needs of tissues and organs.

While a number of vital components comprise an ECMO circuit, including blood pumps, heat exchangers, and blood-contacting tubing, the most critical part is the oxygenator, which contains the gas exchange membranes and guides blood flow in contact with the membrane surface.

Current clinically used oxygenators typically employ hollow fiber membranes; blood flows around bundles of thousands of individual membrane fibers while sweep gas flows through the fiber lumens. This design provides a large cross-sectional area for the blood flow, with millions of potential paths for red blood cells to pass through the interwoven plastic fibers, resulting in a

low pressure drop and correspondingly low fluid shear stress through the oxygenator. However, this design consequently allows blood to follow a path of least resistance through the oxygenator, leading to incomplete utilization of the gas exchange capability of all hollow fibers. This inefficiency requires the use of excessive membrane area, on the order of 1 m^2 , to meet the gas exchange requirements of adult patients.

The purpose of the work outlined in this dissertation is to evaluate an alternative gas exchange membrane, in which a micron-thin polydimethylsiloxane (PDMS) film is mechanically supported by a silicon micropore membrane (S μ M) with highly uniform pore geometry and distribution. The PDMS-S μ Ms revisit some of the earliest work on membrane oxygenators using new technologies derived from the semiconductor industry and the field of soft lithography to create a robust, planar gas exchange membrane. These membranes allow rapid gas exchange per unit area and also open the possibility for new oxygenator geometries in which blood flow is tightly controlled, as in the alveolar capillaries of the native lung, enabling highly efficient gas exchange in parallel plate oxygenators with surface areas less than one tenth of existing designs. Using microfabrication techniques, I fabricated an oxygenation membrane consisting of a $4.63 \text{ }\mu\text{m}$ thick PDMS film supported by a rigid S μ M with 500 nm wide rectangular pores, which provided a planar gas exchange surface without the need for structural supports in the blood channel, capable of tolerating transmembrane pressure loads of 76 cmHg . Membrane mass transfer coefficients for oxygen and carbon dioxide were measured to be 5.49 ± 0.89 and $31.76 \pm 0.80 \text{ mL STP min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$, respectively. As a proof of concept, full oxygen saturation of porcine whole blood was achieved in a miniaturized *ex vivo* circuit for 3 hours without formation of gross clots, as well as demonstration of respiratory assist in a live ovine model, with an observed maximum oxygen exchange with blood of $1.94 \pm 0.02 \text{ mL min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$.

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Chapter 1: History of Gas Permeable Membrane

Development for Extracorporeal Membrane Oxygenation

This chapter has been accepted for publication in *Artificial Organs* as “Evolution of Gas Permeable Membranes for Extracorporeal Membrane Oxygenation”.

1.1 Introduction

Extracorporeal membrane oxygenation (ECMO) is a life support method used to oxygenate blood and ventilate carbon dioxide without the need for functioning native lungs. In its simplest form, venous blood with low oxygen and elevated carbon dioxide content is withdrawn from the patient, flowed across a membrane oxygenator to exchange oxygen and carbon dioxide between the blood and a sweep gas, and then returned to the body^{1,2}. ECMO is capable of maintaining healthy organ function, allowing a patient to survive and heal from cardiopulmonary surgery, traumatic injury, infection, or inflammation of the lungs over periods of hours to weeks. ECMO is also used as a bridge to lung transplant^{3,4}, allowing patients to maintain stable blood gas levels and, perhaps equally importantly, to remain awake and ambulatory^{5,6} while awaiting a donor organ. ECMO technology has advanced considerably since the earliest development on artificial lungs began in the 1930s⁷, including revolutionary and evolutionary improvements in blood pumps, tubing, gas exchangers, and surgical practices. This review will focus on the evolution of the core component of modern ECMO, the oxygenator membrane, and the future of this technology. As summarized in Table 1.1, oxygenators have progressed from exposed blood films, to sandwiched parallel membrane arrays, to dialyzer-like hollow fibers, to microfluidic

capillary systems that mimic the physiology of the alveoli in the native lung. All of these technologies, with their inherent strengths and weaknesses, have made vital contributions to the field of extracorporeal life support that can inform future oxygenator designs.

Table 1.1. Summary of technical and clinical milestones in ECMO.

Year	ECMO Milestone	Reference(s)
1954	First cardiopulmonary bypass, using blood film directly exposed to atmosphere.	7,8
1955	Blood oxygenation demonstrated using sheets of polymer membrane between blood and sweep gas (parallel plate oxygenator).	9,10
Early 1970s	Introduction of hollow fiber oxygenators, derived from renal dialyzers.	11
1972	First successful clinical use of ECMO.	12
Mid 1980s	Development of hollow fiber oxygenators with extraluminal “cross-flow” of blood.	13
Late 1990s-present	Research begins on microfluidic oxygenators.	14-16

1.2 Early development of gas exchange membranes – 1950s-1960s

The first successful cardiopulmonary bypass was performed on a human patient in 1954 by John Gibbon, Jr.⁸. Venous blood was drained from the patient using finger cot pumps and cascaded down a rotating cylinder. The centrifugal force exerted on the blood caused it to spread into a thin film on the interior surface of the cylinder, where it was directly exposed to an oxygen-rich atmosphere, as shown in Figure 1.1; fully oxygenated blood was returned through an arterial cannula. The product of more than two decades of development⁷, the heart-lung machine was designed to provide gas exchange while open heart surgery was performed, typically lasting less than one hour. This groundbreaking system informed much of the preliminary work in extracorporeal life support.

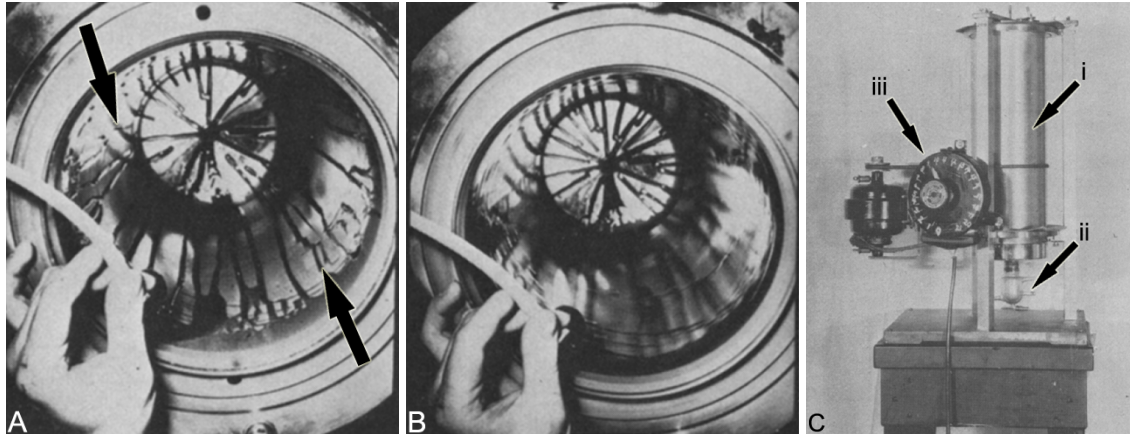


Figure 1.1. Gibbon blood film oxygenator. A) Blood flowing down the cylinder in rivulets (indicated by arrows) when the cylinder was stationary. B) Blood film produced by rotating the cylinder. C) The first oxygenator used, showing the revolving cylinder (i) and the stationary cup (ii) at the bottom that returned blood to the patient. The rheostat (iii) controlled the rate of revolution of the cylinder. Adapted from Gibbon⁷.

As had been witnessed earlier by Gibbon and colleagues, researchers seeking to develop new oxygenators found that direct exposure of blood to atmosphere, whether in a rotating cylinder, rotating disc¹⁷, screen cascade¹⁸, or bubbling system¹⁹, would cause foaming of the blood. The foaming action led to blood trauma and loss of blood products during and following oxygenator usage^{19,20}. While brief atmospheric exposure could be accommodated during cardiopulmonary bypass, the rapid consumption of blood products and risk of arterial gas emboli during life support sessions greater than several hours generated demand for new oxygenator designs. Seeking to eliminate the blood-gas interface in oxygenators, Clowes and colleagues performed pioneering work in the use of plastic sheets for gas transfer in a parallel plate, or sandwich, geometry⁹. Several plastic films were tested as diffusion membranes between a pure oxygen

supply at 760 mmHg and a reservoir of continuously mixed blood. One such polyethylene film, of 25 μm thickness, was capable of transferring $11.2 \text{ mL O}_2 \text{ m}^{-2} \text{ min}^{-1}$; although thinner polyethylene films were capable of higher gas exchange, contemporary manufacturing techniques produced pinhole defects that allowed oxygen bubbles to enter the blood channel ⁹. Clowes later demonstrated successful oxygenation via diffusion through 25 μm thick ethylcellulose membranes in a 6 m^2 stacked parallel plate system¹⁰, providing oxygen exchange of $14.6 \text{ mL O}_2 \text{ m}^{-2} \text{ min}^{-1}$. However, ethylcellulose allowed water to seep into the gas channel, and the brittle material was difficult to support mechanically. The pressure of the sweep gas was used to control the separation distance between two plates and adjust the height of adjoining blood channels, but excessive gas pressure often resulted in emboli in the blood channel. While contemporary artificial lungs relied on Teflon and silicone rubber in flat sheets or tubes due to availability of preexisting industrial materials, in 1969 Galletti and colleagues proposed that blood flow could be more closely controlled by machining capillary channels into the membrane sheets²¹. A parallel capillary channel pattern could be imprinted on a microporous substrate by rollers, then skinned with a 10 μm thick silicone film; such silicone-coated fabric sheets were suggested to provide mechanical strength to thin but fragile membranes²². Technical challenges that could not be adequately addressed at the time included maintaining the desired plate separation, which allowed blood shunting to poorly oxygenated regions, and water condensation on the microporous substrate that limited gas exchange. In order to overcome material defects and resulting gas embolism in 76 μm thick silicone films supported by Dacron and fiberglass meshes, Kolobow and colleagues employed a hypobaric oxygen sweep gas²³ in a spiral-wound parallel plate membrane oxygenator, as shown in Figure 1.2. Blood could then leak through any membrane holes into the lower pressure sweep gas

chamber, rather than allowing gas bubbles to infiltrate the blood channel. This improved the safety of the device at the cost of a decreased oxygen partial pressure gradient across the membrane; using a membrane surface area of 1.2 m^2 with sweep O_2 pressure of 500 mmHg provided a gas transfer rate of $82 \text{ mL O}_2 \text{ m}^{-2} \text{ min}^{-1}$. Since the oxygenator did not feature fixed structural supports in the blood channel, the channel height could be dynamically varied around a mean height of 80 microns by fluctuating the sweep gas pressure, which mixed the blood and improved gas exchange when compared to static channels. Later developments enabled the coating of $13 \text{ }\mu\text{m}$ silicone rubber on microporous fabric substrates to provide greater gas transfer²².

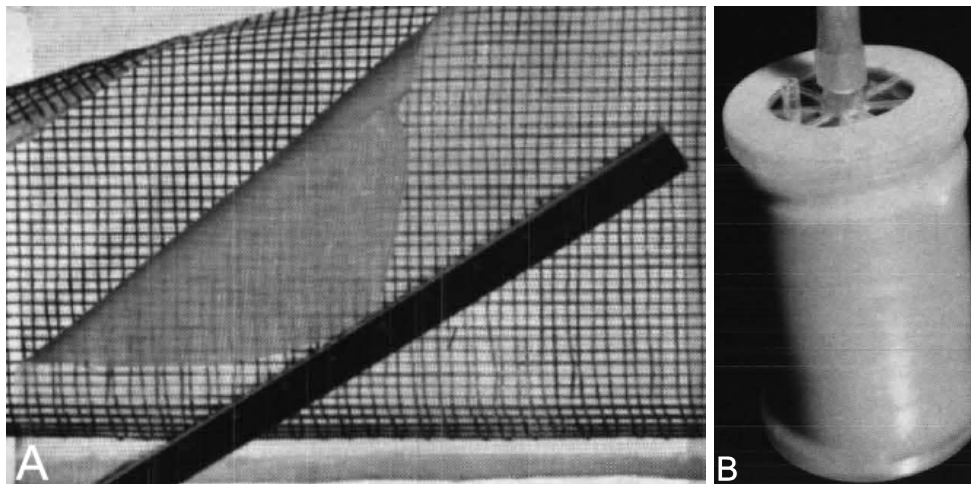


Figure 1.2. Kolobow cylindrical oxygenator. A) Silastic coated Dacron screen with fiberglass supporting screen used for gas exchange membrane. B) Assembled cylinder oxygenator consisting of wrapped layers of silastic coated Dacron and fiberglass. Adapted from Kolobow²³.

Despite the promising gas exchange performance of the early membranes, the manufacturing processes were not yet optimized, resulting in inconsistent performance⁹. Clinical adoption was

also limited by the time consuming preparation and cleaning processes required for operation and reuse of oxygenators.

1.3 Parallel plate optimizations and the rise of clinical ECMO – 1960s-1970s

In an effort to produce a clinically useable membrane oxygenator, the Bramson lung was developed as a 6 m² parallel plate system comprised of 15 individually transfused blood channels, shown in Figure 1.3. The blood channel was enveloped by 51 µm thick reinforced silicone sheets to form concentric gas and water chambers, which oxygenated and heated the blood, respectively^{24,25}. The surrounding water chamber had the added benefit of compressing the plates to control blood channel height without requiring adjustment of sweep gas pressure.

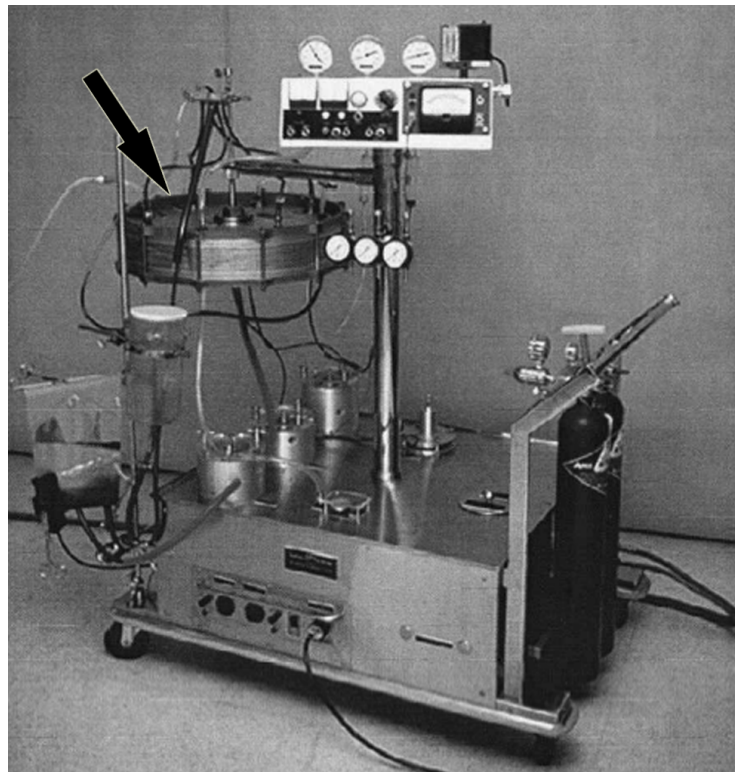


Figure 1.3. Bramson membrane heart-lung machine, adapted from Schulte²⁵. The stacked parallel plate oxygenator, with total surface area of 6 m², is indicated by the arrow.

A similar clinically-scaled device, the Landé-Edwards oxygenator, shown in Figure 1.4, utilized silicone copolymer membrane sheets to form a stack of 58 parallel plates with 3 m² total membrane area²⁶⁻²⁸. Blood channel height was controlled using corrugation of the membrane sheets by a grooved plastic support wafer to define 1,440 capillary channels per plate, with a 3 cm blood path length²⁸. Pulsatile modulation of the sweep gas pressure was used to vary the blood layer thickness between 76 and 127 µm and promote mixing. The design avoided costly and difficult assembly of small membrane sections by pleating a single large membrane sheet to form a stack of alternating blood and gas channels²⁶; multiple oxygenators could be used in parallel to form a modular life support system for larger patients. The preassembled oxygenator was also disposable, greatly simplifying setup for clinical procedures.

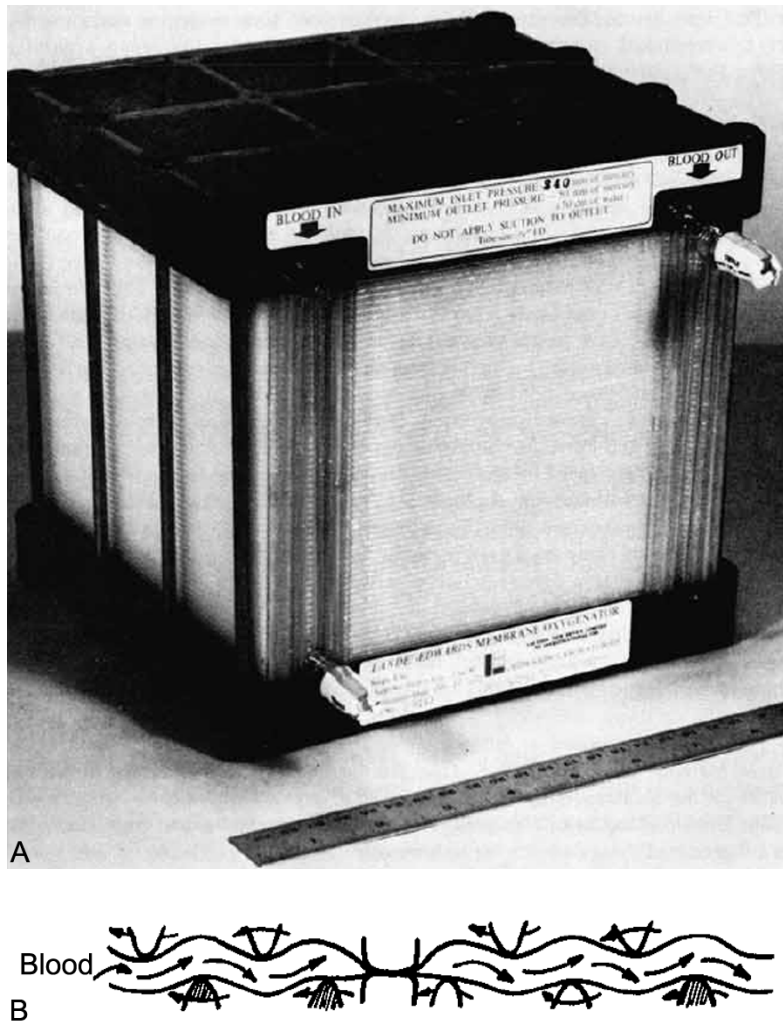


Figure 1.4. A) Landé-Edwards parallel plate oxygenator assembled from folded silicone membrane sheets with 3 m² total area, reproduced from Carlson²⁸. B) Diagram of blood flow between membrane layers supported by corrugated plastic structure. The change in direction of blood flow was designed to induce mild non-turbulent mixing of the blood layer; reproduced from Landé²⁶.

Due in part to the large (150-1500 μm) plate separation distances imposed by manufacturing technology at the time, Gaylor and Mockros determined that parallel plate oxygenators incorporating woven nylon mesh screens in the blood channel could surpass the performance of

open blood channels²⁹. While the mesh screens roughly doubled the total foreign material surface area in contact with blood, the interruption of blood flow induced turbulent mixing to greatly enhance the rate of gas exchange and reduce the required membrane area by approximately half. These features provided the advantage of smaller oxygenators with lower priming volume, while the mesh also served as a structural support to maintain the membrane plate separation. This design was employed commercially in the Travenol oxygenator, shown in Figure 1.5.

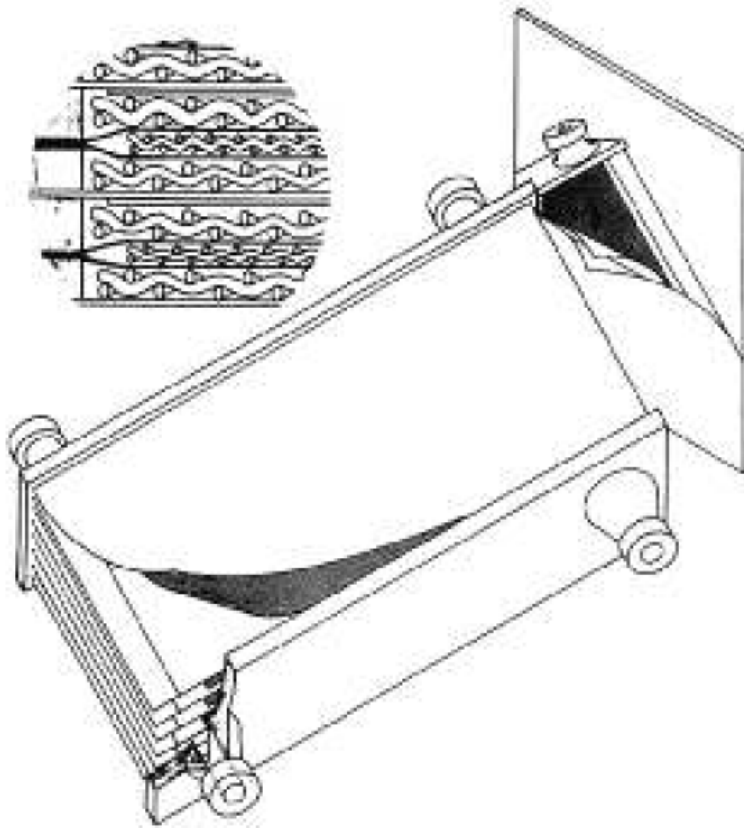


Figure 1.5. Diagram showing the mesh support structure in the blood channels of the Travenol oxygenator, reproduced from Trudell³⁰. Mesh screens, shown in the inset, increased the total foreign material surface area in contact with blood, but interruption of blood flow induced turbulent mixing to enhance the rate of gas exchange and reduce the overall membrane area.

Planar parallel plate oxygenators such as the Bramson or Landé-Edwards, mesh screen-supported plate oxygenators such as the Travenol³⁰, and commercial variants of Kolobow-type spiral oxygenators were of particular interest to clinicians due to their disposable nature. Rather than requiring costly and time consuming cleaning and reassembly of membranes, which had led many clinicians to continue using less expensive and easier to prepare bubble oxygenators³¹, the relatively simple construction encouraged the wider adoption of membrane oxygenators. The first successful long-duration use of ECMO to support a human patient was reported in 1972¹², using a Bramson oxygenator to enable recovery from “shock lung”, or acute respiratory distress syndrome, over a period of 75 hours. Meanwhile, ECMO support of neonatal and pediatric patients was performed by Bartlett and colleagues using Landé-Edwards oxygenators, successfully treating 4 out of 13 patients³².

1.4 Hollow fiber oxygenators become standard of care – 1970s-present

The extracorporeal life support field began transitioning to the use of hollow fibers following the demonstrated success and wide availability of hollow fiber dialyzers for hemodialysis³³, with the first large-scale hollow fiber oxygenator reported in 1971¹¹. Blood was routed through a manifold into the lumens of tens of thousands of hollow fibers with lengths of 10-18 cm; sweep gas flowed through a jacket surrounding the fibers, as shown in Figure 1.6. Mathematical models of luminal flow hollow fiber oxygenators were developed during this time to guide the design of clinically relevant oxygenators^{34,35}.

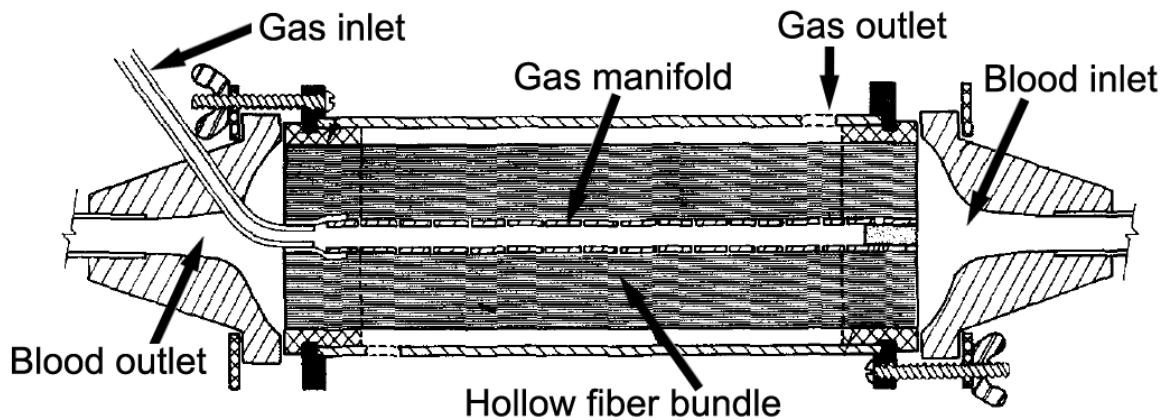


Figure 1.6. Schematic of intraluminal blood flow hollow fiber oxygenator, adapted from Kaye³³.

The high surface to volume ratio of the hollow fiber lumens allowed high gas exchange at the expense of high resistance to blood flow through individual fibers.

Although luminal flow hollow fibers were theoretically capable of high gas exchange due to their circular cross section and correspondingly maximized surface to volume ratio, the 200-300 μm diameter lumen, lacking surface perturbations that could induce turbulent mixing, resulted in the formation of a plasma boundary layer in contact with the membrane surface, requiring longer fibers to ensure adequate diffusion of oxygen into the blood. The hydraulic resistance, which is inversely proportional to the fourth power of the fiber lumen diameter, also imposed large blood pressure drops across the oxygenator, risking hemolysis and requiring the use of powerful blood pumps.

Coagulation issues associated with silicone hollow fibers³⁶ were reduced and gas transport was greatly improved by the adoption of microporous polypropylene hollow fibers³⁷. The microporous structure provided open pores on the order of 1 μm in diameter for direct gas

exchange between the sweep gas and blood³⁸, as shown in Figure 1.7, without exposing red blood cells to the liquid-gas interface.

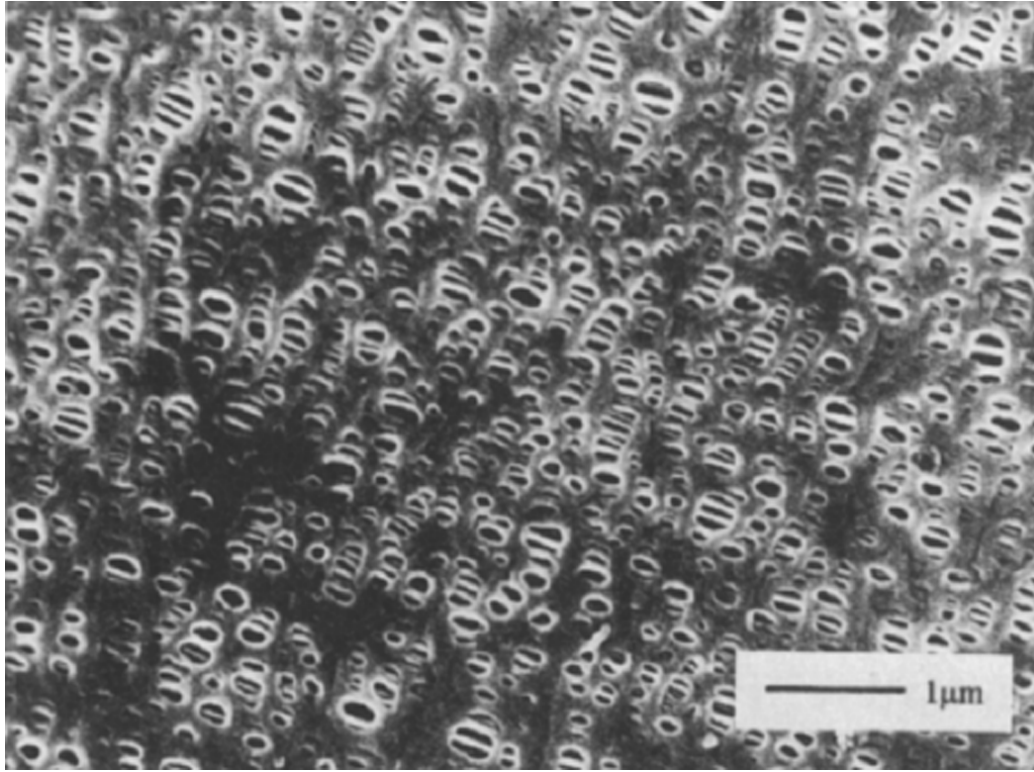


Figure 1.7. Scanning electron micrograph of microporous surface of a single hollow fiber, reproduced from Kim³⁸. Open pores of less than 1 μm diameter form direct channels between the sweep gas and blood sides of the membrane.

However, this introduced a new challenge of oxygenator wetting, in which blood plasma gradually infiltrated the micropores and greatly inhibited gas transfer. Several mechanisms were suspected of inducing pore wetting, including plasma evaporation and condensation in the cooler sweep gas³⁹, ultrafiltration of plasma through the micropores driven by high blood pressure⁴⁰, and wetting of micropores by phospholipids⁴¹. Blood phospholipids bind non-specifically to the hollow fiber, creating a hydrophilic surface at the pore openings; plasma is then able to infiltrate

the pore via capillary action, allowing phospholipids to bind further along the pore. The process continues until the entire pore is wetted and filled with plasma. The much lower diffusivity of oxygen in water compared to air results in greatly diminished gas transfer across the membrane. Although increasing the sweep gas pressure can counteract plasma wetting, it risks introducing gas emboli into the blood stream. Consequently, plasma wetting eventually necessitates the replacement of the oxygenator and reconditioning the patient's blood to the new foreign surface. Hydraulic resistance and boundary layer formation were overcome, not through the use of larger arrays of narrower fibers, but by employing "cross-flow" hollow fiber oxygenators¹³. In this design, blood flowed outside of cross-woven hollow fibers while oxygen flowed in the fiber lumens, thereby providing a larger cross sectional area for blood flow and presenting a more chaotic blood path to induce mixing.

In order to address the plasma wetting issue, Kawahito and others explored the use of microporous hollow fibers skinned with silicone rubber⁴²⁻⁴⁵. The hydrophobic silicone rubber prevented passage of water into the sweep gas channel; although purely diffusive transport of gas through the silicone diminished the rate of gas exchange, it was viewed as an acceptable tradeoff for increased oxygenator longevity.

The turn of the 21st century saw the introduction of a novel membrane material, polymethylpentene (PMP), which provided a microporous structure with a water-impermeable skin layer in contact with blood. This addressed the need to prevent plasma infiltration of pores, while presenting minimal resistance to diffusive transport of oxygen and carbon dioxide. Cross-flow hollow fiber oxygenators such as the Medos Hilite 7000LT⁴⁶ and Maquet Quadrox_D⁴⁷ (shown in Figure 1.8) were developed to bring PMP into clinical use.

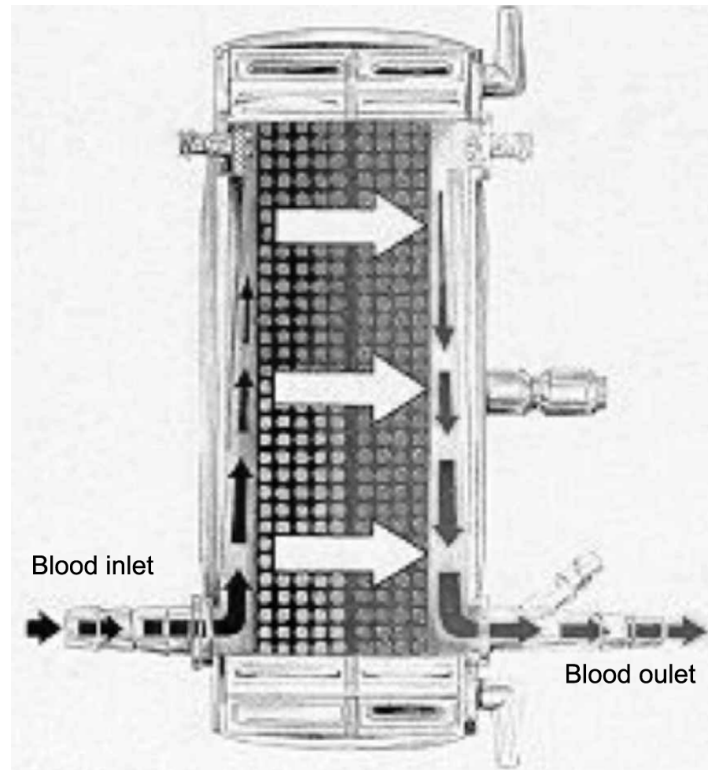


Figure 1.8. Cross section of Maquet Quadrox oxygenator, illustrating cross flow of blood (white arrows) through mesh of hollow fibers oriented perpendicular to the blood flow path. Adapted from Horton et al⁴⁷.

The turbulent mixing and large cross sectional area permitted by cross-flow hollow fiber oxygenators, allowing high blood flow at sub-100 mmHg driving pressures, has also enabled a new class of specialized carbon dioxide removal devices. The Novalung interventional lung assist (iLA)⁴⁸ uses a PMP hollow fiber cartridge for pumpless extracorporeal carbon dioxide removal (ECCO₂R) in an arterio-venous blood circuit, while the ALung Hemolung RAS⁴⁹ utilizes an integrated centrifugal pump to drive blood through a fiber bundle and reduce fluid boundary layer thickness. Both systems provide oxygenation as well as carbon dioxide removal, however the blood flows supported are approximately 1.5 L/min for the Novalung iLA and 0.5 L/min for the Hemolung, making them less suitable for full respiratory support.

Hollow fiber oxygenators have become the standard of care for cardiopulmonary bypass and bedridden ECMO, with support of awake and ambulatory patients becoming increasingly common^{50,51}. However, improvements in reliability and ease of use are still needed to make ECMO feasible outside of specialized care centers. Despite the commercial use of immobilized heparin coatings on membrane surfaces⁵², systemic anticoagulation is still necessary and increases the risk for bleeding, both internally and at cannulation sites. Oxygenator and circuit priming volumes in excess of 100 mL often require blood transfusions to initiate ECMO, especially for pediatric and neonatal patients. Additionally, the complex and fragile nature of the oxygenator and ECMO blood circuit make unassisted ambulatory ECMO a risky endeavor.

1.5 Microfluidics mimic native lungs – 1990s-future

In the native lung, red blood cells of approximately 8 μm diameter flow single-file through alveolar capillaries whose diameter can be as small as 3-5 μm , causing the red blood cells to deform and sweep along the capillary lumen⁵³. These tiny physical dimensions minimize the plasma layer through which oxygen must diffuse and permit capillary lengths on the order of 1 mm. The geometry and manufacturing techniques used in hollow fiber oxygenators do not allow for such tight tolerances, with the result that their performance is limited by blood-side diffusive transport. However, the growing field of microfluidics⁵⁴ has inspired the use of soft lithography to define capillary blood channels for blood oxygenation.

Mockros and colleagues explored the theoretical benefits of microfluidic lungs to better mimic native lung physiology¹⁴, concluding that parallel plates or large arrays of parallel capillary channels with critical blood channel dimensions approaching 10 μm would remove the majority of blood side resistance to gas diffusion, allowing the use of sub-1 cm blood flow path lengths

and priming volumes below 50 mL to supply gas exchange needs for blood flows in excess of 4 L min⁻¹. Proof of concept was demonstrated using small scale devices with 100 µm thick silicone rubber membranes mechanically supported by a 280 µm thick wire mesh spanning a 5 mm wide blood channel⁵⁵. Additional experiments demonstrated the feasibility of an open rectangular blood channel 15 µm high with a 130 µm thick membrane and integrated support columns fabricated from polydimethylsiloxane (PDMS) using soft lithography⁵⁶. This design indicated that arbitrarily wide blood channels were possible in a microfluidic device with a single critical dimension for gas transport - blood channel height - enabling oxygenators that were more tolerant of blood clots.

Burgess et al fabricated monolithic PDMS membranes consisting of stacked arrays of parallel capillary channels with segmental cross sections. Each capillary channel had a maximum height of 33 µm, width of 105 µm, and length of 1.8 cm; gas exchange membranes tested were 64 or 146 µm thick¹⁵. While the permeability to both oxygen and carbon dioxide was limited by the thickness of the membrane, it demonstrated the potential for PDMS-only capillary oxygenator arrays.

Potkay and colleagues expanded on the capillary array concept by using dramatically thinner 15 µm PDMS gas exchange membranes to enhance gas transfer^{16,57-59}; an example of this capillary channel geometry is shown in Figure 1.9. Blood channels in these devices were 10-20 µm high, 88 µm wide, and less than 1 mm long. Meanwhile, Rochow et al used PDMS to define the blood channels, testing both 6 µm thick microporous polycarbonate membranes or 20 µm thick PDMS for gas exchange. This enabled blood channels with 80 µm height and 500 µm width in a stackable design⁶⁰⁻⁶². The high gas permeability of the thin PDMS membranes enabled the use of

ambient air as a sweep gas, which could make dedicated pure oxygen supplies and gas mixers unnecessary.

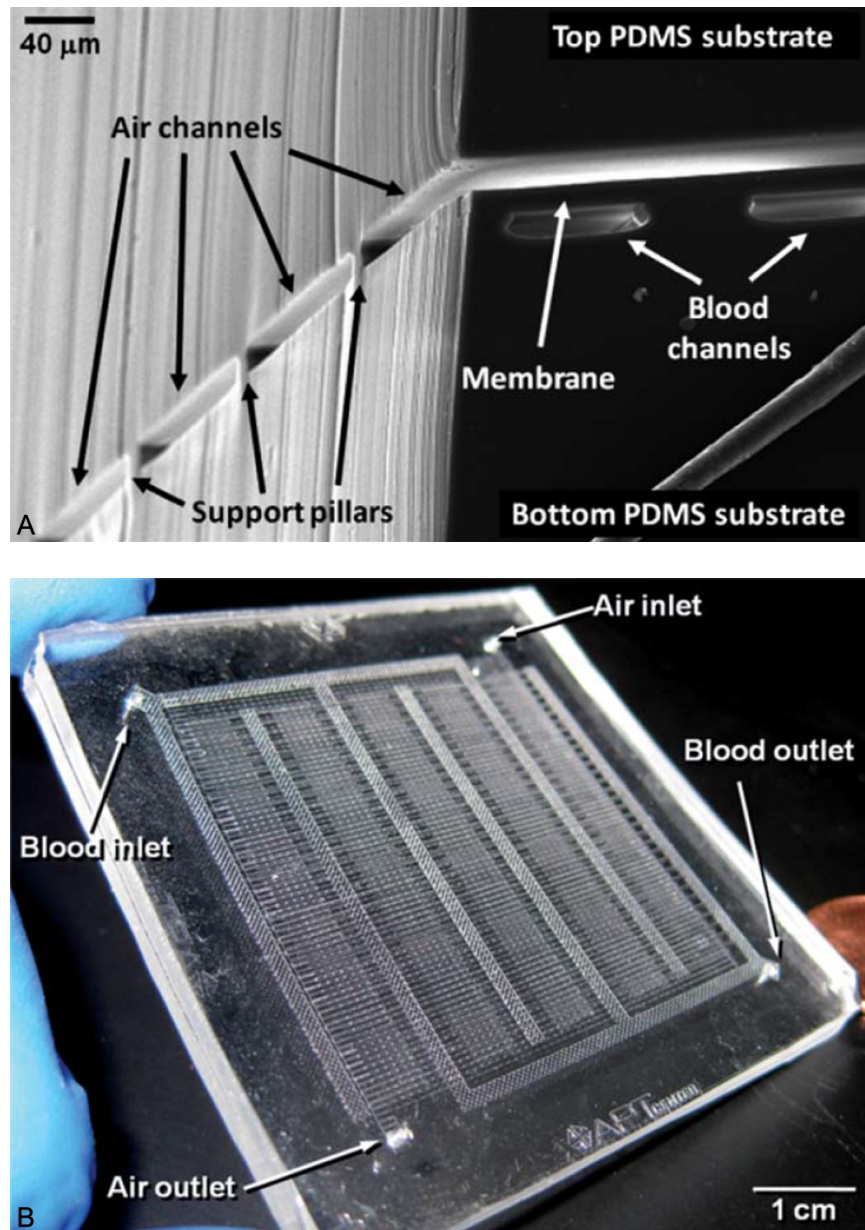


Figure 1.9. Microfluidic artificial lung. A) 15 μm tall blood channels and 20 μm thick gas exchange membrane fabricated from PDMS using soft lithography. B) Array of capillary channels in a prototype oxygenator. Reproduced from Potkay⁵⁷.

Although individual capillary channels impose large resistance to blood flow, the use of thousands of capillaries in parallel works to overcome this effect; however, the manifolds at the blood inlet and outlet constitute the greatest source of hydraulic resistance⁵⁷. In order to control blood shear and minimize hydrodynamic pressure drop, especially at the blood inlet and outlet, recent work from the Potkay group and Draper Lab has focused on employing branching capillary channels that closely match the branching ratios found in the native lung⁶³⁻⁶⁶; an example of this geometry is shown in Figure 1.10. The <50 mmHg pressure drop across optimized microfluidic systems could allow the use of smaller, less powerful blood pumps, or operate in a pumpless arterio-venous circuit.

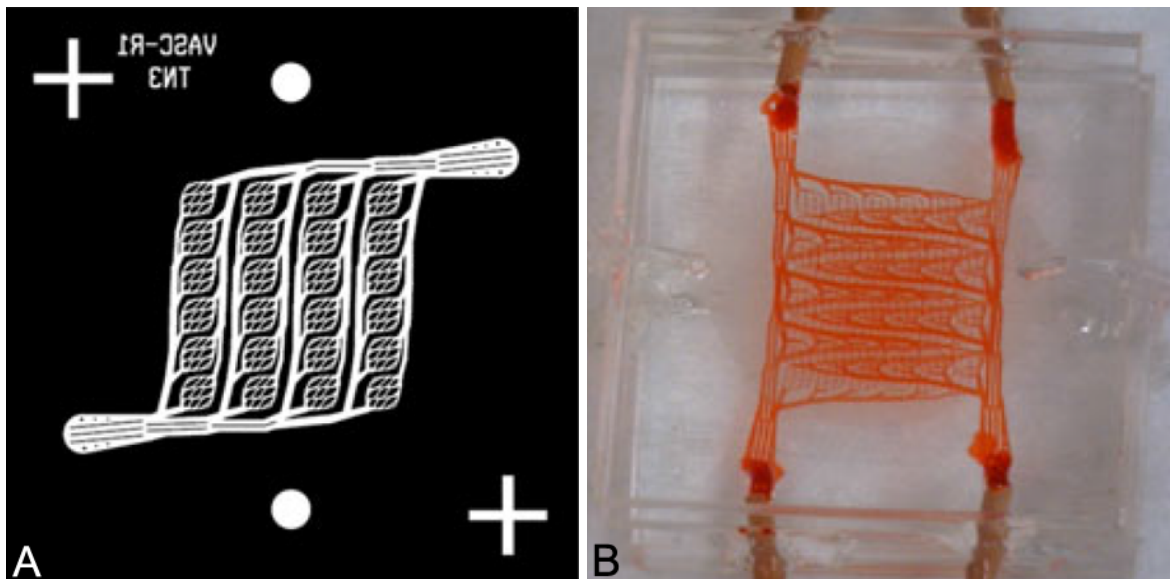


Figure 1.10. A) Schematic of biomimetic branching capillary design for a microfluidic lung, reproduced from Kniazeva⁶⁴. B) Assembled stacked parallel plate microfluidic gas exchanger using branching capillaries, reproduced from Kniazeva⁶⁵.

Taken together, recent developments in microfluidic oxygenator designs make them a compelling avenue for further progress in ECMO technology towards compact, wearable systems that support unassisted ambulatory patients. However, the use of monolithic PDMS structures in recent designs could have detrimental consequences. Due to the hyperelastic mechanical properties of PDMS, capillary channels must be narrow in width ($\sim 500\text{ }\mu\text{m}$ or less) to avoid channel collapse or distension due to pressure differences between the sweep gas and blood. The side walls of each capillary do not contribute significantly to gas exchange, but add to the total surface area in direct contact with blood, making the narrow capillaries vulnerable to occlusion by clots⁶⁷.

A potential solution to these challenges could be found by combining the mechanically supported parallel plate geometry of Mockros et al^{55,56} with the sub- $20\text{ }\mu\text{m}$ PDMS membranes of recent capillary oxygenators. An oxygenator incorporating these design features would benefit from the high gas permeability of plasma-impermeable solid membranes, the low blood side resistance of $\sim 10\text{ }\mu\text{m}$ channel heights, and the greater clot tolerance of centimeter-scale channel widths. Such a system would in effect be an optimized version of the parallel plate oxygenators of the 1950s and 60s.

1.6 Conclusion

As the evolution of ECMO continues, it is becoming possible to overcome past limitations of blood-side resistance to gas exchange. PDMS thin films can be produced at less than $20\text{ }\mu\text{m}$ thickness and greatly surpass the low permeability of early polymer membranes^{16,57,61,62}, and modern fabrication techniques can reliably produce defect-free membranes that minimize the risk of gas embolism⁴⁷. The stacked parallel plate blood channels used in the first clinical

membrane oxygenators²⁴⁻²⁸ can now be reproduced using soft lithography to yield sub-10 μm channel heights⁵⁶, significantly reducing plasma boundary layers. This approach allows for the use of shorter blood channel lengths with lower pressure drops and correspondingly decreased priming volume to more closely mimic the physiology of the native lungs. By revisiting membrane concepts and challenges from the 1950s and 60s with state-of-the-art microfabrication technology, we are even closer to realizing a true artificial lung that can bridge the gap between sickness and health.

Chapter 2: Design and Fabrication of Silicon-Supported Polydimethylsiloxane Gas Exchange Membranes

2.1 Introduction

Extracorporeal membrane oxygenation (ECMO) is a respiratory support method wherein blood is pumped out of the body, flows over a gas permeable membrane to exchange oxygen and carbon dioxide, and returns to the systemic circulation¹. When conventional modes of respiratory support, including mechanical ventilation, are unable to provide sufficient gas exchange, ECMO is used as a bridge to recovery⁶⁸ or lung transplantation³⁻⁵. The current generation of membrane oxygenators utilizes polymethylpentene (PMP) hollow fibers oriented perpendicular to the blood flow path, with a total membrane surface area on the order of 1 m². The hollow fibers occupy a blood channel with a large cross sectional area, resulting in a low hydraulic pressure drop between the oxygenator blood inlet and outlet of approximately 50 mmHg^{69,70}. The interruption of the flow path by hollow fibers leads to a large distribution of fluid velocities and shear stresses^{71,72}, allowing low flow regions to develop where blood can stagnate and clot^{15,16,73}. The open nature of the blood conduit, coupled with redundant membrane area, allows hollow fiber oxygenators to tolerate some degree of clot formation.

To more closely mimic the scale and geometry of alveolar capillaries in the native lung, a number of microfluidic ECMO devices have been developed^{59,74} that utilize a parallel plate geometry, in which blood is channeled between two gas exchange membranes made of polydimethylsiloxane (PDMS). This approach allows for much shorter gas diffusion distance in

the blood channel compared to hollow fiber oxygenators, and PDMS is highly permeable to both oxygen and carbon dioxide. However, the low elastic modulus of PDMS constrains the geometry of single-material microfluidic oxygenators, requiring blood channels on the order of 100 μm wide with membrane thickness of 10-50 μm ^{57,65}. These narrow blood channels possess impose high resistance to blood flow, and the channel sidewalls contribute significantly to the total device surface area without providing gas exchange. Taken together, these factors contribute to the risk of thrombosis in the device, with the potential for individual channels to become blocked by thrombi during prolonged exposure to blood⁵⁹.

I propose an intermediate solution between open hollow fiber arrays and tightly closed microchannels: using a PDMS thin film supported by a rigid porous membrane in a parallel plate geometry, it is possible to provide wide blood channels on the order of 1-10 cm with controlled channel height of less than 200 μm . This design expands the cross-sectional area of the blood channel to reduce blood flow resistance, while also achieving the short blood-side diffusion length inherent to microfluidic ECMO systems. The mechanical strength afforded by these asymmetric membranes allows the use of PDMS films of 0.5-10 μm thickness. I aim to minimize the membrane surface area required for adequate oxygenation in a parallel plate geometry, thereby reducing the extent of blood-material interaction and creating more uniform shear stress in the blood flow path to reduce the risk of thrombosis.

2.2 Design

In a simplified model of diffusive gas transport across a membrane¹⁶ shown in Eq. 2.1, gas flux, Q (mL STP min^{-1}), across a membrane with a partial pressure difference between the sweep gas, $pO_{2,gas}$ (cmHg), and blood, $pO_{2,blood}$ (cmHg), is directly proportional to the membrane mass

transfer coefficient, S (mL STP min⁻¹ m⁻² cmHg⁻¹), and membrane area, A (m²). Mass transfer is inversely proportional to membrane thickness, T (m), as shown in Eq. 2.2. While material choice dictates the permeability, K (mL STP min⁻¹ m⁻¹ cmHg⁻¹), membrane thickness can be manipulated by adjusting fabrication parameters.

$$Q_{O_2} = (p_{O_{2,gas}} - p_{O_{2,blood}}) \cdot S \cdot A \quad (2.1)$$

$$S = \frac{K}{T} \quad (2.2)$$

Gas transport can be enhanced by decreasing the membrane thickness or increasing the partial pressure of oxygen in the sweep gas to create a larger concentration gradient. However, a thin membrane made of highly elastic PDMS can deform due to differences between the absolute pressures in the sweep gas and blood (P_{gas} (cmHg) and P_{blood} (cmHg), respectively), illustrated by Eq. 2.3, where u (m) is deflection out of the membrane plane, E (Pa) is membrane elastic modulus, and W (m), L (m), and T (m) are width, length, and thickness of the membrane, respectively⁷⁵. This can lead to ballooning or collapse of the blood channel, as illustrated in Figure 2.1.

$$u \propto \frac{(P_{gas} - P_{blood}) \cdot W^5}{E \cdot T^3 \cdot L} \quad (2.3)$$

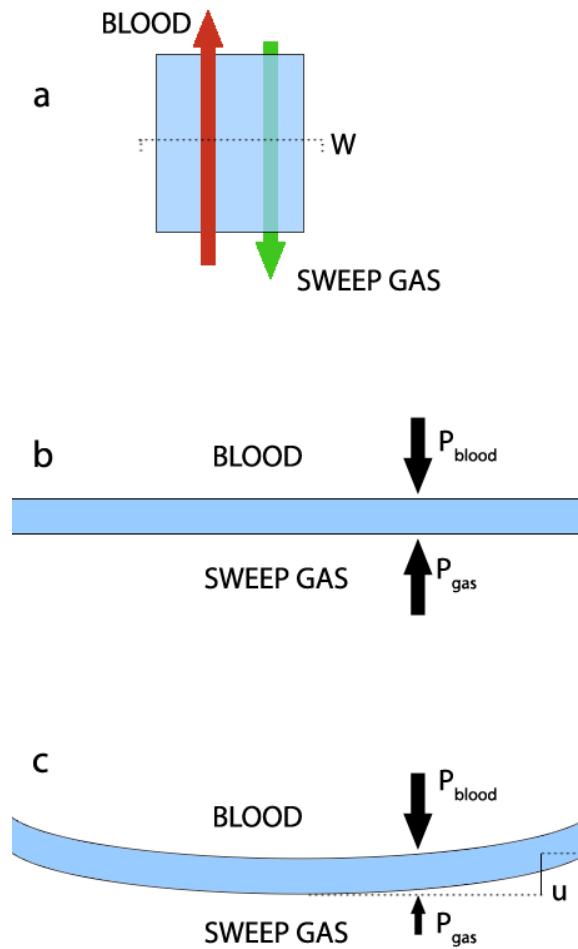


Figure 2.1. Illustration of thin membrane deflection under differential pressure load between sweep gas and blood channels. (a) Plan view of a membrane spanning a channel of width W with sweep compartment below and blood compartment above the plane of the membrane. (b) When sweep gas and blood compartment pressures are equal, the membrane remains undistorted in a cross section view. (c) If a pressure differential exists between the compartments, the membrane will deflect a distance u , as a function of the difference in pressure, as well as the geometry and material properties of the membrane, as detailed in Eq. 2.3.

Deformation of the gas transfer membrane can restrict blood flow or increase the critical length for diffusion of gas through the blood plasma to reach red blood cells, reducing the oxygenation and ventilation efficiency of the ECMO circuit. Historically, pressure imbalances between sweep gas and blood compartments has also led to mechanical rupture of the membrane, resulting in gas embolization into the blood stream or leaking of blood plasma from the circuit^{23,45}. In order to produce a gas exchange membrane capable of withstanding large pressure differentials (on the order of 76 cmHg) to drive gas diffusion, without relying on support pillars in the blood channel, I adapted a silicon hemofiltration membrane^{76,77} to provide mechanical support for a sub-10 μm PDMS film in a parallel plate geometry.

The silicon membrane incorporates nested arrays of high aspect ratio rectangular pores; from Eq. 2.3, long but narrow pore openings can minimize PDMS deformation while maximizing the total pore area available for gas exchange. Each membrane die is composed of a 6 mm long by 6 mm wide array of rectangular “windows” through a 400 μm thick silicon wafer; each window is approximately 250 μm long by 50 μm wide. The silicon is overlaid with a 0.5 μm thick film of polysilicon that spans all windows, as shown in Fig 2.2a. The polysilicon over each window is patterned with an array of rectangular micropores, with length of 4 μm and width on the order of 1 μm , spaced 0.5 μm apart, shown in Fig 2.2b, constituting a silicon micropore membrane (S μ M). The PDMS thin film is bonded to the polysilicon surface, spanning the micropores, as shown in Fig 2.2c, completing the PDMS-S μ M.

Due to the demonstrated mechanical stability of the silicon hemofilter membrane⁷⁸, I elected to conserve most of the original design, including the window dimensions and micropore length and pitch, while adjusting the micropore width and PDMS film thickness. Our design goals were to: (1) maximize polysilicon membrane porosity to enhance area available for gas transfer (A in

Eq. 2.1); (2) minimize thickness to increase membrane mass transfer via Eq. 2.2; and (3) limit membrane deformation under a transmembrane pressure load of 76 cmHg to $2.5\text{ }\mu\text{m}$ out of plane, equivalent to 10% of the height of a $50\text{ }\mu\text{m}$ tall by 1 cm wide blood channel in a parallel plate geometry.

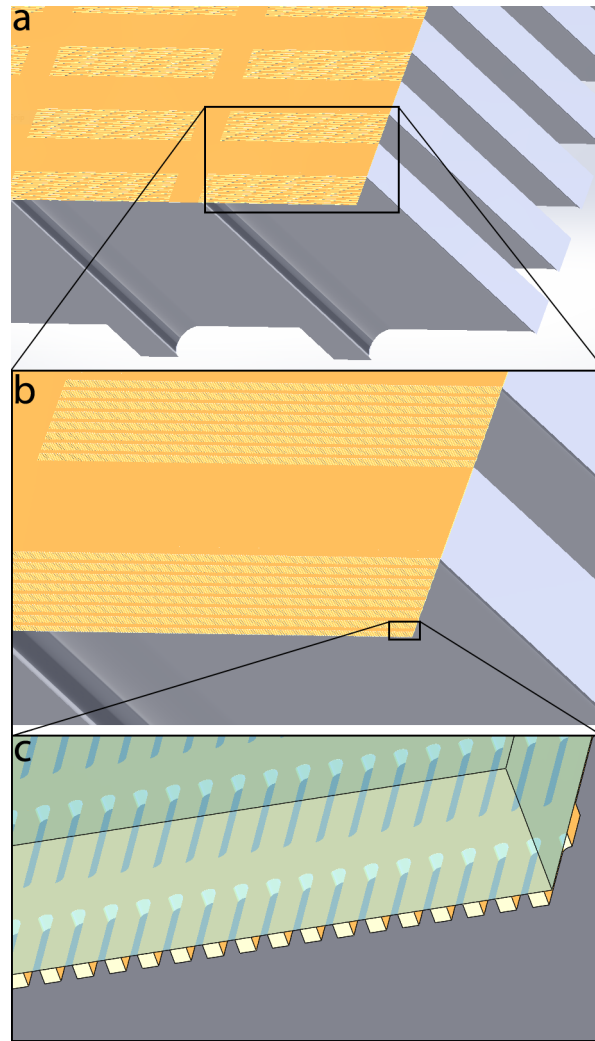


Figure 2.2. Schematic of asymmetric membrane design. (a) Each membrane die is composed of a 6 mm long by 6 mm wide array of $250\text{ }\mu\text{m}$ long by $50\text{ }\mu\text{m}$ wide rectangular “windows” through crystalline silicon (grey), overlaid by polysilicon (orange). (b) Polysilicon spanning the windows is patterned with arrays of rectangular micropores with length of $4\text{ }\mu\text{m}$. (c) A thin film of PDMS covers the membrane, spanning the micropores in the polysilicon.

I used ANSYS Mechanical finite element analysis software (ANSYS, Inc., Canonsburg, PA) to conduct parametric modeling of the deformation of membrane components under transmembrane pressure loads of 76 cmHg. While die and window size, pore length, and pore pitch were held constant, micropore width and PDMS film thickness parameters were evaluated at 0.5, 1, 2, and 4 μm and 0.5, 1, 2, 5, and 10 μm , respectively. Due to the computational complexity of modeling the entire membrane, mechanical simulations were broken into three components: at the die level, the crystalline silicon membrane was modeled with an array of open windows; at the window level, a film of polysilicon spanning one window was modeled with an array of open micropores; at the micropore level, a film of PDMS spanning one micropore was analyzed. For each model, maximum deformation at the center of the membrane area was analyzed. Due to the large difference in length scales between the die, window, and micropore components, it was assumed that deformation of one component, such as the die, would not significantly alter the geometry of another component, such as a single window.

The die and window models assumed identical mechanical properties for both monocrystalline silicon and polysilicon, with elastic modulus of 169 GPa and Poisson ratio of 0.22. Since PDMS is a hyperelastic material, a second order Ogden model⁷⁹ was applied to calculate deformation of the PDMS film spanning a micropore with the following Ogden parameters: $\mu_1=63.489$ MPa, $\alpha_1=6.371\text{E-}10$, $\mu^2=0.041103$ MPa, $\alpha_2=3.8117$.

Finite element analysis indicated that a micropore width of 0.5 μm and PDMS membrane thickness less than 5 μm could meet our membrane deformation criteria, as shown in Figure 2.3. Although greater pore width increased the porosity of the silicon, this led to unacceptably large deformation of the S μ M.

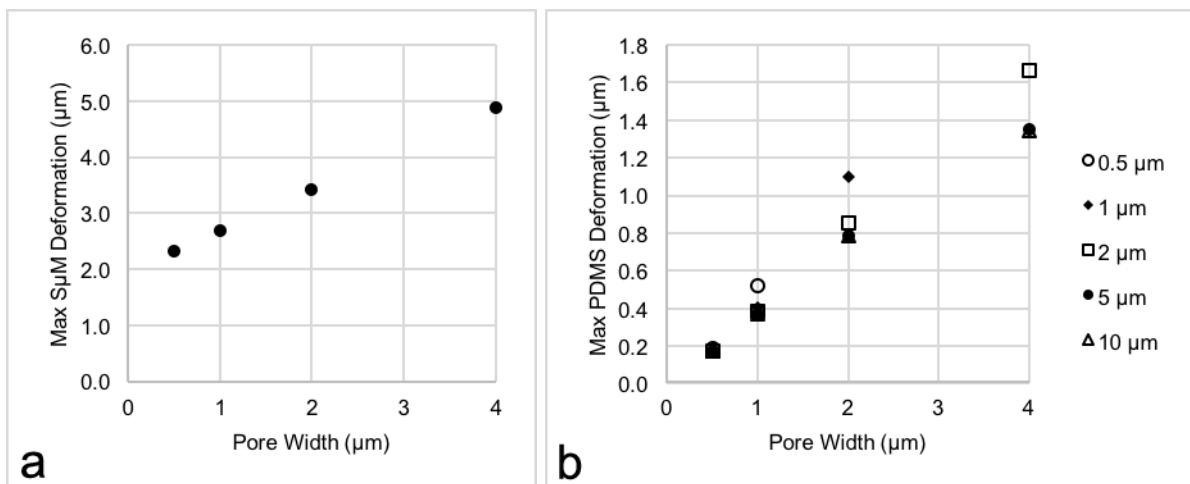


Figure 2.3. (a) Maximum displacement at center of SμM as a function of micropore width; (b) deformation of PDMS spanning SμM micropores as a function of micropore width and PDMS film thickness.

Using Eq. 2.2, scaled by the SμM porosity, and assuming PDMS oxygen and carbon dioxide permittivity of 367 and 1842 mL STP $\mu\text{m min}^{-1} \text{m}^{-2} \text{cmHg}^{-1}$, respectively⁸⁰, a plot of expected membrane mass transfer coefficients was generated, shown in Figure 2.4. This provided a conservative estimate of the expected gas transport across the membrane, as it was assumed that gas diffusion would only occur through PDMS spanning an open micropore. While PDMS films with thickness of 0.5 μm were expected to provide the greatest mass transfer, a 5 μm thick PDMS film was targeted for this proof of concept study due to fabrication constraints.

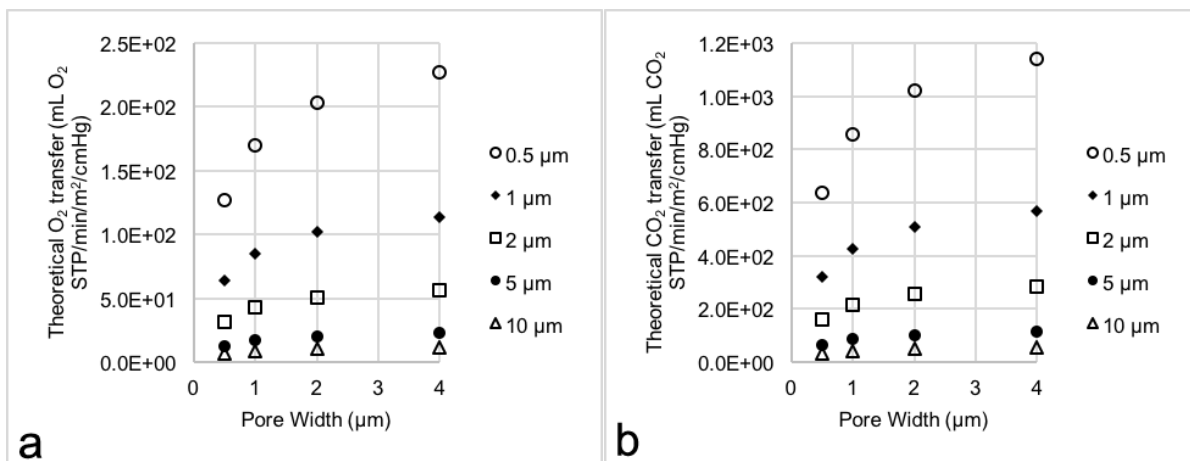


Figure 2.4. Theoretical gas transfer rate for (a) oxygen and (b) carbon dioxide as a function of micropore width and PDMS film thickness.

2.3 Methods

2.3.1 Silicon micropore membranes (SμMs)

SμMs were fabricated on 400 μm thick, <100>-oriented silicon wafers substrate to produce arrays of 500 nm by 4 μm rectangular micropores. First, a 1 μm thick thermally grown silicon dioxide layer was patterned with anchor regions to divide the wafer into 50 μm by 267 μm “window” sub regions. A 500 nm thick polysilicon film was then deposited and patterned via photolithography and reactive ion etching (RIE) to define evenly spaced parallel beams (Fig 2.5a-b). Lines and spaces were both 500 nm wide. The backside of the wafer was then patterned to define the same window dimensions using front-to-back alignment and deep reactive ion etching (DRIE), thereby exposing the backside of the polysilicon beams (Fig 2.5c). Lastly, 49% hydrofluoric acid was used to remove the oxide etch-stop layer and open the membrane pores (Fig 2.5d). For the purposes of this study, the wafers were diced to form 1 cm² membranes containing 1500 windows each, with a total of 3.12E6 pores per membrane and 0.36 cm² effective membrane area.

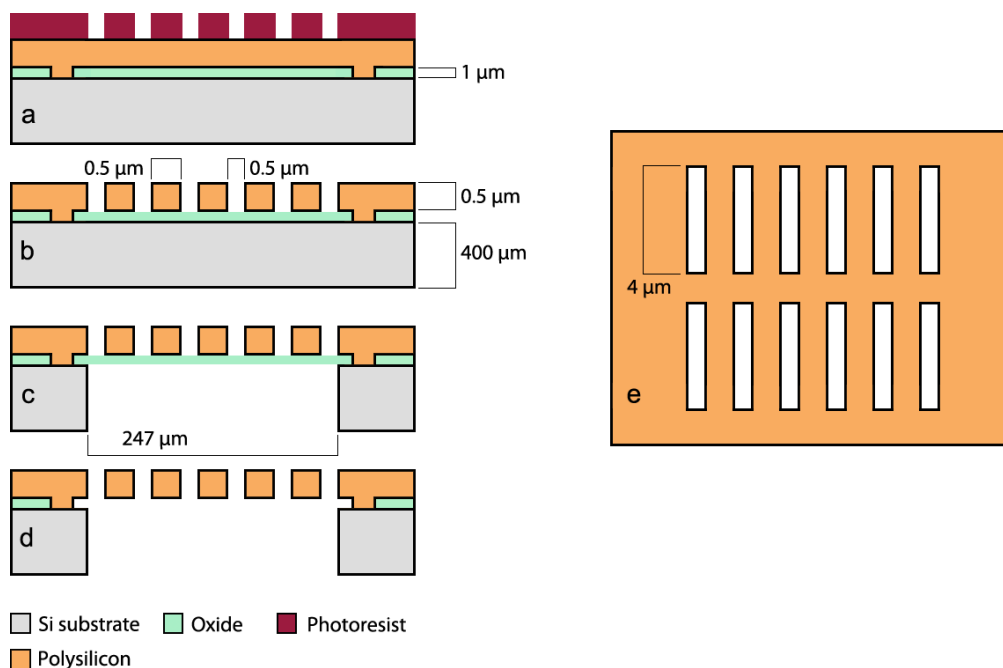


Figure 2.5. Process flow for fabrication of silicon micropore membranes (S μ Ms). Cross-section of a single membrane “window”. Features not drawn to scale. A 1 μ m thick thermally grown silicon dioxide layer was patterned with anchor regions on a silicon wafer to define 50 μ m by 267 μ m “window” sub regions. A 500 nm thick polysilicon film was then deposited and patterned via photolithography and reactive ion etching (RIE) to define evenly spaced parallel beams (a,b). The backside of the wafer was patterned to define the same window dimensions using front-to-back alignment and deep reactive ion etching (DRIE) to expose the backside of the polysilicon beams (c). Hydrofluoric acid was used to remove the oxide etch-stop layer and open the membrane pores (d). In plan view, the finished S μ M consists of an array of 0.5 μ m by 4 μ m rectangular pores (e).

2.3.2 PDMS coating

S μ Ms were coated with PDMS via a liftoff process derived from Thangawng et al.⁸¹ and Park et al.⁶⁹. A 15 μ m thick layer of SU-8 photoresist (MicroChem Corp., Newton, MA) was spin-coated

onto a silicon wafer and baked (Fig 2.6a). Sylgard 184 PDMS (Dow Corning, Midland, MI) was then mixed at a monomer to crosslinker ratio of 3:1 and spin-coated onto the photoresist (Fig 2.6b) at 4500 rpm for 2 min to form an approximately 4.5 μm thick PDMS film; the PDMS was subsequently heat-cured at 80 $^{\circ}\text{C}$ for 2 hr. This film thickness was chosen for ease of fabrication and handling in the available clean room facilities. The $\text{S}\mu\text{M}$ was then bonded to the PDMS layer using oxygen plasma treatment at 150 W for 5 s (Fig 2.6c); a 2 μL drop of isopropyl alcohol was placed on the PDMS prior to contact with the $\text{S}\mu\text{M}$ to ensure a conformal bond as the alcohol evaporated. The complete asymmetric membrane unit was released from the silicon wafer by stripping the photoresist with acetone (Fig 2.6d).

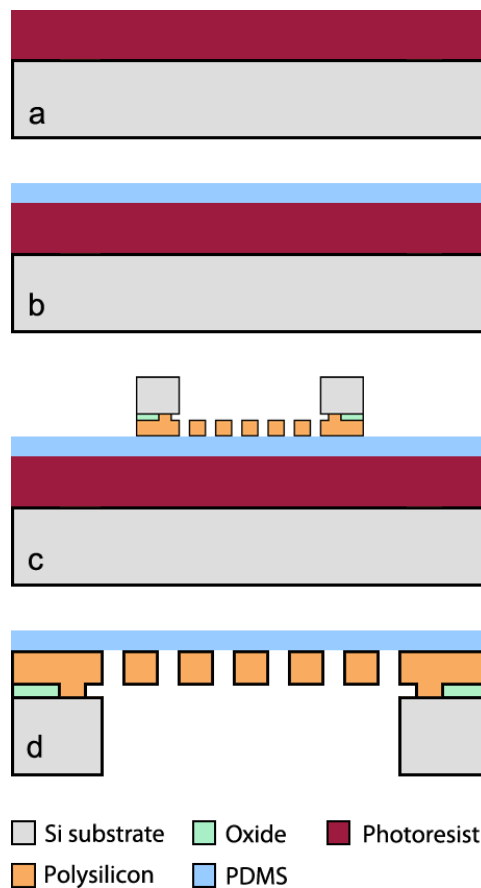


Figure 2.6. Process flow for PDMS bonding to $\text{S}\mu\text{Ms}$. Cross-section of a single membrane “window”. A 15 μm thick layer of photoresist was spin-coated onto a silicon wafer and baked (a).

PDMS (3:1 monomer:crosslinker) was spin-coated onto the photoresist to form an approximately 4.5 μm film (b). The S μM was bonded to the PDMS layer using oxygen plasma treatment at 150 W for 5 s (c). The complete PDMS- S μM asymmetric membrane unit was released by stripping the photoresist with acetone (d).

2.3.3 Membrane structural characterization

S μM dimensions and PDMS film thickness were measured using scanning electron microscopy (SEM). Membrane mechanical robustness was experimentally verified by subjecting the complete PDMS-S μM s to leak testing using a bench top hydraulic permeability testing system⁷¹, which is capable of measuring water flux per unit pressure on the order of nanoliters per minute in response to a transmembrane pressure gradient. Water was flowed in contact with the PDMS side of the membrane at a transmembrane pressure of 26 cmHg, the maximum pressure achievable with the test apparatus, for 30 min. Membrane ruptures could be detected by outflow of water collected in a precision mass balance (Mettler Toledo, Columbus, OH).

2.3.4 Gas diffusion through membranes

The complete PDMS-S μM s were tested for gas exchange in a dry bench-top flow cell connected to a pressurized gas supply and a bubble flow meter (Sigma-Aldrich, St. Louis, MO), as method that has been used to test other artificial lung systems^{15,16}. The pressurized gas, either oxygen or carbon dioxide, was flowed on the sweep gas side of the membrane at a transmembrane partial pressure gradient between 70 and 140 cmHg. Since the PDMS component of the PDMS-S μM formed a solid barrier preventing convective gas transport across the membrane, the only path for gas transport to the opposite side of the membrane was via diffusion. Gas that diffused to the

opposite side of the membrane was collected in the bubble flow meter, displacing a meniscus of detergent to measure the volume of gas transported across the membrane. By measuring the gas flux per unit pressure, gas mass transfer coefficient could be calculated for the PDMS-S μ Ms via Eq. 2.1. Membrane area used for this calculation was the total effective membrane area exposed to blood, $3.6\text{E-}5\text{ m}^2$.

2.3.5 Gas exchange with blood

The PDMS-S μ Ms were tested for gas mass transfer in a flowing blood environment using porcine whole blood, treated with 2 U mL^{-1} heparin. A custom designed flow cell, containing a 1 cm^2 PDMS-S μ M ($3.6\text{E-}5\text{ m}^2$ membrane area), was used as a blood oxygenator and deoxygenator, with the PDMS side of the membrane in direct contact with blood while the silicon backside was exposed to a sweep gas, either oxygen or nitrogen, respectively (Fig 2.7). The blood channel was 3D-printed using PolyJet HD (Solid Concepts, Inc., Valencia, CA, USA), a urethane-based resin, to define a channel over the PDMS-S μ M with dimensions of 10 mm long by 8 mm wide by 50 μm high, tapering at the inlet and outlet to interface with 1/16" Luer lock tubing connectors. The sweep gas channel was machined from acrylic plastic to form a 3 mm tall chamber over the backside of the PDMS-S μ M. The complete device was assembled by compressing a 125 μm thick silicone gasket between the PDMS-S μ M and the sweep gas chamber; the stack of components was secured with machines screws.

A total volume of 2 mL of blood was recirculated over the PDMS-S μ M at a flow rate of 2 mL min^{-1} , chosen to maintain wall shear stress below hemolysis thresholds⁸². Sweep gas pressure was measured using a digital pressure transducer (General Electric, Schenectady, NY). The gas side of the membrane was first exposed to pure nitrogen at a partial pressure of 86 cmHg to

deoxygenate the blood; this pressure was chosen to purge the sweep gas side of the circuit of all ambient air. The gas was then switched to pure oxygen at a gauge pressure of 52 cmHg to create a transmembrane oxygen partial pressure gradient of 128 cmHg and drive oxygen diffusion into the blood; this pressure was chosen to test the ability of the membrane to withstand higher than ambient sweep gas pressures and create a large concentration gradient for oxygen diffusion across the membrane. Blood oxygen partial pressure measurements were acquired at 1 Hz using a NeoFox inline optical oxygen sensor (Ocean Optics, Dunedin, FL), which was coated with an oxygen-quenchable fluorophore. Total blood oxygen concentration was determined from the hemoglobin dissociation model developed by Margaria⁸³. The flow cell was then flushed with saline solution at 2 mL/min for 5 min, then disassembled and examined for visible clots.

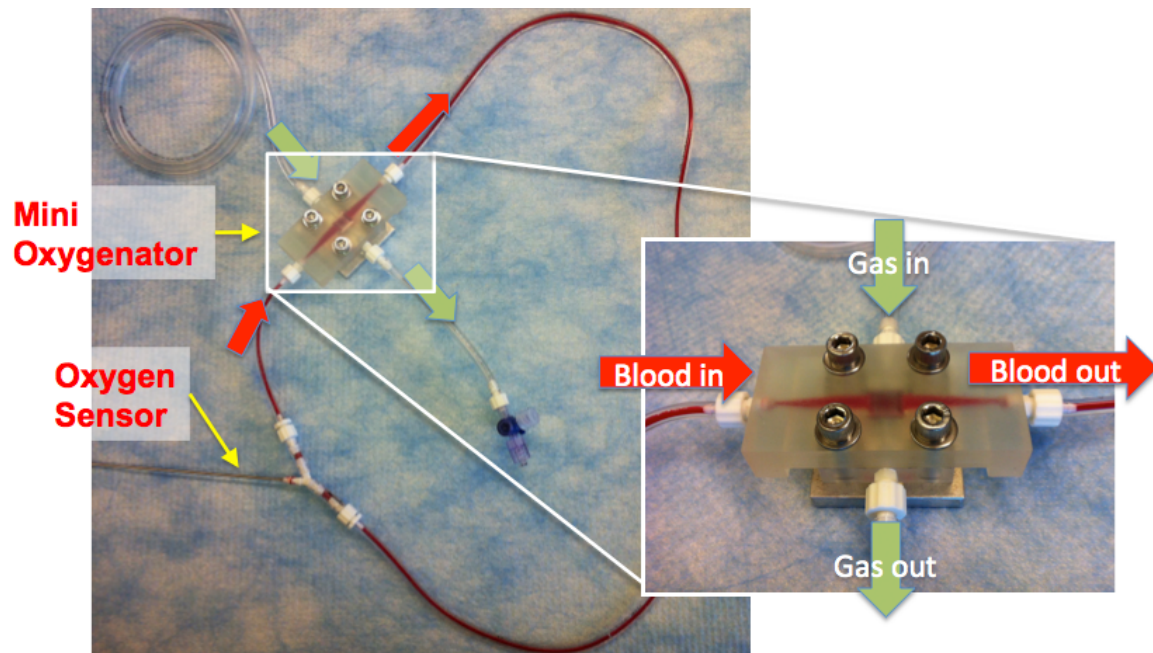


Figure 2.7. *Ex vivo* blood oxygenation circuit with inline optical oxygen sensor.

2.4 Results

2.4.1 Membrane structure

PDMS-S μ M dimensions were characterized using SEM (Fig 2.8a,b), with micropore dimensions of $3.55 \pm 0.03 \mu\text{m}$ long by $450 \pm 20 \text{ nm}$ wide, with a polysilicon membrane thickness of $480 \pm 20 \text{ nm}$. The PDMS film thickness was measured by SEM to be $4.63 \pm 0.11 \mu\text{m}$ (Fig 2.8b).

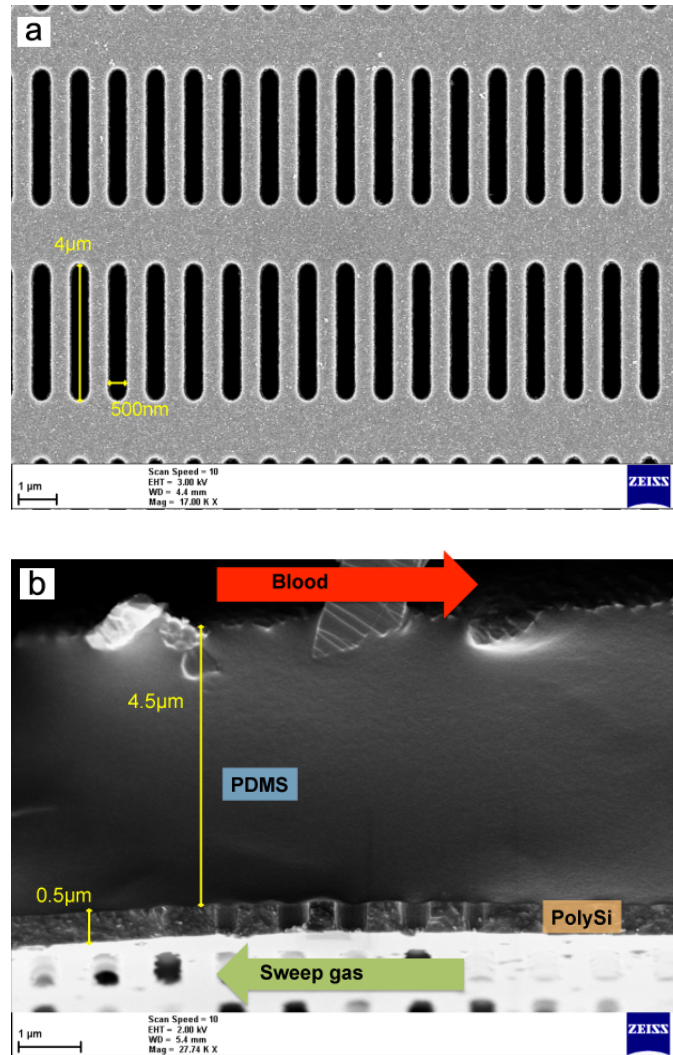


Figure 2.8. a) Top view of S μ M with dimensions of individual pores. b) Cross section of PDMS-S μ M; blood flows in contact with the PDMS film while sweep gas flows on the opposite side of the polysilicon support structure of the S μ M.

Hydraulic permeability testing of the complete PDMS-S μ M was carried out to detect membrane defects that would allow leaking of water under a transmembrane pressure gradient. No water flux across the membrane was detected. This confirmed that there was sufficient conformal bonding of the PDMS and S μ M to prevent water or blood plasma from flowing around the PDMS and wetting the S μ M pores.

2.4.2 Membrane diffusive gas transport

Gas exchange of the PDMS-S μ M was first tested in a dry bench-top flow cell between air at ambient pressure and a pressurized, purified gas source. The volume of gas that diffused to the opposite side of the membrane was measured by a bubble flow meter. Mass transfer coefficients for the PDMS-S μ M were calculated from the measured gas flux per unit pressure via Eq. 1. Mass transfer coefficients for O₂ and CO₂ were found to be 5.49 ± 0.89 and 31.76 ± 0.80 mL STP min⁻¹ m⁻² cmHg⁻¹, respectively (Fig 2.9).

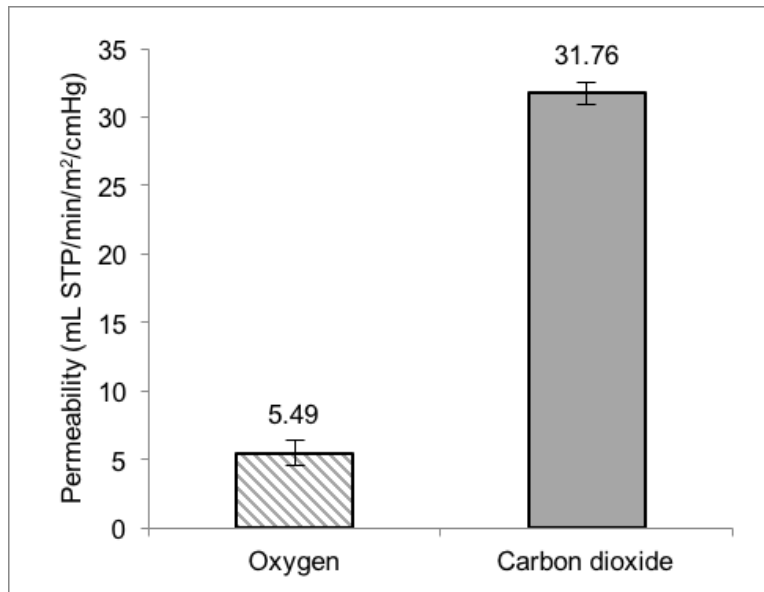


Figure 2.9. Dry gas mass transfer coefficients of PDMS-S μ M.

2.4.3 Gas transport *ex vivo*

Heparinized porcine whole blood was flowed over the PDMS-S μ M in a 50 μ m high by 9 mm wide by 9 mm long channel at 2 mL/min. Repeated oxygen saturation and desaturation of blood was achieved with no gross clots in the flow cell or tubing for 3 hr. Since oxygen partial pressures in the sweep gas and blood were sampled continuously, the time-dependent change of the oxygen partial pressure gradient ($pO_{2,gas}-pO_{2,blood}$) and total blood oxygen concentration (Q_{O_2} , from the oxygen-hemoglobin dissociation curve) was used to solve Eq. 1 for the membrane mass transfer coefficient, S . The effective oxygen mass transfer coefficient of the PDMS-S μ M in contact with blood was calculated to be $1.94 \pm 0.02 \text{ mL min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$ (Fig 2.10), approximately 35% of the oxygen transport achieved with dry gas. The oxygen transfer rate was consistent for the duration of the experiments, indicating negligible fouling of the membrane over the 3 hour period of the experiment.

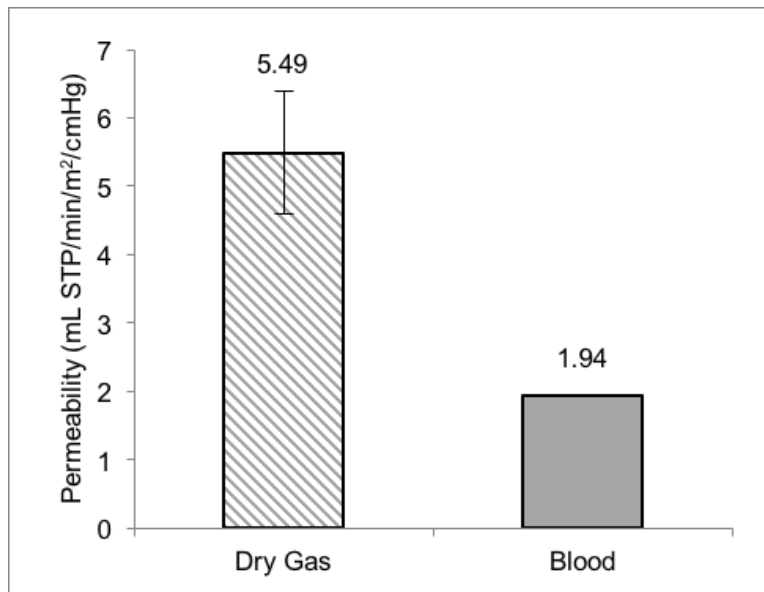


Figure 2.10. Comparison of membrane oxygen mass transfer in contact with dry gas and blood.

2.5 Discussion

2.5.1 Membrane structural characterization

Using SEM measurements, I found PDMS-S μ Ms to have uniform pore geometry with conformal PDMS film coating. Micropore dimensions were $3.55 \pm 0.03 \mu\text{m}$ long by $450 \pm 20 \text{ nm}$ wide, with a polysilicon membrane thickness of $480 \pm 20 \text{ nm}$. The PDMS film thickness was $4.63 \pm 0.11 \mu\text{m}$. The precision of these dimensions is important to the reliability of the membrane, especially at elevated transmembrane pressures, because it minimizes the likelihood that a region of PDMS film will rupture over an irregularly shaped pore and lead to blood plasma leakage or gas embolism. The integrity of the membrane was confirmed by hydraulic permeability tests, which exhibited no detectable flow of water across the membrane under 26 cmHg transmembrane pressure loading. Additionally, no reduction in sweep gas pressure was detected at fixed sweep gas flow rates for the duration of *ex vivo*, nor were gas emboli visible in the blood channel.

2.5.2 Membrane gas mass transfer

The expected mass transfer coefficient of a $4.63 \mu\text{m}$ thick PDMS film to oxygen and carbon dioxide is 79.3 and 397.9 $\text{mL min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$, respectively⁸⁰. Using the mean membrane dimensions measured by SEM in section 2.5.1, the pore area was calculated to be $4.98\text{E-}6 \text{ m}^2$ in a total membrane area of $3.60 \text{ E -}5 \text{ m}^2$, for a S μ M porosity of 13.8%. Assuming that gas exchange only occurred where PDMS spanned micropores in the S μ M, the current PDMS-S μ M design had a theoretical oxygen mass transfer coefficient of $10.98 \text{ mL STP min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$, and carbon dioxide mass transfer coefficient of $55.08 \text{ mL STP min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$.

While PDMS occlusion by the silicon beams of the S μ M reduced the total membrane area available for gas exchange, resistance to gas diffusive transport through the S μ M micropores was

not expected to significantly decrease performance. Using oxygen diffusivity values of $0.2 \text{ cm}^2 \text{ s}^{-1}$ in air and $2 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ in PDMS⁸⁰ as an analogue for permeability in Eq. 2, the S μ M micropores were predicted to reduce total gas exchange by less than 1% compared to an unobstructed PDMS membrane with area equivalent to the micropore area.

The observed PDMS-S μ M mass transfer coefficients for oxygen and carbon dioxide were 5.49 ± 0.89 and $31.76 \pm 0.80 \text{ mL STP min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$, respectively. The lower than expected mass transfer coefficients may have been a consequence of the use of 3:1 PDMS; highly crosslinked PDMS formulations such as this have been shown to undergo an irreversible decrease in gas permeability when exposed to oxygen plasma⁸⁴. Oxygen plasma exposure was used to bond the PDMS film to the S μ M. The PDMS formulation was chosen to make the uncured PDMS less viscous, allowing a thinner PDMS film to be formed at a lower spin coater speed and shorter spin duration.

When compared to the gas exchange achieved in microfluidic oxygenators by Potkay for oxygen and carbon dioxide of 22.2 and $88.24 \text{ mL min}^{-1} \text{ m}^{-2} \text{ cmHg}^{-1}$, respectively¹⁶, it is evident that the PDMS-S μ Ms are limited by the low porosity of the S μ M. However, while the PDMS film covering the S μ M is effectively unavailable for gas transfer, the silicon beams of the S μ M are essential to the mechanical integrity of the membrane. This design tradeoff permits the use of an open blood channel uninterrupted by structural supports, as well as a greater range of sweep gas pressures. Whereas pure PDMS microfluidic oxygenators typically operate with sweep gas at atmospheric pressure (76 cmHg maximum oxygen partial pressure gradient) to avoid deformation of the PDMS membrane into the blood channel, the PDMS-S μ Ms have demonstrated gas exchange at a sweep gas pressure of 52 cmHg relative to the blood channel (128 cmHg maximum oxygen partial pressure gradient). The mechanical strength of the PDMS-

S μ Ms allows for a wider range of sweep gas pressures to meet the variable oxygenation needs of patients.

2.5.3 Blood oxygenation *ex vivo*

Whole porcine blood was repeatedly oxygenated and deoxygenated using a 1 cm² PDMS-S μ M in a flow cell with blood channel height of 50 μ m and width of 9 mm. Oxygen partial pressure in the blood was measured using an inline optical sensor; due to the closed loop nature of the blood circuit and lack of carbon dioxide input, carbon dioxide exchange was not measured. The repeated cycles of oxygenation and deoxygenation by oxygen and nitrogen sweep gas, respectively, demonstrated proof of concept for gas transfer to and from blood using PDMS-S μ Ms. However, the observed oxygen mass transfer coefficient decreased approximately 65% relative to the dry gas transport experiments. This may be a result of boundary layer formation in the blood channel, forcing gas to diffuse through a cell-free layer of blood plasma^{15,85}, with low solubility for oxygen and carbon dioxide, before reaching circulating red blood cells.

A comparison between the current work and similar PDMS-based microfluidic oxygenator platforms is shown in Table 2.1. While the PDMS-S μ M utilizes the thinnest PDMS membrane component, the porosity of the S μ M alone does not account for the disparity in maximum oxygen exchange with blood. Further study is needed to identify the key contributing factors to the decreased gas exchange, including PDMS crosslinking, oxygen plasma exposure, and blood side gas diffusion lengths.

Table 2.1. Comparison of *ex vivo* blood oxygenation with microfluidic oxygenator platforms.

Oxygenator	Maximum oxygen exchange with blood (mL STP min ⁻¹ cmHg ⁻¹ m ⁻²)	PDMS membrane thickness (μm)
Current work	1.94	4.63
Monolithic PDMS microfluidic lung ⁵⁷	14.3	15
Multilayer PDMS microfluidic lung ⁶⁵	4.56	30
Extracorporeal gas exchange device (EGED) ⁷⁴	0.35	90

2.5.4 Design improvements

This first proof of concept and demonstration of PDMS-SμMs illustrates their promise, as well as the limitations of the initial design. A number of options exist for optimizing the membrane and blood channel geometry, which will be pursued in future studies. Decreasing the PDMS membrane thickness to 0.5 μm would increase PDMS-SμM gas mass transfer by nearly an order of magnitude, making the PDMS-SμM competitive with existing microfluidic gas exchange platforms. Our mechanical modeling suggests that, if all SμM dimensions are held constant, a 0.5 μm PDMS film would be able to withstand transmembrane pressures similar to those used in this study, and fabrication of sub-micron PDMS films has been demonstrated by others⁸⁶.

Additionally, given the small calculated deformation of the PDMS membrane component under transmembrane pressure up to 76 cmHg, it appears that 1 μm wide micropores could achieve a 23% SμM porosity with minor effects on the blood channel geometry. This would enable the PDMS-SμM to more closely approach the mass transfer of an unsupported PDMS film. However,

prior studies have noted that the low diffusivity of oxygen and carbon dioxide in blood can impose far greater resistance to gas transport than the membrane itself^{65,74}. Consequently, a thinner membrane will need to be pursued in concert with refinement to the blood flow path. Future iterations of the flow cell design will focus on decreasing the blood channel height to reduce the diffusion path length for oxygen to reach red blood cells from the blood-membrane interface. This could take the form of PDMS or other polymer gaskets to set PDMS-S μ M separation distances on the order of 10 μ m to mimic the critical dimension of alveolar capillaries⁸⁷. Branching capillary networks, which are typically a necessity in other microfluidic gas exchange systems⁵⁹, may be obviated in a PDMS-S μ M oxygenator by the use of blood channels on the order of 1 cm wide. It may also be possible to take advantage of Eq. 2.3 and employ arbitrarily wide blood channels if blood channel length can be held less than or equal to 1 cm. This would have the added effect of reducing the surface to volume ratio of the blood channel by removing the non-functional surface area of sidewalls or supports while maintaining the ratio of *membrane* surface to blood channel volume ratio.

For a human-scale parallel plate oxygenator, however, multiple stacked blood and gas layers will be required to provide sufficient membrane area for gas exchange. In this case, the thickness of the S μ M, approximately 400 μ m, must be taken into account when determining the overall oxygenator size and blood manifold requirements. Assuming the maximum gas exchange of 10.98 mL STP min⁻¹ m⁻² cmHg⁻¹ for oxygen and 55.08 mL STP min⁻¹ m⁻² cmHg⁻¹ for carbon dioxide achieved in this design, with pure oxygen sweep gas at 128 cmHg partial pressure gradient, the respiratory needs of a neonatal patient of 100 mL O₂ min⁻¹ and 80 mL CO₂ min⁻¹ would be met with 0.29 m² total membrane area, due to the lower CO₂ partial pressure gradient. If a hypothetical blood channel 10 cm wide by 1 cm long was achieved, then a stack of at least

29 blood channels would be required. The resulting 58 PDMS-S μ M layers would occupy a thickness of approximately 30 mm, not including the blood and sweep gas channels. Future studies will investigate the scalability of the PDMS-S μ M oxygenator concept.

2.6 Conclusion

I report a planar asymmetric membrane designed for use in a microfluidic oxygenator. I have fabricated a membrane consisting of a 4.63 μ m thick PDMS film supported by a 400 μ m thick rigid silicon micropore membrane (S μ M) with uniform 500 nm wide by 4 μ m long rectangular pores that provides a planar gas exchange surface without the need for structural supports in the blood channel.

Chapter 3: Hemocompatibility Studies of Gas Exchange Membranes

3.1 Introduction

Extracorporeal membrane oxygenation (ECMO) can enable the complete support of respiratory functions, including oxygenation and carbon dioxide ventilation, without the need for contributions from the native lungs. This approach allows patients to rest and recover from traumatic injury^{12,16,73}, disease-induced acute respiratory distress^{59,64,68}, or prepare for lung transplant. A typical ECMO system uses a mechanical pump to withdraw deoxygenated blood from the patient, via large diameter (~1/4") tubing, through a heat exchanger and oxygenator, before returning oxygen-rich blood to the body.

The current generation of clinical ECMO equipment is the product of more than 40 years of development^{12,75} directed towards reducing consumption of both ECMO components and blood products. This is exemplified by work aimed at minimizing circuit priming volume, avoiding shear-induced hemolysis, and increasing oxygenator membrane longevity^{46,70,81,88}. These endeavors have typically employed hollow fiber oxygenators, which are the current clinical standard of care^{69,89}. Hollow fiber oxygenators incorporate blood flow paths with a large cross sectional area to minimize hydraulic resistance, but are interrupted by the hollow fibers oriented orthogonal to the blood flow.

An area of active research is exploring the use of microfluidic gas exchange devices to mimic the anatomy of native lungs. In contrast to hollow fiber oxygenators, microfluidic devices employ

blood channels on the order of 100 μm wide^{59,71}, exhibiting laminar flow⁶⁵ and providing short gas diffusion distances on the order of 10 μm ⁵⁷. Microfluidic gas exchange devices have been mechanically limited by elastic membrane materials, such as polydimethylsiloxane (PDMS)⁶¹, which deform under pressure differences between the blood and sweep gas channels. The small channel widths necessitated by these flexible membranes contribute to a large total blood flow resistance. With a large surface area to volume ratio, microfluidic channels are also vulnerable to occlusion by blood clots unless a sufficient level of fluid shear is maintained. In turn, this requisite shear stress can lead to red blood cell hemolysis.

In order to maximize gas transfer while preventing blood stagnation, I adopted a hybrid approach to the challenge of miniaturization. Using a micron-thin PDMS film supported by a silicon micropore membrane (S μ M), it is possible to maintain a planar membrane surface without the need for support structures that could disrupt blood flow. The mechanical rigidity provided by the silicon substrate allows the membrane to withstand large pressure gradients between the blood and sweep gas without deforming or rupturing. Gas transport is highly dependent on blood flow in contact with the membrane surface⁷², and the PDMS-S μ M enables alternative flow geometries to be investigated, potentially granting much higher gas exchange than is currently possible with a hollow fiber approach and avoiding the hydraulic resistance imposed by narrow microfluidic channels.

With the aim of providing a viable alternative to existing gas exchange devices, the PDMS-S μ M needs to be capable of satisfying US Food and Drug Administration guidance for cardiopulmonary bypass oxygenators (21 CFR §870.4350) to provide respiratory support for at least 6 hours⁹⁰. In the present study, I sought to assess the stability of the membranes during prolonged exposure to whole blood under flow conditions. I hypothesized that membrane gas

exchange would decline as blood products accumulated on the untreated surface. The data collected provided a preliminary measure of the extent of fouling on the membrane surface, as well as the degree to which fouling reduced gas exchange in a miniature ECMO system.

3.2 Methods

3.2.1 PDMS coating of S μ Ms

S μ Ms, prepared as described in section 2.3.1, were coated with polydimethylsiloxane (PDMS) using a lift off process derived from Ingber and colleagues⁹¹. First, a 4-inch silicon wafer was silanized to prevent adhesion to PDMS by exposure to trichloro(1H, 1H, 2H, 2H-perfluorooctyl)silane (Sigma-Aldrich, St. Louis, MO, USA) vapor in a vacuum chamber for 36 hours. Sylgard 184 PDMS (Dow Corning, Midland, MI) was then mixed at a monomer to crosslinker ratio of 10:1 and spin-coated onto the silicon wafer at 500 rpm for 20 seconds. The PDMS was heat-cured at 80 °C for 2 hours to form a ~1 mm thick film, denoted as the “thick PDMS” layer (Fig 3.1A). The silanization process was repeated to passivate the thick PDMS.

A second PDMS layer was then prepared, using a 10:1 monomer:crosslinker ratio diluted with 50% hexanes (Sigma-Aldrich, St. Louis, MO, USA) by mass to reduce the mixture viscosity. The PDMS mixture was spin-coated atop the thick PDMS wafer at 6000 rpm for 5 minutes, then heat-cured at 80 °C for 2 hours to form a ~3 μ m thick film, denoted as the “thin PDMS” layer (Fig 3.1B). After curing, the thin and thick PDMS layers were peeled from the silicon wafer as one piece (Fig 3.1C). This allowed the thick PDMS layer to act as a flexible supporting substrate for the thin PDMS, preventing wrinkling of the thin film prior to transfer to the S μ M.

The S μ M and PDMS were both exposed to oxygen plasma at 100 W for 10 s. A 5 μ L drop of isopropyl alcohol was deposited on the surface of the thin PDMS layer, then the S μ M was settled

onto the PDMS, ensuring a conformal bond as the alcohol evaporated. The PDMS and S μ M were allowed to bond at room temperature for 24 hours. The thick PDMS layer was then removed, peeling away nearly parallel to the S μ M surface to minimize out-of-plane stresses on the membrane (Fig 3.1D), leaving the complete asymmetric membrane unit (Figs 3.1E and 3.2). S μ M pore dimensions, membrane polysilicon thickness, and PDMS film thickness were characterized using scanning electron microscopy (SEM).

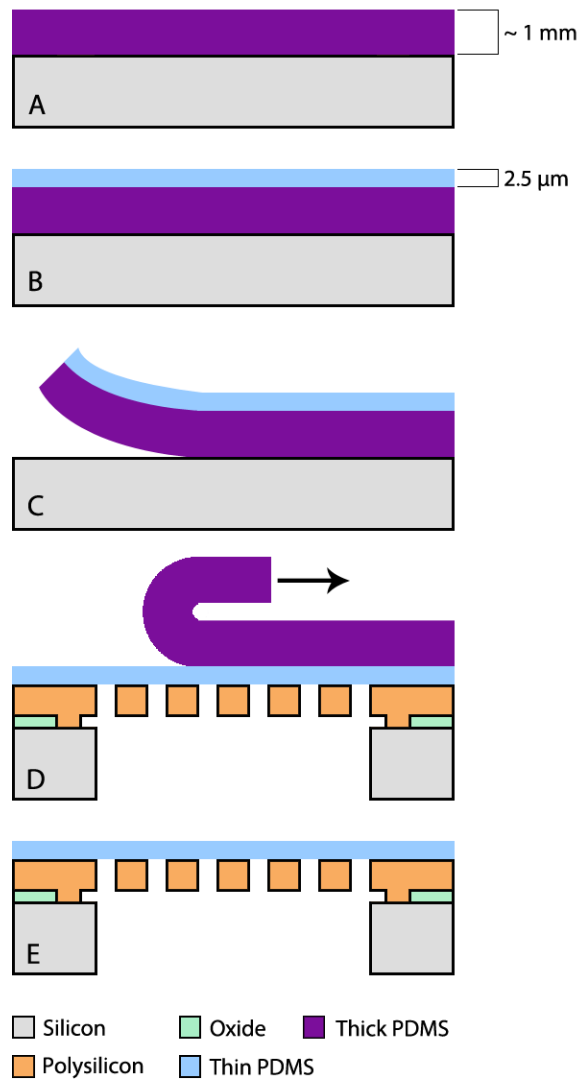


Figure 3.1. Process flow for polydimethylsiloxane (PDMS) bonding to S μ Ms. Cross-section illustrates a single membrane “window” (not to scale). (A) Thick PDMS layer (~ 1 mm) is spun onto silanized silicon wafer and heat cured. (B) Thick PDMS is silanized and spin coated with hexane-diluted PDMS to define thin PDMS film. (C) Thick and thin PDMS layers are peeled from silicon wafer as single sheet. (D) Thin PDMS layer is plasma-bonded to S μ M; thick PDMS is peeled away. (E) Complete PDMS-S μ M.

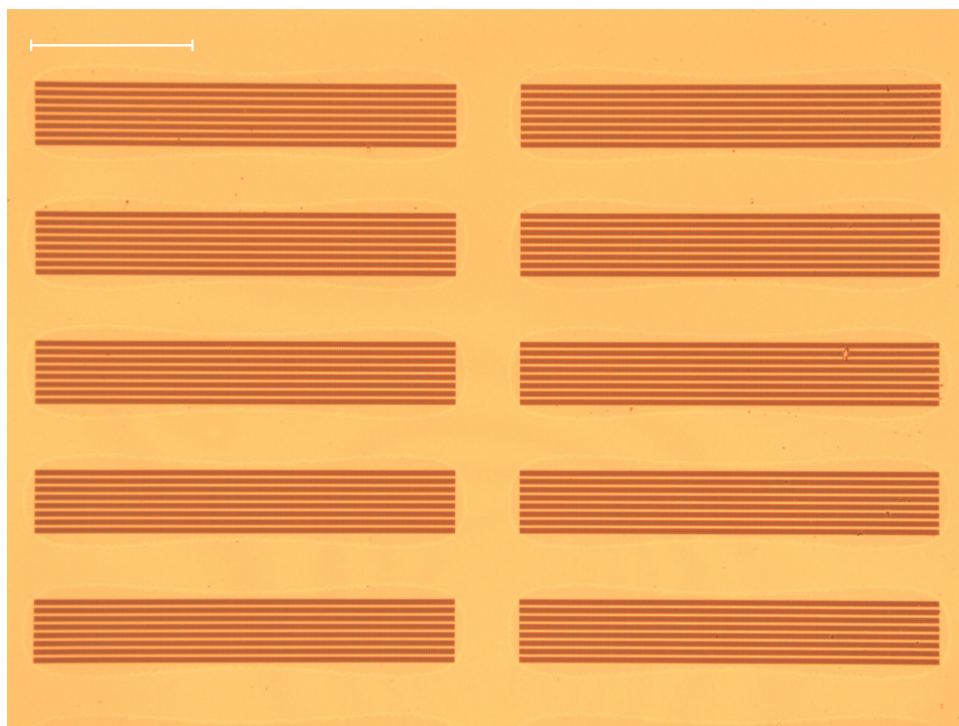


Figure 3.2. Light microscope image of PDMS-SμM. Dark regions are SμM micropores. Scale bar is 100 μm .

3.2.2 Membrane pressure loading

Membrane mechanical robustness was experimentally verified by subjecting the complete PDMS-SμMs to leak testing using a bench top hydraulic permeability testing system⁷¹, which is capable of measuring water flux per unit pressure on the order of nanoliters per minute in response to a transmembrane pressure gradient. Water was flowed in contact with the PDMS side of the membrane at a transmembrane pressure of 26 cmHg for 30 min. Any water that passed through fractures or tears in the membrane was collected and measured in a humidified chamber on a mass balance.

3.2.3 Gas diffusion testing

The PDMS-S μ Ms were tested for gas permeability in a dry bench-top flow cell connected to a pressurized gas supply and a bubble flow meter (Sigma-Aldrich, St. Louis, MO, USA), similar to a setup used by Burgess et al¹⁵. The pressurized gas, either oxygen or carbon dioxide, was applied to one side of the membrane to form a transmembrane partial pressure gradient between 70 and 140 cmHg. As gas diffused across the membrane, it displaced a meniscus of detergent in the bubble flow meter, which allowed direct measurement of the volume of gas transported across the membrane. By measuring the gas flux in the bubble flow meter, gas permeability could be calculated for the PDMS-S μ Ms as a function of gas flux per unit membrane area.

3.2.4 Blood channel and sweep gas channel geometry

The blood channel was 3D-printed using PolyJet HD (Solid Concepts, Inc., Valencia, CA, USA), a urethane-based resin, to define a channel over the PDMS-S μ M with dimensions of 1000 μ m x 800 μ m x 200 μ m (L x W x H), tapering at the inlet and outlet to interface with 1/16" Luer lock tubing connectors, shown in Fig 3.3. The sweep gas channel was machined from acrylic plastic to form a 3 mm tall chamber over the backside of the PDMS-S μ M. The complete device was assembled by compressing a 125 μ m thick silicone gasket between the PDMS-S μ M and the sweep gas chamber; the stack of components was secured with machine screws.

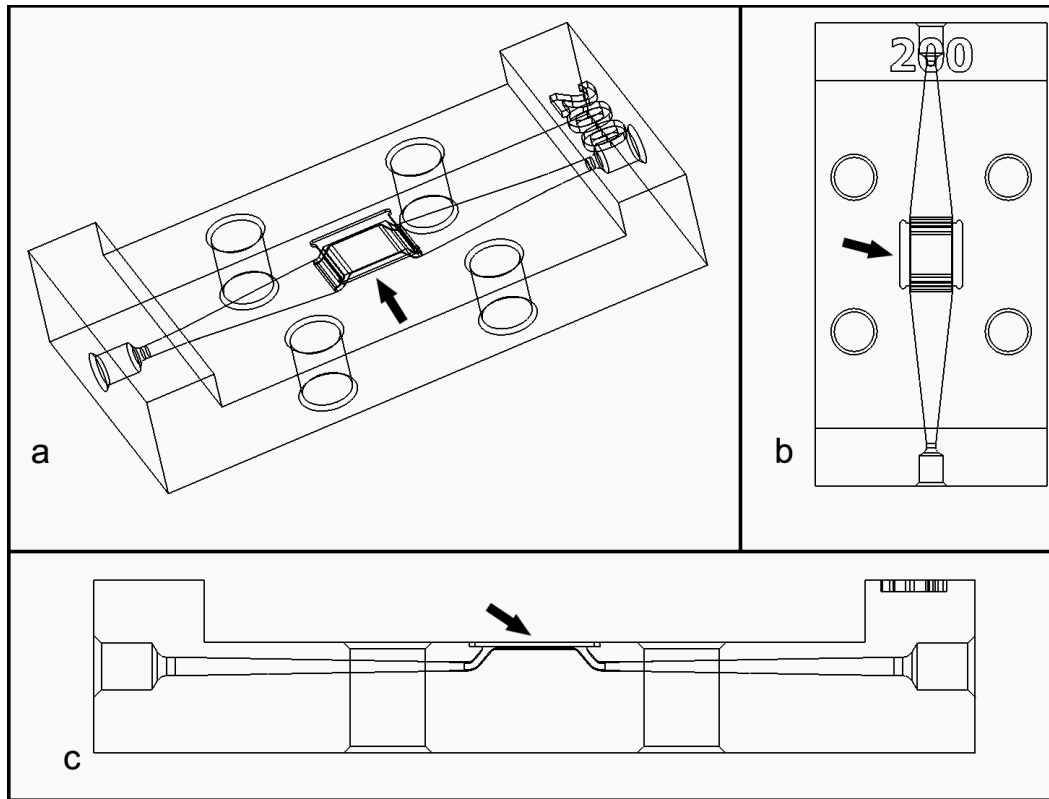


Figure 3.3. Schematic of blood side of flow cell. Membrane area with 200 μm tall blood channel is indicated by black arrows in isometric (a), top (b), and side (c) views.

3.2.5 Gas exchange *ex vivo*

Whole ovine blood was used in a 200 μm blood channel device. The blood was collected in citrate phosphate dextrose adenine (CPDA-1) bags from anesthetized sheep immediately prior to planned termination for an unrelated experiment. Testing was conducted over a 3-hour period. Blood was maintained in a warming bath at 39°C throughout the experiment and a peristaltic pump (Cole-Parmer, Vernon Hills, IL, USA) was used to circulate blood through the device with a digital pressure gauge (General Electric Measurement & Control, Billerica, MA, USA) monitoring blood inflow pressure continuously (Fig 3.4A). The blood channel, gas channel, and PDMS-S μM were assembled dry, then primed with 20 Units/mL heparin saline for 15 minutes

prior to introduction of blood into the circuit (Fig 3.4B). Pure oxygen sweep gas was supplied to the device at a flow rate of 2.5 L/min, maintaining sweep gas at a gauge pressure of 58 cmHg. Blood flow rates were set at 0.1, 0.2, 0.5 and 1 mL/min. Blood flow rates through the device were chosen to maintain wall shear stress below hemolysis thresholds⁸². The order of flow rates was determined using a random number generator, providing for two full cycles of the four flow rates. Three blood samples at each flow rate were collected from both the inlet and outlet, and analyzed at six-minute intervals for pO₂ and oxygen saturation (S_{O2}) using an ABL5 blood gas analyzer (Radiometer America, Westlake, OH, USA). The blood gas analyzer was automatically calibrated throughout the experiment. Blood was visually assessed for gross coagulation after each draw.

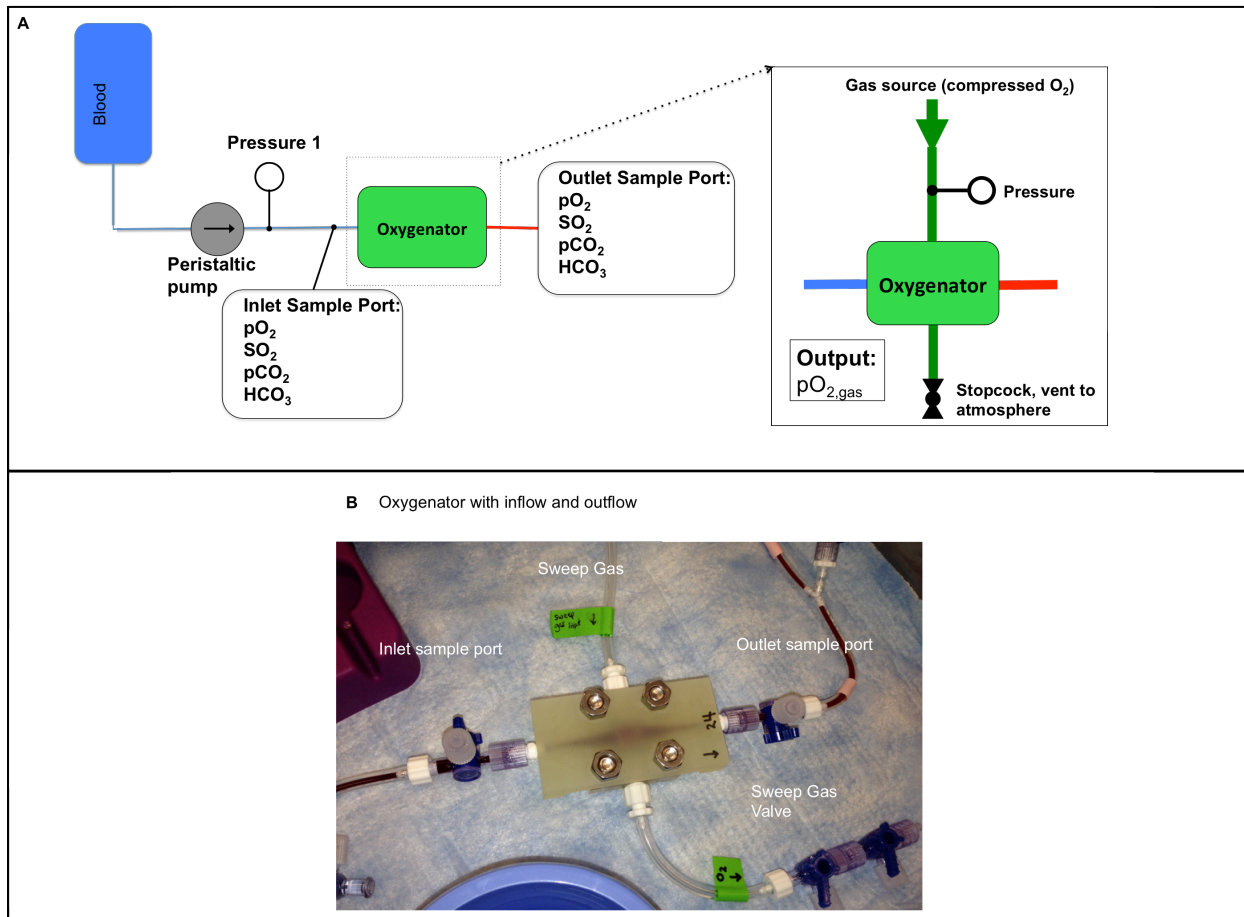


Figure 3.4. (A) Schematic of *ex vivo* gas exchange experiment. Citrated blood maintained at 39°C in water bath was pumped through the oxygenator, with blood samples collected at the oxygenator inlet and outlet in a single-pass manner. (B) Oxygenator with 0.36 cm² membrane area; pure oxygen sweep gas flows across the backside of the membrane while whole blood flows in contact with the PDMS film.

3.2.6 Gas exchange *in vivo*

For *in vivo* testing, a similar circuit with 200 µm tall blood channel was utilized (Fig 3.5A), with the device inflow and outflow ports connected to an adult ewe sheep with bilateral saphenous vein catheters.

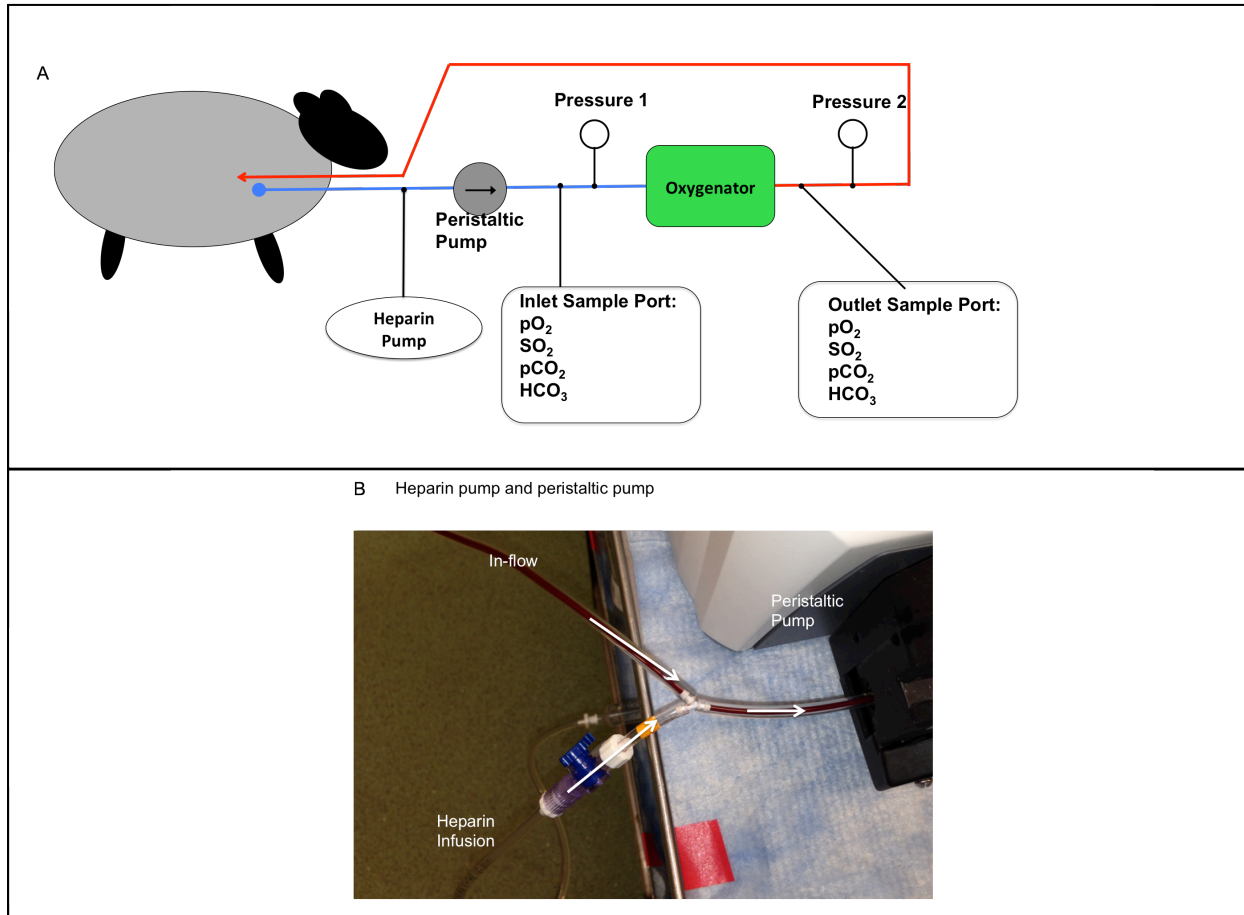


Figure 3.5. (A) Schematic of *in vivo* gas exchange experiment. Venous blood from an adult ewe was withdrawn by a peristaltic pump and anti-coagulated by an inline heparin infusion pump (B). Blood samples were collected at the oxygenator inlet and outlet before returning to systemic circulation via a separate venous line.

The venous inlet on the right leg used 8 Fr tubing, while the venous return to the left leg used 7 Fr tubing. The animal was sedated with a continuous drip of ketamine at $0.3 \text{ mg kg}^{-1} \text{ min}^{-1}$, diazepam at $0.002 \text{ mg kg}^{-1} \text{ min}^{-1}$, and fentanyl at $1 \text{ } \mu\text{g kg}^{-1} \text{ hr}^{-1}$ for anesthesia and analgesia using an internal jugular vein catheter. Hemodynamics were monitored continuously through a femoral arterial line. The ewe was maintained on room air for the duration of the experiment without

advanced airway control. A heparin bolus of 100 U kg^{-1} was administered immediately prior to connection of the saphenous catheters to the device and a continuous infusion of heparin at 20 U min^{-1} from a syringe pump (KD Scientific, Holliston, MA, USA) was used to prevent coagulation in the device (Fig 3.5B). A peristaltic pump (Cole-Parmer, Vernon Hills, IL, USA) was used to circulate blood through the device with a digital pressure gauge (General Electric Measurement & Control, Billerica, MA, USA) monitoring blood inflow pressure continuously. The blood channel, gas channel, and PDMS-S μ M were assembled dry, then primed with 20 U mL^{-1} heparin in 0.85% saline for 15 minutes prior to introduction of blood into the circuit. Pure oxygen sweep gas was supplied to the device at a flow rate of 2.5 L min^{-1} , maintaining a sweep pressure of 52 cmHg for a maximum oxygen partial pressure gradient of 128 cmHg. Blood flow rates were set at 0.1, 0.2, 0.5 and 1 mL min^{-1} . The order of flow rates was determined using a random number generator, providing for two full cycles of the four flow rates. Three blood samples at each flow rate were collected from both the inlet and outlet, and analyzed at six-minute intervals using an ABL5 blood gas analyzer (Radiometer America, Westlake, OH, USA). At the conclusion of the experiment, the animal was euthanized while sedated using sodium pentobarbital. The experimental protocol was approved by the Institutional Animal Care and Use Committee at the University of California San Francisco.

3.2.7 Platelet and blood endothelial cell adhesion on membranes

Following blood exposure, PDMS-S μ Ms were fixed in 4% paraformaldehyde, then incubated with CD31 primary antibodies and FITC-conjugated secondary antibodies to label adhered platelets and other blood endothelial cells. Membrane images were obtained using an epifluorescent microscope (Nikon 6D from UCSF Nikon Center). Image analysis was conducted

using NIH ImageJ (National Institutes of Health, Bethesda, MD). Images were color thresholded to exclude background fluorescence and reflection from the PDMS-S μ M; the area of the image above the threshold (indicating fluorescent signal from labeled blood products) was measured, allowing calculation of the percentage of the membrane surface that was occluded by adhered platelets and other blood cells.

3.3 Results

3.3.1 Membrane characterization

Scanning electron micrographs of the PDMS-S μ M confirmed the presence of a conformal PDMS film with a thickness of $3.25 \pm 0.08 \mu\text{m}$; the polysilicon support layer of the S μ M was measured to be $0.96 \pm 0.06 \mu\text{m}$ thick (Fig 3.6A). S μ M pore dimensions were $0.48 \pm 0.01 \mu\text{m}$ wide and $3.57 \pm 0.01 \mu\text{m}$ long (Fig 3.6B). No water flow was detected across the PDMS-S μ M during hydraulic permeability testing up to a maximum applied transmembrane pressure of 26 cmHg, confirming the integrity of the PDMS gas exchange membrane.

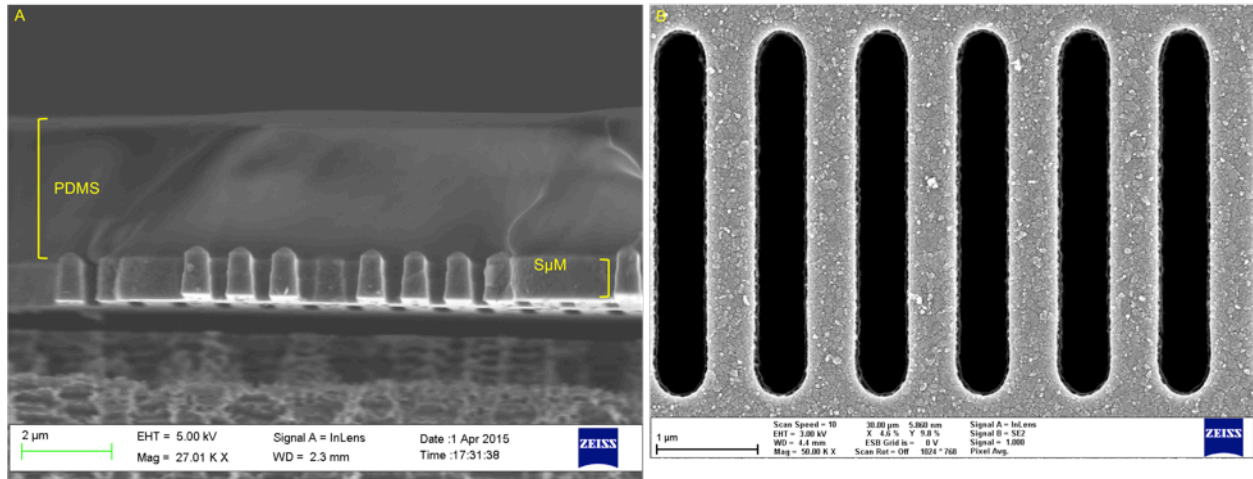


Figure 3.6. (A) Cross section SEM of PDMS-SμM. Blood flows in contact with the PDMS film, while sweep gas flows on the silicon membrane side, diffusing through the PDMS to the blood. (B) Top view SEM of SμM, showing repeated micropores.

3.3.2 Membrane gas mass transfer

Collection of 100 μL carbon dioxide and 10 μL oxygen gas permeate was conducted three times for each membrane. The volumes were chosen to allow rapid collection of the target gas before the gas concentration gradient on each side of the membrane became equalized. A set of six PDMS-SμMs were tested, producing gas permeability results of 6.70 ± 0.80 mL

STP/min/cmHg/m² for oxygen and 43.26 ± 5.80 mL STP/min/cmHg/m² for carbon dioxide (Fig

3.7). Two of the most similar PDMS-SμMs were selected for comparative studies between *in*

vivo and *ex vivo* blood oxygenation experiments. For *in vivo* testing, the selected membrane had

the following permeability: 6.21 ± 0.84 mL STP/min/cmHg/m² for O₂ and 47.32 ± 1.31 mL

STP/min/cmHg/m² for CO₂. The membrane selected for *ex vivo* testing exhibited similar

permeability: 6.22 ± 1.01 mL STP/min/cmHg/m² for O₂ and 47.48 ± 7.93 mL STP/min/cmHg/m² for CO₂.

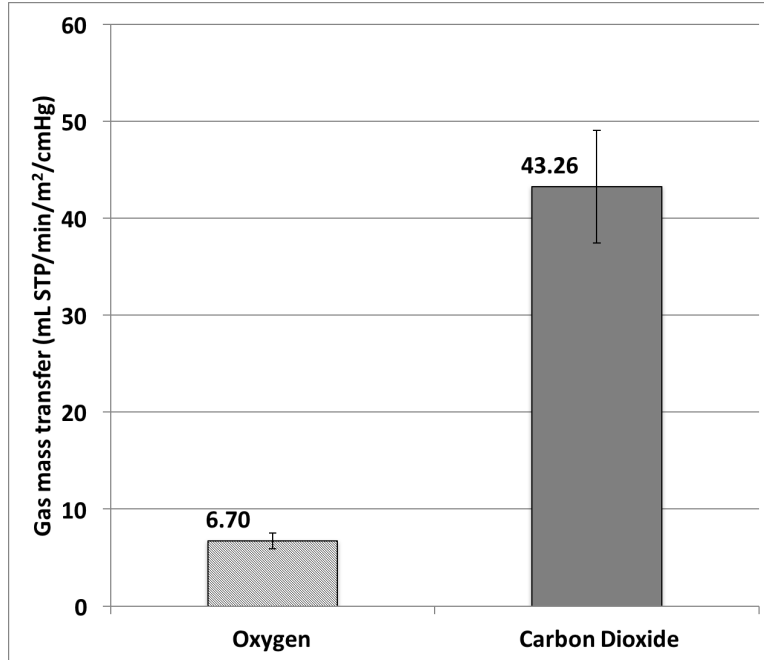


Figure 3.7. Membrane mass transfer coefficients for oxygen and carbon dioxide. Transport was measured by transmembrane diffusion from pure sample gas to room air.

3.3.3 Blood oxygenation *ex vivo*

Citrated whole ovine blood was flowed along a PDMS-S μ M in a 200 μ m high channel for 3 hours in a single-pass experiment. Blood pressure drop across the device remained below 5 mmHg (Fig 3.8), with no visible obstructions to the blood flow across the membrane for the duration of the experiment (Fig 3.9). No visible coagulation was detected in blood drawn from the inlet or outlet sample ports. The pH, pCO₂, and pO₂ of blood at the inlet sample port remained stable throughout the 2 hr experiment, with pH 6.97 ± 0.12 , pCO₂ 93.5 ± 3.7 mmHg, and pO₂ 40.8 ± 1.7 mmHg. Oxygen mass transfer as a function of blood flow rate is plotted in Fig 3.10. Maximum mass transfer for oxygen was 2.65 ± 1.75 mL STP/min/cmHg/m² at 0.5 mL/min blood flow.

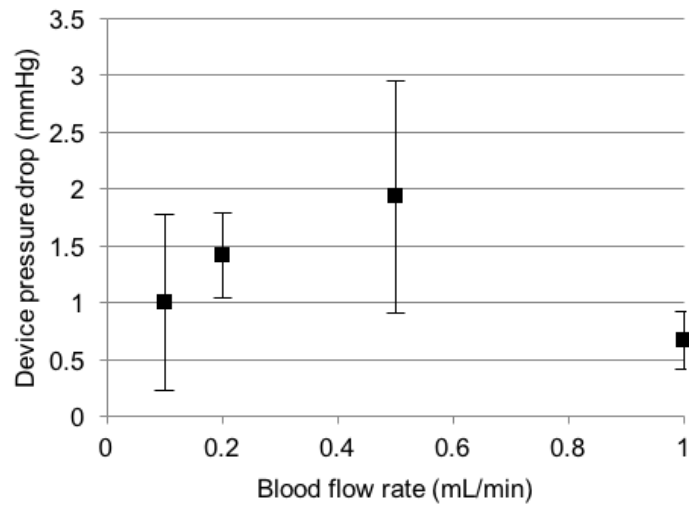


Figure 3.8. Device hydraulic pressure drop versus blood flow rate during *ex vivo* experiment.

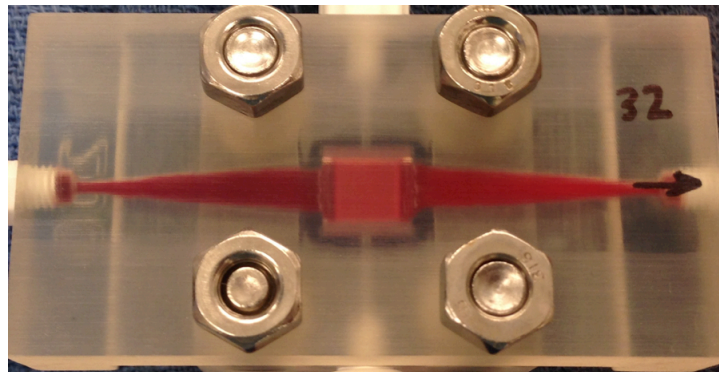


Figure 3.9. Citrated whole blood flowing through 200 μm high blood channel during *ex vivo* testing.

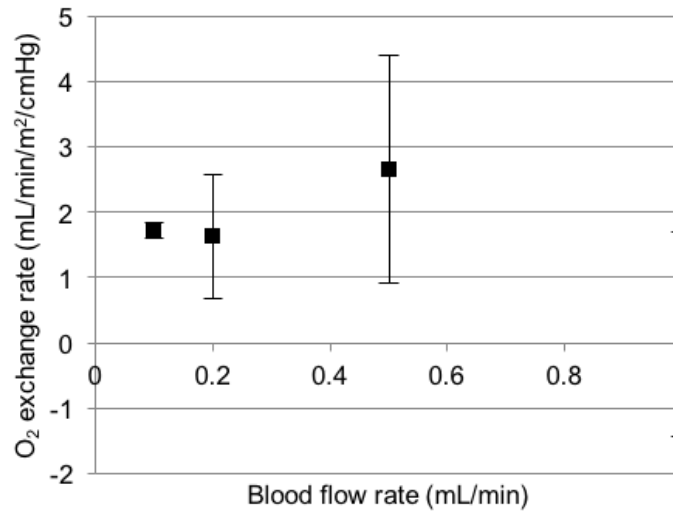


Figure 3.10. Ovine blood *ex vivo* gas exchange versus blood flow rate.

3.3.4 Blood oxygenation *in vivo*

Heparinized venous whole blood from an adult ewe was flowed over the PDMS-S μ M in a 200 μ m high by 10 mm long by 9 mm wide channel at 0.1, 0.2, 0.5, and 1 mL/min, before returning to the systemic circulation. The pH, pCO₂, and pO₂ of blood at the inlet sample port remained stable for the duration of the 1.5 hr experiment, with pH 7.36 ± 0.01 , pCO₂ 43.2 ± 2.7 mmHg, and pO₂ 45.0 ± 5.6 mmHg. Hydraulic pressure drop across the oxygenator flow cell remained between 5-11 mmHg throughout the experiment, as shown in Fig 3.11, although disruption to the blood flow path was visible at the conclusion of the experiment, as shown in Fig 3.12. Blood gas measurements were used to calculate the oxygen transport rate, which was plotted against blood flow rate through the oxygenator circuit in Fig 3.13. Maximum mass transfer for oxygen was 1.21 ± 0.32 mL STP/min/cmHg/m² at 0.5 mL/min blood flow.

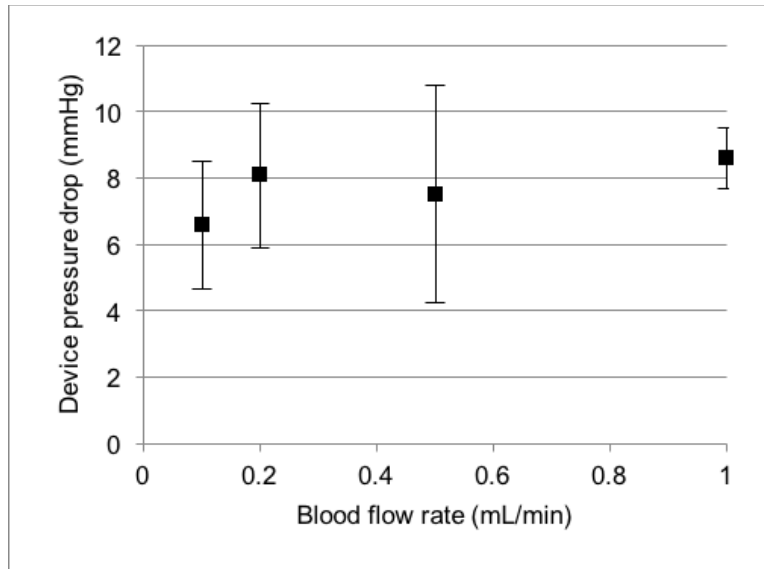


Figure 3.11. Device hydraulic pressure drop versus blood flow rate during *in vivo* experiment.

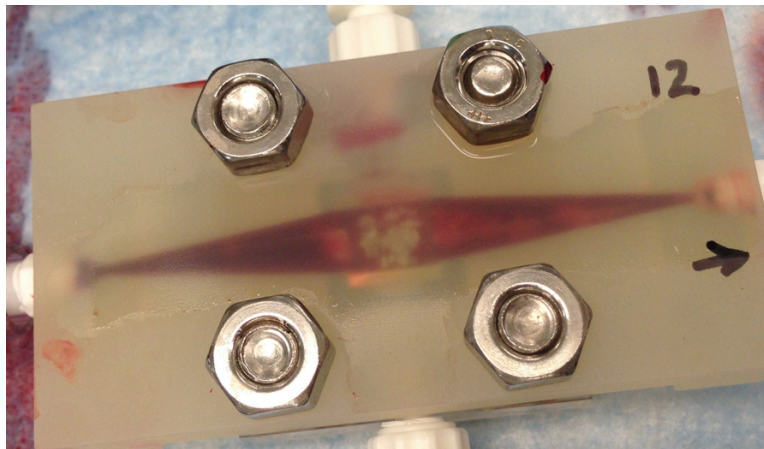


Figure 3.12. Heparinized whole blood flowing through 200 μm high blood channel at conclusion of *in vivo* testing; note disruption of blood flow over membrane surface.

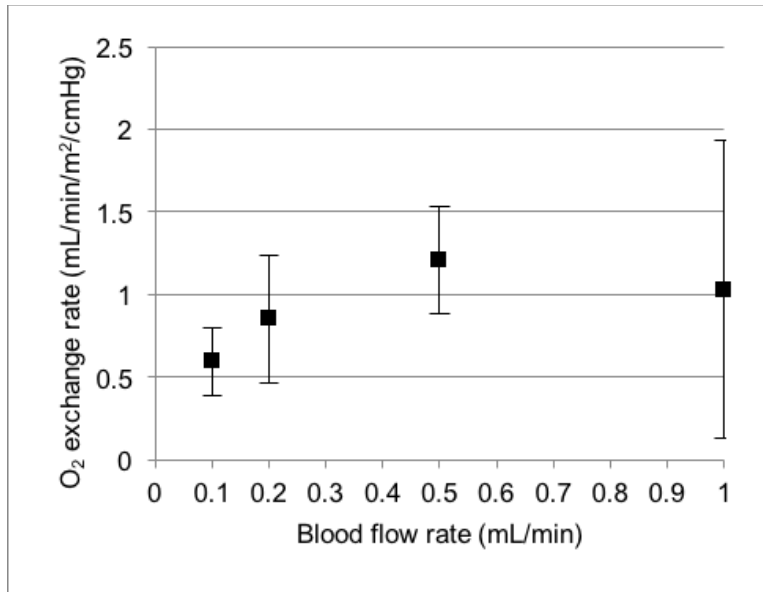


Figure 3.13. Ovine *in vivo* gas exchange versus blood flow rate.

3.3.5 Platelet and blood endothelial cell adhesion on membranes

CD31-stained membranes showed minimal adhered cells after exposure to citrated blood *ex vivo* (Fig 3.14A), with less than 0.05% occlusion ($<0.0002 \text{ cm}^2$) of the total 0.36 cm^2 membrane area. However, 12.5% of membrane area (0.045 cm^2 out of 0.36 cm^2) was occluded by cells and platelets after exposure to heparinized blood *in vivo* (Fig 3.14B).

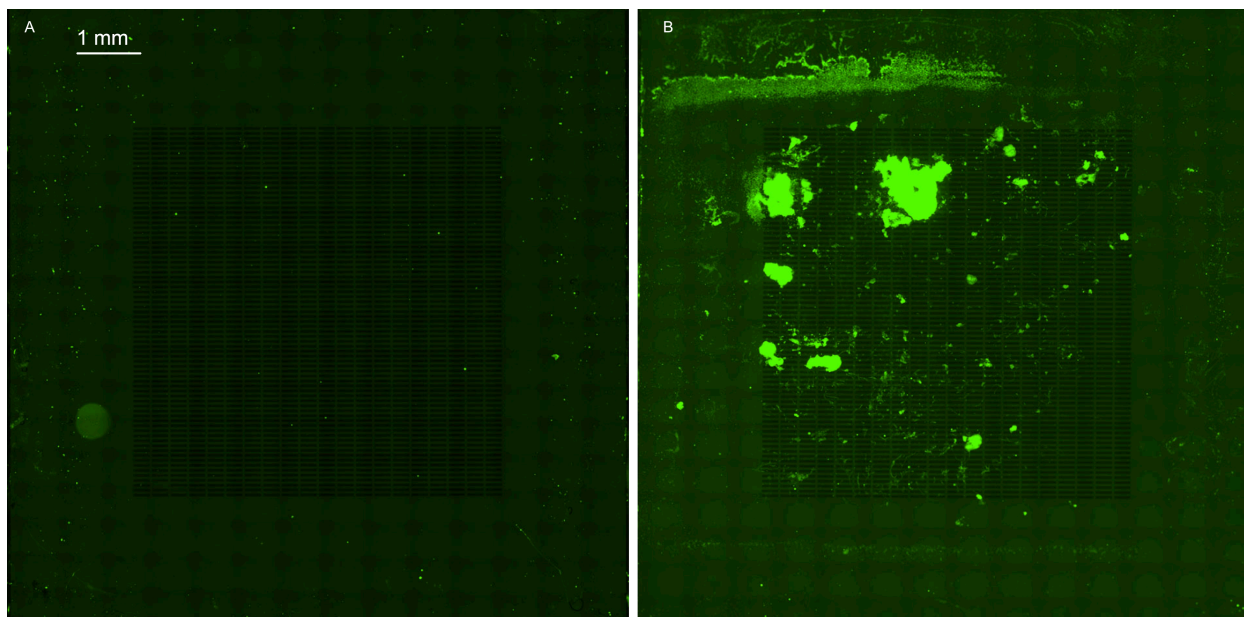


Figure 3.14. (A) Epifluorescence image of CD31-labeled PDMS-S μ M following conclusion of *ex vivo* blood oxygenation experiment; <0.05% membrane surface area is occluded by adhered platelets and other blood endothelial cells. (B) CD-31 labeling of adhered blood cells on PDMS-S μ M following *in vivo* blood oxygenation experiment showed 12.5% occlusion of membrane surface area.

3.4 Discussion

3.4.1 Gas transport from pure gas to ambient air

In 2009, Burgess et al. utilized a gas exchange device comprised entirely of PDMS, with a 146 μ m thick membrane and 100 μ m wide microchannels¹⁵. Potkay used similarly all-PDMS design with a membrane thickness of 15 μ m spanning an array of 132 μ m wide microchannels¹⁶. The membrane used for the current study is competitive with the other designs when gas exchange performance is normalized for transmembrane partial pressure gradients; the thinner PDMS film in the PDMS-S μ M counteracts the effects of membrane occlusion by the polysilicon membrane components. It should be noted, however, that the PDMS-S μ M is designed to operate under

sweep gas partial pressures in excess of 120 cmHg, enabling much higher overall gas exchange, especially of oxygen.

3.4.2 Blood oxygenation *ex vivo*

Although the observed membrane mass transfer with dry air was 6.70 ± 0.80 mL STP/min/cmHg/m², the maximum transport achieved between pure oxygen sweep gas and blood *in vivo* was 2.65 ± 1.75 mL STP/min/cmHg/m², which was achieved at a blood flow rate of 0.5 mL/min. Gas exchange rate was likely limited by the formation of a plasma boundary layer at the interface between the membrane surface and blood. Under no-slip boundary conditions, blood plasma near the membrane surface is static, forcing oxygen to diffuse through plasma before reaching red blood cells. The native lungs minimize this issue by using blood channels of the same diameter as the red blood cells⁹², forcing the alveolar capillary endothelium and red blood cell membrane into nearly direct contact and allowing full oxygen saturation of blood with minimal capillary residence time. Due to material biocompatibility limitations, it is important to reduce blood exposure to the device surface, making the use of capillary channels less attractive than wide rectangular channels.

3.4.3 Blood oxygenation *in vivo*

In the *in vivo* demonstration with an adult ewe, a 200 μ m blood channel was used for gas exchange in order to reduce the surface to volume ratio of the blood circuit, and thereby decrease the risk of clot formation near the membrane. At blood flow rates of 0.1, 0.2, 0.5, and 1 mL/min, the measured membrane oxygen transport was 0.59, 0.85, 1.21, and 1.03 mL min⁻¹ m⁻² cmHg⁻¹, respectively. However, the large variations in oxygen transport measurements at 1 mL/min blood

flow make it difficult to accurately determine the maximum gas exchange for this membrane and blood channel geometry combination. Additional experiments are needed to evaluate the extent to which increased blood flow rate and correspondingly increased shear may enhance gas exchange.

3.4.4 Differences between oxygen transport *in vivo* and *ex vivo*

While the initial cycle of blood flow rates produced similar oxygen exchange in both *ex vivo* and *in vivo* experiments, the apparent effects of membrane fouling were much more apparent in the heparinized blood *in vivo*, whereas the citrated blood *ex vivo* successfully achieved oxygen saturation at low flow rates during the final cycle of blood flow rates. This is likely to result from the different anticoagulation regimens; heparin was used *in vivo* to avoid the calcium chelation effects of citrate⁹³.

3.4.5 Membrane fouling

Analysis of membranes fluorescently labeled for CD31 showed less than 0.05% coverage of membrane area by adhered platelets and blood endothelial cells *ex vivo*, while 12.5% of the membrane surface area was occluded after 3 hours exposure to flowing blood *in vivo*. The most significant difference in blood conditions between the two experiments was the use of citrated blood *ex vivo* and heparinized blood *in vivo*. Citrate acts as a chelating agent to remove calcium from blood plasma, which is a key factor in the coagulation cascade⁹³, while heparin functions on a single part of the coagulation cascade by activating antithrombin⁹⁴. Since a greater than 12.5% decline in gas exchange (from 1.38 to 1.03 mL min⁻¹ m⁻² cmHg⁻¹ at 0.5 mL min⁻¹ blood flow) was observed in the *in vivo* experiment, and non-CD31 expressing red blood cells were not

visible on the membrane surface, it is possible that non-specific adhesion by blood proteins also inhibited gas transfer to a greater extent in heparanized blood *in vivo* versus the citrated blood *ex vivo*. Additionally, the non-uniform blood flow over the membrane surface *in vivo* likely was a result of blood coagulation in the device inlet, which was not dislodged after flushing with saline upon conclusion of the experiment.

3.4.6 Performance comparison with other microfluidic gas exchange membranes

A comprehensive list of existing experimental microfluidic gas exchange membranes and their corresponding gas exchange performance with blood has been reviewed by Potkay⁵⁹. Due to the much higher sweep gas partial pressure (>120 cmHg) used in the PDMS-S μ M system, the oxygen exchange rate is competitive with other oxygenator designs, at 317 mL O₂ STP/m²/min. However, the carbon dioxide mass transfer with blood needs to be further evaluated for the PDMS-S μ Ms.

3.5 Conclusion

I have demonstrated, *ex vivo* and *in vivo*, a novel PDMS-silicon gas exchange membrane in a parallel plate geometry. While diffusive transport of both oxygen and carbon dioxide between pure gas and room air provides gas exchange comparable with clinical oxygenators, limitations in the design of the blood channels used in our study restricted gas exchange with blood *ex vivo*.

Chapter 4: Future Directions

PDMS-S μ Ms fit between the two paradigms of hollow fiber (macro scale blood flow) and microfluidic (micro scale blood flow) oxygenators, more closely approaching the design goals envisioned for the parallel plate oxygenators of the 1960s. Due to their mechanical robustness, PDMS-S μ Ms enable blood flow through wide, rectangular channels free of disrupting support structures; the design results in a linear decrease in hydraulic pressure drop across the oxygenator when compared to the capillary channels present in current microfluidic research platforms. Simultaneously, the uniform planar structure of the PDMS-S μ Ms allows for blood channel heights approaching the 10 μ m scale found in the alveolar capillaries of the native lungs; the small dimension results in a dramatically reduced boundary layer between the membrane surface and the red blood cells and provides for much more rapid gas exchange. Taken together, these features make it possible for future oxygenators to not only match the blood-friendly flow characteristics and thrombus tolerance of current hollow fiber oxygenators, but also to exceed the gas exchange capabilities of both hollow fiber and microfluidic capillary oxygenators. The work discussed in this dissertation provides an intriguing proof of concept of using PDMS-S μ Ms for gas exchange in both bench top and *in vivo* environments. While further improvements to the membrane design, including thinner PDMS films and greater S μ M porosity, will enhance gas permeability and require lower sweep gas pressure, the observed discrepancy in gas exchange between dry air and blood environments suggests that improvements in the blood flow path alongside the membrane could yield the most noticeable advances. Initially, this will entail the fabrication of new blood channels using PDMS or other suitable blood contacting material

that can be molded or machined with an 8-10 μm channel height and surface roughness matching the PDMS surface of the PDMS-S μM . These modifications will allow for demonstration of gas exchange approaching that observed in dry air. Ultimately, scale up of a PDMS-S μM oxygenator will require several key steps: 1) dicing of larger S μM wafers to define wide ($\sim$ 6-10 cm) channels; 2) molded or machined spacers of PDMS or other material to set the blood and sweep gas channel heights and allow true parallel plate geometry with membranes on both “floor” and “ceiling” of the channel; 3) design and fabrication of a blood manifold to safely route blood from a single inlet catheter into multiple parallel blood channels. These tasks will allow the production of larger oxygenators for more clinically relevant experiments with more complete respiratory support of live animals, and ultimately, human patients.

While current experiments have shown that inline heparin administration can enable 3-hour oxygenation trials *in vivo*, extended duration tests will require the application of hemocompatible coatings to the membrane surface. Polyethylene glycol⁶⁷ and slippery, liquid-infused, porous surfaces (SLIPS)⁹⁵ have both been demonstrated as viable blood-contacting coatings on PDMS. An additional avenue of investigation is the use of PDMS-S μM s for ECMO as an adjunct therapy in support of other treatment regimens. Historically, ECMO has often been used in combination with mechanical ventilation⁹⁶ to allow low blood flow and low ventilation settings that minimize hemolysis and barotrauma, respectively, while meeting the full respiratory requirements of the patient. More recently, research has focused on the use of low blood flow ECMO for carbon dioxide ventilation, known as extracorporeal carbon dioxide removal (ECCO₂R)⁹⁷⁻¹⁰¹. ECCO₂R devices such as the Novalung rely on membrane surface areas equivalent to conventional oxygenators⁴⁸, but can operate at lower blood flows (1-2 L/min in adult patients) to remove carbon dioxide and combat hypercapnia in patients whose oxygenation

needs are already met with other methods. The advantage of ECCO₂R lies in its low blood flow, which allows low resistance oxygenators to operate in a pump-free manner when connected between an arterial and venous blood supply, as is commonly possible with femoral cannulation. However, the size and placement of current ECCO₂R systems necessitates that patients generally remain bedridden. A more compact PDMS-S μ M-based ECCO₂R device, made possible by lower surface area and priming volume, could be connected to a smaller blood supply, such as in an arm fistula, thereby providing carbon dioxide removal to ambulatory patients.

A long-term goal is to develop a wearable PDMS-S μ M oxygenator, with an integrated ventricular assist-type blood pump, to supply full respiratory support to awake and ambulatory patients. Whether it is used to help patients recover from illness, heal from surgery, or prepare for a lung transplant, such a device will provide a true bridge from sickness to health.

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Appendix: Membrane Fabrication Methods

A.1 Direct spin coating of PDMS on SNMs

PDMS coating of silicon membranes was first attempted using silicon nanopore membranes (SNMs) identical to those used for hemofiltration as part of an implantable artificial kidney^{76,77,102}. To achieve initial proof of concept, SNMs were secured polysilicon-side-up on a silicon wafer using Kapton polyimide tape (DuPont, Wilmington, DE, USA) and approximately 1 g of uncured PDMS mixture with monomer:crosslinker ratio of 3:1, 5:1, or 10:1 was deposited on the SNM face. The wafer was then spun in a spin coater at 3000, 4500, or 6000 rpm for 2 minutes. The wafer and PDMS-SNM were cured in an oven at 80°C for 2 hours, after which the PDMS-SNM was removed from the wafer. Due to the sharp boundary between the tape-covered and PDMS-coated regions of the SNM, the PDMS film thickness could be readily measured using a contact profilometer. An example of a complete PDMS-SNM is shown in Fig A.1. The average PDMS film thickness is shown in Fig A.2.

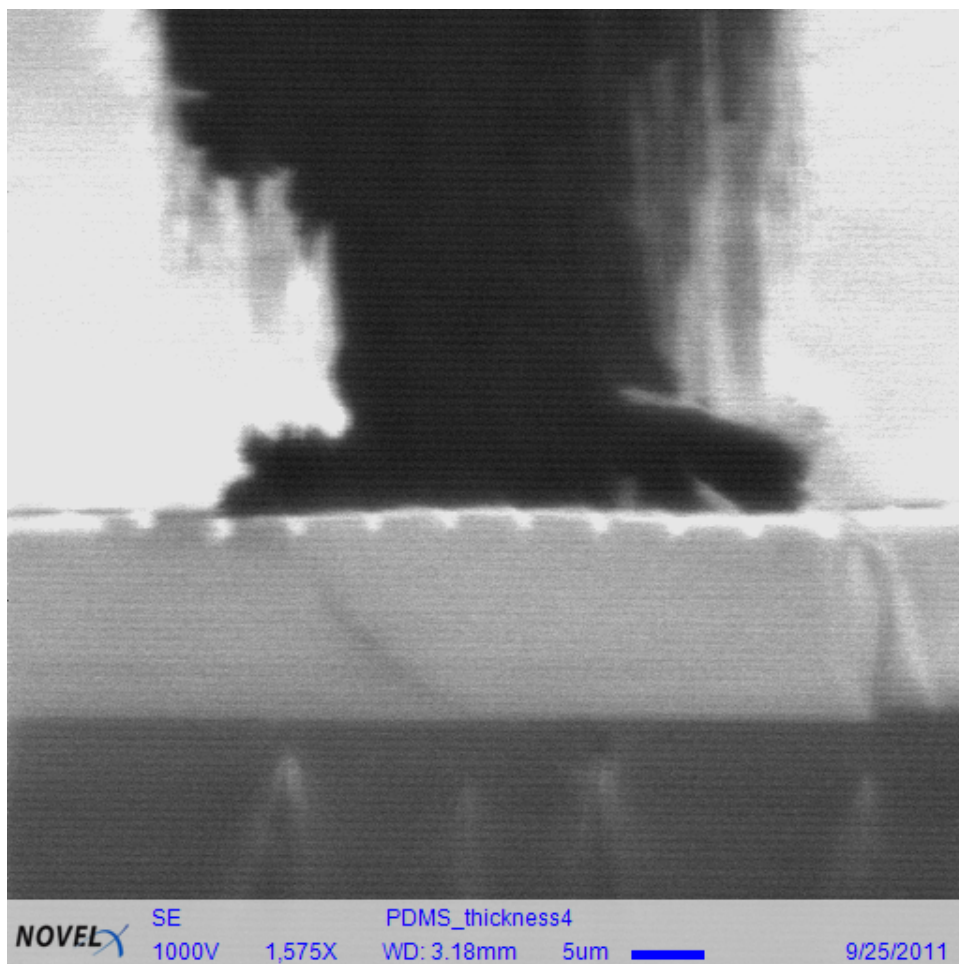


Figure A.1. Cross section of PDMS-SNM. PDMS film is oriented below the polysilicon layer of the SNM. The cavity at the top of the image is the SNM window.

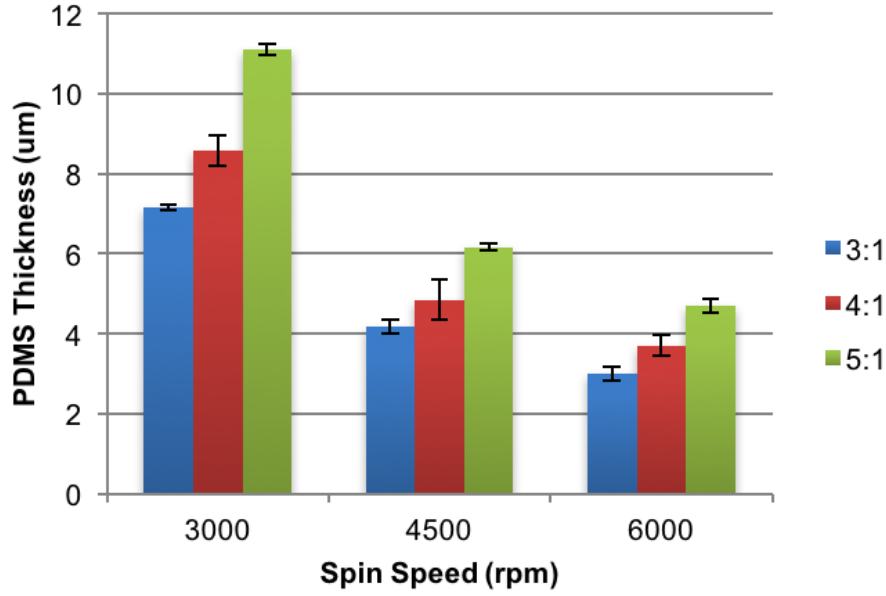


Figure A.2. PDMS film thickness achieved at varying spin coating rotational speed using 3:1, 4:1, and 5:1 PDMS monomer:crosslinker mixtures.

Using n=6 PDMS-SNMs with 3:1 PDMS film spun at 6000 rpm for 2 minutes, giving an approximate PDMS film thickness of 3 um, gas permeability was tested using a bubble flow meter and pressurized sources of pure oxygen and carbon dioxide. Oxygen mass transfer was measured to be $2.82 \pm 0.45 \text{ mL O}_2 \text{ STP cmHg}^{-1} \text{ min}^{-1} \text{ m}^{-2}$, and carbon dioxide mass transfer was measured to be $10.9 \pm 2.15 \text{ mL CO}_2 \text{ STP cmHg}^{-1} \text{ min}^{-1} \text{ m}^{-2}$.

The gas mass transfer observed for PDMS-SNMs was found to be negatively affected by uncured PDMS infiltrating open pores in the SNM during spin coating, resulting in a gas diffusion path through the PDMS that included the film thickness, as well as much of the pore length of the SNM. The capillary pressure acting to drive PDMS into the SNM pores was estimated as $P_c = \gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right)$, where R_1 and R_2 are the radii of curvature of the PDMS as it

contacts the wall of the SNM nanopores, described as $R = \frac{a}{\cos\theta_c}$. The uncured PDMS surface tension is $\gamma = 2.15 \times 10^{-2}$ N/m, the PDMS contact angle on polysilicon is $\theta_c = 50^\circ$, and a is the half-width or half length of the SNM nanopore, as shown in Fig A.3.

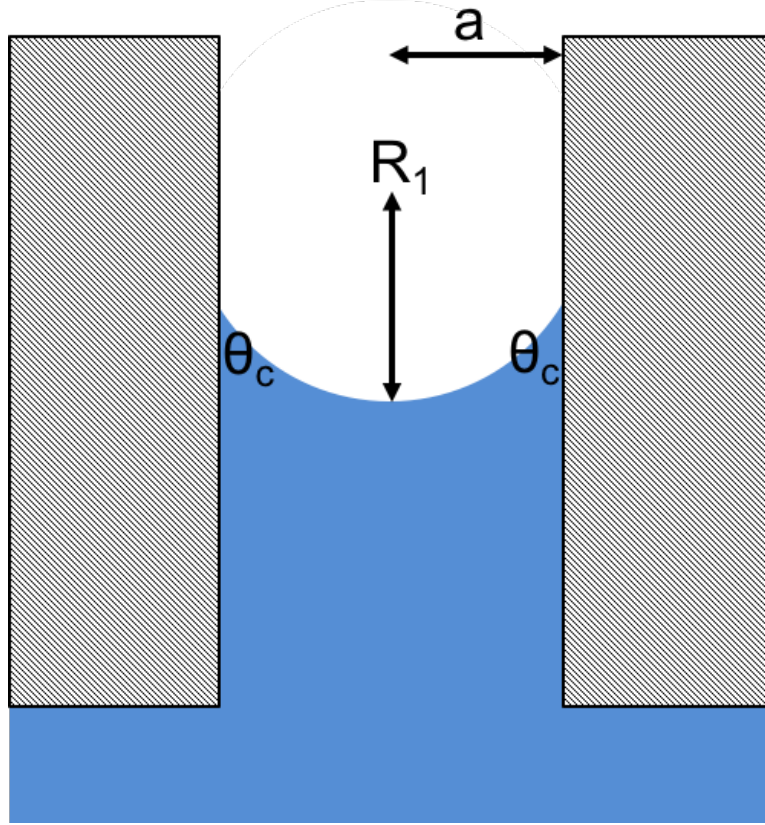


Figure A.3. Illustration of PDMS (blue) infiltration in to SNM nanopore.

In order to clear PDMS from the SNM pores, exposure to 49% hydrofluoric acid (HF) was used to erode¹⁰³ the cured PDMS while the rest of the SNM was protected in a PDMS enclosure. The backside of the SNM was exposed to HF for 1 min, then washed 2x 5 min and 1x 1 hr in DI H₂O. While the gas mass transfer of HF-treated PDMS-SNMs was approximately double that of untreated membranes, if the HF etched through the PDMS filling the nanopores, it could detach the PDMS film from the SNM and induce wrinkles in the PDMS film, as shown in Fig A.4.

Although the PDMS film was not compromised, the added surface texture was not considered suitable for blood contact.

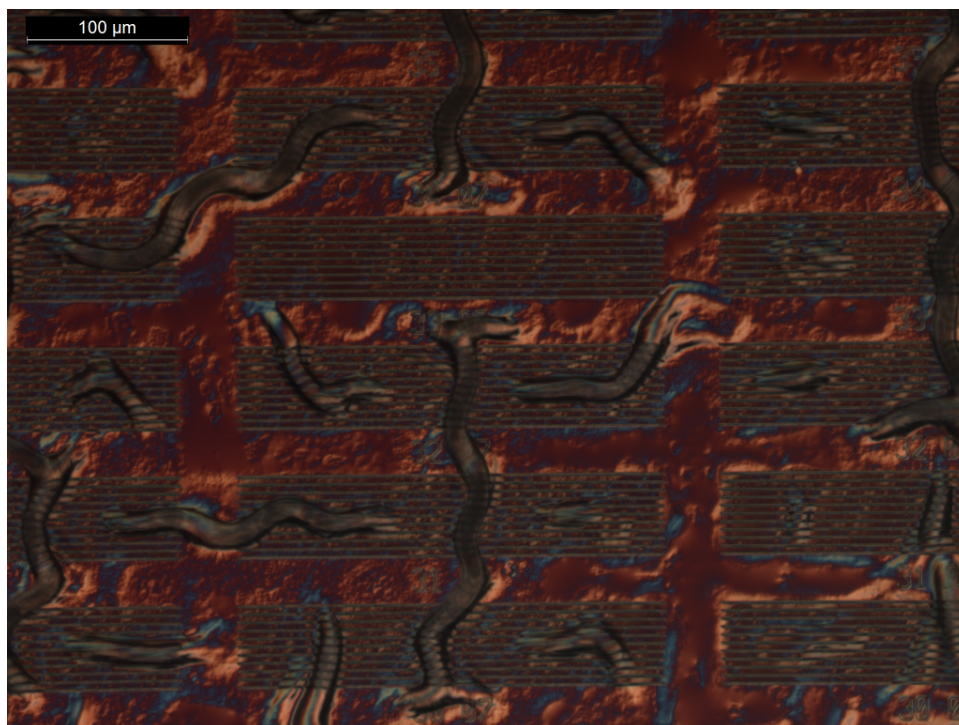


Figure A.4. Differential interference contrast image of wrinkled PDMS film on SNM following backside etching with hydrofluoric acid.

In order to more controllably etch the PDMS filling the SNM nanopores, 10:1 buffered oxide etch (BOE) was substituted for HF. The backside of PDMS-SNMs were exposed to BOE for 40 min, then rinsed with DI H₂O for 2x 5 min and 1x 1 hr. The resulting membranes provided approximately 10x greater mass transfer than unetched membranes, and the BOE etching process did not affect the PDMS adhesion to the SNM surface, as shown in Fig A.5.



Figure A.5. Differential interference contrast image of PDMS film on SNM following backside etching with buffered oxide etch.

A.2 Photoresist liftoff method

In the pursuit of more repeatable and easily fabricated membranes, the PDMS film was prepared separately and then bonded to the SNM or S μ M. First, SU8-2100 photoresist was spin coated on a silicon wafer to a thickness of approximately 20 μ m and hard baked to provide a smooth surface on which to spin coat the PDMS film. The PDMS film was prepared as described above. The silicon membrane was then bonded to the PDMS using oxygen plasma exposure of 100 W for 10 s. Following bonding, the photoresist and PDMS coated wafer with bonded SNM or S μ M was washed in acetone for two hours, after which the photoresist was stripped away and the PDMS-S μ M could be detached from the wafer, as illustrated in Fig A.6.

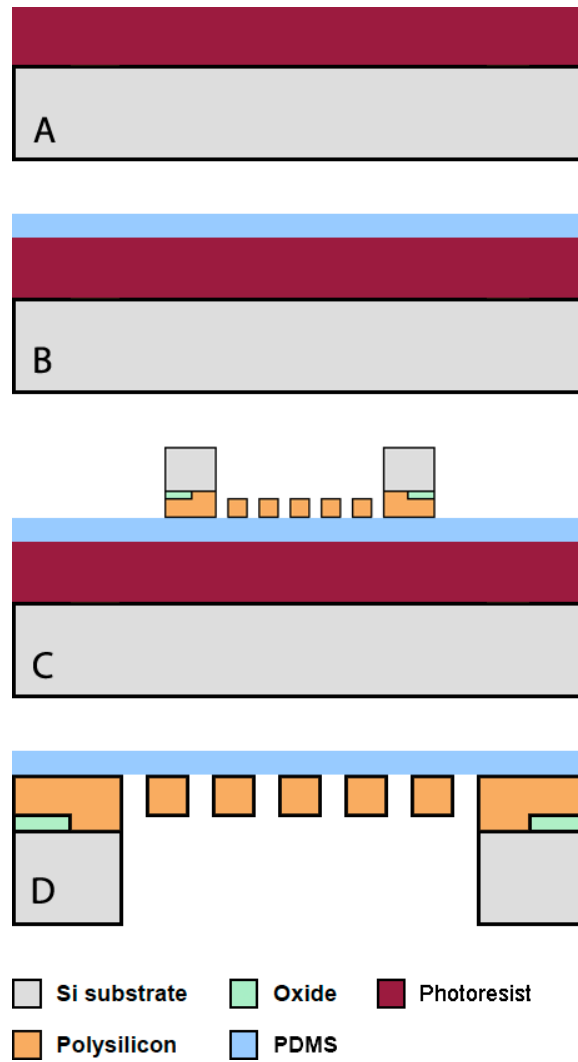


Figure A.6. A) Photoresist spin coated on silicon wafer. B) PDMS film spin coated on top of photoresist. C) SμM bonding to PDMS by oxygen plasma exposure. D) PDMS-SμM detached from silicon wafer by stripping photoresist with acetone.

The gas mass transfer of the photoresist liftoff membranes is shown in Fig A.7. Due to the exposure of PDMS to oxygen plasma, it was observed that the PDMS surface appeared crystallized, which may have inhibited gas exchange.

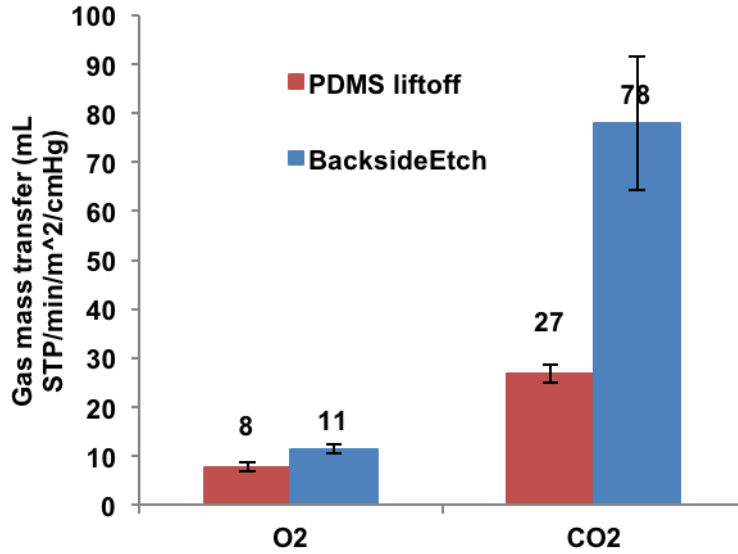


Figure A.7. Comparison of mass transfer between photoresist PDMS-liftoff and backside etched PDMS-spin coated PDMS-SNMs.

A.3 PDMS liftoff method

As an alternative to using photoresist as a sacrificial layer for PDMS liftoff, a dual layer PDMS system was used to enable casting of a thin film of PDMS on top of a thick (~1 mm) flexible layer of bulk PDMS to enable direct bonding and liftoff of PDMS-S μ Ms, as shown in Fig A.8. This method also allowed for direct measurement of the PDMS film by measuring the step height between the thick PDMS and the edge of the thin PDMS film formed during liftoff of the PDMS-S μ M, as shown in Fig A.9. However, careful liftoff of the PDMS-S μ M was required to prevent excessive out-of-plane deflection of the S μ M, which could fracture the membrane, as shown in Fig A.10.

The gas exchange achieved with PDMS-S μ Ms using this fabrication method was comparable to that observed in photoresist liftoff PDMS-S μ Ms, due to similar oxygen plasma exposure. The measured mass transfer coefficients for oxygen and carbon dioxide are detailed in chapter 3.

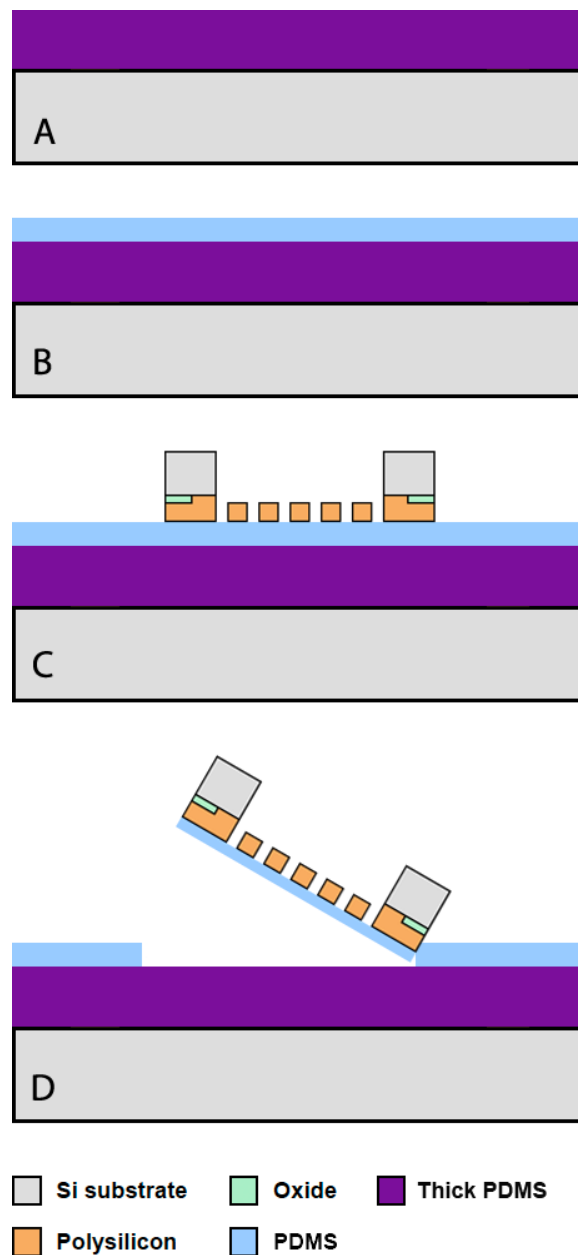


Figure A.8. A) Thick (~1 mm) PDMS layer cast on silicon wafer, then treated with perfluorooctyl silane to prevent adhesion to other PDMS layers. B) Thin PDMS film spin coated on top of thick PDMS. C) SμM bonded to thin PDMS film via oxygen plasma exposure. D) PDMS-SμM is peeled away from thick PDMS layer.

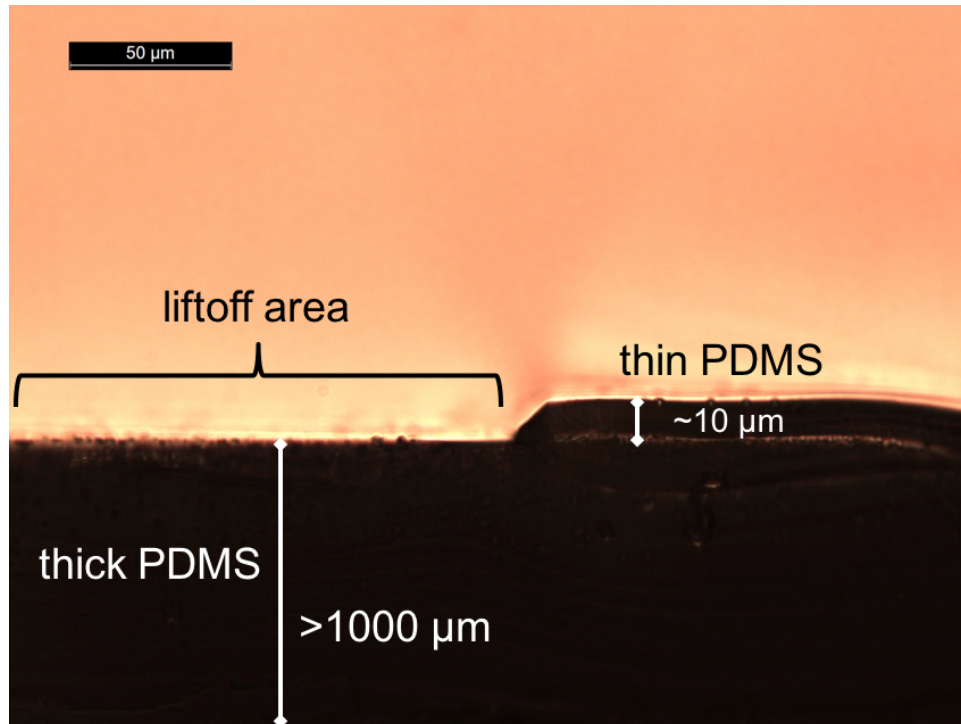


Figure A.9. Thin PDMS film on bulk “thick” PDMS, showing region that was bonded to $\text{Si}\mu\text{M}$ and peeled away from thick PDMS.

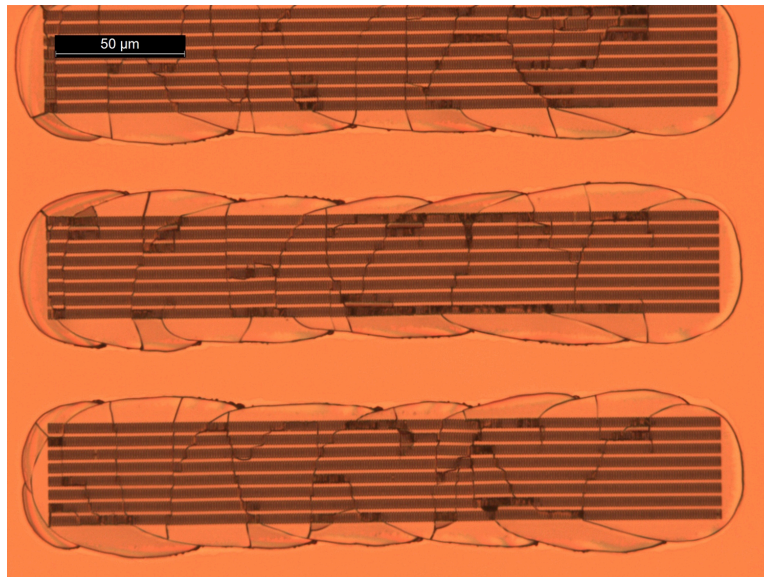


Figure A.10. Silicon membrane fractured due to out of plane deflection during PDMS liftoff detachment.

A.4 Future fabrication methods

Due to equipment limitations, spin coating speeds greater than 6000 rpm for durations greater than 2 min could not be attained, but spin coating speeds of 10000 rpm are attainable with modern spin coaters and could lead to sub-micron PDMS film thickness.

Additionally, PDMS precursor dilution with hexanes has been tested and shown to decrease the viscosity of the precursor, enabling thinner PDMS films to be generated at lower spin coater speeds. This also allows the use of 10:1 PDMS, which has a greater permeability to oxygen and carbon dioxide than 3:1 PDMS following exposure to oxygen plasma.

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