Working title: Optimizing Sacrificial Core Formation in the Fabrication of Nanopore Biosensors

Background

Molecular biomarkers are molecules, such as proteins, DNA, or RNA, that may indicate a disease or condition if detected in the body. One method of detecting these molecular biomarkers is to use a solid-state nanopore[1] submerged in a fluid with an electrical current flowing through the nanopore. As shown in Figure 1, the measured electrical current is approximately constant[2] when there is no particle translocating the nanopore, but there is a measurable blockage of current when the particle is translocating the nanopore. This allows individual biomarker particles to be detected. The detection of molecular biomarkers using this method has many advantages, including the flexibility to detect a wide variety of biomarkers.

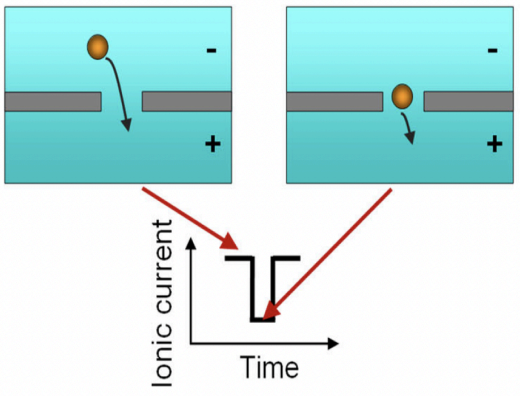

Fig. 1[3]

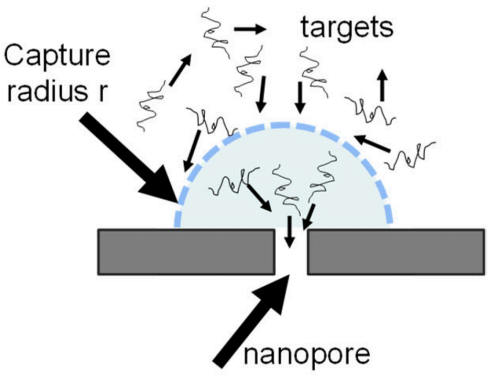

Fig. 2

One challenge with this nanopore method is the requirement for a high concentration of biomarkers to be present near the nanopore. For example, given the typical concentration of molecular biomarkers in a human body fluid sample (10^3 particles/mL), the translocation rate (2^{-8} particles/s) of biomarkers would be so slow that it would take about 30 days for a meaningful amount of particles to be detected. On the other hand, if the same concentration of biomarkers is in the 10um capture radius shown in Figure 2, a majority of the particles would translocate and be detected in about a minute.

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[1] A solid-state nanopore is a nanoscale opening made through a thin membrane made of a material such as SiO2. Often it is placed at a location where fluid can flow through the nanopore carrying particles through the small hole.

[2] In practice, the current line is not that flat and clean. There is a significant amount of noise from the power source, although the noise is significantly less in magnitude than the current drop that occurs when a particle passes through the nanopore and reduces the electrical current flow.

[3] Figures 1 and 2 were taken from a proposal written by Dr. Hawkins and collaborators for a project involving the use of nanopores and silicon based optofluidic devices to detect biomarkers. https://drive.google.com/file/d/1PdJ81W9pwqDJos9KuQV5SsjVBWAOcVTG/view?usp=sharing

To solve this challenge, Dr. Hawkins' research teams have developed devices that trap polystyrene carrier beads within a 10um radius of a nanopore. The polystyrene carrier beads are engineered to bind to the smaller biomarker particles and help transport them to a region near the nanopore. There are several versions of these devices, but the most current design uses a filter-like method, called a bridge[4], to trap the polystyrene carrier beads at the nanopore region.

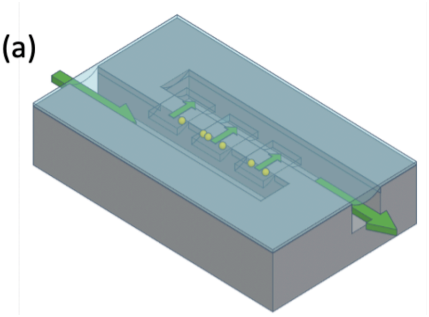


Fig. 3(a)[5]

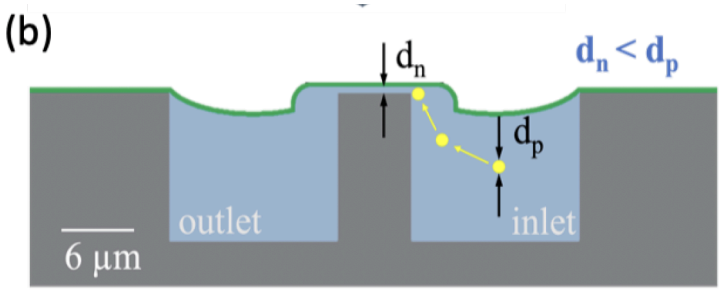
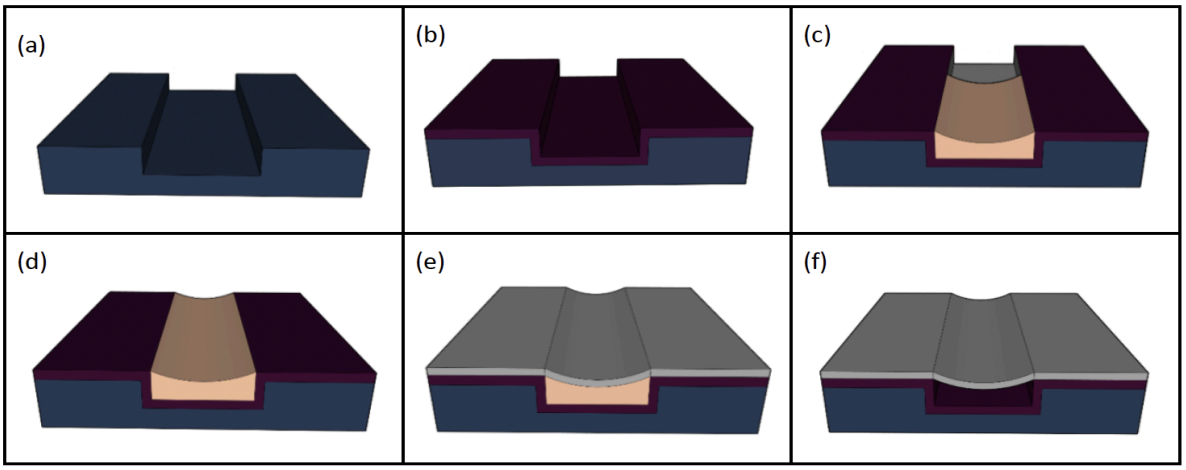


Fig. 4(a)

Figure 3a depicts a version of these devices where polystyrene beads, shown in yellow, are carried through the channel with the flow of water represented with green arrows. The transparent teal covering over the channels is a thin SiO2 membrane. When the beads reach the end of the inlet channel shown in Figure 4a, they are trapped at the bridge. The bridge is a thin gap with a thickness of d_n located between the inlet and outlet channels. Since d_n is less than d_p it has a filter-like effect, keeping the polystyrene beads at the trapping region while the water continues to flow through the bridge to the outlet channel. This method allows enough beads to be trapped near the nanopore for detection to be viable. Once the beads are trapped, the wafer is heated up causing the beads to release the biomarkers which can then translocate through the nanopore and be detected.



[6]Fig. 5

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[4] Wells, Tanner N. *Design and Fabrication of Passive Microfluidic Devices for Enhancing Membrane-Based Biosensors.* 2024. Brigham Young University, PhD diss., BYU ScholarsArchive.
[5] These figures were taken from pg. 102 of Tanner Well's dissertation published at BYU Provo.
[6] These figures are from Zach Walker's paper titled Solid-State Membranes Formed on Natural Menisci" doi:10.1088/1361-6528/aba711.

The method of fabricating the hollow solid-state membrane covered channels used in the above devices was a novel technique developed by Dr. Hawkins and some of his students[7]. Figure 5 above shows the process of forming the fluid channels covered with a SiO2 membrane. First, a trench in the shape of the channels is reactive ion etched into a Si wafer (Fig. 5a). After a thin SiO2 membrane is thermally grown on the surface (Fig. 5b), a negative photoresist (SU8 2000.5) acting as a sacrificial core is flowed through the channels (Fig 5c and 5d). This sacrificial core along with the rest of the wafer is covered with a PECVD SiO2 membrane. The ends of the channels are exposed using reactive ion etching, and the sacrificial core is removed using piranha[8].

Research Problem

The current process to fabricate the mechanical trapping devices works, but requires both long etch times and manually applying individual droplets of SU8 photoresist in each reservoir to fill the channels through capillary flow.

Project Purpose

Develop a method for filling microfluidic channels with a sacrificial core material that results in membrane covered channels equal to or better in quality than those created by the current capillary flow method and uses processes that can be done in a commercial semiconductor fab.

Project Importance

Currently, the qPCR test is the gold standard diagnostic tool for detecting viruses such as Covid-19. The qPCR test works by amplifying[9] DNA or RNA in a sample then using dyes or fluorescent DNA probe binders. This test is accurate, but it is very complex, expensive, can easily be inhibited by contaminants, and requires samples obtained from a person to be sent to a lab. On the other hand, the nanopore biosensor method is simpler and requires no amplification of DNA and RNA. It works by isolating the desired biomarker particles, concentrating them, then detecting them as they pass through a nanopore. Dr. Hawkins and other researchers recently published their results[10] that the nanopore biosensor method they developed was as good as the qPCR test at detecting Covid-19 and Zika virus. In some cases, the devices were able to detect viral RNA in the body fluid samples even when the qPCR test did not detect anything. This nanopore biosensor has also recently been used to successfully detect biomarkers for a rare form of cancer[11].

Since this system can be adapted to detect a wide variety of different biomarkers, it has the potential to revolutionize diagnostics. One key issue keeping this nanopore biosensor from entering the market is the viability of commercially fabricating them. There are several steps

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[7] Walker, Zach, et al. “Solid-State Membranes Formed on Natural Menisci.” *Nanotechnology*, vol. 31, no. 44, 2020, article 445303, doi:10.1088/1361-6528/aba711.

[8] A mixture of sulfuric acid and hydrogen peroxide often used to remove organics, such as photoresist.

[9] This involves making additional copies of a certain DNA or RNA sequence

[10] Sampad, Mohammad Julker Neyen, et al. "Label-free and amplification-free viral RNA quantification from primate biofluids using a trapping-assisted optofluidic nanopore platform." *Proceedings of the National Academy of Sciences* 121.16 (2024): e2400203121.

[11] The details for this research are still pending publication and are not currently available to the public.

in the current fabrication process of these nanopore biosensors that are not suitable for mass manufacturing, since they were developed for small batch manufacturing processes. One step in this process that this thesis attempts to improve on is the creation of the sacrificial cores used as a template to apply a SiO2 membrane over channels. Currently, this step requires manually applying small drops of photoresist to over 100 reservoirs, and would require the creation of new fabrication equipment to produce these devices. If this manual step can be replaced, it will help solve one processing challenge keeping the nanopore biosensors from being manufactured on a large scale and introduced into the market.

Project Overview

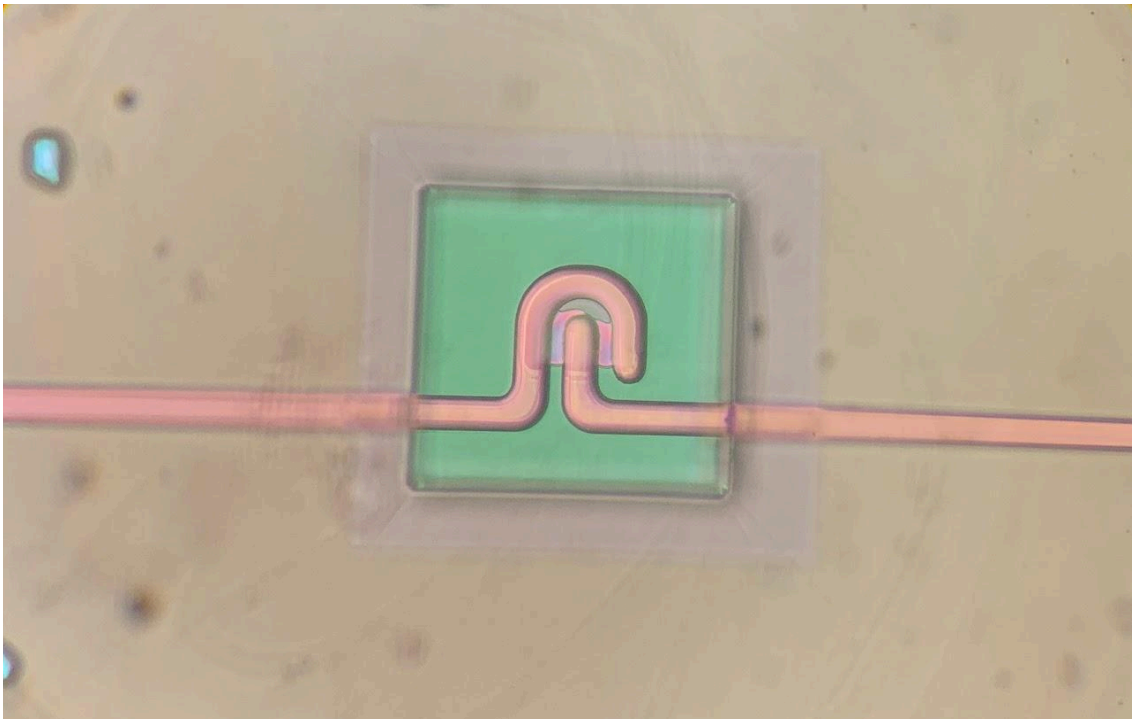

Fig. 6 Mechanical trapping device with thin membrane and TMMF produced with the old capillary filling method.

Addressing the problem of Long etch times: I have helped identify and obtain samples for a photodefinable film, called TMMF, which can be used to replace the SiO2 membrane covering the majority of the channel. However, TMMF is too thick for forming nanopores, so a thin SiO2 membrane still needs to be produced over the trapping region. Edward Marcos, a PhD student in the research group, has optimized a recipe for applying the TMMF to nanopore-based chips. The process of applying TMMF will be used later to ensure that the methods developed in this thesis are compatible with other processes used to produce these devices. In Figure 6, the green colored area is where the thin SiO2 membrane is. Note how the SiO2 membrane is a square that overlaps beneath the TMMF membrane which is the brown colored material. The device shown in Figure 6 was created using a process that formed sacrificial cores with capillary filling.

Addressing the problem of manually forming the SU8 sacrificial core

This problem will be the primary topic of this thesis. The objective will be to develop a method to fill the channels with SU8 or other similar material through dewetting. The goal

would be to leave a region around the channels where there is no photoresist, while filling the channels to an acceptable height.

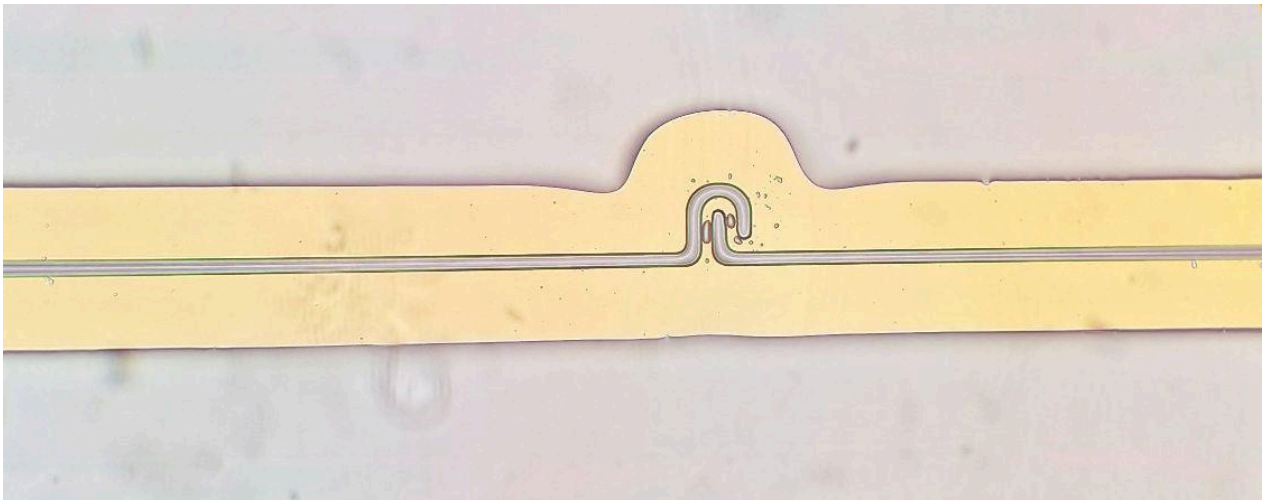

Fig. 7 Mechanical trapping device trenches with dewetting effect

Proposed Solution 1: Fill Channels Using the Dewetting Effect

Dewetting is an effect that is observed on thin liquid films coating a substrate that might be slightly phobic to the liquid. When the liquid is heated up, defects, ridges, or grooves on the surface of the substrate cause holes to form in the liquid film which may expand in size. Figure 7 shows etched channels of a mechanical trapping device with this dewetting effect. In the figure, the gray material in the channels and outside the channel is SU8, while the light colored yellow region is the surface of the wafer where there is no photoresist. This effect is normally avoided when applying photoresist to a substrate, since it results in poor coating of the substrate. This is due to unpredictable patches where photoresist is not covering the substrate, or uneven surfaces making it difficult to do photolithography. Based on my preliminary tests where SU8 was spun onto devices similar to those shown in Figure 7, the dewetting effect consistently leaves SU8 in the channels while leaving a region outside the channel without SU8. Thus it is hypothesized that the dewetting effect can be used to achieve the goal of this thesis.

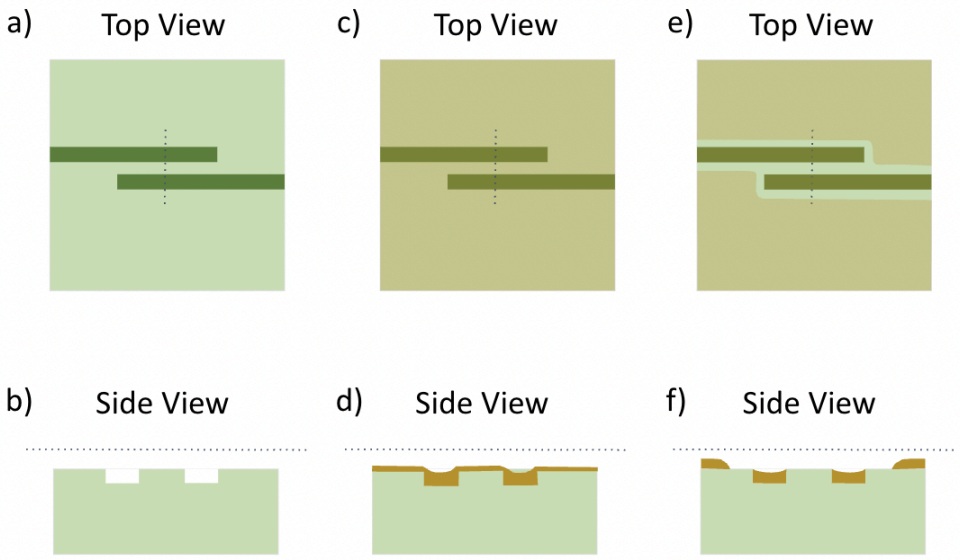

Fig. 8 Dewetting process

The first method to accomplish the first proposed solution would be utilizing the dewetting method to fill the channels, but to not remove the photoresist left in the field. Figure 8a and 8b show 2 views of the device before SU8 is spun onto the surface of the wafer. Figure 8c and 8d show two views of what it looks like after SU8 is spun onto the wafer. Figure 8e and 8f shows 2 views of a device after dewetting has occurred. Note that after dewetting occurs, there is photoresist in the channels, but a small gap with no photoresist around the channels. After this, if a thin SiO2 membrane[12] can be successfully grown on the surface of the wafer with the photoresist left in the field, it will be the best method because it will minimize the number of process steps. The best case scenario for this method would only require spinning photoresist onto the surface of the wafer then baking it, which would be significantly faster than the current method of manually applying droplets to 101 individual reservoirs.

If this first method does not work, an alternative method to to use the dewetting effect to fill the channels is using a photomask to expose the photoresist inside the channel to light and cross-linking it, while protecting the photoresist outside the channels from light which so it can be developed away. Figure 9 shows what this extra step would look like for a device.

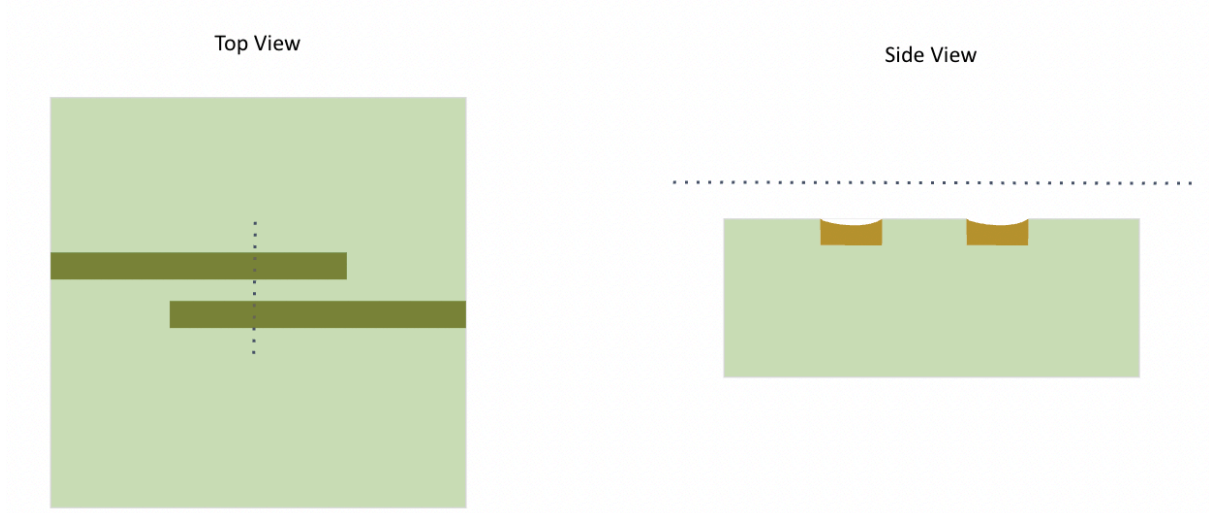

Fig. 9 Device after exposure of the channels and development of the photoresist on the field

If the first method is unsuccessful, this second method will be used because the surface of the wafer will be clean from the photoresist, and it will remove the variability caused by an unclean wafer surface. The best case scenario for this second method would only require a step to spin on the sacrificial core material, a step to expose a mask to remove material everywhere except for the reservoirs and channel, then a step for developing away the field resist. This would still be better than the current method of manually applying droplets to each reservoir.

[12] The green square from Figure 6 is an example of what that thin membrane would look like.

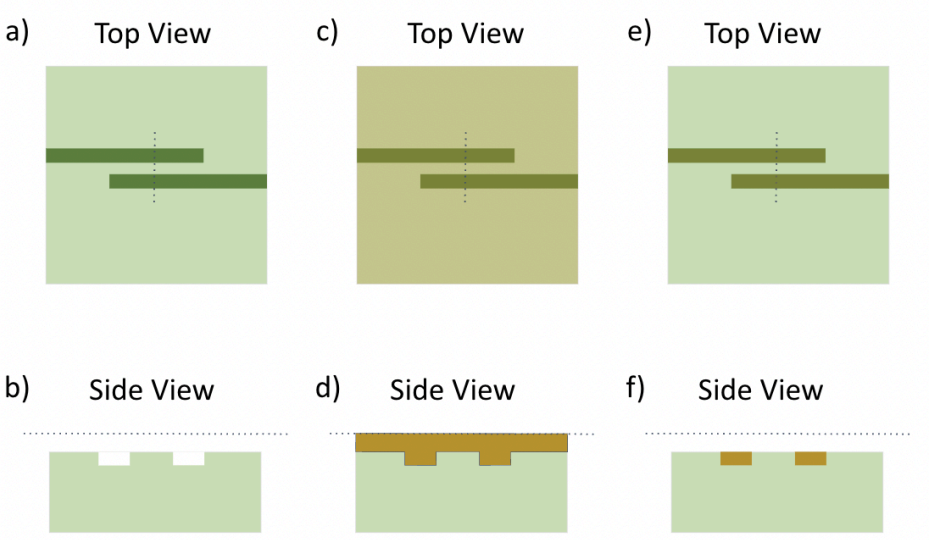

Fig. 10 SU8 etchback process

Proposed Solution 2: SU8 Etchback with Plasma

This will involve spinning on a SU8[13] layer that fills the trenches and has a uniform surface and experiments with recipes of plasma etching to etch-back the surface of the sacrificial core material to leave only SU8 in the channel.

The first goal will be to find a recipe for applying SU8 or other sacrificial core material that has smooth surface with feature variation of less than 10nm, fills the 10um deep trenches, but is as thin as possible[14]. Parameters to vary include the number of layers, viscosity of resist for each layer, bake temperatures for each layer, length of bakes for each layer.

After applying a uniform layer of SU8 on the surface of the wafer that can fill the trenches, the SU8 would be plasma etched until there is only photoresist left in the trenches. Plasma etching SU8 would use O2 plasma or other gas mixtures that can etch SU8. This process will be tested to verify it can remove SU8 from the field while leaving a sacrificial core in the channel that is as uniform as possible. The 2 biggest challenges for this method will be the final uniformity of the SU8 in the channels across the wafer and process time.

Figures 10a and 10b show 2 views of a device before SU8 is spun on. The dark green shapes represent channels that are etched into the silicon. Figures 10c and 10d show 2 views of a device after a uniform layer of SU8 is applied that also fills the channels. Figures 10e and 10f show what the device looks like after the SU8 is etched back with plasma. Note how the channels are still filled with SU8 while the top surface of the device no longer has SU8.

Proposed Solution 3: AZ3312 Etchback with Developer

This solution should also follow the progression shown in Fig. 9 and described in proposed solution 2. The difference is that the sacrificial core material is now a positive photoresist like AZ3312. This positive photoresist will be applied to test if it can adequately fill the channels

[13] SU8 is a negative photoresist where the material is strengthened when exposed to light and easily rinsed away when not exposed to light.
[14] meaning that the amount of material on the surface of the wafer is as little as possible. Adding a lot of material on the surface of the wafer will result in longer etch times.

with a uniform thickness across the wafer. Another difference is that developer instead of plasma will be used to etchback the photoresist until the field is clear and there is only photoresist in the channel.

Research Plan

Samples will be created for each of these 3 methods, then evaluated using the methods below to determine the quality of the sacrificial core produced.

Evaluation method

The sacrificial core characteristics that will be measured for each method are: meniscus shape, meniscus depth, how much of the channel is filled, and consistency across the wafer, a 10nm coating of chromium will be applied to the wafer over all the devices using the E-beam Thermal Evaporator, then 3d scanned using the Zeta 3D profilometer. The coating makes the sacrificial core opaque enough for the Zeta 3D profilometer to perform the optical scan. Scans will not work well on transparent or semi-transparent materials. The profilometer will return a 3D scan where the above sacrificial core characteristics can be determined using digital tools provided with the machine.

Performance parameters for the best method to create a sacrificial core

A meniscus shape: In previous tests, we have determined that a sacrificial core that is slightly lower than the surface of the wafer and not a meniscus shape will require a larger bridge shape which we have shown will not hold up during piranha etching. The meniscus must also create a continuous curve from one edge of the channel to the other edge. Any sharp corners caused by the meniscus not extending to the top of the channels will result in places where the SiO2 membrane is very likely to break.

A meniscus that is as flat as possible while continuously connecting the sidewalls: Ideally, the difference between the edge of the meniscus to the lowest point of the meniscus is less than 1um.

Consistent channel filling depth across all devices: This means that the sacrificial core shape and fill depth does not vary significantly for devices across the wafer.

No sacrificial core material within 15 um of the channel edges: Ideally, there is only sacrificial core material in the channels and not on the surface of the wafer. For negative photoresists, as long as there is no sacrificial core material within 15um of the channel edge, a mask can be created that can get rid of the photoresist outside the channels.

A manufacturable process: The process should be reproducible using commercial fab machinery, processes, and supplies.

A process that can be completed in a reasonable time frame: For example, a process that has the above characteristics, but takes multiple days to complete will not meet this requirement.

Test Procedure

After determining which method is best at creating a sacrificial core of the desired attributes[15], test whether this new method of forming a sacrificial core can allow a thin SiO2 membrane to be formed over the channel that is strong enough to withstand piranha etching. The testing procedure is listed out below.

[15] The desired attributes: flat or meniscus shape, fills the channel, only leaves photoresist in the channel, and very little photoresist close to the channel.

1. Apply a 3312 bridge to the devices.

2. Cover the bridges by depositing a 300nm-400nm SiO_2 membrane on the surface of the wafer using the PECVD 3 in the cleanroom.

3. A 168um by 168um photoresist mask, most likely AZ 3330, will be applied to the wafer centered over the bridge region. This would protect a 168um x 168um square SiO_2 membrane above the bridge region.

4. Use the Trion to plasma etch the SiO_2 everywhere except under the above mask. This would leave a thin membrane above the bridge region, and expose the majority of the channels.

5. Etch the sacrificial core in Piranha, leaving hollow membrane covered channels.

6. View each device under the microscope to visually determine the number of devices on the wafer that survived. Edward has shown that it is possible to create this 300-400nm thin SiO_2 membrane over devices with a high yield when placed over sacrificial cores created using the current capillary flow method. A high yield above 80% or comparable to the yield of devices created by Edward would indicate that the sacrificial core recipe is suitable.

The final step within the scope of this project will be to show that a TMMF membrane can be fully applied to the devices created using the new sacrificial core method without breaking the devices. The procedure is listed out below.

1. The wafer is prepared with a pretreatment to enhance adhesion of the TMMF.

2. TMMF is laminated onto the surface of the wafer.

3. A short bake smoothes out the TMMF layer and helps with adhesion.

4. The wafer is exposed with UV light and a mask to open up holes above the bridge area, and above the reservoirs.

5. The wafer is developed in a fresh solution of PGMEA[16].

6. View each device under a microscope to determine the percent of devices that successfully developed (no TMMF blocking the channels) and still have an intact membrane (for devices that had an intact membrane before the TMMF was applied).

Thesis Committee

Faculty Advisor: Dr. Aaron Hawkins, PhD, Department of Electrical Engineering

Faculty Reader: Dr. William Pitt, PhD, Department of Chemical Engineering

Department Honors Coordinator: Dr. Karl Warnick, PhD, Department of Electrical Engineering

Qualifications of the Thesis Committee

Dr. Aaron Hawkins:

I have worked in Dr. Hawkins Nanopore research lab for about 2.5 years. This thesis is a sub-project of a larger project that he has been leading that I have helped work on.

“Aaron Hawkins earned the B.S. degree in Applied Physics from Caltech and the Ph.D. degree from the University of California, Santa Barbara in Electrical and Computer

[16] This is a solvent that can dissolve TMMF that is not crosslinked.

Engineering. Before joining the faculty at BYU in 2002, he was a cofounder of Terabit Technology in Santa Barbara, California, and later worked as an engineer for CIENA and Intel. He is a Fellow of the IEEE and OSA. He served as the Editor-in-Chief for the IEEE Journal of Quantum Electronics and currently serves as the Vice President for Publications for the IEEE Photonics Society. He has authored or coauthored nearly 400 technical papers and was the co-editor of the Optofluidics Handbook, a defining text on the new field of optofluidics. He also co-authored the textbook Practically Magic, A Guide to Electrical and Computer Engineering. At BYU, Dr. Hawkins directs the university's cleanroom facility and co-directs a flagship undergraduate research program called IMMERSE."[17]

Dr. William Pitt:

"His research and publications are in the general areas of biomedical polymers, blood, bacteria and drug delivery, with emphasis in the use of ultrasound in actuated drug delivery and chemotherapy, bacterial separation from infected blood, protein adsorption to polymers, nanoparticle synthesis, polymer synthesis, polymeric composite materials, polymer surface chemistry and modification, and novel biomedical materials. He has published over 150 peer-reviewed journal publications, and has an H-index of 49. He holds 9 patents with several others pending."[18]

Dr. Pitt is also the Honors Coordinator for the Chemical Engineering Department, so he has significant experience with the process and writing required for a honors thesis. In addition, his expertise in polymer surface chemistry is of particular value to this thesis because one part uses surface chemistry effects to work.

Project Timeline

April 2025-September 2025: Began preliminary tests of 3 sacrificial core creation methods and familiarized myself with the 3 sacrificial core creation methods, identified potential roadblocks, acquired required materials, refined thesis topic and project.

September 2025: Thesis Approval

September 2025-November 2025: Finish testing the 3 sacrificial core creation methods (Dewetting, SU8 etchback with plasma, Positive photoresist development), refine a recipe for the best method

October 2025: Identify a conference or journal to submit a final paper by the end of the month

November 15, 2025: Apply for graduation by this date

November 2025-December 2025: Evaluate the 3 sacrificial core creation methods, summarize results, create figures/charts representing results, start first drafts of the honors thesis

January 2026-February 2026: Continue revising the thesis and finalize the thesis

February 13, 2026: Thesis Defense information submission by this date

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[17] https://hawkins.byu.edu/about-professor-hawkins
[18] https://independent.academia.edu/WilliamPitt2

February 2026: start drafting paper to be submitted to a conference or journal, schedule a Thesis Defense date

March 13, 2026: Thesis Defense completed by this date

March 16, 2026: Submit Thesis Defense result by this date

IRB or IACUC Approvals: N/A

Funding

500 mL of SQ 2 photoresist $470.80 + $25 shipping[19]: This is the material used to create the sacrificial cores. A sample will first be tested or obtained before purchasing the full bottle.

2 masks $55 x 2: These will be produced at the BYU cleanroom and used to develop the photoresist leftover on the surface of the wafer after the dewetting step.

1 box of 25 silicon wafers $200 + $25 shipping: These will be the primary substrate that the devices are fabricated on.

Additional funding may be needed to buy more chemicals used in the experiments, as well as to make additional masks.

total: $830.80 + shipping

Culminating Experience

The results of this thesis will be compiled into a paper and published in a journal. I am not sure which journal will accept this paper, but journals relevant to the research field of this thesis include: Journal of Micromechanics and Microengineering, Micromachines, Nature Microsystems & Nanoengineering, or Biomedical Microdevices. It may also be presented at a conference such as MicroTAS.

Conclusion

Significant preparation has been done before this prospectus was submitted to ensure that I have a starting point for the three proposed solutions. Enough materials required to start implementing the three proposed solutions immediately have also been acquired, so that I do not have to wait for the additional materials purchased with Honors funding to arrive before working on the project. I have also been working on the nanopore project for over 2 years, so I have a lot of experience with the processes and machinery required to complete this project.

[19] This is an estimation based on previous orders.