

Small Project Final Quarterly Report

DOE Office of Nuclear Physics (NP)
Facilities and Project Management Division

Proposal Name:

Improved Production and Separation Technologies for Non-standard PET Radionuclides

Report Date: December 1st 2012 (Final Report)

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Work-scope Highlights:

Project 1. Development an optimized high-power inclined solid target system for the production of ^{64}Cu at Washington University

^{64}Cu is currently the most widely used of the PET radioisotopes produced by solid targets. Although we have achieved relatively high yields with our current system, our production yields have been limited due to the amount of beam current with which we can irradiate the target. The development of high powered targets, particularly for this isotope will result in higher yields for shorter bombardments, thus saving on valuable cyclotron time.

We have designed and manufactured new target bodies to allow for irradiation of the target material at an angle, thus in effect spreading out the cyclotron beam to increase heat dissipation which was previously our limiting factor. We have also adapted a pre-existing target station from the JSW cyclotron for use on the CS-15 cyclotron, which is our dedicated solid target cyclotron. This involved development of a new mounting flange, controller and associated equipment.

Project 2. Improved Separations of Non-standard PET Isotopes

In task 2 of this project we proposed to develop microfluidic systems capable of performing liquid - liquid extractions (LLX) of cyclotron produced radioisotopes of interest for PET imaging. Scaling back to a shorter project length we are currently focusing solely on the LLX processing of Cu-64.

Brief summary of activity issues, concerns, successes:

Project 1 is completed. We have optimized plating parameters with the new target bodies and slanted target plating system. The target station has been mounted on the end of the beamline, service lines have been installed to allow for helium and water cooling. We have routinely produced copper-64 using the new slanted target system in conjunction with our automated system.

In project 2, we successfully fabricated and tested microfluidic extraction devices made out of two organic solvent-resistant polymers, thiolene and SIFEL. Initially, we developed analytical and computational models to describe the extraction process, and used the model to design the microfluidic devices. Then we optimized the microfabrication procedures to manufacture microreactors, followed by optimization of the operational parameters to obtain a stable aqueous-organic interface, which is critical

for efficient extraction. When we tested the thiolene devices for extraction of copper-64, we observed very low extraction efficiencies (less than 5%) due to adhesion of copper to thiolene. However, we observed very high extraction efficiencies with SIFEL devices (greater than 95%), which are due to the high interfacial area for extraction and shorter diffusion lengths.

Milestones

Project 1.

Project 1.1 Adapt solid target station for CS15

The new target station for irradiation of slanted targets will consist of an adaptation of a pre-existing target station. Completed

The target station has been mounted on the end of the beamline and water and helium cooling has been plumbed. Completed

Project 1.2 Design & Fabricate new targets

The new target body has been designed and several variations have been constructed. Completed

Project 1.3 Development of ellipsoid plating system

The plating system has been designed, fabricated and accommodates the new slanted target design. Completed

Project 1.4 Optimization of target irradiation parameters

We have conducted many irradiations on this target and have succeeded in ramping up beam currents $>35 \mu\text{A}$ on target. Completed

Project 2.

Project 2.1.1 Modeling of μLLX (microfluidic liquid - liquid extraction)

1. Since the proposed μLLX involves the interplay between the stability of the aqueous-organic interface and extraction kinetics determined by diffusion and reaction rate constants, we developed a numerical model allowing for the systematic design of the microreactor.
2. Incorporation of experimental Cu-64 extraction data has allowed a refinement of the numerical model and microreactor design.
3. Analytical model has been modified to incorporate unequal flow rates between the organic and aqueous streams

Project 2.1.2 Fabrication / Testing of prototype devices

1. We fabricated and tested devices using thiolene and SIFEL.
2. We tested different device designs, operational parameters and surface functionalization to optimize the stability of the aqueous-organic interface.

Project 2.2.2 Testing / operation protocol development

1. We tested the thiolene devices for extraction of copper-64, and observed very low extraction efficiencies (less than 5%) due to adhesion of copper to thiolene.

2. We observed very high extraction efficiencies with SIFEL devices (greater than 95%), which are due to the high interfacial area for extraction and shorter diffusion lengths.

Budget

Summary of total expenditures:

ID #	Item/Task	Baseline Total Cost (AY\$)	Costed & Committed (AY\$)	Estimate To Complete (AY\$)	Estimated Total Cost (AY\$)
1	Increased isotope production	\$172,627	\$172,627	\$0	\$172,627
2	LLX separation	\$247,373	\$247,373	\$0	\$247,373
Totals:		\$420,000	\$358,005	\$0	\$420,000

Summary of expenditures by fiscal year (FY):

	FY 2010	FY 2011	FY 2012
a) Funds allocated	\$ 420,000.00	\$ 420,000.00	\$ 420,000.00
b) Actual costs to date	\$ 4,131.83	\$ 277,254.22	\$ 420,000.00
c) Uncosted commitments	\$ 226,428.17	\$ 80,753.78	\$ 0
d) Uncommitted funds (d=a-b-c)	\$ 189,440.00	\$ 61,995.00	\$ 0

Details on, or further, issues/concerns

Project 1.

Plating of new target design

New targets and plated apparatus were designed and constructed as outlined in the previous progress reports. Plating parameters have been optimized and targets can be plated with enriched nickel-64 in a reproducible fashion.

Quality control of copper-64

Several bombardments of the new system have been conducted. The target was plated with enriched nickel-64 in our custom plating system and bombarded as previously described. The produced copper-64 was separated from the nickel-64 target material on our standard processing system. While yields of copper-64 produced with the new target system have increased as expected, specific activities (radioactivity per total mass of metal contaminates) are lower than previously achievable with the standard target systems. Investigations are ongoing and have resulted in a thorough analysis of sources

of metal contaminants during production of copper-64 and development routine procedures for measuring specific activity of radiometals. This includes a comparison of chelate titration, ion chromatographs and ICP analysis. Data is being analyzed and a manuscript on this work is in preparation. Support from this grant will be acknowledged.

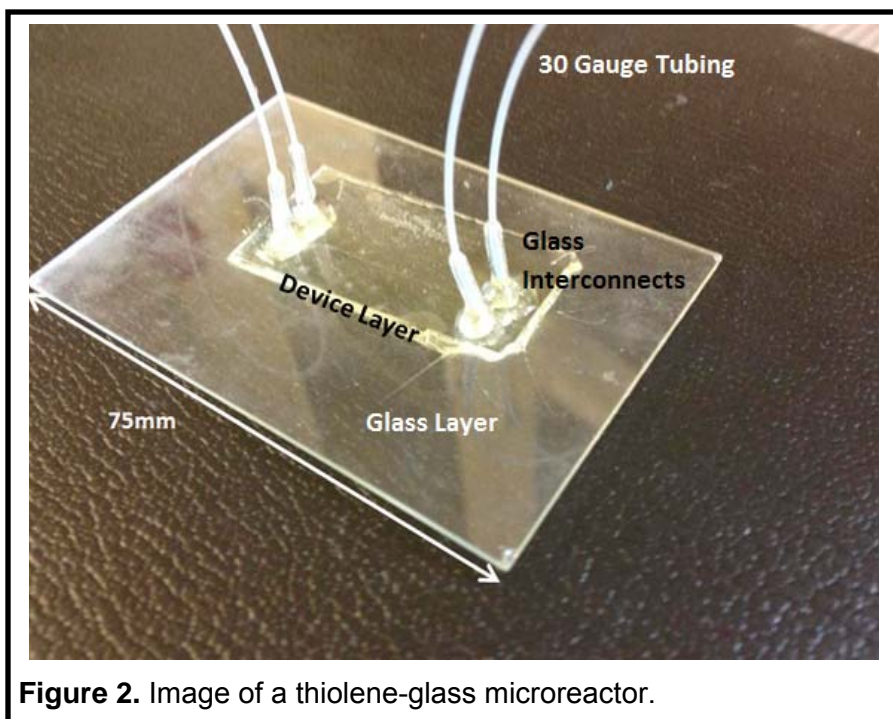
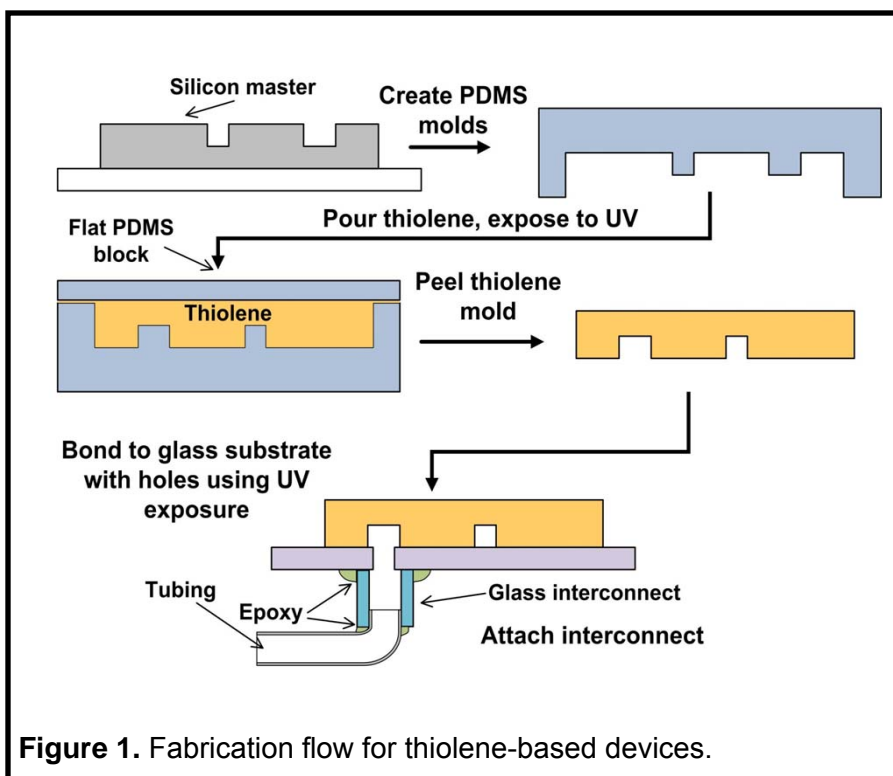
Project 2.

Fabrication of thiolene-based microreactors

In the last quarterly report, we proposed exploration of solvent-resistant polymeric materials for fabricating microreactors for liquid-liquid extraction (LLX), since the separation of radioisotopes by LLX requires the use of non-polar organic solvents (*e.g.*, toluene). We chose thiolene, an ultraviolet (UV)-curable epoxy, for the following reasons: (1) high-resolution features (as small as 1 μm) can be fabricated using thiolene, (2) thiolene is resistant to many non-polar organic solvents, typically used in LLX, (3) thiolene is optically translucent, and (4) the short fabrication time enables rapid prototyping.

We had to modify the fabrication procedure from the previously described method in order to aid in stabilization of the aqueous-organic interface. The main modification was to replace a thiolene substrate with a glass substrate. This modification avoided the blockage issue at the interconnects that resulted due to incomplete curing of the thiolene substrate.

The modified fabrication flow for thiolene-based devices is shown in figure 1. The thiolene used was NOA81, which was purchased from Norland Products. The microreactor channel patterns were transferred to silicon using photolithography and deep reactive ion etching. Then, the silicon master was used to create a negative pattern of the features in poly(dimethylsiloxane) or PDMS. Thiolene features were created by pouring thiolene on to the PDMS molds, and curing the thiolene under UV exposure. Finally, the thiolene features were bonded to a glass substrate, and glass interconnects were glued to the device. Figure 2 shows an image of a fabricated microreactor.



Stabilization of the aqueous-organic interface

In a previous progress report, we had suggested two strategies to obtain a stable aqueous-organic interface (AOI): (1) use of hydrophobic patterning to ensure better wetting of the microchannel walls by toluene, and hence better separation of the phases at

the exit, and (2) splitting the overall extraction length into smaller segments, since a stable AOI is easier to achieve with shorter lengths. We systematically investigated both strategies to stabilize the interface.

As mentioned in the previous report, when we did not use any surface functionalization, we obtained a stable AOI throughout the extraction length, but the toluene phase leaked into the aqueous phase at the outlet. Figure 3 shows optical micrographs of different sections of the device with two-phase flow. We observed that the interface was stable throughout the extraction length, but the toluene phase slightly leaked into the aqueous phase at the outlet, as evident from the optical micrograph of the device outlet. For the operating conditions shown in figure 3, we observed that approximately 10% (by volume) of the exiting aqueous stream contained toluene.

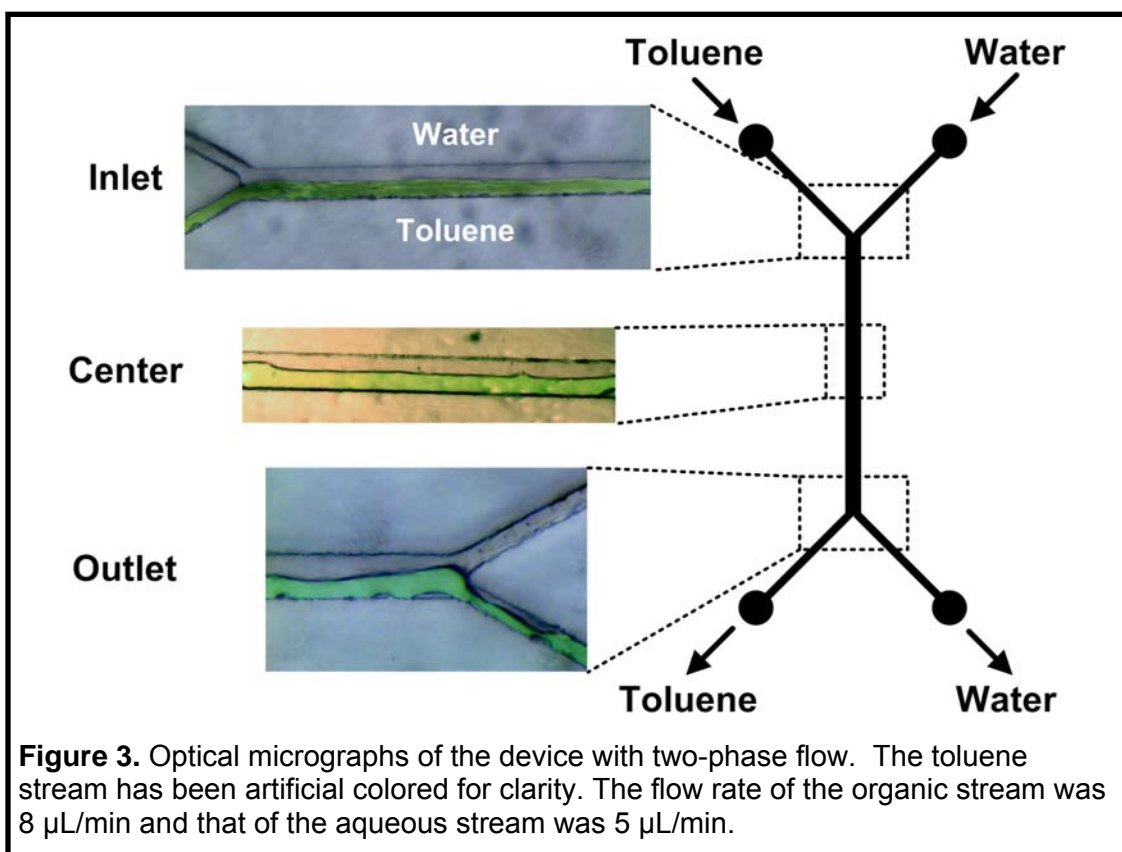
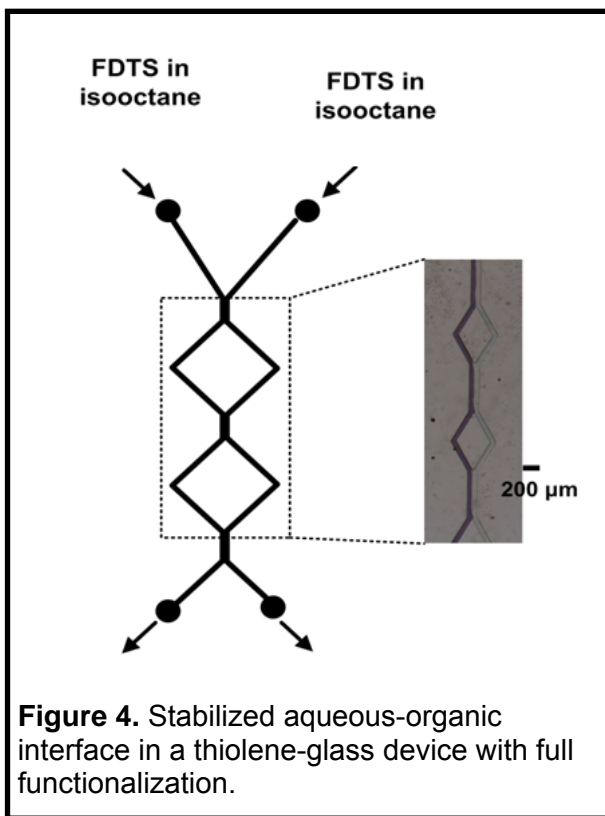


Figure 3. Optical micrographs of the device with two-phase flow. The toluene stream has been artificial colored for clarity. The flow rate of the organic stream was 8 $\mu\text{L}/\text{min}$ and that of the aqueous stream was 5 $\mu\text{L}/\text{min}$.

We hypothesized that constraining the toluene phase to one half of the microchannel will minimize leakage. Our strategy to constrain the organic phase was to partially modify the microchannel surface (half the channel) to be hydrophobic. The surface modification procedure was adapted from previous research, where a silane solution (perfluorodecyltrichlorosilane or FDTS) was flowed over the desired surface to make it hydrophobic. In this research, 1% silane in isooctane solution was flowed through the inlet for the toluene phase, while pure iso-octane solution was flowed in the second inlet.

We observed that partial surface functionalization reduced the leakage; however, the phase separation was still not ideal. We speculated that the functionalization was not effective at the exit, due to mixing of the streams prior to exiting during functionalization.



To address this issue, reverse-functionalization was used, which involved first forward functionalizing the device according to usual protocols, then reversing the direction of functionalization, so that the outlets in the previous stage were inlets during the second stage. Reverse functionalization improved the phase separation at the exit.

As a control experiment, we functionalized all the microchannel surfaces with the hydrophobic coating. Surprisingly, we observed that full functionalization resulted in a more stable AOI compared to that obtained using partial functionalization. This observation was counter-intuitive as microchannels with full functionalization are expected to behave similar to channels with no functionalization. However, in case of

channel with no functionalization, one of the contacting surfaces is glass and the other is thiolene, which have different hydrophilic or wetting properties. Hence, fully functionalized microchannels led to stable AOI, since all the surfaces have similar wetting behavior (equally hydrophobic), due to presence of a hydrophobic coating. To explain improved stability of AOI for fully functionalized microchannels compared to partially functionalized channels, we note that during partial functionalization the streams mix at the interface, which may lead to non-uniform functionalization at the interface. This non-uniform functionalization could lead to the observed leakage at the exit. In case of a fully functionalized microchannel, the uniform hydrophobic nature of the contacting surfaces led to minimal leakage. We speculate that this uniform wetting behavior of surfaces is more important than confinement of phases by partial functionalization to obtain a stable AOI. This theory is confirmed by our observations on stability of AOI in SIFEL microreactors, where all the contacting surfaces were made out of the same hydrophobic material (details in a later section). Figure 4 shows an image of a stable interface with full functionalization for a thiolene-glass microreactor. A brief summary of the studies on surface functionalization, found that in terms of the effect on stability of AOI: **No Functionalization < Partial Functionalization < Reverse Functionalization < Full Functionalization.**

Next, we tested the strategy of splitting the overall extraction length into smaller segments to stabilize the AOI. The idea for this strategy germinated from our observation that the AOI was more stable when the extraction length was 4 mm compared to 10 mm. The reason for this unstable interface in the 10 mm device is that

deviation of the interface from the central axis (δ) is lower for shorter lengths (assuming angle of deviation, θ , is constant), which results in better separation of phases at the outlet (figure 5). Thus reduction of the contact length of the device will lead to reduced δ , which in turn should lead to better phase separation. Hence, we decided to test the strategy of splitting the extraction length into smaller segments, which we refer to as the branched design.

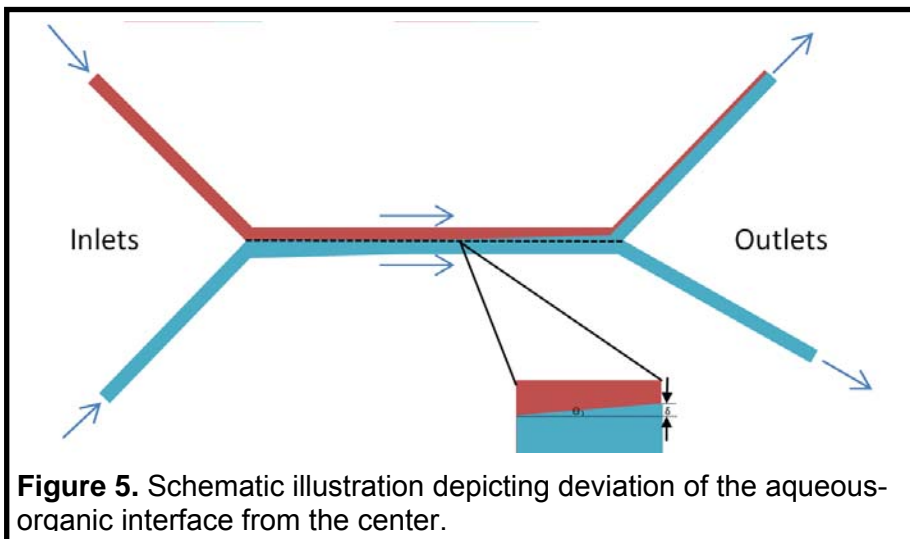


Figure 5. Schematic illustration depicting deviation of the aqueous-organic interface from the center.

The branched design (figure 6) comprised 10 smaller segments of length 1 mm, so that the overall extraction length was still 10 mm. We observed that the AOI was more stable for a branched design (figure 4) compared to that obtained in a straight 10 mm long microchannel. We conclude from these experiments that a branched design is preferable to a straight microchannel from point of view of interface stability.

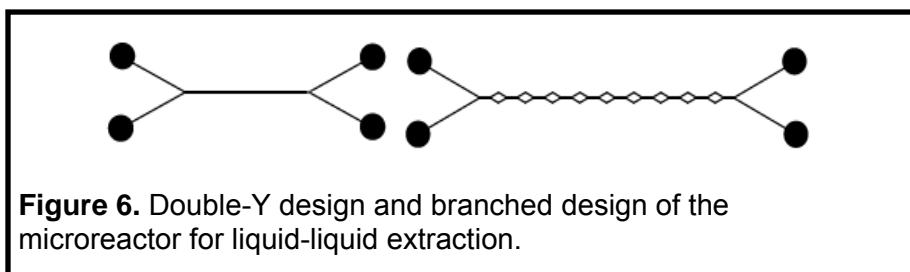


Figure 6. Double-Y design and branched design of the microreactor for liquid-liquid extraction.

Application of the thiolene-based microreactors for extraction of copper-64

After developing an optimized thiolene-glass microreactor, we used the reactor to extract copper-64 from an aqueous solution (0.1 M HCl) into a toluene solution consisting of HOBO, where HOBO is the extracting ligand. We observed a very low extraction efficiency (less than 15%), in spite of a stable AOI. We hypothesized that this low efficiency was due to adhesion of copper to the SH bonds in thiolene. To confirm the hypothesis, we co-flowed an aqueous solution of copper-64 and toluene solution without HOBO in the thiolene microreactor to mimic the extraction conditions. We observed that 45% of the copper was retained in the microreactor during the experiment, which explains the low extraction efficiency.

To address this issue, we decided to use another polymer SIFEL, an organic solvent-resistant polymer to fabricate the microreactors. SIFEL is a Teflon-like material, and hence the adhesion of copper was expected to be minimal.

Fabrication of SIFEL-based microreactors

Figure 7 shows the fabrication flow for SIFEL-based microreactors. Briefly, the device features were patterned on silicon using standard photolithography. Then, SIFEL (1:1.5 ratio of curing agent to monomer) was spun on the patterned features; a thin layer of SIFEL was used to reduce wrinkling of SIFEL that occurs in thicker layers. Then, a thin layer of PDMS was spun on the SIFEL, followed by bonding of a cyclic-olefin copolymer (COC) sheet with predrilled holes for vias. A thin layer of PDMS was used to bond the SIFEL to the rigid COC sheet. Interconnects were attached to the COC sheet, and the assembly was removed from the silicon mold. Then, a thin layer of SIFEL (1.5:1 ratio of curing agent to monomer) was spun on silicon to act as the substrate layer for the microreactor. The SIFEL device layer was bonded to the SIFEL substrate by heating. Figure 7 shows an image of a fabricated SIFEL microreactor.

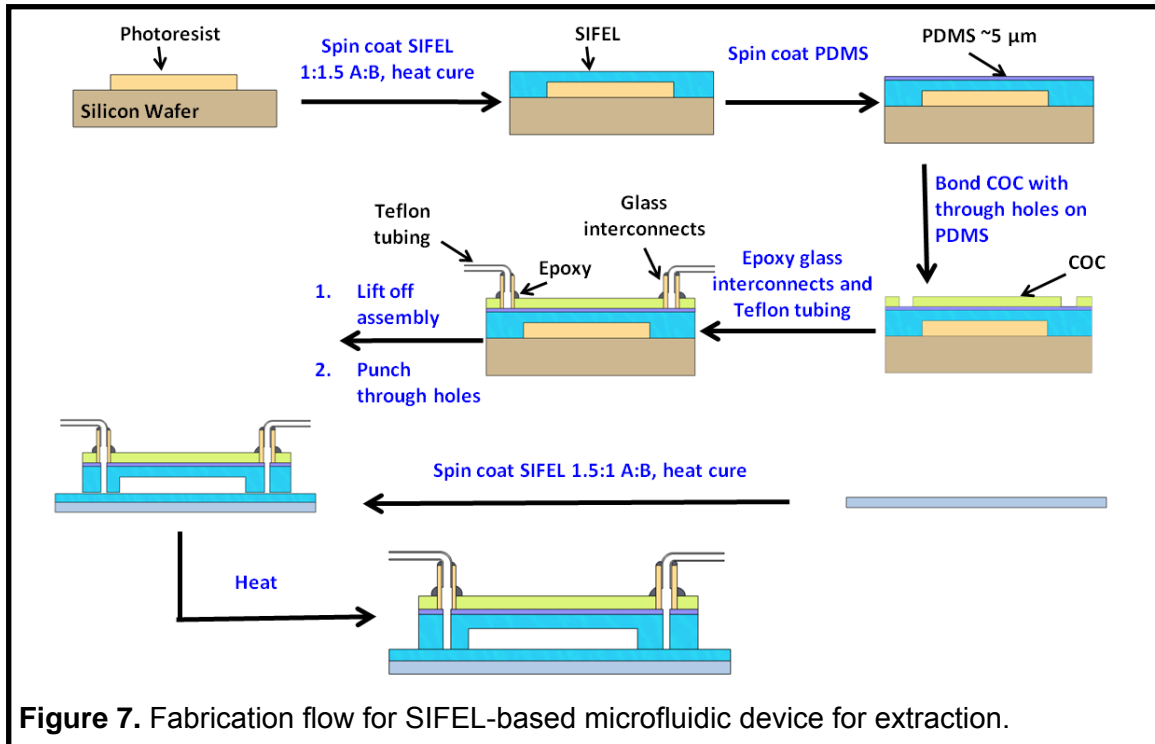
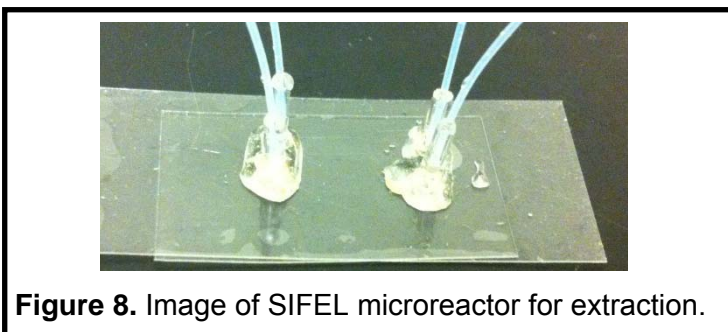
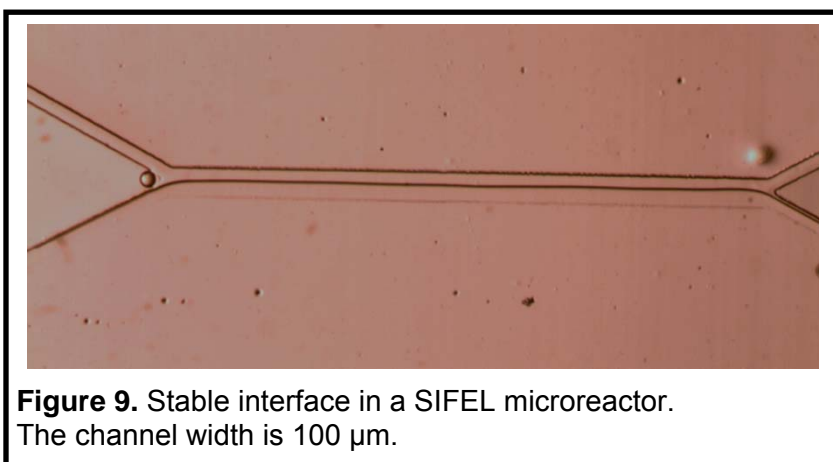


Figure 7. Fabrication flow for SIFEL-based microfluidic device for extraction.



Application of the SIFEL-based microreactors for extraction of copper-64

We initially optimized the operation of the device to obtain a stable AOI. We observed a stable AOI for a SIFEL device with 10 mm extraction length with minimal leakage. We did not observe significant differences in leakage between a straight and branched design, and hence decided to use a straight design. We did not explore surface functionalization of the microchannels, due to the inertness of the CF_4 groups on SIFEL. However, the leakage was minimal (less than 10%), and we decided to use the microreactor without any surface functionalization (figure 9).



We initially tested the adhesion of copper to SIFEL microreactors by co-flowing an aqueous solution of copper-64 and toluene solution without HOB0 to mimic the extraction conditions. We observed that less than 5% of the copper was retained in the microreactor during the experiment, which validates the inertness of SIFEL.

Then, we used the SIFEL microreactors to extract copper-64 from an aqueous solution (0.1 M HCl) into a toluene solution of HOB0, where HOB0 is the extracting ligand. The flow rates of the aqueous and organic phases were 20 and 35 $\mu\text{L}/\text{min}$, respectively, which resulted in a contact time of approximately a few milliseconds. We used three different devices and two different concentrations of HOB0. In all cases, we observed that the extraction efficiency was very high (more than 95%). These high values for extraction efficiency are due to (1) the high interfacial area at the microscale resulting from a large surface-to-volume ratio, and (2) shorter diffusion lengths (less than 25 μm on an average). Such high extraction efficiency corroborated with analytical

modeling, where we assumed that the extraction is a diffusion-limited process due to the large excess of HOBO.