

Abstract:

Today, more than ever, the United States (US) health system is faced with an increasing incidence and prevalence of cancer as the whole population lives longer. Consequently, there is an increasing need for better utilization of oncology treatment resources. One recent answer has been the development of home-based chemotherapy systems (HBCs), which have shown to not only reduce hospital burden, but also deliver better treatment outcomes, especially for the elderly. Nonetheless, current HBCs employ complex, costly, and cumbersome pole-based infusion pumps. Current alternatives, such as Iontophoretic drug delivery patches, however, fall short. While they address the cumbersome factor, they fall short in that they 1) require chemotherapy drug reformulation, 2) can only deliver 1 drug. As such, we have developed ChemoPatch, a low-cost, disposable, and electronic patch-based cancer chemotherapy device designed to be not only be simple, automated, and unobtrusive, but that also 1) delivers chemotherapy drugs as they exist and that 2) delivers up to 3 drugs at once. Our device comprises of 5 components: 1) a novel micropump for drug delivery; 2) a drug reservoir that contains up to 3 separate chemotherapy drugs; 3) a microneedle array; 4) an electronic circuit for complex programmable delivery scheduling capability; and 5) a padded and bendable circular 2.0" diameter patch to package all of the other components. Through developing this device, we aim to bridge the gap between technology and cost-effectiveness/comfort in high-quality home-based cancer care.

Introduction and Background:

Today, more than ever, the United States (US) health system is faced with an increasing incidence and prevalence of cancer as the whole population lives longer.¹ In practical terms, oncology organizations have to support an increasing number of patients requiring more therapeutic interventions, long lasting care, and longer follow-up time.^{1,2,3} Consequently, there is an increasing need for oncology treatment centers to manage this growing market, a large bulk of which is now becoming the burgeoning baby-boomers. Thus, oncology organizations need to better utilize treatment resources so as to be able to offer high quality cancer care to all those who require it.

One recent answer has been the development of home-based chemotherapy systems.^{2,3} It can be seen that the three main treatment modalities for cancer are radiotherapy, surgery, or chemotherapy.¹⁵ Of the three, chemotherapy has the greatest potential for widespread implementation in CPCHCs, as it has the fewest associated equipment requirements. As such, in a strict sense, home-based cancer care as they exist refer to the full home-based administration of intravenous chemotherapy. CPCHCs have been shown to be particularly appropriate for treatment of elderly patients, as on average they yield better treatment outcomes than hospital or outpatient-based chemotherapy systems for the elderly.³

Nonetheless, the current method for administration of chemotherapy drugs within these systems has been primarily through a complex, costly, and cumbersome pole-based infusion pump setup.^{3,4} These setups are needed to administer complex drug schedules and as a result, infusion pumps have prevented home-based chemotherapy from becoming an attractive/viable alternative to hospital or outpatient-based chemotherapy administration both economically and comfort-wise.

Iontophoretic electronic and patch-based disposable drug delivery was first introduced to the market in the 2000's as an alternative to infusion based setups that could potentially rival such standards while addressing all of their shortcomings.⁴ It was a breakthrough at the time in that it was able to deliver a wider range of drugs than would be allowed by simple, diffusion-based passive patches. Nonetheless, it was never proven an adequate alternative to the standard pole-based infusion pumps for 2 main reasons: 1) it requires chemotherapy infusion drugs to be reformulated for storage in the Iontophoretic patch reservoir and 2) it only allows for 1 drug at a time.⁵

Our solution (device), named ChemoPatch™, fills both of these technology gaps. The ChemoPatch is a low-cost, disposable, and electronic patch-based cancer chemotherapy device designed to be simple, automated, unobtrusive, and easy-to-use by cancer patients outside of the hospital, yet cutting-edge in its ability to deliver quality home-based chemotherapy.

It address the first issue in that chemotherapy drugs can be loaded as they currently exist, as it allows for any liquid drug to be injected for storage in the drug reservoir. It addresses the second issue because the ChemoPatch™ is an electronic device and is able to administer 3 different chemotherapy drugs at specific time intervals. Furthermore, it is unobtrusive because the delivery is automated via preprogrammed settings, allowing patients to receive quality care with reduced hospital visits. Thus, our device is not only much less costly than traditional infusion pumps, but it also reduces the need for excessive medical intervention by automating the delivery process.

The ChemoPatch™ consists of 5 components: 1) a novel micropump for drug delivery; 2) a drug reservoir that contains up to 3 separate chemotherapy drugs; 3) a microneedle array for the painless administration of drugs; 4) a novel microcontroller-based electronic circuit for complex programmable delivery scheduling capability; 5) a padded and bendable circular 2.0" diameter patch to package all of the other components.



At present, the standard method of administration of cancer chemotherapy drugs remains the pole-based infusion pump setup. However, the costs of purchasing and maintaining standard multiple drug infusion pumps (Figure 1) are, on average, \$25,000 USD and those of the equipment for standard single drug infusion pumps (Figure 2) are, on average, \$9,000 USD.⁵ Furthermore, such infusion machines have typically been rooted in hospital or outpatient care settings, thus requiring patients to remove themselves from their daily lives and routines to receive treatment.² Thus, the high costs associated with drug infusion pumps for intravenous chemotherapy, as well as the time cost of disrupting patients' daily lives for prolonged periods of time has prevented intravenous chemotherapy from becoming readily accessible.

One of the primary reasons why pole-based infusion pumps have remained the gold-standard in chemotherapy care is that they can deliver not just one, but up to three chemotherapy drugs simultaneously, all at specific time intervals and in very accurate dosages.

Iontophoretic (Figure 3) electronic and patch-based disposable drug delivery was first introduced to the market in the 2000's as an alternative to infusion based setups that could potentially rival such standards while addressing all of their shortcomings. The Iontophoretic electronic patch (Figure 3), which applies an electric field to the skin prior to delivering drugs, was a breakthrough at the time in that it was able to deliver a wider range of drugs than would be allowed by simple, diffusion-based passive patches.⁷ Nonetheless, it has still proven an inadequate alternative to the gold-standard pole-based infusion pumps for 2 main reasons. Firstly, though it can now administer nearly all chemotherapy drugs with respect to their molecular weight, whereas passive patches could not, incorporation of drugs within the gel or absorbent pad-based reservoir of Iontophoretic electronic patches requires extensive efforts on the part of pharmaceutical companies to properly reformulate current intravenous cytotoxic cancer chemotherapy drugs. Secondly, current commercially available Iontophoretic electronic patches only allow for delivery of 1 drug at a time, whereas cancer chemotherapy treatment protocols often require simultaneous administration of up to 3 chemotherapy drugs from physically disparate reservoirs.¹

Through extensive R&D efforts, we managed to improve upon the Iontophoretic patch technology via our development of the ChemoPatch (Figure 4). The ChemoPatch, which is an electronic and disposable device, includes a novel patent-pending micropump. This micropump matches the accuracy of the Iontophoretic electronic patch while overcoming both of their limitations. Firstly, recent advancements have allowed pharmaceutical companies to develop more stable, selective, and concentrated cytotoxic chemotherapy drugs. Thus, the ChemoPatch is able to store and administer a large majority of chemotherapy drugs not only in their existing formulations, but also for up to 1 week at a time. Secondly, the ChemoPatch has built-in flexibility to allow for up to 3 chemotherapy drugs to be stored in physically disparate reservoirs and delivered either separately or in combination. By doing so, we have set the stage for dramatically increasing convenience, and, as a consequence, access to high-quality cancer chemotherapy care.

Our innovations can be broken down into 3 design modules: 1) micropump development, 2) circuit development, and 3) microneedle development. Firstly, we developed the first completely plastic-based micropump. Though micropumps sufficiently accurate for medical dosing are commercially available, they are silicon-based, thus requiring complex and costly manufacturing setups, rendering them indisposable. Consequently, our micropump is the first one that is truly disposable. Secondly, we developed an intelligent circuit, as well as a desktop java executable program that allows a user to program not only precise volume deliveries, but also at future dates and times, as the device can automatically wakeup for pre-programmed drug administration. Thirdly, we developed a novel microneedle array for painless administration of chemotherapeutics into the subcutaneous layer of the skin, as opposed to a large needle, which often is quite painful.



Figure 1: Multi-Drug Chemotherapy Infusion Pump⁸



Figure 2: Single Drug Chemotherapy Infusion Pump⁸



Figure 3: Iontophoretic Drug Delivery Patch⁸

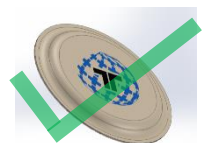
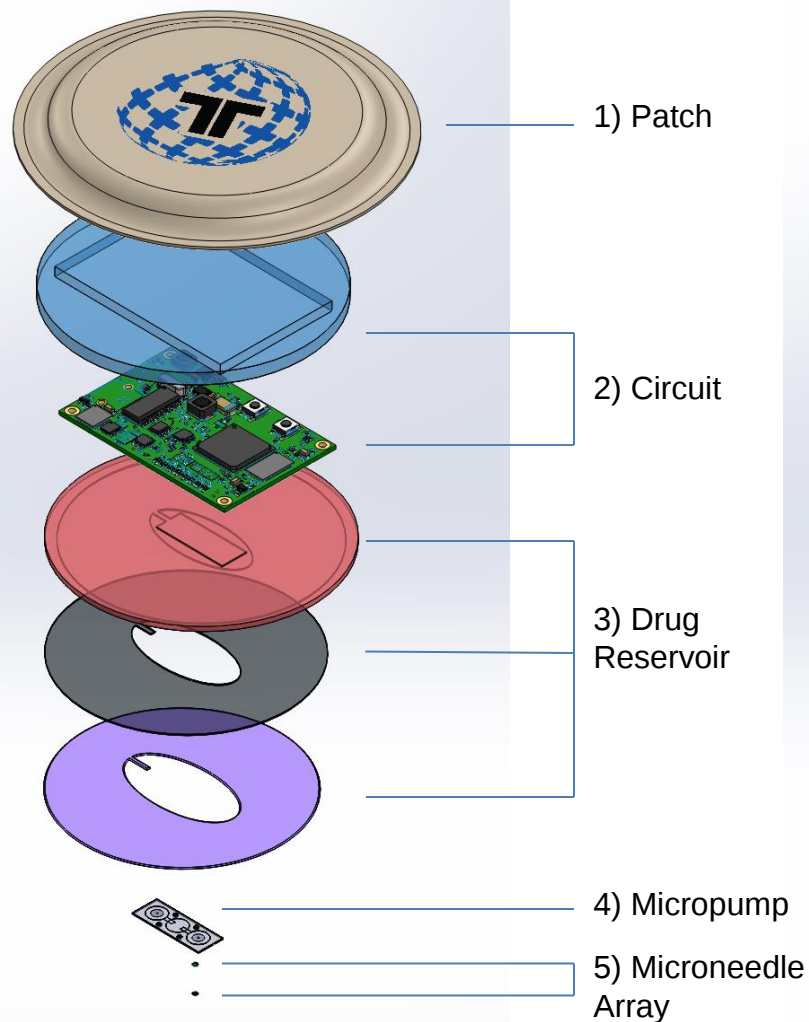
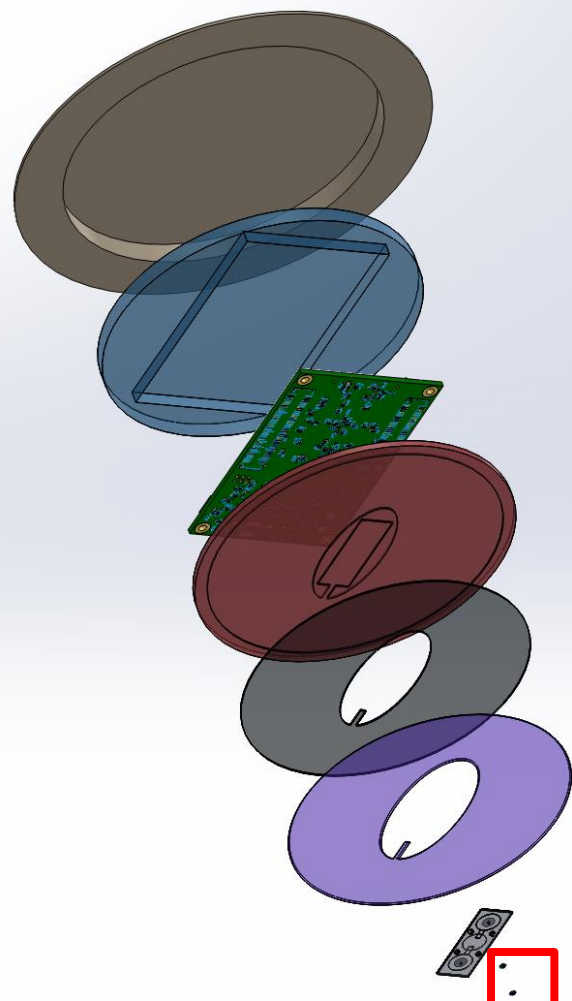


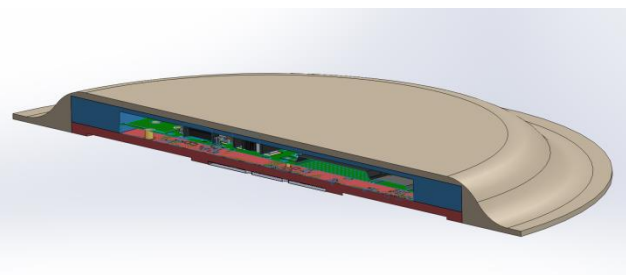
Figure 4: Our Solution: The ChemoPatch



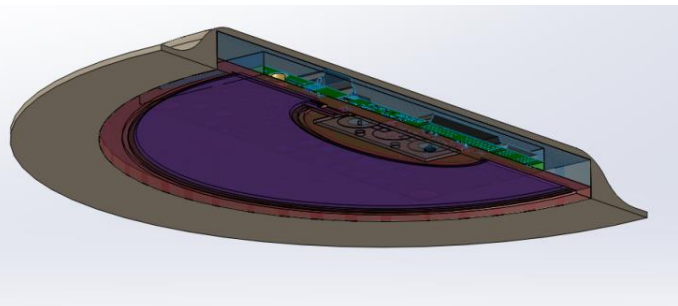
Topside Exploded View



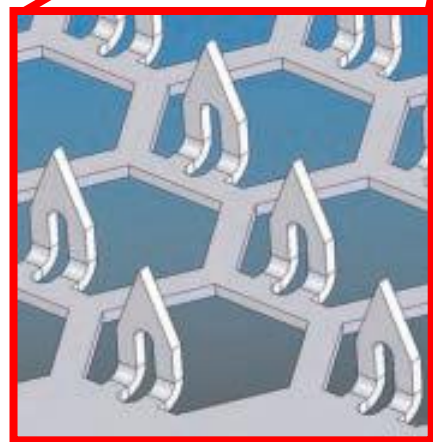
Backside Exploded View



Topside Assembled View



Backside Assembled View



Close-up of Microneedle Array



Methods:

Within module I, we first designed a piezoelectric micropump that would be of small dimension, low cost, low power consumption, high backpressure, adequate flow rate, and high accuracy, which are all key to high quality microdosing of chemotherapy drugs.^{7,9,10,11}

We did so by first laying out a SolidWorks (CAD) model of the micropump, as shown in exploded view on the right (see Figure 5). We decided to employ a passive valve design to create a completely solid state micropump to minimize chances of pump failure, which are much more common in mechanical pumps that involve moving parts. Secondly, we manufactured each of the components with a variety of techniques. Firstly, we used a CO₂-based precision laser to cut the coverplate, valve seats, Kapton valve, chamber spacer, membrane, and fixing bar components. Secondly, we purchased a custom-ordered piezoelectric actuator (bimorph rectangular piece). The layers were then all fixed to each other using laser-cut Kapton double-backed adhesive.

Second, we sought to evaluate the micropump in terms of the flow rate and back pressure it could generate when pumping minute quantities of water. We employed a thermal mass microflow meter from Brooks Instruments to accurately measure both the flow rate (microliters/minute) and the backpressure (millibars). As shown in Figure 6 we measured the flow rate or dosing of liquid water from the outlet hole of the micropump (see Figure 5). We employed a lab-bench function generator to produce a variety of waveforms. The micropump is a piezoelectric actuator-based one, and thus, requires an inverting signal. We decided to employ a sine waveform so as to create smooth motions of the micropump when pumping. We fixed the voltage at 100 V and as can be seen in Figure 7, we varied the frequency from 0.1 Hz to 200 Hz and measured the flow rate. As shown in Figure 7, we chose select frequencies (0.5 Hz, 1 Hz, 2 Hz, and 10Hz).

Results:

First, the results in Figure 6 demonstrate that we can precisely control when and how much of a loaded chemotherapy drug is released using our electronic circuit board, thus allowing for highly controllable and precise chemotherapy drug delivery. Next, as shown in Figure 6, we measured the downstream pressure (backpressure) that resulted at different flow rates or drug dosages.

Secondly, the resistance of the skin subcutaneous layer is approximately 70 millibars or 7 kiloPascals and the resistance of a standard set of microneedles is approximately 20 millibars or 2 kiloPascals.⁷ As can be seen in Figure 7, the micropump was able to generate over 400 millibars of pressure at a variety of frequencies, which is far above the requirement. We demonstrated that the micropump unit would generate more than enough pressure to counteract the resistance to the pumping of a chemotherapy drug into the subcutaneous layer of the skin.⁷

Thirdly, we found that the pump operates optimally from both a functional and power-efficiency standpoint. It operates optimally from a functional standpoint because at 10 Hz, it is able to maintain flow in the linear regime of the flow rate vs. frequency graph, which drastically improves the chances of it being able to reproduce that same flow rate at 10 Hz.(ref) It operates optimally from a power-efficiency standpoint in that it is able to generate a fairly high flow rate at the low frequency of 10 Hz, which also satisfies the pressure requirement. This is opposed to other pumps, which often require frequencies as high as 100 Hz to generate a pressure above the opposing pressure of a combination of the skin subcutaneous layer and a set of microneedles.

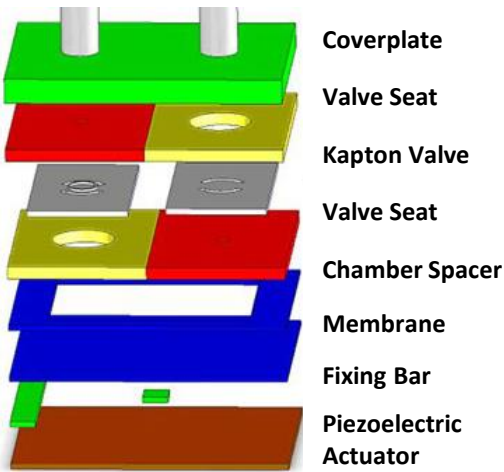


Figure 5: Exploded view of micropump assembly

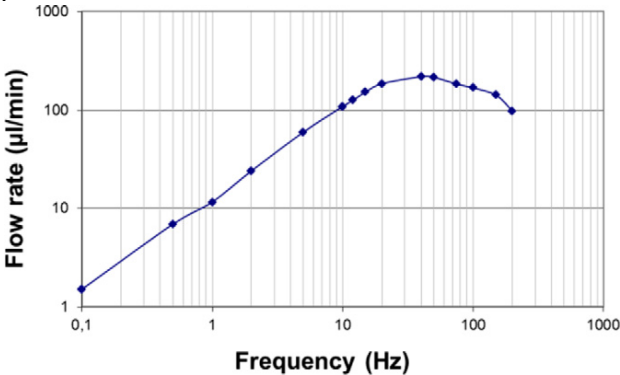


Figure 6: Flow Rate vs. Frequency

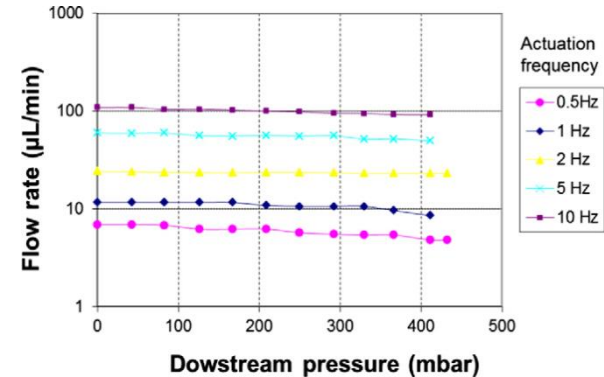


Figure 7: Flow Rate vs. Downstream Pressure



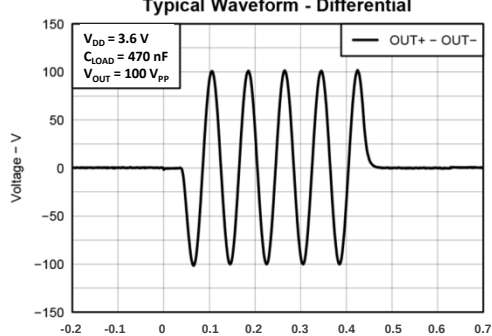
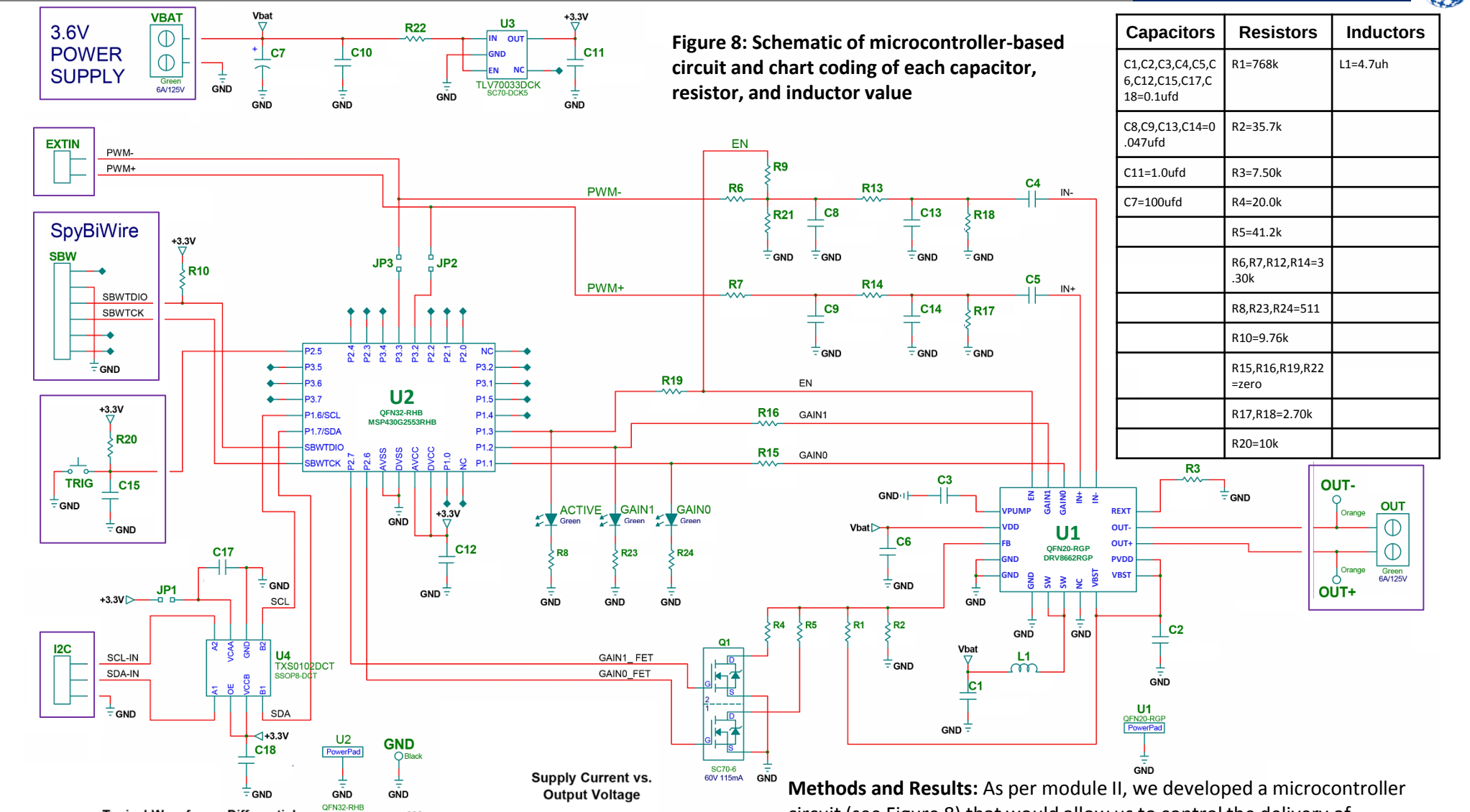


Figure 9: Sine Waveform at 100 V, 10 Hz

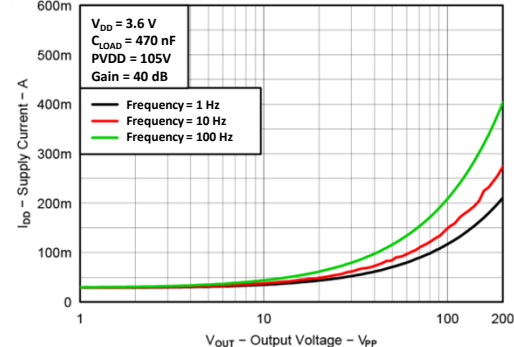


Figure 10: Current Consumed vs. Voltage

Methods and Results: As per module II, we developed a microcontroller circuit (see Figure 8) that would allow us to control the delivery of chemotherapeutics using the micropump engineered in module I. The circuit involved 3 silicon-based chips from Texas Instruments (labeled as U1, U2, U3, and U4), as well as a number of capacitors, resistors, and inductors. We tested the circuit in terms of the waveform it generated, as well as the power it consumed. We demonstrated function of the circuit at a voltage of 100 V and 10 Hz (these were the optimal micropump operation parameters as per the results of Module I), as in Figures 9 and 10. Figure 9 shows that the circuit can produce a high resolution and accurate sine waveform for pump control at 10 Hz and 100 V and Figure 10 shows that the circuit consumes only 150 mA when running, making the device power-efficient enough to pump continuously for over 4 hours on a standard coin cell battery.

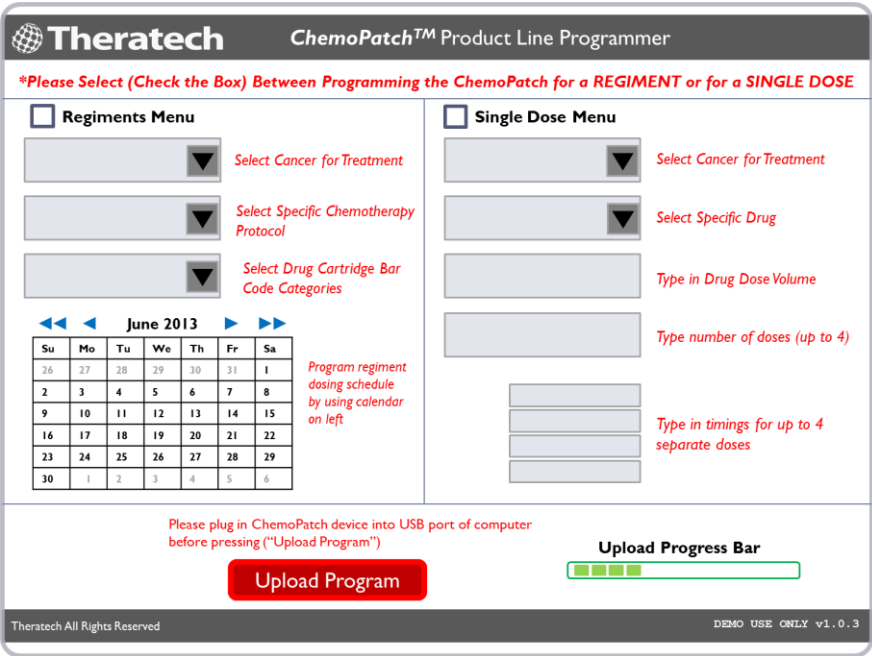


Figure 11: Java .exe GUI program that allows for drug delivery scheduling

Methods:

First, we sought to fabricate a microneedle array that would allow for more painless drug delivery. Microneedle arrays have not yet caught on within the drug delivery industry due to the fact that most microneedle arrays are difficult to manufacture economically.^{12,14}

Additionally, microneedle arrays such as the gold-standard hollow microneedles suffer from clogging when inserted into tissue, which prevents effective perfusion of the subcutaneous, layer of tissue, which is often the targeted layer of the tissue for drug delivery.^{13,15}

We developed an array that employed a cheap, robust, and accurate manufacturing process while maintaining a microneedle array that was able to perfuse tissue. We developed a microneedle array that employs needles that bend out of a laser cut metal sheet (see Figure 12a, 12b, 12c).

Results:

Finally, after optimizing the geometry to withstand breaking when purposely pricked, we placed it on human tissue samples obtained from Prof. David Mooney of Harvard SEAS. A blue dye was injected into the skin samples As can be seen, the needles effectively pierced the outer layer of the skin (see Figure 13b) and also perfused the target skin layer (the subcutaneous layer-see Figure 13a).

Methods and Results (Cont'd):

After having completed the circuit for controlling the micropump, we developed a Java executable program we developed for use on Windows PCs that allows a clinician to customize the delivery schedule of a number of chemotherapy drugs via the ChemoPatch device (see Figure 11).

The program is preloaded with standard chemotherapy protocols for a number of cancers, as per the latest literature and clinical trials.

Additionally, the user can either program the device for long-term use (regiment) use or short-term use (single dose)



Figure 12: 12a-SolidWorks (CAD) depiction of microneedles, 12b-SEM image of microneedles, 12c-Actual photograph of microneedles

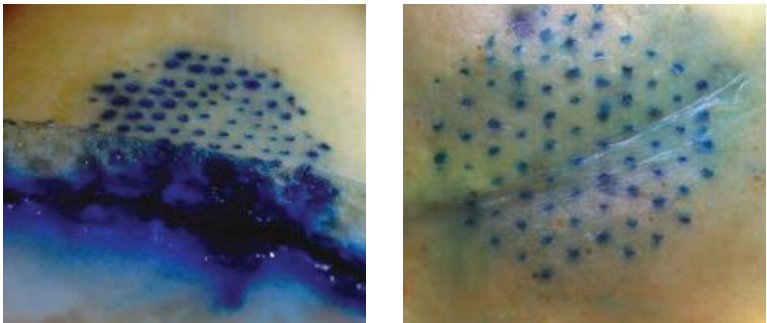


Figure 13: 13a-Cross section of tissue depicting infusion of skin fat and subcutaneous layers, 13b-Top view of tissue depicting infusion of skin



References

1. Tralongo, P. (2011). Cancer patient-centered home care: a new model for health care in oncology. *Therapeutics and Clinical Risk Management*, Dovepress. 1. Benizri, F. (2008). Stability of antineoplastic agents in use for intravenous chemotherapy. *Pharmacy World Scientific*.
2. (2010). Home therapy. *Bazian*.
3. Lin, C.C. (2013). *Association Between the Availability of Medical Oncologists and Initiation of Chemotherapy for Patients With Stage III Colon Cancer*. Health Care Delivery.
4. Raphaël Remonnay, Yves Devaux, Franck Chauvin, Eric Dubost and Marie Odile Carrère (2002). ECONOMIC EVALUATION OF ANTINEOPLASIC CHEMOTHERAPY ADMINISTERED AT HOME OR IN HOSPITALS. *International Journal of Technology Assessment in Health Care*, 18, pp 508519.
5. ECRI Institute. (n.d.). *Healthcare product comparison system*. Retrieved from https://www.ecri.org/Documents/HPCS_Infusion_Pumps.pdf 2. Bohm, S. (1999). *A plastic micropump constructed with conventional techniques and materials*. (Master's thesis, University of Twente, Enschede, Netherlands).
6. Chandika, S. (2011). *Design and analysis of piezoactuated micropump for fuel delivery in automobiles*. (Master's thesis, Kongu Engineering College, Erode, India).
7. Ochoa, M. (2012). *Polymeric microdevices for transdermal and subcutaneous drug delivery*. Publication, School of Electrical and Computer Engineering, Purdue University, West Lafayette, IN.
8. *Monet medical inc.* (n.d.). Retrieved from <http://www.monetmedical.com/products/catalog/product/view/id/2400/s/alaris-imed-gemini-pc-4-infusion-pump/category/151/>.
9. Jang, L. (2007). *Peristaltic micropump system with piezoelectric actuators*. (Doctoral dissertation, National Cheng Kung University, Tainan, Taiwan).
10. Kim, J. (2003). *Laser-based fabrication of polymer micro pump*. Publication, Mechanical Engineering, Purdue University, West Lafayette, IN.
11. Li, X. (1999). *Electromechanical behavior of pzt-brass unimorphs*. Publication, Materials Engineering, Princeton, Princeton, NJ.
12. Rohan D. (2012). *Microneedle Technology for Advanced Drug Delivery: A Review*. *International Journal of PharmTech Research*.
13. Kim, Y.C. (2012). *Microneedles for drug and vaccine delivery*. *Advanced Drug Delivery Reviews*.
14. Nordquist, L. (2013). *Novel Microneedle Patches for Active Insulin Delivery are Efficient in Maintaining Glycaemic Control: An Initial Comparison with Needle Subcutaneous Administration*. *Pharmaceutical Research*.
15. Martanto, Wijaya. (2010). *Microinfusion Using Hollow Microneedles*. *Pharmaceutical Research*.