122nd ASEE Annual Conference & Exposition
June 14 - 17, 2015
Seattle, WA
Seattle Making Value for Society

Paper ID #13578

Microfluidic Medical Diagnostics Devices: Instructive Student Projects for Product Development in the Coming Decade

Dr. Michael G Mauk P.E., Drexel University
Dr. Richard Chiou, Drexel University (Eng. & Eng. Tech.)

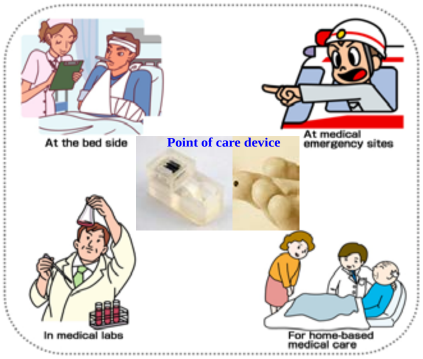
Work in Progress:
Microfluidic Medical Diagnostics Devices-
Instructive Student Projects for Product Development
in the Coming Decade

1. Introduction and Background.

Portable devices and systems that enable medical diagnostics outside of traditional laboratory settings will likely be an important component of future healthcare. The recent SARS and Ebola pandemics underscore the pressing need for simple, low-cost, easy-to-use devices to rapidly test for pathogens in places such as airports, border crossings, and schools. So-called *point of care* diagnostics at doctors' and dentists' offices, hospital bedsides, rural clinics, and even at home, will foster more efficient, sustainable and streamlined delivery of healthcare, especially for the developing world. Point-of-Care (POC) diagnostics and other field-deployable bioassay test devices can be realized with microscale fluidic systems. Typically, a POC test cartridge is formed on credit card-sized plastic substrates that hosts a miniaturized network of chambers, conduits, filters, valves and flow control components. The cartridge or 'chip' is mated with a portable processing device that provides the chip with controlled temperatures, fluid actuation and flow control, and optical sensing, such as for measuring a fluorescence signal. These microfluidic "Lab on a Chip" (LOC) devices can process and analyze medical specimens (whole blood, plasma, saliva, urine), food and water, and environmental samples to detect viruses, bacteria, parasites, toxins, and bioterrorism agents. Continued progress and affordability in rapid prototyping (3D printers, laser cutters, soft lithography), Computer-Aided Design (CAD), microcontrollers, Smartphone cameras and other CCD-based imaging, miniature sensors, freeze-dried reagents, and optical components and materials (e.g., LEDs, laser diodes, photodiodes, optical fibers, filters, fluorescent dyes) make the design, fabrication, and testing of Lab on a Chip diagnostics devices accessible to engineering students. We describe Student Design Projects to demonstrate LOC diagnostics devices to meet current needs for healthcare, public safety, and sustainable development. These projects provide a gateway for engineering students to learn biomedical applications of engineering, gain experience with product development, and integrate knowledge of materials, instrumentation, control, rapid prototyping, and applied optics in products with considerable near-term commercial potential and/or as appropriate technology for resource-limited areas of the world.

2. Overview.

POC systems are portable handheld devices for rapid tests of viral, bacterial and parasite infections or assessing immune response in humans and animals. Similar point-of-test (POT) devices can be made for assurance of food and water safety, environmental monitoring, detection of bioterrorism agents, and tests for hereditary disorders, markers of cancer and other diseases, and genetically modified organisms. POC technology is expected to foster a paradigm shift in healthcare, and the projected global POC diagnostics market for 2018 is over $25 billion [http://www. marketsandmarkets.com]. Student Senior Design teams can invent, develop, and prove innovative POC devices to enhance healthcare and offer medical testing options to the developing world using appropriate technology.



Senior Design Teams (groups of 3 to 5 students with an academic advisor and a clinician/researcher or industrial stakeholder as co-advisor), working over an 8- or 9-month period conceptualize, design, prototype, and test novel POC and related devices, and if technically successful, can take the first crucial steps towards commercialization. Senior Engineering students develop state-of-the-art diagnostics devices, utilizing and leveraging recent developments in microfluidics technology, rapid prototyping, smartphones and wireless communications, low-cost CCD cameras, microcontrollers, sensors, and biological assay kits with freeze-dried reagents. These tools and resources make POC technology readily accessible to schools and educational institutions.

The Senior Design projects can be structured to include: 1) demonstrating working prototypes of novel POC diagnostics devices, 2) defining an invention by way of a provisional patent application and drafting patent claims, 3) developing material and data to support and write an SBIR (Small Business Innovative Research) proposal, and 4) familiarization with a 510(k) FDA application for regulatory approval of a diagnostics device. The patent and mock SBIR serve as realistic exercises that inform and instruct students in the components of a successful technology venture and the competitive nature of securing funding for a start-up company.

The drafting of patent claims is instructive in defining an invention with respect to the prior art, and gauging its strengths and weaknesses regarding infringement: the value of a project is ultimately in the strength of any ensuing patent claims. The SBIR proposal has a standardized format that will compel students to review the competing technologies; make a rationale for the approach; define technical objectives; organize the research effort by formulating a detailed work plan with specific tasks, milestones and schedules, and contingency plans; identify needed facilities and resources; determine required expertise, budget the effort, and make persuasive, realistic plans for commercialization. Student SBIR proposals can be scored and evaluated using the same criteria as funding agency reviewers. The invention disclosure and SBIR proposal will help crystallize the issues and problems to be addressed in contemplating further product development and commercialization strategies.

Thus, point-of care-diagnostics can provide instructive and productive projects for students on the basis of their immediate feasibility, wide range of sophistication at many technical levels, modest requirements for available resources, and exemplary integration of scientific, engineering, managerial, and marketing disciplines. Also, we emphasize that it will not be necessary for students to work with any dangerous or infectious agents as there are numerous safe surrogates (harmless, deactivated specimens) that are commercially available and are widely used for educational purposes in schools and test labs.

What is Point-of-Care Diagnostics? Point-of-care diagnostics systems are typically based around a credit-card sized, plastic microfluidic cassette or cartridge (“chip”), pre-loaded with reagents, buffer solutions, and lyophilized (freeze-dried) biological reagents (such as enzymes) as a very low-cost, self-contained single-use (disposable) test vehicle (**Figure 1**). The cassette features a microfluidic network where the sample is processed and analyzed. The sample (blood, saliva, urine, food particles, drinking water, insect samples, etc…) is loaded into the cassette at the point of medical care or in-field testing. The cassette is then inserted into a small portable instrument (**Figure 2**), operated by the caregiver or health worker, that provides the cassette with regulated heating or cooling, fluid pumping, and interrogation for an-easily interpreted read-out test report based on an optical signal due to fluorescence. The generic advantages of microfluidics include reduced reagent consumption and waste generation and retention of waste for easy disposal, automated operation, faster test results, reduction in cross contamination of tests, and better protection of medical personnel against infectious materials. The test can be performed by non-technical personnel. Each test requires from 10 to 40 minutes, and testing costs of $1 to $10 per test are feasible. There are thousands of designs, operating principles, materials, and applications for POC microfluidics reported in the scientific and patent literature, and there is still much opportunity for innovation and new insights.

Why Is Point-of-Care Diagnostics Important? POC diagnostics is an enabling technology that will foster distributed health care in non-traditional venues by facilitating rapid medical tests, improving the quality and lowering the costs of healthcare by avoiding the need for expensive testing in central clinical laboratories, and providing more tools for the control of epidemics, especially in the developing world. The recent epidemics of SARS and Ebola, and the worldwide decades-long scourges of HIV, tuberculosis, malaria, hepatitis, and numerous other viral, bacterial, and parasite infections underscore the need for rapid diagnostics tests, including means to test the safety of water, food, living quarters, and air. In the developing world, POC tests will find wide use in doctors’ and dentists’ offices, hospital bedsides, nursing homes, schools, food processing plants and distribution and retail centers, restaurant kitchens and cafeterias, and at-home patient monitoring for drug therapy. The later applications underscore the role of POC diagnostics in personalized medicine, where therapy is tailored according to individual genetics and life history. Recent market surveys project near-term global markets for POC technology in excess of $25 billion. A recent development is coupling smartphones to POC systems for communications, computation, and archiving data. For instance, smartphone-enable POC devices testing for HIV, malaria, or Ebola can transmit test results to a central control point, and the spread of an epidemic can be monitored. Similarly, outbreaks of food poisoning or terrorists incidents could be tracked.

Students Making Point-of-Care Technologies: Tools and Capabilities

Several technical developments make design and prototyping POC technology readily accessible to students and include:

- ***Microfluidics.*** Miniaturized fluidic circuits formed in palm-sized plastic substrates (“chips”) can process and analyze samples in ways previously limited to laboratories equipped with varied, bulky, expensive and/or sophisticated benchtop instruments such as centrifuges, water baths, thermal cyclers, electrophoresis gels, hoods, refrigerators, freezers, and pure water systems. We fabricate the chips as plastic laminates of acrylic, polycarbonate or similar clear plastics. The chips can be operated manually with syringes, or with programmable syringe pumps. Other methods of fluid actuation are possible and are often a design objective of the student project.

- ***Assay Kits and Protocols.*** There are commercially available reagent kits containing all the materials and protocols needed to test for most common disease targets and analytes of biomedical or biological interest. Therefore, no chemistry development is needed. The technical task is instead to adapt the benchtop protocol and materials of a commercial laboratory kit to a microfluidic chip.
- ***Lyophilized reagents.*** Reagents that normally had to be frozen or refrigerated are now available as freeze-dried pellets, avoiding the need for ‘cold chains’ and enabling simplified microfluidic implementations with chips pre-loaded with reagents. For instance, the polymerase chain reaction (PCR) is used to amplify DNA and is a central process step in many diagnostics tests. PCR kits for educational and commercial purposes can be purchased where all the reagents are premeasured and formulated as a 1-mm diameter lyosphere, to which sample and water are added and heated to effect the amplification reaction.
- ***Safe Surrogates.*** Many of the diagnostics kits provide ‘mock’ samples and safe substitutes for viruses and bacteria, which can be used to develop and test POC systems. These surrogate samples are widely used in educational settings and pose no danger to students. The same bioassays can be used to detect viruses, bacteria, and other organisms by using different primer sets (specific nucleic acids that initiate the amplification reaction used to detect pathogens) and minor modifications in the temperature cycling protocol. Thus, safe
- ***CAD/CAM/Computational Fluid Mechanics.*** The chips can be designed and simulated with various CAD software (SolidWorks®, FEMLAB®).
- ***Rapid Prototyping Tools.*** Rapid prototyping tools (3D-printers, engravers, laser cutters, and CNC machines) can be used to make chips and parts for the instruments (**Figure 3**). For example, a 30-watt CO2 laser cutter can be used to cut a fluidic circuit in 0.1- to 2-mm thick acrylic sheets. The chips are then sealed by bonding a top and bottom sheet, using either solvent bonding, thermal-pressure bonding, adhesives, or double-sided tape.
- ***Microcontrollers*** (e.g., Arduino™) can be used to make functional instruments to operate the chip. For example, we use the Arduino to implement a PID programmable controller for a 12.5mm x 12.5 mm thermoelectric element and measure temperature with a thermocouple or RTD.
- ***Sensors.*** There are a wide variety of inexpensive sensors (temperature, pressure, light, GPS, motion, pH, etc…) that can interfaced with Arduino or similar microcontrollers for various operational schemes.
- ***Smartphones,*** ubiquitous in the developing world, can be coupled with POC instruments, leveraging their power for communications, computation, and control. One of our Senior Design student projects used a Smartphone CCD camera as a fluorescence detector. A blue LED excited the fluorescence generated by a dye that binds DNA, and the cellphone camera (along with an appropriate optical filter) was used to detect the fluorescence signal.

3. A Senior Design Structure and Format

In one implementation of Senior Design, the student Senior Design teams can be tasked with the following objectives and activities (see **Table 1**):

1. ***Identify a Specific Need of Opportunity for Point-of-Care Devices.*** Students search the literature, or respond to specific interests of medical researchers, to identify POC and related POT opportunities. There are over 4000 pathogens that infect humans, and many others that infect animals, insects, and crops. Further, related devices can find numerous applications in agriculture, food safety, environmental and wildlife monitoring, homeland security, cancer and genetic diseases, dentistry (dental caries and tooth infections), pet care, and the like.
2. ***Market Study and Business Plan.*** Students can assess the current diagnostics options. What tests are now available? How many tests are performed per year and at what cost? What are typical features of the test (performed in what types of laboratories?)? Are they covered by insurance?
3. ***Design Conceptualization.*** The diagnostics tests can be flow charted, a protocol and a bill of materials determined based on or modified from current laboratory procedures and reagents in commercial kits. The chip and instrument case will be designed with CAD and the microfluidic chip simulated with computational fluid mechanics if appropriate.
4. ***Invention Disclosure, Patent Search, Invention Analysis and Drafting of Patent Claims, Provisional Patent Application.*** An invention disclosure leading to a provisional patent application can serve as one means of reporting progress and achievements. Although provisional patents do not normally require claims, claim drafting for the student invention can be included as an instructive exercise.
5. ***Demonstration and Proof of Concept, Data Supporting Feasibility, Working Prototype*.** The design is rapid prototyped and tested, and demonstrated to intended users. Technical publications in the scientific literature, where appropriate and where proprietary technology is protected by patent applications, are encouraged.
6. ***Draft of SBIR Proposal.*** As a summary written report of their project, students can write a mock SBIR proposal in response to current solicitations or similar solicitations topics (NIH, NSF, DOD, NASA, USDA, CDC, and DOC). The proposal would include, as required, sections on Identification and Significance of Opportunity and Need, Background, Description of Related Work, Technical Objectives, Work Plan including tasks, milestones, contingency plans, alternative methods, schedule of tasks and level of effort, commercialization plans, key personnel, facilities, relation to future R&D, plus a budget allotting hours of effort, materials, supplies, capital equipment purchases, and overhead.
7. ***Regulatory Issues and Plan for Approval.*** Students can review FDA 510(k) form for approval of diagnostics devices and other regulatory issues as it pertains to their particular application.

4. Example Student Senior Design Projects

Several 9-month (three terms) Senior Design Projects are described as representative examples of the scope and issues addressed in making point-of-care diagnostics systems.

In the first project, students adapted the materials of commercial chemical heating mixtures, as available in ‘ready-to-eat’ meals and hand warmers, to provide autonomous heating for a microfluidic system, i.e., a portable diagnostics system that does not require electrical power for heating the sample or reagents such as required in various incubation steps (**Figure 4**). A recurring issue in this project was related to students’ appreciation of the challenges and advantages of miniaturization. Several design iterations progressed through smaller and smaller devices: from the size of small lunchbox to a palm-sized device. In the second project, students built and Arduino-based POC device that adapted a Smartphone camera as a fluorescent detector (**Figure 5**). This project involved writing Android code for the cellphone. In a third project, students used focused optical beams to selectively heat phase change material with high expansion volumes to push liquids through a chip channel (**Figure 6**). This device demonstrated a novel microfluidic format. In a fourth project, a syringe was molded into a microfluidic cassette for manual but precise fluid actuation in the chip.

5. Sidebar: Medical Diagnostics as Unit Operations

Microfluidics for bioassays and diagnostics provides a familiar engineering perspective to laboratory biotechnology. Chemical and process engineers use a *unit operations* approach for the analysis and design of chemical and industrial processes. Unit operations encompass reactors (e.g., continuous-flow, stirred tank, packed-bed, and batch reactors), separations (e.g., distillation, extraction, adsorption), and physical processes (mixers, heat exchangers, crystallizers). Historically, this methodology has been applied to the scale-up of benchtop and pilot operations to the chemical plant, but can also be applied to biotechnology and biomedical laboratory work implemented in a microfluidic format in scaling down processes to fit on a chip. For medical diagnostics, the relevant unit operations are cell sorting, cell lysis, nucleic acid isolation, amplification, and detection. Each of these steps can be performed on a chip. Then, the unit operations are integrated into a single chip. The unit operations approach can serve as an effective gateway to biotechnology for engineering students.

References

1. B. Monegain, "Point-of-Care Diagnostics Market Headed to $16.5 Billion" *Healthcare News* (Jan 6 2012)
2. C. Liu, M.G. Mauk, R. Hart, M. Bonizzoni, G. Yan, and H.H. Bau, “A Low-Cost Microfluidic Chip for Rapid Genotyping of Malaria-Transmitting Mosquitoes” *PLoS One* (Aug 3, 2012) **7(8)** e42222.
3. Michael G. Mauk, Changchun Liu, Paul Corstjens, and Haim H. Bau, “Streamling Point of Care Devices” *IVD (in vitro Diagnostics)* Magazine (Nov/Dec 2011).

4. Nitika Pant Pai, C. V. “Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low-and Middle-Income Countries” *PLOS Medicine* , (2012) *9* (9), 1-7.

5. M.G. Mauk, C. Liu C, M. Sadik, H.H. Bau “Microfluidic devices for nucleic acid (NA) isolation, isothermal NA amplification, and real-time detection”. *Methods Mol Biol*. (2015) 1256:15-40.

6. Y. Song, Y.-H. Huang, X. Liu, X. Zhang, M. Ferarri and L. Qin, “Point of care technologies for molecular diagnostics using a drop of blood” *Trends in Biotechnology* 32, 3 (2014) 132-139.

Table 1: Suggested Senior Design Microfluidic POC Diagnostics Projects Timeline

Schedule of Project	**Month of Senior Design Project**							
Task	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1 Identify Need/Opportunity POC diagn.	🟧	🟧						
2 Market Study/Business Plan	🟧	🟧						
3 Design Conceptualization		🟧	🟧	🟧				
4 Invention Disclosure/Prov. Pat. Appl.					🟧	🟧	🟧	🟧
5 Demonstration/ Proof of Concept			🟧	🟧	🟧	🟧	🟧	
6 SBIR Proposal					🟧	🟧	🟧	🟧
7 510(k) forms and related						🟧	🟧	
Final Report and Presentation								🟧

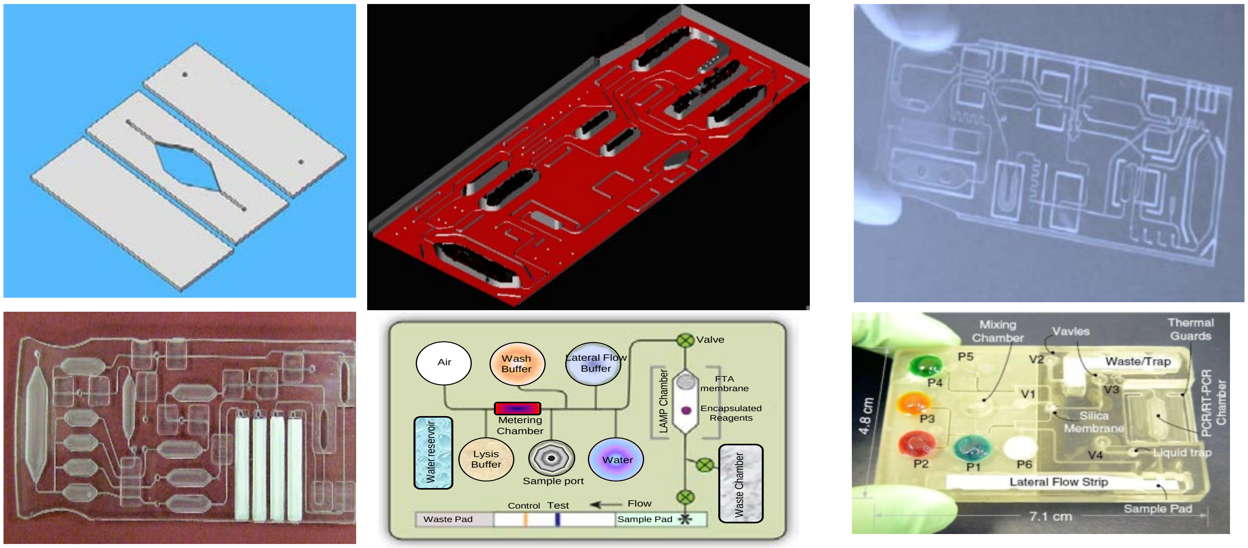


Figure 1: Various disposable plastic sample processing microfluidic ‘chips’ for POC diagnostics.

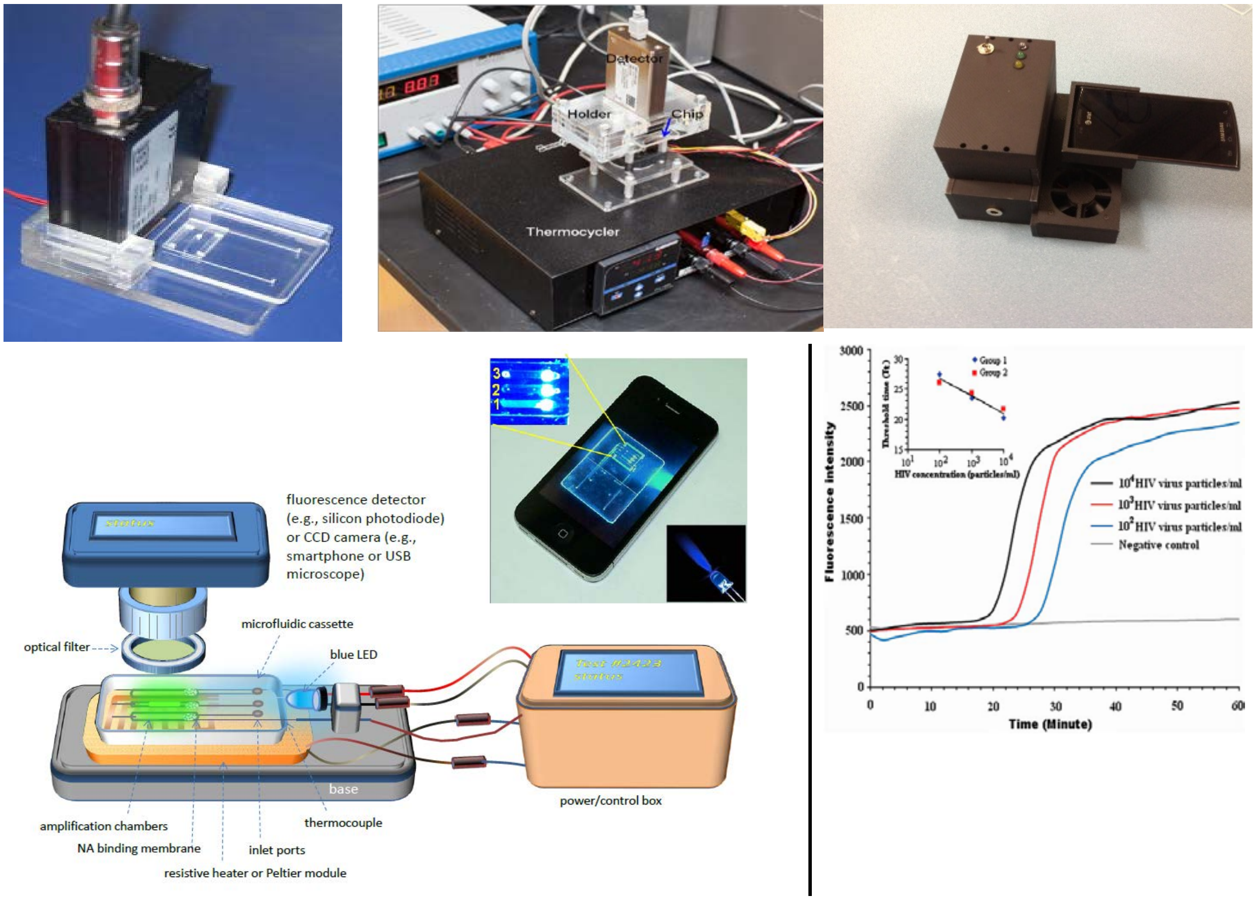


Figure 2: Various companion instruments used to operate chips: Bottom right: fluorescence curves from cellphone coupled to instrument to detect virus load from microfluidic chip.

Figure 3: Rapid Prototyping Tools: CNC mill, CO2 laser cutter, 3-D printer.

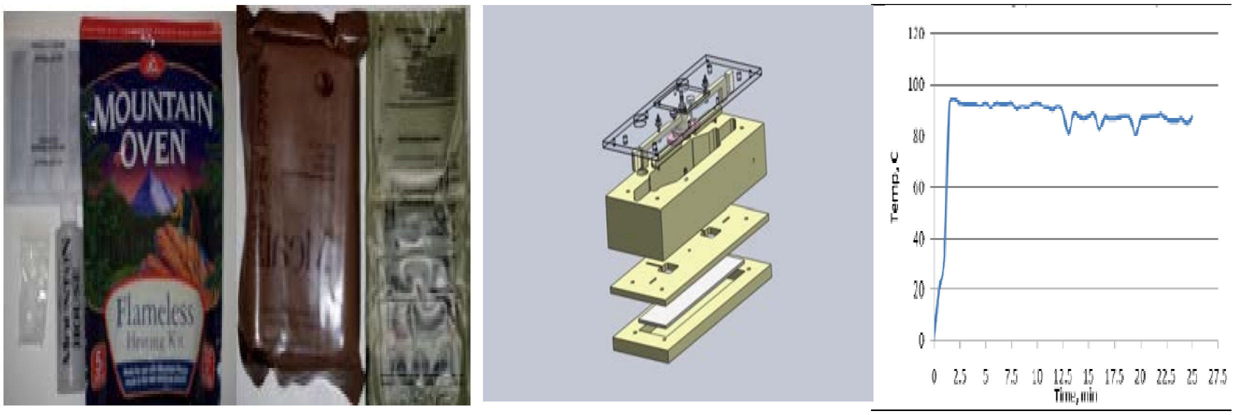


Figure 4: Commercial mixes for heating by exothermic chemical reactions, student design for a chemical heater for a microfluidic diagnostic device; and time-temperature plot of device performance.

Figure 5: Cell phone based diagnostic system: SolidWorks design (left), captured image of fluorescence nucleic acid amplification chamber on chip (center), and quantitation of fluorescence signal (right).

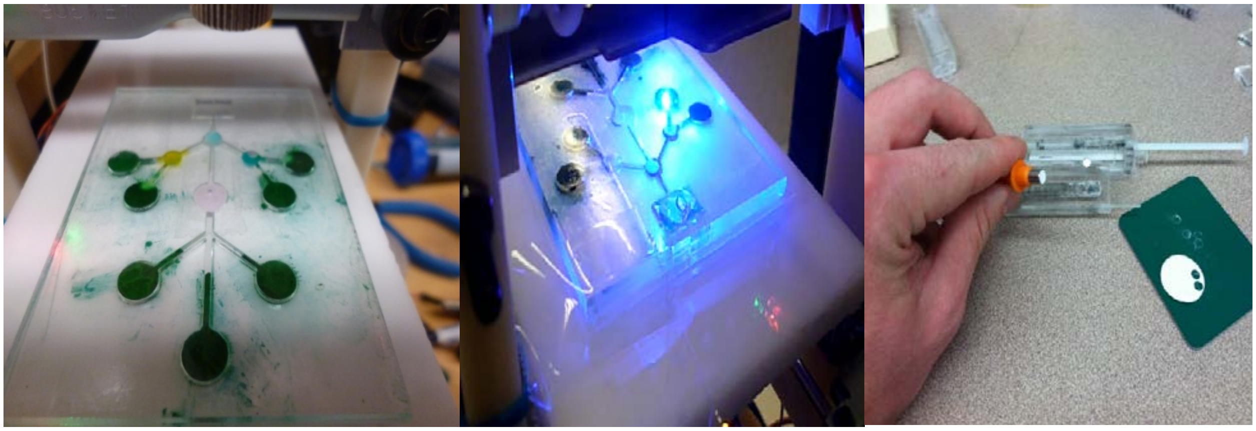


Figure 6: Optically heated fluid actuation and manual syringe-powered chip (left and center) and chip incorporating syringe for fluid actuation (right).