Low Cost Solution of Thermal Cycler for LifeFoundry, Inc.

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1 Introduction

1.1 Objective

A thermal cycler is a device that repeatedly raises and lowers the temperature of liquid samples in microplates during a synthetic biological process. It is widely used to conduct polymerase chain reaction (PCR), a technique to make particular copies of DNA segments under high temperature with enzymes and primers [1]. The PCR reaction usually requires around 30 cycles of such heating / cooling operations, which can take several hours to run. It has a long list of potential applications, including but not limited to: identification, gene sequencing, and drug development. However, current products on the market are expensive and require much training before one can operate on them.

We are planning to design and build a prototype thermal cycler with water cooling capabilities with a \$400 budget. The reason we chose to use water cooling is because water removes heat from the microplate much faster compared to traditional fans. If our sponsor eventually deploys our design, there are possibilities to further reduce costs, such as clustering a few thermal cyclers around a shared water tank and radiator. In addition, the design fits well for our sponsor's application, and the finished product will not require a lot of training for the operator.

1.2 Background

Compared to existing products on the market, our device has several advantages. First, it is less than half of the price of most competitors. The average starting price of commercial solutions cost more than \$1,000 [2], not to mention professional and premium products with higher capacities and higher throughputs that cost north of \$10,000 [3]. Second, existing products require manual input while our device operates nearly automatically, so researchers do not need to be physically in the lab to enter inputs while conducting the experiment. Third, unlike most existing products that cool microplates with airflow generated by fans, our device cools with water, which is faster and more effective for repetitive cooling operations. The addition of a water cooling unit gives researcher more flexibility when a large number of heating and cooling operations are needed.

We are building this device for LifeFoundry, Inc., a startup based in the Research Park focusing on the automatic control of synthetic biological processes. Throughout the semester, we will be getting financial and technical support from LifeFoundry, Inc.

1.3 High-level Requirements

- The prototype must cost less than \$400 to build to serve our original purpose in providing a cheap alternative to overpriced commercial products.
- The device must be able to operate 25 continuous cycles of experiments without human supervision.
- Each cycle should be able to finish in 7 minutes under water cooling according to typical PCR procedure.

2 Design

2.1 Block Diagram

Figure 2.1 shows how every part gets connected. Our power source is converted from 110V AC to 5V and 12V DC respectively. In the power-on process, the microcontroller will try to read from the two temperature sensors as a self-test to see if signals are indeed being read. If self-test fails, the device will not start as a safety precaution. When performing regular tasks, the microcontroller will directly talk to these two thermocouples.

As thermocouples feed data into the microcontroller, it will start each cycle with PID control as programmed. It will then instruct the heating pad and the water pump to perform heating/cooling cycles, as long as it keeps getting streams of temperature data. In the meantime, it will send data to the LED display to show the current status. Buttons are used to reset the microcontroller.



Figure 2.1 High-level block diagram

2.2 Physical Design

Figure 2.2 is a sketch of the hierarchical version of our physical design solution. The aluminum sample plate sits on top of other components for ease of frequent access. The sample plate is attached to a thick plastic lid, and all major components will be enclosed by a plastic casing. Two thermocouples will be housed in the drilled holes on the bottom of the sample plate. The heating pad and the water block are the major components for heat exchange. Since the sample plate, the heating pad, and the water block are all made of heat conductive materials, we should be able to easily inject or remove heat from the system. To amplify the thermal conductivity, liberal amount of thermal paste will be applied in between the three components to close air gaps.

The water cooling unit is a bit more complex. It consists of a water tank, a pump, a water block, and a radiator. When the device is in a cooling cycle, water is pushed through the water block to absorb heat, and then the heat is released as water runs through the radiator. Since water has roughly five times the specific heat capacity of aluminum [4], a decently sized water tank and a good radiator will guarantee proper cooling.



Figure 2.2 High-level physical design

2.3 Functional Overview

2.3.1 Control Unit

Microcontroller

The microcontroller will poll data from the temperature sensors and calculate the derivative of temperature to determine the rate at which temperature is changing. The microcontroller then uses this data to control the water pump module and the heating pad module, both of which work together to control the temperature. There will be a PID algorithm to regulate this process.

Inputs interface: signal from buttons for selection, signal from thermocouple, 5V voltage Outputs interface: PWM signal [5] for water pump, modulated signal for heating pad, data for LED display

2.3.2 Heating and Cooling Unit

Heating Pad

The heating pad is placed under the microplates. It is designed to generate heat via a matrix of resistors. The heating pad will heat the samples to the designated temperature and preserve the temperature for a period of time. Input interface: signal from microcontroller, 12V voltage Output interface: heat flow to the microplate

Water Pump, Water Tank, Radiator and Tubings

They will work together as the water-cooling unit. Water will be at room temperature and the water pump will be part of the water cycle. Water pump will push water through the water block and the radiator. Both the water block and the radiator will be purchased as off-the-shelf parts, for preventing leaking and enhancing cooling efficiency. The best material for the water block and the radiator is copper; however, if we experience budget issue, we can also use aluminum parts as a decent alternative. Input interface: PWM signal from microcontroller, 12V voltage Output interface: pump water through cooling unit

2.3.3 Sensor Module

Thermocouple

There are two types of temperature sensors: thermocouple and thermistor. Environmental temperature change will result in thermistors' resistance change and thermocouples' voltage change. Our application requires accurate and timely temperature inputs. Therefore, we chose thermocouple over thermistor because thermocouple is more

sensitive to temperature change[6]. Thermocouples will be placed below the microplate, adjacent to samples, ensuring accurate temperature measurement. They are used to generate real-time temperature data from the samples and microcontroller will poll data from them.

Input interface: temperature of the microplate

Output interface: analog voltage between 0-5V back to microcontroller

2.3.4 Power Module

AC to DC converter

Our power module consists of 110V AC source and an AC to DC converter. The voltage supply for both the heating pad and the water pump will be at around 12V, and the voltage supply for the microcontroller will be at 5V.

Input interface: 110V AC voltage Output interface: 5V and 12V DC

2.3.5 User Interface

LED display

LED display will display the current temperature collected from temperature sensors to user, so user would know which cycle the microplate is going through. Input interface: 5V voltage, data from microcontroller Output interface: display value in human readable format

Buttons

Buttons are used to reset the system in the middle of a heating/cooling cycles so user does not need to unplug then plug the power cord.

Input interface: user interaction

Output interface: 5V signal to microcontroller

2.4 Block-level Requirement

Block-level requirement is listed below in table 2.1.

Control Unit	Microcontroller	Requirement 1: microcontroller should be able to convert analog data from temperature sensors to decimal number.
		Requirement 2: microcontroller should be able to process and send signal to BJT to turn on and off the heating pad.

		Requirement 3: microcontroller should be able to send PWM signals to BJT to turn on and off the water pump. Requirement 4: if microcontroller loses temperature signal, the whole system should be shut down for overheat protection.
Heating and Cooling Unit	Heating pad	Requirement 1: heating pad should be able to raise the temperature to 95 degree Celsius. Requirement 2: heating pad should be able to keep microplates at constant temperature.
	Water pump, water tank, radiator and tubing	Requirement 1: water pump will be able to eject water to 45 centimeters high at max.
Sensor Module	Thermocouple	Requirement 1: the sensor must operate in the range of 20 degree celsius to 100 degree celsius. Requirement 2: the sensor must be able to send analog temperature data back to the microcontroller, in an amplified version. Requirement 3: pins need to be high impedance.
Power Module	AC to DC power converter	Requirement 1: major heat generation is done by the heating pad, which will take roughly 150 watts. The cable should allow 5A of current to pass through it. Requirement 2: power module should be able to accept 110V to 120V AC voltage as an input and output DC voltage 5V and 12V with error within 10%.
User Interface	LED display	Requirement 1: LED display should be able to display to user the temperature and the time that the PCR machine has been running.
	Buttons	Requirement 1: Buttons should be able to generate a 5V signal when they are pressed.

Table 2.1 Block-level Requirement Table

2.5 Risk Analysis

Whether we can successfully control the temperature of microplates is a great risk on the success of the project. First, in the development stage, if water gets leaked from the cooling system, we might damage the PCB board and substantially delay our project. Second, while the cycler goes through the constant temperature phase, the temperature and amount of current going through heating pad is nonlinear. Heating rate cannot be easily controlled because when the temperature gap between heating pad and the environment gets larger, heat transfer rate increases. Third, although the PID control algorithm enables more precise control over the temperature, it increases the complexity of our project and therefore increases the risk of project failure.

3 Ethics and Safety

Several ethical issues may arise during the development and usage of our product because it enables individuals with the greater power to make copies of DNA. Our device could be unethically used to create bio-hazardous materials or even produce biological weapons. Such kind of action violates IEEE Code of Ethics, #1 "to accept responsibility …" [7]. However, preventing that from happening is out of our capabilities. We believe the release of this product should facilitate the research in bioengineering field according to IEEE Code of Ethics, #5. What we can do instead, is to make our product as safe as possible, complying with the IEEE Code of Ethics, #9. Because both the heating pad and the water cooling unit are installed inside the device, there are quite a few safety concerns in different scenarios.

Most obviously, the water cooling unit must operate as a circulatory system with reliable seals. If water leaks to other components of the device, it could short and the circuit and potentially lead to a fire. Leaking could also cause electrical shocks due to the conductivity of water. To alleviate these risks, connections between the tubings of water cooling unit will be carefully sealed. Furthermore, our group has planned to run an extensive test of the water cooling unit to minimize the possibility of leaking before it goes live.

Excessive heat generated from the heating pad is another concern since many links could fail when regulating the heating process. A fancy cooling unit is futile unless it receives proper commands from our controller to start/stop cooling. To do that, the temperature sensors need to function correctly with enough redundancy for error. To eliminate the risks of overheating, our group has decided to add a protection mechanism that shuts down the device when the temperature rises to an unsafe level or the temperature signal is lost.

As our thermal cycler is designed to operate at a maximum of 95°C, all working components will be housed in a thick, heat-resistant case made of plastic or similar material to keep the end user away from potential dangers related to heat and shock. Besides, we will ensure to use a power cord with a ground. That is one of the reasons we choose off-the-shelf AC to DC power converter. We will attach a label on the surface of the device to indicate the potential risks associated with using it.

Finally, we need to consider biosafety for our end user because they may place biohazardous material on and around the device. Even though it is the user's responsibility to prevent harms, there should be a biohazard sign on the device to meet ACM Code of Ethics and Professional Conduct, #1.2 [8]. Our product is designed to operate at Biosafety Level 1 [9].

4 References

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