BMEN 411

LabVIEW Interface Design to Monitor and Control a Bioreactor

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Introduction

A bioreactor is a device used in bioprocess engineering in which whole cells or free enzymes are used to transform raw materials into biochemical products. There are various configurations of bioreactors such as batch reactors or continuous stirred-tank reactors[1]. In a batch reactor the cells are inoculated into fresh medium and left undisturbed until the desired product is generated. A continuous stirred tank reactor is a reactor in which the cells are in suspension in a vessel and feed is introduced at the same rate effluent is removed. The type of reactor chosen for a given application depends on the cell system being used, its parameters, and the desired output of the system. For example, if a company wants to produce a very large amount of a single-cell product, such as a protein, then the continuous stirred-tank bioreactor is often chosen because the growth rate of the cells and production of the product can be precisely controlled by modifying the dilution rate of the system. However, if a company wants to produce a small amount of product on a smaller timescale then the batch reactor system is often chosen because it is easier to manage and is quicker than continuous culturing techniques. Batch reactor systems are also often used in research laboratories because there is less risk of contamination as no nutrients are added and less risk of mutation because the culturing timescale is shorter[2,3].

Cells are incredibly complex and can only fulfill their intended function under ideal conditions. Therefore, it is crucial to understand how the parameters of a bioreactor affect the productivity and usefulness of different designs. As an example, in aerobic fermentation, the temperature, pH, present chemical constituents, and dissolved oxygen all affect the growth and productivity of the bioreactor. These parameters guide the designs of bioreactors by informing engineers on what components are necessary for a given cell type and process. If a certain process generates more heat than others, then the bioreactor will need a better cooling system. If

a certain cell type is only able to operate within a narrow pH window, then the bioreactor will need stringent pH regulation. Due to the complexity of these bioreactor designs it is necessary to have powerful software tools that allow effective modeling of the designs. This software must have an easily usable graphical user interface (GUI) to allow the engineers to quickly adjust parameters and their relationships in the design model. Software such as LABVIEW is therefore the perfect tool for creating a model of a prospective bioreactor design. The LABVIEW software can also be applied to create virtual instruments that will replace expensive mechanical equipment. For example, an analog-to-digital converter can be replaced with a virtual oscilloscope, which aids in reducing costs and mechanical complexity for chemical plants and bioreactor designs[4].

To illustrate the usefulness of LABVIEW as a software for modeling and designing bioreactors, this paper will discuss the bioreactor modeling market and provide an example of a LABVIEW hematopoietic stem cell (HSC) bioreactor model. HSCs are multipotent primitive cells that can differentiate into myeloid and lymphoid-lineage blood cells. These cells are commonly found in the bone marrow, but can also be found in the blood[5]. In certain cancers, such as leukemia, there is stimulation of osteoblastic cell production which thereby lowers the abundance of HSC maintenance factors. It is also possible that treatment of these cancers will adversely impact the HSCs found in bone marrow[6]. A common treatment option is HSC transplantation, also known as a bone marrow transplant. Therefore, the creation of a bioreactor that facilitates quick and simple growth of HSCs for transplantation will have a profound impact on clinician's ability to treat these cancers.

Market Analysis

One of the main companies involved in the automation and control of bioprocess software is ThermoFisher. This company combines automation software with controllers to create a singular interface that can store and monitor processes and changing conditions within a bioreactor. One of the main drawing points to this device is its compatibility with ThermoScientific bioreactors as well as many third-party bioreactors to provide a universal measuring technique among different devices.[6] An additional company involved in bioreactor modeling interfaces is Dynochem Biologics. This company highlights its ability to ensure uniformity among measurements of different bioreactor machines to better understand key attributes and components in varying environments. It also contains a library of up and downstream operations that allow for a simple user base.[7] Sartorius created its BioPAT Process Insights Software to improve process transfer across many different scales while also containing an earlier transfer risk detection in process workflows in comparison to other software on the market. This interface has been shown to better predict bioreactor scalability, mitigate risk, and simplify bioreactor scaling making it a high competitor for bioreactor interfaces today.[8]

The use of software including LabVIEW falls under the umbrella of GUIs to help model and control varying types of bioreactors used in the industrial setting. Additional interface methods that are being explored include the hierarchical structure control system (HSCS) and flat organizational control system (FOCS). The HSCS has become the dominant physical structure used while the FOCS has become more recently used due to its more concise process control solutions.[9]

The target buyers for these interfaces would most prominently be biomedical industrial companies that are attempting to frequently use bioreactors to rapidly increase cell growth. These

interfaces could also be beneficial in research labs, hospitals, etc., and should provide an easy user guide that would allow it to be used by more than just engineers. A research lab often needs a quick accumulation of cells to run an experiment and this simple model to monitor the effectiveness and alter the controls would make it very easy to maintain. In a medical setting, for treatments including CAR-T therapy, the maintenance of the T-cells is imperative to a successful transfusion. With the simple interface for the user, monitoring these cells will become easier and more efficient which will cause high demand in the medical market as well as in the environments stated prior.

The competition would be the large biomedical companies that have large connections to many of the industrial companies being targeted with this new interface. There is a large group within the Biotechnology community on LinkedIn that discusses and compares different bioreactor models and control interfaces. Connecting within this group could allow for an outlet to gain exposure and attraction to this device and pull some clients away from the big biotechnology companies that have created the previous interface models.

Model Design

Several assumptions were made to make this model. Firstly, it is assumed that the endogenous metabolism of the cells in the reactor is negligible. It was also assumed that the substrate levels would be depleted linearly after every doubling period and would therefore be represented as a percent. Since the reactor is continuous, pressure is assumed to be constant as there is no change in volume.

The model involves a continuous flow reactor that has equal flow rates into and out of the reactor. This means the volume of the reactor remains constant at 1.5L throughout the simulation. The reactor operates between 32-40º C, 0.5-1.5 atm, and substrate levels above 0%.

Any values outside these ranges will trigger alarms in the system which will alert the user with a popup message and then end the program as the reactor is now compromised. After the user inputs the system's initial parameters, the temperature increase for every doubling period (24 hours) is calculated. The program then simulates the depletion of substrate and rise of reactor temperature. Every real-time second corresponds to 12 hours of simulated growth. The elapsed time and the mass of cells in the reactor are actively returned to the user with every iteration of the doubling period.

The LabVIEW model consists of a front end and a back end. The front end displays the tank volume, pressure, temperature, and substrate levels as well as a cluster of set-up parameters for the user to input. The backend of the program consists of two main parts embedded in a while loop. The first of these parts calculates the temperature change of the reactor for each doubling period. This info is then inputted into the second half of the block diagram which simulates the reactor. This half consists of three case structures that correspond to the pressure, temperature, and substrate levels of the tank. During each iteration of the while loop, these parameters are evaluated to identify if any of the parameters are outside their thresholds. If a parameter is above or below the threshold, the true case of its respective case structure will run and will send an alert to the user. If any parameter exceeds its respective threshold, a boolean value is returned to the stop condition of the while loop which terminates the loop and therefore the program.

LabVIEW Front Panel and Block Diagrams

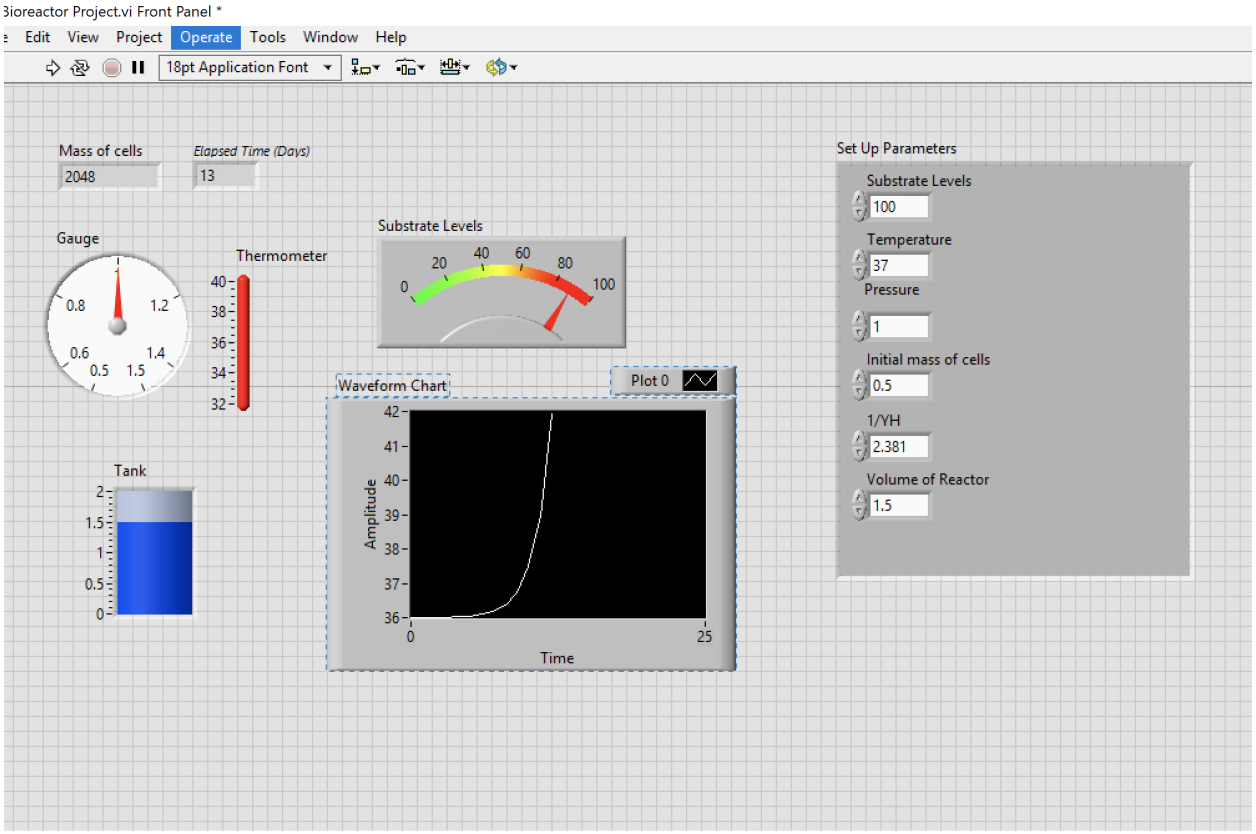

Figure 1. Front panel of the program resulting from the optimal setup parameters.

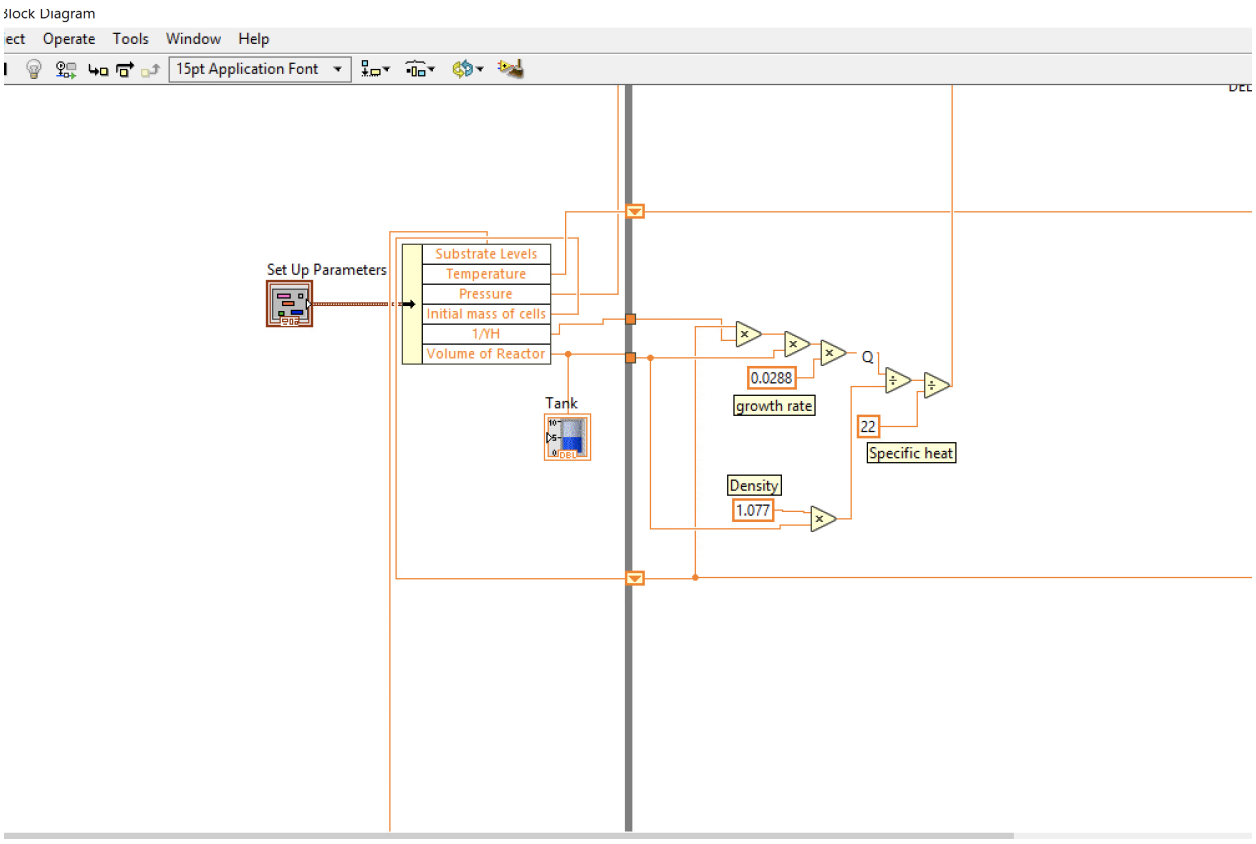

Figure 2. Block diagram calculation of ΔT for each iteration of the while loop. Setup paramters are taken from the cluster for this calculator.

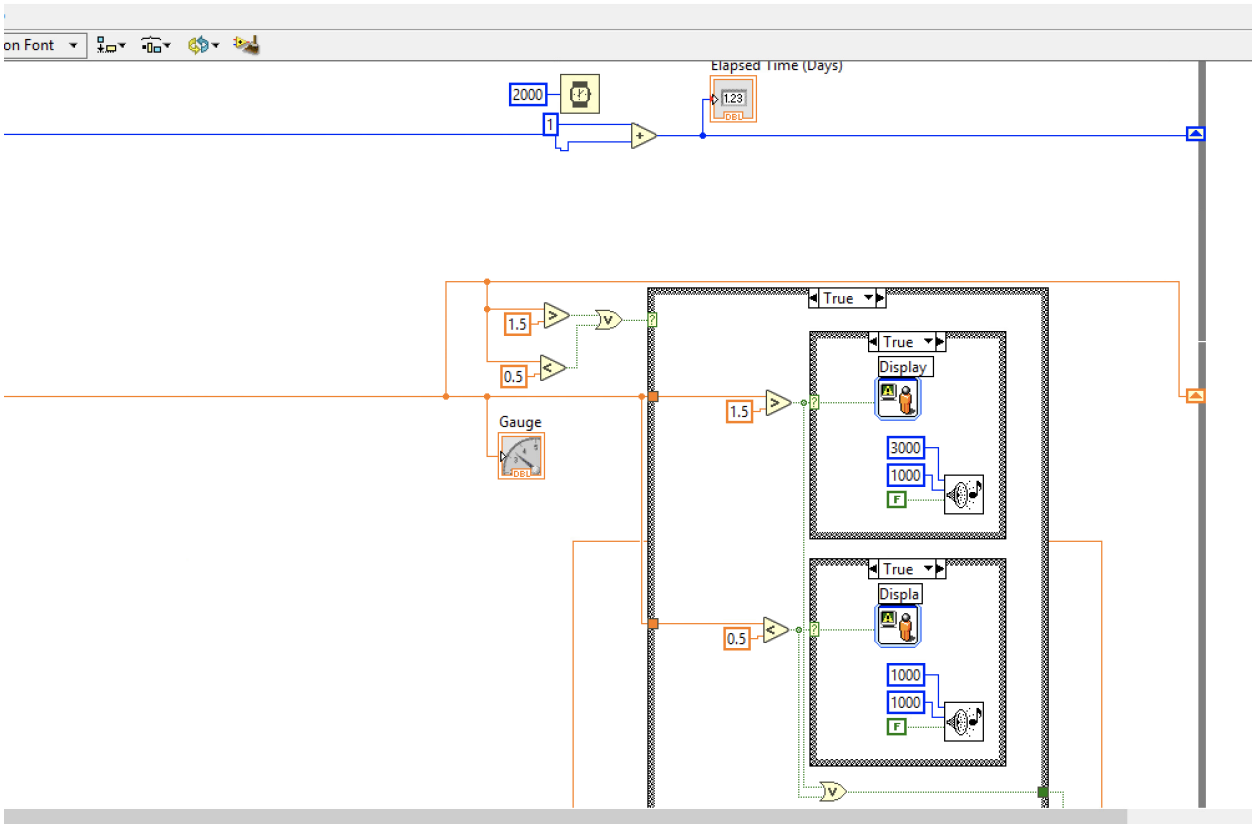

Figure 3. Pressure case structure which alerts the user in the true case if the pressure is outside the allotted threshold. The false case is empty and would allow the program to continue. The wait feature and the elapsed time are also in this section.

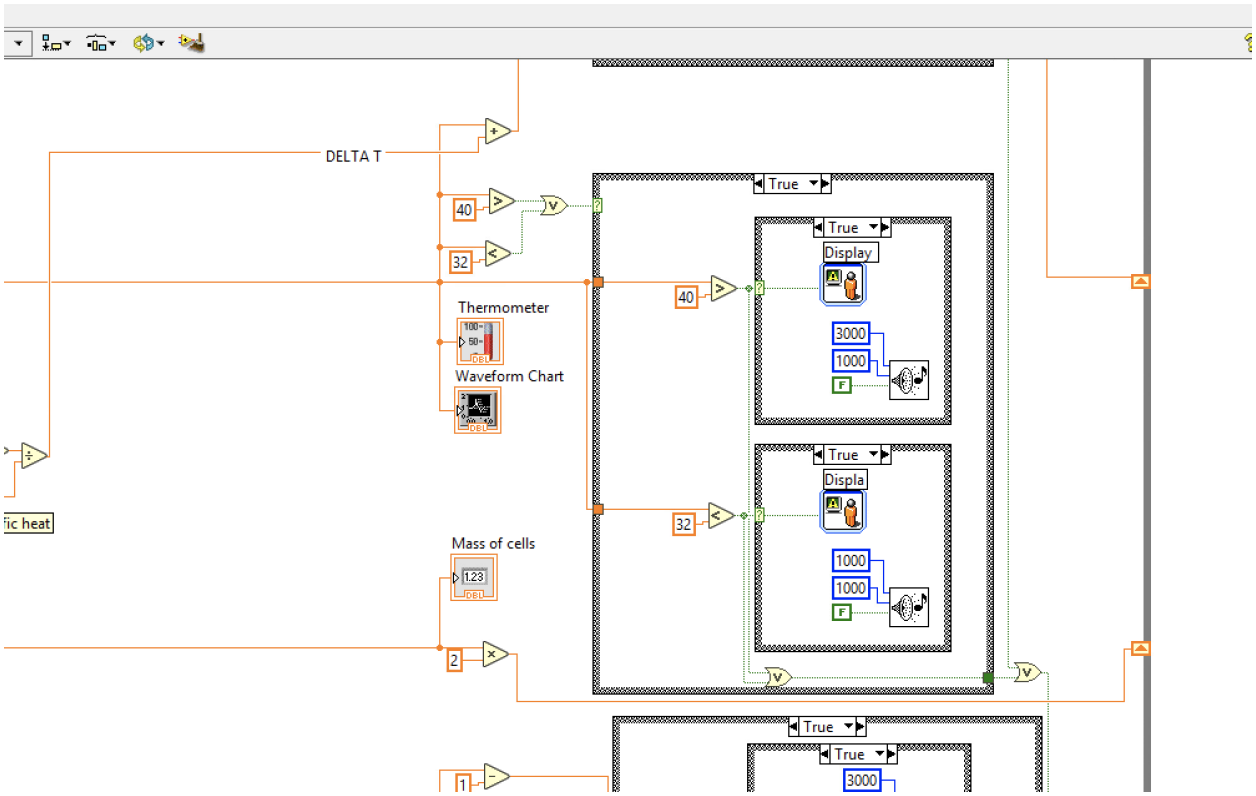

Figure 4. Temperature case structure which alerts the user in the true case if the temperature is outside the allotted threshold. The false case is empty and would allow the program to continue. The waveform chart is attached to the thermometer reading.

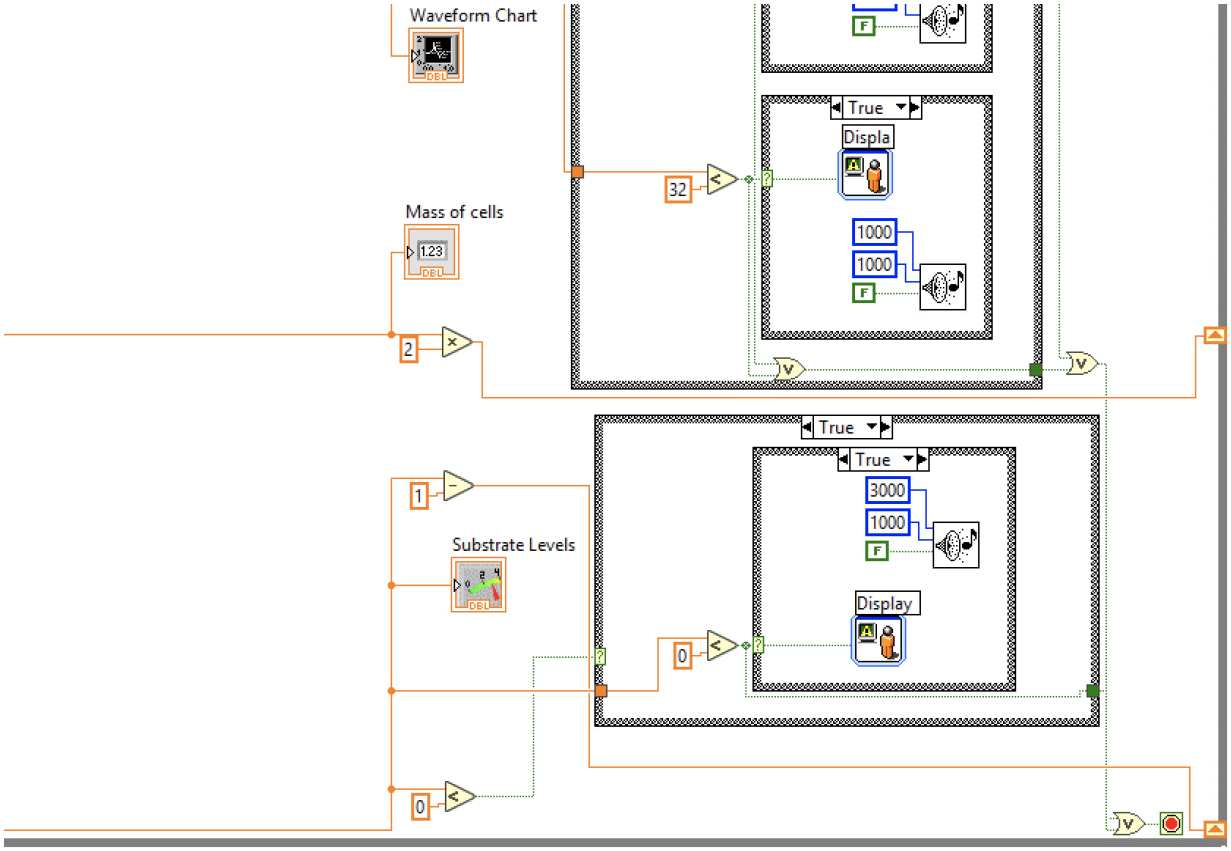

Figure 5. Substrate levels case structure which alerts the user in the true case if the level is outside the allotted threshold. The false case is empty and would allow the program to continue. The stop condition is attached to all three case structures via OR gates which stop the program if any value is true.

Results

After running several simulations, the optimal performance was conducted with a pressure of 1 atm, a temperature of 37ºC, a metabolic heat of 2.381 Kcal/g, 100% substrate levels, 0.5 g of initial cell mass, and a volume of 1.5 L. These parameters allowed the reactor to run for 13 days straight before the temperature exceeded the threshold and produced 2048g of cells. The waveform chart shows the rapid increase in temperature as cells in the reactor grow. Figure 1 shows the optimal set-up parameters and resulting simulation.

Conclusion

Bioreactors allow for the rapid growth of a large number of cells and their metabolites by providing ideal growth conditions and substrates. Herein, we describe the design of a continuous reactor for the growth of hematopoietic stem cells (HSCs) which are a highly valuable subclass of stem cells that gives rise to all red and white blood cells in the body through the process of hematopoiesis in the red bone marrow of adults. HSCs are often used to treat immune disorders such as cancer, and therefore the ability to rapidly produce these cells is greatly important.

The continuous reactor we proposed here was able to create 2,048 grams of cells in the span of 13 days before the temperature in the system reached a value that caused rapid denaturation of the cells and subsequent death of our system. Further testing of key parameters may produce more optimal setups and reactors that can run for longer without overheating.

Ideally, a more accurate model would account for the endogenous metabolism of the cells and the production of product, which at a large cell number, would greatly hamper the large growth of the cells seen here. A more complex model would also account for the concentration of the cells, as at the high concentrations seen in our system, the cells would stop growing exponentially and enter a stage of stationary growth and death due to the lack of available space for further growth. A more clinically relevant model would also automatically regulate the temperature of the system so as to prolong the exponential growth phase of the cells.

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