Chemical Synthesis Automation

A Major Qualifying Project

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By

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Abstract

Exothermic reactions can yield different products depending upon the available heat energy. In order to maximize the rate and efficiency of chemical syntheses, an expression of acceptable limits of temperature vs time for a chemical synthesis can be used by a synthesis robot to control the rate of reaction. A markup language, such as Chemical Markup Language (CML), could usefully support this expression. The robot, informed by the temperature profile and real time data sensors in the form of a thermocouple, could automate synthesis and improve the yield of desired products for a chemist.

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Introduction

Our sponsor Abbvie has requested a robot to aid in the automation of a chemical synthesis. The specific synthesis is extremely exothermic and difficult to complete in a lab, so this step is currently outsourced. Our MQP group focused on finding a way to automate a robot to complete the synthesis by monitoring the temperature of the reaction over time and making informed decisions on when to slow or stop the release of reactant, therefore controlling the rate of reaction.

Exothermic Reactions

The rate of chemical reaction is in most cases dependent on temperature. Generally, as the temperature of the reaction increases, the rate of reaction also increases. However, in a laboratory setting, there is a reasonable temperature range in which the reaction can be completed safely and successfully. Factors like boiling, bumping, burning, and evaporation all limit the effect temperature has on increasing the rate of reaction, and in some cases even decrease yield. In order to maximize the rate and efficiency of chemical syntheses, an upper temperature threshold can be put in place to control the reaction. We intend to make an extension to CML that allows for a chemist to specify a temperature profile for an automated chemical synthesis.

The Robot

A list of potential equipment for current and future compatibility with the robot consisted of both common equipment used during synthesis and from lists given from our sponsor at AbbVie. For each piece of equipment, a brief synopsis of its purpose was given along with a proposed action that the robot could direct it to do. Below is a list of instruments that are currently used with the robot and their functions as they will be seen in Labview. After choosing equipment, Labview will prompt the chemist to input instructions on how to complete a given action as well as time and temperature restrictions. The Labview server will then communicate with the robot to complete the action, and use sensors, such as thermocouples, to send feedback. In the future, we hope to continue adding instrument actions to the Labview server so that the robot can support more instruments, and in turn, support a wider range of chemical reactions.

<u>Heating Mantle/Hot Plate/Hot Plate Stirrer Combination (Heat Only)</u>: Heats at a certain temperature of or dial setting (ie. 100 degrees Celsius, Dial Setting 6)

Choose Instrument: Heating Mantle, Hot Plate, Hot Plate Stirrer Combination
    Instrument Setting Unit: Degrees Celsius, Fahrenheit, Kelvin, or Dial Settings
    Instrument Setting: real numbers > 0, range and precision based on instrument model
Choose Action: *"Heat"/"Raise Heat"/"Lower Heat" to X degrees/setting X*
    Threshold: Temperature Thresholds
Type of Action: Event Triggers End
Type of Trigger Event: Temperature Threshold Reached, Safe Temperature Range Exceeded

<u>Stir Plate</u>: magnetic stir bar (~size of a black bean) goes inside the flask and magnetic stir plate propels it. For this reason, the flask needs to be touching or very close to the stir plate.

Choose Instrument: Stir Plate, Hot Plate Stirrer Combination
Instrument Setting Unit: rpm, or Dial Settings
Instrument Setting: real numbers > 0, range and precision based on instrument model
Choose Action: *"Stir" to setting X, "Stir" at X rpm*
Threshold: Stir Speed Threshold
Type of Action: Time Duration
Type of Trigger Event: Safe Stir Speed Exceeded

Rotovap: Solution is put in the pear-shaped flask (the one at an angle) and rotated while it is dropped into a hot water bath. An arm controls the height of the flask in or above the bath.

Choose Instrument: Rotovap
Instrument Setting Unit: rpm, or Dial Settings, Temperature, Arm Height (cm, in, ft)
Instrument Setting: real numbers > 0, range and precision based on instrument model
Choose Action: *"Rotate" vial at X rpm, "Heat" bath to X degrees, "Raise/Lift" arm to height X*
Threshold: Rotation Threshold, Height Threshold, Temperature Threshold
Type of Action: Time Duration (rotations) Event Triggers End (heat and arm)
Type of Trigger Event: Safe Rotation Speed/Temperature Reached, Max/Min Height Exceeded

Vacuum Filtration/Air Valves: Special glassware with a filter on top and vacuum suction beneath. The solution is pulled through the filter and the precipitate (aka the desired product) is left on the filter and is dried. This may need to be repeated to maximize product yield.

Choose Instrument: Vacuum Filtrations, Air Valves
Instrument Setting Unit: Pressure (psi), and/or percent valve opening
Instrument Setting: real numbers > 0, or real numbers 0-100% capacity
Choose Action: *"Increase/Decrease" vacuum pressure to X psi/to 50% capacity*
Threshold: Pressure Threshold, Glassware/Material Threshold
Type of Action: Time Duration
Type of Trigger Event: Glassware Threshold Exceeded, Pressure Threshold Exceeded

Phase Separator: liquid-liquid/gas-liquid separation, separates emulsions into components

Choose Instrument: Phase Separator
Instrument Setting Unit: Applied Pressure (psi/bar), Flow Rate (ml/min)
Instrument Setting: real numbers > 0
Choose Action: *"Pressurize" solution at X psi/bar, "Separate" solution at ml/min*

Threshold: Pressure Threshold, Flow Rate Threshold, Blockage Threshold

Type of Action: Time Duration

Type of Trigger Event: Pressure Threshold Exceeded, Maximum Flow Rate Exceeded, Blockage

Normal Phase Silica Gel Chromatography: flash chromatography workstation with a built in UV-Vis absorbance detector, and an integrated fraction detector. Separates compound based on polarity across a silica gel stationary phase, using applied air pressure to increase flow rate over column chromatography

Choose Instrument: Flash Chromatography Workstation

Instrument Setting Unit: Applied Pressure (psi), Flow Rate (ml/min),

Instrument Setting: real numbers > 0

Choose Action: *"Test" sample X at Y psi with flowrate X ml/min*

Threshold: Pressure Threshold, Flow Rate Threshold, Blockage

Type of Action: Event Triggers End

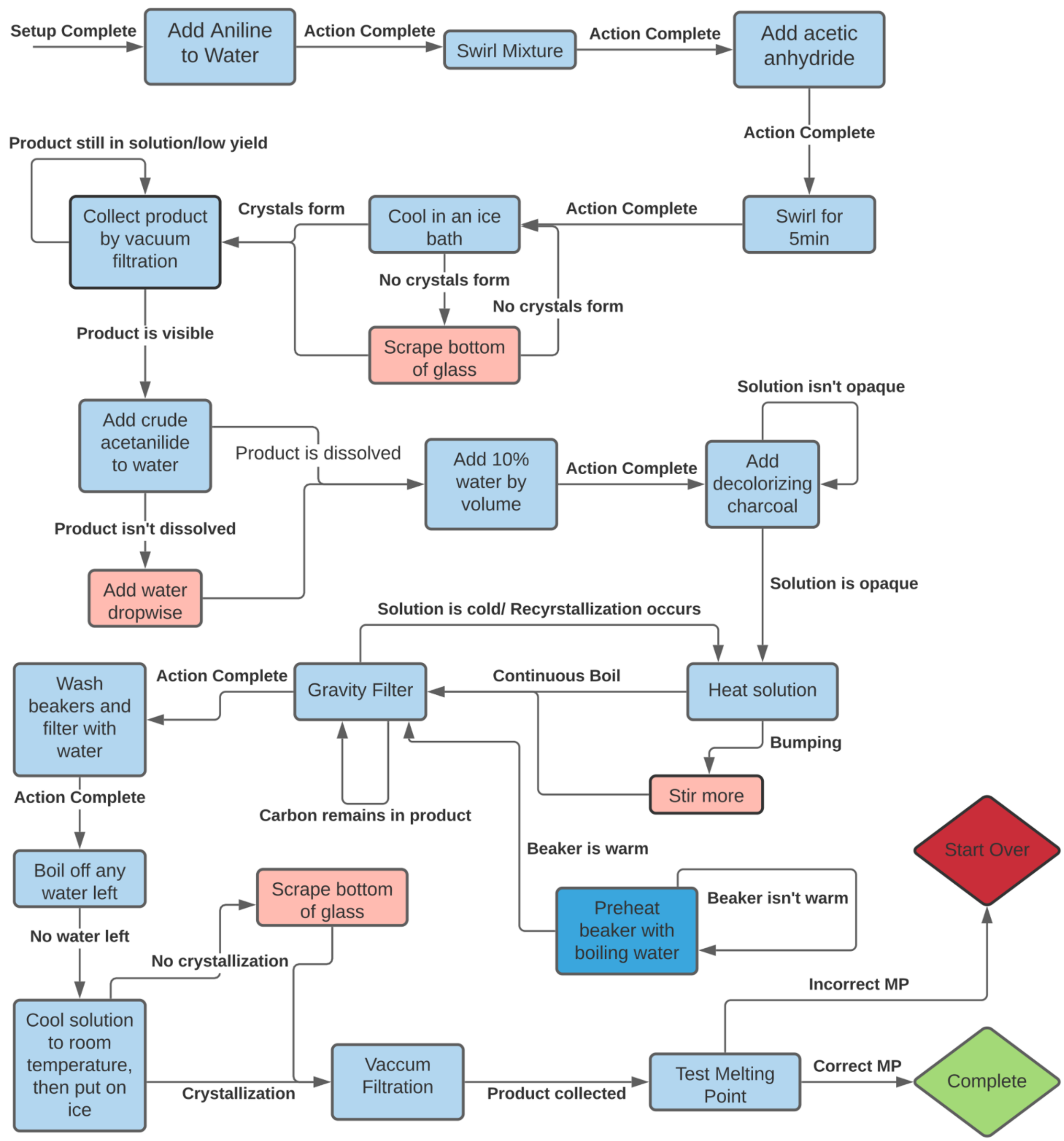
Type of Trigger Event: Pressure Threshold Exceeded, Maximum Flow Rate Exceeded, Blockage

System Error/Tray Error

Process Control

Process control is primarily concerned with monitoring for mistakes or issues in a process and then making dynamic changes to correct them. There are two ways this can be achieved: by making judgements on what actions to take once a mistake has occurred or by using an automated process.[1] To demonstrate the first example of how a process control engineer would fix a mistake, we used a state transition diagram to show the thought process that could be used to correct mistakes in a synthesis.

As an example, we used the synthesis of acetanilide, a compound formerly used as a non-prescription drug to treat pain and fevers and has a very similar structure to a more common drug, acetaminophen, which is Tylenol.[2] We took synthesis instruction for this compound and transferred them to an intermediate flow chart form which could then be better understood by both the chemists and the computer scientist and robotic engineers working on the robot so that the chemists' language could be translated easier to the computer language. This also gave the group a better idea of how a common user would expect a state transition diagram to function within the robot. After thoroughly understanding the process itself and the many checks and balances that need to be put in place to ensure proper synthesis, we then plan to transfer the flow chart's information into CML code. For ease of viewing, the exact measurements were removed, and only basic commands are visible on the chart and the chart assumes that set up has already been completed. The chart works by including color coded action boxes driven by conditional arrows.



Flow Chart of the Synthesis of Acetanilide

The light blue boxes represent actions that drive the synthesis such as adding, heating, mixing. These would be the actions the robot would instruct each individual machine to do. The arrows represent the checkpoints that the robot, or user, will be looking for before completing the next action. These include time (i.e., Stir for five minutes), temperature (i.e., heat to 30 degrees

Celsius), and qualitative properties like light, color, opacity, odor, texture, etc. The red boxes represent situations where the arrow conditions are not meant, and the synthesis must deviate from the original path in order to get back on the right path. The dark blue box represents an action that is done concurrently alongside the main synthesis. This may be something that is required for the synthesis but does not need to be completed in order like actions in light blue boxes. Lastly, the diamonds represent the outcome of the synthesis, green for a successful synthesis of the product after analytical testing, and red for errors in synthesis. The red error may not require the user to completely start over but will require human intervention to decide what to do from there.

Applications of XML in Process Control

Chemical automation can dramatically improve the yield and safety of chemical reactions, therefore, it has application in the field of process control. By taking the information from a chemical synthesis, and breaking it down into specific actions as seen above, computer scientists can transform the instructions into code that can be read by the robot. When searching for an existing database of chemical information that could be used for this application, Chemical Markup Language, or CML, was found and contained a schema of molecules, compound, reaction and spectra.[3] Our group consulted the Journal of Loss Prevention in the Process Control Industry and other journals, and found that no such extensible language existed for the process control industry.[4] For this reason, we proposed an extension to CML that caters to the process control industry.

Citations

1. U.S. Department of Commerce. (2012, April) What is process control? *Engineering Statistics Handbook*. NIST Sematech.
2. NIST Chemistry Workbook. *Preparation of acetanilide*. Gordon College.
3. Murray-Rust, P., and Rzepa, H. (2010) Chemical Markup Language. *CML*. CMLC.
4. Journal of Loss Prevention in the Process Industries. *Elsevier*.