

# Chemical Synthesis Automation

A Major Qualifying Project

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By

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## **Abstract**

The Chemical Synthesis Automation team continued the work of previous MQPs towards developing a robot platform that can automate steps of a chemical synthesis process. We examined the robot's equipment and reaction mechanisms to ideate an intuitive user interface by which chemists can input synthesis instructions. We designed a graphical LabView interface for manual input, and proposed the construction of an intermediate language to compile the input into a finite state machine.

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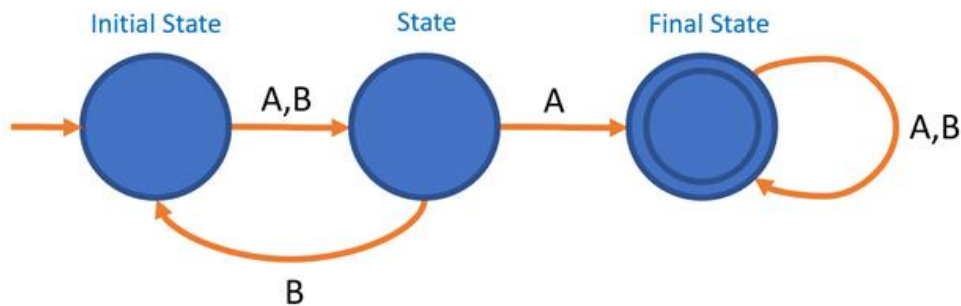
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# Chapter 1: Introduction

## 1.1 Model Checking

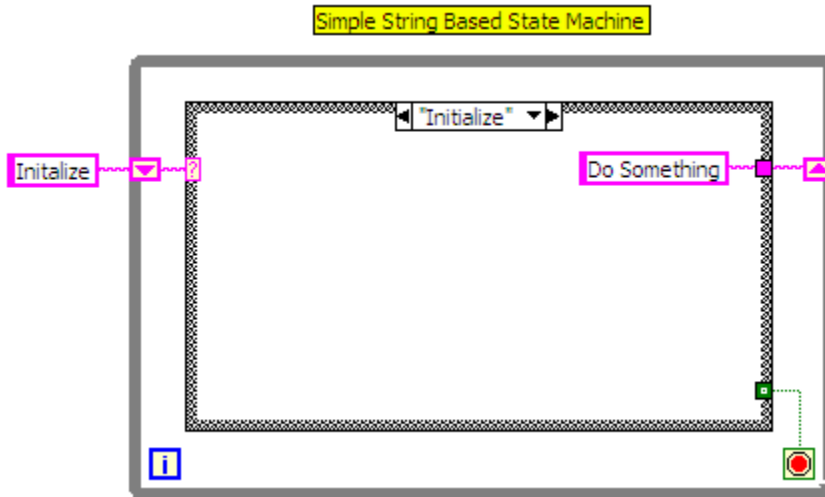
State machines, also called finite-state automata, are a method of encoding computer systems whose behavior depends on a series of inputs. They have a wide variety of uses, including specifying a program which responds to control commands and sensor readings (MIT OpenCourseWare). State machines consist of states, inputs, and transition functions. States are conditions that the machine can be in at any given point in time. They include an initial state, in which the machine starts, and final states, in which the machine is allowed to stop. Inputs, or events, are information received and processed by the machine. Transition functions determine how the machine reacts to receiving inputs. These functions generally change the machine from one state to another state, depending on where it starts and which input it receives (Myers).



*Figure 1: A graphical representation of a simple state machine. Blue circles represent the states, black text represents the inputs, and orange arrows represent the transition functions.*

State machines are an important design element in LabVIEW. They are implemented using a case structure placed inside a while loop. The case structure contains all the different states of the machine, and its case selector processes the given input to choose the initial state. Inputs can be

either direct user input or programmed calculations, and the transition functions are handled by a shift register (LabViewWiki).



*Figure 2: An example of a LabVIEW state machine (LabViewWiki). The outermost loop is the for loop, and the inner loop is the case structure, with a state called "Initialize". The pink text boxes and wiring represent the inputs and transition functions.*

Model checking is an algorithm to determine whether a state machine system behaves as intended. It requires defining a set of properties which indicate the correctness. For instance, model checking for a microwave might specify the property that the heat should not turn on unless the door is closed. These properties must then be expressed as logical statements (Schneider). Then, the state machine is simulated with various inputs, and the property statements are evaluated at each state the machine reaches. If the statements hold true along every transition path, then the machine obeys the properties correctly. If a statement evaluates as false at any point, then the machine can provide a counterexample to show that there is a problem where the machine does not work as intended and must be debugged (Sinha).

# Chapter 2: Examination of Equipment

## 2.1 Types of Equipment

A list of potential equipment for current and future compatibility with the robot was comprised 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. The equipment was split up into four categories based on the portion of the synthesis it would be used for. The first section, “Set Up”, entailed devices that were used to prepare the reactants for synthesis, including measurements devices and glassware. The second section included devices that aid in the reaction portion of the synthesis such as heating and stirring. The third section includes devices used to isolate the product of the synthesis such as evaporation. The fourth and final section of the equipment list covers analytical equipment used to determine the chemical composition of the product, such as chromatography or spectroscopy. This MQP project will focus mainly on set up and reaction mechanisms while giving recommendations for future applications for product isolation and analytical tests.

## 2.2 Set Up

- **Measurement**
  - o Syringe Pump
    - § Details

- Depresses the syringe at a set rate over a given time (ie. 10 ml/min, 1 mL/hr)

#### § Actions

- Depress to X Volume (or height)
  - o  $X \text{ Volume} / \text{Rate} = \text{Amount of Time}$
- Pull Back to X Volume (or height)
- expand

#### o Scale<sup>1</sup>

#### § Details

- Scale requires both doors to close, has much more precision than the syringe pump

#### • Glassware<sup>2</sup>

- o See footnote

### React

#### • Heating

- o Heating Mantle

#### § Details

- Almost glove shaped, sometimes sand is used to fill in gaps to maximize surface cover

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<sup>1</sup> Much like in baking, sometimes mass is a better indicator than volume. This is because reaction quantities are calculated by moles (or mass/molar mass). Therefore, the volume will accumulate more error because it is a derived measurement. In general, a scale will have more precise measurements (think +/- 0.001 g vs +/- 1 mL)

<sup>2</sup> There are many potential glassware setups for different kinds of chemical reaction types.



§ Actions

- Heat to Setting X
  - o Rotate dial to Setting X
  - o Heat to X
  - o Once Temperature Reaches X, Turn Off

o Hot Plate/ Combination Hot Plate Stirrer

§ Details

- Can either have just hot plate or have stirrer attached

§ Actions

- Rotate dial to Setting X
- Heat to X
- Once Temperature Reaches X, Turn Off

o Bunsen Burner

§ Details

- Rarely Used

• **Stirring**

o Stir Plate and Magnetic Stir Bar/ Combination Hot Plate Stirrer

§ Details

- Can either have just hot plate or have stirrer attached, magnetic stir bar (size of a black bean) goes inside the flask and magnetic stir plate propels it. For this reason, flask needs to be touching or very close to stir plate

§ Actions

- Rotate dial to Setting X
    - Stir for X minutes then Turn Off
  - Reflux
    - o Details
      - § Need to talk to AbbVie to see if this is necessary

## **Isolate Product**

### **§ Distillation**

- o Fractional Distillation

### **§ Evaporation**

- o Rotovap

- Details

- Product is in solution and solution needs to be evaporated off.

Solution is put in the pear-shaped flask (the one at an angle) and rotated while it is dropped into a hot water bath

- Actions

- Set rotation to setting/dial X
    - Set water bath to X temperature
    - Lower/raise arm

### **§ Separation**

- o Separation Funnel

- Details

- It seems like last year's group had a system in place already to do this

## § Vacuum Filtration

- Details
  - 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.
    - Usually before this step, the solution is cooled in an ice bath in order to help crystals form. If you don't see crystals, it may need to be cooled more.
- Actions
  - Turn on vacuum/turn on air valve
    - The air valve is usually found on the outside of the fume hood and is attached to the glassware by tygon tubing (small rubber hosing)
  - Dispense X solution onto the filter paper

## Analytical Tests

### § Chromatography

- Gas Chromatography (GC)
- High Pressure Liquid Chromatography (HPLC)
- Thin Layer Chromatography (TLC)
- Gravity Columns/Column Chromatography
- Silica Gel Chromatography

## § Spectroscopy

- Infrared Spectroscopy (IR)
- Ultraviolet Spectroscopy (UV Vis)
- Nuclear Magnetic Resonance (NMR)
  - H NMR
  - C NMR

## § Physical Characteristics

- Melting Point Analysis
- Water Content
  - Karl Fischer Titration (KFC)
    - Details
      - Determines the water content of a solution by titrating it automatically. The volume and solution type are input before hand so the calculations are also automatic
    - Actions
      - Set solution type to X
      - Set volume to X
      - Dispense X mL of solutions
      - Send results to server

## Chapter 3: LabVIEW Interface

### 3.1: LabVIEW Details

Consider the sample list of chemical synthesis steps provided below:

Quench Bot Chemical Language/Sequence

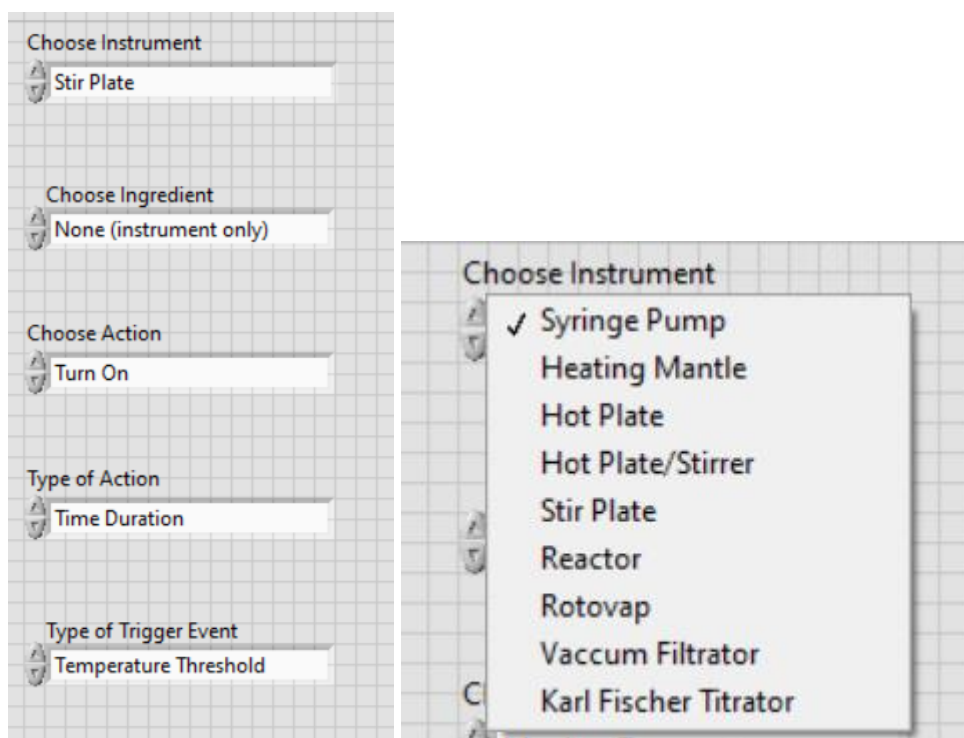
1. Turn on stir plate (300 rpm)
2. Charge syringe 1 (100 mL) with reactive reagent
3. Charge syringe 2 (100 mL) with quenching solution
4. Dose syringe 2 into reactor 10 mL/min
5. Stop dosing syringe 2 after 5 mins (50 mL)
6. Charge syringe 2 (50 mL) with quenching solution
7. Dose syringe 1 and 2 simultaneously into reactor at 10 mL/min
8. Monitor temp of reactor
9. If temp exceeds 35°C stop dosing syringe 1 and 2
10. Monitor temp of reactor
11. Once temp of reactor reaches 25°C start dosing syringe 1 and 2 at 10 mL/min
12. Continue until syringe 1 and 2 have completely dispensed
13. Fill syringe 1 (100 mL) with cleaning solvent (methanol)
14. Dose syringe 1 into reactor (50 mL/min) (2 mins)

15. Fill syringe 2 (100 mL) with cleaning solvent (water)

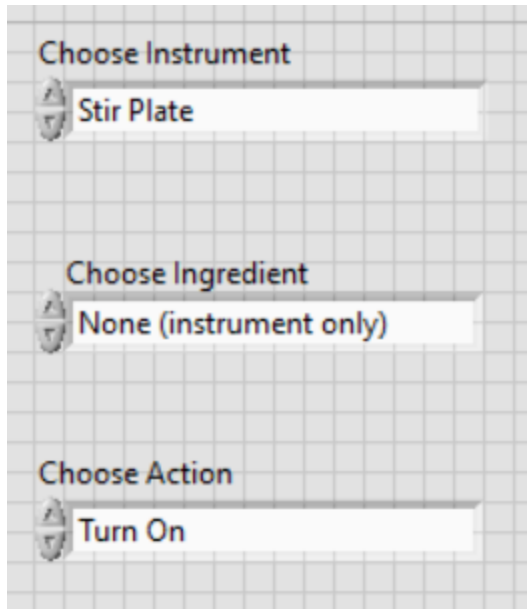
16. Dose syringe 2 into reactor (50 mL/min) (2 mins)

17. Turn stir plate off.

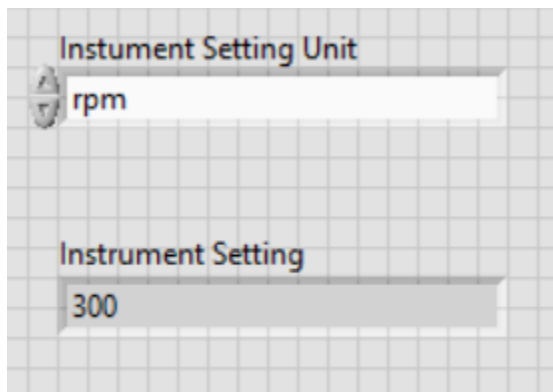
In order for the robot to carry out a synthesis such as this, chemists must be able to enter these steps in a manner that the robot can understand. A LabVIEW interface makes this possible.



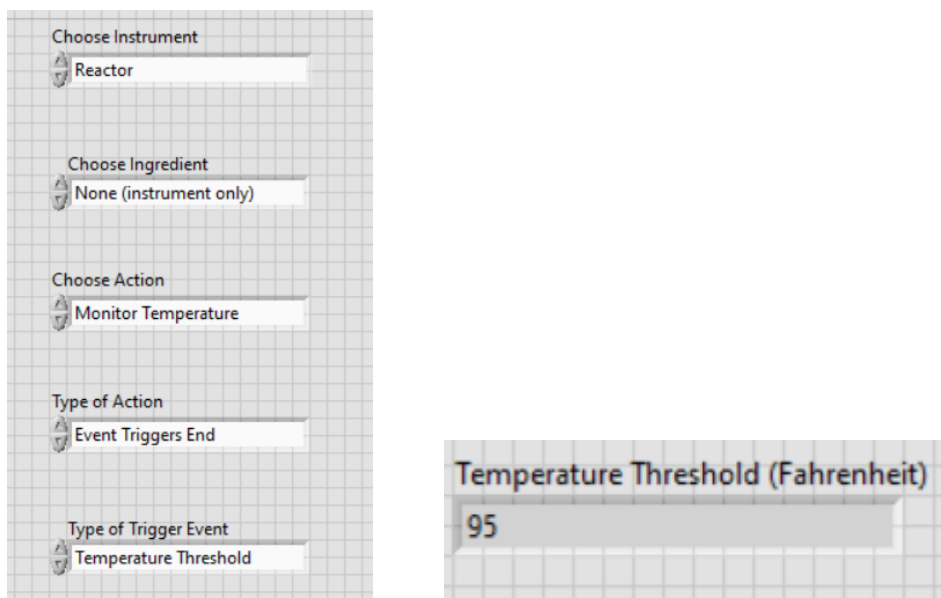
The drop-down menus and boxes above help chemists enter the details of each individual synthesis step. Consider step 1 of the example synthesis found above - “turn on stir plate (300 rpm)”.



The selections above instruct the robot to focus on the stir plate and complete the “turn on” action with no ingredients involved, since the plate must only be turned on. The user is then prompted to specify the setting that the instrument is to be set to.



These menus specify that the stir plate should be set to operate at 300 RPM, as said in the instructions. However, consider a more complicated instruction that requires a stop condition, such as example step 9, which asks for the dosing to stop when a certain temperature is reached.



The instructions specify that this step has a stop condition. In the previous step, a switch just had to be flipped and the plate turned on. In this case, the robot must continuously monitor the temperature and trigger a new event when the threshold is released. This command tells the system to send a notification when the temperature reaches the threshold and move to the next step. The system is also prepared to deal with other stop conditions such as time limits.

### 3.2 Natural Language Processing

The LabVIEW interface still leaves a lot of technical details up to the chemist. In order to make their job easier and stay in a language that they completely understand, adding natural language processing to this project may eventually become a viable option. For example, consider spaCy, an industrial-strength natural language processing open-source library written in Python. This technology takes natural text and can separate it into a series of commands that a computer can understand. For example, consider the instruction “charge syringe 2 (100 mL) with quenching solution”. The library will split the sentence into its various parts. It will recognize



“charge” as a verb, and translate this to a command that the robot can understand. “Syringe 2” will be recognized as a noun and will be translated to a particular port on one of the Arduinos for the command to be sent to. “100 mL” will be seen as a quantity and will become a translatable part of the command for the robot.

Furthermore, this library utilizes deep learning. This means that the model used to understand a chemist’s speech would come to automatically recognize objects and instruments more quickly. Common commands and chemicals would be stored in a database so syntheses could be repeated with ease. Adding natural language processing gives the chemist the ability to utilize instructions as complicated as they need to without having to think about entering it through the LabVIEW interface. Since chemists are not typically trained to understand robotic technology, entering complicated commands through drop-down menus may end up causing errors in synthesis that lead to a ruined project or a dangerous situation.

### **3.3 Flow Charts as a Representation for State Transition Diagrams**

In order to represent a state diagram from a chemist’s perspective, we first started with a flow chart. 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.<sup>3</sup> 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

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<sup>3</sup>The difference between acetanilide and acetaminophen is the presence of an alcohol (-OH) group para to the amine group on acetaminophen.

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 into a state transition diagram. The synthesis was transcribed into steps as follows.

### Synthesis of Acetanilide

1. Add 7.0 mmol of aniline to 15 mL of deionized water in a 50. mL Erlenmeyer flask
2. Swirl the mixture thoroughly.
3. Add 8.3 mmol of acetic anhydride to the mixture.
4. Swirl the mixture for 5 minutes
5. Cool in an ice bath until crystal formation is visible. If no crystals form, it may be necessary to scrape the bottom of the flask.
6. Collect product for vacuum filtration. Product should be visible on the filter paper. If desired yield is not met or if product is still visible in the dissolved portion of the filtration, repeat filtration.
7. Add the crude acetanilide and 5 mL of water to a 25 mL beaker. If the solution does not dissolve, continue to add water dropwise until it is just dissolved.
8. Add additional water equal to 10% of the volume of the dissolved crude acetanilide.<sup>4</sup>
9. Add enough fine powder charcoal to so that the solution is opaque, even when swirled.<sup>5</sup>
10. Heat the solution until it boils while continuously stirring.

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<sup>4</sup> For example, if after dissolved, the solution is 10 mL, add 1 mL additional water

<sup>5</sup> This step is to remove any impurities present after the initial synthesis, as well as to remove any color present in the solid

11. Prepare the beaker with a small amount of boiled water (0.5 cm) and a glass filtration funnel affixed with a fluted filter paper. The beaker should be warm so that the shock of adding hot solution does not break the glassware
12. Using gravity filtration, pour small amount of the charcoal-acetanilide solution through the filter paper at a time. Keep the solution hot in between pours by returning it to the heat. If the solution starts to recrystallize before filtration or on the filter paper, reheat and filter again.
13. Add boiling water (2 mL) to the flask containing the charcoal solution to wash the remaining solution through the filter paper. Additionally, add boiling water to the filter paper dropwise to filter any remaining acetanilide. If any decolorized carbon remains in the filtered product, repeat filtration back to Step 10, adding more water if necessary and by using a new clean filter paper.
14. Remove any additional water by boiling the solution.
15. Once concentrated, remove the solution from heat and allow it to. Cool to room temperature. Then place on ice. If no crystallization occurs, you may need to scrape the bottom of the glassware. If the crystallized product still looks impure (i.e., color or texture) Repeat recrystallization.
16. Collect product by vacuum filtration, and dry overnight.
17. Analyze the final product by testing its melting point.<sup>6</sup>

These steps were then transformed into a flow chart. For ease of viewing, the exact measurements were removed, and only basic commands are visible on the chart and the chart

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<sup>6</sup>The melting point will be depressed if water is still present in the product.

assumes that set up has already been completed. The chart works by including color coded action boxes driven and conditional arrows.

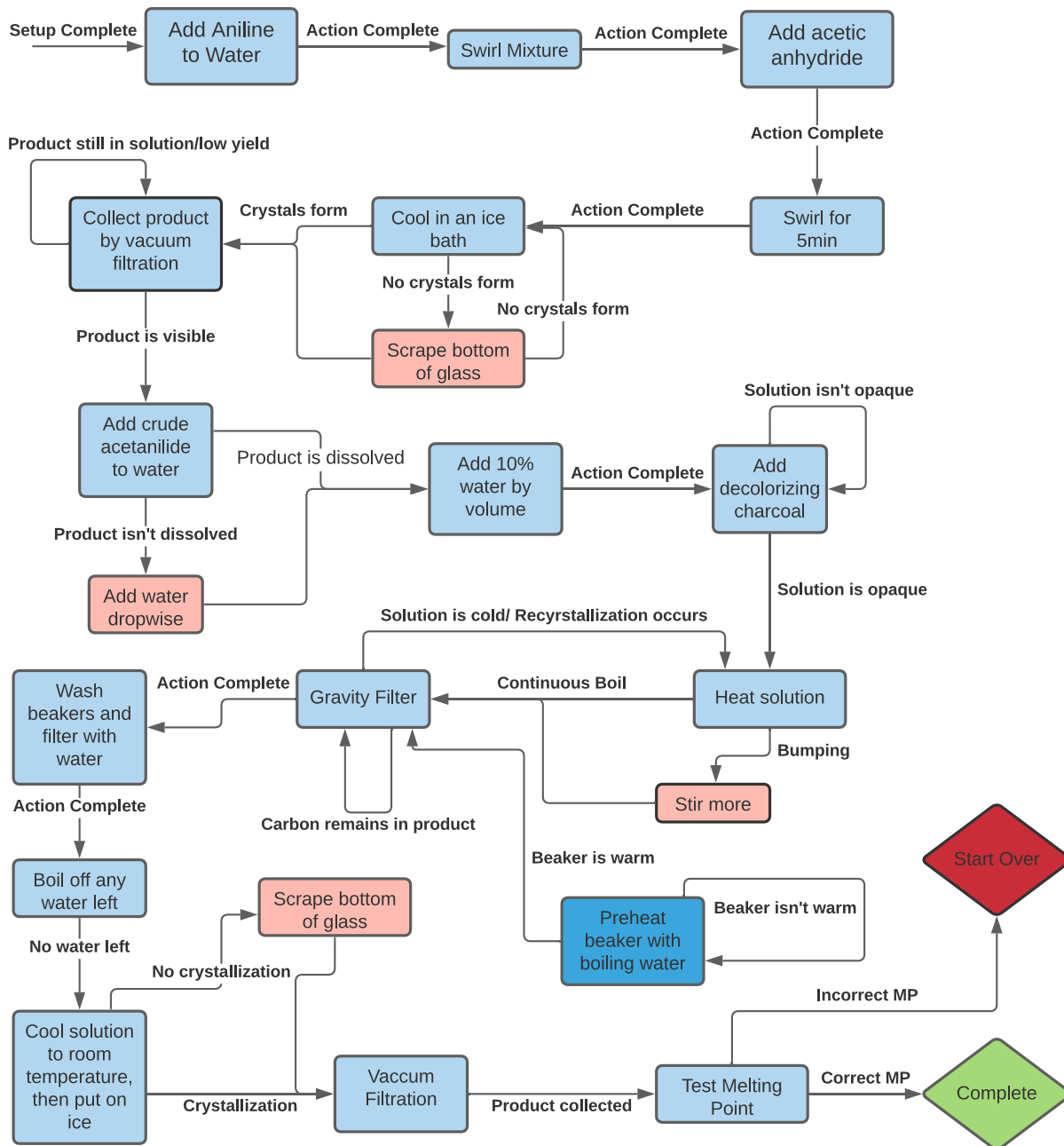


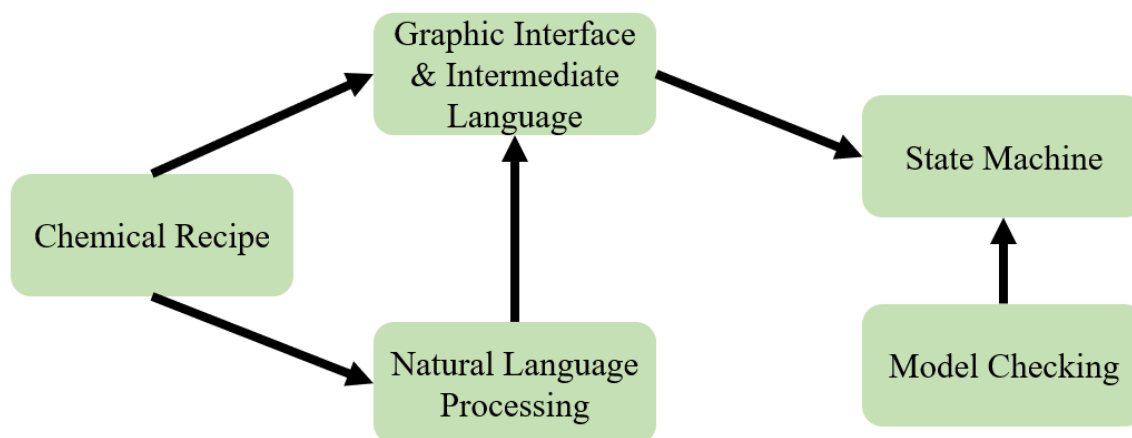
Figure 3: Flow Chart of the Synthesis of Acetanilide

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.

## Chapter 4: Program Ideation

### 4.1 Software Structure

The chemical synthesis robot will need software to interpret a chemical recipe into instructions that the robot can process. We worked on defining a potential base structure for this software, which could be implemented in future work.



*Figure 4: A diagram representing a potential structure of components for the software.*

Figure 4 shows a diagram of what this program might look like. The first piece is a chemical recipe, the directions for the synthesis process as written by chemists in natural language.

This recipe must then be converted into a computer-readable form. One way to do this would be through a graphical user interface in LabView. We discussed this interface earlier, under “LabView Details”. It uses dropdown menus to allow chemists to select and input commands, and is designed to be intuitive even without coding experience. A compiler would

then convert this graphic program into a specially constructed intermediate language. This intermediate language would use a Lisp-style parenthesis notation, with a set of verbs describing the actions that can be taken by the synthesis robot. It would be designed to be relatively human-readable, but also easily interpretable into a state machine. As an alternative to using the graphical interface, a chemist could learn the intermediate language and code with that directly.

Another input route would be to use natural language processing to automatically interpret the written chemical recipe into the intermediate language form. This could then potentially employ the graphical interface to display the interpreted instructions, allowing chemists to double-check the results and edit if necessary.

The intermediate language instructions, which are ultimately obtained from any of these input methods, must then be compiled into a state machine. This machine contains the final code which would be used to tell the robot how to carry out the synthesis process. Finally, before these state machine instructions are ever executed, the software would employ model checking to ensure that the state machine is correct.

## **4.2 Additional Tools**

One tool which we believe would be useful to implement in future work is a reaction calculator, which would allow chemists to specify a desired amount of product or limiting reactant, and from that compute how much of the other reaction components would be needed or produced. For instance, if using the equation for salt  $\text{Na} + \text{Cl} \rightarrow \text{NaCl}$ , the chemist could input the desired amount of sodium chloride to be produced and learn from the calculator how much sodium and chlorine would be required to make it. We envision that the quantities could be specified in grams or molar. The calculator would need to have access to a database which

holds the molecular weights of each chemical; beyond that it would just use a set of equations, so we think this would be very possible to implement.

	Na	+	Cl	→	NaCl
g					
M					

*Figure 5: A table representing what the calculator interface might look like. Entering a quantity in one of the white boxes on the table would calculate the quantities for each of the other boxes.*



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