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# **Development of a continuous-flow based process for AI-guided polymer synthesis**

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## **Abstract**

The need for reliable, rapid and precise polymer synthesis for therapeutic materials led to the democratization of flow chemistry in research labs. In this view, programmable high-throughput platform for scalable polymer synthesis has been improved. It comprises a web-based user interface, capable of controlling up to eight syringe pumps for flow chemistry. A database has been developed, aiming at storing large amounts of data about experimental polymer synthesis. Such a system will enable the implementation of a predictive artificial intelligence to guide this synthesis. In-flow characterisation and live feedback has also been initiated, and will soon be fully functional.

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# Introduction

## IBM Research | Almaden

The International Business Machines Corporation, or IBM, was originally founded in 1911 by Charles Ranlett Flint and Thomas J. Watson Sr. The company now operates in more than 170 countries and counts 350,000 employees. The main focus of IBM are computer hardware and software, but its activity also comprises material science, physics, Artificial Intelligence development and more.

IBM Research employs more than 3000 scientists around the globe, which makes it one of the largest corporate research group in the world. With 9100 patents in 2018 and more than 110,000 since its creation, IBM is the leader US company in terms of number of granted patents[1–3].



Fig. 1 Photograph of IBM Almaden research center [4]

The 22-week placement was carried out at the IBM Almaden research center in San Jose, California, in the heart of Silicon Valley. It is one of the twelve satellites of IBM's

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Research and Development division, on the borderline between academic and industrial research. It especially focuses upon different aspects of computer science, fundamental physics, nanotechnology and polymer synthesis.

## Interest of Flow Chemistry for research

The main interest of flow chemistry most probably lies in its higher precision and reproducibility as compared to the more conventional batch chemistry. Ten years ago, this discipline was reserved to industry and large scale applications, but the miniaturization of apparatuses enabled the use of flow chemistry in research labs[5].

There are several reasons why flow chemistry is more reproducible than batch reactions. Indeed, efficient mixing, better heat transfer and much more precise reaction timings all tend to reduce experimental and human-induced errors. This comes at the price of a different way to prepare reactions: volume ratios are replaced by flow rates, but programmatic reaction control is able to efficiently counter this inconvenience. In addition, once a new material has been developed in-lab using a flow reactor, its scale-up process is greatly facilitated.

In the frame of this internship, polylactones and polylactides were synthesized. These materials are part of a biocompatible and biodegradable class of materials, enabling the development of macromolecules for therapeutic and antimicrobial applications[6, 7], as well as diversified other biomedical applications[8–11]. In order to synthesize these materials in flow, the most convenient approach is the ring-opening polymerization of cyclic monomers [12].

Another crucial matter is the introduction of artificial intelligence guided chemistry, as evidenced by the creation of IBM RXN, a web service able to predict chemical reactions. As of today, very few articles have been published on the subject of predictive artificial intelligence for polymer synthesis, which makes it a perfect field of study.

In view of these elements, a question emerges:

**How to develop a fully automated polymer flow-reactor that would enable AI-guided material synthesis?**

The first step towards the implementation of Artificial Intelligence for polymer synthesis is making the process dependable and accessible to all lab scientists[13].

The main goal of this internship is to improve the current polylactides and polylactones syn-

thesis method by making it faster, more straightforward, and more reliable for researchers. Overall, the existing flow reactor needs more control and feedback on the experiment. In this regard, the pre-existing Python program controlling the reactor has been recast. A User Interface has also been developed in order to facilitate the work of researchers having no programming knowledge. To ensure the most precise results, in-line live characterization and direct feedback on the reactor's settings has been achieved. Additionally, several polymer synthesis were carried out as a proof of the good operation of the computer-controlled system, as well as a demonstration of its versatility.



Fig. 2 Photograph of the flow reactor set up



# Chapter 1

## State of the art of the system

Before any improvement could be done on the reactor, it is primordial to understand how it was previously working and what functionalities needed to be enhanced or added to the system. Also, in order to quantify the ability of a system to synthesize polymers, the chemical principle of the reaction will be discussed, as well as the working principle of three characterization techniques.

### 1.1 Chemical Theory

A polymer is a large molecule composed of a number of smaller repeating units. In order to synthesize a polymer, small organic molecules named monomers must chemically react and form a chain. The polymer is then a series of these monomers, structurally rearranged. Four main characteristics are to be considered. First, the Degree of Polymerization (DP) is the length of the chain in terms of repeating units. Next is the architecture: A polymer can be constituted by a single type of monomer, in which case it is a homopolymer, or by two or more different monomers, in which case it is a copolymer. A block-copolymer for instance is a series of one monomer units followed by a series of units from another different monomer. In the frame of this study, only homopolymers and block-copolymers were synthesized, but many other monomer arrangements are possible. Then, one has to consider a more global scope and take into account characteristics that directly result from the polymer synthesis. Conversion is a figure of merit of the quality of this synthesis. It is simply the percentage of monomers molecules that reacted to form a polymer. The last critical indicator for our study is the dispersity of the polymer, and represents the homogeneity of molecule sizes in the polymer solution. These values will be discussed in

more details during the explanation of their measurement method.

First of all, let's focus on the chemistry aspect of the project. In order to test the synthesis method at lower costs, commercially available cyclic monomers are used, namely  $\delta$ -Valerolactone, L-Lactide and  $\epsilon$ -Caprolactone. All three are esters, which means that they contain R-COOR' groups (see figure 1.1), that can be polymerized by Anionic Ring Opening Polymerization (ROP). It is assumed that if this method works with these esters,

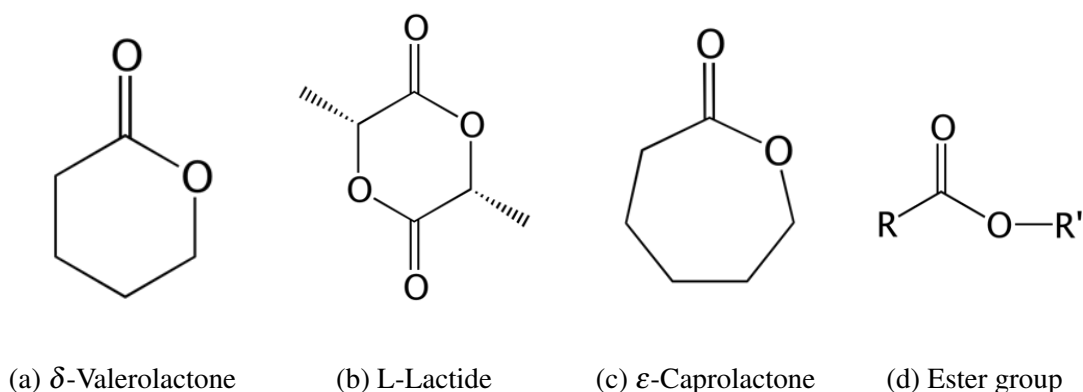


Fig. 1.1 Cyclic monomers used for the project

the very same method can be easily adapted to more costly monomers of the same type. The Anionic Ring Opening Polymerization is a 3 steps process. The reaction starts with the initiation, during which a negatively charged compound called initiator interacts with a cyclic monomer and opens it (see Figure 1.2). This reaction usually does not occur

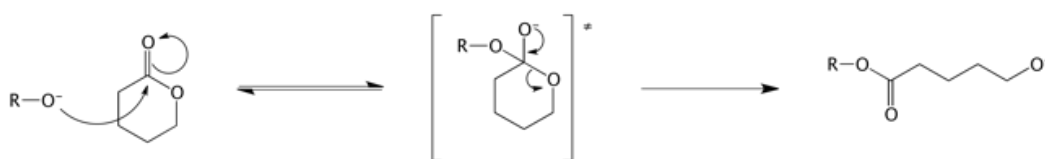


Fig. 1.2 Initiation reaction

naturally if the initiator and the monomer are put together in solution. In order for the initiator to open the ring, the use of catalyst is needed. In this project, urea are used as catalysts because of their fast and selective properties [14]. For more details about how the use of a urea facilitates the reaction, see Appendix A.1. In practice, the urea used are referred to as Urea 7 and Urea 5. Their chemical structure is shown in figure 1.3. For the reactions at stake, even though it is sufficient to use the same molar quantity of initiator and urea, a (urea:initiator)=(3:1) ratio is used for better reproducibility[15].

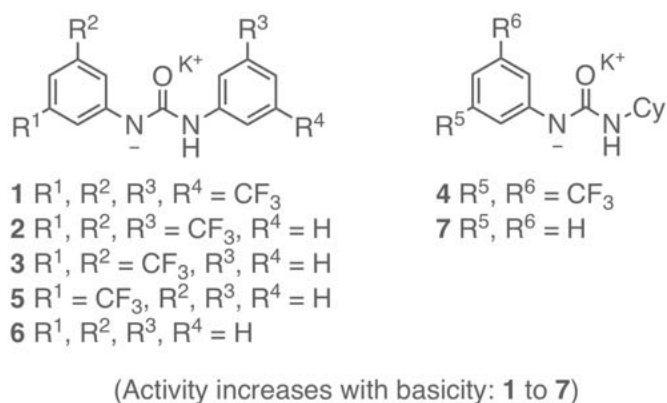


Fig. 1.3 Different urea used during the internship. In practice, Urea 7 and Urea 5 were the most used. Extracted from [15]

After the Initiation, the molecule formed is made of the initiator and an opened negatively charged monomer ring. The same reaction now happens between the anionic chain end and another monomer, until, in theory, all the monomers in solution have become part of the polymer chain (see Figure 1.4). The degree of polymerization can be calculated

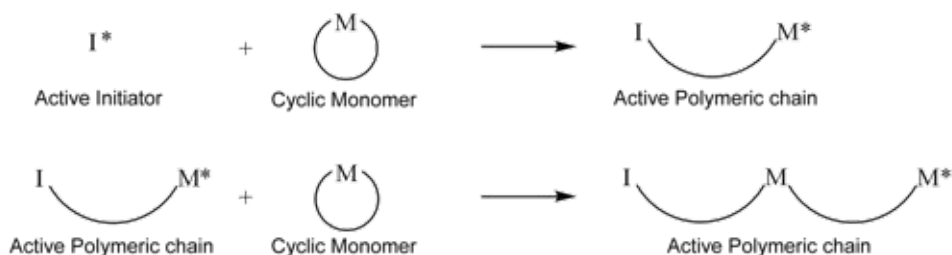


Fig. 1.4 Ring opening polymerization mechanism. By convention, as they are catalyst, urea do not appear in the chemical equation. Adapted from [16]

as the molar ratio of Monomer over Initiator in the reactor. In reality, the reaction will stop before all the monomers in solution have reacted. Indeed, an chemical equilibrium is reached between the cyclic monomer and the polymer chains[17]. The concentration of the monomer in solution at which this equilibrium is reached is referred to as the Equilibrium Monomer Concentration. For instance, the equilibrium monomer concentration of  $\delta$ -Valerolactone is 0.1M (where M is mol/L). Therefore, based on the equation 1.1 extracted from Tobolsky's work[18], mixing Valerolactone, Urea and Initiator in a ratio (50:3:1) with in-reactor molar concentrations (1:0.06:0.02) will form a homopolymer of DP 45 at best. It is also very important to note that because of that equilibrium concentration, the conversion of such a reaction cannot go higher than 90% (see equation 1.2).

$$DP = \frac{\text{Monomer Concentration in reactor} - \text{Equilibrium Monomer Concentration}}{\text{Initiator Concentration in reactor}} \quad (1.1)$$

$$\text{Conversion}_{max} = 100 \times \left(1 - \frac{\text{Equilibrium Monomer Concentration}}{\text{Monomer Concentration in reactor}}\right) \quad (1.2)$$

From this point, forming a block-copolymer does not add much more complexity to the reaction. A new catalyst is used, so that its activity matches the reactivity of the second monomer, in a process called catalyst switch[15]. After a given time, the reaction is quenched using benzoic acid, which will provide enough hydrogen atoms to stabilize the polymer. Indeed, without a negative charge on its last unit, the polymer's reactivity will drop.

One of the goal here is to reduce the reaction time as much as possible, while still reaching full conversion. Indeed, the longer the reaction time, the longer the probability of transesterification of the polymer backbone which will result in a broader range of molecular weights amongst the polymers synthesized, reflected by an increase of the dispersity[15]. If the quality of the final polymer is altered by too long a reaction time, it is also the case if the reaction time is too short. In this case, the equilibrium cannot be reached, which means that the conversion is lower than expected. Thus, as all the monomers did not have enough time to open and lengthen the polymer chains, the ratio (monomer : initiator) is reduced. In the end, the polymer synthesized will be shorter than desired.

## 1.2 Real life system

The reaction set-up is shown in figure 1.5.

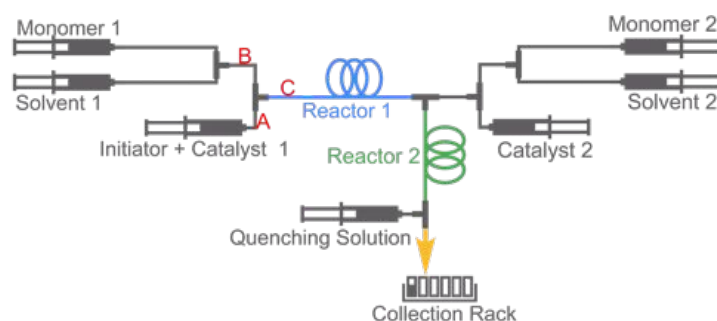


Fig. 1.5 Schematic view of the reactor set-up

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First, the first monomer is mixed with the first catalyst and the initiator. A solvent syringe is used in order to decrease the monomer concentration while keeping a constant flow rate in tube B. As the initiator+catalyst flow rate is fixed (tube A), the flow rate in tube C is also fixed. By doing so, it is possible to vary the (initiator : monomer) ratio and obtain different degrees of polymerization while keeping a given reaction time. The same process is repeated for the second block. Finally, a benzoic acid solution quenches the reaction before the collection in a vial.

In March 2019, the set-up was comprised of:

- One Python script
- 4 syringe pumps (2 models : 33DDS and PhD Ultra), capable of controlling 2 syringes each
- Tubing, mixers and connectors forming the reactor

The Python code would allow to choose the reactions parameters such as the concentrations of the different solutions, the volume of the syringes, the equilibrium monomer concentration, the total flow rates in the reactors, the injection duration and a list of DPs for both blocks. It would then handle the calculation of the flow rates for each syringe and control of the pumps accordingly.

In order to start a reaction, one had to:

- Directly alter the Python code in order to specify the reaction parameters
- Calculate by hand the quantities of chemicals to be prepared
- Prepare the solutions and transfer them to syringes, all of which are the same size
- Connect the pumps one by one by USB and specify their USB Address manually to the code
- Start the reaction by running the program

Several concerns can already be raised. First, modifying a script manually before each and every reaction is perilous in the sense that all parameters to be specified do not stand out the rest of the code. Also, forgetting to save before running, not noticing a typo or a USB Address assignment error will make the reaction fail and all the preparation steps will have to be redone. A hardware damage risk adds up to that 'human error' possibility. In fact, in order to protect the pumps Non Volatile Random Access Memory, any external control program must start by sending a 'protection' command[19, 20]. As no distinction

was made between the two models of pumps in the code, 2 pumps were running without safeguard. The majority of the other commands being shared by the two types of pumps, operations such as ‘Injection at a given flowrate’ could be achieved anyway.

In a more practical view, it is important to note that in a situation in which several different polymers are made successively, the output of the reactor has to be manually held and positioned above a vial, resulting in recurring spills of solvent and polymer solution. Also, the communication with the pumps being unilateral, any stalling of one pump could not be automatically detected. The other pumps would continue injecting and the rest of the reaction would be wasted.

Let’s now have a closer look at the characterization techniques. For homopolymers and block-copolymers synthesized by ROP, Spectroscopy by Nuclear Magnetic Resonance (NMR) and Gel Permeation Chromatography (GPC) were used. Infrared Spectroscopy (IR) was then needed in order to include a live feedback loop control on a flow polyurethane synthesis. Just after the polymer synthesis, the product gathered is comprised of the polymer molecules, catalysts, left over monomers and quenching molecules. This fraction is called crude sample and can be analyzed by NMR. Integrating different regions of the output spectrum gives key information concerning the proportions of each chemical compound in the crude solution. By comparing the amount of polymer material in it with the quantity of monomer leftover, the conversion can be determined. Then the sample is cleaned (see procedure in Annex A.2) in order to isolate the polymeric portion of the solution. This clean sample can then be analyzed by NMR again, in order to determine the number of repeating units for one initiator group, hence deriving the Degree of Polymerization. Finally, a GPC analysis will confirm the DP previously found and tells us about the weight distribution of the cleaned polymer by calculating  $M_w$  the mass-average molar mass and  $M_n$  the number-average molar mass. The dispersity is derived from there.

### **1.3 Working principle of the NMR [21, 22]**

The Nuclear Magnetic Resonance Spectroscopy (NMR) exploits the interaction between protons and magnetic fields to obtain information about the environment of hydrogen atoms. In general, superconductor materials build a strong magnetic field  $B_0$  through the sample to be analyzed. By doing so, all the spins of the protons line up with the field. Their energy  $E_1$  is now taken as a reference. Now that they are all parallel and in a stable state, a radio frequency excitation is applied. The goal here is to move the protons spin away

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from their initial position,  $90^\circ$  being the optimal value. They now resonate at an energy  $E_2$ , higher than  $E_1$  and specific to each proton. Then the excitation is turned off and the protons relax to their first state  $E_1$ . In the process, they will emit an electromagnetic wave of frequency  $\nu$ , with an energy equal to  $E_2 - E_1$  (see equation 1.4). The signal is received by a coil and converted into a chemical shift  $\delta$  in part per million (or ppm) (see equation 1.3)

$$\delta_{ppm} = \frac{\text{resonance frequency} - \text{reference resonance frequency}}{\text{spectrometer frequency}} \times 10^6 \quad (1.3)$$

$$\nu = \frac{E_2 - E_1}{h} \quad (1.4)$$

The interesting property is that this chemical shift varies depending on the environment of the excited proton. Indeed, an electronegative atom will tend to withdraw electrons, lowering the electron density around him. If a proton is located in this area, it is said that it is deshielded, and it will be more sensitive to a variation of magnetic field. Thus, a deshielded proton will have a high chemical shift. Conversely, a proton located around less electronegative atoms will be shielded, leading to a lower chemical shift. If several protons have a similar environment, they are equivalent and will have the same chemical shift. This will be converted into a peak proportionally more intense than a single proton on the spectrum. Finally, neighboring protons also have an influence on the chemical shift. Thus, a neighboring proton B will split the chemical shift of proton A into two very close shifts. Proton C will split the peak again, to give a total of 3 shifts. Then, N neighboring hydrogen atoms will split a chemical shift into N+1 peaks. This phenomenon is known as the N+1 rule.

The intensity, shift and splitting information are then used to determine or verify the composition of a sample.

This technique enables the calculation of both conversion and degree of polymerization of a polymer. Indeed, the analysis of a crude sample will give the conversion of the reaction. As cyclic monomers and polymerized monomer units do not have the same environment, their chemical shift are different. Integrating their respective peaks will then give their quantitative ratio, and thus the conversion (equation 1.5). Also, after cleaning of the sample, only the polymer remains, comprised of the monomer units and the initiator. The ratio of their quantities gives the degree of polymerization (equation 1.6).

$$\text{Conversion} = \frac{\text{Polymer quantity}}{\text{Monomer quantity} + \text{Polymer quantity}} \quad (1.5)$$

$$DP = \frac{\text{Polymer quantity}}{\text{Initiator quantity}} \quad (1.6)$$

## 1.4 Working principle of the GPC [23]

The Gel Permeation Chromatography (GPC) gives information about the size of molecules. The working principle is the following: The sample to be analyzed is pumped through a gel-filled column. The gel contains pores, in which smaller molecules can be trapped for some time. Conversely, bigger molecules will not fit into the pores as easily and will reach the end of the column more quickly. At the output, a refractive detector observes the amount of molecules exiting the column, and provides an intensity versus retention time spectrum. The use of standards for calibration allows us to determine the total molecular weight of the molecules based on their retention time, and the ratio  $M_w/M_n$ , where  $M_n$  is the number-average molar mass and  $M_w$  the mass-average molar mass. The difference between  $M_n$  and  $M_w$  is the following:  $M_n$  is simply the average molar mass, where the contribution of each molecule is one, whereas  $M_w$  is the average molar mass where the statistical weight of each molecule is its own molecular weight (see equations 1.7 and 1.8, Where  $M_i$  is the molecular weight of a chain and  $N_i$  the number of chains of that molecular weight). The dispersity is calculated as the ratio of  $M_w$  over  $M_n$  and is always greater than one (see equation 1.9). It gives an idea of the homogeneity of the molecules analyzed.

$$M_n = \frac{\sum N_i \times M_i}{\sum N_i} \quad (1.7)$$

$$M_w = \frac{\sum N_i \times M_i^2}{\sum N_i \times M_i} \quad (1.8)$$

$$D = \frac{M_w}{M_n} \quad (1.9)$$

## 1.5 One real life experiment example

Now that the reactor set up and the characterization techniques are known, it is interesting to sum it up by focusing on what an experiment really looks like.

For example, the synthesis of four block-copolymers composed of 5, 10, 15 and 20 units of  $\delta$ -Valerolactone respectively, to which 25 units of L-Lactide are added. First, seven syringes are prepared, containing:

1. Monomer 1 : 2.5mL of  $\delta$ -Valerolactone at a concentration of 2.5M
2. Initiator / Catalyst 1 : 7.5mL of Potassium methoxide at 0.04M and Urea 7 at 0.12M
3. Monomer 2 : 4.25mL of L-Lactide at 2M



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4. Catalyst 2 : 4mL of Urea 5 at 0.24M
5. THF 1 : 5.55mL of THF
6. THF 2 : 7.25mL of THF
7. Quenching solution : 7.5mL of Benzoic acid at 2M

For DP20  $\delta$ -Valerolactone and DP25 L-Lactide:

The injecting rate ratios must be calculated, so that in the reactor 1 the molecular ratio is (Monomer 1 : Initiator) = (25:1). Indeed, the equilibrium monomer concentration of  $\delta$ -Valerolactone is 0.1M. 30mL/min is arbitrarily chosen in the reactor 1 and the flow rate of the Initiator/Catalyst 1 syringe is set to 15mL/min. To respect the molecular ratio,  $\delta$ -Valerolactone must be injected at 6mL/min, and THF1 at 9mL/min.

In the second reactor, the flow rate is chosen to be 60mL/min, and the Catalyst 2's is 7.5mL/min. This way, once in the reactor 2, the second catalyst has the same concentration as the catalyst 1 in reactor 1. L-Lactide and THF 2 share the remaining 22.5mL/min so that their molecular ratio in reactor 2 is (Monomer 2 : Initiator) = (27:1), once again because the equilibrium monomer concentration of L-Lactide, 0.02M, is to be taken into account. The reaction can be summarized in terms of molecular ratios (Initiator : Monomer1 : Monomer2 : Catalyst1 : Catalyst2) = (1:25:27:3:3). In the end, the reaction is quenched with excess Benzoic acid. The same method is applied for  $\delta$ -Valerolactone at DP 5, 10 and 15.

To get an idea of the physical reactors, here are its dimensions: 1mm-diameter tubing is used to make all the reactor and junctions, 0.5mm T-Mixers make the connections. The reactor 1 is 22cm long and reactor 2 is 16cm long, so that the reaction times are 0.36s and 0.13s respectively (see Figure 1.6). The NMR spectra of these polymers are shown in Figure 1.7.

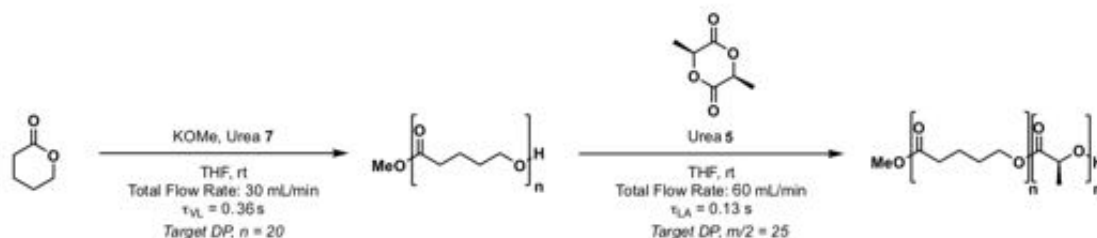
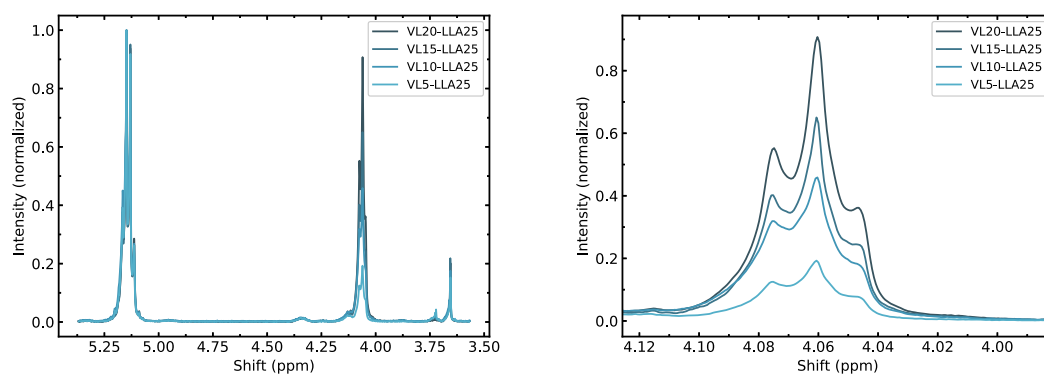


Fig. 1.6 Reaction equation for poly(VL)<sub>20</sub>-block-poly(L – LA)<sub>25</sub>

transition



(a) NMR trace of the four cleaned polymers synthesized, normalized. Around  $\delta=5.15\text{ppm}$  is the poly L-Lactide peak, while the poly  $\delta$ -Valerolactone is at  $4.06\text{ppm}$ . The Initiator's peak used to calculate the DP is at  $3.65\text{ppm}$

(b) Close up view of the poly  $\delta$ -Valerolactone peak. Here, the decreasing intensity of the peak with decreasing DP is evidenced

Fig. 1.7

## Chapter 2

# Coding for the automated polymer synthesis

As mentioned in the previous part, the automated synthesis procedure was rudimentary. The goal here was to find a way to control the pumps in a way that is safe for the hardware and the human operator. In addition, in view of integrating an AI system to the reactor, an efficient way to save reaction data was to be developed. Finally, as no programming skill should be required by the lab workers to run a reaction, a user interface was created.

This second section will then be dedicated to the implementation of a Web-based User Interface able to fully control a reaction as well as an automated fraction collector. The reaction data will be stored on a database, which will also contain the necessary information to provide a preparation procedure to the user.

### 2.1 Running the pumps and collecting fractions

First and foremost, the Python code needed an update in order to be able to manage the fraction collector and the database. Here is a simplified view of its latest architecture (Figure 2.1).

In view of simplifying the reaction procedure as much as possible for the users, a startup procedure was written. Once all the pumps are hooked up to the computer, the script locates all the USB modem connected and sends them a request asking for their version. If the USB modem replies, it is most likely a pump. Then, the USB address of these modems are isolated and a new request is made, asking for their Pump address. The pump address is a two digit number set up by hand directly on the pump, and is different from the USB address. Finally, each USB modem is assigned to a virtual pump object that contains the information needed to communicate with the real pump. The Python class

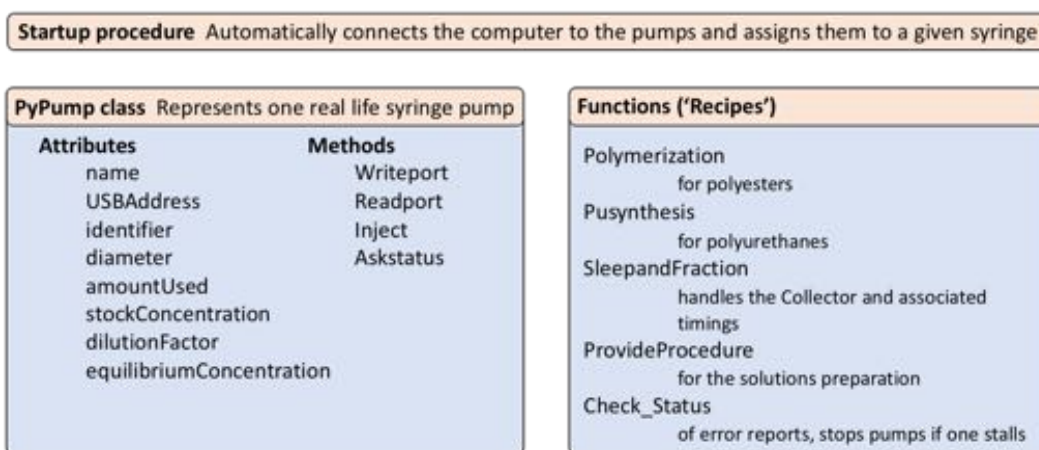


Fig. 2.1 Simplified view of the Python code running the pumps. Attributes are variables that define a particular PyPump object, methods are functions that can be applied to any PymPump object

created for that purpose is called PyPump and contains several attributes. The USBAddress and identifier are used to communicate with the physical object via USB. The diameter is a characteristic of the syringe that is being emptied by a pump, and will be transmitted to the pump before every injection. It is derived from the volume input given by the user. Finally, the amountUsed, stockConcentration, dilutionFactor and equilibriumConcentration are used for the calculations of the flow rate and quantities of chemicals needed to prepare the reaction. Besides, the Methods are functions that are specific to the PyPump objects. 'Writeport' and 'Readport' facilitate the USB communication by making it more human-friendly, while 'Inject' and 'Askstatus' let the program send command to the pumps. Inject will make the pump infuse at a given flow rate for a given period of time and Askstatus collects the error report from the pump.

Now the Fraction collector could be integrated to the reactor. The addition of such an apparatus to the system was crucial. Indeed, not only does it reduce the risk of spilling and inhalation of solvent vapors by the user to zero, it also handles the waste and fraction time so that only the steady state part of the reaction is collected. For other longer reactions, as discussed in section 3.1, the fraction collector will enable fully automatized synthesis of multiple polymers. Such a reaction could be started at night and analyzed by the operator the day after. In practice, the fraction collector is connected via USB to the computer, which will send commands the same way it communicates with the pumps. The only two instructions this machine can handle from an external source are "start fraction", which will actuate the valve and redirect the flow from the reactor's output to the test tube, and

“stop fraction and advance”, which will redirect the flow to the waste container and move the nozzle above the next test tube.

With that level of control over the pumps, it is now possible to create reaction protocols, which in reality are simply ‘recipes’, timed series of injection and timing instructions sent to the pumps and the fraction collector. For the polyester homopolymer and block copolymer synthesis, a loop over the degrees of polymerization was added, so that different polymers could be synthesized one after the other. In more details, the ‘Polymerization’ function calculates the flow rate ratios between the different pumps according to the stock concentration of each monomer, catalyst and initiator solutions, taking the equilibrium monomer concentration into account. Then it calls ‘SleepandFraction’: As only the steady state part of a given synthesis is to be collected, the sequence of instructions sent to the fraction collector is waste – fraction – waste. It has been experimentally observed that throwing away the first and last 10% of the synthesis gives the best trade-off between amount wasted and quality of the final polymer. To do so with the only two commands available, the end-waste of polymer N has to be combined with the start-waste of polymer N+1. Thus, the sequence of instructions is :

With ‘Polymerization’:

1. start polymerization

With ‘SleepandFraction’:

2. Stop fraction and advance if this is the first polymerization
3. Wait 10% of injection time
4. Start fraction
5. Wait 80% of injection time
6. Stop fraction and advance
7. Wait 10% of injection time

After a reaction, or even after each iteration of the loop, it is possible to get an error report directly from the pumps. The most important information contained in this brief report is whether or not a pump stalled. If one does, an emergency stop is triggered, so that all other pumps stop too. This way, the next reaction will not start and the solution remaining in the syringes can be reused after the error is cleared.

Moreover, the preparation of the reactions can be simplified. Indeed, instead of having to calculate the masses and volumes of each solution to be prepared by hand, it is possible to have the program compute it. By simply simulating the reaction, namely by skipping the association with the pumps and all the timing-induced wait times, one can know how

much of each solution is needed. Then, as the concentration of each solution is specified by the user, the mass of a given chemical can be determined with equation 2.1. As the concentration used are usually quite high, the volume occupied by the monomer, catalyst or initiator to be dissolved is to be taken into account. The approximation is made that one gram of chemical will fill 1mL (density 1mg/cm<sup>3</sup>). The volume of solvent needed is then the total volume found by simulation, minus the volume needed for the chemicals.

$$\text{mass} = \text{molecular weight} \times \text{concentration} \times \text{volume} \quad (2.1)$$

## 2.2 Storing data : MongoDB

In view of storing the reaction parameters for each reaction and their measured characteristics, a database has been added to the system. MongoDB, a document-oriented database program was chosen, for its simple and efficient communication with Python. The database runs on a local server, and comprises collections, which are in turn made up of JSON-like documents. JSON documents are a type of data storage relying on text key-value pairs. For the present project, the MongoDB database contains several collections, each one for

```

_id: ObjectId("5d28ca0f6ca3e5b7a8cd17c7")
name: "materials"
nbblocks: 2
Monomer 1: "Valerolactone"
StartDP1: 40
StopDP1: 50
StepDP1: 5
initiator: "KOMe"
Catalyst 1: "Urea 7"
THF 1: "THF"
Monomer 2: "Lactide"
StartDP2: 20
StopDP2: 40
StepDP2: 10
Catalyst 2: "Urea 5"

_id: ObjectId("5d28ca0f6ca3e5b7a8cd17d1")
name: "rates"
monomer1PlusTHFFlowRate: 15
catalyst1FlowRate: 15
monomer2PlusTHFFlowRate: 22.5
catalyst2FlowRate: 7.5
washFlowRate: 15

_id: ObjectId("5d28ca0f6ca3e5b7a8cd17cb")
name: "times"
waitTime: 1.5
prerinseTime: 2
washTime: 2

_id: ObjectId("5d28ca0f6ca3e5b7a8cd17cf")
name: "concentrations"
monomer1StockConcentration: 2.5
equilibriumMonomer1Concentr_ : 0.1
initiatorStockConcentration: 0.04
monomer2StockConcentration: 2
equilibriumMonomer2Concentr_ : 0.02

_id: ObjectId("5d28ca0f6ca3e5b7a8cd17c9")
name: "syringesvolumes"
Monomer1SyringeVolume: 10
THF1SyringeVolume: 3
Catalyst1SyringeVolume: 20
THF2SyringeVolume: 10
Monomer2SyringeVolume: 10
Catalyst2SyringeVolume: 10

_id: ObjectId("5ce6bda252f9594c734a1f5c")
name: "Lactide"
molecular_weight: 144.12

_id: ObjectId("5ce6bda252f9594c734a1f5e")
name: "Valerolactone"
molecular_weight: 100.12

_id: ObjectId("5ce6bda252f9594c734a1f60")
name: "Caprolactone"
molecular_weight: 114.14

```

(a) Example set of reaction parameters from the polyesters collection (b) Example set of Monomer data

Fig. 2.2 Examples of documents in JSON format, extracted from the software MongoDB Compass

a different usage. Four of them store the name and molecular weights of a number of Monomers, Catalysts, Initiators and Solvents. Two others contain several documents that

## Coding for the automated polymer synthesis

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are used to store all the reaction parameters in a structured way (see figure 2.2) for two different reactions (polyurethanes and polyesters). Finally, two collections are controlled automatically by MongoDB and are used to store files that are uploaded by a user.

The main goal is to store generic information about the chemicals used, in order to calculate the quantities required for a given reaction, and to save all the experimental data that can be acquired by a lab worker. In this view, a data model was to be defined, so that a polymer could be fully characterized by a set of key values. One document corresponds to one sample of one experiment, so for the synthesis of 5 different polymers in one experiment, 5 documents are created. These documents are automatically filled with the reactions parameters entered before the reaction, and can be completed later on, once the user made the analysis. In addition, the GPC and NMR files can be uploaded to the database. This way, all the information collected for a given reaction is stored in the same place. This enables the implementation of a predictive Artificial Intelligence system, capable of matching input parameters with material properties. For this study, a shorter data model was selected, containing only the information having the most impact on the synthesis and results (see figure 2.3).

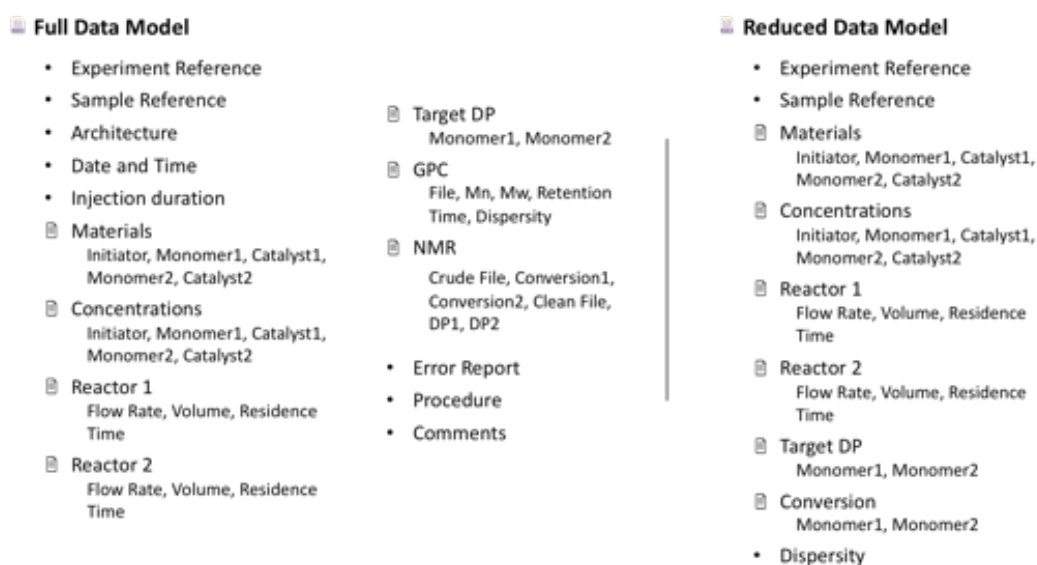


Fig. 2.3 Full data model for data storage (left) and reduced model for predictive AI implementation (right)

## 2.3 Web-based User Interface

Finally, a web based user interface was coded, aiming at reducing the complexity of running a reaction to the minimum. The ensemble formed by the entities that enable the display of the interface and the processing of the data input by the user is called an App.

The flask Python module was used to run a local server and display a web page accessible with any browser. It uses HTML and CSS to show the front-end, while the back end is managed with Python. Here, a page is dedicated to the polyester reaction, and another one to the polyurethanes synthesis. The user can enter all the reaction parameters in a form and choose whether he wants to prepare or to run a reaction. If he selects the former, a printable table will show up containing all the preparation procedure, and if the latter is chosen, the program will start the pumps and run the reaction. Other pages are available:

The screenshot displays a web interface with two main sections. On the left, a table titled "Procedure for CD-001-45" lists reagents and their quantities. On the right, there are three tool panels: "Materials reminder" with chemical structures for L-Lactide, Valerolactone, Caprolactone, and TMC-Bn; a "Urea" section with seven numbered chemical structures and their substituents; and two calculators: "Tube length Calculator" and "Tube volume Calculator", each with input fields for residence time, diameter, and flow rate, and a "Calculate" button.

Procedure for CD-001-45				
Reagents	mol (mmol)	mol.weight (g/mol)	mass (mg)	volume (mL)
THF 2				9.67
THF 1				2.25
Valerolactone	22.50	100.12	2252.7	
THF				6.75
KOMe	0.45	70.13	31.56	
Urea 7	1.35	218.3	294.7	
THF				10.92
Lactide	14.40	144.12	2075.3	
THF				5.12
Urea 5	1.35	280.0	378.0	
THF				5.25

(a) Example of a procedure table

(b) Tools web page

Fig. 2.4

localhost:3000 is the homepage and contains tips for practical use of flow reactors, compiled during the past few months.

localhost:3000/tools contains a reminder of the Lewis representations of monomers and urea, as well as tube length calculator for given flow rate, diameter and residence time, and tube volume calculator for given length and diameter.

## 2.4 Results

The operation of the whole system can be summarized in 7 steps (see figure 2.5). First, a Python App uses Flask to run a website on a local server. It uses HTML and CSS to display the pages via any web browser. The user then inputs the reaction parameters that are saved into the database and are processed by the App. Next, the pumps and fraction



## Coding for the automated polymer synthesis

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collector are controlled by a python script. Finally, the error report from the pumps is displayed to the user and saved into the database (see figure 2.5)

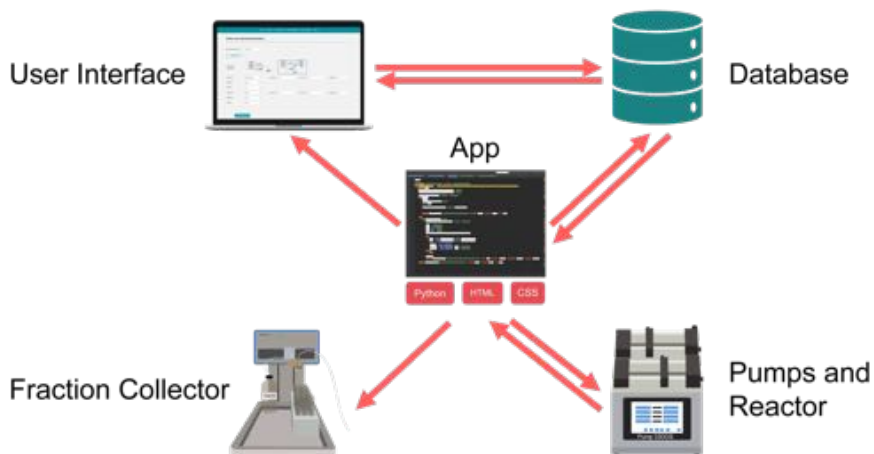


Fig. 2.5 Schematic representation of the global system, comprised of a an App handling a user interface, a database, several pumps and a fraction collector

The global system has then been tested with a well known reaction, to make sure that the polymer synthesis was working correctly. Experimentally, the homopolymers and block-copolymers synthesised using the App have a quality similar to those made by controlling the pumps manually. As the procedure is now provided, the time needed for the preparation of solutions is greatly reduced. In addition, the risk of making errors inputting the reactions parameters is cut down, and the set up time required to connect the pumps is shorten to zero. Finally, all the experimental data can now be stored in a dedicated database.

# Chapter 3

## Feedback loop

In view of producing a polymer as close as possible to the desired one, a live measurement can be performed and a correction on the flow rates can be applied accordingly. Also, the addition of such a correction to the system will remove the need of a kinetic study to determine the reaction time.

### 3.1 Integration to a reactor

In the first instance, this system is added to the polyurethane synthesis system, for it is the easiest reaction to monitor with IR spectroscopy. Almost no knowledge of the actual chemical reaction is needed in order to implement a feedback loop. The only important information derived from the spectrum is the concentration of diisocyanate in solution at the output of the system. Indeed, the intensity of the corresponding peak has a linear relation to the concentration of diisocyanate, which happens to be directly related to the conversion of the reaction (see equation 3.1). A schematic of the reactor is shown on figure 3.1.

$$\text{Conversion} = \frac{\text{Concentration at reactor input} - \text{Current concentration at output}}{\text{Concentration at reactor input}} \quad (3.1)$$

To simply and efficiently implement a live feedback and correction system, the instantaneous flow rate is chosen as the input parameter, and the conversion as control value. The challenge lies in the long reaction time of such a reaction, which we know is around 20 minutes. Indeed, the system has to update its flow rate at a much greater rate than the reaction time if we want it to reach the wanted conversion in a relatively short period of time. Also, too long a reaction time will increase the conversion too much, increasing the viscosity of the polymer solution dramatically, ending up clogging the tubes. A ‘prediction’

## Feedback loop

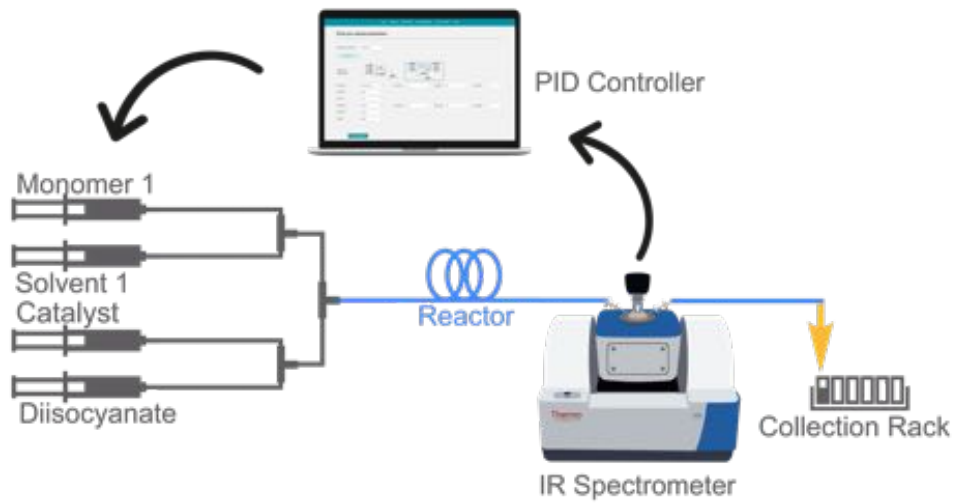


Fig. 3.1 Schematic view of the polyurethane synthesis set-up

has to be made to avoid excessive change in the flow rate, most probably resulting in an overshoot in reaction time and clogging the tubes. The correction system must then be able to find the right flow rate quickly, with minimal overshoot. A correctly tuned proportional–integral–derivative (PID) controller perfectly fills these requirements (see Figure 3.2)

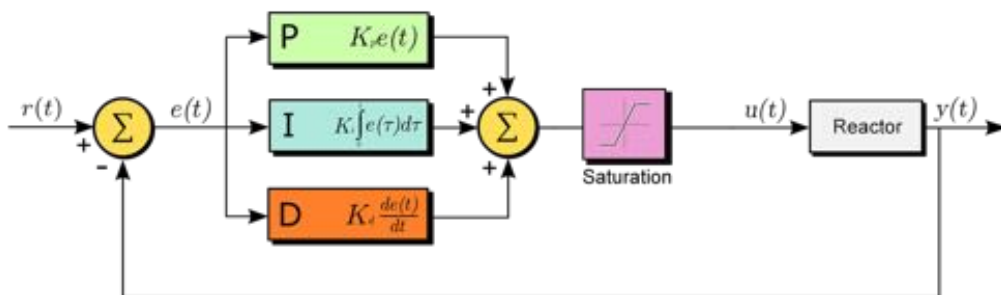


Fig. 3.2 Schematic representation of a PID Controller with saturation. Here,  $r(t)$  is the input from the user: the desired conversion.  $e(t)$  is the error, which is the difference between  $r(t)$  and the current conversion measured at the output of the system  $y(t)$ .  $u(t)$  is the signal sent to the reactor, namely the flow rate of all the pumps. Finally,  $K_p$ ,  $K_i$  and  $K_d$  are the coefficient to be tuned, the proportional, integral and derivative coefficients respectively. Adapted from [24]

## 3.2 Simulation

Because of the time and cost of tweaking the parameters on a real life experiment, a simulation of the system was first made. The model contains a list of all changes made to the system, namely the instantaneous flow rate and time of the change. The time spent in the reactor by a given fraction is derived from this list, and logarithmically converted into a conversion value. Then the input flow rate is modified and a new (time, flow rate) couple is added to the list. A first estimation of the controller's coefficients was made using Ziegler-Nichols method[25]. Indeed, after an extensive research, no system similar to the flow reactor with a conversion target was found [26–29]. The more general Ziegler-Nichols was then used, and manually adjusted. Here the  $K_d$  is much higher than  $K_i$  or  $K_p$ , in order to account for the long reaction time and avoid overshoot. This allows the system to predict the evolution of the conversion in time, but as the derivative part has by far the largest influence on the new flow rate, a perturbation of the system or of the conversion measurement will result in a wrong estimation. To counter that, a saturation is added on the maximum change in flow rate between two iterations of the PID Controller. In practice the largest possible change goes from 20% to 2% as the reaction runs. This will force the system to stabilize to a given optimal flow rate. Also, a minimum flow rate is fixed, in order to avoid clogging the system if the target conversion is too high to be reached without producing a very viscous polymer. After tuning, the simulations results are satisfactory enough to try the controller on the real life system (Figure 3.3).

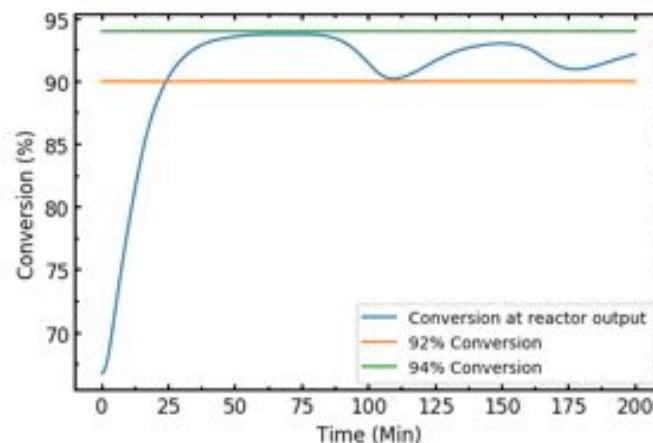


Fig. 3.3 Conversion curve as a function of time, from the simulation. A 2% error is considered as acceptable. For this simulation, the maximum possible conversion was 100%, which means that the PID controller worked fine. The parameters were  $K_p=0.9$ ,  $K_i=0.1$ ,  $K_d=700$

### **3.3 Real life implementation**

The system has been tested in real life conditions. But because of leaking syringes, the catalyst was not correctly infused into the reactor and the reaction was not happening. Due to a lack of time, the PID controller has not been tested a second time during the internship.



# Chapter 4

## Versatility and demonstration

For the purpose of demonstrating the proper functioning of the system and its versatility, polymer with new architectures were synthesized.

### 4.1 New architectures

In order to be able to use a variety of alcohols as initiators, the reaction was slightly different from the polymerisation of esters explained previously. Indeed, as previously,  $\delta$ -Valerolactone and L-Lactide were used as monomers but the urea were replaced by Potassium tert-butoxide. The details about the chemical interactions leading to the polymerization can be found in annex A.3. The interesting element is that the initiation can begin on any alcohol group. Thus, a monofunctional alcohol, which has one alcohol group, can be used as initiator to form a homopolymer or a block-copolymer as in section 1.1. But now, there is the possibility to use difunctional or trifunctional alcohols as initiator, and form star polymers, as shown in figure 4.1.

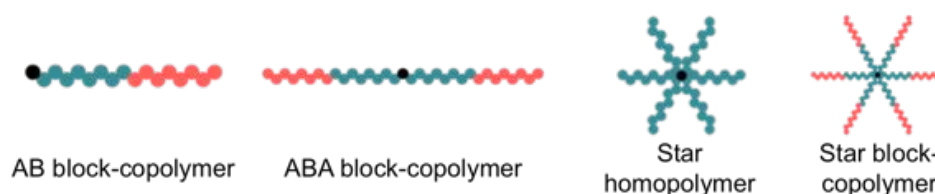


Fig. 4.1 Schematic representation of new accessible architectures. The black dots represent initiators, blue dots represent a monomer unit and red units from a different monomer

The first step was to make sure that making a classic AB block-copolymer was still possible using potassium tert-butoxide. Also, it is important get an idea of the reaction

## Versatility and demonstration

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time needed to reach high conversion while keeping the dispersity as low as possible. To do so, a kinetic study was performed, which most interesting results are shown on figure 4.2. In total, nine identical reactions were carried out with reaction times ranging from 5ms to 1s. As the dispersity is greatly impacted by the change in reaction time but the conversion is not, the default reaction time was chosen to be 10ms. 5ms is the shortest reaction time achievable with the system, but in order to reduce the pressure in the tubing, and because the quality of the polymers synthesised was equivalent, 10ms was kept as the optimal reaction time. With a more powerful system, it would have been possible to see the conversion drop with shorter reaction times.

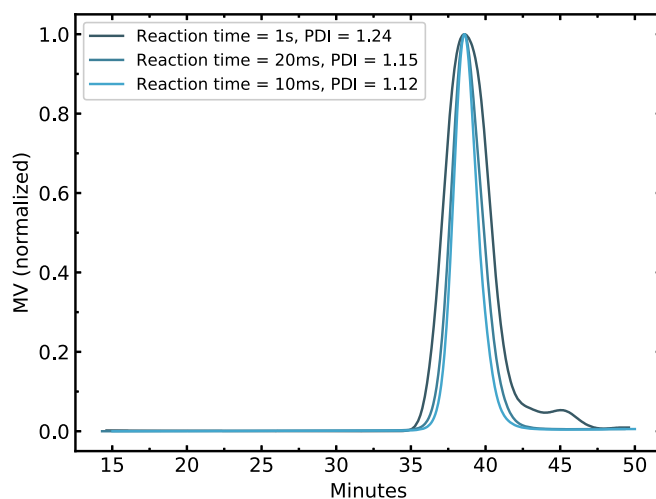


Fig. 4.2 With these graphs from GPC analysis, one can clearly see the impact of reaction time on the dispersity of these polymers. PDI stands for Polymer DIspersity. MV stands for millivolts and is no more than an image of the number of molecules

Then, difunctional (octanediol) and trifunctional (1,1,1-Tris(hydroxymethyl)ethane) alcohols were used, and homopolymers and block-copolymers were all successfully synthesized. A short sum up of the characterization results gives a better idea of the quality of these new polymers (see table 4.1)

Here the results speak for themselves: The system works well and can be used for different reactions. Moreover, it has been tested by other interns on other types of polymerizations and gave promising results.



Initiator type	Block 1		Block 2	
	Conversion	Measured DP	Conversion	Measured DP
Difunctional	89	24	87	19
	89	25		
Trifunctional	90	23	93	18
	88	25		

Table 4.1 Here, the target DP for block 1 was 25, and 20 for block 2

## 4.2 Static mixer

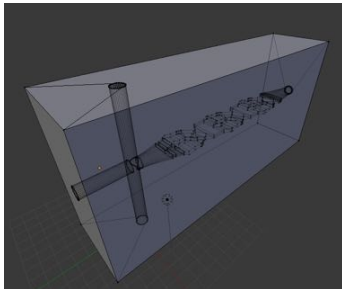
A last element can make this reactor set up better, in particular in terms of mixing efficiency for fast reactions for which timing is very important. In fact, two very simple mixers were used in the reactor: T-mixers (combining 2 fluids) and Cross-Mixers (combining 3 fluids). Properly speaking, they were not really mixer but just hollow connectors. For this reason, it has been observed that the conversion of a reaction could drop unpredictably, especially with cross-mixers. To remedy this situation, a new type of mixer was developed using the 3D modelling software Blender. It has to be noted that only laminar flow was achievable in the reactor. Indeed, the largest Reynold's number was around 700, for a density  $\rho$  approximated to  $1\text{kg}/\text{m}^3$ , a velocity  $u$  of  $0.6\text{m}/\text{s}$  (flow rate  $60\text{mL}/\text{min}$ ), a characteristic dimension equal to the tubing diameter, 1mm and a dynamic viscosity close to water's:  $0.89\text{mPa}\cdot\text{s}$  (see equation 4.1). This is far less than 2300, at which the flow starts to transit to a turbulent behaviour[30].

$$Re = \frac{\rho u L}{\mu} \quad (4.1)$$

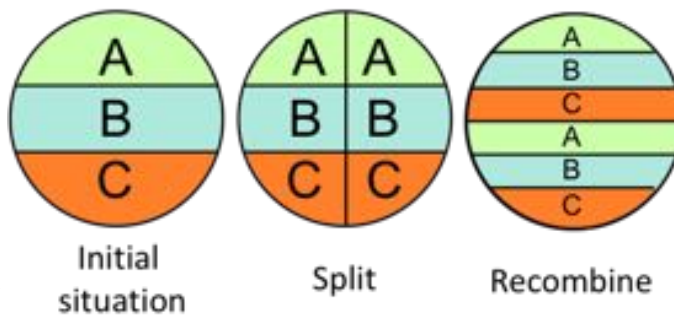
Because of the small diameter of the tubing used, no complex internal structure could be 3D printed to make the mixer. Thus, a 'split and recombine' mixer was chosen for its simplicity and efficiency[31]. The 3D model is shown on Figure 4.3a.

Here, the flow is split and recombined 3 times, which means that for a cross mixer, there are now 24 fluid layers instead of 3 (see Figure 4.3b). The mixing by diffusion is now faster.

After printing, the static mixer was tested with a flow of solvent through it. It rapidly got clogged due to the disintegration of the plastic used for 3D printing. Due to a lack of time, this mixer has not been printed in an other material, and is not ready to use yet.



(a) 3D view of the split and recombine mixer adapted to the flow reactor. The diameter of the inputs is 1mm.



(b) Split and recombine mixer working principle. A,B and C represent 3 different fluids, assuming no mixing by diffusion

Fig. 4.3

## Conclusion and Future work

During this internship, the existing automated polymer synthesis system has been upgraded in view of implementing a predictive artificial intelligence to guide reactions. It is now possible to synthesise polymers in flow rapidly and precisely. Indeed, the time needed to prepare the reagents has been reduced, and the computer connection with the pumps has been facilitated. The process is now more reliable and all the experimental results are stored in a database. The measurement files and properties can also be integrated to the database, so that all the information about a given synthesised polymer can be found and exploited easily. The web-based user interface enables easy access to flow chemistry to researchers having no knowledge of programming. Moreover, a PID controller has been integrated to the system, to guarantee high quality synthesis. Finally, new polymer architectures have been synthesised, as a proof of the potential and versatility of the system.

Yet, several elements can still be enhanced. Indeed, the interface is specific to a reaction, and a more global structure could be developed. Also, the PID controller may not be working optimally on the polyurethane synthesis system, and it could be extended to live NMR measurement and degree of polymerisation. Finally, the static mixer 3D-printed during the internship is not functional yet.

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# Appendix A

## Supplementary Information

### A.1 Role of the urea in the initiation reaction

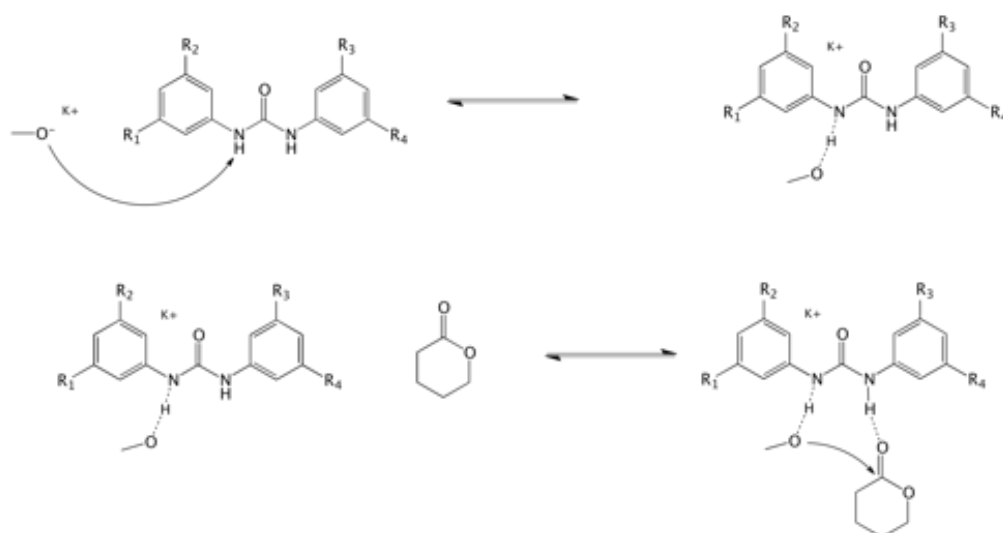


Fig. A.1 Schematic showing the role of the urea in the initiation reaction

At the beginning of the reaction, the initiator is ionic and the urea is not. The Nitrogen atoms of the urea being electronegative, they will attract the electrons around them, leaving their hydrogen with a low electron density. This low electron density will induce hydrogen bondings with the negatively charged initiator and the double bonded Oxygen atom of the monomer, rich in electrons. This will physically gather the initiator and the monomer. In addition, the Oxygen of the initiator is rich in electrons and the double bonded Carbon of the Monomer is completely depleted because of its two electrophilic Oxygen neighbours. A nucleophilic attack will then take place and trigger the initiation.

## A.2 Cleaning of the crude polymer in solution

The crude sample is comprised of the polymer molecules, catalysts, leftover monomers and quenching molecules. In order to clean the sample, one has to isolate the polymer part. To do so, the sample is put in a larger vial of flask and methanol is poured into it. The polymer part is not soluble in methanol, and will precipitate. The other compounds stay in solution. Then, the solid polymer is extracted by centrifugation and filtration.

## A.3 Polymerization with Potassium tert-butoxide (tBuO K)

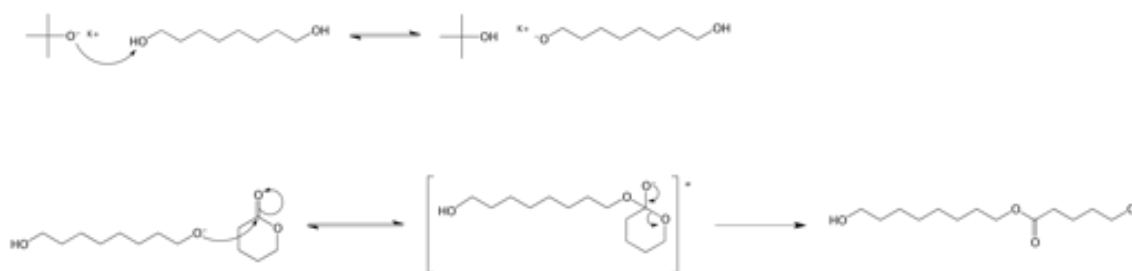


Fig. A.2 Schematic showing the initiation reaction with tBuO K and octanediol, followed by an initiation reaction with  $\delta$ -valerolactone. This reaction also occurs on the second alcohol group

# **Appendix B**

## **Additional requirements**

### **B.1 Planning of the internship**

See Figure B.1

### **B.2 Cost estimation**

For IBM, the cost of having me as an intern is estimated to 75.000\$. This includes 6000\$ of salary, 4000\$ of chemical glassware and syringe pumps and 2000\$ of chemicals. The rest covers personal for the visa and administrative procedures, as well as the lab space and facilities.



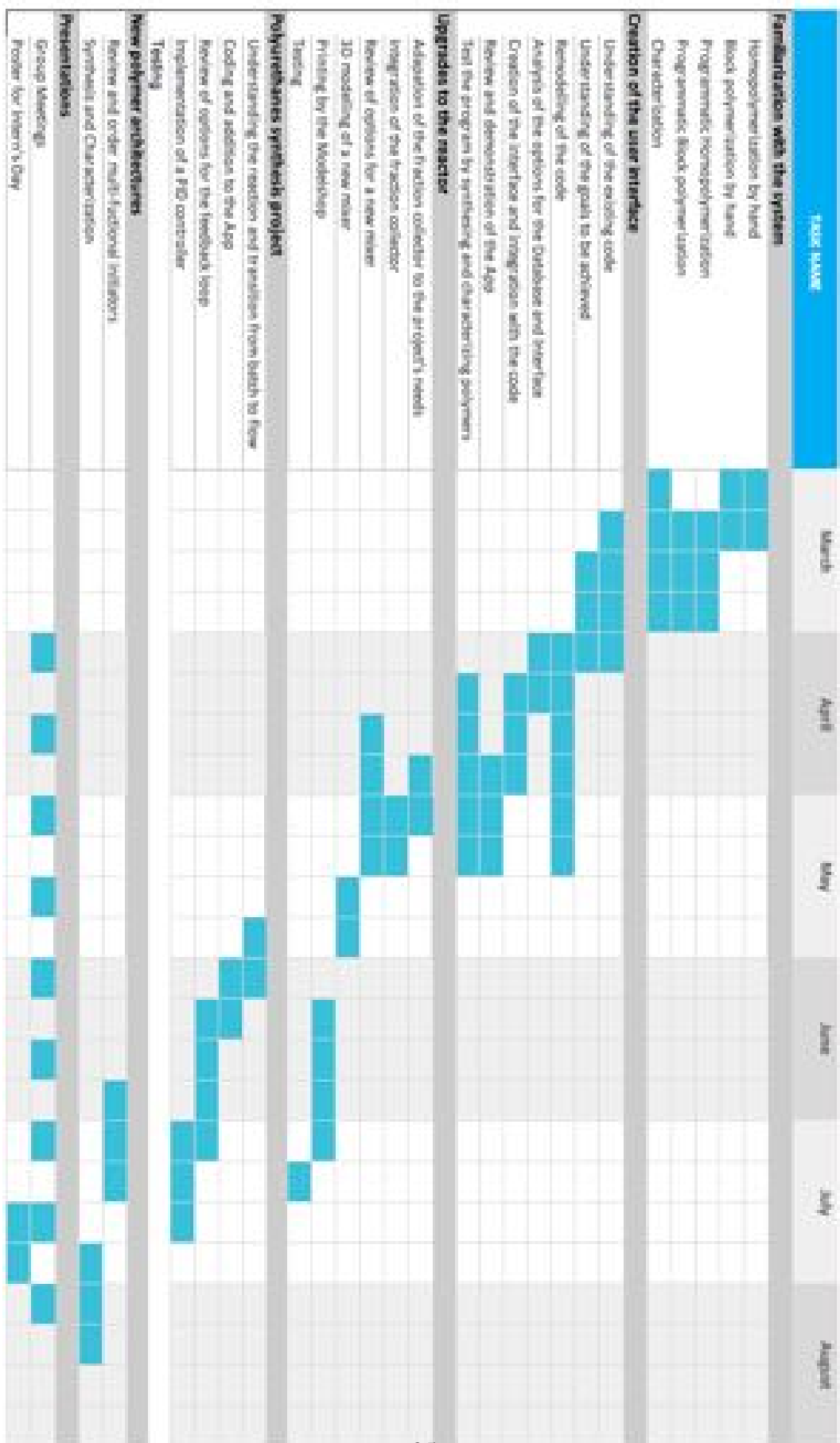


Fig. B.1 GANTT diagram representing the tasks realized during the internship

# Appendix C

## Summary / Résumé

During this internship, the existing automated polymer synthesis system has been upgraded in view of implementing a predictive artificial intelligence to guide reactions. It is now possible to synthesise polymers in flow rapidly and precisely. Indeed, the time needed to prepare the reagents has been reduced, and the computer connection with the pumps has been facilitated. The process is now more reliable and all the experimental results are stored in a database. The measurement files and properties can also be integrated to the database, so that all the information about a given synthesised polymer can be found and exploited easily. The web based user interface enables easy access to flow chemistry to researchers having no knowledge of programming. Moreover, a PID controller has been integrated to the system, to guarantee high quality synthesis. Finally, new polymer architectures have been synthesised, as a proof of the potential and versatility of the system.

Au cours de ce stage, le système de synthèse de polymères existant a été amélioré, en vue d'implémenter un intelligence artificielle capable de guider des réactions. Il est désormais possible de synthétiser des polymères en flux continu rapidement et avec précision. En effet, le temps de préparation des réactions a été réduit, et la connexion des pompes avec l'ordinateur de contrôle a été simplifié. Le procédé est maintenant plus fiable et tous les résultats expérimentaux sont stockés dans une base de données. Les fichiers de mesures ainsi que les propriétés des matériaux peuvent également être ajoutés à la base de données, de façon à centraliser les informations concernant les polymères synthétisés et à faciliter leur exploitation. Une interface utilisateur permet un accès à la chimie en flux aux chercheurs n'ayant pas de connaissance en programmation. De plus, un correcteur PID a été intégré au système pour garantir la qualité des synthèses. Finalement, de nouvelles architectures ont été synthétisées, prouvant ainsi le potentiel et la polyvalence de ce système.