Development of a Low-Cost Multi-Wavelength Inline Detector for Slug Detection in Continuous Flow

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Herein we describe our expansion upon previously published low-cost inline detectors. Using an Adafruit AS7341 10-channel light/colour sensor, a Raspberry Pi, and a white LED we were able to simultaneously monitor infrared and multiple visible spectrum absorption wavelengths. This allowed even challenging colourless slugs within a colourless carrier solvent to be detected and characterised as they progressed through a flow reactor. The sensor data is displayed in graphical form in real-time and stored on the device for reference afterwards.

In this publication we provide details on the design and development of a Raspberry Pi based, low-cost inline detector suitable for use with flow chemistry systems (**Figure 1**).

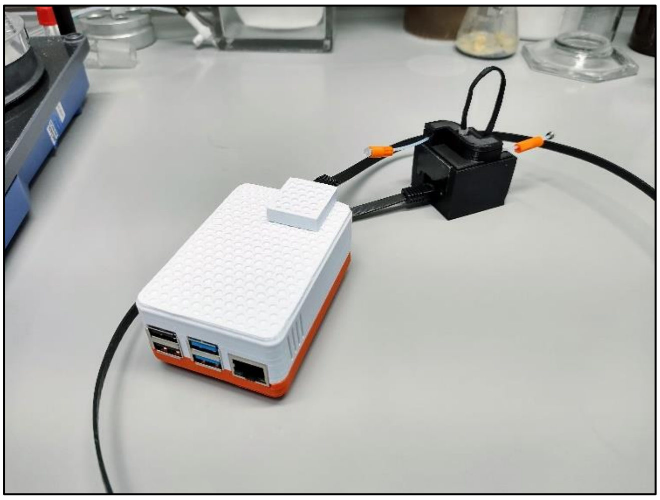

Figure 1 - Our completed design - a low cost detector module connected to a Raspberry Pi computer

Flow chemistry enables reactions to be performed as a continuous process with precise control of reaction conditions such as temperature, pressure, and stoichiometry. [1] Flow reactions can be performed in two regimes – continuous or slug flow. In continuous flow the entire fluidic system is filled with reagents, intermediate or formed product. Conversely in slug flow much of the fluidic system is filled with carrier solvent, small discrete reaction slugs then flow through the system (**Figure 2, A**). Although slug flow reactions are being performed on a much smaller reaction scale, on a microfluidic scale the same reaction is performed. This means at identical positions within the flow reactor an identical profile is observed in both the slug and continuous flow regime. This linear scalability makes slug flow chemistry ideal for library synthesis in flow.

Two critical considerations when performing slug flow chemistry is the timing and profile of the slug. Knowing to a high degree of accuracy where a reaction slug is within a fluidic system that is likely 10 or more times the volume of the reaction slug is crucial to enable effective collection of the product solution. This becomes even more apparent when two reactant slugs need to meet at a t-mixer. For a complete reaction, both slugs need to begin and end with perfect synchronicity (**Figure 2, B**) – where the two slugs do not overlap one reagent does not see the other, meaning no reaction can occur (**Figure 2, C**).

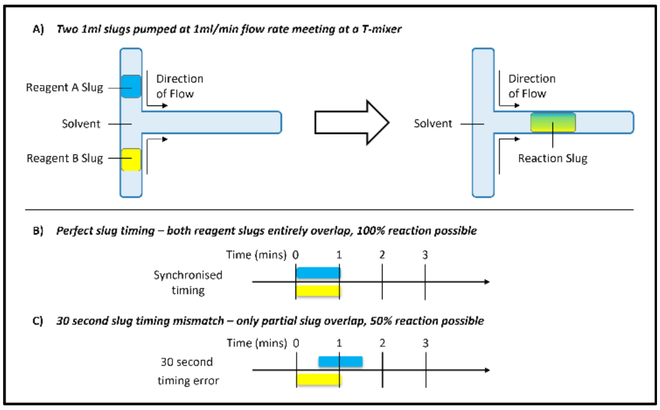

Figure 2 - A) Representation of two reagent slugs meeting at a T-mixer. B & C) The importance of slug timing

Prediction of slug timing within a simple tubular flow reactor can be achieved when both the flow rate and system volume are known to a high degree of accuracy, so long as the flow rate is well controlled. In more complex fluidic systems however – in particular when a solid phase reactor is present – prediction of slug timing can become more difficult to predict due to the chromatographic effect of the stationary phase reaction surface. [2]

If reaction slugs are highly coloured, and see-through PTFE/PFA or similar material tubing is used then slug timing can be corroborated by eye. If either of these factors is not the case however, then inline detection is required to 'see' the reaction slug. Several inline detection technologies are commercially available including inline flow NMR, MS, IR or UV. [3 - 4] All of these commercial examples however are significantly priced and have a sizeable footprint to accommodate within a fume cupboard that likely already contains a large amount of equipment associated with the flow reactor itself. As a result, multiple groups have reported their efforts to overcome these issues, creating low-cost inline detectors relying on the absorbance of visible spectrum light. [5 - 6]

Whilst elegant and likely to generate high quality and sensitive data thanks to the reference measurement being taken, the resultant complex optical setup using a beam-splitter cube and optical fibres of the detector published by Glotz & Kappe [5] makes replication of the literature challenging without sufficient engineering expertise.

The later publication from Höving *et al*. [6] was the basis of a much simpler design. In the Höving *et al.* publication, the flow reactor tube was sandwiched between a coloured LED (Light Emitting Diode) and LDR (Light Dependent Resistor) and held together in a specially designed 3D printed housing. The simplicity of this design made it a much more tangible prospect for us to be able to reproduce. The reliance of the design however, on a single wavelength LED, and typically low sensitivity LDR, made us question if further enhancements could be made to increase the applicability.

With the rise of single board computers such as the Raspberry Pi and Arduino Uno a market has emerged for a wide range of sensors that can easily be incorporated into these systems. For this application, the Adafruit AS7341 sensor looked ideal. [7] The sensor measures light across 10 wavelength 'channels' (IR, 8 visible spectrum wavelengths, and a 'clear' channel that covers that entire spectrum) and can be interfaced with easily using I^2C (Inter-Integrated Circuit). If a white LED was used to irradiate the reactor pipe, then the absorbance of the fluid within the pipe could be determined at multiple wavelengths simultaneously – providing richer data than the previously published inline detectors at a similar low cost.

Measuring absorbance across a wide range of wavelengths would also negate the need to optimise the detector for the substrate you wish to measure. Comparing the absorbance 'fingerprints' of two apparently colourless substances could enable easy identification of colourless slugs within a colourless carrier solvent.

Design and Development

Using the "Version B" flow cell design from the Höving *et al*. publication [6] as a starting point, an initial prototype detector housing was designed in Tinkercad.[8] Although only 2.6 x 1.8 cm in size, the Adafruit AS7341 sensor board is significantly larger than an LDR as used in the previous publication. As a result, modifications were required to encase the

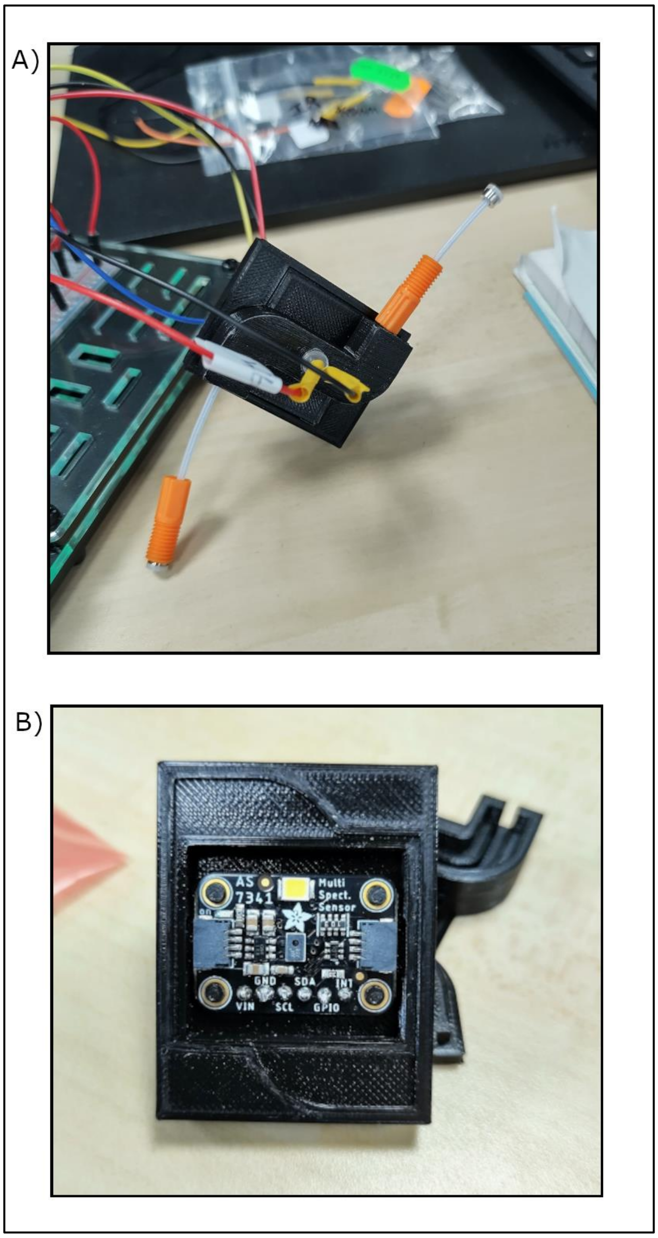

Figure 3 - A) Assembled prototype inline detector B) Sensor within prototype detector module

larger Adafruit AS7341 sensor board to create a light-proof box, whilst exposing the sensor pins to allow circuit prototyping with the Raspberry Pi and a breadboard (**Figure 3**).

To complete the prototype device a white LED was also controlled by the Raspberry Pi, using PWM (Pulse Width Modulation) to optionally control brightness of the LED, allowing the effect of varying irradiation brightness to be tested.

Initial experiments using this prototype device confirmed our hopes. Using the example code provided by Adafruit [7] and pumping test solutions through the flow cell using a hand operated syringe; THF, IPA (isopropyl alcohol) and ethyl acetate showed differences in absorbance, despite all being colourless liquids to the human eye.

To transform the prototype into a useable device that could be housed and operated in a laboratory fume cupboard two major improvements needed to be made: the fragile breadboard prototype circuitry needed to be rigidified and then protected from potential solvent splashes etc, and a better representation of the sensor data also needed to be created rather than using the Adafruit example code.

To consolidate and rigidify the circuitry bespoke printed circuit boards were designed using circuit design software tool Fritzing and then fabricated at a low volume PCB manufacturer, Aisler. A design strategy commonly employed in the single board computer arena was used – a Pi HAT (Hardware Attached on Top) circuit board was designed to contain all the control electronics in an easily attachable/detachable board. A second smaller circuit board was designed for the detector and LED.

On both boards was also included an RJ45 (ethernet) port. An ethernet cable was chosen to consolidate the 6 wires required to power the LED and communicate with the sensor into a single cable (leaving two of the eight wires unused). The choice was made to use a ubiquitous, easily interchangeable cable so that any cable of suitable length could be selected as required dependent on location. This design then allows the detector and Raspberry Pi to be located any distance apart by simply choosing a longer or shorter ethernet cable (**Figure 4**).

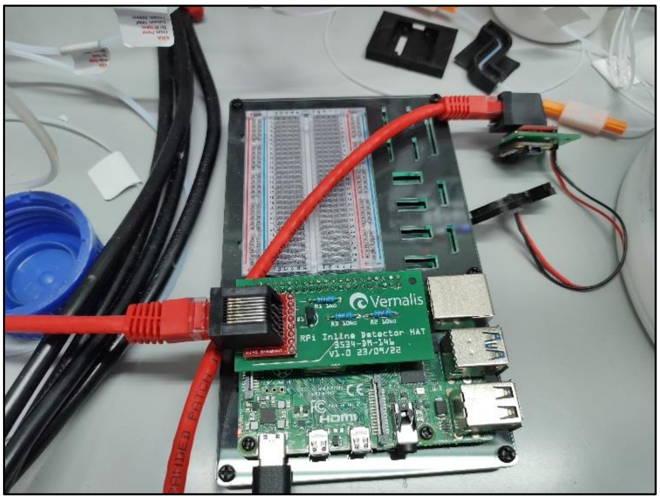

Figure 4 - Custom circuit boards consolidate device electronics, using an ethernet cable to connect the sensor board to the Raspberry Pi HAT

The initial proof-of-concept code supplied by Adafruit displays the sensor wavelength readings in a histogram form, refreshing each time sensor values are read. To allow us to see changes in absorption over time, and thus identify when slugs are passing the detector, the data needed to be represented as a line graph – plotting sensor readings versus time (**Figure 6**). This was achieved using the python programming language: using the "pandas" module for tabular data storage and "matplotlib" to output the data in a graphical form. In addition to displaying the plot in real-time, the tabulated data as a .csv file and a .png image of the graph are also stored.

Further testing of the device was carried out to determine the best operation protocol. It was found slugs were much easier to visualise graphically if the sensor channel data is baselined to the absorbance of the system solvent (see **Supplementary Information, Figure S20**). This then results in a clear positive or negative peak in the trace when a slug is passing the detector. LED brightness was also tested, and full power was found to give the best signal to noise ratio (the LED is not too bright to cause saturation of the detector).

Finally, we needed to provide a secure and protective housing for the new detector circuit board and separately the Raspberry Pi computer. The initial prototype 3D printed sensor housing was modified further to accommodate the RJ45 connector now included. The sensor device is an approximately 4.5 x 4.5 x 4.5 cm cube – still a very small footprint and thus very portable, allowing positioning wherever required in a fluidic system (**Figure 5**). For the Raspberry Pi

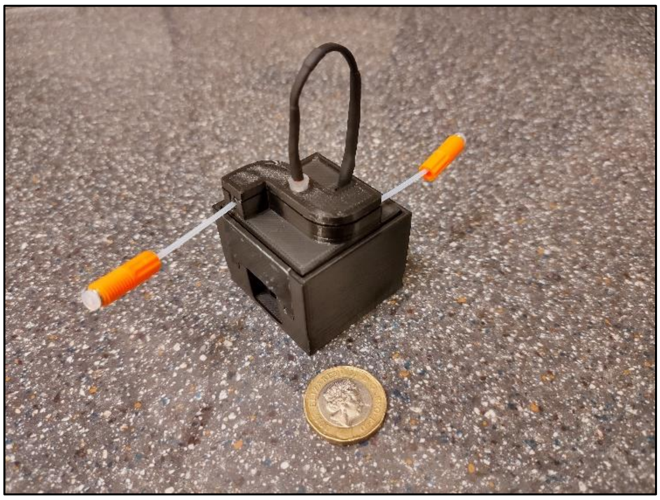

Figure 5 - The finalised detector module. £1 coin for scale

housing, a suitable case available on the Thingiverse was chosen. [9] Minor modifications were made to accommodate the RJ45 connector we introduced, which stands taller than most Pi HAT devices.

With construction of the final design complete we carried out a more thorough validation test using our Syrris Asia flow chemistry system. Running THF as the system solvent we injected sequential slugs of dilute iodine in THF (as a coloured, positive control) followed by IPA and then ethyl acetate. All slugs could be clearly visualised as distinctly different to the THF system solvent – confirming the device works as anticipated (**Figure 6**).

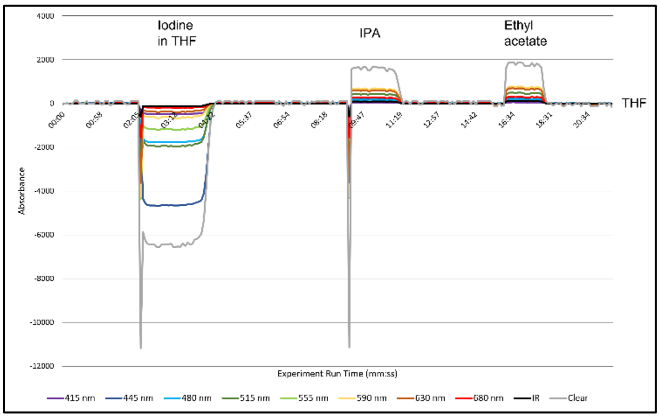

Figure 6 - Graphical output from detector - slugs are clearly detectable versus THF baseline

Conclusion

In conclusion, in this publication we report a significant enhancement on the previously published low-cost inline detector from Höving *et al.* [6] by changing the detector to one that can measure multiple wavelengths simultaneously and changing the irradiation source to a white LED. As a result, we were able to obtain real-time inline spectral data from a flow reactor operating in a slug flow regime, indicating when slugs pass the detector even when undetectable to the human eye.

This device enables slug timing within a flow reactor to be determined in a quick and facile manner. Furthermore, the device could be used to monitor residence time distribution within a system based on shape of the slug peak, along with perhaps estimation of reaction conversion if the optical absorbance profile of starting material and product were known.

Details to construct the device are provided in the supplementary information document, including links to purchase the printed circuit boards directly from the manufacturer we used. Source code, 3D print .stl files and circuit board Gerber files (if you wish to organise manufacture yourself) are all provided on our GitHub repository:

https://github.com/vernalis/digital-lab/tree/main/Inline%20Detector

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