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A Self-Optimising Continuous-Flow Hydrothermal Reactor for Nanomaterial Synthesis

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Abstract

Nanomaterials have emerged as an exciting class of materials with tuneable chemical and physical properties and often enhanced performance when compared to their bulk counterpart. However, the synthesis of nanomaterials remains complex, with a large number of process variables (temperature, reaction time, stoichiometry, pH etc.) having a significant effect on process outcome. Furthermore, traditional optimisation strategies are typically inefficient and often fail to identify factor interactions.

Recent advances in automation, machine learning and optimisation have given rise to the concept of "self-optimisation" in continuous-flow reactors. These integrated cyber-physical reactor systems combine online process analytical technologies with robotics and advanced optimisation algorithms, enabling closed-loop control of reaction outcome and the ability to rapidly optimise a chemical process.

The work presented in this thesis aims to demonstrate the feasibility of self-optimisation in the continuous-flow hydrothermal synthesis of nanomaterials. This Industry 4.0 approach to research and development aims to reduce the timescale necessary for the development of new materials to the point of reliable manufacture. A key objective in this work is the ability to transfer knowledge obtained from bench scale optimisation to pilot and industrial scale production.

A bespoke autonomous reactor platform is presented; capable of generating, analysing and executing experiments without the need for user intervention. Integrating online analytics with process control and machine learning ensures that the system can learn from and predict experiment outcome in real time, continually increasing in confidence over successive iterations.

Following development of the reactor platform, the system was demonstrated across various nanomaterial examples and objectives, including targeted particle size in metal oxides and maximising the surface area in metal-organic frameworks. This work represents the first reported example of self-optimisation in the continuous-flow hydrothermal synthesis of nanomaterials.

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List of Abbreviations

3 Dimensional
4 Dimensional
Attenuated Total Reflectance
Brunauer-Emmett-Teller
1,4-benzenedicarboxylate
Back Pressure Regulator
1,3,5-benzenetricarboxylate
Centred Composite Design
Centred Composite Face
Conventional Electric Heating
Continuous-flow Hydrothermal Synthesis
Core-Shell Nanoparticle
Design of Experiment
Dynamic Light Scattering
Dimethylformamide
Electrochemical
Ethanol
Fourier-transformed Infrared Spectroscopy
Full Width at Half Maximum
Grams
Generation
Genetic Algorithm (Evolutionary Algorithm)
Gas Chromatography
Gaussian Process
Graphical User Interface
Hour
Hong Kong University of Science and Technology
High-Performance Liquid Chromatography
High-Throughput Experimentation
Isopropanol
International Union of Pure and Applied Chemistry
Kilogram
Kelvin

L	Litre
LAI	Light Absorption Imaging
LC	Liquid Chromatography
LED	Light Emitting Diode
М	Molar
MAE	Mean Absolute Error
МС	Mechanochemical
MeOH	Methanol
MIL	Matériaux de l'Institut Lavoisier
min	Minute
mL	Millilitre
ML	Machine Learning
MLR	Multiple Linear Regression
mm	Millimetre
MOF	Metal-Organic Framework
MPa	Mega Pascal
MS	Mass Spectroscopy
MSE	Mean Squared Error
MW	Microwave
nm	Nanometre
NMR	Nuclear Magnetic Resonance
NTA	Nanoparticle Tracking Analysis
OVAT	One Variable at a Time
Р	Pressure
Pc	Critical Pressure
РАТ	Process Analytical Technology
PFD	Process Flow Diagram
PNBU	Pre-Nucleation Building Unit
psi	Pounds per Square Inch
PXRD	Powder X-Ray Diffraction
QD	Quantum Dot
Re	Reynolds Number
rpm	Revolutions Per Minute
RSM	Response Surface Model
S	Second

SC	Supercritical
SEM	Scanning Electron Microscopy
SHYMAN	Sustainable Hydrothermal Manufacture of Nanomaterials
SML	Supervised Machine Learning
SNOBFIT	Stable Noisy Optimisation by Branch and Fit
SOP	Standard Operating Procedure
SPR	Surface Plasmon Resonance
Т	Temperature
Tc	Critical Temperature
TEA	Triethylamine
TEM	Transmission Electron Microscopy
US	Ultrasound
UV-Vis	Ultra-Violet Visible
V	Volume or Volts
XRD	X-Ray Diffraction
ZIF	Zeolithic Imidazolate Framework

Chapter 1: Introduction to Nanomaterials and Optimisation

1.0 Introduction to Nanomaterials and Optimisation

This review highlights two of the key topics which are used extensively throughout this thesis; nanomaterials and their synthesis, as well as automation and optimisation in chemical synthesis. Both of these topics have been areas of intense research in recent years; nanomaterials offer many significant advantages over their bulk material counterparts, while automation and optimisation has potential to significantly streamline the research and development process.

This review therefore exists in two distinct parts. First, an introduction to nanomaterials, their applications and a brief overview of their synthesis methods, with emphasis on the continuous-flow hydrothermal synthesis (CFHS) methods used in this work. Second, an introduction to automation, optimisation and machine learning, as applied to chemical synthesis or processes. This review aims to highlight some of the key reports in literature and provide a useful timeline of how the optimisation process has developed in recent decades, from traditional "one variable at a time" through to fully-integrated self-optimising, autonomous reactors. Furthermore, the optimisation algorithms which have been applied to chemical synthesis are discussed, including their working principles, advantages and limitations.

Finally, the aims and objectives of this PhD are described in greater detail, with overview of the remaining chapters in this thesis.

1.1 Introduction to Nanomaterials

Nanomaterials are defined as materials with dimensions of less than 100 nm in at least one dimension [1]. Nanomaterials have grown in popularity in recent years due to an increased realisation of their range of applications, resulting from a reduction in the achievable primary particle size and adjustable surface chemistry.

Despite the recent advances in both synthesis and applications, nanotechnology is not a new phenomenon and examples can be dated back into ancient civilisations [2]. One such example is the Lycuragus Cup from AD400; embedded with colloidal gold and silver nanoparticles dispersed within the glass, resulting in a colour change which is dependent on the direction of incident light (red or green appearance when front- or back-lit respectively) [3]. It is unlikely that the reasoning for these effects were well understood at the time, however, several manufacturing processes exploited nanotechnology to improve on product performance; Damascus steel swords for instance were renowned for their exceptional strength and sharp cutting edge. While this can be attributed to the highly skilled smiths and their utilisation of suitable materials and techniques, they were almost certainly unaware of the orientated wire-and-tube nanomaterial structures which they were embedding within the blade [4].

Today, nanotechnology is a field of research attributed to the synthesis of materials or building of devices on the nanoscale. The reduction in primary particle size can have significant impacts on the properties of these materials, which can be exploited for application in a wide range of scientific fields; the synthesis strategies and potential for these materials is an area of intense ongoing research and a brief overview of the materials, applications and synthesis methods are discussed throughout this chapter.

1.2 Advantages of Nanotechnology

One of the key and most apparent advantages of nanomaterials stems from their increased surface area to volume ratio. The surface area increases dramatically as particle size decreases, as can be understood from Figure 1, whereby the surface to volume ratio is greatest in the single (smallest) particle, and reduced in the bulk materials. This increased surface area to volume ratio can have dramatic impacts on the material properties and applications as discussed below.



Figure 1: Illustration showing the increased surface area to volume ration associated with particle size [329]

1.2.1 Catalysis

Catalysts can be categorised as homogenous (same phase) or heterogeneous (different phase) and the ideal catalyst exhibits the useful properties of each; heterogeneous catalysts for instance are often limited by their available surface area and interactions, but are easily separable and recoverable from the reaction medium by simple processes such as filtration [5]. An increase in surface area to volume ratio gives rise to an increase in the accessible, and therefore exploitable, surfaces of the material. This feature has dramatic implications in catalytic applications, where the productivity and efficiency is often limited by the available material surfaces.

Further to the available surface area, modifying the size of particles can also impact the electronic state, coordination environment and adsorption energy of surface atoms and reactant molecules [6]. Reducing the particle size to 1-2 nm in metals can result in

electronic structures much closer to that of molecules than the bulk material; for example, the catalytic performance of Au nanoparticles have been explored extensively in relation to their size and shape [7]. Goodman *et al.* demonstrated experimentally that the coordination number of Au nanoclusters supported on TiO₂ was proportional to the particle size, with smaller Au nanoparticles exhibiting a size-dependent electronic environment [8].

1.2.2 Optical & Electrical Properties

It has long been known that nanomaterials exhibit unique and interesting optical properties; one of the earliest scientific recordings is in Faraday's study of gold colloids, following an accidental discovery of the phenomenon while mounting gold leaf onto microscope slides [9]. Today, we understand this to primarily be a product of Surface Plasmon Resonance (SPR); consisting of the collective oscillation of conduction electrons excited by the electromagnetic field of light [10]. Following Faraday's work, Gustav Mie continued the study of the optical effects of nanoparticles, which led to the Mie theory of scattering (also known as Lorenz-Mie or Lorenz-Mie-Debye), describing the scattering of an electronic plane wave by a homogenous sphere [11].



Figure 2: (a) Composite images of 0.6x1.9 mm² QD-LED pixels operating at applied bias voltage of 6, 6, 4, 4 and 5 V for blue, cyan, green, orange and red respectively (right to left). (b) Electroluminescence (Solid) and Photoluminescence (Dashed) spectra of samples from (a). (c) Photograph of chloroform solutions excited by a UV-Lamp with fixed emission at wavelength 365 nm. Reproduced from Anikeeva et al. [14]

As particles approach a critical size, they divert from classical laws of physics and begin to follow quantum mechanics. An example of this is quantum confinement, which is observed as particles approach or are smaller than the wavelength of the incident light; electrons that were previously subject to random motion then become restricted to discrete energy levels [12]. The size, shape and environment of particles all contribute to the variability of the band gap in these discrete energy levels, it is therefore possible to alter the observed opto-electric effects by correctly modifying the particle properties.

While initially observed and studied in noble metals, the opto-electric effects of various other materials have been investigated at small scale. Quantum dots have become an interesting area of increasing research due to the potential applications in photovoltaic devices, quantum dot displays and even in use as fluorescent labels for monitoring drug delivery [13, 14, 15]. Quantum dots of tailored size and shape have been synthesised to achieve precise band gap energies, which interact with specific wavelengths of incident light to absorb or emit energy in the form of absorption and photoluminescence respectively [16].

1.2.3 Magnetic Susceptibility

Certain nanomaterials may also exhibit superparamagnetic behaviour or magnetic susceptibility; the most explored of these are ferrite (iron oxide) nanoparticles in the magnetite crystal structure [17]. Identifying nanomaterials that show superparamagnetic behaviour creates opportunity for applications in catalysis, biosensors and MRI contrast agents, to name a few; the excitement stems from the ability to coat or functionalise Fe₃O₄ nanoparticles with inorganic or organic layers to suit a particular application [18]. Immobilising substances onto magnetite nanoparticles not only enables easy recovery, but the formation of a core-shell particle also serves to potentially reduce the material cost by minimising the volume of inaccessible active substrate, and replacing with typically less costly Fe₃O₄.

1.2.4 Melting Point

Another interesting feature of nanomaterials exists in the variation in melting point of metal nanoparticles relative to their bulk counterpart. While the melting point of bulk metals is normally considered independent of size, there is a direct correlation between the particle size and melting temperature as the particle diameter approaches atomic scale [19]. For example, the melting point of bulk gold is 1064 °C, whereas particles with diameters of 4 and 3 nm have melting points of 581 and 248 °C respectively [20]. This feature extends to other metallic nanomaterials, such as copper where the melting point decreases from 1085 °C in the bulk material to 130 °C in the 3-5 nm diameter range [21]. The ability to depress the melting point of metals by exploiting their size opens opportunities such as the development of nano-metal inkjet formulations for use in printed and flexible electronics. Not only do these formulations require greatly reduced temperatures to sinter particles into an electrically conductive strip, but the small particle size and size distribution aid the fluid dynamic properties of inks [22].

1.3 Synthesis Methods

Many of the properties which make nanomaterials so exciting, i.e. particle size, morphology, surface area, superparamagnetic behaviour, are heavily influenced by the synthesis conditions and methods used. There is no single "best" synthesis method for all materials, as each method will demonstrate particular respective advantages and limitations which may necessitate one synthesis method over another for a given application; a common example is the balance of cost, product quality and time.

Generally, nanomaterial synthesis can be categorised into either "Top-down" or "Bottomup" synthesis methods. "Top-down" refers to the physical pulverisation or leaching of bulk material in the systematic generation of nanomaterials; common techniques in large scale manufacture include mechanical milling, photolithography and anodization [23]. By contrast, "Bottom-up" approaches refer to the assemblage or coalescence of atoms and



Figure 3: Overview of widely-used nanomaterial synthesis methods

molecules to form the nanomaterial through methods such as self-assembly, chemical precipitation and chemical vapour deposition (CVD) [24].

Each of these methods can be further divided into biological, chemical or physical methods [25]. Biological methods are often eco-friendly; they include nanomaterial synthesis by the use of microorganisms, such as bacteria, fungi and algae from aqueous metal salt solutions [26, 27, 28]. While there have been significant improvements in the biological synthesis of nanomaterials in recent years, the process is still inefficient and slow when compared to chemical and physical methods [29]. Further work is needed to develop effective control on particle size and morphology, and so biological methods will not be considered further for use within this work.

Physical methods often constitute the majority of "Top-down" synthesis methods; for example, the bulk material being pulverised down to the required size through mechanical milling. While these methods often exhibit the advantage of being solvent and contaminant-free, they also demonstrate difficulty in consistently achieving the required particle size and shape, resulting in significant waste and poor process economy [24].

1.3.1 Bottom-Up, Chemical Synthesis

Some of the most commonly applied chemical methods for nanomaterial synthesis include sol-gel, co-precipitation and hydrothermal synthesis. Each are discussed in this section, with particular focus on hydrothermal routes, as it will be the primary synthesis method applied in this thesis.

Sol-Gel Methods:

Sol-gel methods are often used in the synthesis of metal oxide nanoparticles, such as TiO_2 , SiO_2 or ZnO. The method is well-studied and has demonstrated the ability to control textural and surface properties in the product materials. These processes typically require five steps; hydrolysis of precursors, condensation, aging, drying and thermal decomposition, as illustrated in Figure 4 [30, 31].



Figure 4: Steps involved in the Sol-Gel method to synthesise Metal-Oxide Nanoparticles. Reproduced from Parashar et al. [31]

One of the most famous examples of the sol-gel method is the synthesis of SiO₂ (Silica) particles in the Stöber process [32]. First described in 1968, the Stöber process is still one of the most widely-used synthesis methods for SiO₂ nanoparticles, owing to the ability to produce particles of controlled, uniform size [33]. A typical synthesis starts with the hydrolysis of silica precursor, often tetraethyl orthosilicate (TEOS), in alcohol, such as ethanol or methanol, with an ammonia catalyst [34]. One of the most attractive features of this method is the simplicity, being a "One-pot" process, with both the hydrolysis and condensation reactions typically occurring in the same vessel. Process conditions, such as concentration, temperature and time, all have significant effects on the particle size and distribution; understanding this enables tuneable synthesis.

However, this method requires significant aging times, often hours or days, which limits the potential scalability of this process [35]. Despite this, sol-gel methods remain a popular option for laboratory nanomaterial synthesis, largely due to the enhanced level of control without the need for specialised process equipment.

Co-Precipitation Synthesis:

Co-precipitation is often considered to be the solid-state analogue to the sol-gel method [36]. Similar to sol-gel, co-precipitation begins with dissolved metal salt precursors; a

precipitation agent, such as base, is then added, resulting in super-saturation of constituent ions and inducing formation of the solid-phase product. Co-precipitation is often fast, with simultaneous occurrence of the nucleation, growth and agglomeration phases that are observed in sol-gel methods [37]. Often, a chemical reaction is necessary to achieve the super-saturation conditions required, as given in the example of ferric oxide nanomaterial synthesis [38].

$$XAy_{(aq)}^{+} + yBx_{(aq)}^{-} \rightarrow AxBy_{(s)}$$

 $Fe_{(aq)}^{2+} + 2Fe_{(aq)}^{3+} + 80H_{(aq)}^{-} \rightarrow Fe_{3}O_{4(s)} + 4H_{2}O_{(l)}$

Co-precipitation has previously been explored for the synthesis of magnetic iron oxide nanoparticles, investigating the effect of reaction temperature and base on particle size and morphology [39]. The main advantages of the co-precipitation method include its speed and simplicity, however, the particle size and morphology have been shown to be heavily dependent on process conditions and the precursors used in synthesis [40]. While sol-gel methods typically utilise short nucleation and long growth periods, co-precipitation methods are unable to control the formation steps independently, often resulting in wide particle size distributions; furthermore, the method cannot be applied if multiple reactant species have significantly different precipitation rates.

Hydrothermal & Solvothermal Synthesis:

Hydrothermal (and solvothermal) synthesis techniques involve the heating of a precursor solution above its typical boiling point within a sealed or pressurised container. Heating water, or other solvents, above their standard boiling point opens up possible chemistries which would not normally be available or practical. Hydrothermal routes therefore enable a great deal of synthesis flexibility through good control of process parameters, such as temperature and pressure [41].

As water is heated to near critical point ($T_c = 374$ °C, $P_c = 22.1$ MPa), the hydrogen bonds between molecules begin to break down, changing from a polar liquid to having reduced pH and a low dielectric constant, as observed in Figure 5. The increased dissociation constant, K_w, results in the breakdown of water molecules to form H⁺ and OH⁻ ions. In these conditions, non-polar molecules can be dissolved, while previously soluble inorganic metal salts become insoluble; it is this principle that forms the basis of hydrothermal synthesis of nanoparticles. The choice of solvents, reagents, additives or pH then enables control of particle size or morphology, and achieving products which may not be attainable by other methods [42].



Figure 5: Simplified Phase Diagram of Water (top) and selected properties of supercritical water (bottom). Reproduced from Dunne et al. [47]
By exploiting the rapid change in solubility described above, inorganic nanomaterials can be formed from the precipitation of metal salt precursor solutions. Under supercritical or near-supercritical conditions, the high concentration of OH⁻ species leads to almost immediate hydrolysis followed by dehydration, generating metal oxide solids which precipitate out of solution due to super-saturation [43]. One of the earliest examples of hydrothermal synthesis for nanomaterials was in 1988 by Ioku *et al.* for the synthesis of hydroxyapatite [44]. Since then, hydrothermal and solvothermal methods have been used extensively for the synthesis of inorganic and metal-organic nanomaterials.

A key aim in nanomaterial synthesis is achieving controlled size and size distribution of particles. Many 'bottom-up' synthesis methods are described through sequential nucleation, agglomeration and growth steps; for effective size control, the process must be designed to ensure these phases do not coincide. In hydrothermal synthesis, this can be likened to the LaMer model of nucleation and growth, first described in 1950 and illustrated in Figure 6 [45, 46]. Upon heating, there is an increase in solution concentration, resulting in a degree of super-saturation; when the concentration exceeds a critical threshold, nucleation occurs. Assuming nucleation occurs at a faster rate than precursor formation, the concentration then falls below the nucleation threshold, however particle growth can continue [47]. Nanoparticle growth can be considered a function of multiple pathways [47, 48]:

- Monomer Addition: deposition of further precursor onto existing nuclei
- Ostwald Ripening: small nuclei dissolve back into solution, which are then deposited on larger, more energetically favourable particles
- Coalescence: multiple nanoparticles combine into larger particles



Figure 6: LaMer model of nucleation and growth. Reproduced from Dunne et al. [47]

Understanding the formation and growth steps of nanomaterial synthesis enables strategies to favour or limit particular transitions. For example, sudden nucleation caused by rapid heating, followed by almost immediate quenching, would favour nucleation and minimise particle growth, resulting in small particles with narrow size distribution. Identifying and pursuing synthesis strategies such as this then leads to the development of sophisticated reactor designs, particularly when considering reaction scale up.

Hydrothermal methods are considered a 'green' alternative to nanomaterial synthesis, chiefly due to the use of water as both a solvent and driving force for nucleation. The concept is fast, scalable and can be achieved at moderate temperature and pressure, when compared to other means.

1.3.2 Batch vs Continuous-Flow

The demand for nanomaterials has increased dramatically in recent decades, creating the need for scalable, economical and sustainable process synthesis. Traditional hydrothermal synthesis of nanomaterials requires the batch heating of a closed container over long reactions times, often hours or days. The high pressure required to maintain liquid or supercritical phase means that thick-walled, Teflon-lined stainless steel autoclaves are often necessary for batch synthesis.

In addition to long reaction times, batch technologies are not easily scalable; a common issue faced in the scaling of batch manufacture is the poor translation of heat and mass transfer from laboratory to plant scale. This is particularly troublesome in nanomaterial synthesis as precursors are subjected to a temperature gradient for extended periods of time. Allowing precursor solutions to remain above the nucleation threshold unnecessarily can lead to the simultaneous nucleation and growth of nanomaterials, resulting in uneven growth rates and increased particle size distribution.

Continuous flow chemistry has become a major enabling technology for synthesis over the last two decades. Bridging the gap between chemistry and chemical engineering, continuous-flow processes demonstrate many advantages over traditional batch counterparts, such as improved control over heat and mass transfer, simpler scale-up and reduced batch-to-batch variability [49]. Transfer of batch synthesis to a continuous process is often straightforward, with many of the same concepts, i.e. stoichiometry and reactor volume.

Historically, hydrothermal and solvothermal reactions were carried out in batch processes, which limited their potential scalability. Continuous-flow hydrothermal synthesis (CFHS) has become an area of increasing interest due to improved process control and significantly reduced reaction times. The process is relatively simple and environmentally friendly, requiring only water as the solvent medium, and has been proven for the production of inorganic nanomaterials [50].

The earliest demonstration of CFHS for nanomaterials is by Adschiri *et al.* in 1992 for the synthesis of seven different metal oxides, from ten different respective salts [43]. The simplest design concept for CFHS constitutes a metal salt solution being heated to near-or supercritical conditions to drive nucleation; however, the extended time at elevated temperature results in the same overlap of nucleation and growth that is observed in batch processes. To solve this, Adschiri *et al.* proposed the mixing of ambient temperature metal salts with a pre-heated flow of water, enabling the rapid heating and cooling of precursors and resulting narrow size distribution [43, 51]. The schematic of this design is shown in Figure 7.



Figure 7: Experimental Apparatus used by Adschiri et al. for the synthesis of metal oxide nanoparticles using CFHS [52]. PG: Pressure Gauge. TC: Themocouple.

Using metal salts of concentration up to 0.10 M and flowrates up to 10 ml.min⁻¹, Adschiri *et al.* were successfully able to produce nanomaterials on the scale of grams per hour (up to 10 g.h⁻¹) [52].

While the overall process proved successful, a key limitation has since been identified in the use of a TEE-piece in lieu of a bespoke reactor, which led to poor mixing regime and resulting in process blockages. Work by Cabañas and Poliakoff in the early 2000's, as part of the Clean Technology Group at the University of Nottingham, initially produced inconsistent products and several experiments were stopped prematurely due to blockages in the process [53]. Figure 8 shows the flowsheet used for nanoparticle synthesis by the Clean Technology Research group [50]. In this design, "R" denotes a Swagelok® TEE-Piece reactor of 0.71 cm internal diameter; supercritical water enters *via* the side of the TEE-piece, while aqueous metal salt is introduced through the top.



Figure 8: Flow diagram for continuous supercritical reactor system used by the Clean Technology Group at University of Nottingham [50]. PH: Pre-heater. R: Reactor. P1: Pump 1. P2: Pump 2. WC: Water cooler. BPR: Back-pressure regulator. F: Filter. P: Pressure controller/transducer.

Subsequent work by the same group, in conjunction with the School of Chemical, Environmental and Mining Engineering (SChEME), investigated the mixing regimes and fluid dynamics within the process, with the aim of developing reactor geometries that would be more suited to particulate synthesis. Blood *et al.* developed the process of Light Absorption Imaging (LAI) in place of CFD modelling; the complex non-Newtonian behaviour of supercritical water meant that CFD was not well-suited to investigating the mixing regime [54]. LAI uses fluids with similar relative densities to supercritical water and the metal salt precursor, in this case methanol and 40 %w/w sucrose solution with methylene blue dye respectively; measuring the light absorbance from the dye before,



Figure 9: Steady-state concentration map using Light Absorption Imaging technique for continuousflow hydrothermal synthesis using a TEE-Piece reactor. Reproduced from Blood et al. [54]

during and after mixing then enables quantitative analysis of the mixing efficiency.

Following refinement of the technique, work by Lester *et al.* highlighted the significance of the relative densities of the supercritical water and metal salt streams; this factor was key in identifying suitable reactor geometries and developing the final patented *Nozzle Reactor* design [50, 55]. Figure 10 shows the schematic of the *Nozzle Reactor* design, illustrating the counter-current mixing regime between the supercritical fluid and metal salt streams

[56]. Several key engineering criteria were used to establish this design; including instantaneous mixing of the two streams, immediate heating of the metal salt stream, a



Figure 10: Schematic of the final Nozzle Reactor design, highlighting the flow profile of both streams and heating/cooling profile [50]

short average residence time to minimise particle growth and strong downstream eddies to transport products away from the reactor [50].

This reactor design has been demonstrated extensively for nanomaterial CFHS research at the University of Nottingham, successfully producing a wide variety of oxides, sulphides, phosphates, metals and metal-organic framework nanomaterials [47, 57, 58, 59, 60].

Following identification of the poor suitability of TEE-piece reactors in CFHS, and development of the LAI technique, several other groups have investigated reactor geometries for nanomaterial synthesis; the most similar of these designs exists in the Darr group at University College London [61]. Darr contributed to the original design of the counter-current reactor, but suggested in later work that certain conditions (high scW flow and low metal salt flow) would lead to jetting at the mixing point [62]. Rotating the reactor about the horizontal axis then led to the proposed Confined Jet Reactor [63]. Darr *et al.*

argued that the co-current mixing regime results in more instantaneous mixing and improved scalability, demonstrating pilot scale production at >1 kg.h⁻¹ of dry weight equivalent nanomaterials [64].



Figure 11: Geometry of the Confined Jet Reactor, showing a co-current mixing regime with scW and metal salt precursor flowing vertically upwards. Reproduced from Gruar et al. [64]

Despite Darr's suggestions of limitations, the counter-current mixing technology has demonstrated remarkable scalability and has been implemented in the large-scale manufacture of nanomaterials through the University of Nottingham spin-out company, Promethean Particles, as part of the SHYMAN (Sustainable Hydrothermal Manufacture of Nanomaterials) project [65, 66, 67]. To date, this is the largest multi-material, continuous-flow hydrothermal synthesis plant for nanomaterial production globally, with capacity of up to 1000 tons per annum of dry weight equivalent product [68].

1.4 Nanomaterials in Continuous-Flow Hydrothermal Synthesis

Many of the methods in continuous-flow hydrothermal synthesis have primarily been developed for the production of metal oxides. Adschiri *et al.*'s pioneering work demonstrated the feasible production of seven different metal oxides from various constituent metal salts [43]. However, the technology has been further refined over the last two decades and now a wide range of materials have been successfully synthesised using these methods.

1.4.1 Metal Oxides

Metal oxide nanomaterials are some of the most widely-produced and utilised nanomaterials in industry today, owing to a wide range of potential applications as pigments, semi-conductors, catalysts and medicines to name a few [69].

Nanomaterial CFHS was first demonstrated and then further developed using a small number of metal oxide examples; however, later research has demonstrated the suitability of CFHS for the production of ZnO, Co_3O_4 and mixed-metal oxides, such as BaTiO₃ and various Ni-Co materials [70, 71, 72].

Iron oxide nanomaterials have been an area of significant interest due to their low toxicity, low cost and change in magnetic behaviour associated to particle size and phase [73, 74]. Both magnetite and maghemite (Fe₃O₄ and γ -Fe₂O₃ respectively) exhibit superparamagnetic properties, which creates potential for biomedical applications such as magnetic resonance imaging (MRI) contrast agents. Hematite (a-Fe₂O₃) is the alpha polymorph of maghemite, with the same chemical composition but different crystal structure; by contrast, hematite shows only very weak magnetic susceptibility [75].

Further details of metal oxide synthesis will be outlined later in this work in Chapter 5, however, the general expression for the formation of metal oxides using supercritical water is as follows (L = counter ion, e.g. (NO₃)) :

Hydrolysis: $ML_x + xOH^- \rightarrow M(OH)_x + xL^-$

Dehydration: $M(OH)_x \rightarrow MO_{x/2} + \frac{x}{2}H_2O$

The first reaction step involves the hydrolysis of the metal salt to produce the metal hydroxide, followed by dehydration to the metal oxide. Various metal salts follow this reaction route, although Adschiri *et al.* noted that some salts result in different products, for instance use of $Fe(NO_3)_3$ results in hematite, while $Fe(NH_4)_2H(C_6H_5O_7)_2$ at the same conditions resulted in magnetite [43]. It was proposed that the thermal decomposition of citrate produced CO gas, which then partially reduced the Fe^{3+} cations, highlighting the significance of precursor selection.

Metal oxides produced by CFHS often have a roughly-spherical morphology, with particle sizes that typically increase with reaction temperature [47]. This suggests a fast nucleation mechanism and it is likely that growth can be attributed to the additional time required for the process stream to cool down from higher temperatures.

1.4.2 Metals

Metallic nanoparticles have drawn much interest for applications in both biotechnology and wider engineering. Noble metal nanomaterials, such as gold, silver or platinum, have been applied in contrast agents for medical imaging or in drug delivery systems. Gold in particular is the most common, owing to unique physico-chemical properties, and ability to synthesise targeted sizes and morphologies with relative ease. Au nanoparticles, like other noble metals, exhibit the phenomenon surface plasmon resonance, as previously described. The combined absorbance and scattering of light (extinction) in both the visible and near-infrared (NIR) regions is proportional to the particle size and shape, making it useful in computed tomography (CT) scanning and photothermal therapy [76, 77].

The most commonly used synthesis method for colloidal Au nanoparticles is the chemical reduction of AuHCl₄ with aqueous citrate solution, known as the Turkevich method [78]. Aside from simplicity, the popularity of this method stems from the ability to finely tune particle size, size distribution and morphology by altering process conditions, such as precursor concentration, temperature and reaction time [79]. Recent research has shown the ability to synthesise Au nanoparticles from biological sources using hydrothermal synthesis [80, 81].



Figure 12: Transmetalation process of Ag onto CuNPs to form Cu-Ag Core-shell Nanoparticles. Adapted from Grouchko et al. [85]

Both Aq and Cu have been successfully synthesised by CFHS, and have demonstrated suitability for dispersion into conductive ink formulations, used in printed electronics [82, 83, 84]. Cu nanoparticle dispersions represent a low-cost alternative to Ag or Au, meaning it is potentially better-suited to the electronics industry. However, a known limitation of Cu is the spontaneous oxidation at ambient conditions, which detracts from the conductive properties. A potential solution is the formation of Cu-Ag core-shell nanoparticles (CSNPs), whereby the bulk material constitutes the lower-cost Cu, surrounded by a thin protective layer of conductive Ag. The formation of Cu-Ag CSNPs was successfully achieved by Grouchko et al. using a multi-step chemical method; initially Cu nanoparticles were synthesised through reduction of $Cu(NO_3)_3$ with an excess of hydrazine, followed by transmetalation of the outmost Cu layer with Ag⁺ ions, as illustrated in Figure 12 [85]. The transmetalation process is possible due to the difference in standard redox potential for Ag and Cu, equal to 0.46 V, meaning that Cu metal at the surface of the nanoparticle can reduce Ag⁺ ions. The standard redox potential of metals can therefore be used to guide the transmetalation process for a variety of other bimetallic CSNPs, with examples such as Ni-Cu, Co-Ag, and Co-Ni having been successfully synthesised [86].

Although only previously demonstrated using batch methods, CSNPs could potentially be well-suited to continuous-flow methods; Grouchko *et al.* commented that a key step in the formation of Cu-Ag CSNPs was the removal of hydrazine, which if not removed would result in the formation of free Ag metal particles. As previously discussed, continuousflow methods are well-suited to multi-step synthesis and could potentially simplify the process.

1.4.3 Other Inorganic Nanomaterials

Other commonly synthesised inorganic nanoparticles include sulphides and phosphates. Metal sulphides, such as ZnS, PbS and CdS, are better-known as quantum dot materials, with applications in medical imaging, photovoltaic cells and LED displays [16].

The most well-known synthesis method for quantum dot synthesis is hot-injection, whereby the metal salt is dissolved and heated in a high-boiling point solvent. Nucleation is initiated by the injection of sulphur-containing compounds, and growth is controlled through successive precursor injections.

Hydrothermal synthesis represents a much greener alternative to the hot-injection method, largely due to the use of water as a solvent, in place of the high-boiling point solvents. Dunne *et al.* were the first to demonstrate CFHS for metal sulphide nanoparticles, using the counter-current mixing reactor previously described. By varying process parameters to favour either nucleation or growth mechanisms, Dunne *et al.* were able to successfully control the particle size of ZnS, CdS, PbS, CuS, $Fe_{(1-x)}S$ and Bi_2S_3 nanomaterials [60].

The synthesis of metal sulphides *via* CFHS presents the challenge of identifying a suitable sulphur source to promote synthesis of the metal sulphide in preference to the metal oxide. Although H₂S or HS⁻ can be produced by the hydrothermal breakdown of many common sulphur-containing compounds, the high toxicity and volatility of these materials limit their practicality. Dunne *et al.* demonstrated the suitability of thiourea as a H₂S precursor, identifying the advantages of being odourless and water-soluble; the reaction scheme for the synthesis of metal sulphides using thiourea is shown below:

$$NH_2CSNH_2 \leftrightarrow NH_4SCN$$

 $NH_4SCN + 4H_2O \rightarrow HS^- + (NH_4)_2CO_3^- + H_2O$

$$M^{x+} + xHS^- \rightarrow MS_{x/2} + \left(\frac{x}{2}\right)H_2S$$

When compared to the co-precipitation method described earlier, OH⁻ ions are substituted by HS⁻ for precipitation of the solid compound. By generating HS⁻ *in situ*, Dunne *et al.* were able to promote either the nucleation or growth mechanism as required; pre-heating of the thiourea solution in the reactor Downflow meant that an excess of HS⁻ was available at the mixing point, favouring nucleation. Whereas growth could be favoured by the mixing of cold thiourea and metal salt solutions prior to contact with the superheated water flow. The two methods are illustrated in Figure 13.



Figure 13: Simplified schematic of counter-current continuous flow reactor used for metal sulphide synthesis. Reproduced from Dunne et al. [60]

Phosphate nanomaterials have also seen growth as an area of research in recent years, most prominently due to the potential of lithium iron phosphate (LiFePO4) as a next-generation material for batteries [87]. LiFePO4 exhibits several major advantages to traditional metal oxide cathode materials, most notably its low toxicity, alongside a high stability and capacity. While bulk LiFePO4 suffers relatively low conductivity in electrochemical systems, nano-LiFePO4 has potential to improve this by controlling particle size and shape to improve the Li⁺ ion diffusion path length [88]. Several groups have demonstrated the suitability of CFHS for the synthesis of LiFePO4 nanomaterials, and have further investigated the effect of various process conditions, such as precursor

concentration, residence times from 9-72 seconds and also temperature between 300-400 °C [89, 90].

The hydrothermal synthesis of LiFePO₄ remains challenging due to the potential formation of iron oxide by-products, which is particularly apparent under sub-critical conditions, although carefully degassing solvents and utilising supercritical conditions improves upon the product purity. In 2011, large-scale CFHS was realised as Hanwha Chemicals completed construction of the world's first supercritical hydrothermal plant for the synthesis of LiFePO₄ nanomaterials, with capacity of up to 100 tonnes per annum [91, 92].

Another highly-investigated phosphate nanomaterial in CFHS is hydroxyapatite (calcium phosphate, Ca₅(PO₄)₃OH), with applications in biomedicine as a potential replacement for damaged bone [93]. The first reported synthesis of hydroxyapatite in CFHS is from Chaudhry *et al.* in 2006 using the counter-current mixing reactor previously described. [94] Since then, further research has investigated the effect of pH and temperatures between 200-400 °C on particle size and shape, as well as consideration to doped materials [95, 96].

1.4.4 Metal-Organic Frameworks

Metal-Organic Frameworks (MOFs) have emerged as a promising class of highly porous, crystalline materials, consisting of metal ion centres co-ordinately bonded to organic ligands, forming 3D periodic networks with large pore volumes and exceptionally large specific surface areas – ranging into the 1000's of m^2g^{-1} [97].

Part of the scientific excitement surrounding MOFs is the ability to modify, or 'tune' the material by altering its composition and structure through the correct selection of metal ion, organic ligand or process conditions, creating a potentially infinite number of MOFs to be synthesised [98, 99]. As such, MOFs have huge potential in applications such as gas storage and separation [100, 101, 102], catalysis [103], energy storage [99, 104] and drug delivery [105] to name a few.

MOF components are referred to as primary and secondary building units, representing the metal ion and metal-oxygen-complexes respectively. In most conventional synthesis methods, a metal salt or oxide is used as a precursor; with the exception of electrochemical synthesis which uses metal rods. The organic linker, used to connect metal ion centres, must contain a suitable functional group, capable of forming a coordinate bond; such as carboxylate, amine or phosphate.

MOF synthesis entails the self-assembly of secondary building units (SBUs) into a 3D periodic network; the secondary building unit (SBU) is responsible for the topology of the MOF [106]. Although advances in MOF research have given rise to successful synthesis with microwave [107], sonochemical [108], electrochemical [109] and mechanochemical [110] techniques, the vast majority of commercially available MOFs are produced under solvothermal conditions in batch processes. Conventional synthesis involves the mixing of metal ion salts and organic linkers in sealed vessels with long reactions times, typically hours or days, under solvothermal conditions to facilitate the nucleation and growth of MOF crystals [111, 112]. The long residence times, combined with the inherent difficulties achieving the reliable scale-up of batch manufacture, result in very few examples of MOFs being manufactured at scale. Furthermore, MOFs which have been produced at industrial

scale are often high-cost, despite their constituents often being relatively simple, low-cost and commercially available.

Gimeno-Fabra *et al.* achieved the first continuous-flow solvothermal synthesis of MOFs in 2012, synthesising HKUST-1 (Cu₃(BTC)₂) and CPO-27(Ni) (also known as MOF-74) [113]. Further examples of MOF continuous-flow hydro/solvothermal synthesis have since been reported, with Rubio-Martinez *et al.* and Munn *et al.* both demonstrating scalable methods with exceptionally high space time yields and product quality that meets or exceeds previous examples [114, 115].



Figure 14: Structures of four prototypical MOFs whose flow synthesis has been studied. The linkers present in the structures are presented above the structures with blue polyhedral units showing the local coordination of metal ions. Reproduced from Dunne et al. [116]

The high potential applicability of MOFs have made them an area of significant research in recent years, with many groups aiming to develop industrially-viable and scalable production methods [116]. While there has been significant success in recent years, our current understanding remains too limited to accurately guide process optimisation to the point of scalable and reliable manufacture for many MOFs. Further to this, the nucleation and growth of MOF crystals is often complex and heavily dependent on several process parameters, such as temperature, stoichiometry, pH, residence time, mixing dynamics and solvent or additive selection [117, 118].

1.5 Overview & Introduction to Optimisation

Process optimisation is the act of improving a specified variable while keeping all others within their respective constraints; a common goal is to maximise yield of a particular product, or to achieve a target yield but minimise cost of production. The goal of an optimiser is to minimise or maximise an objective function, which relates the outcome to the design and operating variables [119].

Assuming time and cost had no measurable impact to R&D, the ideal optimisation method would depict a simple grid search of all parameters at the highest attainable precision; in doing so, the chemist or operator would gain an almost complete insight into the process output in response to the input. However, the time and resources necessary to achieve such a method are simply not feasible, and instead efforts are applied to developing more efficient search methods to better suit given problems.

The oldest and most commonly taught optimisation method is the "One variable at a time" (OVAT) approach, whereby all variables but one are fixed; once the best result is achieved from varying the free input, it becomes fixed at the new value and another is varied. While this approach is methodical, it assumes that the problem is simple or 'flat' in all directions, and there are no interactions between variables [120]. In chemical synthesis, this is often not the case, and OVAT methods fail to identify the true optimum values in complex systems.

Various optimisation methods have been developed in recent decades which aim to improve upon the traditional OVAT approach; these range from statistical methods, such as Design of Experiments (DoE), all the way through to the integration of machine learning and 'self-optimising' processes. This section aims to provide an overview of current optimisation strategies in chemical synthesis, with particular focus on the development of 'self-optimisation' methods which are applied in this work.

1.6 Automation & High-Throughput Experimentation

High-throughput experimentation (HTE) is the process of integrating automation, experimental design and rapid experimentation into scientific exploration. This is often in the form of integrating robotics with suitably designed parallel or serial reactors, with the intention of creating large volumes of data to aid technical understanding [121].

A fundamental part of the HTE strategy is the use of suitable computational methods to control equipment, as well as for the design and analysis of experiments. Recently, Clayson *et al.* published a review discussing the recent advances of HTE in the synthesis, characterisation and optimisation of porous materials [122]. Porous and crystalline materials often exhibit additional challenges in HTE when compared to traditional solution-based flow chemistry; namely the need in many cases to grow, handle and separate or process solids from the as-synthesised materials prior to analysis. Nevertheless, the authors provide an excellent coverage of HTE development in zeolites, MOFs and COFs, despite there being significant differences in the chemistries and challenges for each case.

High-throughput experimentation can focus predominantly on the advancement of experimental synthesis, material processing and characterisation, or computational screening and prediction of experimental outcome. Perhaps the simplest example of a high-throughput reactor would be the implementation of robotics for the handling of either solid or liquid reagents for automated synthesis; this is often combined with multi-well plates (Shown in Figure 15) for the parallel screening of various precursor combinations or process conditions.

Some of the earliest examples of batch HTE for MOF synthesis have been from the Stock group, from 2004 to 2012, screening synthesis parameters and their effect on particle morphology and topology using parallel synthesis multi-claves [123, 124, 118, 111]. The wealth of information available from such methods mean the practice is still used today in a number of MOF optimisation studies [125, 126, 127]. The most extensive study in porous materials, was carried out by Banerjee *et al.* for the high-throughput synthesis of ZIFs for applications in CO₂ capture [128]. Using 9600 different combinations of solvent,



Figure 15: Multiclave used for the screening of synthesis parameters on the formation of metalorganic frameworks. The stainless steel reactor block contains 24 reaction chambers with inserted miniaturized Teflon® *Reactors organized in a 4x6 array [118]*

metal source, linker, stoichiometry and process conditions (temperature range 65-150 °C and time 48-100 hours) in multi-well microreactor plates, the authors were able to discover 16 previously unknown compositions and structures, as well 5 topologies which had previously been unobserved in zeolites.

The simple design and operation of multi-well plates (multiclaves) make them an attractive first step in HTE [123, 124]. However, this technology exhibits limited suitability for the exploration of process conditions, particularly reaction temperature, as it often requires all samples from a single plate to experience similar conditions. The method has advanced beyond conventional heating methods to include examples in both sonicated and microwaves synthesis. These synthesis methods are well-suited to HTE in MOFs as they have been shown to significantly reduce the required reaction time, further increasing the overall speed of experimentation [129, 130].

While these studies have all resulted in large volumes of data for optimisation, including some leading to the discovery of new structures, they are all batch-based and so will suffer the inherent limitations of batch technologies, when considering scale-up or process variability. To date there have been no reported studies of HTE in MOF flow synthesis, which represents a significant potential step forward in this methodology.

1.6.1 High-Throughput MOF Synthesis – Post-processing & Characterisation Depending on the process bottleneck, it is advantageous to apply HTE methodology to either the synthesis or sample characterisation step. However, MOF synthesis and experimentation often results in the formation more than just the targeted crystalline compounds, i.e. impurities or by-products. After a successful synthesis, it is therefore important to be able to isolate the targeted solid product from the surrounding assynthesised material.

MOF separation most often consists of either centrifuging or filtering processes [131], and manually processing each sample would be extraordinarily time consuming. It is no surprise then that some groups have attempted to integrate robotics and automation into the processing stages, including the ability to wash and dry products through customised parallel-filtration devices in preparation for further characterisation [132, 133].

Following any required isolation or washing stages, characterisation of the synthesised product is essential. A commonly applied characterisation method for high-throughput MOF synthesis is powder X-ray diffraction (PXRD); with the ability to rapidly identify sample crystallinity and being the standard analytical method for crystalline materials, PXRD can be well-suited to HTE and fast characterisation for nanomaterials [131]. However, the analysis becomes more complex if diffraction patterns are unable to be recognised automatically; from unknown or overlapping peaks, for instance.

A fast alternative to determine initial success in crystallisation is the use of optical microscopy, as demonstrated in Banerjee *et al.*'s 9600 sample study of ZIFs for CO₂

capture [128]. While this method provides no information regarding composition or application suitability, the ability to screen large numbers of samples using a relatively simple technology means that seemingly successful syntheses can be prioritised for further in-depth characterisation.

Often, the primary characterisation methods used to identify MOF quality surrounds gas uptake and adsorption, but these methods often require several hours and therefore far too time consuming for HTE. In such cases, the only option is to parallelise characterisation to achieve the required throughput [134, 135].

1.6.2 Refining HTE Methods: Optimisation & Machine Learning

One of the main advantages of HTE is that, once developed, the relative cost of additional experiments is low. However, this can in some cases encourage a 'brute force' approach, systematically running experiments in a grid search pattern. This approach can be beneficial when there is a lack of prior knowledge or understanding of the design space, but is highly inefficient as the number of required experiments increases dramatically with the experiment dimensionality [136].

Incorporating reaction feedback into HTE can greatly reduce the need for a blanket approach by prioritising experimental exploration. A relatively simple way to implement this is to run and analyse experiments in groups or batches, before generating the next batch of experiments. This approach has been demonstrated in MOF synthesis by Maniam *et al.* for the discovery of new copper-based MOFs [137]. However, one of the most recent and advanced examples is demonstrated in the work of Moosavi *et al.* who developed a combined robotic microwave synthesis and computational approach to the optimisation of HKUST-1 synthesis [138].

Using sample crystallinity as evaluated by the extent of diffraction peak broadening as their fitness evaluation, the authors use genetic algorithms (GA) across nine variables and three generations to achieve the highest reported surface area for HKUST-1 to date, as 2045 m²g⁻¹. This was achieved through the ability of the GA to mimic the 'chemical intuition' a chemically trained operator would input into the decision-making process. By

analysing both the successful and unsuccessful reactions throughout the 90 experiments, the authors train a supervised machine learning (random forest) model to both predict reaction outcomes to reasonable accuracy, as well as 'learn' the weighted importance of particular variables. A chemist might instinctively develop a similar understanding of the process throughout optimisation, but to consider nine variables simultaneously is almost certainly beyond human capability.

The developed machine learning model can be used to provide experiment predictions *in silico* which then helps to minimise the experimental cost associated to conditions which are expected to perform poorly. A useful feature of the developed model is the ability to give a weighted importance to each variable (See Figure 16), which can be used to explore the high dimensional design space with greater efficiency, or can be potentially applied to similar studies. This is demonstrated in Moosavi *et al.*'s subsequent synthesis of Zn-HKUST-1, successfully producing MOF crystals in far fewer attempts than would have been statistically necessary, albeit with low purity and requiring further optimisation.



Figure 16: Relative impact of 9 parameters on HKUST-1 synthesis, obtained from Random Forest machine learning (Left) & Multidimensional scaling of experimental conditions across successive generations [138]

To date, this approach represents one of the most advanced applications of highthroughput experimentation to MOF synthesis. One of the key benefits lies in requiring no prior knowledge of the chemical system, as well as the ability to learn important features of synthesis from both successful and unsuccessful reactions. To encourage other scientists to work in this way, the authors published their optimisation and machine learning algorithms in a user-friendly web application, the Synthesis Condition Finder (SyCo Finder) [139].

While Moosavi *et al.* have expertly integrated automation, optimisation and machine learning into MOF synthesis, they are limited by their selection of process technology. By establishing their system around a batch process, they will always experience the inherent limitations, such a batch variation and poor scalability. These limitations can be potentially mitigated through the implementation of continuous-flow synthesis, as previously discussed.

1.7 Online Process Analytical Technologies (PATs)

Advances in continuous flow chemistry have been echoed and supported by the development of online process analytical technologies (PATs). The integration of online PATs in chemical synthesis enables the real-time analysis of reaction progress; in addition to secondary features, such as the ability to monitor catalyst activity or precursor quality [140]. Applying this same methodology to flow chemistry further enhances these capabilities, particularly as process conditions can be modified relatively quickly to either improve synthesis outcome or to minimise disturbances.

Online PATs are typically better suited to generating large volumes of data when compared to traditional sampling methods. As such, the process output in response to changes in conditions, i.e. temperature, stoichiometry or flowrate, can be far better explored; this enables the rapid understanding of the process and can be used to develop kinetic and thermodynamic models from real data.

Both 'on-line' and 'in-line' terms refer to methods of analysis which do not require manual transfer from the process; in-line describes systems where all of the process flow passes through the analytical equipment, while on-line methods typically refer to representative sampling [141]. A key distinction between the two setups is the time taken to both analyse the sample and generate data; in-line systems must inherently be able to analyse representative samples faster than the process can be modified or fluctuate in order to be suitable, while on-line systems generally have more time available for analysis and can often provide more detailed information of the sample.

Sans and Cronin reviewed the majority of analytical techniques which have been, or could be, applied to flow chemistry, with the overarching aim of complete integration and the development of 'Self-Optimising' reactors [142]. Many of the techniques described have since been demonstrated in a number of further case studies, and the greatest recent advancement can be attributed to the algorithms employed or reactor designs; this is discussed in greater detail in the remainder of this chapter.

1.8 Self-Optimisation in Chemical Synthesis

Self-Optimisation is the combination of robotics, on/inline analysis and machine learning algorithms for the autonomous optimisation of chemical synthesis. In the simplest sense, this constitutes a reaction feedback loop based on experiment output, i.e. quality, % by-product or yield, where the experiment inputs can be iteratively modified within a defined range of parameters, as illustrated in Figure 17. Using this self-optimising methodology means that complex processes can be optimised with very little *a priori* information; this is particularly useful in the case of nanomaterial synthesis, where the formation mechanisms are not fully understood.



Figure 17: Basic Schematic of a Self-Optimising Flow Reactor. Online analysis is used to score experiments against a predefined objective function. Process conditions (Temperature, flowrate etc.) are modified iteratively, dependent on the selected optimisation and machine learning methods.

The closed-loop design of this system enables iterative optimisation, whereby the experiment outcome can be scored against a predefined objective function and new synthesis conditions can be generated for subsequent experiments. A key feature of this methodology is the ability to optimise these processes with almost-no user involvement, freeing the chemist or user to focus on more skilled tasks.

The choice of machine learning and optimisation methods determine the proportion of experiments devoted to exploration or exploitation; many optimisation methods utilise random exploration, although recent works in literature have begun to investigate more intelligent and efficient exploration methods. Table 1 gives an overview of automation and self-optimisation studies available in literature, from Krishnadasan *et al.*'s 2007 study of CdSe quantum dots nanoparticles optimised using inline spectroscopy in combination with SNOBFIT [143]. Many of the self-optimisation examples in literature utilise solution flow chemistry, using online techniques such as HPLC, GC or MS to attain quantitative information regarding the yield or reaction by-products; while this is inherently unsuitable for the formation of particles, it provides useful reference for the use and implementation of advanced algorithms, such as TSEMO or Bayesian optimisation [144, 145].

Recently, UV-Vis spectroscopy has been used extensively as an inline analytical method for particle size tuning in quantum dot synthesis [146, 147, 148, 149, 150]. While the reaction process is somewhat similar to that of Krishnadasan *et al.*, there have been significant advances in the machine learning and optimisation methods applied; particularly in the generation of new conditions and building of suitable models to conduct experiments *in silico* to reduce experimental cost.

A large variety of methodologies and optimisation algorithms exist and in many case studies, several algorithms may be suitable. To better understand the advantages, limitations and suitability of these algorithms to particular chemical examples, a brief background and the functionality is discussed in this chapter. Table 1: Timeline of Self-Optimised experiments reported in literature from Jan 2007 to March 2021, showing PAT and Algorithms used. First author is shown. PAT: Process analytical technology. DoE: Design of Experiments. TSEMO: Thompson Sampling Efficient Multi-Objective. NNE: Neural Network Ensemble. MOAL: Multi-Objective Active Learning. SMSIM: Super-Modified Simplex. HPLC: High-Performance Liquid Chromatography. NMR: Nuclear Magnetic Resonance. MS: Mass Spectroscopy. FTIR: Fourier Transform Infrared. GC: Gas Chromatography. SEC: Size Exclusion Chromatography.

Author	Year	Process	PAT	Algorithm	Ref
Krishnadasan	2007	Synthesis of CdSe nanoparticles	Flow UV- Vis	SNOBFIT	[143]
McMullen	2010	Knoevenagel condensation	HPLC	Simplex, SNOBFIT, Steepest Descent	[151]
McMullen	2010	Heck reaction	HPLC	Nelder-Mead Simplex	[152]
Parrot	2011	Methylation in scCO ₂	GC	SMSIM	[153]
Moore	2012	Paal-Knorr	Flow FTIR	Steepest Descent, Conjugate Gradient	[154]
Skilton	2013	Solvent-free methylation of 1- pentanol	Flow FTIR	SMSIM, SNOBFIT	[155]
Ley	2015	3D Heterogeneous catalytic reaction	Flow FTIR	Modified Simplex	[156]
Sans	2015	Imine formation	Flow NMR	Nelder-Mead Simplex	[157]
Reizman	2016	Suzuki-Miryaura	LC / MS	DoE-Based	[158]
Holmes	2016	Amide coupling + elimination	HPLC	SNOBFIT, DoE	[159]
Zhou	2017	Pomeranz-Fritsch	MS	Deep Reinforcement Learning	[160]
Echtermeyer	2017	Pd-Catalysed C-H activation	Flow UV- Vis & GC	Model-based DoE, MOAL	[161]
Hsieh	2018	Photo-redox dual catalysed cross- coupling	HPLC	DoE-based	[162]
Cortés-Borda	2018	Synthesis of natural carpanone	HPLC & Flow NMR	Custom Nelder-Mead Simplex	[163]

Jeraal	2018	Claisen-Schmidt condensation	HPLC	SNOBFIT	[164]
Poscharny	2018	Photochemical reaction of benzophenone and furan	Flow FTIR	Modified Simplex	[165]
Schweidtmann	2018	SNAr & N- benzylation	HPLC	TSEMO	[144]
Cherkasov	2018	Nitrobenzene hydrogenation	GC	SNOBFIT	[166]
Rubens	2019	Polymer synthesis	SEC	Custom	[167]
Waldron	2019	Esterification between benzoic acid and ethanol	HPLC	Model-based DoE	[168]
Epps	2020	Synthesis of metal- halide quantum dots	Flow UV- Vis	NNE, SNOBFIT	[146]
Li	2020	Discovery of chiral inorganic perovskite nanocrystals	Flow UV- Vis	SNOBFIT	[147]
Li	2020	Inverse temperature crystallisation of perovskite	Flow UV- Vis	Various	[148]
Salley	2020	Shape programmable synthesis of Au nanoparticles	UV-Vis	Genetic Algorithm	[169]
Wang	2020	Parallel millifluidic synthesis of quantum dots	Flow UV- Vis	Nelder-Mead Simplex	[149]
Burger	2020	Photocatalyst mixtures	GC	Bayesian	[145]
Abdel-Latif	2021	Multistep quantum dot synthesis	Flow UV- Vis	NNE	[150]
Hall	2021	Au-catalysed phenol reduction	Flow UV- Vis	SNOBFIT	[170]

1.9 Optimisation & Machine Learning Algorithms

Broadly, optimisation algorithms are described as either local or global methods; the suitability of the algorithm depends largely on the problem to be solved. Local optimisers, for instance are very fast, but suffer the possibility of achieving only the local optimum. By contrast, global optimisers show high probability of achieving the global optimum, but suffer a relatively poor efficiency in exploration. The result of a chemical optimisation study can therefore be greatly impacted by the algorithm selection and application, both in terms of final result and the experimental cost to do so. This section aims to give further detail on the working principles and history of these algorithms where applied to chemical synthesis and optimisation.





1.9.1 Design of Experiments (DoE)

Design of experiments (DoE) is a statistical tool for optimising processes, it is well-studied in literature, and is readily used in both academia and industry [171]. This approach demonstrates many significant advantages over the traditional "One variable at a time", including increased experimental efficiency, the ability to identify factor interactions and high probability of attaining the global optimum, as illustrated in Figure 19 [172]. DoE aims to explore and model the response with respect to each variable in a given design space by simultaneously varying multiple factors according to a predefined set of experiments; the result is the ability to evaluate the effect of significantly more parameters with fewer experiments, compared to traditional methods [173].



Figure 19: Comparison between "One Variable at a Time" (OVAT), Design of Experiments (DoE) Factor Screening and DoE Response Surface Optimization (left-right) within a given design space. Objective response defined by the contour plot. In this example, OVAT fails to identify the optimum region [172].

When considering new materials, or for materials where little is known about factor influences, a DoE will usually begin with a fractional factorial design, with the aim of screening a large number of variables at small experimental cost; both continuous and discrete factors can be investigated at this stage. Factor screening allows the user to determine the relative significance of each variable at an early stage of development, with some indication of factor interaction. However, such designs are not detailed enough to provide accurate predictive models and will usually require a full factorial design or response surface optimisation to follow, often with less-significant factors omitted and a greater number of experimental points for the remaining factors [172].

While DoE has become commonplace among pharmaceutical and life science industries, it has only recently emerged within the field of nanomaterials. At nanoscale, this is arguably more appropriate due to the level of complex interactions between factors and process outputs, which traditional "One variable at a time" methods may miss [174].

Recently DoE has been applied to the optimisation of gold nanoparticle synthesis, where Stiolica *et al.* used a two-level full factorial design to determine the effect of sodium citrate and chloroauric acid concentrations on particle size, using UV-Vis spectroscopy, DLS and ζ -potential to provide particle characteristics [175]. A further example is shown by SadatShojai *et al.* in the optimisation of hydroxyapatite nanoparticles by hydrothermal synthesis. Using a two-level full factorial experimental design and considering reaction temperature, pH, reactant concentration and presence of urea as variables, the authors determined that temperature and pH were the two most significant factors affecting particle morphology [176].

A DoE approach has many significant benefits when compared to more traditional optimisation methods, however, it suffers the drawback that very little is known about the reaction behaviour until all initial experiments are complete [172]. The method also becomes very complex in processes with a large number of factors; for a process with k number of variables, a two-level factorial design would require 2^k experiments. To reduce experiment time and cost, higher order interactions are often assumed less significant to the response, when compared to the main or second-order effects, allowing the number of experiments within the design to be reduced to a quarter or eighth of the original design [174]. Denoting the fraction of the factorial design as p, a two-level fractorial factorial design is generally expressed in the form $2^{k \cdot p}$. Once a full or fractional factorial design is complete, the process can be further optimised through response surface methodology (RSM), whereby the second-order effect of factors can be determined.



Figure 20: Central Composite Design comparison - Circumscribed, Inscribed, Face (Left-Right) [335]

Response surface optimisations most commonly use central composite designs (CCD), which consist of a factorial or fractional factorial design with centre points that are augmented with an additional group called "star points" [120]. Three central composite designs exist; circumscribed, face and inscribed, and are selected depending on the limitations of the process or experiment. The circumscribed design is the original composite design, with start points exceeding the initial factorial design; this allows the generation of new limits for all factors. However, this technique relies on exceeding the original design space, which may not always be possible. Inscribed designs are very similar to circumscribed, but with star points within the initial limits of the factorial design. Both inscribed and circumscribed designs require 5 levels of each factor and exhibit circular, spherical or hyper-spherical symmetry. The face-centred design consists of star points which are at the limit, or face, of the original factorial, requiring just 3 levels per factor to achieve a full quadratic model. These designs are often selected due to their simplicity when compared to rotatable CCDs, but give rise to larger prediction errors for curvature effects [120]. These designs always require twice as many star points relative to the number of factors.

An alternative to traditional central composite designs, Box-Behnken designs, are often used to determine full quadratic models and with typically fewer experiments. Avoiding the corners of the design space, extreme factor combinations are not investigated; similar



Figure 21: Box-Behnken Design as an alternative to traditional central composite designs. [335]

to composite central face designs, this enables an efficient exploration within the design space but leads to poor estimations of factor extremes.

DoE has become a powerful tool for process optimisation, particularly when investigating processes with little prior knowledge; however, DoE suffers several distinct disadvantages or limitations. Relying heavily on statistics, DoE optimisation can be very complex, particularly when considering large numbers of variables, and achieving results which are statistically significant can require several data points for each combination of conditions. In addition, it is often difficult to control or identify all variables which impact the process; while some variables are non-linear, making it difficult to identify optimum conditions [177]. The greatest limitation in DoE is often in the execution, as many failed cases often start with DoE designs but resort to traditional trial and error, with little statistical awareness. It is particularly important in complex investigations to analyse the quantitative data correctly, otherwise misinterpretations can easily occur.

1.9.2 Local Optimisation Methods

Many local optimisation methods originate from the simplex, introduced by Spendley *et al.* in 1962 [178]. The most commonly used of these is the Nelder-Mead simplex algorithm, proposed by John Nelder and Roger Mead in 1965 [179]. The Nelder-Mead simplex is a direct search method of local optimisation, often applied to non-linear problems where the derivatives are not known. This method employs a polytope (simplex) of n+1 vertices in n dimensions, where n is the number of variables.

Operating similar to other "Black Box" algorithms, this method is widely used where the function is not well defined and cannot be easily subjected to analytical methods [180]. The simplex explores the feasible region within a predefined design space; the initial simplex can be randomly generated or defined by the user. Each iteration involves the movement or reshaping of the simplex by adjusting a single vertex, subsequent iterations translate or transform the simplex within the design space until an optimum point is achieved [181].



Figure 22: Graphical representation of the Simplex algorithm. (a) Reflection, (b) Expansion, (c) Outside contraction, (d) Inside Contraction, (e) Shrinking. Blue lines represent the original simplex, nomenclature is as follows: x_h : Worst, x_i : Best, x_s : Second-best, x_r : Reflected, x_c : Contracted, x_e : Expanded. Adapted from Mateos et al. [336]

A simple approach is to replace the worst point of the simplex with one reflected about the centroid of the remaining vertices; if the new position develops a more favourable result, it continues to stretch along that plane. However, if the new position is less favourable, a contraction is used to explore the design space within the simplex itself, causing it to shrink. This algorithm continues to iterate until the maximum number of iterations is reached, the best solution reaches a limit or the minimum simplex size is achieved.

The Nelder-Mead Simplex algorithm is commonly used within machine learning as a fast and efficient optimisation method, however, for more complex applications the method is prone to finding the local optima, which may not be the most favourable solution within the entire design space. The only solution for further exploration is to restart the algorithm with new initial conditions, and selecting the most favourable result across all runs. One of the earliest examples of applying the Nelder-Mead Simplex algorithm to flow chemistry is the integrated self-optimisation of the Heck reaction by McMullen *et al.* [152]. Operating as a "Black box", the system was able to maximize the yield by adjusting the reaction time and equivalents of alkene, while using online HPLC to provide feedback. McMullen *et al.* then scaled up the reaction 50-fold and continued to demonstrate good agreement with initial results. More recently, the Nelder-Mead Simplex has been used in combination of *in situ* flow-NMR for use in a self-optimising system by Sans *et al.* [182]. Here, the authors develop a closed-loop reactor system with the ability to monitor and control organic reactions in real time. The technique is also applicable for a variety of kinetic and mechanistic studies and shows potential for the discovery of new compounds.

Further advancement on the Nelder-Mead Simplex algorithm is the Super Modified Simplex developed by Routh *et al.* in 1977 [183]. In this method, the position of the new vertex is determined through second-order polynomial fitting, allowing much greater freedom in location of the new vertex, enabling the algorithm to more closely follow the system output and accelerate through the design space when necessary. Comparison with the Nelder-Mead Simplex shows fewer required data points and simplicies, as well as a reduced experimental time.

The Super Modified Simplex was demonstrated for chemical synthesis by Bourne *et al.* for the self-optimised methylation of 1-pentanol in supercritical carbon dioxide [184].



Figure 23: Example Nelder-Mead Simplex Optimisation. Reproduced from [181]

Combining online gas chromatography analysis with a continuous-flow reactor system allowed the authors to vary reaction parameters, including temperature, pressure, CO₂ flowrate and methylating agent, to optimise the yield of pentyl methyl; improving upon their previous work, which considered only three of the four variables [153]. During this study, the authors demonstrated the ability to optimise for more than one product from the same reaction mixture, but also noted the ability to optimise instead for alternative factors, such as reducing waste.



Figure 24: Comparison between Nelder-Mead Simplex (Left) & Super Modified Simplex (Right) algorithms. Reproduced from Bourne et al. [184]

An alternative and widely used local optimiser is the gradient-based, 'steepest descent' in minimisation, or 'steepest ascent' in maximisation. Gradient descent methods require initialisation in the form of a 2^k orthogonal polytope about a random or user-defined point. A polynomial is fit within the polytope and the optimisation continues in the direction inverse to the gradient, i.e. following the slope downhill until reaching a valley. As the polytope moves along the surface response, a new local polynomial model is fit, allowing the optimiser to change direction. The steepest descent method was applied to chemical synthesis in McMullen and Jensen's optimisation of the Knoevenagel condensation reaction [151]. A later modification to the gradient descent method, conjugate gradient, was demonstrated by Moore and Jensen's Paal-Knoor self-optimised synthesis [154]. The conjugate gradient combines the weighted sum of the previous search direction and that newly calculated to determine the next set of conditions; doing so prevents large changes


Figure 25: Steepest Descent minimisation of 2 variables using a 2^k orthogonal design. Contours show Blue to be the response minima, while Red is Maxima. Experiment trajectory is shown in Black points and dashed line. Reproduced from Clayton et al. [187]

of direction which can lead the algorithm into surface responses which are difficult to navigate [185].

While local optimisation algorithms are simple to use and are fast-converging, they are highly susceptible to noise factors and likelihood of attaining a local optimum, which may neglect a potentially favourable optimum elsewhere in the design space. To solve this, more complex global optimisation methods are typically needed, which are better able to mitigate noise factors and will often use statistical analysis to develop a more complete model, compared to the simpler "Black box" algorithms.

1.9.3 Global Optimisation Methods

Global optimisers utilise various exploration methods to cover much larger regions of the design space, often fitting a suitable response surface model (RSM) which can be used to estimate process outcome within given constraints, without the need for further experimentation. One such global optimisation method is SNOBFIT (Stable Noisy Optimisation by Branch and Fit) [186]. SNOBFIT generates experiments by random exploration in combination with local fits, and then approximates response values over the region by generating a polynomial surrogate model. Surrogate models are built using process data to estimate the objective response to given variables, these can be optimised *in silico* as a far cheaper alternative to experimental execution. The random exploration of SNOBFIT leads to a generous scatter across the design space, which increases the confidence of attaining the global optimum.



Figure 26: Comparison of SNOBFIT (Orange) and Simplex (Black) for the minimisation of a complex function, restricted at 30 evaluations. Global minimum indicated by a blue cross. Reproduced from Clayton et al. [187]

Until 2018, SNOBFIT was the only single-objective global search algorithm which had been successfully applied to a self-optimising reactor system [187]. The first example of self-optimised synthesis of nanoparticles was by Krishnadasan *et al.* in 2007, using inline spectrometry and an automated microfluidic reactor for the controlled synthesis of CdSe quantum dots [143]. By varying the temperature, reaction time and molar ratio of

components, the system was able to synthesise fluorescent CdSe quantum dots for a specific target emission wavelength, using a custom dissatisfaction coefficient for feedback.

SNOBFIT was further implemented and compared to well-known local optimisation algorithms by McMullen *et al.* for multivariate optimisation of small molecule synthesis, using HPLC to provide feedback [151]. Noting that it is often difficult to determine which algorithm will best-suit a given reaction type, McMullen *et al.* designed their reactor system with the ability to use SNOBFIT as their global search algorithm, as well as Nelder-Mead simplex and steepest descent for local optimisation. The importance of this is highlighted in reactions with non-linear variation, such as solvent composition and pH [188]. By implementing a combination of global and local optimisation methods, the user is better able to identify the true optimum of the reaction without applying *a priori* knowledge, as has been required by previous works [189, 190, 191]. McMullen *et al.* noted that the simpler, local optimisation algorithms used were often much faster at determining the optimum; this is largely attributed to the random search nature of SNOBFIT, compared to the gradient-based local optimisation methods. However, it is likely that a more complex



Figure 27: SNOBFIT optimisation of yield of pentyl methyl ether, optimum region circled. DMC: dimethyl chloride. Reproduced from Skilton et al. [155]

chemistry, exhibiting several local optima would have better demonstrated the global capabilities of SNOBFIT [151].

Skilton *et al.* later compared SNOBFIT with the Super Modified Simplex for the optimised methylation of 1-pentanol with dimethyl carbonate, using real-time ATR-FTIR spectroscopy [155]. Several benefits of SNOBFIT were noted, such as not needing to specify initial conditions for the algorithm, and instead specifying the total search area. Skilton *et al.* concluded that both SNOBFIT and Super Modified Simplex were able to converge upon the same optimum, achieving >99% yield, however the conditions were not the same for each algorithm, suggesting that the optimum can be better represented as a region, rather than a distinct peak. Comparison with a grid of measurements, totalling 252 experiments, confirmed that neither algorithm had missed a more favourable region within the overall design space [155].

SNOBFIT has been successfully demonstrated as a robust global search algorithm within academia and industry; however, it has been noted that SNOBFIT typically struggles with systems of high dimensionality [192]. Simple, single-stage reactions tend to not be affected by this, but it may present significant issues when considering more complex systems with multiple-stage reactions. In addition, SNOBFIT can only optimise continuous variables, eliminating the ability to optimise synthesis routes which consider both continuous and discrete variables [187].

Genetic (Evolutionary) algorithms are a subgroup of stochastic optimisers which iteratively improve upon a solution, taking inspiration from Darwinian evolution. Every iteration of the study consists of a fixed population size, whereby the 'offspring' of high-performing experiments inherit features which had led to their parents' success [193]. An individual experiment is characterised by independent process variables, i.e. temperature, pressure, flowrate, which take the form of 'Genes', the combination of these variables which constitute an experiment is then the 'Chromosome'.

Individuals within a population are measured against a fitness function (objective function) and the probability of selection for reproduction is then proportional to their fitness score. Reproduction occurs in two steps, Crossover and Mutation; crossover combines the genes of two successful parents from the previous generation, while mutation occurs with relatively low random probability in order to maintain diversity and exploration. Over successive populations, unsuccessful chromosomes are not reproduced, until eventually only high performing individuals remain and the process converges.

Genetic algorithms are often used when operating within a complex and diverse design space, such as high dimensional synthesis methods, or where it is known that several local optima exist [194, 195]. While genetic algorithms are very robust, they generally require large sample sets, and so are poorly suited to cases where the experimental cost is high. In addition, selection phases consider only the parent population, and so it is possible to



Figure 28: Overview of Genetic Algorithm Optimisation, depicting the Selection and Reproduction Phases. Gene availability and Population are shown for reference and to aid terminology.

unintentionally repeat experiments across multiple generations. Despite this, and owing to their flexibility, genetic algorithms have been utilised in several chemical synthesis and optimisation studies. Kreutz *et al.* discusses the evolution of catalysts for a plug-based microfluidic device, using the oxidation of methane by molecular oxygen as a model system [196]. The design variables, catalyst, co-catalyst, and ligands, take the form of independent genes, while each experiment constitutes one chromosome. Noting the need for a large number (>300) of experiments across several generations, the authors suggested the potential parallelization of experiments through integration with platforms such as SlipChip for solution preparation [197]. The method proved successful and the authors were able to demonstrate successive generations of greater fitness to their calculated model, as well as identify the most relevant catalytic components and their effect on the objective function.

Genetic algorithms have also been applied by Fernandes *et al.* in the synthesis and optimisation of monodisperse silver nanoparticles using a microfluidic flow reactor [198]. Much of the excitement around this work lies in the use of a multi-objective optimiser to automate the optimisation of synthesis, as well as to reduce sample polydispersity, demonstrating a more holistic optimisation. Using online UV-Vis spectroscopy and dynamic light scattering, the authors were able to identify the effects of each 'gene' with respect to both particle size and dispersity, providing a potentially scalable synthesis strategy for monodisperse silver nanoparticles with little requirement for human skill or intuition, and with greatly reduced development time.

Several other examples of genetic algorithms are discussed by Leardi, including molecular modelling, curve fitting and regression [195]. However, the author notes that while genetic algorithms are a powerful tool for complex problems, it is often highly dependent on the correct structure and application from the onset. Wehrens *et al.* provides a useful set of criteria for the correct structure and performance evaluation of a genetic algorithm, including coverage, reproducibility and evaluation of experiments [199]. The flexibility of design allows genetic algorithms to be very well suited to specific optimisations, with the

user able to define the ratio of exploration to exploitation that best suits the case. This technique has shown high precision and reproducibility in finding the global optima, particularly in cases where a series of local optima exist.

More recently, Bayesian optimisation has been applied to chemical synthesis as a derivative-free global optimiser, using surrogate models to optimise in place of expensive-to-evaluate experiments. In this instance, surrogate models are typically in the form of a Gaussian process, which is a collection of random variables, any finite number of which have consistent Gaussian (normal) distributions [200]. Gaussian process models can be defined by the mean function, m(x), which predicts the output for any set of conditions in the input space, and the covariance (kernel) function, K(x, x'), which is a statistical measure of how variables change together.

$$f(x) \sim \mathcal{GP}\big(m(x), K(x, x')\big)$$

Introducing a noise term allows the algorithms to handle the level of noisy data normally consistent with experimental systems; this is an example of a hyper-parameter which can be tuned to better suit the study and specific datasets. Hyper-parameters have significant impact on the model fit and can therefore be viewed as a limitation of these methodologies. A potential solution lies in the use of Bayesian optimisation to tune the selection of hyperparameters which result in the best, or most suitable, fit; this significantly reduces the computational time and ensures a robust model development.

In self-optimisation scenarios, the surrogate model is used together with an acquisition function to determine the next conditions for evaluation; this ensures a suitable balance of exploration against exploitation, i.e. the likelihood of exploring unknown regions of the available design space, or targeting regions of expected high performance. Common acquisition functions include probability of improvement, expected improvement, entropy



Figure 29: Bayesian optimisation of an arbitrary function. (i)-(viii) represent sequential iterations, whereby the acquisition function is shown in Red and current estimated function with 95 % confidence bounds shown in Blue. Data are shown as red dots, with the next evaluation selected as the point which maximises the acquisition function. Adapted from Clayton et al. [187]

search and upper confidence bounds [201]. Figure 29 shows the Bayesian optimisation (minimisation) of an arbitrary function using expected improvement; initial iterations show high levels of exploration, before focussing on high performing regions [187].

In chemical processes, it is often the case that multiple competing factors require optimisation, such as product quality, sustainability and process economy. Historically, this has best been achieved through the scalarisation of factors into a single objective function, whereby the suitable weightings of each factor need to be identified. More recently, the Bourne Group have demonstrated means of obtaining the Pareto front of a multi-objective optimisation study, whereby an improvement in one variable results in the loss of another; carrying out optimisation in this manner removes the need for *a priori* knowledge which could result in factor bias [202]. This approach provides the ability to simultaneously optimise multiple objectives at various points in the process, giving rise to significant potential savings in both time and resources.

1.10 Aims & Objectives of this PhD

The primary aim of this work is to develop a robust and efficient platform for the optimisation of nanomaterials in order to reduce the time and resources necessary for reliable industrial manufacture.

While the interest around nanomaterials continues to grow, so does the need for fast and reliable methods of development and scale-up. Throughout this chapter, the principal methods of synthesising nanomaterials have been discussed, with a focus on continuous-flow hydrothermal synthesis due to the proven reliability at scale and suitability for automation. The counter-current mixing reactor (*Nozzle Reactor*) and adjoining processes have been demonstrated as a suitable technology for the synthesis and scale up of nanomaterials, but it currently lacks an appropriate methodology for intense optimisation of multiple cases. To further develop this technology, this work has the following aims:

- Automate the continuous-flow hydrothermal synthesis process in a manner suitable for high-throughput experimentation
- Implement suitable online process analytical technologies to provide reaction feedback in real time
- Apply machine learning and optimisation algorithms to efficiently explore and optimise process conditions within a pre-defined design space
- Integrate automation, online PATs and machine learning to enable 'selfoptimisation' of the process
- Demonstrate scalability of the optimised process conditions for industrial manufacture

Using self-optimisation methods previously demonstrated in literature, together with the robust reactor geometry and scalability from Promethean Particles and the University of Nottingham, provides an excellent platform for the closed-loop, self-optimisation of nanomaterial synthesis. Case study materials used in this work are well-known and highly reported. The goal is not to further develop these products, but demonstrate a robust

platform which can be used for the development, optimisation and scale-up of future materials.

Chapter 2 provides an overview of the methods applied in this work; this includes details of process analytical technologies which have previously been implemented in online analysis for flow chemistry or nanomaterial synthesis. Furthermore, the reactor, automation control and optimisation methods are all discussed. The development of the autonomous rig is discussed in Chapter 3, highlighting justifications to the final design.

Chapter 4 is the first experimental chapter, focussing on the optimisation of HKUST-1 MOF using the automated reactor described in Chapter 2 in combination with offline analysis, machine learning and evolutionary optimisation.

Chapter 5 integrates 'self-optimisation' into continuous-flow hydrothermal synthesis through the optimisation of particle size, using online dynamic light scattering and the case study material hematite, a-Fe₂O₃. A customised supervised machine learning (SML) algorithm, which uses a Bayesian-optimised Gaussian process model, is then compared to previously demonstrated methods in literature.

Chapter 6 extends the 'self-optimisation' methodology to CFHS for MOFs, using the case study material Al-Fumarate, with *in situ* FTIR spectroscopy. The synthesis and optimisation of Al-based MOFs in current literature is reviewed, before applying the SML method developed in Chapter 5. The optimum conditions determined from the selfoptimisation study are then demonstrated at pilot and industrial scale in Chapter 7, using the facilities at Promethean Particles.

Finally, the conclusions and recommendations for further research are discussed in Chapter 8.

Chapter 2: Analytical Methods, Reactor Design and Automation

2.0 Analytical Methods, Reactor Design and Automation

This chapter provides details for analytical methods used throughout this work. The working principles of each technique are discussed, as well as the advantages or limitations as applied to nanomaterial characterisation. Furthermore, this chapter includes description of the reactor design and platform setup, highlighting features such as automation and process control which are essential for an autonomous reactor.

Two bespoke graphical user interfaces (GUIs) were compiled for this work, in order to control the reactor instrumentation and machine learning algorithms, respectively. The reactor control GUI (RC-GUI), written using NI LabVIEW, enables remote or autonomous control of the main components of the reactor, including pumps, heaters and sampling functions during experiments; some features such as pressure control, cooling water and alarms were controlled independently for safety purposes. The machine learning and optimisation GUI (MLO-GUI), written in MATLAB 2020a, is responsible for building surrogate models for the process from the available analytical data, and subsequently generating new experiments. Generated experiments can be run *in silico* which is used to balance the exploration and exploitation features of self-optimisation. Several optimisation and machine learning model algorithms are available within the GUI, depending on the required complexity of the experiment case study.

Further details for the setup of the reactor, process analytical technology and optimisation methods are given in each subsequent experimental chapter (Chapters 4-7).

2.1 Nanomaterial Characterisation

The following section outlines the main analytical techniques currently applied in the characterisation of nanomaterials. In each case, a brief explanation of the measurement principle is provided, with emphasis on methods which are the primary source of characterisation in this work.

Characterisation of nanomaterials is often very different to that of the equivalent bulk material owing to their small size. The choice of technique is first determined by the property one wishes to study, followed by the sample state and chemistry [203]. Characteristics such as particle size, shape, composition and surface area are often of particular interest in the synthesis of nanomaterials, however, the product end-use may determine the need for more specific characteristics such as surface charge or morphology [204]. This complexity has given rise to a wide variety of possible analytical techniques, each with their particular advantages and disadvantages; it is therefore imperative to select the appropriate technique, or combination of, to best suit the specific material and property.

Several reviews outlining the current techniques used in the characterisation of nanomaterials currently exist [203, 204, 205, 206], with Mourdikoudis *et al.* providing perhaps the most recent and comprehensive assessment; this includes the classification of each technique based on their operational principles and comparison in relation to the studied property in each case [204]. Often, a sample can be characterised through multiple techniques, with each technique showing respective advantages or limitations, specific to the physical or chemical properties of the sample. To provide detailed characterisation, a combination of techniques is often applied.

2.1.1 UV-Visible Spectroscopy (UV-Vis)

UV-Visible (UV-Vis) spectroscopy is an absorption technique that uses light within the ultraviolet and visible regions of the electromagnetic spectrum, to promote electronic transitions from ground to excited states within molecules of the sample. Absorption or reflection of light from the visible range is directly responsible for the perceived colour of chemical samples.

UV-Vis spectrometry is performed using a spectrophotometer (spectrometer), which measures the intensity of light passing through a sample (I), relative to a known reference (I₀). The ratio of the sample and reference intensity is called generally transmittance, %T, or alternatively absorbance, A. Whereby:

$$\%T = \frac{I}{I_0}$$
, $A = -\log\left(\frac{\%T}{100}\right)$





The spectrometer is responsible for filtering the light source using a monochromator, ensuring that only monochromatic light is passed to the sample and reference, as illustrated in Figure 30. Often, a scanning monochromator is used, which scans the range of available wavelengths, resulting in the recording of an absorption or transmission spectrum.

Where samples contain particles smaller than the wavelength of incident light, light can be elastically scattered, known as Rayleigh scattering. In UV-Vis spectroscopy, this prevents light from returning to the detector, hence influencing the absorption spectra. Using Mie Theory of scattering, the optical cross-section of nanomaterials can be calculated, assuming particles are spherical. The total extinction cross-section is then a function of both the scattering and absorption of light from the sample [207].

Samples in this work were analysed using a Cole-Parmer UV-Visible Spectrophotometer (WZ-83059-15) with a quartz cuvette of 10 mm path length. Analysis was in the wavelength range 250-900 nm, step size 2 nm.

2.1.2 Infrared Spectroscopy (IR)

Infrared (IR) spectroscopy is a tool used to study a material's structural properties at molecular level; most commonly on the absorption of electromagnetic radiation within the mid-Infrared region, with wavenumbers in the range 4000-400 cm⁻¹ (2.5-25 μ m). The technique utilises the principle that molecules will absorb characteristic radiation frequencies dependent on their molecular structure, resulting from the strength of the bond and associated atomic mass [208]. To be considered "IR active", a structure within the molecule must be able to exhibit a "dipole moment", whereby electrons are unevenly distributed within the bond. Different bonds and functional groups will give rise to



Figure 31: Six types of vibrational modes. Arrows depict the type or direction of vibrational motion, red and green arrows depict symmetry or asymmetry, respectively. Both wagging and twisting modes are in and out of plane.

particular frequency absorption, or vibrations, which can be compared to known absorption spectra, allowing the determination of the molecular structure [209].

A molecule can vibrate in several ways, Figure 31 shows the six commonly recognised modes of vibration; these include two stretching modes: symmetric (v_s) and asymmetric (v_{as}), and four bending modes: wagging (ω), twisting (τ), scissoring (δ) and rocking (ρ).

Dispersive spectroscopy measures the absorption of monochromatic light, repeated over a range of distinct wavelengths. Fourier Transformed Infrared (FTIR) spectroscopy differs in that a broadband light source is used, containing the full spectrum to be measured. After determining the absorbance from the initial light source, the beam is modified to contain a different combination of frequencies; this process is repeated several times and the data used to infer the absorption at each wavelength within the spectral range [210]. The two methods commonly applied in IR spectroscopy are Transmission and Attenuated Total Reflectance (ATR).



Figure 32: Example of a multiple reflection ATR Infrared Spectroscopy light path [211]

ATR is often used in infrared spectroscopy due to the ease of sample preparation. In ATR-FTIR, radiation passes through an internal reflection element (IRE) crystal material, as shown in Figure 32. The sample to be measured sits in contact with the crystal, allowing IR light to interact with the sample interface, with a penetration depth of around 1 μ m [211].

Transmission IR spectroscopy instead allows light to pass through the sample, any frequency of light which is not absorbed by the sample is then measured at the detector.

It is therefore important to ensure that the sample path length is so large as to completely absorb all emitted light or saturate the detector [212].

When comparing spectra from ATR and transmission measurements, small variances in peak position and intensity can occur. This due to the difference in refractive index of the sample and ATR crystal at varying frequencies of emitted light; an example is the peak shift demonstrated by a carbonyl band within a molecule, when measured with each method [212]. There are advantages to each technique, transmission spectroscopy often leads to higher quality spectra which can be used for quantitative analysis; whereas ATR is more reproducible and requires significantly less sample preparation. The easy of sample preparation and robust flow cell design means that ATR-FTIR spectroscopy was used throughout this work.

Samples in this work were analysed using a Bruker Alpha II Platinum FTIR Spectrometer fitted with Platinum Diamond-ATR QuickSnap Sampling Module. All samples were measured and analysed using Bruker OPUS 8.5. Measurements were taken in the range 4000-400 cm⁻¹. FTIR spectroscopy is used extensively throughout Chapter 6, and further details specific to this work given the experimental chapter.

2.1.3 Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) is a bulk analytical technique which provides information on the crystal structure and (indirectly) particle size of solid samples, based on their diffraction pattern. During analysis, a sample is illuminated with X-rays of known wavelength, λ ; X-rays impacting the sample are then elastically scattered by electrons within the sample atoms.

In crystalline solids, atoms are arranged in repeating units of long-range order, forming distinct planes. X-rays scattered by crystalline solids result in constructive interference, which are indicative of the spacing, d, between diffracting crystal planes and the incident angle, Θ , of X-rays to the sample, as shown by Bragg's Law [213].

$n\lambda = 2d\sin\theta$

This constructive interference is then detected by the instrument, which records the intensity in relation to the incident angle as a diffraction pattern. A perfectly crystalline material, with no defects, displays a diffraction pattern with vertical lines and no peak broadening.



Figure 33: Schematic representation of the parameters used in Bragg's Law, by X-ray diffraction (XRD). Image reproduced from [339]

Amorphous solids are samples in which there is no long-range order of atoms. In amorphous materials, diffraction patterns lack intense reflections and are often represented by broad asymmetric features across a wide range of incident angles.

In crystallography, a unit cell is the smallest portion of the crystal lattice that repeats across all three dimensions of the crystal. Using Bragg's Law, and by maintaining n constant (n = 1), the inter-planar spacing can be used to determine the lattice parameters of a unit cell, which are unique to each crystal.



Figure 34: Schematic diagram of a Crystal Lattice and a Unit Cell in crystallography. Reproduced from [343]

In this work, the technique requires dry, finely ground material, whereby the average bulk composition and properties can be determined. The sample is prepared to ensure random orientation, and therefore minimise any preferred-orientation effects. Diffraction may only occur if Bragg's law is satisfied, and so a diffraction pattern is created by scanning the X-rays across a range of angles and recording the detected intensity. As the diffraction pattern is a function of the d-spacing and incident angle, the recorded diffraction pattern is then unique to each crystalline solid; this can then be used for phase identification of the sample.

A perfectly crystalline material, with no defects, would display a diffraction pattern as a series of vertical lines. However, a crystal is rarely structurally 'perfect' and any imperfections are represented by broadening of reflections in the diffraction pattern. Broadening effects can also occur due to small particle sizes, sample preparation and environment (e.g. temperature), or from the instrument itself. In the case of size broadening, sub-micron particles are typically small enough so that there are insufficient planes across the particle to ensure complete destructive interference at angles close to the Bragg angle. The breadth of peaks within the diffraction pattern can therefore be used in combination with the Scherrer equation to determine the mean particle size of crystalline materials.

$$\tau = \frac{K\lambda}{\beta\cos\theta}$$

Whereby τ is the mean size of crystalline domain, K is the is Scherrer constant (Value = 0.9, assuming particles are spherical), λ is the X-ray wavelength used for analysis, β is the line broadening at full-width at half-maximum value of the peak (FWHM) and Θ is the Bragg angle.

It is important to remember that broadening can arise from multiple sources, and additional particle effects, such as agglomeration and shape, may lead to significant error in the particle size values determined by XRD alone. It is therefore necessary to combine XRD with other techniques, such as SEM and TEM, for a more complete understanding of particle size and morphology.

The rapid analysis time and ease of availability, in combination with the range of information that can be gathered from this technique, means that PXRD is the primary method of offline analysis used during this work. Samples were analysed using a Bruker D8-Advance Da Vinci Diffractometer with Cu Ka radiation ($\lambda = 1.5418$ Å). Diffraction patterns were recorded across a 20 range of 5-70°, with a step size of 0.05° and 0.2 s per step (8 s per step in Chapter 5). All analysis and processing was completed using Bruker EVA software, which allows comparison to known reference crystalline patterns.

2.1.4 Scanning electron microscopy (SEM)

Following structural identification through X-ray diffraction techniques, nanomaterial samples are often further analysed by scanning electron microscopy (SEM) to study features such as surface morphology, topology or particle size distribution. By contrast to optical microscopy, which uses a visible light source, SEM utilises a beam of electrons which are scanned across the sample surface. Electrons beams are used due to their shorter wavelength when compared to visible light, resulting in much higher possible magnifications, typically between 100 and 100,000 times. The narrow beam also results in a large depth of field, which is responsible for the three-dimensional appearance of images; this feature in particular makes SEM valuable for studying a sample's surface structure.



Figure 35: Schematic Illustration of Scanning Electron Microscope [346]

During analysis, electrons are generated and the beam focused through a series of lenses and apertures before it reaches the surface of the sample. Upon interaction with the sample surface, electrons can either be backscattered or generate secondary electrons; both backscattered and secondary electrons can be used to provide information about the sample. Secondary electrons arise through interaction of incident electrons with the sample surface; secondary electrons are typically lower in energy than backscattered electrons and are primarily used for high resolution imaging or studying the topology of the material. Deeper penetration of the incident electron beam leads to interaction with the nuclei of atoms within the sample; this results in direct backscatter of electrons. As materials of higher atomic mass cause more electrons to backscatter, the sample composition can be investigated through backscattering.

For the purposes of this work, samples are in the form of dry powders, and are fixed to an aluminium stub through the use of carbon tape or glue. Prior to analysis, the sample can be coated with a thin layer of gold or platinum to improve conductivity and give higher resolution. Once the sample stub is placed into the sample chamber, the system is evacuated to produce a vacuum (See Figure 35).

Samples in Chapter 4 were imaged using a FEI Quanta600 MLA SEM. Sample powder was mounted onto a carbon glue coated stub. The stub was allowed to dry before coating with platinum in a Polaron SC7640 set to 2.2 kV, coating was done for 90 seconds.

2.1.5 Transmission electron microscopy (TEM)

Similar to SEM, transmission electron microscopy (TEM) utilises a beam of electrons which are fired upon a sample. In contrast to SEM, TEM operates on the transmission of incident electrons through the sample, producing a projection upon a screen located underneath (See Figure 36). Transmission of electrons is heavily influenced by a sample's composition, density and particle size, which can all be studied through the projected image; for example, a 5 keV can penetrate 400 nm of Al, but only 88 nm for Au [214].

TEM uses a much more focused electron beam, when compared to SEM, which enables higher resolution and magnification up to 1×10^6 times. However, the field of view (FOV) is far smaller, meaning that detailed images are limited to only small regions of the sample.



Figure 36: Schematic illustration of transmission electron microscope [347]

For analysis, samples are first transferred into a volatile solvent, such as ethanol, before deposition onto a copper or carbon grid for imaging. As the solvent evaporates, a thin layer of nanomaterial sample is retained. As before, the chamber is evacuated to ensure a vacuum prior to imaging.

Owing to the many properties which can be investigated by electron microscopy, including particle size, morphology, topology and also composition; both SEM and TEM provide a powerful characterisation tool for this work. Both methods are primarily used to validate the online analytical techniques used for self-optimisation. While the imaging itself is rapid and non-destructive, the sample preparation is still too resource-intensive to consider analysing all samples; for this reason, only select samples from experiments in Chapters 4-7 are analysed *via* SEM and TEM.

Samples were analysed using a JEOL 2100F HRTEM equipped with a field emission gun (FEG) and operating at 100 kV. Samples were transferred into ethanol and sonicated in an ultrasonic bath for 60 minutes to disperse agglomerates, before being distributed on a carbon grid. All TEM images were provided courtesy of Dr Michael Fay of the Nanoscale and Microscale Research Centre (nmRC) at the University of Nottingham.

Particle size analysis using SEM and TEM imaging was completed by Dr Vitaliy Sechenyh as part of the EPSRC project "Cognitive Chemical Manufacturing" (Ref: EP/R032807/1). A custom algorithm written in MATLAB was used for analysis. This method modifies the image contrast to produce a binary profile; particles are automatically detected as "holes" in the image background, whereby the major and minor axis of each particle is measured and counted.

2.1.6 Dynamic Light Scattering (DLS)

Dynamic light scattering (DLS), also known as Photon Correlation Spectroscopy (PCS) is a technique used to determine the hydrodynamic radius of particles in suspension. DLS utilises the principle of Brownian motion by illuminating particles within the solution with a monochromatic laser and analysing the intensity fluctuations in the scattered light, shown in Figure 37 [215].



Figure 37: Diagram showing scattered light falling on a detector [215]

Particles suspended in solution do not remain stationary, but instead undergo Brownian motion. Brownian motion is the movement of particles due to random collisions with molecules of liquid surrounding the particle [216]. As small particles move faster than larger particles, the particle size can be determined using the speed of the particles under Brownian motion, as defined by the Stokes-Einstein equation [217].

$$D = \frac{k_B T}{6_{\pi\eta} R_H}$$

Where D is the Translational Diffusion Coefficient, k_B is the Boltzman constant, T is temperature, η is the solution viscosity and R_H is the hydrodynamic radius.

The DLS instrument measures the fluctuation in scattering intensity and then calculates the particle size. It does this by comparing the degree of similarity between signals over short periods of time and creating a correlation function. Over time, the degree of



Figure 38: Correlation function for small and large particles. The rate of decay of the correlation function is greater for small particles, compared to large particles. [215]

similarity will decrease; if the sample contains large particles, then the particles move slowly and the intensity fluctuation is relatively low. For smaller particles, which move faster, the fluctuation intensity is much greater and therefore the rate of change in similarity is also greater; this effect is shown in Figure 38.

While it is theoretically possible to detect scattered light in every direction, and therefore all angles, as illustrated in Figure 39, most instruments have fixed backscatter (173°) or classical (90°) arrangements. Measuring backscatter has the advantages of not requiring the laser to travel through the entire sample, meaning higher concentration samples can be used while minimising the effects of multiple scattering. This arrangement also reduces



Figure 39: Basic setup of DLS measurement system. Sample is contained within the cuvette and scattered light can be detected at different angles [217]

the scattering effect of dust and other large contaminants as they typically scatter in the forward direction.

DLS measurements in this research were carried out using a Malvern Panalytical Zetasizer Nano ZS, in backscatter arrangement with a detector angle of 173°. For *in-situ* experiments, the measurement time was fixed at 10 seconds per run, and the measurement averaged across 10 runs. Features within the Malvern Zetasizer software enabled optimisation of the measurement position between sampling, as well as the ability to increase or reduce the light intensity through use of the built-in attenuator. A customised standard operating procedure (SOP) was created for each material, and used for all experiments, further details are given in Chapter 5.

2.1.7 Surface Area Analysis (BET N₂ Adsorption)

Gas adsorption using the *Brunauer-Emmett-Teller* (BET) model is a technique used to determine the surface area and pore size of a nanomaterial sample. The technique is based on the adsorption of gas onto a solid surface, and is an extension of the Langmuir theory of monolayer adsorption relative to the pressure of a gas medium at constant temperature [218, 219].



Figure 40: IUPAC classification of adsorption isotherms, n_a represents the quantity of adsorbed gas as a function of partial pressure, p/p0 [220]

Various gases can be selected for BET surface area analysis, however, nitrogen is most commonly used due to its strong interaction with most solids, high chemical compatibility, size and availability in high purity. To increase interaction between the gas and solid surface, the sample is cooled using liquid nitrogen at 77 K, known volumes of gas are then discharged into the sample cell. High precision pressure monitors and transducers then measure the change in pressure within the cell due to adsorption. Data are displayed as an adsorption isotherm, with types I-VI being generally accepted, plotting the adsorbed gas volume as a function of pressure [220]. Figure 40 shows the six possible adsorption isotherms.

Surface area is a key property when developing porous nanomaterials. BET has become a standard analysis method for determining the surface area of microporous materials such as zeolites and MOFs. However, there has been some debate regarding the validity of these measurements, questioning whether the reported surface areas were instead a result of a pore-filling mechanism, rather than the multilayer adsorption for which the test was originally intended [221, 222].

Various MOFs can exhibit pore sizes ranging from below 7 Å (ultra-micropores), between 7-20 Å (super-micropores), or greater than 20 Å (mesopores); it is this complication that can potentially contribute to inaccuracies in the BET equation [223].

Rouquerol *et al.* further analyses the validity of the BET equation for use in microporous materials in 2007 [224]. In that work, Rouquerol *et al.* discusses that neither the BET, nor Langmuir equation should be blindly applied to microporous samples. A "linearity criterion" is provided for analysis of BET plots to ensure consistency between measurements, mitigating subjectivity. To support these findings, Rouquerol *et al.* conducted calorimetric analysis and found it to correspond well with the calculation of BET monolayer content through this criteria [224]. Despite these concerns, BET continues to be used as a standard metric for comparison of microporous materials, and as such is utilised in this work.

Samples in this research were analysed using a MicroMeritics Tristar II 3020, with a preloaded dosing program for surface area calculation. All samples were degassed overnight at 200°C under vacuum to remove any surface water or other impurities which may confound the measurement. Nitrogen gas was used for adsorption at 77 K due to ease of availability, at partial pressures between 0.001 and 0.99.

2.2 Autonomous Reactor Design

This section describes the design and build of the autonomous reactor used for all experiments within this work. The reactor itself is based on previous bench-scale designs of the counter-current flow reactor at the University of Nottingham, with some modifications to better suit an automated platform [56, 67].

All pressurised components of the reactor were constructed from 316L stainless steel, and purchased from Swagelok®, unless otherwise stated. Six high-performance liquid chromatography (HPLC) pumps (Gilson 305) were used for pumping solvent and precursor solutions into the system; pumps were allocated to the Upflow or Downflow based on the requirements of the specific case study, with further details given in experimental chapters (Chapter 4-7). A Eurotherm 3216e PID controller with additional communications accessory was used to control power to a Watlow 1000 W mineral band heater, enabling control of the reactor Downflow. The reactor itself comprises a 0.125" tube inside a 0.375" tube and mixing length of 100 mm, with all components at 0.065" wall thickness.

Following the reactor, a tube-in-tube heat exchanger was used to rapidly cool the process stream (tube side) using recirculating deionised water (5 °C, shell side), controlled by an IKA RC2 Green Control recirculating chiller. All post-reactor tubing was 0.25" in diameter. Pressure was maintained using a Tescom back pressure regulator, combined with a Tescom ER3000 electro-pneumatic valve actuator for automated pressure control. The Tescom ER3000 was operated using Tescom proprietary software and PID control to maintain stable pressure throughout and avoid interference with pressure relief operations.

The process stream from each experiment was set to normally flow to waste, however, a 24 V, two-way solenoid valve, controlled by Arduino through LabVIEW, was used to divert samples flow to online analysis or sample retain. A customised Gilson FC204 Fraction Collector was used to retain up to 50 ml from each sample, using polypropylene centrifuge tubes; up to 35 samples could be collected without intervention.



Figure 41: Schematic of the Autonomous Reactor used throughout this work. Process equipment (Pumps and Heaters) are controlled via RS232 serial communication, using the custom reactor control graphical user interface (GUI) in NI LabVIEW. Online process analytical technology (PAT) is shown in flow-through mode, but can be oriented in parallel or series to the process, depending on the PAT and setup. Heat exchanger and Back pressure regulator are controlled using built-in software and set points constant throughout all experiments. Thermocouples are not shown. Machine learning (ML) and instrument control denotes the custom reactor control and optimisation GUIs.



Figure 42: Front view of the Autonomous Reactor used for all experiments within this work. Pumps 1-6: Gilson 305 HPLC pumps. Temperature Controller: Eurotherm 3216e PID Controller. Pressure Trip: Pressure safety trip – cuts power to pumps and heaters at pressure >4000 psi. Pressurised Reactor: More details given in Figure 43. PC, recirculating chiller and auto-sampler and not shown.



Figure 43: (Left) Autonomous Reactor used throughout this work. R: Counter-current flow reactor. H: Watlow Band Heater (1000 W). NRV: Non-return valve. PRV: Pressure relief valve (4000 psi). PG: Pressure gauge. PT: Pressure transducer. P: Pressure gauge & transducer. HX: Tube-in-tube heat exchanger. BPR: Back pressure regulator (Automated, Tescom). CW: Cooling water. T: Thermocouple. All major components are Swagelok® unless otherwise stated.



Figure 44: Customised Gilson FC204 Fraction Collector utilised as an autonomous auto-sampler for all experiments in this work.

Figure 41 shows the simplified process flow diagram (PFD) for the self-optimising system. Figure 42 to Figure 44 show the autonomous reactor used throughout this work. All components were operated using RS232 control with a single computer, running the bespoke reactor control graphical user interface, unless otherwise stated.

Figure 45 and Figure 46 show the Bruker Alpha II ATR-FTIR spectrometer and Malvern Zetasizer Nano ZS respectively, used for online analysis in self-optimised experiments. Further details are given in experimental chapters (Chapter 5 and Chapter 6).



Figure 45: Bruker Alpha II FTIR Spectrometer, with Platinum ATR-QuickSnap attachment. Bruker flow-through ATR accessory is shown, used for work in Chapter 5.



Figure 46: Lleft) Malvern Zetasizer Nano ZS with flowcell for online DLS analysis, used in all Hematite synthesis experiments. (Right) Quartz Flow Cell (ZEN0023) from Malvern for size and intensity measurements [340]

2.3 Reactor Control Graphical User Interface

The reactor control graphical user interface (RC-GUI) was written and compiled using NI LabVIEW. LabVIEW is a graphical programming platform in which data flow are generated by 'wiring' inputs and user-defined variables to operators and functions. The visual nature of LabVIEW makes understanding the data-flow and overall structure of the GUI much more intuitive than traditional text-based programming methods; this is particularly useful when debugging.

The GUI was built in several stages, starting with remote operation and control of the desired instrumentation, before integrating cyclic automation, allowing the reactor to follow a pre-defined set of automated protocols without user intervention. Finally, the RC-GUI was further developed to read and write text files to mediate the online process analytical technology (PAT), instrument hardware and a separate machine learning and optimisation GUI (MLO-GUI, described later).

The RC-GUI uses a 'Queued Message Handler' (QMH) template, which facilitates sections of code running in parallel and allowing transmission of data between them. Defining each subsection of code as a task (e.g. reading an instrument state), the GUI quickly becomes analogous to a state machine. The front view of the RC-GUI is shown in Figure 47, the programme is too large to be fully described in this thesis; however, the key features and design are highlighted, and the files available on request.

The RC-GUI is designed to enable autonomous experimentation, following a cyclic *Standby-Heating-Run-Flush* configuration. These actions are predefined by the user ahead of a case study, and include inputs such as pump flowrates or temperature during each phase. The RC-GUI moves between phases when triggered by an external state, such as reaching the temperature tolerance or waiting an allocated time. Figure 48 shows a typical flowsheet for autonomous reactor control, integrating online dynamic light scattering (DLS) and experiments generated using the MLO-GUI.



Figure 47: Reactor Control graphical user interface (RC-GUI) created in NI LabVIEW. (a) Reactor and experiment controls (Pumps. Heater and Auto-sampler). (b) Online analysis import and monitoring. (c) Data text file import and export, for external communication with set-point generation.


Figure 48: Reactor automation protocol flowsheet. Example shown uses online dynamic light scattering (DLS). ML: Machine learning.

2.4 Machine Learning & Optimisation Graphical User Interface

As part of the EPSRC project Cognitive Chemical Manufacturing (Ref: EP/R032807/1), a machine learning and optimisation graphical user interface (MLO-GUI) was developed by Dr Vitaliy Sechenyh, using the Statistics and Machine Learning Toolbox from MATLAB 2020a [225]. This GUI was used for all self-optimised experiments (described in Chapter 5 and Chapter 6), using a supervised machine learning (SML) to construct a model from available experiment data and generate predictions in the presence of uncertainty.

Input data are generated from physically running experiments and analysing the outcome against a pre-defined objective function (i.e. particle size, conversion etc.). Input data is used to train a SML model using regression, allowing the continuous prediction of response for previously untested conditions, with indication of prediction uncertainty.

Two methods of regression are primarily used for self-optimised experiments in this work; polynomial and Gaussian process. Polynomial regression models the relationship between a dependent and multiple independent variables, using a polynomial to the *n* degree, whereby *n* is usually the number of independent variables. Polynomial regression in this instance is very similar to multiple linear regression (MLR) which is commonly applied in simple SML problems. For more complex or detailed problems, a Gaussian process (GP) is often used, which defines a distribution over all possible functions for the available data. In this work, following the import of input data, several GP models were built using various hyper-parameters; Bayesian optimisation was used to minimise the re-substitution errors based on deviations of training to predictive data.

Both regression methods were used to generate experiment points across the available design space, with each set of conditions having an associated prediction. The user defines the proportion of exploration (random) and exploitation (high-performance) at the start of the process. Figure 49 shows the MLO-GUI used within this work, with further details for operation available in experimental chapters (Chapter 5 and Chapter 6).

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Figure 49: Options (top) and Model View (bottom) tabs of the Machine Learning and Optimisation graphical user interface (MLO-GUI). Options allows the selection of base model, number of variables and optimiser used for self-optimised experiments. Model view shows the contour plots of generated models at given 2D slices within the design space. MLO-GUI developed by Vitaliy Sechenyh as part of the Cognitive Chemical Manufacturing EPSRC project. (EP/R032807/1)

Chapter 3: Rig Development

3.0 Rig Development & Commissioning

To facilitate self-optimisation of nanomaterial synthesis, a robust, autonomous reactor platform must first be developed. Chapter 2 describes the platform arrangement that was used in all bench-scale experiments presented in this thesis, however, several design iterations were necessary to finalise this design.

The initial goals when designing the high-throughput reactor for use in this work were:

- Maximum working temperature and pressure ($T_W = 380$ °C, $P_W = 24.0$ MPa)
- Suitable for nanomaterial synthesis
- Small internal volume
- Fully automated and/or remote control operation
- Rapid stabilisation after changes to process conditions
- Low energy usage (Heating and cooling)

To achieve this, the original bench-scale reactor design used at the University of Nottingham and Promethean Particles was adapted [56, 67]. The base design has previously been demonstrated to satisfy the working conditions and be suitable for nanomaterial synthesis. However, the development of the self-optimising platform required several iterations to ensure robust yet efficient operation.

This chapter describes the design iterations and justification for the final autonomous reactor system described in Chapter 2 and used in all bench-scale experiments in Chapter 4 to Chapter 7. Early iterations prioritise safe and robust reactor performance; once this was established, the reactor and auxiliary components were further modified to minimise variability across the process and analytical systems.

3.1 Iteration 1 (Initial Design)

Reducing the total internal volume within the reactor minimises the volume of waste material and time required to achieve steady state conditions. This means that for the same given time period, or volume of precursor solutions, more experiments can be executed and hence larger volumes of data.

The original reactor design comprises a 0.125" in 0.375" (all dimensions refer to outer diameter) tube-in-tube counter-current reactor (Nozzle reactor), and 0.250" tubing for all main process lines post-reactor [56]. To reduce the total internal volume of the reactor, this design was scaled down one size, according to the availability of standard Swagelok® parts. The proposed reactor consisted of a 0.0625" in 0.250" counter-current reactor, with 0.125" tubing post-reactor.

Reducing the tube diameter also serves to improve the surface area to volume ratio of tubing, which is particularly important for achieving good heat transfer in heating and cooling applications. However, there are other effects to consider when modifying the reactor geometry, such as adjusting the total flowrate to mitigate changes to the superficial velocity and flow regime of the process fluid.

Further to changes in reactor geometry, the initial design aimed to improve the overall energy efficiency by employing simple methods of heat integration. The reactor Downflow could be pre-heated using the thermal mass of the reactor outlet, this reduces the total heater duty required whilst simultaneously cooling the reactor outlet stream. Furthermore, the Downflow trim heater was designed to wrap around the Nozzle reactor itself, meaning that residual heat from the heater coil and mechanical support would transfer to the reactor through conduction.

The completed initial rig design is shown in Figure 50, with the illustration of fittings and conceptual design shown in Figure 51.



Figure 50: Image of the high-throughput reactor (Iteration 1). R: Counter-current mixing reactor. H: Heater. HX: Heat exchanger (Shell: Downflow preheat, Tube: Reactor outlet). PG: Pressure Gauge. PRV: Pressure relief valve. CW: Cooling water. BPR: Back pressure regulator.



Figure 51: Illustration of the high-throughput reactor (Iteration 1). T: Thermocouple, DF: Downflow, UF: Upflow, NRV: Non-return valve, PRV: Pressure-relief valve, CW: Cooling water, P: Pressure gauge and transducer, BPR: Back-pressure regulator.

The rig was commissioned by increasing the system pressure with 30 ml.min⁻¹ of deionised water and slowly adjusting the back-pressure regulator (BPR) until achieving 24.0 MPa. Following pressure testing, cooling water was recirculated from a large drum and the heater slowly ramped until the Downflow temperature achieved 380 °C. This process was repeated immediately following all modifications to the rig design or parts. The primary constraint is the back-pressure regulator temperature, which must not exceed 40 °C for personnel safety and equipment longevity.



Figure 52: Temperature ramp during commissioning of the initial high-throughput rig design. Downflow temperature achieves 380 °C, while the back pressure regulator (BPR) temperature range: 17-23 °C.



Figure 53: Image of the initial autonomous reactor platform (Iteration 1) during early scoping experiments.

Initial automation of reactor was achieved using RS232 serial communication, with commands sent using MATLAB 2018b. Using multiple pumps meant that a range of flowrates and precursor concentrations were available through dilution in flow. Figure 53 shows the automated rig during operation of initial scoping experiments. As the autonomous platform became more complex (integrating online analysis and optimisation algorithms) the automation methods were transferred into NI LabVIEW 2020, with the design of a new graphical user interface (Described in Chapter 2).

The initial design for the automated CFHS reactor fulfilled many of the design requirements previously described; the total volume of pressurised components was calculated to be 9.2 ml. Furthermore, the heat integration methods applied meant that supercritical water could be achieved using only a 500 W heater, while the outlet process fluid could be cooled to <30 °C prior to the release of pressure at the BPR, using a short (70 mm) cooler.

However, several aspects of the design required improvement before it could applied to the high-throughput experimentation required throughout this work. The primary concern was the presence of large pressure fluctuations and frequent blockages when running scoping experiments. Figure 54 shows the pressure trace during one of the early scoping experiments for the synthesis of metal organic frameworks. The large fluctuations are



Figure 54: Pressure trace during scoping experiments for the initial high-throughput rig design. Pressure trip triggered at 4000 psi, cutting power to the pumps and heater.

most likely attributed to accumulation of solids within sections of the rig, restricting the flow until either the solids are dislodged or the maximum working pressure is exceeded.



Figure 55: Areas of suspected solid accumulation: 0.250-0.125" reducer and 0.125" tubing with a sharp bend and vertical gain.

Figure 55 highlights locations or fittings within the rig that are suspected to have contributed to solids accumulation and blockages. Immediately following the 0.250" reactor outlet, the tubing reduces to 0.125"; furthermore, the vertical gain immediately after the reactor could contribute to uneven transport of solids within the mixture.

In addition to the large fluctuations in the overall system pressure, significant variation between the Upflow and Downflow pressure was also observed, as shown in Figure 56. This can most likely be attributed to the 0.0625" Downflow tube, as this is the narrowest component following the non-return valves; it is possible that solids created during scoping experiments fouled the reactor internal surface of the tube, further restricting the flow.



Figure 56: Discrepancy in Upflow and Downflow pressure during operation. Reactor was not intentionally pressurised, pressure reading shown is a result of backpressure along the Downflow process line.

Issues surrounding pressure fluctuations, solids accumulation and blockages were not observed in all scoping experiments, and were more prevalent in the synthesis of metalorganic frameworks. This is likely due to the greater concentration of solids, increased particle sizes and higher tendency to agglomerate, when compared to the metal oxide materials which were also investigated in this work.

3.2 Iteration 2

After identifying the limitations of the initial design, several components of the highthroughput reactor were modified. The reactor scale was returned to the original 0.125" in 0.625" design; no variation in pressure was observed between the Upflow and Downflow lines after this, suggesting that the lower-scale reactor geometry was a significant contributing factor. Further to this, all tubing post-reactor was changed to 0.250" and arranged to avoid to any elevation gain after the production of solids, as seen in Figure 57.



Figure 57: Image of the high-throughput reactor (Iteration 2). R: Counter-current mixing reactor. H: Heater. HX: Heat exchanger (Shell: Cooling water, Tube: Reactor outlet). PG: Pressure Gauge. PT: Pressure transducer. PRV: Pressure relief valve. BPR: Back pressure regulator.

To simplify the design at this stage, the heat integration previously employed to pre-heat the reactor Downflow was removed; this also served to significantly reduce the average stabilisation time when altering process conditions within the rig. Figure 58 shows a schematic illustration of the design for reference.



Figure 58: Illustration of the high-throughput reactor (Iteration 2). T: Thermocouple, DF: Downflow, UF: Upflow, NRV: Non-return valve, PRV: Pressure-relief valve, CW: Cooling water, P: Pressure gauge and transducer, BPR: Back-pressure regulator.

Figure 59 shows the system setup during further scoping work, investigating the use of inline FTIR analysis as a suitable online process analytical technology. The process flow diagram (PFD) of the autonomous platform is shown in Figure 60.



Figure 59: High-throughput reactor, complete system including process analytical technology (PAT) during scoping experiments.



Figure 60: Schematic of the high-throughput autonomous reactor (Iteration 2). Online process analytical technology (PAT): inline ATR-FTIR spectroscopy. ML: Machine learning.

To minimise user intervention, the manual spring-loaded back pressure regulator (BPR) was replaced with an air-actuated BPR (Tescom, 26-1700 Series), automated through an ER3000 electro-pneumatic controller.

During commissioning of this design, it was immediately clear that the cooler was not sufficient when running at a total process flowrate of 30 ml.min⁻¹. The process fluid at the BPR should not exceed 40 °C, however, the Downflow could only be heated to 150 °C before the BPR temperature limit was reached. This is far below the required temperature of 380 °C, and so the cooler length had to be increased. For reasons of safety and equipment longevity, the outlet stream must not exceed 40 °C, in order to avoid burns to personnel or risk softening of the polymer seal within the BPR. However, when considering online analysis, the outlet temperature must be very tightly controlled to ensure this does not result in measurement error.



Figure 61: Temperature commissioning test for the high-throughput reactor (Iteration 2). As the Downflow (DF) approaches 150 °C, the back pressure regulator (BPR) temperature exceeds 30 °C.

3.3 Iteration 3

Iteration 3 of the reactor involved significantly increasing the cooling capacity. The cooler design from Iteration 2 was repeated and applied in series, effectively doubling the heat exchanger length. Additionally, the cooling water recycle drum was replaced with an IKA RC2 Green Control recirculating chiller, which maintained the cooling fluid temperature close to 5 °C. The modified heat exchanger design is shown in Figure 62.



Figure 62: Image of the high-throughput reactor (Iteration 3). R: Counter-current mixing reactor. H: Heater. HX: Heat exchanger (Shell: Cooling water, Tube: Reactor outlet).

The alterations to the cooling system showed excellent results, allowing the Downflow temperature to exceed 380 °C whilst maintaining a BPR temperature in the range 18-24 °C, throughout the same commissioning tests previously described. This level of control is excellent, especially given the large temperature ranges attainable within the reactor, and is suitable for experiments within this work.



Figure 63: Illustration of the high-throughput reactor (Iteration 3). T: Thermocouple, DF: Downflow, UF: Upflow, NRV: Non-return valve, PRV: Pressure-relief valve, CW: Cooling water, P: Pressure gauge and transducer, BPR: Back-pressure regulator (Automated).

The third iteration of the reactor resulted in a high-throughput reactor design which was safe to operate, could achieve the desired process conditions and had a small reactor volume, at just 16.9 ml. At this point the reactor could reasonably be used for experiments and the generation of data.

However, several sources of possible error were identified, primarily surrounding the stabilisation time and rig dead-volume; these are features which could easily be overlooked and later result in significant experimental error. For example, the automation protocols were developed to ensure the Downflow temperature is stable within 2% of the set-point temperature before starting the experiment. Three reactor volumes were typically sent to waste before then collecting and analysing the synthesised product. Figure 64 shows the temperature trace of automated scoping experiments at various set

conditions. While the process control surrounding the Downflow temperature is quick to respond, it is evident from the temperature trace that the reactor outlet temperature does not stabilise within the experiment time. Observing very similar temperature profiles for the reactor outlet and heater block, it is likely that the integrated reactor-heater design is the cause of the slow stabilisation time. Residual heat from the higher temperature Downflow tubing is transferred into the heater block, and then to the reactor itself. A simple solution lies in increasing the experiment time to allow stabilisation, however, this would result in the unnecessary waste of both time and materials. Instead, the rig was further modified to separate the heater and reactor components, as shown in Iteration 4.



Figure 64: PicoLog trace of automated scoping experiments. Back-pressure regulator (BPR) temperature range 20-26 °C. Reactor outlet temperature does not achieve steady state within thee given experiment time (5 minutes). Dashed line indicates expected temperature profile at extended reaction times.

3.4 Iteration 4

Iteration 4 includes modifications to the heater and changes to the arrangement and fittings selection in order to minimise dead volume within the rig.

To ensure a fast stabilisation time at the reactor outlet, the heater and reactor are separated into two distinct components. Figure 65 shows the new heater design, consisting of a 1000 W mineral band heater from Watlow, surrounding 3 m length of 0.125" tubing on an aluminium mechanical support.



Figure 65: New heater design, consisting of a 3 m length of 0.125" Swagelok® *316SS tubing, a custom aluminium mechanical support and a 1000 W mineral band heater supplied by Watlow.*

Several regions of unnecessary dead volume were identified from Iteration 3; these include the 0.625" cross-piece at the reactor, and non-essential thermocouple locations which require TEE-piece fittings. Dead volume describes regions of recirculation or accumulation of materials within the tubing and fittings of the rig. Dead volume can significantly affect the residence time distribution of fluid parcels, as it flows through the process; depending on the location and conditions of this dead volume, increased residence time could result in increased particle growth, agglomeration of particles, or accumulation of solids which could lead to blockages. For product quality purposes, it is therefore important to minimise unnecessary reactor dead volume, and minimise the fluid residence time distribution. Only dead volume after the reactor mixing point was considered to have any effect on the product quality; several components located before the reactor have intentional dead volume, such as the pressure relief valves and pressure transducers, to act as a buffer and protect these components from potentially damaging reagents.

The final reactor design is shown in Figure 66 and respective illustration in Figure 67; this design was used for all bench-scale experiments in Chapters 4-7 and has an internal working volume of 12.4 ml. Ideally, a study of the residence time distribution before and



Figure 66: Image of the high-throughput reactor (Iteration 4). R: Counter-current mixing reactor. H: Heater. HX: Heat exchanger (Shell: Cooling water, Tube: Reactor outlet). PG: Pressure Gauge. PRV: Pressure relief valve. BPR: Back pressure regulator.

after this iteration would have been performed using a suitable tracer and inline analysis; however, this was not possible due to time constraints and equipment availability.

No operational issues, such as pressure fluctuations, blockages or significant fouling were observed during the experimental work described in this thesis. This was aided by the automation protocols and experiment design, which included reactor flushing phases; this comprises 3-5 minutes of pumping deionised water and a cleaning agent (HNO₃ or NaOH, depending on the material case study – further details given in Chapter 4-7). The flushing phases ensure experiments are not able to 'bleed' into one another and confound results; while this approach is robust, there is a compromise in both the time and cost required per experiment.



Figure 67: Illustration of the high-throughput reactor (Iteration 4). T: Thermocouple, DF: Downflow, UF: Upflow, NRV: Non-return valve, PRV: Pressure-relief valve, CW: Cooling water, P: Pressure gauge and transducer, BPR: Back-pressure regulator (Automated).



Figure 68: Automated thermal cycling to test temperature response rates. Downflow temperature heats from ambient to 350 °C in under 7 minutes. Reactor outlet temperature stabilises within 2% in 2 minutes. Back pressure regulator (BPR) temperature range: 19-25 °C.

Figure 68 shows the temperature profile during a predetermined, automated thermal cycling programme. The process response time is excellent, with the reactor Downflow taking just 7 minutes to heat from ambient temperature to 350 °C, with a Downflow flowrate of 20 ml.min⁻¹. Furthermore, the reactor outlet trace shows that from the start of the experiment (identified by a small change to the temperature profile) the temperature stabilises to within 2% of a plateau in just 2 minutes, resulting in 3 minutes of run time at steady state conditions. A fast stabilisation time is essential for high-throughput experimentation, and the proposed reactor design shows excellent thermal control.

The final modification consisted of two additional Gilson 305 HPLC pumps, bringing the total to six. Having multiple pumps means that a wide range of flowrates, precursor concentrations and additives can be investigated with relative ease. The final PFD is shown in Figure 69.



Figure 69: Process flow diagram of the proposed autonomous reactor system. PAT: Process analytical technology, shown in flow-through (inline) arrangement. ML: Machine learning and optimisation algorithms.

3.5 Process Control

Process control is the ability to monitor and adjust parameters within a process in order to ensure consistency. For the hydrothermal process described in this work, temperature is one of the key parameters which can significantly affect the product quality; it is therefore imperative that these controllers are well tuned to the given process.

Industrial process control typically comprises of either 'On/Off' or three-term control, more commonly referred to as proportional-integral-derivative (PID) control. On/Off is the simplest approach, whereby the output is toggled from 0-100% in accordance to a predetermined dead-band. This results in significant process oscillation and often poor control of the process. Alternatively, PID control is typically far more accurate and responsive, and is often applied where a high degree of process control us required to ensure product quality.

During commissioning of the high-throughput reactor, the temperature controller was tuned using the 'Auto-tuning' function of the Eurotherm 3216e PID controller. Figure 70 shows the temperature trace before, during and after tuning of the controller; the rig demonstrates excellent control over process temperature, which serves to minimise error



Figure 70: Automatic PID tuning of the Eurotherm temperature controller and Watlow heater.

during the experiments in Chapters 4-7. The BPR ER3000 electro-pneumatic controller was also tuned using PID control to ensure fast response times.

3.6 Online Analysis Repeatability

In addition to ensuring reliability in the synthesis process, it is also important to ensure repeatability in sample measurement and analytical results. Using the hematite (a-Fe₂O₃) case study synthesis methods described in Chapter 5, a repeatability test was performed for the online dynamic light scattering (DLS) measurements.

This test was performed automatically using the reactor control graphical user interface (RC-GUI) with process set point conditions of Downflow temperature: 240 °C, Upflow and Downflow flowrates 15 ml.min⁻¹, respectively. All other process conditions were similar to those described in Chapter 5. The PicoLog temperature profile of the experiment is shown in Figure 71; in this case, the process was maintained at steady state conditions for one hour while discrete samples of product were sequentially injected into the DLS Flowcell every 5 minutes. No operational issues were observed within this one hour study. The recorded DLS measurements are shown in Table 2.



Figure 71: Online dynamic light scattering (DLS) analysis test 1, (Red Star): Experiment starts, (Black Stars): Sample injected into the DLS. At each sampling point, the DLS was injected with new sample, to identify steady state variability.

Table 2:	Repeatability	test for the	online	dynamic	light	scattering	(DLS)	instrument	and	injection
loop.										

Sample No.	1	2	3	4	5	6	7	8	9	10
Z-Average (nm)	40.2	38.6	40.4	40.7	35.5	34.9	39.1	43.6	43.5	38.2
Mean (nm)	39.5	(±2.7)								

To identify experiment cycle variation, the same test was performed with 6 repeat experiments, using the automation protocols outlined in Chapter 2; this test follows the same Standby-Heat-Run-Flush phases used for self-optimisation experiments, and so best emulates the potential sampling error for the investigation in Chapter 3.

The temperature trace is shown in Figure 72; each cycle within the test clearly shows the heating, run and flush phases previously described. In this instance, the 'Heating' phase utilises a reduced Upflow flowrate to conserve water; changing from 10 ml.min⁻¹ to 15 ml.min⁻¹ when the Downflow temperature measures between 2% of the set point. The Reactor Outlet trace shows a clear plateau within the 5 minutes of starting the 'Run' phase, and sudden decrease in temperature for the Downflow, Reactor Outlet and Heater Block components during the 'Flush' phases, due maximum flowrate of the water pumps (25 ml.min⁻¹ each) and temperature set point of 0 °C. The overall trace shows excellent reproducibility, which was essential for reducing the experimental error in self-optimised experiments. Prior to each 'Flush' phase, a sample was injected into the DLS instrument, with the recorded measurements shown in Table 3.



Figure 72: PicoLog temperature trace for replicate automated experiments to identify repeatability of process conditions, subsequent sample injection and analysis of particle size by dynamic light scattering (DLS).

Table 3: Repeatability test for the reactor system, online dynamic light scattering (DLS) instrument and injection loop.

Sample No.	1	2	3	4	5	6
Z-Average (nm)	43.0	42.2	46.0	44.5	41.6	43.8
Mean (nm)	43.9	(±1.3)				

Both tests show excellent reproducibility within their respective DLS measurements. It is unclear why there is discrepancy between the average measurements across both tests. One explanation could be a slight difference in the average reactor outlet temperature, at 151 and 155 °C, respectively; if this is the cause, then it demonstrates the sensitivity of the case study to the process conditions. However, there are multiple external sources of error, such as environment temperature, which were uncontrolled throughout these investigations.

3.7 Conclusions:

Following four significant design iterations, an autonomous continuous-flow hydrothermal reactor for nanomaterial synthesis was developed. The proposed final design demonstrates safe and robust operation, while maintaining a rapid response to changes in process conditions. A key feature of this design is range of attainable process conditions, meaning that the same reactor can be used for multiple case studies, providing chemical compatibility is observed.

The final reactor design shown in Figure 66 and Figure 67 was used for all bench-scale experiments, throughout chapters 3-6. The design permits easy modification of pump arrangement (Downflow: Upflow – 5:1, 4:2, 3:3, 2:4 or 1:5 are all feasible), as required. The PFD for each optimisation case study is given their respective chapters, with further details of any other modifications.

The autonomous system has been developed with two available online process analytical technologies (PATs), DLS and FTIR spectroscopy. The autonomous platform can easily be modified to accommodate alternative PATs, such as UV-Vis or Raman spectroscopy without significant changes to the pressurised rig or developed graphical user interfaces. This generalised approach means that many nanomaterial case studies can be investigated with the same primary platform, only altering the auxiliary instrumentation as required.

Chapter 4: Combining Evolutionary Optimisation and Machine Learning with High-Throughput Experimentation

4.0 Combining Evolutionary Optimisation and Machine Learning with High-Throughput Experimentation

This chapter introduces the concepts of machine learning, optimisation and highthroughput experimentation (HTE) to the flow synthesis of metal-organic frameworks (MOFs). Using the well-studied case study material HKUST-1, the autonomous reactor previously described in Chapter 2 is used in combination with evolutionary optimisation, while also training a machine learning model to enable prediction of experiment outcome. A brief overview of the HKUST-1 material, applications and synthesis methods is provided, with a timeline highlighting key publications in literature.

Offline characterisation by powder X-ray diffraction (PXRD), N₂ adsorption and scanning electron microscopy (SEM) are used to evaluate sample crystallinity and specific surface area in relation to the given process variables. Three Generations (1-3) of HKUST-1 experiments are run, across five variables, with a total of 52 experiments. Generation 3 is run in conjunction with an *in silico* search to prioritise expected high performing experiments and minimise unnecessary experimental cost.

The results show the highest surface area achieved in this work to be 1837 m^2g^{-1} which is very similar to the highest reported value produced in continuous-flow solvothermal synthesis, 1852 m^2g^{-1} by Rubio-Martinez *et al.* (See Table 4).

4.1 This work

As discussed in Chapter 1, one of the most recent and advanced examples of HTE in MOF synthesis was demonstrated by Moosavi *et al.* for the optimisation of HKUST-1, using a robotic microwave batch reactor [138]. In this work, the authors achieved the highest-reported surface area to date for HKUST-1, at 2045 m²g⁻¹ (See Table 4), whilst also training a machine learning model to capture 'Chemical Intuition'. The experimental work in this chapter aims to apply the same methodology as presented by Moosavi *et al.* but with the continuous-flow hydrothermal synthesis (CFHS) reactor system previously described to ensure a scalable route to production. HKUST-1 makes for an excellent case study material, and is also used here to enable an easy comparison of methods.

Following initial scoping work and literature studies, five variables; temperature, stoichiometry, flowrate (analogous to residence time and thus crystallisation time) and the %v/v of methanol and ethanol in the solvent. DMF is not used at any point in the process, including washing and activation, ensuring a greener synthesis route.

To reflect the reduced number of variables, the population size of each generation is reduced to 20, compared to 30 in the work by Moosavi *et al.*. Having demonstrated the effectiveness of genetic algorithms and machine learning models for HKUST-1 synthesis, it is therefore reasonable to use the same SyCo Finder application in this work. A minor modification to this strategy is demonstrated in the third generation, where a machine learning model is developed to provide an *in silico* search of new experiments, enabling prioritisation of experimental conditions – a feature discussed but not demonstrated in Moosavi *et al.*'s initial Cu-HKUST-1 optimisation.

The primary aim of this optimisation is to maximise BET specific surface area, however, the objective function is determined by the sample crystallinity, calculated *via* the FWHM of the diffraction pattern peaks. PXRD is used in the analysis of all samples due to the significantly faster method when compared to BET N₂ adsorption; following XRD analysis, the 6 out of 20 most crystalline samples will be further analysed by BET.

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This work therefore represents the first known published example of HTE combined with machine learning and optimisation for the flow synthesis of metal-organic frameworks.

4.2 HKUST-1 Synthesis

HKUST-1 (Hong Kong University of Science & Technology) is one of the most highlystudied MOFs, due to a high specific surface area and large pore volume [226]. First reported in 1999 [227], the most well-known analogue of HKUST-1 consists of Cu²⁺ ion nodes surrounded by 1,3,5-benzenetricarboxylate (BTC) organic linkers. The resulting framework exhibits a bimodal pore size distribution, with large and small pore diameters of 9 Å and 3.5 Å respectively [228].

Several analogues of HKUST-1 exist, typically consisting of metals with a +2 charge to achieve an overall neutral framework, including Mo²⁺, Cr²⁺, Ni²⁺ and Zn²⁺ [229, 230, 129, 231]; although examples using metals with a 3⁺ charge have also been synthesised, resulting in an overall charge for the structure [232, 233].



Figure 73: HKUST-1 2x2x2 Unit Cell Structure, generated from CIF 2300380 [254]

Figure 74 shows the dehydrated and hydrated state of HKUST-1 secondary building unit (SBU). Commonly referred to as a 'Paddlewheel' unit, the SBU consists of four 1,3,5benzenetricarboxylic acid linkers bridging two metal centres. In the hydrated state, one water molecule is coordinated to each of the metal centres; this is often the case when HKUST-1 is handled in air. Activation through vacuum and heating is usually sufficient to remove these water molecules, resulting in a coordinatively unoccupied Lewis acidic site.



Figure 74: Dehydrated (Left) and Hydrated (Right) Secondary Building Unit (SBU) of HKUST-1, demonstrating Paddlewheel type structure. Hydrogen atoms removed for clarity

This site is suitable for the selective binding of polar gas species, leading to the extensive exploration of HKUST-1 for use in gas separation and storage applications, in particular CO₂ adsorption for carbon capture, utilisation and storage (CCUS). Many synthesis routes have been reported for HKUST-1; these include microwave-assisted (MW) [234], mechano-chemical (MC) [235], electrochemical (EC) [236] and ultrasonic (US) [108] methods, however, the vast majority of research has surrounded the Hydro/Solvothermal approach (See Table 4). The vast majority or previously reported synthesis utilise conventional electrical heating (CEH) and batch processes. There have been relatively few reports of continuous flow-synthesis of HKUST-1, despite the potential scalability advantages of flow technologies (See Table 4).

Table 4: Timeline of milestones in HKUST-1 Synthesis, highlighting new synthesis methods or due to high reported surface area. First author is used for reference. US: Ultrasound, MW: Microwave, MC: Mechanochemical, EC: Electrochemical, RT: Room Temperature, TSE: Twin Screw Extrusion. †Langmuir Specific Surface Area. Conventional Electric Heating used unless otherwise stated. ‡Highest reported value.

Author	Year	Synthesis Method	BET Surface Area (m²g⁻¹)	Solvent	Ref
Chui	1999	Solvothermal	692	H ₂ O, EtOH	[227]
Wang	2002	Solvothermal	964 -1333	H ₂ O, EtOH	[237]
Chowdhurry	2008	Solvothermal	1482	DMF, H2O & EtOH	[238]
Li	2009	US	1100	DMF, EtOH	[239]
Seo	2009	MW	1392	H ₂ O, EtOH	[234]
Schlesinger	2010	Solvothermal MW US EC Reflux MC	1143 1321 1206-1499 1119-1421 897-1270 424-1253	H2O, EtOH No Solvent	[236]
Нио	2013	RT Synthesis	1403-1680	H ₂ O	[240]
Kim	2013	Solvothermal, Flow	1673	H ₂ O, EtOH	[241]
Yang	2014	Solvothermal	1922	DMF	[242]
Rubio-Martinez	2014	Solvothermal, Flow	1852	H ₂ O, EtOH	[114]
Crawford	2015	MC	1738	No Solvent	[243]
McKinstry	2017	Solvothermal, Flow MW, Flow	1200-2200† 1857†	EtOH	[244]
Elsaidi	2017	RT Synthesis	2014	MeOH	[245]
Ми	2018	Solvothermal	1542	H ₂ O, EtOH	[246]
Chen	2018	Solvothermal	801-1615	MeOH, EtOH	[247]
Moosavi	2019	MW	2045‡	DMF, H₂O, MeOH, EtOH, iPrOH	[138]
Vepsäläinen	2021	EC	1716	H ₂ O, EtOH	[248]

4.3 Variables & Optimisation

This work adopts a similar synthesis strategy to that shown in the solvothermal route, reported by Rubio-Martinez *et al.* [114]. First, 1,3,5-benzenetricarboxylic acid (H₃BTC) ligand is deprotonated by means of a suitable base and dissolved into deionised water, the resulting ligand solution is then reacted with an aqueous solution of copper (II) nitrate, resulting in the precipitation of the sky blue solid reaction product. Factors such as reaction temperature, stoichiometry and the incorporation of alcohol co-solvents are all investigated with the aim of achieving the maximum crystallinity and specific surface area. Higher crystallinity is determined by means of minimising the full width at half-maximum (FWHM) of the three most intense reflections in the powder X-ray diffraction (PXRD) pattern. Specific surface area is determined by Brunauer-Emmet-Teller (BET) method, using N₂ adsorption at 77 K.

Five variables were considered for the optimisation of HKUST-1, as shown in Table 5. To enable comparison between samples, the concentrations of 1,3,5-benzenetricarboxylic acid and trimethylamine (TEA) are fixed at 0.02 M and 0.06 M respectively in the reactor Downflow. The molar ratio of Cu(NO₃)₂ to 1,3,5-benzenetricarboxylic acid is investigated; while the ideal crystal structure consists of a 3:2 stoichiometry (Cu²⁺:BTC) [227], a wide range of reaction stoichiometry is reported with varying success.

It has previously been shown that incorporating varying ethanol co-solvent concentrations into the aqueous reaction mixture can modulate the growth of HKUST-1 crystals, which affects both the crystallinity and defect density of the product [249]. Here, both ethanol and methanol are investigated independently, allowing a total alcohol concentration range of 0-40 %v/v in the reactor outlet (0-20 %v/v for methanol and ethanol respectively). Methanol was selected due to similarity in physical properties, but significantly reduced cost when compared to ethanol [250].

Process parameters, temperature and flowrate, are also varied to investigate the reaction kinetics. The preheated Downflow has a temperature range of 50-200 °C, before mixing

with the unheated Upflow, to give a total reactor flowrate has range 20-30 ml.min⁻¹, equally distributed between the reactor Upflow and Downflow.

Table 5: Process Constraints for HKUST-1 Synthesis & Evolutionary Optimisation. $H_3BTC = 1,3,5$ -benzenetricarboxylic acid.

Variable	Synthesis Constraints	Notes
Temperature	50 – 200 [°C]	Downflow temperature
Reactant Ratio	1 – 5 [M ratio]	Molar ratio of Cu(NO3)2 to H3BTC ligand
Methanol	0 - 20 [%v/v]	%v/v in reactor outlet
Ethanol	0 - 20 [%v/v]	%v/v in reactor outlet
Flowrate	20 – 30 [ml.min ⁻¹]	Equal ratio Downflow to Upflow

4.4 Reactor Layout:



Figure 75: Schematic of Automated High-Throughput Synthesis Reactor for HKUST-1 Optimisation. BTC = 1,3,5-benzenetricarboxylic acid. TEA = trimethylamine.



Figure 76: Reactor setup during HKUST-1 Evolutionary Optimisation Experiments. (Auto-sampler & PC not shown)

4.5 Experimental & Analysis:

In each generation, the precursor solutions and post-processing steps are as follows. All materials used through this study were purchased from the vendors as specified below. The materials were used as sold, without additional processing or modifications.

Stock solution make-up corresponds to Pumps 1-6. Stock solution 1 & 5 [5 L]: De-Ionised H₂O. Stock solution 2 [1 L]: 0.10 M 1,3,5-benzenetricarboxylic acid (BTC) (\geq 95%, 22.120g – Sigma Aldrich) + 0.30 M trimethylamine (TEA) (\geq 99%, 30.906g – Alfa Aesar). Stock solution 3 [1 L]: Methanol (94-96%, Alfa Aesar). Stock solution 4 [1 L]: Ethanol (94-96%, Alfa Aesar). Stock solution 6 [1 L]: 0.15 M Copper (II) Nitrate Trihydrate (\geq 98%, 36.980g – Sigma Aldrich)

All experimental conditions were determined using the SyCo Finder from Mossavi *et al.* [139]. Experiment conditions were imported into the custom reactor control graphical user interface (RC-GUI) in LabVIEW and converted into process set points (temperature and respective flowrates) based on stock solution concentrations.

For each experiment, the RC-GUI follows a cyclic Standby-Heating-Experiment-Flush pattern. To minimise waste of stock solutions, only water is pumped during the Standby,
Heating and Flush stages. During the heating stage, the GUI does not proceed until the measured heater outlet temperature is within 2% tolerance of the set point.

All samples are collected using a customised Gilson FC 204 Fraction Collector, combined with a 24 V solenoid two-way valve controlled by an Arduino. Prior to collection, each experiment ran for two reactor volumes (where $V_{Reactor} = 50$ ml) to ensure steady state operation.

For each experiment, a 40 ml sample was collected in a 50 ml polypropylene centrifuge tube. The solids were separated from the supernatant *via* sequential centrifugation at 3500 rpm for 5 minutes. After each centrifugation step, the pellet was re-dispersed in methanol. This process was repeated three times to remove any unreacted starting materials from within the MOF pores and replace pore-bound water with more volatile methanol. Samples were then dried overnight at 80°C under vacuum (1000 mbar) to remove any residual solvent and yield the coordinatively unsaturated MOF structure.

Vacuum activation was accompanied by a characteristic colour change from sky blue to navy/purple. Following activation, care was taken to minimise exposure to atmospheric moisture during all subsequent manipulations.

4.6 Generation 1: Initialisation *via* Diverse Set

The initial conditions are determined using the MaxMin method [251] to attain the 20 most diverse possible experiments within the given design space. These experiments are generated using the SyCo Finder application [139], which will be used extensively during this investigation.

Table 6: Experimental Conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 1. Reactant ratio = Ratio of $Cu(NO_3)_2$: 1,3,5-benzenetricarboxylic acid linker. Product mass refers to the dry solid retained after completing the washing and activation steps. Temperature refers to the preheated Downflow temperature.

Exp. Number	Temperature [°C]	Reactant ratio	МеОН [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	Product Mass [g.40ml ⁻¹]
GA_1_1	50.0	1.00	0.00	0.00	20.0	0.0853
GA_1_2	200.0	5.00	20.00	20.00	30.0	0.1329
GA_1_3	50.0	1.00	10.00	20.00	30.0	0.0946
GA_1_4	200.0	1.00	20.00	0.00	25.0	0.0763
GA_1_5	200.0	3.00	0.00	20.00	20.0	0.1149
GA_1_6	50.0	5.00	20.00	10.00	20.0	0.1392
GA_1_7	125.0	5.00	0.00	0.00	30.0	0.0973
GA_1_8	125.0	1.00	20.00	20.00	20.0	0.0961
GA_1_9	200.0	1.00	0.00	10.00	30.0	0.0833
GA_1_10	50.0	3.00	20.00	0.00	30.0	0.1240
GA_1_11	50.0	5.00	0.00	20.00	25.0	0.1332
GA_1_12	200.0	5.00	10.00	0.00	20.0	0.1216
GA_1_13	50.0	1.00	0.00	0.00	30.0	0.0837
GA_1_14	50.0	1.00	0.00	20.00	20.0	0.0916
GA_1_15	50.0	1.00	20.00	0.00	20.0	0.0859
GA_1_16	200.0	1.00	0.00	0.00	20.0	0.0719
GA_1_17	200.0	1.00	20.00	20.00	30.0	0.0936
GA_1_18	125.0	3.00	10.00	10.00	25.0	0.1312
GA_1_19	50.0	5.00	0.00	0.00	20.0	0.1069
GA_1_20	50.0	5.00	20.00	20.00	30.0	0.1309

All experiments within Generation 1 resulted in the production of solids with a light blue colour, as shown in Figure 77, consistent with previous literature reports [252]. In each case, the dry mass of washed product was recorded, which can be later used in combination with the PXRD and BET data to determine the commercially optimum synthesis conditions.



Figure 77: HKUST-1 samples from Generation 1 as-synth, collected via the Auto-sampler (left) and a typical HKUST-1 as-synthesised sample showing light blue colour (right)

Upon washing and activation, there was a noticeable colour change from light to dark blue in all samples, as shown in Figure 78. This is likely due to a change in the coordination number of copper within the sample from six to four; this can be attributed to the removal of water or other coordinated solvents from the copper sites [252, 253].



Figure 78: Typical HKUST-1 as-synthesised sample (left) and representative example of the colour change due to the washing & activation method (right)



Figure 79: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 1 Experiments 1-5. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



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Figure 80: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 1 Experiments 6-10. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 81: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 1 Experiments 11-15. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 82: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 1 Experiments 16-20. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]

Figure 79 to Figure 82 show the diffraction patterns for all samples produced in Generation 1. The samples demonstrate significant variation in both crystallinity and phase purity, which is to be expected, given that the purpose of Generation 1 is to investigate the most diverse range of conditions possible within the 5-dimensional design space.

The diffraction data shows 12 samples with high crystallinity and in close match the simulated pattern [254]. The FWHM was used to rank these samples as a measure of crystallinity; to avoid bias due to preferred orientation effects, the average FWHM of the 3 most intense reflections was used. In all samples, this corresponds to the (200), (220) and (222) reflections at $2\Theta = 6.8^{\circ}$, 9.5° and 11.7° respectively.

There is slight variation in the intensity ratios of the (200) to (220) plane, which could be attributed to the hydration state of powder samples. It has previously been reported that the reduction in intensity of the (111) and (200) planes can be related to the hydration of HKUST-1 and subsequent loss of FCC crystal structure [255, 256].

Samples showing the presence of significant additional peaks in the diffraction pattern, indicating poor phase purity, were represented by a FWHM penalty value of '0.5' to evaluate the fitness function when running the evolutionary algorithm. The samples with the six smallest FWHM values were then characterised using BET N_2 adsorption.

Vacuum activation during N₂ adsorption preparation was accompanied by a characteristic colour change from sky blue to navy/purple. Following activation, care was taken to minimise exposure to atmospheric moisture during all subsequent manipulations.



Table 7: HKUST-1 Generation 2 - BET Specific Surface Area Data & Synthesis Conditions

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	BET Specific Surface Area [m²g⁻¹]
GA_1_3	50	1	10	20	30	1514
GA_1_5	200	3	0	20	20	1663
GA_1_6	50	5	20	10	20	1648
GA_1_10	50	3	20	0	30	1813
GA_1_11	50	5	0	20	25	1767
GA_1_18	125	3	10	10	25	1813

HKUST-1 Generation 1 - N₂ Adsorption Isotherms

The BET isotherms from Generation 1 show specific surface areas within the known range for HKUST-1 (shown in Table 4) with experiments GA_1_{10} and GA_1_{18} showing the highest values at 1813 m²g⁻¹. All samples demonstrate a Type I isotherm according to IUPAC classification, indicating a microporous structure (i.e. pores <2 nm) [235, 257].

The large surface areas exhibited by all samples suggests that the washing, activation and degassing steps used are sufficient to remove guest molecules from within the pores; these steps will therefore remain consistent for subsequent generations.

Interestingly, the six samples showing a high BET surface area were all produced by drastically different synthesis conditions; this suggests that the surface response within the available design space is complex and could potentially contain many local optima, which explains the large range of values reported in literature (See Table 4).

Table 8 shows the synthesis conditions and characterisation data for samples produced in Generation 1. The FWHM data was used to determine a fitness value, which was entered into the SyCo Finder application to generate a new set of conditions [139].

Fitness (*Objective Function*) = 1 - FWHM

Table 8: Synthesis conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 1. Reactant ratio = Ratio of $Cu(NO_3)_2$: 1,3,5benzenetricarboxylic acid linker. Product mass refers to the dry solid retained after completing the washing and activation steps. FWHM = Full width at half-maximum of the 3 most intense reflections in the HKUST-1 pattern. Crystallite size was determined through use of the Scherrer equation and FWHM values. Temperature refers to the preheated Downflow temperature. Yield was calculated based on full conversion of the 1,3,5-benzenetricarboxilic acid linker. \dagger FWHM and crystallite size values could not be obtained due to poor phase purity, a penalty value of FWHM=0.5 is used to enable the algorithm to progress.

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	FWHM	Crystallite Size [nm]	BET Surface Area [m²g ⁻¹]	Product Mass [g/40ml]	Yield [%]
GA_1_1	50.0	1.00	0.00	0.00	20.0	0.5 †	N/A †		0.0853	35.2
GA_1_2	200.0	5.00	20.00	20.00	30.0	0.234	345.7		0.1329	54.9
GA_1_3	50.0	1.00	10.00	20.00	30.0	0.214	381.6	1514	0.0946	39.1
GA_1_4	200.0	1.00	20.00	0.00	25.0	0.5 †	N/A †		0.0763	31.5
GA_1_5	200.0	3.00	0.00	20.00	20.0	0.201	406.1	1663	0.1149	47.5
GA_1_6	50.0	5.00	20.00	10.00	20.0	0.204	400.1	1648	0.1392	57.5
GA_1_7	125.0	5.00	0.00	0.00	30.0	0.215	377.9		0.0973	40.2
GA_1_8	125.0	1.00	20.00	20.00	20.0	0.219	371.7		0.0961	39.7
GA_1_9	200.0	1.00	0.00	10.00	30.0	0.5 †	N/A †		0.0833	34.4
GA_1_10	50.0	3.00	20.00	0.00	30.0	0.182	449.6	1813	0.1240	51.2
GA_1_11	50.0	5.00	0.00	20.00	25.0	0.208	391.4	1767	0.1332	55.0
GA_1_12	200.0	5.00	10.00	0.00	20.0	0.5 †	N/A †		0.1216	50.2
GA_1_13	50.0	1.00	0.00	0.00	30.0	0.5 †	N/A †		0.0837	34.6
GA_1_14	50.0	1.00	0.00	20.00	20.0	0.5 †	N/A †		0.0916	37.9
GA_1_15	50.0	1.00	20.00	0.00	20.0	0.5 †	N/A †		0.0859	35.5
GA_1_16	200.0	1.00	0.00	0.00	20.0	0.5 †	N/A †		0.0719	29.7
GA_1_17	200.0	1.00	20.00	20.00	30.0	0.235	345.3		0.0936	38.7
GA_1_18	125.0	3.00	10.00	10.00	25.0	0.171	482.4	1813	0.1312	54.2
GA_1_19	50.0	5.00	0.00	0.00	20.0	0.269	297.7		0.1069	44.2
GA_1_20	50.0	5.00	20.00	20.00	30.0	0.226	358.7		0.1309	54.1

4.7 Generation 2: Set point generation *via* SyCo Finder & G1 fitness valuation

Following input into the SyCo Finder web application [139], the synthesis conditions for Generation 2 were created. As before, these conditions were run autonomously, collecting 40 ml samples for further processing and analysis. The dry product mass after washing and activation is shown in Table 9, along with the synthesis conditions.

Table 9: Synthesis conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 2. Reactant ratio = Ratio of $Cu(NO_3)_2$: 1,3,5-benzenetricarboxylic acid linker. Product mass refers to the dry solid retained after completing the washing and activation steps. Temperature refers to the preheated Downflow temperature.

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	Product Mass [g.40ml ⁻¹]
GA_2_1	171.0	3.00	4.45	17.41	23.1	0.1325
GA_2_2	50.0	5.00	0.00	0.00	20.0	0.1351
GA_2_3	89.3	1.00	11.27	3.97	30.0	0.0911
GA_2_4	100.1	1.26	5.55	6.63	23.9	0.1218
GA_2_5	50.0	5.00	20.00	19.19	28.2	0.1216
GA_2_6	72.5	3.15	15.45	12.58	30.0	0.1369
GA_2_7	154.5	1.16	9.93	20.00	20.0	0.1101
GA_2_8	73.8	3.07	19.32	20.00	23.4	0.1244
GA_2_9	118.8	2.49	20.00	14.98	30.0	0.1338
GA_2_10	139.3	1.00	0.14	0.00	20.0	0.0892
GA_2_11	82.6	5.00	17.10	4.99	27.1	0.1365
GA_2_12	137.7	5.00	1.16	0.00	23.4	0.1300
GA_2_13	50.0	5.00	0.00	0.01	24.9	0.1250
GA_2_14	55.5	1.69	2.95	2.26	20.0	0.1312
GA_2_15	88.4	2.11	20.00	0.63	30.0	0.1239
GA_2_16	67.2	1.44	20.00	12.23	20.6	0.1423
GA_2_17	50.0	5.00	0.00	20.00	25.0	0.1358
GA_2_18	50.0	1.00	10.00	20.00	30.0	0.0947
GA_2_19	91.9	2.34	9.27	18.06	22.6	0.1423
GA_2_20	74.5	4.25	14.96	20.00	21.3	0.1437

Similar to Generation 1, the average FWHM of the three most intense peaks was used to rank experiments, with the six best performing samples being further analysed by BET N_2 adsorption. Table 10 shows the BET specific surface area for these experiments, with several experiments exhibiting surface areas >1700 m²g⁻¹.



Figure 84: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 2 Experiments 1-5. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



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Figure 85: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 2 Experiments 6-10. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 86: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 2 Experiments 11-15. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



HKUST-1(Cu) Evolutionary Optimisation - PXRD Patterns

Figure 87: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 2 Experiments 16-20. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 88: HKUST-1 Generation 2 - BET N₂ Adsorption Isotherms

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	BET Specific Surface Area [m²g⁻¹]
GA_2_6	72.5	3.15	15.45	12.58	30.0	1563
GA_2_7	154.5	1.16	9.93	20.00	20.0	1682
GA_2_15	88.4	2.11	20.00	0.63	30.0	1809
GA_2_16	67.2	1.44	20.00	12.23	20.6	1778
GA_2_17	50.0	5.00	0.00	20.00	25.0	1784
GA_2_19	91.9	2.34	9.27	18.06	22.6	1650

Table 10: HKUST-1 Generation 2 - BET Specific Surface Area Data & Synthesis Conditions

Table 11: Experimental Conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 2. Reactant ratio = Ratio of $Cu(NO_3)_2$: 1,3,5-benzenetricarboxylic acid linker. Product mass refers to the dry solid retained after completing the washing and activation steps. FWHM = Full width at half-maximum of the 3 most intense reflections in the HKUST-1 pattern. Crystallite size was determined through use of the Scherrer equation and FWHM values. Temperature refers to the preheated Downflow temperature. Yield was calculated based on full conversion of the 1,3,5-benzenetricarboxilic acid linker.

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	FWHM	Crystallite Size [nm]	BET Surface Area [m²g⁻¹]	Product Mass [g/40ml]	Yield [%]
GA_2_1	171.0	3.00	4.45	17.41	23.1	0.222	364.8		0.1325	54.8
GA_2_2	50.0	5.00	0.00	0.00	20.0	0.227	355.4		0.1351	55.8
GA_2_3	89.3	1.00	11.27	3.97	30.0	0.297	270.2		0.0911	37.6
GA_2_4	100.1	1.26	5.55	6.63	23.9	0.326	244.9		0.1218	50.3
GA_2_5	50.0	5.00	20.00	19.19	28.2	0.216	375.9		0.1216	50.2
GA_2_6	72.5	3.15	15.45	12.58	30.0	0.183	448.9	1563	0.1369	56.6
GA_2_7	154.5	1.16	9.93	20.00	20.0	0.159	524.2	1682	0.1101	45.5
GA_2_8	73.8	3.07	19.32	20.00	23.4	0.211	385.0		0.1244	51.4
GA_2_9	118.8	2.49	20.00	14.98	30.0	0.209	388.4		0.1338	55.3
GA_2_10	139.3	1.00	0.14	0.00	20.0	0.291	275.8		0.0892	36.9
GA_2_11	82.6	5.00	17.10	4.99	27.1	0.223	361.8		0.1365	56.4
GA_2_12	137.7	5.00	1.16	0.00	23.4	0.239	337.5		0.1300	53.7
GA_2_13	50.0	5.00	0.00	0.01	24.9	0.199	409.3		0.1250	51.7
GA_2_14	55.5	1.69	2.95	2.26	20.0	0.347	232.0		0.1312	54.2
GA_2_15	88.4	2.11	20.00	0.63	30.0	0.164	506.1	1809	0.1239	51.2
GA_2_16	67.2	1.44	20.00	12.23	20.6	0.160	518.2	1778	0.1423	58.8
GA_2_17	50.0	5.00	0.00	20.00	25.0	0.172	480.5	1784	0.1358	56.1
GA_2_18	50.0	1.00	10.00	20.00	30.0	0.210	386.4		0.0947	39.1
GA_2_19	91.9	2.34	9.27	18.06	22.6	0.174	473.9	1650	0.1423	58.8
GA_2_20	74.5	4.25	14.96	20.00	21.3	0.188	435.7		0.1437	59.4

4.8 Generation 3: Combined SyCo Finder with *In Silico* search

The results from Generation 1 and 2 show a notable increase in the average fitness function value, as well as increased average specific surface area and product mass. It is therefore reasonable to continue the synthesis optimisation with this method until a time, material or cost limit is reached.

While evolutionary algorithms are able to determine favourable regions of the design space with a high degree of confidence, they do not converge upon a single set of conditions unless a specific stop condition is met. Furthermore, genetic and evolutionary optimisers have the inherent flaw of only considering data from the previous generation. This can result in the unnecessary repetition of previous experiments, or mutations which have previously been demonstrated as ineffective.

To avoid the issue of repetition, experiments in Generation 3 were designed using a combination of the SyCo Finder application and an *in silico* search, by means of a supervised machine learning (SML) model. Results from G1 and G2 were combined into



Figure 89: Comparison of Model Prediction against Actual Training Data from Generation 1 & 2 Samples

one dataset and the evolutionary optimiser was then run as before, generating 40 new experiments (Population of G1 + G2).

In parallel, the existing 40 data points were used to develop a machine learning model, trained by Random Forest using the Statistics and Machine Learning Toolbox in MATLAB 2020a [225]. The trained model was then used to provide an *in silico* prediction of the proposed experiments for Generation 3. During this process, 90% of the data was used for training the model, while the remaining 10% was used for validation and testing.

Following conditioning of the trained model (regularisation and shrinking), the number of trees was reduced to 100, corresponding to a mean-squared error (MSE) of 0.11 in the test data, which is suitable for predicting synthesis outcome for the purpose of screening experiments, shown in Figure 90. A significant proportion of the model error is likely attributed to the penalty value applied to samples with low phase purity; applying a more suitable quantitative analysis for all samples would likely reduce the model error further.



Figure 90: Mean squared error plot for the supervised machine learning model, used to provide in silico predictions for Generation 3 experiments.

In addition to predicting experiment outcome, the model can also be used to provide the weighted importance of variables, shown in Figure 91. This knowledge can be implemented in further optimisation during this study to improve exploration efficiency, or can also be applied in the optimisation of similar analogues and MOFs.



Figure 91: Weighted importance of variables for HKUST-1 synthesis, as determined by the supervised machine learning model. ReaRatio = Reactant ratio of $Cu(NO_3)_2$: 1,3,5-benzenetricarboxylic acid.

To produce the experiments for Generation 3, the SyCo Finder is run using the data from both G1 and G2, generating 40 new experiments; these experiment conditions are then run through the machine learning model to provide an initial prediction of reaction success. Using the objective function score, the experiments can be ranked and prioritised to reduce experimental cost. The full list of possible experiments and predicted outcome is shown in Table 12, with highlighted experiments selected for synthesis and analysis. Table 12: In Silico Search using machine learning model, trained using data from G1 & G2. Experiment outcome is predicted. FWHM = Full width at half-maximum of the 3 most intense reflections. †Experiments selected for execution, based on predicted FWHM.

Exp.	Temperature	Reactant	МеОН	EtOH	Overall	FWHM
Number	[°C]	ratio	[%v/v]	[%v/v]	Flowrate [ml.min ⁻¹]	[Predicted]
1 †	129.8	2.5	7.6	12.7	20.5	0.170
2†	137.0	1.5	15.5	20.0	21.7	0.176
3†	128.4	3.7	11.3	20.0	20.9	0.181
4 †	58.8	4.3	1.9	20.0	21.9	0.185
5 †	117.5	3.0	9.7	18.9	17.5	0.191
6†	62.0	2.4	20.0	11.9	20.0	0.194
7 †	55.9	1.2	20.0	12.2	20.3	0.195
8†	70.1	4.6	12.6	13.2	30.0	0.196
9†	105.1	3.0	10.8	12.8	23.5	0.198
10 †	90.6	5.0	10.3	16.0	29.8	0.202
11	50.0	5.0	17.8	12.9	20.8	0.204
12	175.0	1.9	14.9	13.6	20.6	0.205
13	50.0	4.0	20.0	17.9	30.0	0.207
14	148.3	3.7	22.2	19.9	27.7	0.208
15	80.0	2.4	21.1	16.1	28.0	0.212
16	109.5	5.0	0.0	2.2	29.0	0.213
17	50.0	5.0	17.5	13.0	29.4	0.215
18	147.1	2.0	10.0	15.6	28.4	0.218
19	155.3	1.5	17.4	20.0	20.0	0.219
20	98.5	2.4	6.3	9.0	21.8	0.224
21	50.0	3.2	20.0	16.3	27.7	0.225
22	87.9	1.4	20.0	6.7	24.9	0.227
23	126.2	3.2	19.4	2.8	28.5	0.228
24	84.3	2.2	14.4	6.2	25.1	0.228
25	50.0	1.4	14.6	16.2	27.1	0.229
26	50.0	1.7	0.0	20.0	22.0	0.233
27	165.4	1.5	5.9	21.9	29.8	0.233
28	82.0	1.1	5.8	18.6	29.2	0.238
29	147.4	3.8	8.2	0.0	26.4	0.240
30	50.4	2.2	0.3	13.6	23.7	0.250
31	181.4	3.8	2.8	19.5	28.1	0.257
32	50.8	4.0	9.3	1.0	20.3	0.257
33	50.0	3.5	2.8	0.7	27.9	0.259
34	196.3	4.9	20.0	14.2	25.4	0.261
35	68.9	1.0	10.0	20.0	20.9	0.284
36	69.6	2.3	19.1	4.1	22.9	0.284
37	146.7	0.0	13.6	15.8	26.4	0.302
38	99.3	2.2	6.5	8.1	21.0	0.311
39	50.0	1.0	0.0	0.0	30.0	0.492
40	91.6	1.0	0.0	12.1	25.2	0.519

Table 13 shows the synthesis conditions and yield data for Generation 3. Experiments 1-10 were selected based on their generation through the SyCo Finder and ranked using the *in silico* prediction. As before, all samples were analysed *via* PXRD, with the diffraction patterns shown in Figure 92 to Figure 94.

Table 13: Synthesis conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 3. *Experiments 11 and 12 were randomly selected replicates of previous experiments which were used to determine the experimental error. (See section 4.10 Error Analysis)

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	Product Mass [g.40ml ⁻¹]
GA_3_1	129.8	2.50	7.60	12.70	20.5	0.1311
GA_3_2	137.0	1.50	15.50	20.00	21.7	0.1468
GA_3_3	128.4	3.70	11.30	20.00	20.9	0.1395
GA_3_4	58.8	4.30	1.90	20.00	21.9	0.1388
GA_3_5	117.5	3.00	9.70	18.90	20.0	0.1448
GA_3_6	62.0	2.40	20.00	11.90	20.0	0.1448
GA_3_7	55.9	1.20	20.00	12.20	20.3	0.1316
GA_3_8	70.1	4.60	12.60	13.20	30.0	0.1439
GA_3_9	105.1	3.00	10.80	12.80	23.5	0.1500
GA_3_10	90.6	5.00	10.30	16.00	29.8	0.1427
GA_3_11*	88.4	2.10	20.00	0.60	30.0	0.1394
GA_3_12*	50.0	3.00	20.00	0.00	30.0	0.1485

Table 14 shows that in all cases, the experiments in Generation 3 performed better than predicted by the trained model; the size of this error is likely heavily influenced by the use of a penalty value applied to samples with poor crystallinity or phase purity. Retraining the model using only samples which can be more precisely compared would likely reduce the magnitude of this error.

Exp Number	FWHM – Actual	FWHM – Predicted	Error [%]
GA_3_1	0.148	0.170	14.9
GA_3_2	0.153	0.176	15.0
GA_3_3	0.179	0.181	1.1
GA_3_4	0.163	0.185	13.5
GA_3_5	0.166	0.191	15.1
GA_3_6	0.172	0.194	12.8
GA_3_7	0.152	0.195	28.3
GA_3_8	0.177	0.196	10.7
GA_3_9	0.172	0.198	15.1
GA_3_10	0.194	0.202	4.1
		Mean Absolute Error (%)	13.1
		Mean Squared Error (%)	5.56

Table 14: HKUST-1 Generation 3 - Actual vs. Predicted full-width at half maximum (FWHM) Values and Average Error



Figure 92: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 3 Experiments 1-4. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 93: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 3 Experiments 4-6. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



HKUST-1(Cu) Evolutionary Optimisation - PXRD Patterns

Figure 94: X-Ray Diffraction Patterns for HKUST-1 Evolutionary Algorithm Optimisation, Generation 3 Experiments 7-9. Full at half-maximum value used for the fitness function is shown. Simulated pattern generated from CIF [254]



Figure 95: HKUST-1 Generation 3 - N₂ Adsorption Isotherms (Samples 1-6)



Figure 96: HKUST-1 Generation 3 - N₂ Adsorption Isotherms (Samples 7-12)

Table 15: Experimental Conditions and collected sample mass for HKUST-1 Evolutionary Optimisation, Generation 2. Reactant ratio = Ratio of $Cu(NO_3)_2$: 1,3,5-benzenetricarboxylic acid linker. Product mass refers to the dry solid retained after completing the washing and activation steps. FWHM = Full width at half-maximum of the 3 most intense reflections in the HKUST-1 pattern. Crystallite size was determined through use of the Scherrer equation and FWHM values. Temperature refers to the preheated Downflow temperature. Yield was calculated based on full conversion of the 1,3,5-benzenetricarboxilic acid linker. *Samples were selected for replication from previous generations to assess repeatability.

Exp. Number	Temperature [°C]	Reactant ratio	MeOH [%v/v]	EtOH [%v/v]	Overall Flowrate [ml.min ⁻¹]	FWHM	Crystallite Size [nm]	BET Surface Area [m²g⁻¹]	Product Mass [g/40ml]	Yield [%]
GA_3_1	129.8	2.50	7.60	12.70	20.5	0.148	566.5	1815	0.13	54.2
GA_3_2	137.0	1.50	15.50	20.00	21.7	0.153	545.0	1786	0.15	60.7
GA_3_3	128.4	3.70	11.30	20.00	20.9	0.179	458.3	1699	0.14	57.6
GA_3_4	58.8	4.30	1.90	20.00	21.9	0.163	507.5	1820	0.14	57.4
GA_3_5	117.5	3.00	9.70	18.90	20.0	0.166	497.2	1774	0.14	59.8
GA_3_6	62.0	2.40	20.00	11.90	20.0	0.172	477.8	1740	0.14	59.8
GA_3_7	55.9	1.20	20.00	12.20	20.3	0.152	549.0	1721	0.13	54.4
GA_3_8	70.1	4.60	12.60	13.20	30.0	0.177	464.4	1742	0.14	59.5
GA_3_9	105.1	3.00	10.80	12.80	23.5	0.172	480.2	1812	0.15	62.0
GA_3_10	90.6	5.00	10.30	16.00	29.8	0.194	421.6	1721	0.14	59.0
GA_3_11*	88.4	2.10	20.00	0.60	30.0	0.147	571.5	1837	0.14	57.6
GA_3_12*	50.0	3.00	20.00	0.00	30.0	0.161	517.6	1827	0.15	61.4

4.9 SEM Analysis



Figure 97: SEM Images for HKUST-1 GA_3_11 (Left) and GA_3_12 (Right)

The morphology and particle size of two samples from this study was determined from SEM analysis (Figure 97). Images of GA_3_11 and GA_3_12 confirm that the samples are highly crystalline. The two samples show very similar morphologies and primarily octahedral structures, which are similar to those reported by Chen *et al.* [247].

The particle size and distribution is shown in Figure 98 and Figure 99. The crystal sizes are in the range 100-3000 nm, although the mean particle size and distribution is similar for both samples, with a mean particle size of 975 nm (\pm 311) for GA_3_11 and 982 nm (\pm 368) for GA_3_12.



Figure 98: Particle size and distribution from SEM analysis for sample GA_3_11. Mean = 975 nm, Standard Deviation = 311 nm



Figure 99: Particle size and distribution from SEM analysis for sample GA_3_12. Mean = 982 nm, Standard Deviation = 368 nm

4.10 Error Analysis

Automated and robotic reactors have previously been demonstrated as more reliable than comparable manual methods [258]. However, experimental error still exists in highthroughput and robotic reactors and it is important to determine the extent of this prior to finalising process judgement.

Many publications acknowledge error in analytical methods, but few report the repeat of entire experimental datasets, despite the relative cost of repeats being very low in highthroughput reactors. Given the sensitivity of MOF synthesis to minor variations in procedure, one can understand that even very small errors in process conditions could potentially result in large variation in the final product characteristics.

In this work, two experiments (one from G1 and G2 respectively) were repeated to identify to total error in sample mass, crystallinity and BET specific surface area. Comparing variance in this manner represents a far more complete approach than calculation through respective method error.

Experiment Number	Full width at Half- Maximum	BET Specific Surface Area [m²g⁻¹]	Product Mass [g.40ml ⁻¹]
GA_1_10	0.182	1813	0.1240
GA_3_12	0.161	1827	0.1485
% Variation	11.9	0.7	16.5
GA_2_15	0.164	1809	0.1239
GA_3_11	0.147	1837	0.1394
% Variation	10.4	1.5	11.1

Table 16: Error analysis using repeated experiments. Full width at half-maximum determined as an average of the three most intense reflections

Table 16 shows the variation in the two sets of repeat samples. The % Error in BET specific surface area measurements (which is the primary objective for this optimisation) is excellent at just 0.7% and 1.5% for GA_1_10/GA_3_12 and GA_2_15/GA_3_11 respectively. However, the % Error in crystallinity and product mass is significant at >10% for both parameters.



Figure 100: HKUST-1 Generation 1 Sample Preparation for XRD Analysis. [a] Sample GA_1_11 *immediately after preparation,* [b] *within 5 mins of preparation,* [c] *HKUST-1 samples post-XRD analysis, activated equivalents are in vials*

Some error in the product mass can be attributed to mechanical losses during the collection and washing procedures, while the FWHM error could be attributed to the moisture adsorption effects noted earlier. Adsorption of moisture can lead to a reduction in the (200) reflection intensity at $2\Theta = 6.8^{\circ}$, which may lead to a reduced FWHM value [259]. Given that Cu-HKUST-1 is known to absorb moisture from the atmosphere, it is very difficult to mitigate this issue during PXRD sample preparation without the use of specialised equipment and analysis under an inert, dry atmosphere, particularly in the context of HTE. Figure 100 shows the variation in sample colour during PXRD analysis; the colour change from dark to light blue typically occurred in under 5 minutes.

4.11 Conclusions

This optimisation study has resulted in the synthesis of HKUST-1 with high crystallinity, phase purity and BET specific surface area. Generation 3 shows 5 synthesis conditions which result in a specific surface area >1800 m²g⁻¹, and all samples showing specific surface areas >1700 m²g⁻¹, indicating a high quality of MOF product. Furthermore, these results are very close to the highest reported flow synthesis values highlighted in Table 4, suggesting that further increases in surface area are either very difficult to achieve, or simply not attainable through this synthesis method.

Experiment GA_3_11 achieves the overall optimum value for both the fitness function at 0.853 (FWHM = 0.147) as well as the highest BET surface area of 1837 m²g⁻¹. While the optimisation work described above has been extremely effective at generating highly crystalline, high surface materials in line or superior to the vast majority of literature reports (See Table 4), there is still considerable scope for further improvement. A small number of literature sources report surface areas of up to 2045 m²g⁻¹, with a calculated theoretical maximum of 2153 m²g⁻¹ [138].

With a total population of 50 experiments (+2 repeats) this investigation has explored only a small part of the available design space and there is still much potential information to be gained from the remaining unexplored experiments. For comparison, a 3-Level Full Factorial DoE design would require 246 experiments (+3 centre points) in order to estimate a full quadratic model [260].

This chapter demonstrates the ability to successfully optimise the synthesis conditions for Cu-HKUST-1, with no prior information using a combination of the SyCo Finder application and a SML model trained by boosted decision trees. Using only 40 data points, an average relative error of just 13.1% (\pm 7.3%) was attained when comparing model prediction to experiment outcome in Generation 3. The combination of evolutionary algorithms with an *in silico* search not only mitigates the known limitations of evolutionary algorithms, but also enables the prioritisation of experiments based on their predicted outcome. However, it should be noted that in this instance, the ML model was developed on a relatively small

data set, after only one generation of improvement. This inherently limits the exploration features of the optimiser and may have resulted in experimental execution within a localised region of the design space, based on early model predictions. To confidently address this, additional generations or increased population sizes within each generation could be used to provide more data prior to the development and use of the SML model.

This work has focused on the optimisation of MOF synthesis, whereas one should consider both the synthesis and activation methods for holistic optimisation. The activation method used in all experiments during this study is relatively simple and 'green', using only methanol for solvent exchange, followed by low heat under vacuum. However, to confidently achieve the global optimum, alternative solvents such as ethanol or propanol could also be considered to remove unreacted ligand and bound water, as well as consideration given to the number and length of each washing cycle.

This work considers only the optimisation of product quality, primarily through analysis of the sample crystallinity, reasoning that more crystalline materials will inherently give rise to increased surface areas. However, this work doesn't consider the 'cost' of quality, where minor increases in surface area could require significant increases in synthesis cost or sacrifice yield. To promote the large scale production of MOFs, the holistic optimisation would consider scalarisation of multiple factors, such as quality, yield and cost into the objective function, or consider a multi-objective optimisation and generation of the optimisation Pareto front.

Finally, this work required the synthesis, processing and analysis of all samples within a generation prior to obtaining any valuable information, although PXRD provided a valuable and relatively fast screening method in order to minimise BET usage. This represents a significant requirement of operator resource and would be greatly improved with the use of an online screening method to guide the machine learning process in real time, reducing the total number of seemingly unsuccessful experiments which require the same level of post-processing and analysis – this methodology is considered in subsequent chapters.

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Chapter 5: Self-Optimisation of Particle Size using online Dynamic Light Scattering

5.0 Self-Optimisation of Particle Size using Online Dynamic Light Scattering

Many of the key physical properties of nanomaterials arise due to their small size and specific morphology, as discussed in Chapter 1. A major challenge in nanomaterial synthesis exists in determining the correct selection of process conditions which lead to particles with the desired characteristics, whilst still maintaining an economically viable and scalable process. Traditional research and development often relies on 'trial and error' or 'one-variable-at-a-time' (OVAT) methods. These techniques are not only inefficient and costly, but they also risk achieving less-than-optimal results by misidentifying factor interactions or by performing an unnecessary number of experiments.

Chapter 4 demonstrated the advantages of applying machine learning, optimisation and automation to the synthesis of metal-organic frameworks. However, each 'generation' of experiments required significant user intervention in order to process and characterise the as-synthesised material, before new experiments could be generated. The process could be significantly improved through implementation of an appropriate online process analytical technology (PAT) which enables the rapid screening and possibly omission of experiments which show poor initial results. Furthermore, complete integration of the online PAT with machine learning and optimisation algorithms would enable autonomous control of experiment generation and execution, removing the need for user intervention between experiments.

Recently, autonomous, or 'self-optimising', reactor platforms have been developed and reported across multiple research areas, including organic chemical synthesis and in nanotechnology (See Table 1, Chapter 1). The earliest report of a self-optimising continuous-flow reactor was by Krishnadasan *et al.* in 2007 for the synthesis of cadmium-selenide quantum dots (QDs) [143]. In their publication, online spectroscopy was

combined with a microfluidic quantum dot synthesis method to achieve targeted maximum fluorescence at desired wavelengths, through autonomous control of reagent flowrates.

In this work, the continuous-flow hydrothermal synthesis (CFHS) reactor, previously described, is used in combination with online dynamic light scattering (DLS) to determine particle size and size distribution in real time. Following each experiment, the size and distribution results are used to build a supervised machine learning (SML) model, which can then predict experiment outcome for given process conditions. As the platform generates more experiments, and therefore more data, the model updates and gains in confidence for future predictions. The combination of an autonomous reactor and SML platform means that the process can be rapidly optimised without the need for user intervention, representing a significant saving in both time and resources.

To develop and demonstrate the autonomous reactor platform, the case study material hematite (a-Fe₂O₃) was used, due to its relatively simple synthesis, low-cost precursors and high stability in colloidal suspension.

Prior to enabling autonomous experiment generation or 'self-optimisation', a design of experiments (DoE) study was performed to assess the suitability and scope of the online DLS system and process constraints used. Variables considered within this study were temperature, flow ratio and total flowrate. The flow ratio is defined as the proportion of reactor Upflow relative to the reactor outlet, e.g. Flow Ratio = 0.5 (Upflow = Downflow), Flow Ratio = 0.33 (Upflow \approx 0.5 x Downflow).

Following the DoE study, the self-optimising capability of the reactor was demonstrated using a custom SML algorithm, which uses Bayesian optimisation to build a surrogate Gaussian process regression model, from which new experiments are generated. The algorithm is designed to enable tuneable balance of exploration and exploitation; i.e. the probability of random experimentation across the design space in order to build more robust and accurate models, against the generation of experiments which target high performance against a pre-defined criteria.

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The custom SML algorithm used in this work was then validated through comparison to the well-known global optimiser SNOBFIT [186]. SNOBFIT is a branch and fit optimiser which fits both local and global polynomial models and has previously been demonstrated as a robust optimiser in chemical synthesis self-optimisation.

5.1 Hematite Synthesis

Iron oxide exists in several crystalline forms, such as FeO, Fe₃O₄ and Fe₂O₃, due to different oxidising states at atmospheric conditions [261]. The similarities of these materials means that interconversion of one phase to another is possible through appropriate process conditions; for instance, the metastable γ -Fe₂O₃ (maghemite) can be heated in the absence of oxygen to form Fe₃O₄ (magnetite), whereas heating in air forms the more stable α -Fe₂O₃ (hematite).

Hematite is one of the most common and stable forms of iron oxide, with a corundum structure, the same as a-Al₂O₃. Hematite is often used in pigments, wastewater treatment, catalysis and photoelectric devices [262, 263, 264].

Several different bottom-up approaches to synthesising hematite have been reported, including co-precipitation, sol-gel and hydrothermal/solvothermal methods [265, 266, 43]. Previous work at the University of Nottingham has demonstrated the effect of temperature on particle size and crystallinity of hematite produced through continuous-flow hydrothermal synthesis (CFHS) using the counter-current nozzle reactor system previously described [267, 268].

The relatively simple synthesis of hematite, requiring only iron (III) nitrate and rapid mixing with near-critical or supercritical water, as well as its high stability in colloidal suspension, make it an excellent case study material to develop the closed-loop selfoptimising flow reactor herein described. In this work, the process conditions (temperature and respective flowrates) were altered to determine their effect on particle size and crystallinity of the synthesised hematite. Characterisation of particle size and size distribution was achieved through the use of online dynamic light scattering (DLS), while validation of the methodology was achieved using offline characterisation methods, such as UV-Vis spectroscopy, powder X-ray diffraction (PXRD) and transmission electron microscopy (TEM).

All materials used through this study were purchased from the vendors as specified below. The materials were used as sold, without additional processing or modifications.

Stock solutions were prepared in deionised water as follows; iron nitrate solution (0.10 M, 0.50 L): 20.61 g iron (III) nitrate nonahydrate (\geq 98.0% Fe(NO₃)₃.9H₂O, Sigma Aldrich), 0.10 M HNO₃ solution (0.10 M, 1.0 L): 31.852 ml of concentrated HNO₃ (70%, $\rho_{25^{\circ}C} =$ 1.413 g.ml⁻¹, Sigma Aldrich).

5.2 Reactor Layout

All experiments were run autonomously using the custom reactor control graphical user interface (RC-GUI) developed in NI LabVIEW (Described in Chapter 2).

For each experiment, the GUI follows a cyclic Standby-Heating-Experiment-Flush pattern. To minimise waste of stock solutions, only water is pumped during the Standby, Heating and Flush stages. During the Heating phase, the RC-GUI does not proceed until the measured Downflow temperature is within 2% tolerance of the set point. Dilute nitric acid was used for the Flush stage to remove any particle fouling from within the reactor.

A custom parallel sample loop was used for online DLS analysis; using a parallel setup removes the need for a flow-DLS system, which would limit the maximum process flowrate if used in series. The process flow diagram and images of the system setup are shown in Figure 101 and Figure 102, respectively.



Figure 101: Schematic of autonomous high-throughput reactor for metal oxide nanoparticle synthesis. DLS: Dynamic light scattering, using the Malvern Zetasizer Nano ZS. ML: Machine learning.



Figure 102: Images of Reactor and DLS for Self-Optimised Hematite Experiments. PC, Auto-Sampler and recirculating chiller not shown. BPR: Back Pressure Regulator. Precursors: Deionised water, 0.10 M Fe(NO₃)₃ and 0.10 M HNO₃

5.3 Online Process Analytical Technology (PAT): Dynamic Light Scattering (DLS)

A Malvern Zetasizer Nano ZS, equipped with a continuous-flow cell of 3 mm path length (ZEN0023, Malvern) was used to obtain particle size and size distribution measurements in real time. A custom two-way solenoid valve controlled by Arduino and software written in NI LabVIEW was used to inject samples into the flow cell following each experiment.

In each case, three reactor volumes of material was produced from the reactor prior to sample injection to ensure steady state operation. The DLS system was set to continuously obtain measurements using the standard operating procedure (SOP) player in the Zetasizer software. All measurements were exported to a text file, which was then imported into and interpreted by the LabVIEW GUI after completing each experiment.

Measurements were averaged across 10x 10 second scans for before being exported to text file. Prior to each measurement, the attenuator and measurement position was automatically optimised to improve the quality of results and account for increased concentration of particles at higher conversion. Both the Z-average and polydispersity index (PDI) values were recorded from each experiment, which allows results associated to a high (>0.45) PDI value to be excluded. DLS is only suitable for monodisperse samples; as the Z-average or cumulants mean gives only a single value, the PDI is used to assess the suitability of the measurement, generated based on the width of a hypothetical Gaussian distribution [269].

The LabVIEW RC-GUI was developed to import 3 consecutive DLS measurements per experiment, highlighting and excluding values with a high PDI value or where a discrepancy exists in the 3 measurements (due to particle growth, aggregation or settling).

The *in-situ* analysis assumes the synthesised particles to have spherical morphology, with a refractive index of 3.0. The as-synthesised sample is stabilised to standard temperature and pressure prior to analysis, and it is assumed that the viscosity remains constant throughout the study.
5.4 Design of Experiments (DoE)

To determine the attainable design space for self-optimised experiments, and to provide an initial model response, a 3-Level full factorial DoE was constructed using Umetrics MODDE (12.1) with the process constraints shown in Table 17.

Table 17: Process constraints for the Design of Experiments (DoE) Study.

Constraint	Lower	Upper
Downflow: Temperature [°C]	340	380
Upflow Ratio	0.33	0.50
Total Flowrate [ml.min ⁻¹]	25.0	35.0

A total of 30 experiments (27 design and 3 centre points to determine reproducibility) were constructed using a centred composite face (CCF) design. The purpose of replicate experiments is to identify the presence of uncontrolled variables within the process.

Both the particle size and PDI values from each experiment were recorded. Particle sizes associated with a PDI value >0.45 were excluded to ensure measurement validity. All experiments were run in random order to identify response drifts over the course of the study, i.e. due to fouling of the reactor, or changes in environment temperature. All 30 experiments were completed in approximately 7 hours, with no observed operational issues.

The DoE results are shown in Figure 103 to Figure 106. Models were fit using multiple linear regression (MLR) to minimise the sum of the squares of residuals. Initially, a saturated model with all square and interaction terms was generated; while this initial model results in a high R^2 value, the presence of non-significant terms can result in a poor Q^2 value or poor response prediction using cross validation. To achieve a more robust model, non-significant terms were removed to ensure the difference in R^2 and Q^2 was low, as shown in Figure 104.



Figure 103: 4D Contour Plots for model response of Particle Size (top) and PDI (bottom) for the 3-Level Full Factorial Design of Experiments Study. Size refers to Z-average measurement in nm. PDI: polydispersity index.



Figure 104: Summary of fit plots for (Left) Particle Size: R^2 =0.893, Q^2 =0.752, Model Validity = 0.601, Reproducibility = 0.942. (Right) PDI: R^2 =0.703, Q^2 =0.503, Model Validity = 0.808, Reproducibility = 0.710. Size: Z-average from online dynamic light scattering. PDI: Polydispersity index.



Figure 105: Plots of Observed vs. Predicted responses for Particle Size (left) and PDI (right). Points lying close to the straight diagonal indicate a good model fit to the experimental data. Size: Z-average from online dynamic light scattering. PDI: Polydispersity index.



Figure 106: Residuals Normal Probability Plots for Particle Size (left) and PDI (right). A straight diagonal line indicates normal distribution, points outside 4 standard deviations represent outliers and would require repeating. Size: Z-average from online dynamic light scattering. PDI: Polydispersity index.



Figure 107: Coefficient plots for models of (left) Particle Size and (right) PDI. Coefficients which were deemed insignificant were removed during data processing. Size: Z-average from online dynamic light scattering. PDI: Polydispersity index. Temp: Temperature. Flo: Flowrate. Rat: Flow Ratio.

Table 18: Design of Experiments (DoE) study results. *indicates experiments excluded from model to improve fit. †indicates highest-performing experiment. Particle size: Z-average from online dynamic light scattering (DLS) measurements

Run Order	Temperature [°C]	Flowrate [ml.min ⁻¹]	Flow Ratio	Particle Size [nm]	PDI
27	340	30	0.330	43.3	0.248
6	360	30	0.330	56.3	0.210
25	380	30	0.330	83.7	0.103
3	340	35	0.330	45.3	0.546
9	360	35	0.330	34.6	0.494
20	380	35	0.330	73.8	0.252
2	340	25	0.330	41.3	0.226
7	360	25	0.330	56.9	0.210
10	380	25	0.330	90.2	0.113
26	340	30	0.415	42.9	0.528
18	360	30	0.415	38.6	0.314
1	380	30	0.415	71.7	0.217
30	340	35	0.415	43.0	0.518
21	360	35	0.415	43.1	0.213
11	380	35	0.415	88.5	0.253
13	340	25	0.415	62.1	0.623
12	360	25	0.415	36.7	0.414
5	380	25	0.415	70.7	0.232
15	340	30	0.500	101.7	0.455
29	360	30	0.500	63.7	0.599
4	380	30	0.500	49.4	0.282
16	340	35	0.500	93.9	0.501
22	360	35	0.500	51.2	0.665
23	380	35	0.500	81.8	0.298
19	340	25	0.500	87.6	0.527
24	360	25	0.500	50.7	0.587
28	380	25	0.500	56.9	0.236
8	360	30	0.415	34.4	0.297
17	360	35	0.415	33.8	0.400
14	360	35	0.415	33.9	0.392
	Run 27 6 25 3 9 20 2 7 10 26 18 1 30 21 13 12 5 15 29 4 16 22 23 19 24 28 8 17 14	RunTemperature [°C]2734063602538033409360203802340736010380263401836011380303402136011380133401236015340293604380163402236043801634023380193402436083601736014360	Run OrderTemperature [°C]Flowrate [ml.min']273403063603025380303340359360352038035234025736025103802526340301836030303403521360351138030303403511380351138035113803512360255380251534030293603043803523380351934025283802583603017360351436035	Run OrderTemperature [°C]Flow rate [ml.min²]Flow 	Run OrderTemperature [°C]Flowrote [nml.min ⁻¹]Flow RatioParticle Size [nm]27340300.33043.36360300.33056.325380300.33083.73340350.33045.39360350.33034.620380350.33073.82340250.33041.37360250.33056.910380250.33090.226340300.41542.918360300.41543.021360350.41543.111380350.41543.111380350.41562.112360250.41536.75380250.41570.715340300.500101.729360350.50093.922360350.50093.923380350.50081.819340250.50050.728380250.50056.98360300.41534.417360350.41533.814360350.41533.8

Figure 103 shows the 4D contour plot generated for the response models of particle size and PDI, respectively. The results indicate an increase in particle size with reaction temperature, low flow ratio values and lower flowrates. These results are entirely intuitive when considering the LaMer model of nucleation and particle growth; an increase in reaction temperature results in a greater nucleation rate and conversion of Fe^{3+} species to Fe_2O_3 . In this process, this is achieved by an increased Downflow temperature and reduced flow ratio; furthermore, the reduced flowrate gives rise to an increase in reaction residence time, enabling further growth of particles (Further discussion given in subsequent sections).

A key feature of this study was the ability to exclude certain results based on their PDI values. PDI values >0.5 indicate a sample with high polydispersity; in these cases the Z-average response cannot be utilised [215]. Using the PDI values obtained from the DoE study, broad regions of the design space were omitted from subsequent self-optimisation



Figure 108: 4D Scatter of experiments and particle size from the Design of Experiments (DoE) study. Experiments excluded from the final model are not shown.

experiments. The 4D scatter of synthesis conditions and particle size is shown in Figure 108, with excluded experiments omitted from the plot.

The feasible region defined by the PDI value is shown in Figure 109; the highlighted polygon therefore represents the design space and constraints applied further self-optimisation studies in this chapter.

It is possible to repeat the DoE study in the new design space, which would provide a more accurate model for that region. However, a DoE relies on statistical interpolation between predefined experimental conditions; while this provides a useful model for the entire design space, it may not necessarily explore the local region around the optimum. It is therefore useful to consider approaches such as self-optimisation, whereby experiments are generated throughout the study to either focus in on the optimum region, or further explore unknown areas of the design space.



Feasible Region for Fe₂O₃ Self-Optimisation

Figure 109: Feasible region for self-optimisation (yellow polygon), determined from polydispersity index (PDI) values obtained in the Design of Experiments (DoE) study. Total volume indicates the design constraints used for the DoE study.

5.5 Self-Optimisation *via* Supervised Machine Learning (SML)

In contrast to the DoE study, where experiments followed a pre-set table of conditions, the SML algorithm generates experiments based on a pre-defined target and analysis of previous data. To demonstrate self-optimisation, the SML algorithm was set to achieve the maximum particle size within the process constraints shown in Table 19. These constraints were obtained from the feasible region determined from the earlier DoE study. Following completion of self-optimisation using the SML algorithm, the study was repeated using SNOBFIT in order to validate the SML algorithm response and model. The total number of experiments, per study, was limited to 30, taking around 6-7 hours for completion.

Table 19: Constraints for the Supervised Machine Learning (SML) Self-Optimisation Study.

Constraint	Lower	Upper
Downflow: Temperature [°C]	360	380
Upflow Ratio	0.33	0.40
Total Flowrate [ml.min ⁻¹]	25.0	35.0

The SML self-optimisation experiments were initialised using the CCF design shown in experiments N1-N6, shown in Table 20. Initialisation in this manner ensures broad coverage of the design space, reducing the potential for bias early in the study.

Following initialisation, experiments were generated in batches of 6, with the first experiment targeting the highest performing experiment as predicted by the model, and the remaining 5 randomly distributed across the design space. The combination of highpotential exploitation and random exploration increases the likelihood of achieving the global optimum; while the randomly generated data provides a sufficient scatter across the design space to fit an accurate supervised machine learning model.

5.6 Results & Discussion

Both the custom SML algorithm and SNOBFIT self-optimisation studies show increased particle size at elevated temperature, reduced flowrates and lower flow ratios; this result agrees with the initial DoE study, although in a smaller region of the initial design space (See Table 19 or Figure 109).

Figure 110 and Figure 111 shows the 4D scatter of particle size for the process conditions from each experiment in the SML and SNOBFIT studies, respectively. All experiments show a PDI value <0.40, which indicates that the samples are monodisperse and no results require exclusion prior to model generation.

Both algorithms were able to locate the optimum synthesis conditions and maximise particle size within the 30 experiment limit, converging upon the same conditions in each case. Further to maximising the particle size, the exploration feature of both algorithms was used to distribute experiments across the design space, which means a more robust model can be built within the available design space. For the SNOBFIT study, this results in a 3 factorial polynomial, while the SML builds a Bayesian-optimised Gaussian process (GP) regression model. It is clear that in this (relatively) simple case study, the polynomial used by the SNOBFIT optimiser is suitable and very similar in appearance to the GP regression model, shown in Figure 112. Achieving similar model responses through two independent studies and different methods suggests that the response is representative of the true system.

The polynomial model developed during the SNOBFIT study has a much smoother appearance when compared to the GP regression model from the SML study. In this instance, it is likely that the parameters selected for the GP regression model resulted in some overfitting to the given data, capturing experimental noise within the model itself. The SML algorithm used in this work builds several GP regression models with varying hyperparameters upon importing data. Here, Bayesian optimisation is used to optimise the fitting method, kernel function and basis function in order to minimise the residuals from training to predicted data during cross-validation. However, for a model to be

effective in real-world scenarios, it must obtain a balance between over and under fitting, ensuring that it generalises well.

There is a clear difference in the location and level of scatter of experiments across the design space for the two algorithms (See Figure 110 and Figure 111). Both algorithms employ random exploration, however, the SNOBFIT algorithm uses a probability of exploration, which is balanced against exploitation around high performing regions. For the custom SML algorithm, only 17% of experiments intentionally targeted high performance, while the remaining 83% were randomly selected; while this generates a well-distributed scatter across the design space for model generation, it is less efficient at exploring regions close to the optimum. Modifying the algorithm parameters to favour exploitation could significantly improve on this; this could simply be achieved by reducing the batch size of generated experiments, allowing the model to update more regularly with new data. Lowering the batch size to between 1 and 3 would likely give a better balance of targeting predicted high performance and still exploring the remaining design space.

Each study was completed in around 6-7 hours, without any user intervention and using less than 500 ml of the iron nitrate precursor solution. This therefore represents a significant improvement in the time and resources required to for process optimisation.

While the objective in this instance was to maximise particle size, the algorithms can easily be modified to target specific particle sizes, as determined by the online DLS measurements. It is also clear that the optimum region is located in the corner of the proposed design space. The original (DoE) design space constraints were arbitrarily selected based on expected performance after commissioning and some initial scoping work; it is possible that a more interesting surface response could be observed at harsher conditions (i.e. higher temperature and extended residence time), which the reactor is capable of achieving.



Figure 110: 4D Scatter of experiments and particle size from the self-optimised supervised machine learning (SML) study.



Hematite Self-Optimisation using SNOBFIT

Figure 111: 4D Scatter of experiments and particle size from the self-optimised SNOBFIT study.



Figure 112: SNOBFIT Polynomial (top) and Bayesian-Optimised Gaussian process (GP) regression (bottom) 4D Models generated in Hematite Self-Optimisation Experiments.

Exp. Name	Temperature [°C]	Flowrate [ml.min⁻¹]	Flow Ratio	Particle Size [nm]	PDI
N1	360	30.0	0.365	44.5	0.241
N2	370	25.0	0.365	62.5	0.217
N3	370	30.0	0.330	66.4	0.206
N4	370	30.0	0.400	49.1	0.222
N5	370	35.0	0.365	42.1	0.324
N6	380	30.0	0.365	69.8	0.187
N7	380	26.0	0.330	83.9	0.135
N8	370	26.8	0.356	58.7	0.183
N9	373	27.0	0.330	69.0	0.216
N10	373	31.4	0.382	53.3	0.208
N11	371	25.0	0.330	64.0	0.212
N12	368	28.1	0.356	54.5	0.193
N13	380	25.9	0.330	84.3	0.181
N14	380	25.0	0.331	83.3	0.184
N15	380	25.0	0.373	76.8	0.187
N16	364	25.5	0.333	72.1	0.240
N17	361	30.4	0.398	43.2	0.389
N18	378	26.3	0.330	77.9	0.187
N19	380	25.5	0.330	84.9	0.158
N20	380	32.1	0.399	64.4	0.197
N21	367	29.6	0.393	44.9	0.215
N22	380	27.4	0.369	76.0	0.199
N23	360	25.2	0.400	47.0	0.413
N24	361	26.9	0.330	68.7	0.296
N25†	380	25.1	0.330	87.7	0.181
N26	365	28.2	0.383	54.8	0.366
N27	376	26.4	0.388	67.4	0.239
N28	367	28.3	0.374	54.8	0.307
N29	376	26.7	0.35	75.9	0.221
N30	366	30.9	0.358	49.6	0.267

Table 20: Supervised Machine Learning (SML) Self-Optimisation study results. †indicates highest-performing experiment.

Exp. Name	Temperature [°C]	Flowrate [ml.min ⁻¹]	Flow Ratio	Particle Size [nm]	PDI
N1	372	27.2	0.361	62.1	0.216
N2	372	26.9	0.373	64.3	0.209
N3	360	30.0	0.330	56.3	0.210
N4	361	27.5	0.346	57.2	0.228
N5	380	26.3	0.347	75.9	0.184
N6	368	27.9	0.396	51.0	0.231
N7	364	26.7	0.330	68.8	0.238
N8	360	25.0	0.330	58.2	0.201
N9	380	29.2	0.330	83.7	0.137
N10	369	28.1	0.354	59.3	0.217
N11	366	27.7	0.347	57.6	0.204
N12	378	29.3	0.396	60.5	0.202
N13	380	26.0	0.330	81.9	0.177
N14	376	27.6	0.359	64.0	0.212
N15	368	32.1	0.377	44.6	0.230
N16	380	25.0	0.338	77.8	0.164
N17	374	31.5	0.383	51.9	0.174
N18	373	25.0	0.346	60.7	0.173
N19†	380	25.0	0.330	91.1	0.125
N20	364	25.5	0.335	72.8	0.251
N21	380	27.7	0.358	76.0	0.208
N22	365	33.5	0.345	42.7	0.308
N23	378	28.4	0.330	75.8	0.213
N24	377	25.0	0.330	77.7	0.227
N25	376	26.9	0.343	73.9	0.225
N26	377	27.3	0.346	74.5	0.216
N27	380	28.2	0.354	74.5	0.206
N28	380	26.2	0.330	84.1	0.170
N29	380	29.3	0.330	78.7	0.194
N30	380	25.0	0.330	84.4	0.184

 Table 21: SNOBFIT Self-Optimisation study results.
 +indicates highest-performing experiment.

5.7 Offline Characterisation

In order to validate the online DLS system, six additional samples were produced which span the range of particle sizes seen in the self-optimised studies; these samples are shown in Figure 113 (Synthesis conditions and online measurements shown in Table 22, detailed reports available in Appendix: A).



Figure 113: Samples A-F (Left to Right) produced for offline characterisation and validation of the self-optimisation study.

Samples A-D exhibit a dark red colour, while samples E and F exhibit a much brighter rustred colour, indicative of hematite particles which are >20 nm in diameter [270]. Hematite is known to have distinct absorption regions around 300, 420 and 550 nm. Figure 114 shows strong absorbance at 420 and 550 nm for samples E and F, which is the reason for the bright red colours observed in Figure 113. These results agree with those shown by Schwaminger *et al.* in their hydrothermal one-pot synthesis of hematite from FeCl₃ over 1-6 hours [271].

Sample	Temperature [°C]	Flowrate [ml.min ⁻¹]	Flow Ratio	Particle Size [nm]	PDI
A	360	30.0	0.365	45.41	0.195
В	367	28.1	0.356	54.08	0.225
с	370	30.0	0.330	66.95	0.252
D	380	27.4	0.369	76.17	0.214
E	380	26.0	0.330	84.05	0.131
F	380	25.0	0.330	91.71	0.122

Table 22: Synthesis conditions, particle size and polydispersity index (PDI) obtained by online dynamic light scattering analysis.



Figure 114: UV-Vis Absorbance spectra of samples A-F, used for offline characterisation.

Schwaminger *et al.* shows that ferrihydrite is the first stable product in the hydrolysis of the iron salt precursor. The authors rationalise that the formation mechanism and growth of iron oxide nanomaterials follows the nucleation of ferrihydrite seeds, which then agglomerate and undergo a phase transition into hematite. In order to distinguish the iron oxide phase of samples A-F, characterisation by PXRD was performed.

Hematite offers an interesting challenge in obtaining useable PXRD data from the available equipment; in most cases, nanomaterial suspensions are washed and separated *via* centrifugation and the pellet is subsequently dried to form a powder for analysis. Owing to the small size and stability of the hematite particles, separation *via* centrifugation was not possible; furthermore, simply concentrating the as-synthesised samples by boiling off water could potentially result in changes to the sample phase.

To solve this challenge, a 2 ml aliquot from each sample was mixed with 1 ml of ethanol. These mixtures were then added dropwise onto the surface of a background-free silicon wafer, allowing the water-ethanol mixture to gently evaporate at ambient temperature and pressure, slowly building a layer of the solid sample (Figure 115). This process was done over several hours to minimise changes to the crystal phase.



Figure 115: Dropwise addition of hematite samples C-F, used for powder X-ray diffraction analysis. Samples A and B were prepared in the same way. The Wet (Left) and Dry (Right) samples are both shown.

The PXRD patterns shown in Figure 116 show good agreement of the simulated hematite pattern to all samples A-F. Sample crystallinity can be estimated using the full width at half-maximum (FWHM) of the five most intense reflections. It is possible that some overlap exists in samples A and B with poorly crystalline ferrihydrite, as suggested by Schwaminger *et al.*, however, samples C-F show clearly crystalline patterns which confirm the synthesis of hematite. Unfortunately, samples E and F show distinct peaks at 29.4, 31.9 and 39° which do not agree with the simulated hematite pattern; this is most likely attributed to the presence of NaNO₃ in the samples. Synthesis of the hematite particles yields free NO₃⁻ ions, which appear to have reacted with contaminant Na⁺ to form NaNO₃ salt. The origin of this contamination is unclear, but can most likely be attributed to poorly washed or handled sample vials. The contaminant peaks do not interfere or overlap with the known hematite peaks, which still enables calculation of the crystallite size using the FWHM values and Scherrer equation (results summarised in Table 23).



Figure 116: PXRD Patterns for samples A-F, used for validation of the inline Dynamic Light Scattering method. Simulated hematite pattern calculated from CIF: [341]



Fe₂O₃ Self-Optimisation - PXRD Patterns

Figure 117: PXRD patterns for samples E and F, compared to the simulated patterns for hematite (Simulated Fe_2O_3) and sodium nitrate (Simulated $NaNO_3$). Simulated patterns from CIF files [341] and [342]

The TEM images for samples A-F show various stages in the generation and growth of hematite nanoparticles (More images available in Appendix B).



Figure 118: TEM Images of Hematite samples A, C and F (left to right). Scale bar at 200 nm. Samples A and B primarily show spherical-cubic particles in the range 5-10 nm (See Appendix: B), as conditions move to favour increased conversion of precursor to product, i.e. increased temperature and residence times, these begin to aggregate and cluster into larger particles. There is a significant change in samples E and F compared to the previous samples, where distinct cubic a-Fe₂O₃ are clearly visible and show good crystallinity, suggesting an Ostwald ripening or oriented attachment growth process, rather than merely agglomeration of smaller particles [48]. Figure 119 illustrates the hydrolysis, seeding and growth stages of hematite synthesis proposed from the study data, adapted from a similar process outlined by Schwaminger *et al.* [271]. Although it is likely that this work follows the same mechanism of ferrihydrite nucleation and seeding, it is not possible to prove or disprove this with the methods applied in this work.



*Figure 119: Illustration of proposed hematite synthesis mechanism, from hydrolysis of initial ferric precursor to distinct a-Fe*₂O₃ *particles. Adapted from Schwaminger et al.* [271]



Figure 120: Particle size analysis for Hematite samples A-F, determined from transmission electron microscopy (TEM) images

Figure 120 shows the particle size distribution obtained for samples A-F from TEM imaging (TEM images available in Appendix: B). The particle size determined by DLS analysis suggests a linearly distributed range from 41-92 nm, however, the TEM images clearly show a range from 5-40 nm. Interestingly, there is an even progression in the particle size observed in samples A-D, from 5-11 nm (\pm 3). However, samples E and F exhibit much larger particles and size distribution at 27 nm (\pm 8).

The purpose of the offline characterisation was to validate the online DLS system. Table 23 shows the particle size determined by DLS, PXRD and TEM imaging; while there is some similarity in the PXRD and TEM data, there is a clear overestimation of particle size from the DLS measurements. This is likely attributable to the measurement of hydrodynamic diameter in DLS, rather than measurement of the particle itself; furthermore, the TEM images show significant levels of aggregation, which can easily be misinterpreted for larger particles by DLS.

Further sampling and comparison of the techniques could potentially allow the conversion of one measurement to another; however, the six samples produced for validation do not sufficiently cover the design space to enable confident prediction. The automated reactor system could easily produce a large sample set, complete with DLS data, however, this would require further user resources associated to the offline PXRD and TEM characterisation.

Samples E and F showed strong absorption bands in the visible spectrum at 420 and 550 nm, observed in Figure 114. This is attributed to the larger particle sizes of the samples, and reports in literature suggest a blue shift in absorbance suggest larger particle sizes [270]. This represents a potential alternative online PAT for determining the particle size during hematite synthesis.

Table 23: Comparison of particle size and distribution characterisation by Dynamic Light Scattering (DLS), Powder X-ray Diffraction (PXRD) and Transmission Electron Microscopy (TEM). FWHM = Full width at half-maximum, averaged across the five most intense peaks. PDI = Polydispersity index.

Sample	DLS [nm]	PDI	FWHM	PXRD [nm]	TEM [nm]	
Α	45.41	0.195	0.828	10.0	5.4 ±3.0	
В	54.08	0.225	0.811	10.3	7.1 ±4.1	
С	66.95	0.252	0.569	15.0	9.1 ±2.7	
D	76.17	0.214	0.466	18.2	10.7 ±3.2	
Ε	84.05	0.131	0.376	22.6	27.1 ±8.2	
F	91.71	0.122	0.360	23.7	27.0 ±7.8	

5.8 Conclusions

This work represents the first reported self-optimised continuous-flow hydrothermal synthesis for nanomaterials. The autonomous generation, execution and analysis of experiments minimises the need for user intervention; this not only increases experiment efficiency, but also allows the user to focus on more complex tasks.

The work presented in this chapter demonstrates the self-optimising capability of the continuous-flow hydrothermal reactor for metal oxide synthesis. An online DLS system was used to provide real time information of particle size and distribution, which was then used to guide subsequent experiments.

A DoE study was performed to determine the surface response within an extended design space, as well as identify a feasible region for subsequent self-optimised experiments based on the PDI value. The custom SML and SNOBFIT algorithms used in the selfoptimisation studies performed equally well, with both methods identifying the global optimum and resulting in similar surface response models. However, the high degree of random exploration used for the SML algorithm demonstrates poor efficiency in balancing exploration against exploitation. In this instance, the algorithm efficiency had little effect on real parameters, such as experiment time and cost, as the number of experiments was predetermined and a low cost case study material was selected. However, in circumstances where time and resources are limited, or precursors represent significantly more experimental cost, the poor optimisation efficiency becomes limiting.

The SML algorithm is designed to allow modification to the exploration parameters, which can be altered to suit a particular optimisation problem; for example, a process which is expensive to evaluate would favour a high level of exploitation. In this study, the SML algorithm obtained a result within 3% of the global optimum after just 7 experiments, indicating that the earliest model was able to identify the optimum region. Identifying this region early in the optimisation process allows more detailed investigation of the local area.

Offline characterisation of select samples showed the DLS significantly overestimated the particle size, when compared to PXRD and TEM analysis. This can likely be attributed to the measurement of the hydrodynamic radius from DLS, as well as the misinterpretation of particle aggregates. This autonomous optimisation platform is designed to suit several case study materials, but can be further improved with the incorporation of more refined or suitable online PATs, such as *in situ* particle or nanoparticle tracking analysis (PTA or

NTA, respectively) [204]. A distinct advantage of these methods is they are not biased towards measurement of larger particles or aggregates, which may have confounded the results for this study using hematite [269]. However, it is also important to consider the additional cost associated with the increased precision and accuracy of such technologies.

The primary objective of this chapter was to commission and demonstrate the selfoptimising capability of the autonomous platform. Although there are possible improvements in both the selected PAT and optimisation parameters, the autonomous reactor was able to self-optimise for maximum particle size, with no operational faults and no user intervention. The same self-optimising methodology can therefore be considered for more complex case studies.

Chapter 6: Self-Optimisation of MOF Synthesis using inline FTIR Spectroscopy

6.0 Self-Optimisation of MOF Synthesis using inline FTIR Spectroscopy

The synthesis of metal organic frameworks (MOFs) can be complex, with several synthesis parameters affecting product quality, as discussed in Chapter 4. Applying high-throughput experimentation enabled the optimisation of HKUST-1, however, the work was limited in the need to process and characterise all samples within a generation before initiating the next.

This chapter aims to apply the same self-optimised methodology demonstrated in Chapter 5, for the synthesis of MOFs. Al-Fumarate (AlFu, MIL-53(Al)-FA, Basolite® A520) serves as a case study due to the simple structure, low toxicity and low cost of precursors. Online Fourier transform infrared spectroscopy (FTIR) is employed as an online process analytical technology (PAT), further details are given in Section 6.2. A brief introduction to the MIL-53 structure, of which Al-Fumarate is an isoreticular analogue, is given in addition to applications and synthesis methods (See Section 6.1).

Prior to self-optimisation using the supervised machine learning (SML) method described in Chapter 5, a design of experiments (DoE) study was performed. This was done in order to assess the practicality of *in situ* FTIR spectroscopy with the autonomous reactor and gain an initial understanding of the surface response.

The primary aim of this chapter is to determine synthesis conditions which enable a 'green', scalable route to producing Al-Fumarate using continuous-flow hydrothermal synthesis. Offline analysis through powder X-ray diffraction (PXRD) and N₂ adsorption was used to validate the objective function score given by the online PAT.

6.1 MIL-53(Al) and Al-Fumarate

MIL-53(Al) is one of the most well-studied Al-based metal-organic frameworks (MOFs), belonging to the MIL-53 (Matériaux de l'Institut Lavoisier) structural family first reported by the Férey group in 2002 [272]. The MIL-53 structure contains terephthalate-based ligands interconnecting inorganic [M-OH] chains; the first published MIL-53 MOF consisted of 1,4-benzenedicarboxylate linkers (terephthalic acid, H₂BDC) and Cr³⁺ ions (See Figure 121). However, several analogues have since been reported with trivalent metal centres, including V³⁺, Al³⁺, Fe³⁺, In³⁺, Ga³⁺ and Sc³⁺ [273, 274, 275, 276, 277]. In addition, MIL-53 structures have been reported incorporating divalent or tetravalent metal ions instead, such as Fe²⁺, Co²⁺, Mn²⁺, Ni²⁺ or V⁴⁺, respectively [275, 278, 279, 280, 281].



Figure 121: MIL-53(Cr) structure, generated using CIF File from Mulder et al. [345]

The chemical diversity of the MIL-53 structure means that a wide range of possible applications have been reported, including gas separation and storage, catalysis, sensors and energy storage [282, 283, 284, 285]. MIL-53(AI) (aluminium terephthalate, commercially known as Basolite® A100), in particular has drawn much attention due to its low toxicity, relatively low-cost precursors and high thermal and chemical stability [286]. The high stability of MIL-53(AI) creates opportunity for applications in hot or humid conditions, but also means that biological or environmental applications are also possible, such as in drug delivery [287].

MIL-53 structures are notable for their flexibility, with many exhibiting a "breathing effect" whereby the pore cross section reversibly changes in response to external stimuli, such as the chemical adsorption of guest molecules, mechanical pressure or changes in temperature [288]. This results in as much as 50% volume change within the MOF pores, as noted in the high and low temperature forms (MIL-53-ht and MIL-53-lt respectively) by Llewellyn *et al.* [289].

The original MIL-53 structure comprises of terephthalate as the organic linker, however, several analogues have since been reported employing a variety of functionalised terephthalate linkers. A comprehensive review of the isoreticular analogues of MIL-53 can be found by Millange and Walton in 2018 [290].

MOF materials with the MIL-53 topology can also be generated from non-terephthalatebased linkers, provided they maintain the same linear arrangement of carboxylate groups to that of terephthalate; an example of this is the use of fumarate with Al³⁺ ions to produce Al-Fumarate (Al-Fum, MIL-53(Al)-FA), commercially known as Basolite® A520. By contrast, Al-Fumarate does not exhibit the same flexible breathing structure as MIL-53(Al), but does maintain several other useful features, such as reversible water uptake, as well as high thermal and chemical stability [291]. Furthermore, Al-Fumarate offers significant promise in mechanical energy storage, water adsorption or in heat pump applications [292, 293, 294].

The precursors and conditions required for Al-Fumarate synthesis are typically of low cost and toxicity making it an excellent case study material for the development of a selfoptimising hydrothermal reactor platform, it is therefore the primary target material throughout the remainder of this work. Given the structural and chemical similarities, it is also reasonable to suggest that the same methodology developed for Al-Fumarate can be extended to MIL-53(Al), and other similar analogues.



Figure 122: Structure of hydrated Al-Fumarate MOF (H atoms have been omitted for clarity). Generated using CIF file from Alvarez et al. [291]

The synthesis of Al-Fumarate, was originally achieved through a solvothermal approach, using *N*,*N*-dimethylformamide (DMF) as the reaction solvent, over several hours [295]. However, the need for expensive, harmful and environmentally damaging solvents and long reaction times limited process scalability; recent research has therefore focused on suitable alternatives such as aqueous, hydrothermal or mechano-chemical methods, with some reports demonstrating excellent promise in both product quality and production scalability (See Table 24).

Aqueous and hydrothermal routes make up the vast majority of Al-Fumarate synthesis research, owing to ease of synthesis and ability to achieve high quality product (specific surface area >1000 m²g⁻¹). The process improves upon traditional solvothermal synthesis in both reaction time and simplicity through the use of base to deprotonate and solubilise the organic linker in water, in place of the solvents previously employed. As deprotonation of the linker precursor is a slow process (often the rate limiting step in MOF synthesis), dissolving the ligand in aqueous solution as the carboxylate salt promotes a fast coordination and thus a faster MOF formation [296].

A range of process conditions, i.e. reaction time and temperature, as well as stoichiometry exist throughout the reported literature shown in Table 24. In the literature, it is often the optimised value that is reported, although in some cases the optimisation process is also well documented. Table 24: Timeline of Al-Fumarate synthesis. FA = Fumaric Acid, DMF = Dimethylformamide, TSE = Twin Screw Extrusion. In each case, first author is shown. Aqueous synthesis denotes pressure <1.5 bar.

Author	Year	Synthesis Method	BET Surface Area (m²g⁻¹)	Reactants	Ref
Kiener	2009	Solvothermal	1033	FA, DMF, Al ₂ (SO ₄) ₃	[295]
Leung	2012	Aqueous	1033	FA, NaOH, Al2(SO4)3	[297]
Jeremias	2014	Solvothermal	1021	FA, DMF, AICl₃	[298]
Alvarez	2015	Aqueous	1025	FA, NaOH, Al ₂ (SO ₄) ₃	[291]
Crawford	2015	Mechano- chemical, TSE	1010	FA, NaOH, Al ₂ (SO ₄) ₃	[243]
Karmarkar	2016	Aqueous	1156	FA, NaOH, Al2(SO4)3	[299]
Rubio-Martinez	2016	Hydrothermal, Continuous-flow	1015-1084	FA, NaOH, Al ₂ (SO ₄) ₃	[300]
Zhou	2017	Aqueous	925	FA, NaAlO ₂	[301]
Rubio-Martinez	2017	Hydrothermal, Continuous-flow	1054	FA, NaOH, Al ₂ (SO ₄) ₃	[302]
Тео	2018	Solvothermal, Modulated	792	FA, DMF, AICl ₃ , Formic Acid	[303]
Kashanaki	2018	Aqueous	780	FA, NaAlO ₂	[304]
Jung	2018	Aqueous	330.3	FA, NaOH, Al2(SO4)3	[305]
Tannert	2018	Dry-Gel Conversion	983-1189	FA, NaOH, Al2(SO4)3	[306]
Tannert	2019	Aqueous	780-1254	FA, NaOH, Al ₂ (SO ₄) ₃	[307]
Peng	2019	Aqueous	1160	FA, Urea, Al ₂ (SO ₄) ₃	[308]

Improving on early batch processes, scalable continuous-flow hydrothermal synthesis of both MIL-53(AI) and AI-Fumarate has been demonstrated by Rubio-Martinez *et al.*, utilising a continuous-flow process with a space-time yield (STY) of up to 97,159 kg m⁻³ day⁻¹ [300]. The authors were able to demonstrate suitability of the hydrothermal route using reactor volumes of 10 mL to 1.394 L, representing a 139 times increase in scale, without changes to the process conditions or significant impact on MOF quality. In addition to reactor geometry, a key difference in the reactor reported by Rubio-Martinez *et al.* is the mixing of precursors before heating in the tubular reactor, necessitating a residence time of 1 minute (although investigation into lower residence times were not reported). By contrast, the Downflow precursor solution in the counter-current reactor is heated before mixing of the two solutions. Preheating the Downflow solution has been reported to enhance the mixing regime in the reactor, due to respective buoyancy effects [55]. Furthermore, if Al-Fumarate synthesis is enhanced by rapid coordination or the organic linker and metal ion, then it is hypothesised that preheating the precursor solutions may act to decrease the necessary residence time while still producing high quality product.

For synthesis using the continuous-flow hydrothermal reactor described in this work, the same self-optimisation methodology demonstrated in Chapter 5 was applied to the synthesis of Al-Fumarate. Given the large range of reported surface areas shown in Table 24 (330-1254 m²g⁻¹), the aim of this work is to achieve a specific surface area that is similar to, or exceeds, the highest reported flow synthesis, which is 1084 m²g⁻¹ by Rubio-Martinez *et al.* [300].

The primary aim of this work is to determine process conditions which are suitable for 'green' and scalable synthesis of high quality MOF material; to achieve this, the synthesis must only use commercially available precursors and solvents which can be easily recycled. Furthermore, the synthesis must be rapid, which would make the process suitable for continuous post-processing, rather than requiring significant aging time for crystallisation.

6.2 *In Situ* Analysis of MOF Synthesis

One of the greatest difficulties in applying high-throughput experimentation and selfoptimisation to MOF synthesis is the need for suitable online process analytical technologies (PATs), which can provide synthesis feedback in real time [122]. *In situ* analysis of MOF crystallisation enables investigation into the effects of reaction parameters, identification of intermediates and further elucidation of the MOF formation steps. Incorporating *in situ* analysis therefore has the potential to significantly increase the speed of optimising synthesis conditions.

Van Vleet *et al.* recently published a review of the studies and *in situ* techniques previously reported for MOF synthesis [309]. Many *in situ* studies of MOF synthesis primarily monitor the nucleation and growth phases, using techniques such as X-ray diffraction (XRD) and nuclear magnetic resonance (NMR) spectroscopy [310, 311, 312]. Millange *et al.* report one of the earliest time-resolved studies of MOF synthesis, using energy dispersive X-ray diffraction (EDXRD) for the solvothermal synthesis of HKUST-1(Cu) and MIL-53(Fe) [313]. The authors note that one of the main advantages of using high-energy X-rays to monitor crystallisation is their non-destructive penetration of lab-ware, whilst still maintaining elevated temperature and pressure within the synthesis vessel. *In situ* monitoring of the MIL-53 system enabled Millange *et al.* to observe the transient appearance of another crystalline phase, later identified as MOF-235 [313].

Applying techniques such as XRD or NMR *in situ* can provide high quality and detailed information of the nucleation and growth phases in MOF crystallisation. However, *in situ* XRD is a developmental technique and not currently accessible in most industrial applications, while NMR would require the use of a high-field solid-state spectrometer [312].

A commonly-used process analytical technology (PAT) which can potentially be employed to investigate MOF synthesis is Fourier transform infrared (FTIR) spectroscopy. FTIR spectroscopy can be used to monitor chemical bond vibrations by measuring the

absorbance or emission of infrared radiation, which allows identification of distinct functional groups in a substance.

Recently, Embrechts *et al.* applied simultaneous *in situ* FTIR and Raman spectroscopy in combination with turbidity measurements to monitor the formation mechanism of MIL-53(Al) MOF in solvothermal synthesis [314]. Embrechts *et al.* demonstrated in their work that bands assigned to the metal-linker complex, or pre-nucleation building units (PNBUs), increased in absorbance with both time and temperature during synthesis. Upon reaching a maximum threshold, the PNBU bands rapidly declined with the simultaneous formation of bands assigned to the solid MIL-53 product.

Embrechts *et al.* determined that the FTIR band at 780 cm⁻¹ was attributable the metallinker complex or PNBUs. Following analysis of the time-resolved FTIR spectra, this band was observed to grow in intensity with both time and temperature, before a rapid decline. *In situ* Raman spectra and turbidity measurements showed this decline to coincide with formation of solid MIL-53. It was therefore proposed that the relative contribution of colloidal MOF species and MOF nuclei to IR absorbance was much greater than that of the solid species. This was credited to the sensitivity bias of FTIR to measurement of the liquid phase over solid, and the short penetration depth of the evanescent wave in ATR-FTIR spectroscopy.

Later work by Embrechts *et al.* demonstrated the advantages of *in situ* spectroscopic analysis for MOF synthesis by studying the formation of the isomers MIL-68(AI) and MIL-53(AI), despite the frameworks exhibiting near-identical FTIR and Raman spectra [315]. Using *in situ* FTIR and Raman spectroscopy to monitor the δ (COO⁻) and δ (CH) bonding modes of the PNBUs and solid MOFs, respectively, allowed the authors to more closely investigate the modulation mechanism of formic acid. Previously thought to act as a competitive modulator through interaction with the metal node, it was determined that formic acid instead forms hydrogen bonds *via* the carboxylate group of the organic linker, subsequently slowing the pre-nucleation and growth phases. MIL-68(AI) has previously been identified as an intermediate in MIL-53(AI) synthesis, but better understanding the

formation steps through *in situ* spectroscopic analysis enabled the authors to target either MIL-53(AI) or MIL-68(AI) through low-temperature, modulated synthesis in DMF.

Prior to the work published by Embrechts *et al.*, only one study, by Ren *et al.*, had been reported which employs *in situ* IR monitoring, investigating the modulated synthesis of Zr-Fumarate in both hydrothermal and solvothermal syntheses [100]. Ren *et al.* used a phased-addition approach while collecting *in situ* FTIR spectra, and was able to identify several peaks which were not observed in pristine precursors. Upon heating, new peaks at 670, 983 and 1585 cm⁻¹ were observed to grow and plateau, corresponding to the formation of Zr-Fumarate. By employing *in situ* FTIR analysis, Ren *et al.* were able to monitor the consumption of the formic acid modulator in the DMF-based, solvothermal synthesis method, which was not observed in the hydrothermal system.

Work by Embrechts *et al.* and Ren *et al.* has demonstrated the feasibility of spectroscopic techniques for monitoring MOF synthesis in real time. This work aims to apply *in situ* ATR-FTIR spectroscopy as an online PAT to provide reaction feedback in the synthesis of Al-Fumarate, using a similar self-optimising method to the work in Chapter 5. A customised fitness function was used, based on the relative intensities of the carboxylate group attributed to as-synthesised solid product and unreacted organic linker (See section 6.4).

6.3 Al-Fumarate Synthesis

The Al-Fumarate synthesis in this work employs a similar hydrothermal method to that previously described by Bayliss *et al.* and Rubio-Martinez *et al.* for the synthesis of MIL-53(Al) and Al-Fumarate; whereby the organic ligand is first solubilised by the addition of NaOH [296]. A similar method, albeit with terephthalate in place of fumarate, was used by Bayliss *et al.* to synthesise MIL-53(Al) using the same counter-current reactor described in this work [316]. In this instance, the solubilised sodium fumarate precursor solution acts as the preheated reactor Downflow and is mixed with ambient-temperature Al₂(SO₄)₃ solution in the reactor Upflow. Reaction temperature, stoichiometry of ligand to metal salt and concentration of base were all varied to promote fast coordination between the carboxylate groups of the organic linker and metal ions.

All materials used through this study were purchased from the vendors as specified below. The materials were used as sold, without additional processing or modifications.

Stock solutions were prepared in deionised water as follows; Ligand Solution (0.50 M, 1 L): 117.244 g fumaric acid (\geq 99.0%, Sigma Aldrich) solubilised with NaOH (1.0 M, 1 L): 125 g NaOH 32 %w/w aqueous solution (Sigma Aldrich). Metal Salt Solution (0.25 M, 1 L): 168.182 g Al₂(SO₄)₃·18H₂O (\geq 99%, Sigma Aldrich). Dilution in flow enables the screening of a wide range of precursor concentrations without altering the total flowrate. Additional NaOH solution (1.0 M, 500 ml): 62.5 g NaOH 32%w/w aqueous solution (Sigma Aldrich) is used to alter the concentration of NaOH and flush the reactor between cycles. Ethanol (94-96%, Alfa Aesar) was used during the post-processing & washing steps.

The as-synthesised product (40 ml) was processed *via* sequential centrifugation (3500 rpm, 5 minutes) and washing steps. The retained product was washed twice with fresh deionised water (40 ml) and once with ethanol (40 ml). The washed material was oven dried overnight at 80°C under ambient pressure.

Variable	Synthesis Constraints	Notes
Temperature	50 – 200 [°C]	Downflow temperature
Al ₂ (SO ₄) ₃	0.05 – 0.15 [M]	Concentration of Al ₂ (SO ₄) ₃ in

reactor Upflow

Downflow

Concentration of NaOH in reactor

Table 25: Process constraints for Al-Fumarate synthesis throughout this work

0.40 - 0.80 [M]

Concentration

Concentration

NaOH

6.4 Online Process Analytical Technology (Inline FTIR Spectroscopy)

Figure 123 shows the ATR-FTIR spectra for Al-Fumarate MOF and the precursor sodium fumarate solution (0.50 M fumaric acid + 1.00 M NaOH). The premise for this work is straightforward, upon coordination of the Al³⁺ metal ion to the organic linker, there is an observable ~50 cm⁻¹ blue shift of the 1558 cm⁻¹ v_{as}(COO⁻) and 1368 cm⁻¹ v_s(COO⁻) stretching vibrations to 1609 and 1422 cm⁻¹ respectively, alongside the growth of new bands at lower wavelength attributed to Al-O vibrational modes. Figure 123 shows comparative spectra of the organic linker precursor solution and Al-Fumarate product.

Due to overlap with the *H-O-H* bending mode of water at 1640 cm⁻¹, higher energy $v_{as}(COO^{-})$ band is not used for evaluation of the fitness function, to mitigate the effect of



Figure 123: ATR-FTIR Spectra for washed Al-Fumarate MOF (top) and Fumaric Acid precursor (bottom). Samples analysed in solution, with water absorbance subtracted for spectral clarity.

subtraction error. It is theoretically possible to use the 968, 803, 692 or 647 cm⁻¹ bands, attributed to Al-O or Al-HBDC complexes, however, the low intensity, combined with overlap with the Al₂(SO₄)₃ precursor, make these impractical (See Figure 124).

The fitness function is therefore evaluated as the intensity ratio of the $v_s(COO^-)$ bands of the coordinated and uncoordinated ligand, as shown below.

$$Fitness \ Function = \frac{Abs_{1422}}{Abs_{1368}} \left[\approx \frac{Absorbance_{MOF}}{Absorbance_{Ligand}} \right]$$

In situ ATR-FTIR spectra were recorded using a Bruker Alpha II spectrometer, with Platinum ATR attachment and commercially available flow-through cell. Spectra acquisition occurred every 1.5 seconds and is averaged across 8 scans before being exported to the reactor control graphical user interface (Described in Chapter 2). Exported spectra were processed using a 1-D low-pass filter (sampling frequency = 4, low cut-off frequency = 0.125) to reduce noise, prior to subtracting a deionised water spectrum, obtained at the start of experiments. The weighted subtraction of the water spectrum is calculated to achieve a near-zero baseline in the region 1500-1000 cm⁻¹, up to a maximum multiplier of 1 (i.e. up to 1x the water spectrum can be subtracted to prevent negative



Figure 124: Signal processing of In-situ ATR-FTIR spectra, showing the Unprocessed (yellow, top), Background Subtracted (red, mid) and Background Subtracted & Filtered Spectra (blue, bottom). All spectra were normalised, the unprocessed signal (yellow, top) was normalised to 1/5th intensity to account for increased absorbance of water.

values). Figure 124 shows the representative effect of the baseline subtraction and data processing steps used this work, prior to recording analysis for each experiment.

It should be noted that filtering of the FTIR spectra results is a slight loss of spectral clarity, as well as a slight shift in peak maxima position, as observed in Figure 124. However, this data processing step is necessary to ensure that spectral noise does not interfere with the FTIR Objective function score assigned to each experiment.

Figure 125 shows the time-resolved *in situ* ATR-FTIR spectra from initial scoping work, while developing the platform. The time-resolved spectra shows good clarity in the symmetric $v_s(COO^-)$ region of fumarate, at wavenumbers 1350-1450 cm⁻¹. Additional peaks are clearly visible, assigned to the S-O bond of Al₂(SO₄)₃ at 1100 cm⁻¹, as well as the metal-organic complexes between 700-850 cm⁻¹. The low intensity and poor clarity of the 700-850 cm⁻¹ region make it unsuitable for primary analysis in this work.


Figure 125: Time-resolved, processed in-situ ATR-FTIR Spectra for Al-Fumarate synthesis, obtained during initial scoping work while building the reactor platform. The $v_s(COO^-)$ band at 1350-1420 cm⁻¹ can be attributed to the coordination of metal ions to the organic linker, which is used for the self-optimisation fitness function. Each spectrum had the water background subtracted and data filtered prior to collation and analysis.

6.5 Reactor Layout

The reactor was setup to run in a cyclic *Standby-Heat-Reaction-Flush* protocol, whereby each cycle represents one experiment. During each experiment, the reactor Downflow temperature was set according to the experiment conditions, and allowed to stabilise to within 2% tolerance of the set-point before starting the *Reaction* phase. To minimise the waste of precursor materials, only water was pumped during the *Standby* and *Heat* cycles. Pressure was maintained at 1000 psi throughout the study using a back pressure regulator.

Post-reaction, the product stream was cooled *via* tube-in-tube heat exchanger to 20°C and then depressurised to ambient conditions. Prior to collection and recording analysis, each experiment ran for 100 ml (equivalent to 3x reactor volumes) to ensure steady-state operation. 40 ml samples were then collected automatically *via* the customised Gilson FC204 Fraction Collector and two-way valve operated by Arduino.



Figure 126: Reactor Schematic for Al-Fumarate Self-Optimisation

6.6 Design of Experiments

To develop an initial understanding of the surface response across the design space, a Design of Experiments (DoE) study was performed. A central composite face (CCF), fractional factorial design was selected to determine a basic quadratic model with relatively few experiments, while 3 centre-point experiments were run to determine reproducibility.

All experiments were run autonomously with the conditions shown in Table 26. Following each experiment, the FTIR objective function (objective function) was obtained in real time.

In all experiments, a white precipitate was produced; the product mass was obtained from processing 40 ml of as-synthesised product using the auto-sampler. Experiments were run in random order (run order shown in Table 26) to identify drift in either the analytical equipment or as a result of reactor fouling.

Table 26: Design of Experiments study for Al-Fumarate Optimisation. FTIR objective function was determined by the relative intensity of ligand to MOF $v_{\rm S}({\rm COO}^{-})$ absorbance values. *Denotes the maximum Objective function result from this study. †Sample 16 was processed the following day to determine if yield increased overnight.

Exp No.	Run Order	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	Product [g.40ml ⁻¹]
N1	14	50	0.40	0.05	7.584	0.0906
N2	2	200	0.40	0.05	20.480	0.2345
N3	16	50	0.80	0.05	3.227	0.0000
N4	4	200	0.80	0.05	2.059	0.0410
N5	5	50	0.40	0.15	7.440	0.0000
N6*	8	200	0.40	0.15	26.055	0.3479
N7	10	50	0.80	0.15	8.798	0.7154
N8	13	200	0.80	0.15	19.322	0.5495
N9	7	50	0.60	0.10	7.998	0.5329
N10	3	200	0.60	0.10	22.510	0.5024
N11	1	125	0.40	0.10	16.700	0.3926
N12	11	125	0.80	0.10	7.670	0.4608
N13	6	125	0.60	0.05	6.224	0.2507
N14	9	125	0.60	0.15	14.502	0.5367
N15	15	125	0.60	0.10	13.441	0.3607
N16†	17	125	0.60	0.10	11.081	0.7003
N17	12	125	0.60	0.10	11.089	0.4096

Figure 127 to Figure 132 show the response surface model and model quality of for both the FTIR objective function and mass of product obtained from each sample after processing. Models were fit using multiple linear regression (MLR) without transformation or further processing or experimental data.

The FTIR objective function model, shown in Figure 127, suggests that ligand to MOF conversion rate is increased at elevated temperature, lower NaOH concentration and slight excess of $Al_2(SO_4)_3$. Furthermore, an interaction was detected in the FTIR model for the concentrations of NaOH and $Al_2(SO_4)_3$. The initial saturated model was generated with all square and interaction terms; removing non-significant terms resulted in a model with improved Q^2 and validity values, shown in Figure 129.



Figure 127: Response surface of FTIR objective function for Al-Fumarate synthesis, calculated from the relative intensity of the $v_{\rm s}(COO^{-})$ carboxylate groups of the organic linker.



Figure 128: Response surface for mass obtained after processing 40 ml as-synthesised product. "Yield" denotes mass of dried product (g).



Figure 129: Summary of fit plots for (Left) FTIR ObjFnc: R^2 =0.933, Q^2 =0.778, Model Validity = 0.705, Reproducibility = 0.953. (Right) Yield: R^2 =0.981, Q^2 =0.849, Model Validity = 0.884, Reproducibility = 0.955. Reproducibility was determined from replicate experiments and infers model sensitivity towards factor effects



Figure 130: Plots of Observed vs. Predicted for the models of FTIR Objective function (left) and product mass from 40 ml of as-synthesised sample (right) in Al-Fumarate CFHS. A straight diagonal line indicates a good fit to experiment data.



Figure 131: Residuals normal probability plot for FTIR Objective function (Left) and Product mass from 40 ml of as-synthesised sample (right) in Al-Fumarate CFHS. A straight diagonal line indicates normal distribution, whereas experiments outside of 4 standard deviations represent outliers which should be repeated.



Figure 132: Coefficient plots for the FTIR Objective function (left) and Product mass from 40 ml of as-synthesised sample (right) in Al-Fumarate CFHS. Terms were determined from creation of a saturated model with all square and interaction terms, and removal of terms with low significance (p<0.05).

The PXRD patterns of all samples (See Figure 133 to Figure 135) confirm the synthesis of Al-Fumarate, with most samples exhibiting good agreement with the simulated pattern; only samples N7, N12 and N13 show additional, unidentified peaks at 16.4° and 42.6°. There is a clear range in broadening of the (011) reflection at 10.48°, which Alvarez *et al.* attributes to the sample hydration state; although the presence of small particles or structural defects could also be the contributory factor [291].

To validate the proposed FTIR objective function, offline N₂ sorption measurement analysis was used to determine specific surface area *via* the BET method (See Figure 136). Comparing results from experiments N6 and N15 shows an increase of 93.85% in the FTIR Objective function score and 98.64% increase in the specific surface area of activated product, suggesting that the proposed FTIR objective function is indeed suitable for this study.



Figure 133: PXRD Pattern for Design of Experiments study samples N1-N8. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 134: PXRD Pattern for Design of Experiments study samples N9-N13. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 135: PXRD Pattern for Design of Experiments study samples N14-N17. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 136: N₂ Adsorption Isotherms at 77 K for experiments N6, N15 and N16 in the DoE Study of Al-Fumarate CFHS.

Table 27: FTIR Objective Function score and BET Surface Area for experiments N6, N15 and N16. **N16 was processed the following day to assess completeness of crystallisation in other samples.*

Exp. No.	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	BET Surface Area (m²g⁻¹)
N6	200	0.40	0.15	26.055	1111
N15	125	0.60	0.10	13.441	559
N16*	125	0.60	0.10	11.081	1085

To determine completeness of the reaction, experiment N16 (replicate of N15 and N17) was processed the following day, allowing 24 hours for crystallisation of the solid product to occur; this resulted in an increased product yield of 81.80% and increase of 93.95% in specific surface area (Results summarised in Table 28). This suggests that an initially midrange FTIR objective function score can still result in a high quality MOF product and yield if the as-synthesised product is processed some time later, signifying that crystallisation can indeed occur at ambient conditions. However, a key aim in this work is to identify synthesis conditions which allow the immediate processing of synthesised product, rather than requiring the product to crystallise over significant time periods. As demonstrated by the results in experiment N6, the high FTIR objective function score gives rise to a high specific surface area, despite immediate processing of the sample.

The high BET surface areas of both samples N6 and N16 (>1000 m²g⁻¹) suggest that the washing, activation and degassing steps used were sufficient to remove residual precursor molecules within the pores, as these are in line with high values reported in literature (See Table 24).

Table 28: Summary table for Al-Fumarate Design of Experiments (DoE) study. *†* denotes the maximum value obtained for the in situ FTIR analysis. *Insufficient solids produced post-processing, therefore no value provided. *‡* Sample processed the following day to determine proximity to complete crystallisation. FWHM: full-width at half-maximum of the (011) reflection at 10.48°. Product was determined from processing 40 ml of as-synthesised material. Yield is calculated based on full conversion of the organic ligand to MOF.

Exp. No.	Run Order	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	Product [g.40ml⁻¹]	Yield [%]	PXRD FWHM	BET Surface Area (m²g⁻¹)
N1	14	50.0	0.40	0.05	7.584	0.0906	12.3	0.494	
N2	2	200.0	0.40	0.05	20.480	0.2345	31.9	0.385	
N3*	16	50.0	0.80	0.05	3.227	0.0000	0.0 *	N/A *	
N4*	4	200.0	0.80	0.05	2.059	0.0410	0.0 *	N/A *	
N5*	5	50.0	0.40	0.15	7.440	0.0000	0.0 *	N/A *	
N6 †	8	200.0	0.40	0.15	26.055	0.3479	47.4	0.366	1111.1
N7	10	50.0	0.80	0.15	8.798	0.7154	97.4	0.506	
N8	13	200.0	0.80	0.15	19.322	0.5495	74.8	0.275	
N9	7	50.0	0.60	0.10	7.998	0.5329	72.6	0.393	
N10	3	200.0	0.60	0.10	22.510	0.5024	68.4	0.309	
N11	1	125.0	0.40	0.10	16.700	0.3926	53.5	0.520	
N12	11	125.0	0.80	0.10	7.670	0.4608	62.8	0.653	
N13	6	125.0	0.60	0.05	6.224	0.2507	34.1	0.812	
N14	9	125.0	0.60	0.15	14.502	0.5367	73.1	0.417	
N15	15	125.0	0.60	0.10	13.441	0.3607	49.1	0.468	559.2
N16 ‡	17	125.0	0.60	0.10	11.081	0.7003	95.4	0.421	1084.9
N17	12	125.0	0.60	0.10	11.089	0.4096	55.8	0.408	

6.7 Self-Optimisation *via* Supervised Machine Learning (SML)

In parallel to the DoE study, the custom supervised machine learning (SML) method, discussed previously in Chapter 5, was applied to the self-optimisation of Al-Fumarate synthesis. In this study, an identical experimental setup was used (precursor makeup, data acquisition and process constraints), however, experiments were generated autonomously, following analysis of those previously run and the generation of a surrogate model.

A total of 30 experiments were performed, with a total run time of approximately 7 hours. Experiments 1-5 were used for initialisation of the SML algorithm, generated *via* the MaxMin method to distribute experiments across the design space, without inducing early bias [251]. Following initialisation, the algorithm generated conditions to solely target high-performance in the experiment outcome. Experiment generation occurred in a batch size of 1, immediately following analysis of the most recently completed experiment. Figure 137 shows the 4D scatter of FTIR objective function against process variables from this investigation.



Figure 137: 4D Scatter of FTIR Objective function score at given synthesis conditions, proposed by the Supervised Machine Learning Self-Optimisation method. After some initial exploration, the algorithm converges into a high performing region at elevated temperature, decreased NaOH concentration and slight excess of $Al_2(SO_4)_3$.

Table 29: Synthesis conditions and initial results from Al-Fumarate Self-Optimisation. † Experiment 16 resulted in the maximum FTIR Objective function score, therefore considered to be the global optimum. *Experiment 24 had no recorded product mass due to a mechanical fault in the auto-sampler.

Exp. No.	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	Product [g.40ml ⁻¹]
1	50.0	0.400	0.050	4.14	0.0675
2	200.0	0.800	0.150	9.47	0.5437
3	125.0	0.800	0.050	1.25	0.0331
4	200.0	0.400	0.100	25.43	0.2661
5	50.0	0.600	0.150	5.75	0.3443
6	188.4	0.452	0.090	16.79	0.2734
7	148.8	0.798	0.140	5.22	0.5300
8	195.0	0.658	0.125	14.90	0.4460
9	186.7	0.706	0.096	5.41	0.3815
10	156.8	0.421	0.092	11.82	0.1703
11	185.0	0.451	0.111	19.74	0.2791
12	190.8	0.434	0.127	22.25	0.2684
13	195.7	0.436	0.108	27.17	0.3538
14	193.9	0.432	0.089	23.75	0.2953
15	193.7	0.467	0.134	26.13	0.3598
16†	199.8	0.467	0.104	30.16	0.4370
17	199.8	0.503	0.074	14.55	0.3066
18	199.8	0.452	0.052	10.15	0.1943
19	199.5	0.414	0.149	27.33	0.2710
20	196.9	0.416	0.135	26.58	0.3013
21	199.8	0.467	0.099	27.99	0.3734
22	196.9	0.441	0.105	21.64	0.3362
23	193.3	0.442	0.108	22.31	0.3778
24	198.4	0.428	0.129	23.70	*N/A
25	194.5	0.449	0.142	20.35	0.3273
26	197.2	0.478	0.138	20.45	0.4033
27	199.1	0.494	0.149	27.08	0.4142
28	197.2	0.405	0.110	27.41	0.2938
29	196.1	0.450	0.116	24.54	0.3477
30	158.8	0.511	0.089	9.29	0.2296

6.8 *In Situ* ATR-FTIR Spectroscopy

In situ ATR-FTIR spectroscopy was used to provide immediate feedback on experiment outcome. The FTIR Objective function score recorded for each experiment was obtained by analysis of spectra after producing three reactor volumes of product to ensure steady state operation. The flow-through design of the ATR Flowcell enabled continuous data acquisition, meaning that time-resolved spectra can easily be obtained.

For each spectrum, three distinct regions are immediately apparent between 1000-2000 cm⁻¹; they include the symmetric and asymmetric carboxylate stretching modes of the organic linker, as describe earlier, as well as the most intense peak at 1100 cm⁻¹, attributed to the S-O stretching mode from the Al₂(SO₄)₃ precursor. Figure 138 shows the time-resolved, *in situ* ATR-FTIR spectra for experiments 21-23, demonstrating the uniform cyclic behaviour of the reactor, in addition to verifying the Flushing phase is adequate to remove precursor and synthesised material from the reactor between cycles. The time-resolved spectra show a ramp and plateau, suggesting that the reaction time is sufficient to achieve steady-state operation. The full time-resolved spectra for self-optimised experiments 1-30 are shown available in Appendix: C.



Figure 138: In-Situ FTIR Spectroscopy for Self-Optimised Experiments 21 (290-295 mins), 22 (300-305 mins) & 23 (310-315 mins). Individual spectra were first baseline-subtracted (Deionised water) and then filtered, prior to analysis and collation.

6.9 Offline Characterisation

As with the DoE study, the *in situ* FTIR objective function measurements were further validated with offline PXRD and N₂ adsorption analysis. The PXRD patterns were obtained in the range $2\theta = 5-50^{\circ}$, with the patterns for SML experiments 1-30 shown in Figure 139 to Figure 142. As before, the PXRD patterns of all samples confirm the synthesis of Al-Fumarate MOF, with good agreement to the simulated pattern and a range of broadening of the (011) reflection.

 N_2 sorption measurements show that Sample 13 exhibits the highest BET surface area, at 1128 m²g⁻¹, which exceeds the highest value from the DoE study and also the highest reported value using hydrothermal flow synthesis by Rubio-Martinez *et al.* [300]. Surprisingly, sample 16, which attained the highest FTIR objective function score, did not achieve the highest BET surface area; however, the result is still excellent at 1112 m²g⁻¹.

To test the FTIR objective function efficacy, a low-scoring FTIR sample was selected for further characterisation; sample 7 obtained an online objective function score of 5.22 (in a total range of 1.25-30.16), offline characterisation by PXRD resulted in a FWHM score of 0.461 and N₂ adsorption resulted in a surface area of just 123 m²g⁻¹. This could be attributed to poor crystallinity and therefore inaccessible adsorption sites, or due to the presence of molecules or solvent which could not be removed through the washing and activation methods. In this instance, all three characterisation methods suggest a low quality sample, signifying that the online FTIR screening method is initially valid. However, significantly further sampling and analysis would be required to establish a good correlation between methods.

The synthesis conditions, yield and characterisation data are summarised in Table 30.

Table 30: Summary table for Al-Fumarate self-optimised synthesis using supervised machine learning. *†* denotes the maximum value obtained for the in situ FTIR analysis, therefore considered to be the global maximum. *** Insufficient solids produced post-processing, therefore no value obtained. *‡* No offline data due to a mechanical fault with the auto-sampler. FWHM: full-width at half-maximum of the (011) reflection at 10.48°. Product was determined from processing 40 ml of as-synthesised material. Yield is calculated based on full conversion of the organic ligand to MOF.

Exp. No.	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	Product [g.40ml ⁻¹]	Yield [%]	PXRD FWHM	BET Surface Area (m²g⁻¹)
1	50.0	0.400	0.050	4.14	0.0675	9.2	0.520	
2	200.0	0.800	0.150	9.47	0.5437	74.0	0.325	
3*	125.0	0.800	0.050	1.25	0.0331	0.0*	N/A*	
4	200.0	0.400	0.100	25.43	0.2661	36.2	0.366	1097
5	50.0	0.600	0.150	5.75	0.3443	46.9	0.471	
6	188.4	0.452	0.090	16.79	0.2734	37.2	0.355	
7	148.8	0.798	0.140	5.22	0.5300	72.1	0.461	123
8	195.0	0.658	0.125	14.90	0.4460	60.7	0.319	
9	186.7	0.706	0.096	5.41	0.3815	51.9	0.318	
10	156.8	0.421	0.092	11.82	0.1703	23.2	0.479	
11	185.0	0.451	0.111	19.74	0.2791	38.0	0.385	
12	190.8	0.434	0.127	22.25	0.2684	36.5	0.383	
13	195.7	0.436	0.108	27.17	0.3538	48.2	0.361	1128
14	193.9	0.432	0.089	23.75	0.2953	40.2	0.377	
15	193.7	0.467	0.134	26.13	0.3598	49.0	0.383	
16†	199.8	0.467	0.104	30.16	0.4370	50.8	0.368	1112
17	199.8	0.503	0.074	14.55	0.3066	41.7	0.349	
18	199.8	0.452	0.052	10.15	0.1943	26.4	0.403	915
19	199.5	0.414	0.149	27.33	0.2710	36.9	0.371	
20	196.9	0.416	0.135	26.58	0.3013	41.0	0.395	1118

21	199.8	0.467	0.099	27.99	0.3734	59.5	0.378	1130
22	196.9	0.441	0.105	21.64	0.3362	45.8	0.379	
23	193.3	0.442	0.108	22.31	0.3778	51.4	0.412	
24 ‡	198.4	0.428	0.129	23.70	N/A ‡	N/A ‡	N/A ‡	
25	194.5	0.449	0.142	20.35	0.3273	44.6	0.327	
26	197.2	0.478	0.138	20.45	0.4033	54.9	0.403	
27	199.1	0.494	0.149	27.08	0.4142	56.4	0.414	
28	197.2	0.405	0.110	27.41	0.2938	40.0	0.294	
29	196.1	0.450	0.116	24.54	0.3477	47.3	0.348	
30	158.8	0.511	0.089	9.29	0.2296	31.3	0.230	



Figure 139: PXRD Pattern for supervised machine learning self-optimisation experiments 1-8. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 140: PXRD Pattern for supervised machine learning self-optimisation experiments 9-15. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 141: PXRD Pattern for supervised machine learning self-optimisation experiments 16-22. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 142: PXRD Pattern for supervised machine learning self-optimisation experiments 23-30. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 143: N_2 Adsorption Isotherms at 77K for Al-Fumarate samples from self-optimised supervised machine learning synthesis.

Table 31: BET Surface areas for s	select self-optimisation experim	ents during Al-Fumarate synthesis,
determined from N ₂ adsorption a	t 77K.	

Exp. No.	Temperature [°C]	NaOH [M]	Al₂(SO₄)₃ [M]	FTIR Objective Function	BET Surface Area (m²g⁻¹)
4	200.0	0.400	0.100	25.43	1097
7	148.8	0.798	0.140	5.22	123
13	195.7	0.436	0.108	27.17	1128
16	199.8	0.467	0.104	30.16	1112
18	199.8	0.452	0.052	10.15	915
20	196.9	0.416	0.135	26.58	1118



Figure 144: Contour plots of FTIR Objective Function Gaussian process regression model from Al-Fumarate self-optimisation. Plots shown at NaOH concentration of 0.40 M (top), 0.60 M (mid) and 0.80 M (bottom).

6.10 Discussion

The SML self-optimisation methodology has promoted more efficient investigation of process conditions for Al-Fumarate synthesis by planning experiments based on predicted outcome. In contrast to the DoE study, whereby only one experiment (N6) falls in the optimal region, the self-optimised method generated 18 experiments with a high-performing FTIR objective function (\geq 20).

Figure 144 shows the response surface contour plots generated using the Gaussian process (GP) regression model (SML) developed from 30 experiments. The mean absolute percentage error of the trained model is 2.69% and the normalised route mean squared error (NRMSE) is 3.12%, which is excellent for 30 data points.

Both the SML and DoE methods identified the same optimum region of the design space, at elevated temperature, reduced NaOH concentration and slight excess of Al₂(SO₄)₃ (*ca.* 200 °C, NaOH: 0.45 M, Al₂(SO₄)₃: 0.12 M). The synthesis conditions denoted by this optimum region are intuitive, as the high temperature and low concentration of NaOH likely promotes coordination of the metal-linker complexes, resulting in the rapid generation of pre-nucleation building units and subsequent crystallisation.

The response surface models in Figure 127 (DoE) and Figure 144 (SML) show similar outcomes, however, there is clear variation in the scaling and detail provided. The DoE quadratic model shows a much smoother model but provides very little detail in the region defined by an FTIR objective function score \geq 20. By contrast, the GP model obtained during the self-optimised experiments provides a much more comprehensive view of the objective function response where the NaOH concentration is 0.40 M.

As discussed in Chapter 5, for the GP model obtained for hematite $(a-Fe_2O_3)$ selfoptimisation, obtaining a model which precisely fits the experimental data is not necessarily optimum, as the algorithm can easily confuse experiment noise for the true signal. The generation of several local maxima and minima within the design space of the GP model was not corroborated by the DoE study, suggesting some overfitting of the model and failure to generalise effectively. However, it is also possible that the smooth

fit observed in the DoE model can be due to the small number of samples in the experiment design, which may have failed to capture some of the more complex factor interactions or quadratic effects. It is possible that the observed differences between the two models can be attributed to the variation in training data and model structure; the DoE model is built using a CCF design with only 17 data sets, while the SML method uses 30 which are disproportionately located around the predicted optimum region. Fine tuning of these methods was not in the scope of this work, which instead focused on the development and demonstration of the autonomous platform itself. However, when considering real-world applications of these systems, it is important to ensure that the generated model used to guide optimisation is a true reflection of the process.

It is hypothesised in this work that the spectral shift in the $v_s(COO^-)$ band position upon metal ion coordination is suitable for identifying conversion of unreacted ligand precursor to MOF product. This concept appears suitable for these studies, but is limited and prone to noise error. To improve on this, alternative (or multiple) absorption bands could be investigated to better correlate the objective function score obtained from online analysis with the product quality determined by offline characterisation; i.e. correlation between the FTIR score and BET surface area values. Potential alternatives include the 1558 cm⁻¹ $v_{as}(COO^-)$ stretching mode of the organic linker, or the 968, 803, 692 or 647 cm⁻¹ bands, attributed to Al-O or Al-HBDC complexes, all of which were not used due either to low intensity, or overlap with the *H-O-H* bending mode of water at 1640 cm⁻¹. However, the baseline subtraction method used throughout this study was very basic, and a more rigorous 'curve-fitting' approach may be better suited, potentially enabling the use of these spectral features.

The *in situ* ATR-FTIR spectroscopy is not sufficient to fully characterise the as-synthesised product, however, it was able to provide a valuable screening tool which autonomously guided experiments during the study. Given the total number of experiments was fixed at 30, and assuming equal cost per experiment, the system generated 18 experiments

which correspond to a >20 FTIR objective function score. The data in Table 30 shows that for experiments analysed by both FTIR and N₂ adsorption, a high FTIR objective function score resulted in a surface area far exceeding the 1000 m²g⁻¹ threshold previously defined. This suggests that when experiments are guided by a high FTIR objective function score, a greater proportion will result in success. Conversely, the same screening method could also be used to reduce the resource requirement of the offline characterisation method, by automatically rejecting samples which exhibit a low objective function score. While this approach would decrease the total throughput in time-consuming offline characterisation, such as N₂ adsorption measurements, it may also miss important features. One example of this from the SML study is the higher than expected surface area from sample 18, which achieved a respectable surface area of 915 m²g⁻¹, despite the low-mid FTIR objective function score.

It is possible that maximising the objective function (Defined in Section 6.4) could instead favour the increased concentration of pre-crystalline (colloidal) MOF nuclei or prenucleation building units (PNBUs), as suggested by Embrechts *et al.* due to preferential measurement of the solution over solids in ATR-FTIR spectroscopy [314, 315]. However, the authors also demonstrated that the crystallisation step is rapid and can occur at relatively low temperature for MIL-53(Al). Given the similarities of this material to Al-Fumarate, it is reasonable to suggest similar behaviour in this study. Furthermore, the authors showed that increased time in solvothermal conditions was shown to impede MOF quality; demonstrated in reduced surface area measurements at extended residence time. This effect may be attributable to the induction of defects in the crystal structure; it may therefore be beneficial to target synthesis conditions which maximise the concentration of pre-crystalline (colloidal) MOF, on the basis that crystallisation occurs soon after exiting the reactor at ambient conditions. Validation of the online analysis method through offline PXRD and BET showed no indication that pre-crystalline or colloidal MOF was produced, however, this does not necessarily mean that the material analysed *in situ* was crystalline at the time of measurement.

For the purpose of this investigation, the collected product was processed within a suitable timeframe (between 0-60 minutes) and gave no indication that prolonged aging times are required to achieve high quality crystalline MOF. Synthesising materials which do not require significant aging periods promotes scalability, as the volume of stored intermediate products can be reduced.

A key limitation of this work is the use of single-objective optimisation; a more robust approach would be to consider the impact of yield in combination with product quality. While this is difficult to achieve in using the self-optimising methodology applied, a potential simple solution could be to combine chemical or structural analysis with online turbidity measurements, which has previously been applied to MOF synthesis [314]. However, developing more effective or efficient optimisation methods was not a primary objective in this work. Furthermore, attaining single-objective optimal synthesis conditions in within just 7 hours, or 30 experiments, demonstrates a substantial improvement on previous methods.

6.11 Conclusions

The objective for the work presented within this chapter was to apply the self-optimisation methodology previously described in Chapter 4 to MOF synthesis. Al-Fumarate was selected as the case study material due to its low toxicity, high stability and commercially available precursors.

In situ ATR-FTIR spectroscopy was applied to monitor reaction success using a customised objective function, determined by the relative intensity of the $v_s(COO^-)$ peaks attributed to the MOF and ligand peaks. Time-resolved FTIR spectra showed the reactor cycling phases (Standby-Heat-Run-Flush) were effective at preventing overlap of experiments, while the high-throughput reactor was able to perform 30 experiments in approximately 7 hours, using less than 1 L for either the organic linker or metal salt stock solutions.

Comparison of the online and offline analytical methods was achieved through further characterisation of select samples; this indicated that a high FTIR objective function score (>20) results in highly crystalline Al-Fumarate with high specific surface area (>1000 m²g⁻¹).

Measurements from the online FTIR analysis were used to train the custom supervised machine learning (SML) and optimisation algorithm, which generated a surface response model and new synthesis conditions in real time. Experiments were generated to maximise the FTIR objective function, as predicted by the updated SML model, which resulted in identification of an optimum region at *ca.* Downflow temperature: 200 °C, NaOH concentration: 0.45 M and Al₂(SO₄)₃ concentration: 0.12 M.

The yield for each experiment was determined by mass of the dry, processed solids and evaluation against complete conversion of the organic linker; the yield for products with a high specific surface area varied between 41-59.5%. Maximising yield was not an objective throughout this study, but is a critical parameter when considering commercialisation and process scale up. Scalarisation of outputs such as yield, crystallinity and surface area into one output could provide a suitable option for holistic optimisation. However, a more effective approach would be to apply multi-objective optimisation methods, to determine the trade-off between competing factors. This approach was not attempted during this work due to time limitations but offers exciting potential in this area.

Given the structural similarities of Al-Fumarate to MIL-53(Al) and its other analogues, it is reasonable to suggest that the self-optimisation methods described in this chapter could be applied to other MOFs. Although FTIR spectroscopy provides limited information regarding the MOF crystal structure, it provides a useful and relatively low-cost alternative screening method for MOF synthesis, potentially reducing the resource requirement for offline characterisation.

Chapter 7: Scale-Up of MOF Synthesis from Bench-Scale Self-Optimisation

7.0 Scale-Up of Metal-Organic Framework Synthesis

7.1 Introduction

Chapter 6 demonstrated a new methodology for the optimised synthesis of Al-Fumarate metal-organic framework (MOF) at lab scale, using *in situ* Fourier-transform infrared (FTIR) spectroscopy to monitor reaction progress. This represents a significant step forward in the application of automation and supervised machine learning (SML) to optimise continuous-flow hydrothermal synthesis; however, a core objective of this PhD is the development of methods or processes which can be scaled to industrial production.

This chapter aims to utilise the optimised synthesis conditions, determined from bench scale self-optimisation in Chapter 6, for both pilot (g.h⁻¹) and plant (kg.h⁻¹) scale production. Furthermore, the washing and activation methods previously used in Chapter 6 are investigated to identify more cost-effective alternatives to centrifugation and use of ethanol in solvent exchange.

This work was completed with the help and resources available at Promethean Particles, including the pilot and industrial scale continuous-flow hydrothermal reactors, and plateand-frame filtration to process large volumes of synthesised materials.

Offline characterisation methods, such as powder X-ray diffraction (PXRD), Brunauer-Emmet-Teller (BET) N_2 adsorption and transmission electron microscopy (TEM) were used to validate the synthesis and post-processing strategies.

7.2 Al-Fumarate Synthesis

The lab-scale self-optimisation study described in Chapter 6 demonstrated that the optimum synthesis conditions could be represented as a region of the design space, rather than a single point. This is not uncommon in chemical synthesis and allows some flexibility in the process to balance competing factors such as the cost of production or product yield, as required.

Using the SML model, trained using the 30 self-optimised experiments, the optimum synthesis conditions selected for scale-up were as follows:

- Downflow temperature: 200.0 °C
- NaOH concentration: 0.45 M
- Al₂(SO₄)₃ concentration: 0.12 M

The reactor Downflow temperature and concentrations of NaOH and $Al_2(SO_4)_3$ were determined directly from interpretation of the model shown in Figure 144 (Chapter 6).

Maintaining these synthesis conditions for the remaining experiments, the effect of reactor flowrate was also investigated; a parameter that had remained fixed in Chapter 6 for simplicity. The total flowrate was varied at both bench and pilot scale to determine proximity to the nucleation threshold required for rapid MOF crystallisation, further details are given in Section 7.3 and Section 7.5.

7.3 Bench Scale Synthesis & Processing

The self-optimised synthesis study described in Chapter 6 focused on the process conditions required to achieve rapid crystallisation of the Al-fumarate MOF. However, there was no investigation into to the effect of the washing and activation (postprocessing) steps required to remove unreacted precursors and other guest molecules from the MOF pores, and subsequently separate the solid product from the supernatant.

Previously, a 40 ml sample from each experiment was collected in a 50 ml polypropylene centrifuge tube. The solids were separated from the supernatant *via* sequential centrifugation at 3500 rpm for 5 minutes. After each centrifugation step, the pellet was re-dispersed in solvent, this process was repeated twice using deionised water and then once with ethanol to replace pore-bound water with a more volatile solvent. The washed samples were then dried overnight at 80 °C and ambient pressure.

The high surface areas (>1100 m²g⁻¹) achieved by several samples in the self-optimised study suggest that the washing and activation methods were sufficient to remove guest molecules from within the MOF pores. However, it is useful to investigate the use of alternative solvents, as well as further explore the effect of ageing time on the assynthesised material.

In Chapter 6, ethanol was used for the final washing cycle for AI-Fumarate in all samples, however, this could potentially be replaced with the use of methanol as a lower-cost alternative. Furthermore, replacing pore-bound water in AI-Fumarate may not be necessary at all, given the high thermal and chemical stability, and reversible water uptake. Removing the requirement for large volumes of volatile solvent would drastically increase the potential scalability of the process, improving on both the economic and process safety considerations.

Further to the washing and post-processing procedures, the initial design of experiments (DoE) study highlighted the potential increase in yield and surface area by processing the as-synthesised material >12 hours after synthesis, demonstrating 81.8% and 94.0% increases in yield and surface area, respectively (DoE samples N15 and N16). While this

increase is certainly significant, it compares a sample synthesised at conditions which were known to be far from the optimum region. It is likely that sample N16 was at an early stage of crystallisation, with a relatively low concentration of pre-nucleation building units (PNBUs) or colloidal MOF particles. Hence, a much longer ageing time was necessary to see significant changes in the product quality and yield.

7.4 Bench Scale Synthesis & Processing Results

To investigate the effect of flowrate, select samples were synthesised at a reactor flowrate of 40 ml.min⁻¹ (compared to 30 ml.min⁻¹ as before), using the same bench-scale reactor configuration described in Chapter 6.

Stock solutions were prepared in deionised water as follows; Ligand Solution (0.20 M, 1 L): 23.43 g fumaric acid (\geq 99.0%, Sigma Aldrich) solubilised with NaOH (0.45 M, 1 L): 56.25 g NaOH 32 %w/w aqueous solution (Sigma Aldrich). Metal Salt Solution (0.12 M, 1 L): 80.73 g Al₂(SO₄)₃.18H₂O (Tech., ReAgent).

Methanol (94-96%, Alfa Aesar) and ethanol (94-96%, Alfa Aesar) were used for the washing and activation steps.

The ageing time, separation method and solvent used for the final wash are all shown in Table 32. Samples N1-N8 were synthesised using the same reactor setup previously described in Chapter 6; with the exception that samples N1-N6 were synthesised at 40 ml.min⁻¹ and N7-N8 were synthesised at 30 ml.min⁻¹ total flowrate (equally distributed between Upflow and Downflow).

Samples N1, N2 and N6 show a slight increase in surface area, from 1026 to 1086 m²g⁻¹, when the sample was aged for 0, 1 and 12 hours, respectively. While the surface area increases by just 5.6% across the 12 hour ageing time, there is a drastic increase in yield, from 31.4 to 60.1% for samples N1 and N6 respectively.

Comparing samples N2, N3 and N4 shows no significant effect on yield when using ethanol, deionised water or methanol for the final solvent exchange. There is a 3.5% loss in surface

area when using only deionised water, however, this is close to the error limits for the BET measurement and so repeated analysis would be needed to confirm this effect. Given the significant cost savings in both material and equipment costs that could be applied through the use of water in place of volatile solvents, this is a very impactful discovery for industrial manufacture of Al-fumarate.

Comparing samples N1 and N7 shows the effect of reactor flowrate, with an 80% increase in yield, but only 2.3% increase in surface area when the flowrate is reduced from 40 ml.min⁻¹ to 30 ml.min⁻¹. This demonstrates a good example of the economic considerations required in a commercial process, by balancing the loss of yield against the reactor throughput, for a similar quality of product. For comparison, assuming 8 hour production using the bench scale reactor, N1 represents a higher throughput of material, but would only produce 110.8 g of dry material after processing, whereas N7 would produce 149.5 g. This could be better represented as a Pareto front, whereby an increase in one objective results in the loss of another; however, this would require a multiobjective approach to optimisation, which was not implemented in this work due to time limitations.

Interestingly, the effect of flow rate on yield and surface area is significantly reduced when the ageing time of the as-synthesised material is increased to 12 hours; samples N6 and N8 show only a 3.8% change in yield, which is within the range of experimental error. This suggests that the current hydrothermal process produces a high concentration of PNBUs or colloidal MOF particles which are then able to further crystallise at ambient conditions. Embrechts *et al.* noted a similar mechanism with MIL-53(AI) synthesis, whereby the concentration of AI-BDC complexes increases with both time and temperature to a critical threshold, before rapid MOF crystallisation [314]. The separation strategy was also investigated, comparing centrifugation against gravity settling and decanting of the supernatant. Centrifugation is a commonly-used technique in lab-scale synthesis and processing, but it is labour intensive and thus costly to implement scale. Gravity settling offers a low-energy means of washing the material, but at the cost of storing large volumes of material during processing. The highly porous structure and small size of MOF particles leads to a density similar to the solvent, making many separation processes inefficient or impractical [296]; for gravity settling, this results in a large settling time. However, given the above discovery regarding the yield advantageous and so gravity settling could offer a low-energy method to aid separation. Sample N5 was separated *via* three gravity settling washes, using a 200 ml measuring cylinder; the MOF suspension was allowed to settle for 24 hours between washes, before the supernatant was decanted and replaced with fresh deionised water.

Samples N5 and N6 (centrifuge separation method) show no significant variation in yield for the two methods, but a 48.8% decrease in surface area, which suggests that the gravity settling method was not able to remove all unreacted precursor materials from within the MOF pores. Increasing the number of washing cycles could potentially improve the product quality, however, the time and resources necessary mean this approach is not commercially viable.



Figure 145: Gravity settling process used to separate MOF solids from MOF-suspension, sample N5. For each washing phase, the solids settled to around 25% of the working volume, allowing decantation of the liquid supernatant. Images shown are 24 hours apart.

Table 32: Effect of post-processing conditions for Al-Fumarate synthesis. Product mass was determined from processing 40 ml of as-synthesised material. Yield is calculated based on full conversion of the organic linker to MOF. FWHM = Full width at half-maximum of the (011) reflection at 10.48°. †Ageing time was as close to immediate as reasonably possible. Centrifugation was carried out as described earlier. Gravity settling involved sequential settling of MOF under gravity for around 24 hours between washes. ‡Solvent used for the final washing stage.

Exp. No.	Flowrate [ml.min ⁻¹]	Ageing time [hours]	Solvent ‡	Separation Method	Product Mass [g.40ml ⁻¹]	Yield [%]	PXRD FWHM	BET Surface Area [m²g ⁻¹]
N1	40.0	0 +	EtOH	Centrifuge	0.2308	31.4	0.413	1026
N2	40.0	< 1	EtOH	Centrifuge	0.2749	37.4	0.403	1045
N3	40.0	< 1	H ₂ O	Centrifuge	0.2682	36.5	0.344	1011
N4	40.0	< 1	MeOH	Centrifuge	0.2670	36.3	0.426	1047
N5	40.0	> 12	EtOH	Gravity settled	0.4343	59.1	0.296	730
N6	40.0	> 12	EtOH	Centrifuge	0.4418	60.1	0.403	1086
N7	30.0	0 +	EtOH	Centrifuge	0.4153	56.5	0.392	1051
N8	30.0	> 12	EtOH	Centrifuge	0.4255	57.9	0.384	1098



Figure 146: PXRD Patterns for experiments N1-N4 in the Post-Processing study. Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 147: PXRD Patterns for experiments N1-N4 in the Post-Processing study. Simulated pattern calculated from CSD-Refcode DOYBEA [291]

The PXRD patterns of all samples confirm the synthesis of the desired Al-Fumarate MOF structure, exhibiting good agreement with the simulated pattern and no additional or unidentified peaks (See Figure 146 and Figure 147). The N₂ adsorption isotherms are shown in Figure 148, with very similar measurements for all samples, with the exception of N5 (gravity settled).



Figure 148: N_2 Adsorption Isotherms at 77K for Al-Fumarate samples from Post-Processing study, BET surface areas are given in Table 32.

7.5 Pilot Scale Synthesis

The pilot scale reactor uses the same tube-in-tube, counter-current flow design as the bench scale system [317]. However, the reactor itself is much larger, using a 1.50" outer tube with 0.188" wall thickness and a 0.50" inner tube with 0.065" wall thickness. A Cast-X 3000 27 kW heater is used to preheat the Downflow process stream, prior to mixing with the ambient temperature Upflow. Similar to the bench scale system, a tube-in-tube heat exchanger cools the process stream prior to the release of pressure at the back pressure regulator (BPR).

Key dimensions used for further calculations are given in Table 33.

Table 33: Pilot rig volume and residence time calculations. HX = First heat exchanger following the reactor. BPR = Back pressure regulator and rig outlet.

Description	Volume [L]	Residence Time [s] (Q = 26.4 L.h ⁻¹)	Residence Time [s] (Q = 51.0 L.h ⁻¹)
Total	1.4		
Reactor	0.26	35.5	18.4
Reactor \rightarrow HX	0.12	16.4	8.5
Reactor \rightarrow BPR	0.39	53.2	27.5

Following investigation of the post-processing parameters, two pilot scale productions were performed (Pilot 1 and Pilot 2 respectively). Pilot 1 was performed at the optimum conditions stated earlier (Downflow temperature: 200 °C, NaOH concentration: 0.45 M, Al₂(SO₄)₃ concentration: 0.12) and a total reactor flowrate of 26.4 L.h⁻¹, representing a 14.5x increase compared to the original lab-scale synthesis. Pilot 2 was performed at 51 L.h⁻¹ (maximum reactor throughput) to further assess the effect of reactor flowrate at increased scale. The effect of flow rate on the flow regime within the reactor is discussed in Section 7.8.
P1 and P2 produced 17 and 37 L of as-synthesised material respectively, in a total time of approximately 40 minutes for each run. In each case, the initial 3 L of produced material was discarded to ensure steady state operation of the reactor prior to sample collection.

All materials used through this study were purchased from the vendors as specified below. The materials were used as sold, without additional processing or modifications.

Pilot 1 Synthesis:

Stock solutions were prepared in deionised water as follows; Ligand Solution (0.20 M, 10 L): 234.34 g fumaric acid (\geq 99.0%, Sigma Aldrich) solubilised with NaOH (0.45 M, 10 L): 562.50 g NaOH 32 %w/w aqueous solution (Sigma Aldrich). Metal Salt Solution (0.12 M, 10 L): 807.27 g Al₂(SO₄)₃.18H₂O (Tech., ReAgent).

Pilot 2 Synthesis:

Stock solutions were prepared in deionised as follows; Ligand Solution (0.20 M, 20 L): 468.69 g fumaric acid (\geq 99.0%, Sigma Aldrich) solubilised with NaOH (0.45 M, 20 L): 1125.00 g NaOH 32 %w/w aqueous solution (Sigma Aldrich). Metal Salt Solution (0.12 M, 20 L): 1614.55 g Al₂(SO₄)₃.18H₂O (Tech., ReAgent).

In both cases, pressure was maintained at 1000 psi throughout the process through use of the BPR.

7.6 Plant Scale Synthesis

In addition to the pilot scale investigation, a plant scale production run was performed to produce 1000 L of as-synthesised material, using the industrial continuous-flow hydrothermal plant at Promethean Particles [65, 67].

The plant scale reactor uses the same reactor geometry as the pilot scale system previously described. However, the plant also utilises a heat recovery system in combination with a 1400 kW natural gas boiler to pre-heat the reactor Downflow. The heat recovery system uses a tube-in-tube heat exchanger, whereby the reactor outlet stream is used to heat the Downflow inlet. After heat recovery, the process stream is cooled to ambient temperature and pressure is released at the BPR. Key dimensions used for further calculations are given in Table 34.

Table 34: Plant volume and residence time calculations. $^+$ The same reactor geometry used for the pilot scale reactor is used for the industrial plant. HX = First heat exchanger following the reactor. BPR = Back pressure regulator and rig outlet.

Description	Volume [L]	Residence Time [s] (Q = 3 m ³ h ⁻¹)		
Total	230			
Reactor †	0.26	0.3		
Reactor \rightarrow HX	25	30		
Reactor \rightarrow BPR	50	57		

Stock solutions were prepared as follows; Ligand Solution (0.20 M, 500 L): 11.72 kg fumaric acid (\geq 99.0%, Sigma Aldrich) solubilised with NaOH (0.45 M, 500 L): 28.13 kg (20.83 L) NaOH 32 %w/w aqueous solution (Sigma Aldrich). Metal Salt Solution (0.12 M, 500 L): 40.36 kg Al₂(SO₄)₃.18H₂O (Tech., ReAgent). Pressure was maintained at 1000 psi throughout the process through use of the BPR.

The plant scale production followed the same process conditions as defined for the pilot synthesis, with the exception of flowrate, which was 3000 L.h⁻¹. 50 L of as-synthesised material was discarded to ensure steady operation, resulting in 950 L of product. No operational issues were observed throughout the production run.



Figure 149: IBC (1000 L) of as-synthesised Al-Fumarate from Plant production (left) and 25 L of as-synthesised Al-Fumarate from Pilot 2 production (right)



Figure 150: As-synthesised Al-Fumarate produced at Plant scale (1000 L). Sample was washed with a combination of gravity settling (in the IBC as shown) and plate and frame filtration.

7.7 Post-Processing: Filtration

The increased volume of as-synthesised material produced in the pilot and plant scale productions enabled the investigation of plate and frame filtration for processing.

A filter press is a mechanical solid-liquid separator; one of the oldest and well-known designs is the plate and frame filter (also known as the membrane plate filter), which consists of alternating plates and frames supported by rails, with filter membranes between each pair [318]. A Shuangfa SFP200-10 filter press was used with 100% cellulose filter cloths (5-13 micron, SLS).



Figure 151: Shuangfa SFP200-10 Filter press used for filtration and dewatering of the Al-Fumarate Pilot and Plant scale productions

For continuous operation, the solid-liquid separation takes place through the filter cake, built up on the filter membranes; in this work, this was achieved by recycling of the MOF suspension through the filter until the supernatant was visibly clear. After each washing step, the supernatant was discarded, and the filter cake re-dispersed into fresh deionised water before repeating. Following three washes, the dewatered cake was then dried overnight at 80 °C and ambient pressure. This same process was repeated for all pilot and plant production studies. Further to trialling the filtration method, a 50 ml sample was washed and separated though sequential centrifugation, allowing comparison of the bench, pilot and plant scale synthesised products. All washes were completed using only deionised water.

Due to the limited capacity of the plate and frame filter available, a combination of gravity settling and filtration was used for the material synthesised on the plant. The assynthesised product was settled to 25-30% of the initial volume (Shown in Figure 150), before the clear supernatant was discarded and replaced with fresh deionised water; this process was repeated three times with 24 hours between cycles. Simultaneously, the concentrated suspension was filtered in five distinct batches, using the same plate and frame filter process previously described and then recombined after filtration. The earlier post-processing study had shown gravity settling to be insufficient as a standalone washing method, which necessitated the combination of gravity settling with filtration. The dewatered cake was then dried overnight at 80 °C and ambient pressure.

7.8 Results & Discussion

Samples from the pilot and plant productions were further characterised by PXRD and BET N_2 adsorption. Yield was determined from the mass of dried product obtained from 50 ml of as-synthesised material and calculated from the theoretical full conversion of organic linker to MOF. The 50 ml samples were taken from the bulk as-synthesised product and processed *via* centrifugation to enable comparison of the synthesis methods. The surface area and yield of all scale-up syntheses are shown in Table 35.

Table 35: BET surface area and Yield for Pilot and Plant scale synthesis, comparison of 50 ml sample processed via sequential centrifugation and Bulk samples processed via filtration. Yield calculated from 50 ml sample taken for centrifugation and full conversion of the organic linker to MOF. Yield for filtration not calculated due to large mechanical losses, which are not representative of the method. *†* % increase from the 50 ml sample process via centrifugation to the bulk filtration method.

Sample	Processing Method	BET Surface Area [m ² g ⁻¹]	Yield [%]
Pilot 1	Centrifugation	1135	83.5
	Filtration	1144 (+0.79%) †	-
Pilot 2	Centrifugation	1087	66.8
	Filtration	1112 (+2.30%) †	-
Plant	Centrifugation	1135	93.3
	Filtration	1155 (+1.84%) †	-

Table 35 shows that in all cases, the BET surface area was greater in samples processed *via* filtration, compared to the sequential centrifugation method used previously; this could suggest that filtration offers a more suitable washing and separation method for MOF processing. However, it is also important to consider the increased time required for filtration (up to 8 hours); earlier investigations demonstrated a slight increase in yield and product quality when samples were subject to increased ageing times. It is therefore possible that the small increase in surface area could instead be attributed to the additional time required to process litre-volumes of material *via* filtration.



Figure 152: Comparison of Sample (blue) and Bulk (red) BET Surface area for Pilot 1, Pilot 2 and Plant synthesis. % increase denotes increase in surface area from 50 ml sample processed via centrifugation to bulk sample processed via filtration.



Figure 153: PXRD for AI-Fumarate samples at Pilot and Plant scale synthesis, comparing initial sample (Centrifugation) and representative bulk sample (Filtration). Simulated pattern calculated from CSD-Refcode DOYBEA [291]



Figure 154: N₂ Adsorption isotherms at 77 K for AI-Fumarate samples at Pilot and Plant scale synthesis, comparing initial sample (Centrifugation) and representative bulk sample (Filtration)

The increase in flowrate from 26.4 to 51 L.h⁻¹ for pilot scale synthesis shows a 4.2% decrease in surface area, and 20.0% decrease in yield; which corroborates the findings of the earlier lab scale post-processing study. This could stem from the reduced residence time at elevated temperature when increasing the reactor flowrate.

Interestingly, the greatest BET surface area and yield exhibited was from the plant scale synthesis, achieving $1155 \text{ m}^2\text{g}^{-1}$ in the final product; which is the highest result throughout this work and far exceeds the highest value reported for continuous-flow hydrothermal synthesis, by Rubio-Martinez *et al.* at 1084 m²g⁻¹ [300]. This can likely be attributed to the improved mixing efficiency and increased nucleation rate of the turbulent flow regime in the plant reactor, resulting from the significantly higher flowrates and disproportionately-scaled reactor geometry.

The increase in reactor flowrate is not equal to the increase in reactor scale and geometry, resulting in changes to the flow regime, reaction time and space time yield, as shown in Table 33, Table 34 and Table 36. The Reynolds number (Re) is calculated immediately after mixing point to the reactor outlet as follows:

$$Re = \frac{\rho D_H v}{\mu}$$

Where Re is the dimensionless Reynolds number, ρ is the fluid density (kg.m⁻³), D_H is the hydraulic diameter of the tube (m), v is the mean velocity of the fluid (m.s⁻¹) and μ is the dynamic viscosity (Pa.s).

Given the tube-in-tube design of the reactor, the hydraulic diameter and cross-sectional area are calculated from the annulus formed from the inner surface of the outer tube (D_{a} in) and the outer surface of the inner tube ($D_{\beta-out}$). This is illustrated as the green shaded region in Figure 155.



Figure 155: Cross-section of the annulus created by the tube-in-tube design of the counter-current heat exchanger. $D_{a-in} =$ inner diameter of outer tube, $D_{\beta-out} =$ outer diameter of inner (Downflow) tube. Shaded region (green) illustrates reactor cross-sectional area.

The flow regime becomes transitional at Re>2300 and turbulent at Re>4000 [319]. This calculation suggests that in all bench and pilot scale studies, the flow regime is well within the laminar region; however, the dramatic increase in flowrate and similar reactor geometry from pilot to plant scale results in a flow regime that is clearly turbulent.

The changes in flow regime and reactor geometry could potentially result in changes to the particle size and morphology. A similar study using these reactors was reported by Clark *et al.* for the scale up of Zn₂Al-CO₃ layered double hydroxides, reporting some

changes to the crystal domain length and surface area when moving between reactor scales [320].

Table 36: Synthesis scale and comparison between flowrate, Reynolds number, flow regime and space time yield. For comparative purposes, the properties of water at 100°C and used for calculation.

Scale	Flowrate [Lh ⁻¹]	Reynolds Number	Flow Regime	Space Time Yield [kg.L ⁻¹ h ⁻¹]
Bench	1.8	212	Laminar	4.8
Bench	2.4	283	Laminar	4.3
Pilot	26.4	770	Laminar	1.2
Pilot	51.0	1488	Laminar	1.9
Plant	3000	87507	Turbulent	158.2

7.8.1 TEM Analysis

The TEM image in Figure 157 (Pilot 1 synthesis) shows lozenge-shaped particles, which is similar across all samples characterised by TEM in this work and agrees with previous reported images of Al-Fumarate in literature [291]. Size analysis considered both the minor and major axis of particles, defined in Figure 156. Figure 158 shows the size distribution for samples taken from the bench, pilot and plant synthesis; in all cases the bench scale synthesis shows the smallest particles and size distribution. The major axis increases from an average particle size of 31 nm at bench scale to 45 nm for the industrial scale synthesis. Many of the TEM images, used for size analysis, are included in Appendix D.

The cause of the increased particle size distribution for the samples produced at industrial scale is unclear. One explanation could be the change in flow regime from laminar to turbulent flow within the reactor; however, it may also be an artefact of the TEM images

used for size analysis (See Appendix D). The images show far fewer particles and significant agglomeration, which when processed *via* the size analysis algorithm in this work, could easily give rise to a misrepresentative response.



Figure 157: Transmission Electron Microscopy (TEM) image of Al-Fumarate from Pilot 1 synthesis.



Figure 156: Definition of Major and Minor axis of lozenge-shaped Al-Fumarate samples for transmission electron microscopy (TEM) size analysis.



Figure 158: Size analysis of Al-Fumarate from transmission electron microscopy (TEM) images. Samples were synthesised at Bench, Pilot and Plant scale.

7.8.2 Error Analysis: Yield & Surface Area

To assess the sampling error in BET characterisation and yield calculations, five 50 ml samples were taken from the Pilot 1 synthesis and processed using the sequential centrifugation steps previously described. The N₂ adsorption isotherms and yield show excellent consistency across the five independent samples, with an average BET surface area of 1128 m²g⁻¹ (±4) and yield of 83.9% (±0.5).



Figure 159: N₂ Adsorption Isotherms at 77 K for Pilot 1 samples A-E.

Table 37: Mean BET Surface area and Yield for five 50 ml samples taken from Pilot 1 synthesis. Yield calculated from full conversion of the organic linker.

Sample	BET Surface Area [m ² g ⁻¹]	Yield [%]	
Pilot 1: A	1129	83.7	
Pilot 1: B	1131	83.3	
Pilot 1: C	1126	84.4	
Pilot 1: D	1135	83.5	
Pilot 1: E	1121	84.5	
Average	1128 ± 4	83.9 ± 0.5	

7.9 Conclusions

This chapter has demonstrated the scalability of the Al-Fumarate synthesis conditions for obtaining high surface area product, determined from the self-optimisation study in Chapter 6. Prior to scale-up, the washing and activation methods were assessed to determine the effect of ageing time on the optimised product, as well as the significance of volatile solvent during the washing stages. The results indicated a 91% increase in product yield when as-synthesised material was aged for over 12 hours. Additionally, the surface area and sample crystallinity were not significantly affected, suggesting that non-crystalline MOF or intermediates were removed during the post-processing steps of samples which were processed immediately.

The optimised synthesis conditions were trialled at pilot and plant scale, demonstrating excellent scalability with the full-scale production $(3 \text{ m}^3\text{h}^{-1})$ producing 1000 L of assynthesised material (approximately 12 kg of dry product). Following processing through a combination of plate and frame filtration and gravity settling, the final BET Surface area for the bulk material was 1155 m²g⁻¹, which exceeds the highest value reported for continuous-flow hydrothermal synthesis, by Rubio-Martinez *et al.* at 1084 m²g⁻¹ [300].

Calculation of the Reynolds numbers at bench, pilot and plant scale show that the flow regime of the bench and pilot systems is likely laminar, whereas the high flowrate and similar reactor geometry of the plant reactor result in a turbulent flow regime. This likely contributes to far more efficient mixing, when compared to the bench and pilot systems, resulting in an increased nucleation rate, and subsequently higher yield and quality of MOF product. It is possible that the turbulent flow regime in the industrial scale synthesis was responsible for the large variation in particle size; however, the PXRD and N₂ adsorption analysis gave no indication of reduced product quality.

Although the synthesis method has demonstrated excellent scalability, the need for suitable washing and solid-liquid separation of the as-synthesised material presents a significant challenge in the overall process. Through use of a plate and frame filtration method, the large volumes of as-synthesised materials could be processed during this study, however, the limited capacity meant that several batches were required. Furthermore, the method required recycling of the filtrate in order to build a filter cake on the filter membrane, significantly increasing the time required for processing. Notably there is no technical barrier to post-processing by this method; in the future this limitation can be trivially addressed by the purchase of commercially available, large capacity filtration apparatus should commercial volume requirements warrant it.

Further investigation of inline filtration methods could significantly improve the scalability of MOF production. Rubio-Martinez *et al.* has previously demonstrated the use of megasonics as a fast and cost effective processing strategy for Al-Fumarate and MIL-53(Al) MOFs; while Munn *et al.* have investigated the use of ultrasound in the activation of ZIF-8, with both groups reporting excellent surface areas for their respective materials [296, 115].

While filtration, ultrasound and megasonics have been demonstrated as suitable for scale, there is still the need for optimisation of the processes, such as the number of washing cycles, or power and frequency of the ultrasound technologies.

The work in this chapter utilised the optimised conditions determined at bench scale and demonstrated their suitability for pilot and plant scale production. The synthesis conditions have shown excellent scalability, however, the process is not yet well-understood, and small changes in the reactor geometries or flow regimes can potentially have significant impacts on characteristics such as particle size and morphology, crystallinity and surface area. In order to attain the optimum conditions needed at pilot or plant scale, a similar self-optimisation process to that of the bench system could be applied at scale. This would pose significant engineering and economic challenges. However, the potential to self-optimise large scale synthesis could drastically reduce the timescales required for industrial production. Furthermore, if well-designed, an autonomous large scale reactor combined with in-line monitoring could respond quickly to variation in process.

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Chapter 8: Conclusions and Further Work

8.0 Conclusions and Further Work

8.1 Overview

The primary objective of this PhD has been to develop an autonomous, continuous-flow hydrothermal reactor, capable of self-optimising nanomaterial synthesis; with a focus towards industrial scale-up and manufacture.

A background literature review of the applications and synthesis methods was presented in Chapter 1, with an emphasis on continuous-flow hydrothermal synthesis. Selfoptimisation in flow-chemistry is a relatively recent but advancing area of research. The review gives a timeline of reported examples, algorithms employed and an overview of their methodologies and limitations.

8.2 Chapter 4: Evolutionary Optimisation of HKUST-1

In Chapter 4, HKUST-1 metal-organic framework (MOF) synthesis was optimised using the autonomous reactor system and the SyCo Finder web application published by Moosavi *et al.* [139]. The optimisation of HKUST-1 synthesis was structured around the genetic (evolutionary) algorithm used in the SyCo Finder application; three generations of experiments were produced, whilst also 'training' a machine learning model to predict experiment outcome. This approach was based around work by Moosavi *et al.* in their optimisation of HKUST-1 using a robotic microwave batch reactor, which achieved the highest reported surface area to date, at 2045 m²g⁻¹ [138].

Samples were optimised to achieve the highest crystallinity from powder X-ray diffraction (PXRD) analysis, as determined from the average full-width half maximum (FWHM) values of the three most intense reflections. Samples showing the highest crystallinity from each generation were further analysed by N₂ adsorption to determine the surface area by BET method; with 1837 m^2g^{-1} being the highest surface area achieved. Whilst this is lower than the reported value by Moosavi *et al.*, this is an excellent result for a scalable synthesis process.

This approach demonstrated that high-throughput experimentation could be successfully combined with machine learning and optimisation algorithms for MOF flow synthesis, however, a significant limitation exists in the need to collect, process and analyse all samples within a generation before any information could be gained. A possible solution could be to automate the processing and analysis stages, which would reduce the time and resource required of the user. Furthermore, this approach would be more efficient if unsuccessful experiments could be identified immediately following synthesis, which would minimise the necessary processing throughput of collected samples.

8.3 Chapter 5

Chapter 5 introduces autonomous, self-optimisation for the synthesis of hematite (a-Fe₂O₃), using online dynamic light scattering (DLS) to maximise particle size. In contrast to Chapter 4, experiments were self-guided and executed by a custom supervised machine learning (SML) algorithm, which uses Bayesian optimisation to build a surrogate model.

The availability of particle size information in real time facilitated far faster and more efficient exploration of the design space. This self-optimised approach required significantly less time, requiring just 7 hours to run and analyse 30 experiments, compared to the several days required to process and analyse the samples in Chapter 4.

Optimisation of hematite considered three variables; temperature, flow rate and the ratio of Upflow to Downflow within the reactor; online DLS indicated that larger particle sizes could be obtained at increased temperature and residence time, and lower Upflow ratios.

Offline analysis *via* PXRD, UV-Vis spectroscopy and transmission electron microscopy (TEM) showed the DLS measurements significantly overestimated the particle size in each case. This could be attributable to DLS measuring the hydrodynamic diameter of particles, or particle agglomerates. Notwithstanding, the autonomous reactor platform was able to self-optimise using an online process analytical technology (PAT) and is the first known example of self-optimisation in a continuous-flow hydrothermal reactor.

While the reactor itself worked well, immediate improvements in accuracy could be achieved in selection of the PAT. Given the significant variation between DLS and size analysis by TEM imaging, a potentially better-suited alternative could be nanoparticle tracking analysis (NTA), which is less prone to measurement bias where large particles or agglomerates exist in the sample, however, this method also represents significant additional cost.

8.4 Chapter 6

In Chapter 6, the autonomous platform was further demonstrated by self-optimising the synthesis of Al-Fumarate MOF; a custom objective function was used, employing online-FTIR spectroscopy for reaction evaluation.

The same SML algorithm used in Chapter 5 was applied in Al-Fumarate self-optimisation, however, exploration parameters were set to prioritise regions of predicted high performance, in order to improve experiment efficiency. 30 experiments were run in approximately 7 hours, varying the Downflow temperature and the concentration of NaOH and Al₂(SO₄)₃. The system converged upon an optimum region at elevated temperature, reduced NaOH concentration and a slight excess of Al₂(SO₄)₃ (ca. 200 °C, 0.45 M_{NaOH} and 0.12 M_{Al2(SO4)3}).

Offline PXRD showed good crystallinity in multiple samples produced within the optimum region, while N₂ adsorption showed surface areas in excess of 1100 m²g⁻¹ by BET method, suggesting a high quality of product. This result far exceeds the highest reported value for Al-Fumarate by continuous-flow synthesis, at 1084 m²g⁻¹ by Rubio-Martinez *et al.* [300]. Product yield for high quality samples varied between 41.0-59.5%, although the reason for this variation is unclear.

The self-optimisation methodology was developed to maximise conversion of organic linker precursor to the MOF product, however, it is difficult to distinguish between pre-nucleation building units (PNBUs), colloidal MOF or the crystalline final product from the methods used. Combining inline FTIR spectroscopy with additional PATs, such as Raman

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spectroscopy or turbidity measurements could further develop the autonomous platform for self-optimising the synthesis of MOFs [321, 322, 323].

8.5 Chapter 7

Chapter 7 directly follows on from the self-optimisation work described in Chapter 6. The optimum synthesis conditions determined at bench scale were applied at pilot and industrial scale manufacture, resulting in a final surface area of $1155 \text{ m}^2\text{g}^{-1}$ for the industrial scale product.

The effect of reactor flowrate was studied at pilot scale through two productions, at 26.4 and 51.0 L.h⁻¹ respectively. The investigation showed a 16.7% decrease in product yield at the higher flowrate, which is likely attributable to a lower residence time at elevated temperature within the reactor.

The industrial scale synthesis resulted in the highest surface area of all Al-Fumarate syntheses within this work, and an estimated yield of 93.3% from initial sampling. The significant increase in yield and surface area is most likely due to the changes in the reactor flow regime, from laminar at bench and pilot scale to turbulent at industrial scale, which improves mixing within the reactor.

Prior to synthesis at increased scale, the washing and activation methods were investigated. It was shown that using only water (instead of either methanol or ethanol) for the washing stages did not adversely affect the measured surface area or sample crystallinity; this is a very impactful and promising discovery for the industrial scale synthesis of Al-Fumarate. The separation of solids from the mixture was also investigated, comparing centrifugation, filtration and gravity settling. Filtration using a plate-and-frame filter press was effective at both washing and separating the solids from the as-synthesised mixture, although the capacity of equipment available meant that a combination of gravity settling and filtration was necessary at industrial scale.

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8.6 General Comments & Further Work

This work represents the first reported self-optimising continuous-flow hydrothermal synthesis reactor. The final reactor design and auxiliary platform has shown excellent applicability to the synthesis of nanomaterials, with a robust design that was used to optimise the synthesis of MOFs and metal oxides. However, the experimental case studies highlighted several areas of improvement in the methods and equipment used for this work.

8.6.1 Materials

The autonomous platform described in this work is intended for use with multiple material groups and case studies. The autonomous bench scale reactor was developed to achieve a Downflow temperature range of ambient to 400 °C, with a maximum reactor flowrate of 50 ml.min⁻¹. Using multiple pumps and dilution in flow ensures that a range of precursor concentrations and flowrates can be rapidly investigated.

The continuous-flow hydrothermal synthesis reactor design, from which this platform is based, has previously been demonstrated for the synthesis of several nanomaterials, as discussed in Chapter 1. As there are no significant alterations to the reactor geometry or working principle, there is no reason this system cannot easily be applied to the synthesis and optimisation of these materials. To further demonstrate the applicability of automation, machine learning and optimisation to nanomaterial synthesis, the range of case study materials should be expanded to include examples such as metals, phosphates, sulphides and other inorganic nanomaterials, which were not attempted during this PhD.

The system is designed so that the process can be rapidly self-optimised if a suitable PAT is available; however, for more complex materials, high-throughput experimentation, sampling and offline analysis may prove to be more effective, similar to the process described in Chapter 4 for HKUST-1 synthesis.

8.6.2 Process Analytical Technologies

Two online PATs were applied in this work: DLS and FTIR spectroscopy. These methods were effective at demonstrating the potential of self-optimisation with the reactor system but were limited in the information they could provide.

DLS measurements were shown to significantly overestimate the particle size of hematite in Chapter 5, when compared to offline PXRD and TEM imaging. DLS measurements are sensitive to the presence of large particles, agglomeration or polydisperse samples, meaning that useful information is only available in regions of close proximity to the desired product. Regions of the design space which are far from the optimum were shown to give invalid responses, which can easily confuse a machine learning algorithm if not correctly identified. In this work, this was overcome through the use of Design of Experiments (DoE) for the initial experiments to identify a feasible region for selfoptimisation; while this approach was effective, it detracts from the autonomous purpose of the self-optimising platform.

Inline FTIR spectroscopy was able to effectively guide the self-optimising platform to synthesise high-quality Al-Fumarate. However, the measurement method was not able to distinguish between colloidal and crystalline MOF; while this did not demonstrate any significant hindrance in this work, more complex MOF products or syntheses may be more limited.

Depending on the material and application, an idea ideal system would employ a more advanced analysis method, such as PXRD. However, this represents significant additional cost and complexity, and is perhaps poorly suited to an industrial environment for which this system is intended.

8.6.3 Machine Learning and Optimisation Algorithms

A significant portion of the success in this work can be assigned to the machine learning and optimisation (MLO) algorithms which were employed. Several MLO methods were applied, including DoE, genetic (evolutionary) optimisation, SNOBFIT and Bayesian optimisation in combination with a surrogate Gaussian process model. In each case, these methods were able to perform at least as well as would be expected from a trained chemist; while training the machine learning models meant that the weighted importance of variables could be identified.

Development and testing of these MLO methods through parameter selection (e.g. exploration vs. exploitation) was not a main objective of this work, and so it is likely that the performance of these algorithms could be further improved and each method compared more effectively.

Throughout this work, only single-objective optimisation was considered, because of time limitations. Given that this work is intended for industrial application, it is therefore imperative to consider holistic optimisation of the process. It is often the case in real-world examples that multiple conflicting objectives exist, such as the cost of production versus product quality. Scalarisation of multiple objectives offers an immediate solution, but requires in-depth prior knowledge of the system to ensure variables are correctly weighted. The need to simultaneously optimise multiple environmental and economic factors means that a more suitable alternative would be the multi-objective optimisation of key or competing parameters, which could be used to identify the optimum region or Pareto front, whereby a gain in one variable inherently results in the loss of another [144, 324, 325].

Furthermore, this work focused on the synthesis stage of the product, whereas in reality, the post-synthesis processing, washing and formulation stages are just as significant. Optimising each stage individually simplifies the task but is analogous to the "one-variableat-a-time" synthesis approach, of which this work has aimed to avoid.

The choice of algorithm depends heavily on features such as the experiment cost, time available and primary objective (i.e. fast and efficient optimisation or to generate an accurate model). As research in this area continues, more advanced and efficient

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algorithms are continually being developed, which could easily be applied to this autonomous platform, with only minor modifications.

8.6.4 Reactor Design

The autonomous self-optimising platform worked well for the case study materials in this PhD and, in the case of Al-Fumarate, the optimum conditions were shown to scale very well at pilot and industrial scale manufacture. However, it was evident in Chapter 6 that each reactor exhibits different flow regimes and residence times, dependent on the reactor geometry and process equipment employed. Through rigorous investigation across multiple materials and process conditions, it is possible to model and predict the effect of moving from one reactor to another. However, this approach limits applicability to wellknown materials.

An alternative approach would be to develop the same integrated cyber-physical system demonstrated at bench scale, to the existing pilot and industrial scale facilities. If welldesigned, such a system could explore and self-optimise within an optimum region previously identified at bench scale, meaning that the optimum conditions for a given reactor and environment could be rapidly identified. Autonomous process control would also enable these reactors to respond quickly to disturbances, such as a drop in catalyst activity or the presence of poor quality precursors.

Integrating online analysis and automation into reactors of increased scale represents a significant additional cost, which must be justified against the cost and sensitivity to process disturbances in the product. However, these challenges could be overcome with appropriate and existing engineering solutions, meaning that autonomous chemical plants could be a viable future direction in industrial scale manufacture.

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Appendix A: Chapter 5 – Detailed DLS Reports



Count Rate (kcps): Cell Description:	420.8 Quartz flow cell	Measurement Position (mm): 4.20 Attenuator: 6			
			Size (d.nm):	% Intensity:	St Dev (d.nm):
Z-Average (d.nm):	54.08	Peak 1:	73.67	100.0	45.47
Pdl:	0.225	Peak 2:	0.000	0.0	0.000
Intercept:	0.931	Peak 3:	0.000	0.0	0.000

Result quality : Good



Figure 160: DLS Size & Distribution Reports for Sample A (top) and B (bottom)



Figure 161: DLS Size & Distribution Reports for Sample C (top) and D (bottom)



Count Rate (kcps): 272.0 Cell Description: Quartz flow cell

Measurement Position (mm): 4.20 Attenuator: 4

			Size (d.nm):	% Intensity:	St Dev (d.nm):
Z-Average (d.nm):	91.71	Peak 1:	105.9	100.0	41.25
Pdl:	0.122	Peak 2:	0.000	0.0	0.000
Intercept:	0.951	Peak 3:	0.000	0.0	0.000
Result quality :	Good				



Figure 162: DLS Size & Distribution Reports for Sample E (top) and F (bottom)

Appendix B: Chapter 5 – TEM Images



Figure 164: TEM Image for Sample A, Scale bar at 200 nm (top) and 20 nm (bottom)



Figure 164: TEM Images for Sample B. Scale bar at 200 nm (top) and 20 nm (bottom)



Figure 166: TEM Images for Sample C. Scale bars at 200 nm (top) and 100, 20 and 10 nm respectively (bottom, left to right)



Figure 166: TEM Images for Sample D. Scale bar at 200 nm (top) and 20 nm (bottom)



Figure 168: TEM Images for Sample E. Scale bar at 200 nm



Figure 168: TEM Images for Sample F. Scale bar at 200 nm (top) and 20 nm (bottom)

Appendix C: Chapter 6 – *In situ* FTIR Spectra during self-optimisation



Figure 169: In-Situ FTIR Spectroscopy for Self-Optimised Experiments 1-6. Individual spectra were first baseline-subtracted (Deionised water) and then filtered, prior to analysis and collation.



Figure 170: In-Situ FTIR Spectroscopy for Self-Optimised Experiments 7-14. Individual spectra were first baseline-subtracted (Deionised water) and then filtered, prior to analysis and collation.



Figure 171: In-Situ FTIR Spectroscopy for Self-Optimised Experiments 15-22. Individual spectra were first baseline-subtracted (Deionised water) and then filtered, prior to analysis and collation.



Figure 172: In-Situ FTIR Spectroscopy for Self-Optimised Experiments 23-30. Individual spectra were first baseline-subtracted (Deionised water) and then filtered, prior to analysis and collation.

Appendix D: Chapter 7 – Al-Fumarate TEM Images



Figure 174: TEM Images for Pilot Scale Synthesis of Al-Fumarate



Figure 175: TEM Images for Plant Scale Synthesis of Al-Fumarate

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