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Recent Developments in Process Digitalisation for Advanced Nanomaterial Syntheses

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Digitalisation and industry 4.0 are set to profoundly change the way chemical and materials discovery and development work. The integration of multiple enabling technologies such as flow synthesis, automation, analytics, and real-time reaction control lead to highly efficient, productive, data-driven discovery and synthetic protocols. For instance, the development of flow chemistry enables the fine control and automation of process parameters such as flow rates, temperature, and pressure, which inherently enhances process efficiency. Flow chemistry presents a more sustainable means of manufacturing in terms of waste minimisation, as it enables the integration of synthetic processes with downstream processing. Furthermore, it allows the integration of analytical techniques to provide in situ process monitoring of large amounts of process and product data. The application of Artificial Intelligence (AI) and/or Machine Learning (ML) techniques allows rapid decision making that can optimise existing processes, and it has also been applied in the discovery of novel materials, synthetic pathways and chemicals. All this is contributing to an effective digitalisation of chemical and material synthetic processes from the laboratory to large-scale industrial deployment.

This paper presents recent developments in the effective digitalisation of chemical synthetic processes which integrates continuous flow synthesis, analytics and artificial intelligence technologies. Specifically, this paper illustrates the emerging trend of process digitalisation through the advanced syntheses of materials with catalytic, optical and optoelectronic applications.

1. Introduction

Process digitalisation is set to transform chemical and materials industry, with a profound transformation of synthetic processes, enabling rapid, on-demand and efficient synthetic processes, which both improve the properties of the materials synthesised and reduce the waste generated.[1] An effective digitalisation of the synthetic process requires: 1) Full automation of the synthetic process. Microfluidic reactor systems are key to achieve this, by eliminating the manual handling steps inherent to batch procedures. 2) Real-time data generation about the properties of the nanomaterials fabricated, to rapidly correlate the inputs (concentrations, flow rates, temperature, etc.) with the outputs (particle size, size distribution, physico-chemical properties, etc.). 3) Advanced modelling to rapidly optimise the properties of the materials, and also for the discovery of emerging properties. The application of artificial intelligence technologies offers a broad range of possibilities to process chemistry, by rapidly developing models that establish meaningful connections between the process parameters and the properties of the materials synthesised. The combination of these three aspects opens new windows of opportunity to develop robust and reproducible fabrication processes. In this work, we present some representative advances in the field to illustrate the potential of this emerging paradigm.

2. Discussion

Continuous flow syntheses, also known as flow chemistry, are efficient processing technologies which are gaining relevance for the production and commercialisation of nanoscale and structured materials,[2] including perovskites, quantum dots, noble metal/metal oxide nanoparticles and porous materials (e.g., MOFs). These advanced materials have a broad range of applications including optoelectronics, catalysis, photovoltaic devices, LEDs and energy conversion and storage,[3] drug delivery, hyperthermia medical treatments, amongst others.[4] However, the bottleneck in the application of nanomaterials in industry is their scale-up to a commercial manufacturing level whilst keeping the material quality. Many of these nanomaterials can be crystallized from solution, and their desirable properties are highly dependent on their chemical and physical properties (e.g., composition, size, shape, etc.) and the nanocrystal dispersity formed during synthesis. Therefore, it is of utmost importance to provide a controlled and reproducible chemical (e.g., *pH*) and physical (e.g., *temperature*) environment during synthesis resulting in well-defined nanocrystal properties.

Currently, batch synthesis of nanomaterials is most widely used in industry. However, due to inconsistent mixing and

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localised concentration and temperature variations within batch reactors, reproducibility and scalability issues arise. The use of microfluidic reactors, in the context of flow syntheses, can overcome these limitations due to the large surface area to volume ratios which enhance heat and mass transfer resulting in faster reactions and higher yields.[4c,5] In the context of flash chemistry, chemical transformations take place very quickly and are solely controlled through the mixing process. Therefore, the enhanced mixing within microfluidic systems enables fast consecutive reactions involving unstable intermediates to take place[6] and the resulting homogenous environment enhances the selectivity towards the desired product, increasing the reaction yield. Furthermore, flow chemistry allows the isolation of unstable reactive species before they decompose by controlling the residence time of the reaction,[7] either through adjusting the reactants' flow-rates or microreactor length.

High mixing is a key advantage in microfluidic systems, although dominated by slow diffusion under the laminar flow regime.[8] The resulting parabolic velocity profile within the microchannels results in a broad residence time which inevitably develops particle size dispersity,[10,35] as shown in Figure 1A. Promoting convection and enhancing mixing within the microchannels is one way to reduce this polydispersity, for example, by introducing Dean vortices through corners and bends or introducing Taylor vortices through segmented liquid-liquid/liquid-gas flow,[10,36] as shown in Figure 1B.

Furthermore, the strict control over reaction parameters in flow chemistry is a major advantage for standardisation of reaction conditions across laboratories, thus increasing the level of reproducibility of experiments.[10] In terms of safety, the consumption of smaller amounts of hazardous reagents associated with microfluidic systems reduces safety risks and allows the use of extreme chemical conditions otherwise deemed unsafe in batch reactors.[9] Thus, it provides extra control over exothermic reactions particularly. Furthermore, the continuous operation of microfluidic systems enhances parameter screening during optimisation studies which results in lower reagent consumption making the process more environmentally friendly. Finally, scale-up of production can be achieved by increasing both the flow-rate and reactor length, maintaining the residence time, or by numbering up the microreactors operating simultaneously in parallel,[11] avoiding the detrimental product quality associated with batch up-scaling. Nevertheless, the high sensitivity inherent to the reactions involved in the synthesis of nanomaterials, including steps of nucleation, growth, ripening, etc. represents a true challenge for the effective scaling-up due to changes in the heat and mass transport properties and mixing when reactor dimensions are increased.[12] Numbering up of microreactor units also poses challenges to generate and maintain stable flow conditions, which are critical to achieve steady state flow conditions that guarantee a uniform residence time distribution.[13] In many cases the materials are produced in relatively small amounts and with a high added value. For instance, 145 g per day of CdTe nanocrystals were achieved with five parallel flow reactors, which is considered a significant production rate for high quality quantum dots. Expanding the

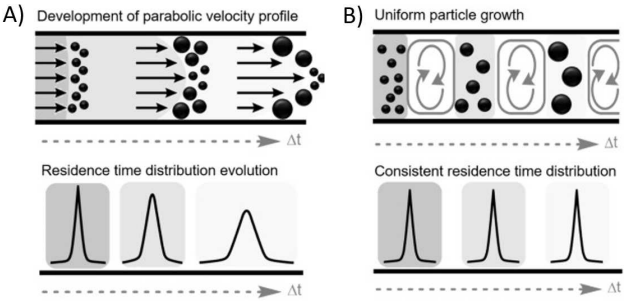

Figure 1. A) The fluid parabolic velocity profile due to friction near the walls. The resulting residence time distribution gets broader over time. B) More uniform particle growth is obtained when chaotic mixing is induced in a segmented flow process. Each segment represents an ideal batch reactor resulting in consistent residence time distribution over the reactor length. Reprinted from Ref. [9], Copyright (2020) with permission from Elsevier.

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parallel reactor system could be relatively easily adapted to achieve a scale of Kg per day, enough to satisfy industry requirements.[14]

During recent years, 3D printing, also known as additive manufacturing (AM), has been used to fabricate advanced geometrical reactor shapes at increasingly high resolutions. It enables the manufacture of complex structures layer-by-layer using 3D model data.[15] Thanks to AM, reactor geometry can be finely tuned for the optimisation of mixing and, more interestingly, the implementation of advanced mixing features such as serpentine structures or the split/recombination of flow channels.[16] The optimised mixing also allows process up-scaling by increasing reactor dimensions to the milli- or mesoscale.[17] Figure 2A showcases an example of a continuous oscillatory baffled reactor (COBR) manufactured with 3D printing used for the synthesis of silver nanoparticles and, as shown in figure 2B, the combination of an oscillatory flow regime and periodic obstructions (baffles) results in high mixing at low Reynolds numbers, which makes the reagents more evenly distributed in the reactor. A geometry like the one shown in Figure 2C, can create a swirling flow that resembles a coiled tube if oscillation is applied, and the authors suggest

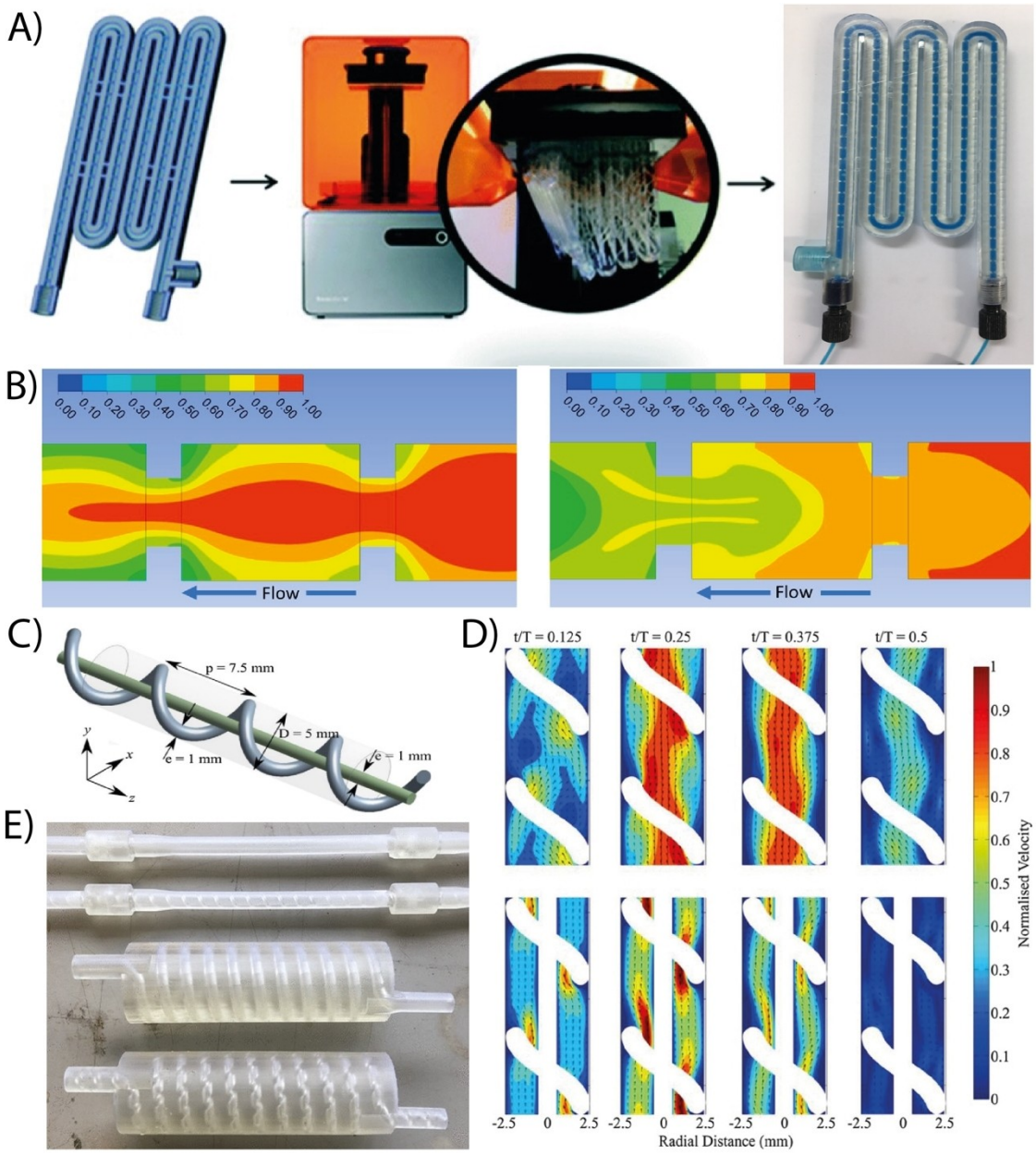

Figure 2. A) 3D printing of a continuous flow oscillatory baffled reactor with advanced mixing for the synthesis of silver nanoparticles. Adapted from Ref. [17a], Copyright (2017), RSC. B) CFD analysis of a 3D printable oscillatory baffled reactor showing improved mixing under oscillatory conditions. Adapted from Ref. [22] under CC BY 4.0. C) Design of a helical baffle with central rod. D) CFD simulations of velocity profiles of helical oscillatory baffle reactor: top without central rod, bottom with central rod. Reprinted from Ref. [18], Copyright (2019) with permission from Elsevier. E) Reactors fabricated using 3D printing, featuring a Coil-in-Coil Reactors (bottom). Reprinted with permission from Ref. [23]. Copyright (2019) American Chemical Society.

additive manufacturing for its construction.[18] Figure 2D illustrates the velocity profiles obtained by CFD simulations for the helical baffled oscillating reactor: the inclusion of the central rod makes the velocities more consistent across the domain. Furthermore, 3D printing enables the design of structures with tailored surface area for supporting different active catalysts,[19] biocatalysts[20] and other advanced functionalities.[21] This would serve as an alternative to the packed bed reactors used in the industry, trading operational difficulties due to the intrinsic randomness of particle-based beds, like pressure drop, flow maldistribution or non-uniformity of the available catalytic surface, with a more reliable control over reactor parameters that can be digitally validated before initial experiments.[20b] In this way, 3D printing enables the evolution from simple straight tubular or random packed reactors to more complex systems, including baffled reactors (Figure 2A–B), coiled tube featuring periodic inserts (Figure 2C–E) and other advanced geometries (Figure 2E)[17a,22]

In-line analytics offer great synergy with continuous flow systems, since they are techniques that continuously record the output of the reactors.[24] The properties of nanoparticles are highly dependent of size and shape, so constant control of the output is key for properly controlling their synthesis.[12] The chosen techniques must be rapid enough to monitor the changes on real time and sensitive enough at small volumes, also it is preferred that they are non-destructive.[25] This synergy enables to swiftly evaluate the effect of modifying reaction parameters or detecting reaction intermediates otherwise undetectable using offline methods like Gas Chromatography (GC) or High Performance Liquid Chromatography (HPLC).[26] However, these techniques have a limited range of applications for nanomaterial syntheses. Spectroscopic techniques are commonly used along microfluidic systems for the synthesis of advanced materials, thanks to their capabilities for fulfilling the aforementioned requirements and the optoelectronic properties presented by many of these materials.[27] Furthermore, some studies report the formation of an amorphous phase of unstable intermediates during nanoparticle synthesis deviating from the traditional particle formation mechanisms.[28] Undertaking the reaction in a microfluidic system allows the steady-state operation to "freeze" transient reaction states locally[4a] since chemical species are transforming through both time and space, therefore providing better understanding of the stages of particle formation.

UV-VIS absorption spectroscopy is widely used in the flow synthesis of nanoparticles of materials such as gold or silver.[17a,29] The radiation absorption properties of this kind of materials allow to monitor their formation, and the implementation of Mie-based algorithms enables to estimate the size of the synthesised particles in real time.[30] In the case of materials with photoluminescence properties, such as quantum dots, photoluminescence spectroscopy offers great sensitivity and real-time information of their physical properties.[27] As seen on Figure 3, there is correlation between physical properties like particle size distribution and the width of the maximum emission peak. Furthermore, other properties like quantum yield or fluorescence lifetime of quantum dots can be measured

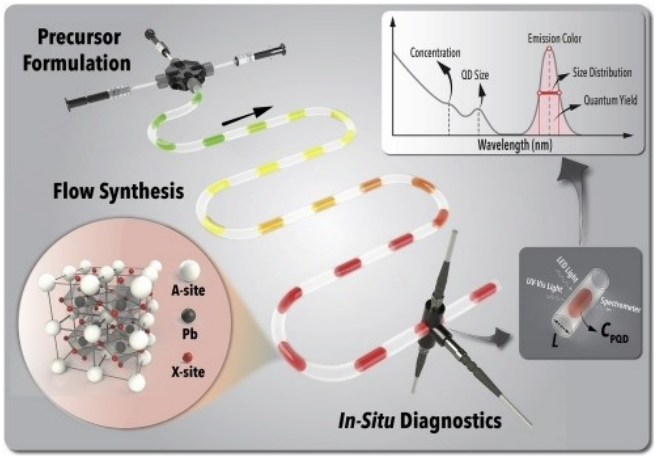

Figure 3. Schematic of a flow system for the synthesis of lead halide perovskite quantum dots featuring simultaneous both UV-VIS absorption and fluorescence spectroscopies for the in situ characterisation of products. Reprinted from Ref. [3a], Copyright (2020) with permission from Elsevier.

in real time,[31] therefore, their synthesis can be tailored to efficiently achieve the desired properties. However, these techniques are not enough for providing insight in properties like crystal structure, surface ligand population or crystal nucleation dynamics,[3a] hence new tools need to be developed.

X-Ray spectroscopic measurements are an essential tool in the study of crystalline materials, however the analysis times classically required are too long for a direct implementation in microfluidic systems and hence setups need to be adapted.[27] In this regard, there are reports of systems that enable the use of X-Ray Absorption Spectroscopy (XAS) to monitor the evolution of gold nanoparticles oxidation states during their synthesis[32] or the combination of Small Angle X-ray Scattering (SAXS) and Wide Angle X-ray Scattering (WAXS) for studying the nucleation and growth of nanoparticles.[33] In the case of Fe_3O_4NPs, their co-precipitation from solution is a very simple, cheap, and safe method, however, the nucleation of nanocrystals is so quick that reaction mechanisms are not well understood.[4a] In-situ Small Angle X-ray Scattering (SAXS) and in situ synchrotron X-Ray Diffraction (XRD) can be integrated at different positions of the reactor length as shown in Figure 4 for capturing reaction states. It is even possible to simultaneously measure SAXS/WAXS and UV-VIS to systematically study all the factors that may influence crystal nucleation and model nanoparticle growth for materials such as gold.[34] Transmission electron microscopy (TEM) is another technique whose potential for in-line monitoring has also been demonstrated. The use of liquid flow cell TEM permitted to directly observe how two dimensional double hydroxide nanostructures attach, and give insight into the parameters that influence the formation mechanism.[35]

Albeit they are more traditionally used for the characterisation of organic molecules, Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopies can be implemented in setups for the synthesis of advanced materials. For example, FTIR has been used to monitor precursor

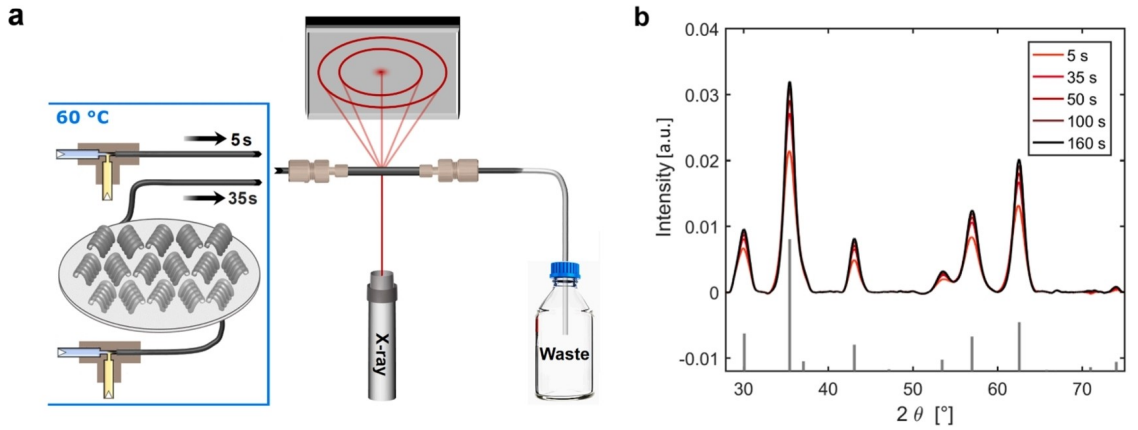

Figure 4. A) Schematic of set-up for in situ XRD studies, capturing the temporal reaction states after mixing the reactant solutions by adjusting the coiled microreactor tube length before the flow cell (residence time between 5–160 s). B) XRD pattern during the first 160 s after mixing the reactant solutions. The bars at the bottom show the peak positions and relative intensities of Fe_3O_4NPs. Reprinted from Ref. [4a] Copyright (2020), with permission from Elsevier.

consumption during the synthesis of CdS nanocrystals. The obtained data was combined with UV-VIS to understand the mechanism of their growth via mass balance.[36] NMR is another technique classically used during the synthesis of organic molecules, but recent developments have shown its integration in the flow synthesis and functionalisation of iron oxide nanoparticles. The magnetic properties of this material and their correlation with particle size enable to monitor particle size in real time during synthesis.[37]

As it has been previously discussed, flow synthesis offers better control of reaction parameters and reproducibility of results over batch synthesis, however there is still room for improvement. The translation of reaction parameters (temperature, pressure, flow, injection time…) into digital values that can be controlled by software, also known as digitalisation, makes flow synthesis of advanced materials prone to automation. The total control of reactor conditions by a computer, minimizing the quantity of uncontrolled variables or differences due to human intervention, further improves the reproducibility of the results.[38] With the addition of in-line analytics for real time characterisation of the products, those reaction parameters can be directly related to material properties and transform syntheses into sequences of sets of parameters.[29]

However, as complexity of the systems increase, and more variables need to be controlled, the search for the ideal conditions by changing only one variable at a time becomes very time consuming to the human researcher. The use of statistical techniques like "Design of experiments" (DoE) allows to study different parameters by creating a matrix of combinations of reaction conditions to evaluate their influences; so time, resources consumption, and waste are reduced.[39] Nevertheless, if the number of parameters to be evaluated grows even further, the number of experiments required becomes too large.[40] The use of optimisation algorithms that interpret the data to maximise/minimise the desired output of the reactions is an alternative tool that can help enhancing the speed of discoveries.[26] This approach involves mathematical models with closed loops where the recorded information of an experiment influences the experimental conditions for the following ones.[41] The more extensively used algorithm for self-optimisation is the Nelder–Mead Simplex Method,[42] but there are also examples of the use of others like a modified version known as Complex,[43] Mie,[4b] TSEMO[44] or SNOBFIT.[45]

Figure 5 illustrates the general workflow for automated self-optimising systems: Initial experimental conditions are set, the output of the reactor is recorded and according to the received

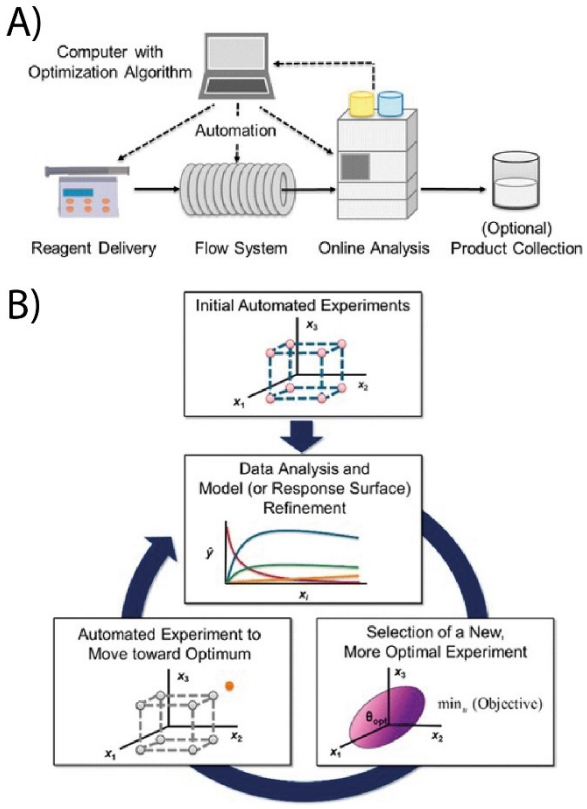

Figure 5. A) Schematic for the setup of self-optimising synthesis platform. B) Illustration of how a self-optimisation algorithm works. Reprinted with permission from Ref. [46]. Copyright (2016) American Chemical Society.

signal new experimental conditions are chosen by the algorithm.[46] The system keeps working until a stop condition is reached. There are different criteria for finishing the process, some examples include a fixed number of iterations, the difference between two consecutive experiments being within a chosen tolerance[41] or the minimisation of a dissatisfaction coefficient compared to a target value.[47] More complex models include multivariable target optimisation functions, based on Pareto front optimisation.[48]

Machine learning (ML) is a further advanced application of optimisation algorithms. It's an Artificial Intelligence based technology that enables the recognition of patterns within complex datasets.[49] ML can be used during reaction planning, like in the selection of reaction pathways that yield the desired material geometries;[50] or execution, to constantly improve the results until target properties are achieved.[51] ML techniques offer potential advantages over cognitive rational experiment design, by selecting non-biased experimental conditions that can contribute to process discovery.[52] There are several available techniques, some examples include artificial neural networks, decision trees, linear regressions or support-vector machines.[53] The application of these techniques during any part of the chemical research workflow, or even during the whole process, can significantly accelerate discoveries. Its potential has been demonstrated in applications such as finding new perovskite single-crystal crystallisation conditions,[54] maximising the yield and antibacterial properties of ZnO nanoparticles[55] or optimise perovskite quantum dots bandgap.[51]

Machine learning algorithms require training to achieve predictive character. Training is classified according to the kind of data supplied to the algorithm, hence it is divided into supervised learning (with previously labelled data), unsupervised learning (with unlabelled data), semi-supervised learning (a combination of both) and reinforced learning (each action is linked to a score that the system tries to maximize).[56] In advanced material synthesis, the predominant use of machine learning methods has been to fit already available data into surrogate models that can be used for supervised learning techniques.[57] This can be used for establishing relationships between different datasets, such as a material composition and its properties, and therefore predict target properties such as a perovskite bandgap[58] or the dimensionality of the crystalline phases[59] depending on the perovskite chemical composition before synthesizing them. The applications of unsupervised learning in advanced materials development are less common, nonetheless it can help in uncovering hidden relationships within big datasets of unlabelled data. This has been reported in applications such as finding the key structural parameter that governs charge losses in halide perovskites.[60] One of the inconveniences of supervised learning is the need to have enough labelled data, something than can be very expensive. Semi-supervised learning can be used to generate a model from part of the labelled data using unsupervised learning and then use supervised learning to label the remaining data.[61] Reinforced learning is often used at parameter self-optimisation processes, for instance, achieving target properties in perovskite quantum dots.[51]

The data required can come in different formats but can be categorized in material properties from experiments/simulations, chemical reaction parameters, image data and data extracted from literature. At the same time, this information can come in diverse formats such as text, vectors, tensors, images, weighted graphs….[63] The source for obtaining this data can be really diverse but some examples include libraries of previous in-house experiments,[3a] mining the available literature for synthesis data,[50] generating an initial set of experiments to be labelled and then used for the training[64] or open available databases. In the case of material science, there are many databases. For instance the Cambridge Structural Database contains crystallographic data of reported structures;[65] the Materials Project[66] or AFLOW[67] contain physico-chemical properties (formation enthalpies, band structures, material porosity…). There are also databases specialised in the specific properties like the Harvard Clean Energy Project for organic photovoltaic materials; or contain experimental conditions and the properties of obtained materials like HTEM.[68] One factor that would enrich experimental databases would be inclusion of failed experiments. This could also accelerate the development of ML techniques by increasing the availability of information, something that would also reduce human bias and therefore improve the versatility of the models.[69] It should be considered that, before training the machine algorithm, there is a need to process the data so that its format matches the requirements of the algorithm, and potential variations depending on the source of the data should be considered, so information should be unified.

The machine learning model selected and the desired accuracy determine the quantity of data needed for the training. Generally, the amount of data required for machine-learning applications is large, but in fields like material science the quantity of high-quality points available is only in the order of hundreds or thousands so this becomes an issue.[70] Therefore, the development of models that rely on minimal amount of data for achieving accurate enough predictions is essential.[71] However, it's even possible to work without any previous data as illustrated by the Figure 6 two-step algorithmic strategy for minimization of the number of datasets required: initially, a Bayesian optimisation algorithm selects batches of 15 experiments that are used to train a deep neural network (DNN). Once enough data has been generated, the predictions of the DNN are compared against the results while more 15 experiment batches are run. Finally, once DNN accuracy is stablished, it can be used for predicting the spectra of silver nanoparticles and the matching synthesis conditions. Nevertheless, currently, ML approaches are more suited for fast syntheses. Slow and multistep processes remain a challenge due to the higher number of uncontrollable parameters that cause variability (flow fluctuations, fouling, ageing of solutions, etc.) and thus would require higher complexity models with periodic training.[4b]

The transformation of controllable variables into digital inputs, along automation and monitorisation of processes,

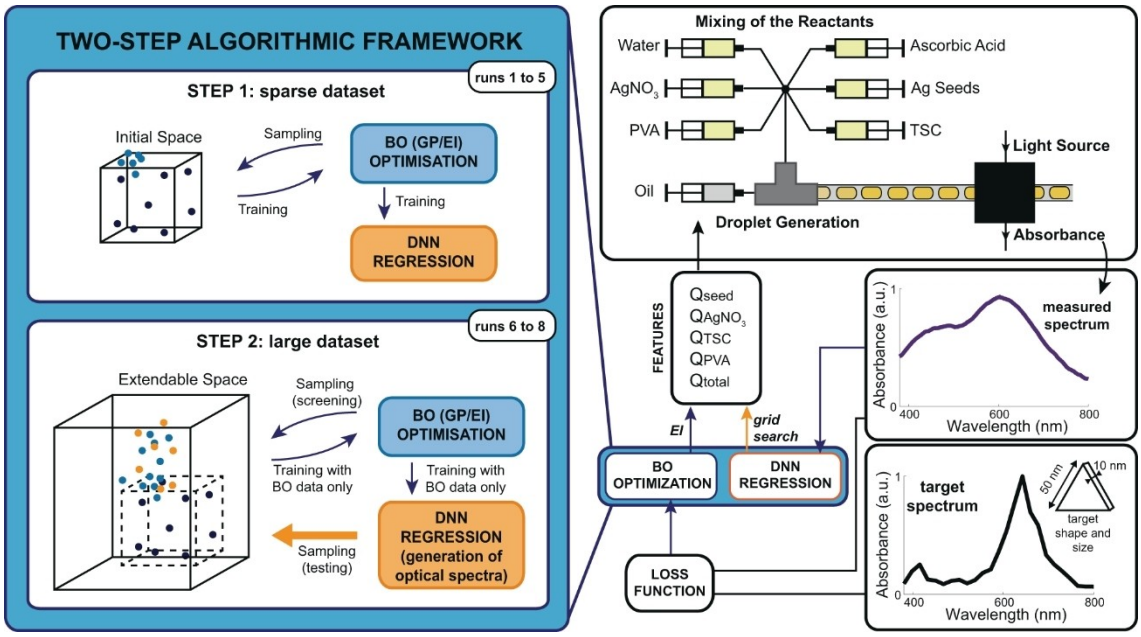

Figure 6. Two-step training of a deep neural network (DNN) for the synthesis of silver nanoparticles. The trained DNN can predict optical properties of the nanoparticles and required synthesis parameters different from the originally targeted. Reproduced from Ref. [62] under the terms of CC BY 4.0.

increases their reproducibility and the speed of discoveries, as previously discussed. Moreover, this digitalisation of the chemical workflow paves the way to further control of processes using computers. The usual chemical reaction workflow can be divided into different modular operations and, hence, they could be assimilated into different digital commands. The term *chemputation* embodies this mindset: to transform classically written chemical reactions into programmable code analogous to computer software. All the factors (e.g., needed operations, reagents, temperature, vessels, etc.) are coded as variables that a computer could process to send the required commands to a robotic platform.[72]

One of the challenges in the development of *chemputing* is the need of process standardisation: the reaction sequence and the reported results must follow a standard so they can be universally shareable (analogous to the code hosting platform GitHub).[72] Moreover, the integration of different software and hardware parts may cause interoperability issues between the different parts so a unified approach is needed to democratize automation, using tools such as knowledge graphs.[73] The development of a programming language for chemistry processes, like Universal Chemical Description Language (χDL), and the creation of open source tools that allow to reproduce experiments without conflicts of different software licences between labs would also help in this matter. Those initiatives are akin to others like the standardisation of flow chemistry protocols,[6] the creation of open experimental databases[68] or labware development tools.[74] Higher standardisation would further enhance the reproducibility of results between laboratories and help in the global sharing of knowledge. Furthermore, the availability of standardized information would have a positive impact in the creation of surrogate models for supervised machine learning techniques.[57]

However, there is also the need to develop reconfigurable hardware compatible with this approach. The possibility of carrying out many different unit operations within a single system requires complex automated platforms. Many of the reactions described in the literature are made in batch, so the transition to coding may be easier due to more established workflows and its likeness to the sequential nature of programming. Sequences can be done by either programming an apparatus with different modules used for individual operations[75] or cartridge based methods.[76] The transition to multistep flow syntheses requires additional factors to be considered like changes of solvent phase, parallelisation of processes or the calculation of times required for achieving steady state. Nevertheless, solutions are being developed like modular interchangeable flow reactor systems[77] or radial platforms where a central station rotates to connect different modules.[78] Most of the reported development regarding these kinds of platforms are within the field of organic synthesis, however, there are reports of a reconfigurable multistage platform for the synthesis of advanced materials which allows the synthesis of different quantum dots with adjustable core/shell compositions.[79] The use of chemical programming could be used to program the desired properties of the nanomaterials synthesised, while the synthetic platforms allow minimal optimisation steps and less waste generation. Furthermore, with the implementation of cloud computing technologies, these platforms could be made accessible from all over the world so scientists could benefit from them without the need of sharing physical location with the laboratory.[80]

3. Conclusions

In order to further develop technologies based on advanced nanomaterials on a broad range of applications, ranging from antimicrobial, catalysts to optoelectronic devices, their syntheses have to be fully controllable and scalable. Continuous-flow syntheses of nanomaterials has emerged as a key technology to achieve this goal, thanks to fine control of the reaction parameters, including temperature and mixing. Furthermore, the use of continuous-flow facilitates the automation of key variables controlling the overall process and also allows to generate real-time data of the conversion and selectivity observed. This also paves the way to the application of AI algorithms, which increase the speed of optimisation of reaction parameters, the knowledge about unexplored conditions and eventually the discovery of new materials.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Continuous-flow · Digitalisation · In-line analytics · Machine learning · Process automation.

[1] J. Kimmig, S. Zechel, U. S. Schubert, *Adv. Mater.* **2021**, *33*, 2004940.
[2] S. Marre, K. F. Jensen, *Chem. Soc. Rev.* **2010**, *39*, 1183–1202.
[3] a) K. Abdel-Latif, F. Bateni, S. Crouse, M. Abolhasani, *Matter* **2020**, *3*, 1053–1086; b) S. A. Khan, C. Li, A. Jalil, X. Xin, M. Rauf, J. Ahmed, M. A. M. Khan, B. Dong, J. Zhu, S. Agathopoulos, *Chem. Eng. J.* **2021**, *420*, 127603; c) A. Kostopoulou, K. Brintakis, N. K. Nasikas, E. Stratakis, *Nat. Photonics* **2019**, *8*, 1607–1640.
[4] a) M. O. Besenhard, A. P. Lagrow, A. Hodzic, M. Kriechbaum, L. Panariello, G. Bais, K. Loizou, S. Damilos, M. Margarida Cruz, N. T. K. Thanh, A. Gavriilidis, *Chem. Eng. J.* **2020**, *399*, 125740; b) B. Pinho, L. Torrente-Murciano, *Adv. Energy Mater.* **2021**, *11*, 2100918; c) J. Mahin, L. Torrente-Murciano, *Chem. Eng. J.* **2020**, *396*, 125299.
[5] M. O. Besenhard, A. P. LaGrow, S. Famiani, M. Pucciarelli, P. Lettieri, N. T. K. Thanh, A. Gavriilidis, *React. Chem. Eng.* **2020**, *5*, 1474–1483.
[6] C. A. Hone, C. O. Kappe, *Chem. Methods* **2021**, *1*, 454–467.
[7] a) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 327–360; b) Y. Tomida, A. Nagaki, J.-i. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 3744–3747.
[8] K. S. Elvira, X. C. i Solvas, R. C. R. Wootton, A. J. deMello, *Nat. Chem.* **2013**, *5*, 905–915.
[9] N. Zaquen, M. Rubens, N. Corrigan, J. Xu, P. B. Zetterlund, C. Boyer, T. Junkers, *Prog. Polym. Sci.* **2020**, *107*, 101256.
[10] C. J. Richmond, H. N. Miras, A. R. de la Oliva, H. Zang, V. Sans, L. Paramonov, C. Makatsoris, R. Inglis, E. K. Brechin, D.-L. Long, L. Cronin, *Nat. Chem.* **2012**, *4*, 1037–1043.
[11] Z. Dong, Z. Wen, F. Zhao, S. Kuhn, T. Noël, *Chem. Eng. Sci.: X* **2021**, *10*, 100097.
[12] V. Sebastian, *Nanoscale* **2022**, *14*, 4411–4447.
[13] A. Woitalka, S. Kuhn, K. F. Jensen, *Chem. Eng. Sci.* **2014**, *116*, 1–8.
[14] A. M. Nightingale, J. H. Bannock, S. H. Krishnadasan, F. T. F. O'Mahony, S. A. Haque, J. Sloan, C. Drury, R. McIntyre, J. C. deMello, *J. Mater. Chem. A* **2013**, *1*, 4067–4076.
[15] A. J. Capel, S. Edmondson, S. D. R. Christie, R. D. Goodridge, R. J. Bibb, M. Thurstans, *Lab Chip* **2013**, *13*, 4583–4590.
[16] V. Hessel, H. Löwe, F. Schönfeld, *Chem. Eng. Sci.* **2005**, *60*, 2479–2501.
[17] a) O. Okafor, A. Weilhard, J. A. Fernandes, E. Karjalainen, R. Goodridge, V. Sans, *React. Chem. Eng.* **2017**, *2*, 129–136; b) P. J. Kitson, M. H. Rosnes, V. Sans, V. Dragone, L. Cronin, *Lab Chip* **2012**, *12*, 3267–3271.
[18] J. R. McDonough, S. M. R. Ahmed, A. N. Phan, A. P. Harvey, *Chem. Eng. Process. Process Intensif.* **2019**, *143*, 107588.
[19] D. Valverde, R. Porcar, M. Zanatta, S. Alcalde, B. Altava, V. Sans, E. García-Verdugo, *Green Chem.* **2022**, *24*, 3300–3308.
[20] a) E. Peris, O. Okafor, E. Kulcinskaja, R. Goodridge, S. V. Luis, E. Garcia-Verdugo, E. O'Reilly, V. Sans, *Green Chem.* **2017**, *19*, 5345–5349; b) A. Valotta, M. C. Maier, S. Soritz, M. Pauritsch, M. Koenig, D. Brouczek, M. Schwentenwein, H. Gruber-Woelfler, *J. Flow Chem.* **2021**, *11*, 675–689.
[21] V. Sans, *Curr. Opin. Green Sustain. Chem.* **2020**, *25*, 100367.
[22] E. Alvarez, M. Romero-Fernandez, D. Iglesias, R. Martinez-Cuenca, O. Okafor, A. Delorme, P. Lozano, R. Goodridge, F. Paradisi, D. A. Walsh, V. Sans, *ACS Sustainable Chem. Eng.* **2022**, *10*, 2388–2396.
[23] J. R. McDonough, J. Armett, R. Law, A. P. Harvey, *Ind. Eng. Chem. Res.* **2019**, *58*, 21363–21371.
[24] D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner, S. V. Ley, *Rapid Commun. Mass Spectrom.* **2012**, *26*, 1999–2010.
[25] J. Nette, P. D. Howes, A. J. deMello, *Adv. Mater. Sci. Technol.* **2020**, *5*, 2000060.
[26] V. Sans, L. Cronin, *Chem. Soc. Rev.* **2016**, *45*, 2032–2043.
[27] R. M. Maceiczyk, I. G. Lignos, A. J. deMello, *Curr. Opin. Chem. Eng.* **2015**, *8*, 29–35.
[28] J. Baumgartner, A. Dey, P. H. H. Bomans, C. Le Coadou, P. Fratzl, N. A. J. M. Sommerdijk, D. Faivre, *Nat. Mater.* **2013**, *12*, 310–314.
[29] V. Sans, S. Glatzel, F. J. Douglas, D. A. Maclaren, A. Lapkin, L. Cronin, *Chem. Sci.* **2014**, *5*, 1153–1157.
[30] a) J. Yue, F. H. Falke, J. C. Schouten, T. A. Nijhuis, *Lab Chip* **2013**, *13*, 4855–4863; b) B. Pinho, L. Torrente-Murciano, *React. Chem. Eng.* **2020**, *5*, 342–355.
[31] I. Lignos, R. M. Maceiczyk, M. V. Kovalenko, S. Stavrakis, *Chem. Mater.* **2020**, *32*, 27–37.
[32] G. Tofighi, H. Lichtenberg, J. Pesek, T. L. Sheppard, W. Wang, L. Schöttner, G. Rinke, R. Dittmeyer, J.-D. Grunwaldt, *React. Chem. Eng.* **2017**, *2*, 876–884.
[33] D. Radajewski, L. Hunter, X. He, O. Nahi, J. M. Galloway, F. C. Meldrum, *Lab Chip* **2021**, *21*, 4498–4506.
[34] X. Chen, J. Schröder, S. Hauschild, S. Rosenfeldt, M. Dulle, S. Förster, *Langmuir* **2015**, *31*, 11678–11691.
[35] N. A. Jose, H. C. Zeng, A. A. Lapkin, *Nat. Commun.* **2018**, *9*, 4913.
[36] J. Li, H. Wang, L. Lin, Q. Fang, X. Peng, *J. Am. Chem. Soc.* **2018**, *140*, 5474–5484.
[37] J. Bemetz, A. Wegemann, K. Saatchi, A. Haase, U. O. Häfeli, R. Niessner, B. Gleich, M. Seidel, *Anal. Chem.* **2018**, *90*, 9975–9982.
[38] V. Dragone, V. Sans, A. B. Henson, J. M. Granda, L. Cronin, *Nat. Commun.* **2017**, *8*, 15733.
[39] R. W. Baker, L. Forfar, X. Liang, P. J. Cameron, *React. Chem. Eng.* **2021**, *6*, 709–719.
[40] C. Houben, A. A. Lapkin, *Curr. Opin. Chem. Eng.* **2015**, *9*, 1–7.
[41] C. Mateos, M. J. Nieves-Remacha, J. A. Rincón, *React. Chem. Eng.* **2019**, *4*, 1536–1544.
[42] J. A. Nelder, R. Mead, *Comput. J.* **1965**, *7*, 308–313.
[43] D. E. Fitzpatrick, C. Battilocchio, S. V. Ley, *Org. Process Res. Dev.* **2016**, *20*, 386–394.
[44] S. T. Knox, S. J. Parkinson, C. Y. P. Wilding, R. A. Bourne, N. J. Warren, *Polym. Chem.* **2022**, *13*, 1576–1585.
[45] a) N. Holmes, G. R. Akien, A. J. Blacker, R. L. Woodward, R. E. Meadows, R. A. Bourne, *React. Chem. Eng.* **2016**, *1*, 366–371; b) A. J. Parrott, R. A. Bourne, G. R. Akien, D. J. Irvine, M. Poliakoff, *Angew. Chem. Int. Ed.* **2011**, *50*, 3788–3792; *Angew. Chem.* **2011**, *123*, 3872–3876.
[46] B. J. Reizman, K. F. Jensen, *Acc. Chem. Res.* **2016**, *49*, 1786–1796.

[47] S. Krishnadasan, R. J. C. Brown, A. J. deMello, J. C. deMello, *Lab Chip* **2007**, *7*, 1434–1441.
[48] A. M. Schweidtmann, A. D. Clayton, N. Holmes, E. Bradford, R. A. Bourne, A. A. Lapkin, *Chem. Eng. J.* **2018**, *352*, 277–282.
[49] M. Elbadawi, B. Muñiz Castro, F. K. H. Gavins, J. J. Ong, S. Gaisford, G. Pérez, A. W. Basit, P. Cabalar, A. Goyanes, *Int. J. Pharm.* **2020**, *590*, 119837.
[50] Z. Jensen, E. Kim, S. Kwon, T. Z. H. Gani, Y. Román-Leshkov, M. Moliner, A. Corma, E. Olivetti, *ACS Cent. Sci.* **2019**, *5*, 892–899.
[51] R. W. Epps, M. S. Bowen, A. A. Volk, K. Abdel-Latif, S. Han, K. G. Reyes, A. Amassian, M. Abolhasani, *Adv. Mater.* **2020**, *32*, 2001626.
[52] V. Duros, J. Grizou, W. Xuan, Z. Hosni, D.-L. Long, H. N. Miras, L. Cronin, *Angew. Chem. Int. Ed.* **2017**, *56*, 10815–10820; *Angew. Chem.* **2017**, *129*, 10955–10960.
[53] C. Chen, Y. Zuo, W. Ye, X. Li, Z. Deng, S. P. Ong, *Adv. Energy Mater.* **2020**, *10*, 1903242.
[54] Z. Li, M. A. Najeeb, L. Alves, A. Z. Sherman, V. Shekar, P. Cruz Parrilla, I. M. Pendleton, W. Wang, P. W. Nega, M. Zeller, J. Schrier, A. J. Norquist, E. M. Chan, *Chem. Mater.* **2020**, *32*, 5650–5663.
[55] N. A. Jose, M. Kovalev, E. Bradford, A. M. Schweidtmann, H. Chun Zeng, A. A. Lapkin, *Chem. Eng. J.* **2021**, *426*, 131345.
[56] L. Zhang, M. He, S. Shao, *Nano Energy* **2020**, *78*, 105380.
[57] C. W. Coley, N. S. Eyke, K. F. Jensen, *Angew. Chem. Int. Ed.* **2020**, *59*, 23414–23436; *Angew. Chem.* **2020**, *132*, 23620–23643.
[58] S. Lu, Q. Zhou, Y. Ouyang, Y. Guo, Q. Li, J. Wang, *Nat. Commun.* **2018**, *9*, 3405.
[59] Z. Li, P. W. Nega, M. A. N. Nellikkal, C. Dun, M. Zeller, J. J. Urban, W. A. Saidi, J. Schrier, A. J. Norquist, E. M. Chan, *Chem. Mater.* **2022**, *34*, 756–767.
[60] G. Zhou, W. Chu, O. V. Prezhdo, *ACS Energy Lett.* **2020**, *5*, 1930–1938.
[61] S. Chibani, F.-X. Coudert, *APL Mater.* **2020**, *8*, 080701.
[62] F. Mekki-Berrada, Z. Ren, T. Huang, W. K. Wong, F. Zheng, J. Xie, I. P. S. Tian, S. Jayavelu, Z. Mahfoud, D. Bash, K. Hippalgaonkar, S. Khan, T. Buonassisi, Q. Li, X. Wang, *npj Computational Materials* **2021**, *7*, 55.
[63] J. Wei, X. Chu, X.-Y. Sun, K. Xu, H.-X. Deng, J. Chen, Z. Wei, M. Lei, *InfoMat* **2019**, *1*, 338–358.
[64] J. Kirman, A. Johnston, D. A. Kuntz, M. Askerka, Y. Gao, P. Todorović, D. Ma, G. G. Privé, E. H. Sargent, *Matter* **2020**, *2*, 938–947.
[65] C. R. Groom, I. J. Bruno, M. P. Lightfoot, S. C. Warda, *Acta Crystallogr. Sect. B* **2016**, *72*, 171–179.
[66] A. Jain, S. P. Ong, G. Hautier, W. Chen, W. D. Richards, S. Dacek, S. Cholia, D. Gunter, D. Skinner, G. Ceder, K. A. Persson, *APL Mater.* **2013**, *1*, 011002.
[67] C. E. Calderon, J. J. Plata, C. Toher, C. Oses, O. Levy, M. Fornari, A. Natan, M. J. Mehl, G. Hart, M. Buongiorno Nardelli, S. Curtarolo, *Comput. Mater. Sci.* **2015**, *108*, 233–238.
[68] A. Zakutayev, N. Wunder, M. Schwarting, J. D. Perkins, R. White, K. Munch, W. Tumas, C. Phillips, *Sci. Data* **2018**, *5*, 180053.
[69] S. M. Moosavi, A. Chidambaram, L. Talirz, M. Haranczyk, K. C. Stylianou, B. Smit, *Nat. Commun.* **2019**, *10*, 539.
[70] K. T. Butler, D. W. Davies, H. Cartwright, O. Isayev, A. Walsh, *Nature* **2018**, *559*, 547–555.
[71] A. Vikram, K. Brudnak, A. Zahid, M. Shim, P. J. A. Kenis, *Nanoscale* **2021**, *13*, 17028–17039.
[72] A. J. S. Hammer, A. I. Leonov, N. L. Bell, L. Cronin, *JACS Au* **2021**, *1*, 1572–1587.
[73] J. Bai, L. Cao, S. Mosbach, J. Akroyd, A. A. Lapkin, M. Kraft, *JACS Au* **2022**, *2*, 292–309.
[74] W. Hou, A. Bubliauskas, P. J. Kitson, J.-P. Francoia, H. Powell-Davies, J. M. P. Gutierrez, P. Frei, J. S. Manzano, L. Cronin, *ACS Cent. Sci.* **2021**, *7*, 212–218.
[75] S. H. M. Mehr, M. Craven, I. Leonov Artem, G. Keenan, L. Cronin, *Science* **2020**, *370*, 101–108.
[76] A. G. Godfrey, T. Masquelin, H. Hemmerle, *Drug Discovery Today* **2013**, *18*, 795–802.
[77] A.-C. Bédard, A. Adamo, C. Aroh Kosi, M. G. Russell, A. Bedermann Aaron, J. Torosian, B. Yue, F. Jensen Klavs, F. Jamison Timothy, *Science* **2018**, *361*, 1220–1225.
[78] S. Chatterjee, M. Guidi, P. H. Seeberger, K. Gilmore, *Nature* **2020**, *579*, 379–384.
[79] J. Baek, Y. Shen, I. Lignos, M. G. Bawendi, K. F. Jensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 10915–10918; *Angew. Chem.* **2018**, *130*, 11081–11084.
[80] R. A. Skilton, R. A. Bourne, Z. Amara, R. Horvath, J. Jin, M. J. Scully, E. Streng, S. L. Y. Tang, P. A. Summers, J. Wang, E. Pérez, N. Asfaw, G. L. P. Aydos, J. Dupont, G. Comak, M. W. George, M. Poliakoff, *Nat. Chem.* **2015**, *7*, 1–5.

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