Online detection and automation methods in microfluidic nanomaterial synthesis

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Microfluidic reactors are increasingly being recognized as a promising tool for the synthesis of bespoke and high quality nanomaterials. Herein, we discuss currently available methods for interfacing microfluidic reactors with online analysis systems such as photothermal, fluorescence, absorbance, X-ray, backscattering and correlation spectroscopies. Integration of appropriate on-line detection methods enables the facile extraction of information relating to size, shape and chemical composition of the formed nanoparticles, thus greatly enhancing control over the synthetic process. Furthermore, we discuss recent approaches aimed at implementing 'intelligent' algorithms that use such extracted information for optimization and parameter space evaluation. Lastly, we provide brief opinion about future directions of this emerging field.

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Introduction

The discovery of novel properties and processes at the nanoscale has created a myriad of opportunities for the formation of new materials and devices possessing tunable physicochemical properties, with applications in biological sensing [1], energy conversion [2], energy storage [2], biomedical imaging [1] and catalysis [3]. The synthesis of such exceptional materials demands that critical parameters including reagent concentration, temperature and pressure be uniform throughout the reaction mixture; in turn allowing the formation of particles with nearly identical size, shape and chemical composition [4]. Such requirements are difficult to realize in macroscale reactors, due to inhomogeneous mixing and inefficient heat transfer [5,6•]. Indeed, whilst conventional flask-based reactors are often used to prepare nanoparticles in large quantities, they are not always successful in delivering nanoparticle populations of consistent size and size distribution [6•].

Over the past decade the use of microfluidic technology has been at the forefront of many key developments in synthetic chemistry and biology, point-of-care diagnostics and nanomaterial synthesis [5]. The benefits of microfluidic reactors over flask-based methods for high-throughput experimentation and nanocrystal synthesis have been disseminated in more than 200 papers and reviews since 2002 [6•]. In the context of nanomaterial synthesis, microfluidic reactors benefit from rapid mixing, independent control of nucleation and growth as well as fast and controllable heat transfer; all being essential elements for preparing high quality nanocrystalline materials [6•,7], as is evident from the examples shown in Figure 1.

Inspired by these advantages, our research group demonstrated the first use of microfluidic reactors for the synthesis of CdS quantum dots [12••]. Since then many research groups have successfully used continuous-flow and segmented-flow microfluidic reactors to synthesize a wide range of nanomaterials including SiO_2, TiO_2, Ag, Au, Fe_3O_4, poly(lactic-co-glycolic acid) (PLGA), $CaCl_2$, CdS, CdSe, ZnS and ZnSe [6•].

Recent developments in the field of miniaturized analysis have enabled the development of microfluidic platforms with integrated real-time detection systems [13]. Such platforms are able to extract important information regarding the size, shape and chemical composition of nanoparticles on a millisecond timescale, and together with algorithms that are able to effectively map the accessible parameter space of a reaction system, facilitate rapid reaction optimization and synthesis of a wide range of high quality nanomaterials possessing bespoke physicochemical characteristics. The importance of rapid and efficient analysis of nanomaterials in such reaction formats cannot be overstated, and accordingly we provide a short overview of the state-of-the-art in online monitoring and 'intelligent' microfluidic reactor technology. More general overviews of nanomaterial synthesis using microfluidic methods can be found elsewhere [14•,15,16].

Online detection methods

Online spectroscopic methods for analysis of chemical reactions in microfluidic reactors permit direct control of the synthetic process, decrease development times by directing changes in synthetic parameters and enable the

Figure 1

Current Opinion in Chemical Engineering
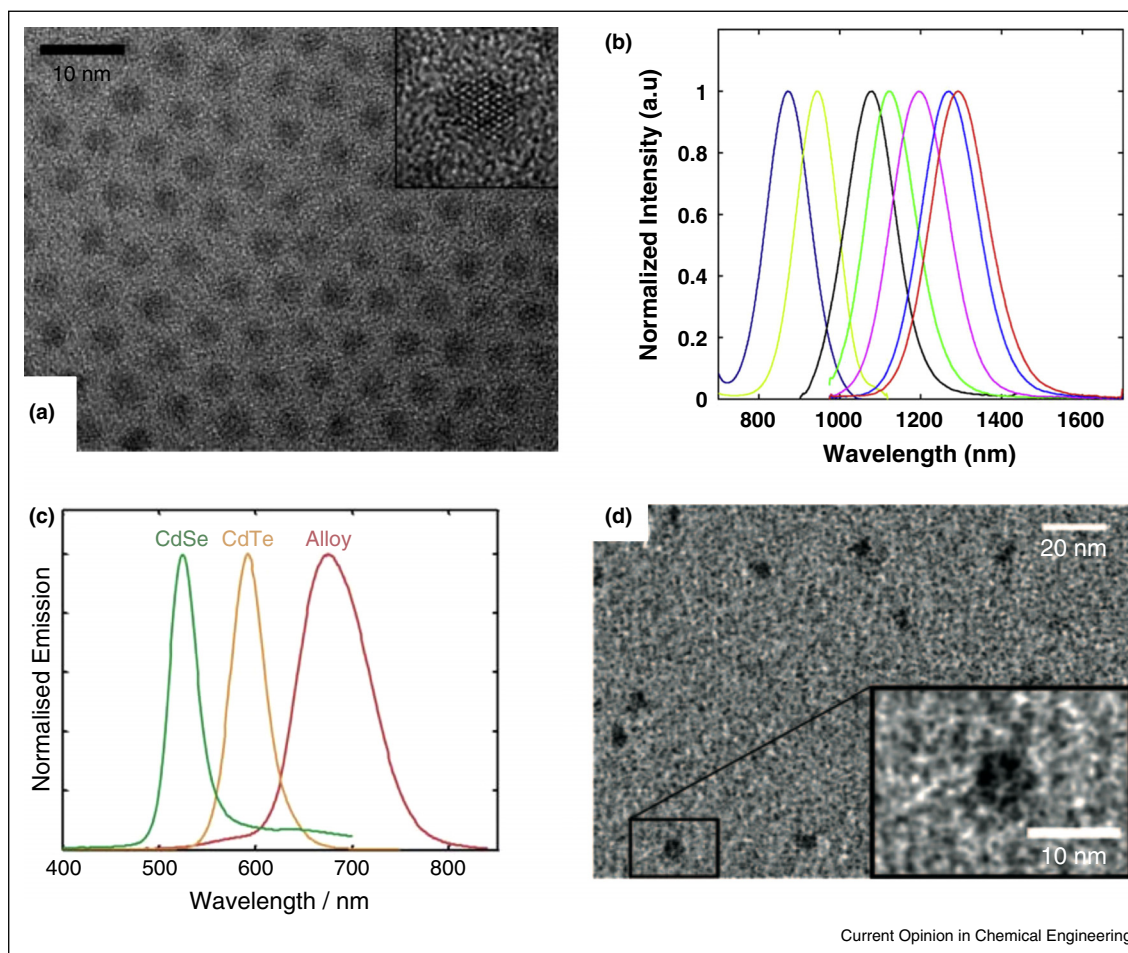
(a) Transmission electron micrograph of CdSe nanocrystals produced in a glass microfluidic reactor. Reprinted (adapted) with permission from Ref. [8]. Copyright (2005) American Chemical Society. **(b)** In-line NIR fluorescence spectra of PbS quantum dots demonstrating the size variability achievable in a microfluidic reactor. Reprinted (adapted) with permission from Ref. [9]. Copyright (2014) American Chemical Society. **(c)** Photoluminescence spectra of CdSe, CdTe and alloyed CdSeTe quantum dots synthesized in a large scale microfluidic reactor. Reprinted (adapted) with permission from Ref. [10••]. Copyright (2013) Royal Chemical Society. D) Transmission electron micrograph of InP quantum dots synthesized in a glass microfluidic chip. Reprinted (adapted) with permission from Ref. [11] Copyright (2009) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

use of automated algorithms for reaction optimization. Such methods need to be sensitive, applicable for use in small volume environments and rapid enough to allow analysis on millisecond timescales. A variety of techniques are available for probing organic reactions [17,13] but frequently these cannot be transferred directly to nanoparticle analysis for a range of reasons. In this section we review currently available methods that are particularly relevant to nanomaterial synthesis and that have or can (in principle) be interfaced with microfluidic reactors.

Fluorescence spectroscopy is widely used in conjunction with microfluidic processing due to its outstanding sensitivity which enables the rapid analysis of sub-nanoliter sized samples with ease. The most prominent class of emissive nanoparticles are compound semiconductor quantum dots [18]. Their photoluminescence spectra correlate directly with physical properties. For example, the position of the band-edge emission maximum is dependent on the average size of the particle population, with the full width at half maximum being an indicator for size dispersion [19]. Other features such as defect emission on the low energy side of the band-edge emission give information about surface properties and defect sites [20]. Several studies have evaluated the photoluminescence spectra of microfluidically produced quantum dots emitting in the visible (CdSe, InP, and CdSeTe) [8,11,21,22••,23–25] as well as the near-infrared (PbS) [9] regions of the electromagnetic spectrum, online and interfaced directly with a microfluidic reactor.

In contrast, obtaining *absorption spectra* is more challenging due to the small pathlengths and low analytical concentrations that typify microfluidic environments. This is unfortunate since extraction of absorption spectra provides critical information relating to particle concentrations and reaction yields [26]. Reports of absorption spectroscopy [27,28] for real time analysis of nanoparticle synthesis are scarce and further investigations are required before this becomes a routine tool for online nanoparticle characterization.

Instead of measuring absorbance via the (conventional) comparison of incident and transmitted light intensities, *photothermal spectroscopy* (PS) probes the heat released by non-radiative decay into the medium surrounding a nanoparticle. Any temperature increase changes the refractive index of the medium, thereby creating a thermal lens that refracts a secondary beam of a wavelength that is not absorbed by the sample [29]. PS is in principle more sensitive than fluorescence spectroscopy for particles possessing a fluorescence quantum yield below 50% and has been shown successful in detecting single gold nanoparticles as small as 5 nm in diameter [30]. Unfortunately, to date it has not been possible to extract particle sizes directly from the recovered PS signal. Such an innovation would be highly desirable and allow for size determination of non-fluorescent nanoparticles using a low-cost and compact optical setup.

Ignatovic *et al.* have utilized interferometric measurement of the amplitude of backscattered laser radiation from nanoscale particles by superimposing the backscattered beam with a reference beam [31]. This is much more sensitive then direct intensity measurements since the amplitude of backscattered radiation scales with the third power of particle radius as opposed to the intensity that is proportional to the sixth power. Such a signal is nearly background free and can be used to determine the size of single nanoparticles as small as 7 nm in real time and with a detection throughput of around one millisecond per particle. This method can also distinguish silver and gold nanoparticles dispersed in the same solution [32]. A limitation of this method in its current embodiment is that the cross-sectional size of the detection channel must be as close as possible to the size of the focal point of the detection laser ($\approx$250 nm) to avoid distortion caused by particles passing through the beam outside of the focal spot. Moreover, the optical setup is much more complex than the aforementioned thermal lens microscope.

Correlation spectroscopy (CS) involves measurement of the fluctuation of an optical signal due to Brownian motion in and out of a probe volume. The signal is autocorrelated against time and then fit to a theoretical autocorrelation function, the form of which is dependent on the diffusive behavior and thus size of the analyzed particles. A range of methods for nanoparticle analysis based on correlation spectroscopy have been reported. However, correlation methods are typically limited to resting dispersions. So far only confocal CS [33] in fluorescent as well as non-fluorescent mode is able to analyze particles as small as 5 nm within microfluidic flows.

X-ray spectroscopy is a valuable tool for the analysis of nanomaterials since it can provide information on the atomic level such as local order, oxidation state and crystal structure. X-ray spectroscopic measurements require long analysis times to extract high quality data, thus making it ill-suited to accessing the millisecond time resolution required to probe reaction kinetics. To address this problem Chan *et al.* [34] studied the kinetics of the CdSe-to-Ag2Se nanocrystal cation exchange reaction by letting two reagent solutions mix and flow through a microchannel at constant flow rate. The distance from the mixing point corresponds to the reaction time allowing arbitrary long measurements with sub-second reaction time resolution by focusing the beam on a fixed point. Similar concepts have since been employed to study the formation of CdSe and Gold nanoparticles [35,36].

Figure 2 contains schematic representations of selected examples mentioned in this section.

Intelligent synthesis

A microfluidic reactor integrated with real time product detection and a control system can in theory carry out and analyze thousands of reactions within very short timeframes. Embracing such an advantage demands the substitution of widespread but inefficient, one-parameter-at-a-time methods with more sophisticated and specialized 'intelligent' algorithms. Trial-and-error scanning of experimental parameter space can identify local optima but often fails at finding global optima, despite the great experimental effort that is needed. Especially in the field of nanomaterials, reagents and products are often toxic, hazardous and expensive, thus minimizing material usage in the development stage is of paramount importance. Despite the clear potential advantages of combining microfluidic reactor technologies with optimization algorithms, only a few reports have addressed the intelligent synthesis of nanomaterials.

Krishnadasan *et al.* [37••] were the first to realize this concept. CdSe quantum dots were synthesized in a temperature controlled microfluidic reactor combined with online photoluminescence (PL) spectroscopy and automated syringe pump handling. The flow rates of the individual precursor streams provided control over average residence times as well as precursor concentration ratios. Extracted spectra were analyzed in real time and reduced to a dissatisfaction coefficient (DC) that quantified experimental success. A *Stable Noisy Optimization by Branch and Fit* (SNOBFIT) algorithm (Figure 3c) was

Figure 2
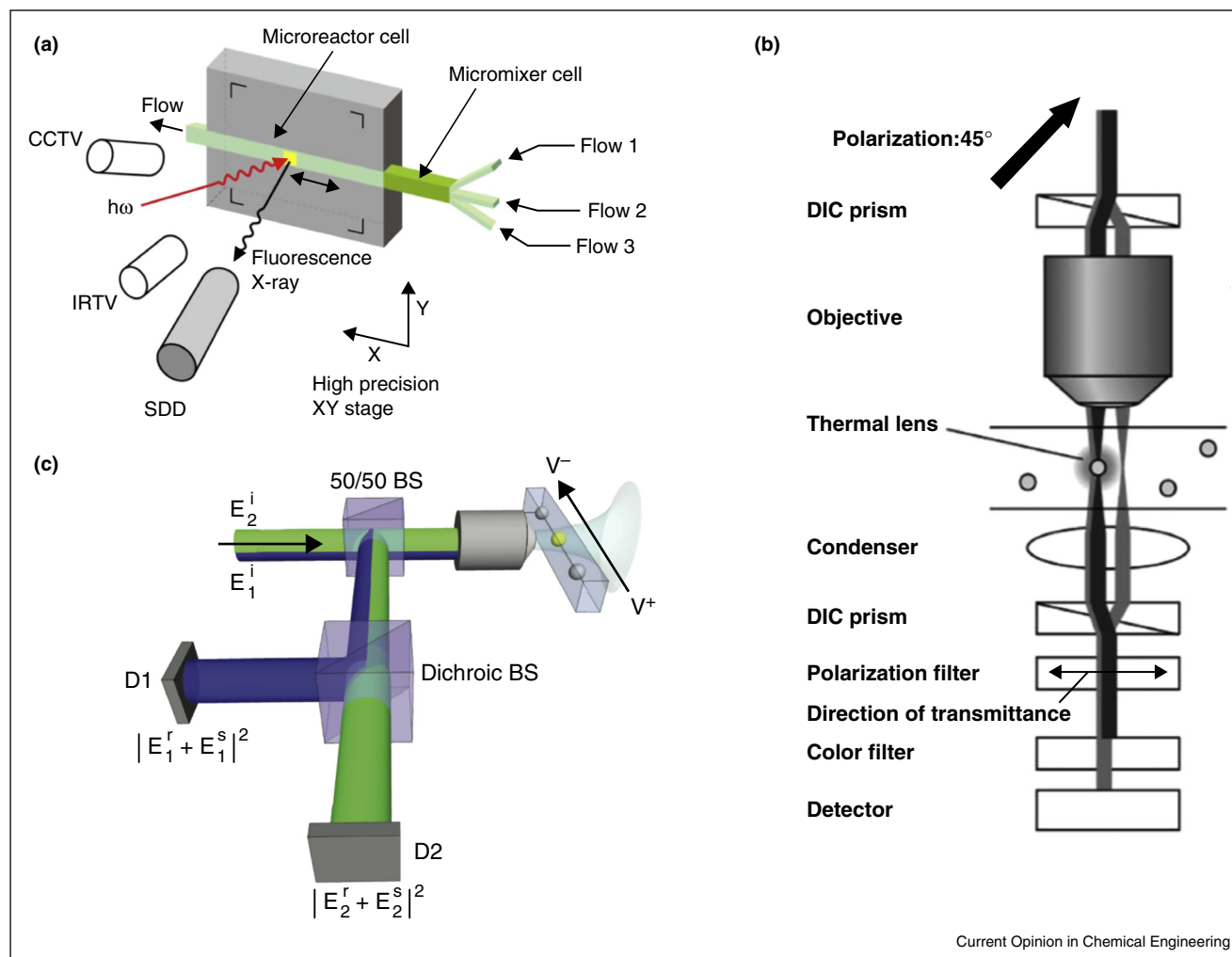
Examples of online detection methods suitable for nanoparticles in flow. **(a)** *In situ* EXAFS measurements on CdSe nanoparticle formation. Reprinted (adapted) with permission from Ref. [36]). Copyright (2009) AIP Publishing LLC. **(b)** Differential interference contrast thermal lens microscopy. The 0°-polarized probe beam is split in two whereas the 45°-polarized excitation beam is deflected to one side only by the DIC prism. The probe beam is reunited to allow interferometric comparison. Reprinted (adapted) with permission from [30]. Copyright (2009) American Chemical Society. **(c)** Interferometric detection of nanoparticles in electroosmotic flow. E^i represents the incident, E^r the reflected and E^s the scattered field. Reprinted (adapted) with permission from Ref. [32]. Copyright (2011) American Chemical Society.

then used to choose further experimental parameters based on the previous results until it arrives at a threshold DC value. The algorithm was successful in reaching this threshold, thus obtaining optimal conditions for the synthesis of particles with given PL characteristics, after approximately 100 evaluations. This method provides a useful tool for the bespoke synthesis of nanomaterials and produces particles of exceptionally high quality, but does possess some undesirable attributes that need to be addressed.

The translation of product specifications to an objective function via weighting coefficients can lead to the exclusion of (in reality) desirable synthesis conditions. A change of desired product parameters and thus of the objective functions generally means that the optimization routine must be repeated. Also, the 'directed' character of the SNOBFIT algorithm makes the discovery and elimination of systematic errors difficult. Previously measured conditions might be wrongly excluded due to measurement error or discarded sections of the parameter space may become desirable during the course of the measurement due to reactor degradation. A random evaluation with an appropriate experimental design can mitigate this problem. Lastly, the 'black-box' character of optimization algorithms prevents a quantitative understanding of how synthetic parameters influence product outcome. This knowledge is extremely valuable, for example, in process control.

Figure 3
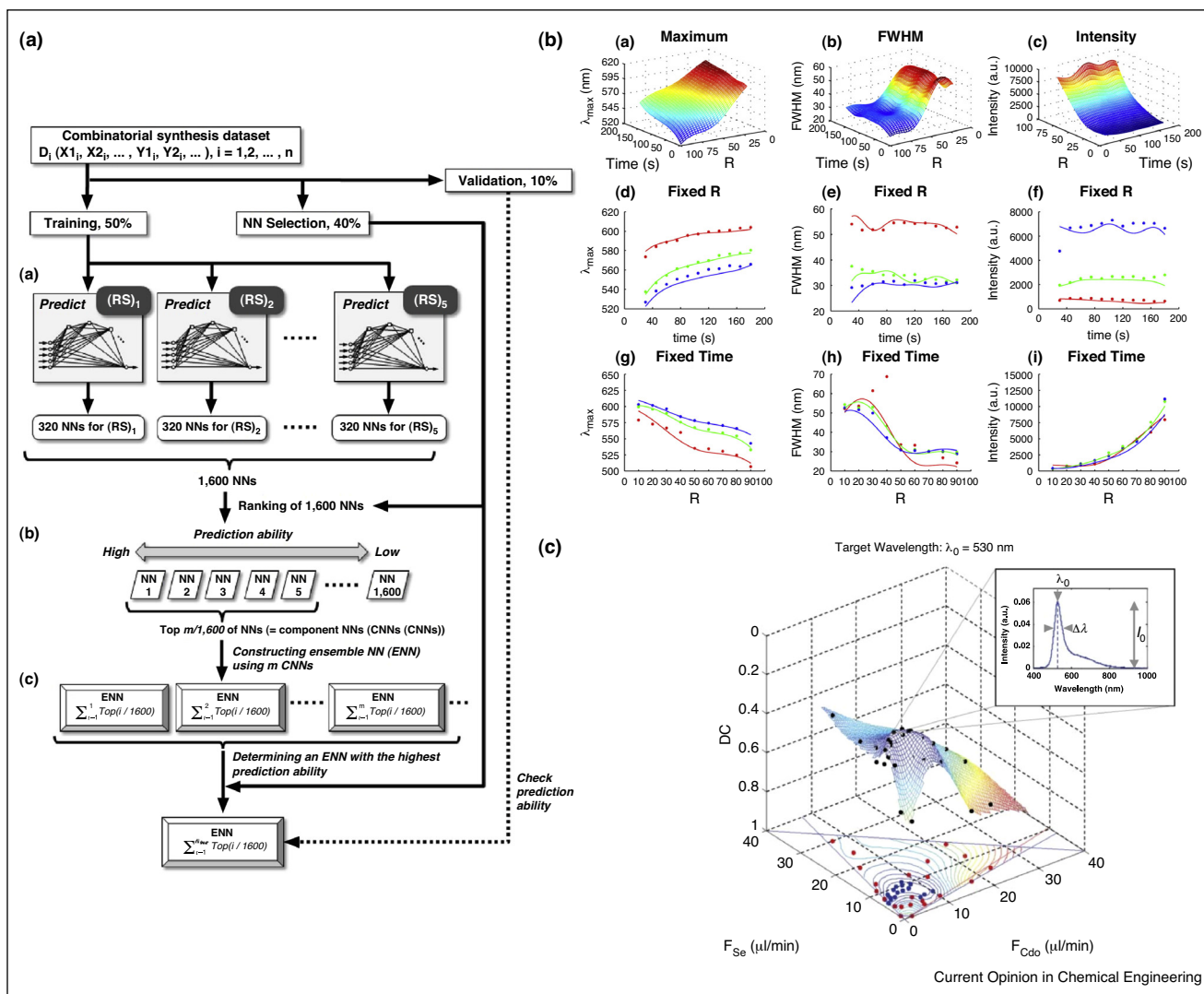
Examples for optimization and modeling methods for nanoparticle synthesis. **(a)** Wide range search and validation procedure for optimal neural networks. Reprinted (adapted) with permission from Ref. [38**]. Copyright (2012) American Chemical Society. **(b)** Kriging metamodels for CdSe synthesis. The first row shows the obtained metamodels of maximum, FWHM, and intensity. The second and third row represent the results of the validation experiment. The solid lines represent the predictions whereas the dots correspond to the data obtained during the validation experiment. Reprinted (adapted) with permission from Ref. [22**]. Copyright (2014) American Chemical Society. **(c)** SNOBFIT method for bespoke CdSe synthesis. showing the influence of the injection rates of CdO (F_{CdO}) and Se (F_{Se}) on the value of the dissatisfaction coefficient (DC) for a target wavelength of 530 nm and a fixed reaction temperature of $220°C$. Reprinted (adapted) with permission from Ref. [37**]. Copyright (2007) Royal Chemical Society.

More recently, Toyota *et al.* [27] developed a reactor for CdSe synthesis consisting of five parallel reaction channels to evaluate the dependence of PL maximum, PL quantum yield, PL full-width-half-maximum, particle size and product yield on temperature, reaction time, and dodecylamine concentration. The obtained data proved highly reproducible and were consistent with previous reports on CdSe synthesis, whilst giving a superior insight on how synthetic parameters influence key product characteristics. A drawback of this method is that the number of experiments that have to be carried out is high and no quantitative prediction is made for the regions between data points. Interestingly, the same group [38**] reported an improved method by using *artificial neural networks* to predict reaction outcomes at unsampled points (Figure 3a). This method can predict reaction outcomes with satisfactory precision. Nonetheless, the implementation of the neural network algorithm is complicated and consumes significant computational resource.

Most recently, Maceiczyk *et al.* [22••] used a *Kriging metamodeling algorithm* in combination with a fully automated microfluidic reactor for the synthesis of CdSe and CdSeTe quantum dots. The reactor scanned experimental parameter space in a random fashion while monitoring reaction products on-line via fluorescence spectroscopy. A computer program then analyzed the resulting spectra to extract FWHM, PL maximum and intensity data that were subsequently used to fit a Universal Kriging metamodel. They then tested the predictions for accuracy in a further experiment (Figure 3b). The algorithm is computationally inexpensive and has the ability to predict reaction outcomes at unsampled points with high accuracy and reliability.

Conclusion

The ability to interface a microfluidic reactor with a detection system capable of extracting relevant information concerning product quality and stability on-line and in real-time is a major advantage over traditional batch chemistry. The availability of characterization data during a synthetic process enables adjustment of synthetically relevant parameters to optimize or stabilize desired product features directly, thus accelerating the development process as well as greatly minimizing reagent consumption and waste. The optimized process can be used directly for continuous production of the material (after scale out) thus taking advantage of the control and reproducibility associated with microfluidic reaction systems. This stands in stark contrast to batch methods, which require significant development on transferral from the lab to a commercial production environment. Of course, microfluidic systems are unsuitable for the production of large scale, low cost chemicals with its strength lying in the synthesis of high-value products with high demands on quality and purity that are used in mg to g quantities. A back of the envelope calculation reveals that a capillary reactor (500 μm inner diameter) can easily synthesize 100 mg of CdSe quantum dots in 1 hour. Considering current market prices the products have increased their value compared to the starting materials by roughly a thousand times. A combination of scale out and scale up can easily increase the production rate to tens of grams without any detrimental effects on product quality [10••].

In this article we have highlighted that only a few on-line nanoparticle detection and optimization methods are available and established. This deficit together with the lack of reactor designs and methods for automated nanoparticle synthesis is inconsistent with the anticipated importance of nanomaterials for future technologies and may be a primary factor why research groups and industrial manufacturers still have not adopted microfluidics as a route for the direct synthesis of nanomaterials. We believe that further development of optimization and detection methods is a key challenge for the progression of microfluidic reactor technology and that the application

of these technologies in synthesizing new nanomaterials that are impossible to access using traditional methods would present a significant breakthrough in nanoscale science. We are confident that in the near future, turn-key systems as well as microfluidic components for nanoparticle synthesis will be available to non-specialized groups and industries. Such developments are expected to be analogous to other areas of microfluidics, where a wide range of pre-configured devices and components are the norm.

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