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Closed-loop optimization of nanoparticle synthesis enabled by robotics and machine learning

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SUMMARY

Colloidal nanoparticles are attractive materials for various energy and chemical applications. Due to their strictly tunable structure-function relationships, reproducibly synthesizing structurally homogeneous nanoparticles is a critical step toward making the nanoparticle technology commercially viable. However, due to a lack of general theoretical foundations for complex nanoparticle formation phenomena, the current synthesis optimizations of nanoparticles are mostly conducted based on the intuitions and trial-and-error-driven manual processes that are slow to explore a large synthesis parameter space. To accelerate these time-consuming and resource-demanding conventional synthesis approaches, we here describe a closed-loop pipeline that consists of robotic synthesis, automated materials characterization, machine-learning optimization, and computational prediction of desired structure-property relationships. We discuss the need and the current levels of automation in different parts of nanoparticle synthesis experiments with future directions and outlook.

INTRODUCTION

Colloidal nanoparticles are important functional materials in systems of energy conversion, chemical conversion, and optoelectronics.[1–3] They have strong quantum effects originating from their finite sizes.[2] The resulting unique electronic structures of nanoparticles, which are intrinsically size and shape dependent, provide a wide range of tunability for their chemical, physical, and electronic properties. In addition, the high surface-to-volume ratio of nanoparticles makes them attractive materials in applications where the access of surface specific chemical or optical interactions is required. For example, diverse types of nanoparticles, including metals, alloys, and oxides, have been used as highly active heterogeneous catalysts in thermal and electrochemical conversion reactions due to the high surface area with uniquely exposed surface atomic structures.[1] Semiconductor nanoparticles are another class of nanoparticles widely investigated in photo-absorption, photo-conversion, and light-emitting devices due to tunable band-gap structures that depend on the size and structure.[4] Introduction of dopants is a promising way to expand the chemical space of existing materials to modify electronic structures and relevant optical transitions in semiconductor nanoparticles.[5] More recently, using chiro-selective surface interaction of small molecules during the synthesis of nanoparticles allowed a production of chiro-optically active metal nanoparticles.[6] These chiral nanoparticles have a great potential as a catalyst for the synthesis of chiral molecules, optically active chiral materials, and artificial enzymes.[6,7] In all of these applications of nanoparticles, controlling the size, morphology, and bulk/surface

PROGRESS AND POTENTIAL

Progress is currently being made at an unprecedented pace in synthesis robots, operando characterizations, and machine-learning algorithms needed to automate the entire workflow and close the loop for accelerated materials discovery. Among different applications of the closed-loop approaches, nanoparticle synthesis optimization is particularly promising due to a necessity to navigate a wide experimental parameter space repeatedly in routine experimental settings to fine-control the particle structures. Full robotic automations guided by artificial intelligence to more efficiently explore the synthesis space can dramatically speed up the reliable synthesis of nanoparticles with the target structures. Such optimizations still require customized developments of different stages of the nanoparticle synthesis, but the current momentum will soon make the needed technical developments attainable for various target applications at a laboratory scale as well as more practical pilot-scale synthesis.

atomic arrangements during synthesis is critical since they determine the reactivity, functionality, durability, and recyclability of these materials.

Challenges in nanoparticle synthesis

While adjustable structure-functional relationship of nanoparticles is a key driving force for a wide range of applications of nanoparticles in modern chemistry as briefly described above, the optimization of the nanoparticle synthesis, usually conducted with a colloidal method, is not trivial in practice. Because a given synthesis batch would yield a distribution of nanoparticles in different sizes and structures,[8,9] to ensure well-defined properties of an ensemble of nanoparticles, it is important to optimize the synthesis conditions to have structurally homogeneous nanoparticles.[10,11] However, in the absence of the unified theory of nanoparticle synthesis and satisfactory understanding of the nanoparticle growth processes at present, most current experimental syntheses of nanoparticles are based on the expert experiences and trials of a small number of experimental conditions. For example, for synthesizing InP-based core/shell quantum dots, it is well known that the growth of shell materials and the surface protection by ligands are the important variables to tune the structures and functionality of the nanoparticles.[12,13] The exhaustive search of the set of synthesis parameters to achieve the desired structure, however, would require hundreds of experimental syntheses and characterizations, a task that is nearly intractable to be executed manually and routinely in the laboratory for different target nanoparticle systems. Added to this synthesis condition optimization of a single nanoparticle compound, such a fine control of the structures of ensemble nanoparticles must be considered by simultaneously varying the compositions, adding a challenging extra dimension of optimization, namely chemical design. Finally, even if the chemical design and synthesis condition optimization are reasonably completed, a further practical aspect to consider is to scale up the optimized synthesis recipes in the laboratory (on a scale of hundreds of milliliters) to a larger scale (at least gram scale) where the mass and thermal transport behaviors are very different from the lab setting.[14] This would potentially yield completely different nanoparticle structures and functionalities at larger scales. To overcome these challenges and expedite the materials discovery based on colloidal nanoparticles, a new paradigm that enables automated navigation of the synthesis parameter space and the property space, and the closed-loop synthesis optimization in multiple scales, is highly desired. The overall workflow we suggest for this development is summarized in Figure 1.

AUTOMATED NAVIGATION OF EXPERIMENTAL PARAMETER SPACE IN NANOPARTICLE SYNTHESIS

The colloidal method for the synthesis of nanoparticles has a large number of experimental parameters to control. Types and concentrations of precursors, solvent, surface passivating ligand, reaction volume, temperature, and retention time need to be explored to synthesize desired nanoparticles. Those parameters are independently operated but their roles and effects are strongly inter-dependent during the formation of nanoparticles in a flask. In addition, many of reagents commonly used in nanoparticle synthesis are pyrophoric. Depending on the reactivities of reagents toward the air and humidity, synthesis of nanoparticles often requires an operation under inert gas conditions. Sometimes as-synthesized nanoparticles may need storage in an inert condition before the active surfaces are protected for downstream processing for applications. These characteristics of the nanoparticle synthesis imply that the scanning of the experimental parameter space for the synthesis optimization is complicated and extremely time consuming. This necessity of searching through a

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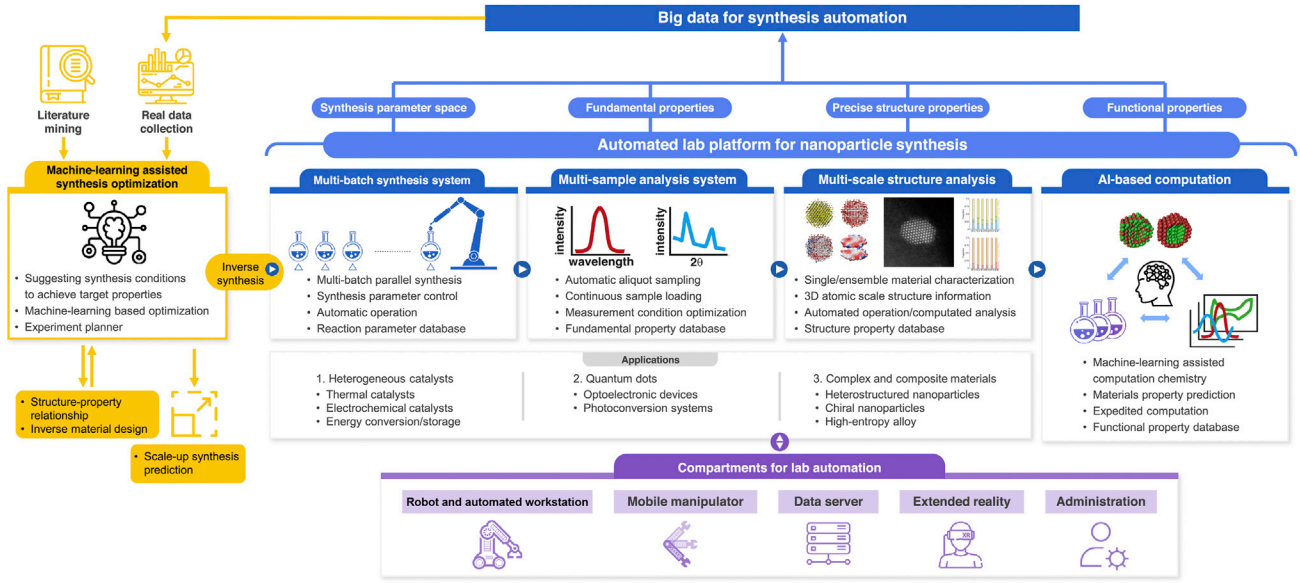

Figure 1. An overview of the workflow for closed-loop optimization of nanoparticle synthesis enabled by robotics and ML

ML-assisted synthesis optimization heavily relies on the database that is to be continuously enriched by accumulating data from repeated nanoparticle syntheses with changing synthetic parameters. A streamline is composed of multiple steps, each of which constructs a different class of datasets that will be accessed by ML optimization. From the synthesis step, synthetic conditions can be logged into the database. The fundamental properties of nanoparticles, such as optical extinction and emission, are readily characterized right after the synthesis in an automated fashion and associated with the pre-logged synthesis conditions. As-synthesized nanoparticles, then, are further characterized to acquire their structural information by a microscopic method and functional properties depending on their target applications. Such obtained information regarding structures and functional properties is also linked to the existing database. Once detailed structural information is obtained, it can be used in computational calculation to mine important characteristics of synthesized nanoparticles that are difficult to access experimentally. The predicted properties from the computation are also added in the database. As a result, the database has inter-connected information between the synthesis parameters, fundamental property, structural property, and functional property from one set of synthesis. As repeating these rounds of processes with different initial conditions, the database self-develops to continuously incorporate multiplexed information covering a wide synthesis parameter space. It will be input in the ML optimization for the desired nanoparticle synthesis. This loop of optimization can be repeated in an automated fashion, continuously improving the accuracy of optimization of the nanoparticle synthesis. At the initiation of repeating the close-loop processes, there are not sufficient data for training the optimization algorithm. Literature mining that classifies information from the published results can be an effective starting strategy. A full automation of all steps in the loop would be highly desired for a completely automated optimization of nanoparticle synthesis. However, the level of difficulty and urgency of automation is not identical for each process, needing a careful consideration for evaluating the priority in development.

large parameter space is what makes the current nanoparticle synthesis experiments performed by human intuitions inefficient and ideally suited for automation.

Indeed, such an automated nanoparticle synthesis workflow has recently been applied in the synthesis of plasmonic and quantum dot nanoparticles with a target extinction property using machine-learning (ML)-assisted parameter optimization to improve the search efficiency.[15–20] In this approach, synthesis in a microfluidic system was conducted to quickly explore synthetic parameter space in a small volume scale. Even if the systems considered in those studies cover important examples that are simple compared with other practical nanoparticle synthesis, a successful demonstration of combining microfluidics synthesis and ML optimization is notable and promising.

The more efficient approach to explore complex reaction parameter space will be a utilization of advanced robotic systems of automated workstation and mobile robotic chemist.[17,21–26] Robotic systems are supposedly free from the non-detectable operational errors that are inevitable in manually operated synthesis, ensuring reliable and reproducible runs of synthesis. They are ideally suited for a rapid

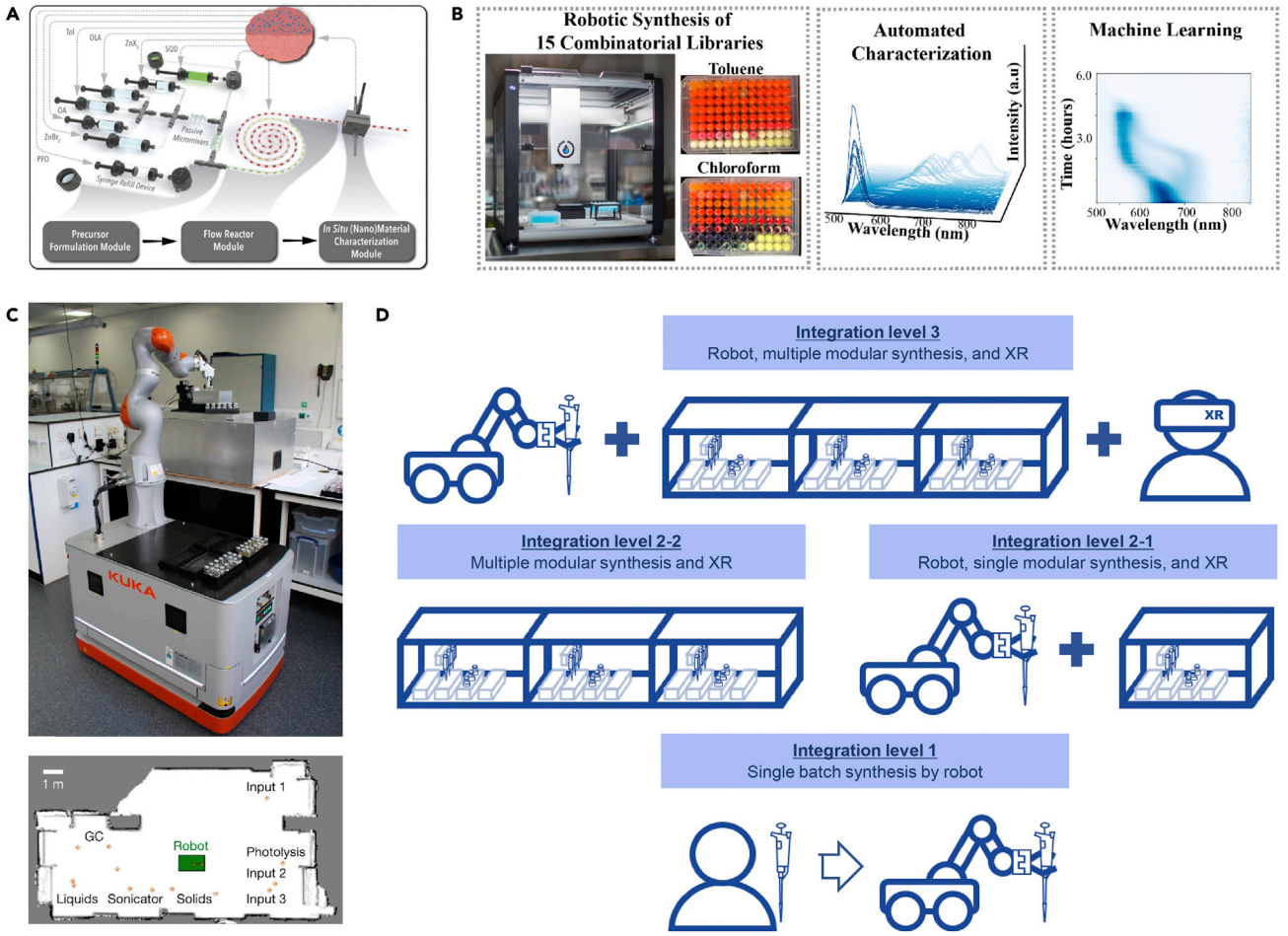

Figure 2. A hierarchical development strategy for the integration of modular robotic-synthesis system, mobile synthesis robot, machine-learned optimization, and extended reality

(A) The development of an Artificial Chemist, a self-driving nanoparticle synthesis platform based on high-efficiency microfluidic reactors and an ML algorithm for experiment design.[20]

(B) The integration of modular synthesis robots, an automated characterization tool, and a ML algorithm for the synthesis of quantum dot nanoparticles.[29]

(C) The development of the mobile synthesis robot applied for the synthesis optimization of photocatalysts materials.[26]

(D) The development strategy for integration. An advanced mobile synthesis robot can be integrated to operate a modular robotic-synthesis system, enabling automated runs of multiple batches of synthesis. Parallelizing the modular synthesis system is an important step for an accelerated navigation of the experimental parameter space. Ultimately, for a completely automated optimization of the nanoparticle synthesis driven by ML and a big database, the delicate robotic manipulator is to be integrated with the parallelized modular robotic-synthesis system. The operation of the integrated platform can be supervised by an advanced administrative system based on the extended reality.

navigation of diverse synthesis parameters. Robotic-synthesis workstations, where essential steps of the nanoparticle synthesis (e.g., injection of reagents, setting the reaction temperature and gas environment, and stopping the reaction by cooling the reaction mixture) can be fully automated, would be an ideal platform. A system called WANDA has been developed and was successfully utilized to map multidimensional synthesis parameters for CdSe, CdTe, and La-doped $NaYF_4$ nanoparticles.[27,28] These modular synthesis systems have an advantage in that multiple syntheses with differently controlled parameters are carried out at the same time, expediting the scan over a wide experimental space. It has also been demonstrated that an auto-pipetting robot, called Opentron, improves the efficiency and accuracy of synthesis optimization for perovskite nanoparticles (Figure 2B).

Examples that utilized automated workstations and mobile robotic chemists for synthesizing various types of nanoparticles are summarized in Table 1.

An automated synthesis enabled by a mobile robotic chemist has been introduced as another approach to run multiple synthetic tasks in a reliable way (Figure 2C).[26] A mobile robotic chemist in a human-free laboratory space basically mimics the manually operated synthesis carried out by researchers. The successful demonstration of the mobile robotic chemist was an important step toward a fully automated synthesis laboratory. Nonetheless, the speed of synthesis operation by the mobile robot has to be improved to efficiently run many syntheses and produce enough data for machine-learned optimization. In addition, the current robotic manipulator is only capable of simple tactical operations. For reproducing complex nanoparticle synthesis, the mobile manipulator needs to be more sophisticated.

Integration of a modular synthesis system and a synthesis robot operated by a mobile manipulator is likely to advance the process of navigating the complex synthesis parameter space and ultimately to construct a big database for ML-assisted optimization (Figure 2D). Improving delicacy of the mobile manipulator to a level similar to a human researcher who can carry out diverse tasks and actively respond to unexpected problems occurring in the synthesis laboratory will be an important step for the development of a fully automated synthesis laboratory. Parallelizing the modular synthesis system is a straightforward step to further accelerate the navigation of the experimental parameter space. The operation of the entire robotic system can then be supervised by an advanced administrative system based on the extended reality.

AUTOMATED NAVIGATION OF PROPERTY SPACE OF SYNTHESIZED NANOPARTICLES

The characterization of the synthesized nanoparticles provides datasets that can associate the synthesis parameter space with the corresponding property space. For each synthesis conducted by the automated robotic system, a set of physical and chemical properties can be measured and linked to the assigned synthesis condition. Depending on the type of nanoparticles and targeting application, different classes of properties are supposed to be measured.[44] For example, in the synthesis optimization of fluorescent quantum dot nanoparticles, the basic characterizations needed to explain fundamental properties of the synthesized quantum dots include absorption spectroscopy, emission spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, inductively coupled plasma (ICP) spectroscopy, X-ray diffraction (XRD), and transmission electron microscopy (TEM). Information from the series of those measurements constructs the property-space information for a given synthesis set, which can be incorporated into the database and can be used for the ML optimization for target properties.

Ultimately, a completely automated optimization of the nanoparticle synthesis requires the entire characterization steps, from aliquoting, preparing samples for measurements, and acquiring measurement data, to be fully automated by robotic systems. However, such complete automation in the characterization process needs more advanced technical improvement in the robotic system since each type of measurement has a different sampling procedure and a different level of tactical complexity. In the above example for quantum dot synthesis, as an example, the measurement systems for absorption and emission spectroscopy can be integrated

Table 1. Summary of major cases of robotics-assisted synthesis of nanoparticles

Nanoparticles	Synthesis method	Note	Reference
Au	millifluidic system	real-time optical property analysis is integrated in the reactor for quality control of the products	30
Au	microfluidic system	the morphologies of Au nanoparticles are controlled by synthesizing the nanoparticles within small aqueous droplets dispersed in an oil phase	31
Au	microfluidic system	oscillatory segmented flow is introduced to synthesize Au nanorods with targeted length. The optical extinction is monitored by *in situ* spectroscopy	18
Au	self-driving microfluidic system	self-driving platform assisted by ML algorithm is developed to synthesize nanoparticles with targeted property. On-line characterization results are learned by the ML algorithm	15
Au	robot-assisted flask synthesis with genetic algorithm	GA is used to discover synthesis conditions of Au nanoparticles with different shapes. On-line characterization provides inputs for the genetic algorithm	16
Ag	multiphasic microfluidic system	two-step ML framework is developed to synthesize nanoparticles with desired properties. Optical property is monitored by on-line characterization tool, and the results are used for optimizations	32
Au/Ag core/shell	microfluidic system	combinatorial method for *in situ* screening of parameters and real-time analysis of optical property is used to control the Ag shell thickness	33
SiO_2	microfluidic system	properties of the segmented flow within microfluidic devices are characterized and their effects on the polydispersity of nanoparticles are examined	34,35
CdSe	automated workstation with deck slots	WANDA platform is developed to automate traditional flask synthesis and characterization with high flexibility in inert environment	27
CdSe	microfluidic system	rapid screening of the experimental parameter space is enabled with a microfluidic reactor capable of high-temperature synthesis	36,37
CdSe	feedback-controlled microfluidic system	on-line spectrometer and control algorithm are implemented to automatically control the reaction conditions to achieve desired products	38
CdSe	microfluidic system	oscillatory flow is utilized to synthesize CdSe quantum dots while the optical extinction is monitored *in situ*	19
CdTe	automated workstation with deck slots	WANDA platform is developed to automate traditional flask synthesis and characterization with high flexibility in inert environment	27
Lanthanide-doped $NaYF_4$	automated workstation with deck slots	WANDA platform is developed to automate traditional flask synthesis and characterization with high flexibility in inert environment	27,28
$Cu_{1-x}Ag_xInS_ySe_{1-y}$	automated workstation with deck slots	automated workstation with deck slots mixes precursor solutions and characterizes optical properties of products	39
$CsPbBr_3$	feedback-controlled microfluidic system	flow monitoring sensor is used for feedback control of the flows segmented into multiple droplets. The products are further characterized by on-line characterization tools	40
$CsPbBr_3$	self-driving microfluidic system	with ML algorithm and microfluidic reactor, nanoparticles with target properties are synthesized automatically with high-throughput, without prior knowledge	20
Chiral $CsPbBr_3$	self-driving microfluidic system assisted with fixed-base collaborative robot	intelligent cloud laboratory with cloud server and AI is constructed. Products are monitored via on-line and offline characterizations, from which the results are learned by the AI	41
Polyoxometalates	microfluidic system assisted with ML algorithm	ML algorithm is developed to efficiently search experimental parameter space for crystallization reaction	42

(*Continued on next page*)

Table 1. *Continued*

Nanoparticles	Synthesis method	Note	Reference
Carbon nanotube	AI-controlled CVD-type microreactor	closed-loop platform in which AI controls an automated CVD reactor and *in situ* characterization results are learned by the AI	[43]

WANDA, Workstation for Automated Nanomaterials Discovery and Analysis; AI, artificial intelligence; CVD, chemical vapor deposition; CNT, carbon nanotube.

into a modular synthesis robot whereby a series of steps including aliquoting, laser irradiation, and spectrum acquisition are sequentially conducted in a fully automated way. On the other hand, measurements such as ICP and NMR require more complicated sample preparation procedures. An initial development may thus focus on the automation of the sample aliquoting where a precise amount of nanoparticle solution is taken out and diluted with the desired ratios. The rest of the steps for ICP and NMR measurements may then be conducted by an administrative researcher. Nonetheless, with the promising pace of progress in the tactical level to which the robotic chemist can operate, it will be possible to accomplish a full automation of the materials characterizations in the future.

One of the very important classes of characterization to optimize the property of nanoparticles is to obtain the structure information of the synthesized nanoparticles. As described above, the properties of nanoparticles, regardless of their target applications, depend on their structures and are sensitive to deviations in atomic scale. Using XRD, it is possible to obtain crystallographic structures and a rough estimation of the average size for the synthesized nanoparticle population. XRD measurement typically requires a dense powder sample of the synthesized nanoparticles deposited within a small spot whose dimension is comparable with an X-ray probe size (less than 1 mm). Methods that can be utilized for the automated synthesis of nanoparticles, including microfluidic and modular synthesis systems, provide a sufficient nanoparticle population for XRD measurement. It needs an incorporation of automated processes in aliquoting multiple solutions from multi-batch synthesis and depositing them onto one XRD plate. As-prepared XRD plate with multiple powder spots can be loaded onto an X-ray diffractometer by a robotic manipulator, followed by automatic scanning of multiple XRD patterns. In addition, TEM can offer the detailed structure information of the individual nanoparticles at atomic resolution. It is notable that there have been significant technical developments for the 3D structure characterization of the synthesized nanoparticles (Figure 3). There are two major TEM-based approaches for the 3D structure analysis of nanoparticles. Scanning TEM (STEM) tomography is to investigate 3D structures of an individual nanoparticle by aligning tilt-series STEM images obtained by rotating holder-mounted nanoparticles (Figure 3B).[45,46] In another approach, called Brownian one-particle reconstruction (Figure 3A),[9] it is possible to obtain the 3D structures of many nanoparticles since one field of view can capture 2D projections of many nanoparticles. The resolutions of the 3D structures from the two methods are already sufficient to map coordinates of the entire constituent atoms of individual nanoparticles, revealing the atomic structural details, which are closely related to their physical and chemical properties. This 3D structural information offers an important additional class of property datasets that is associated with a given synthesis parameter, completing the necessary synthesis-structure-property relationship for the automated synthesis optimization.

A typical workflow for TEM analysis, from deposition of the nanoparticle solution on a TEM grid, loading a prepared TEM grid into a transmission electron microscope,

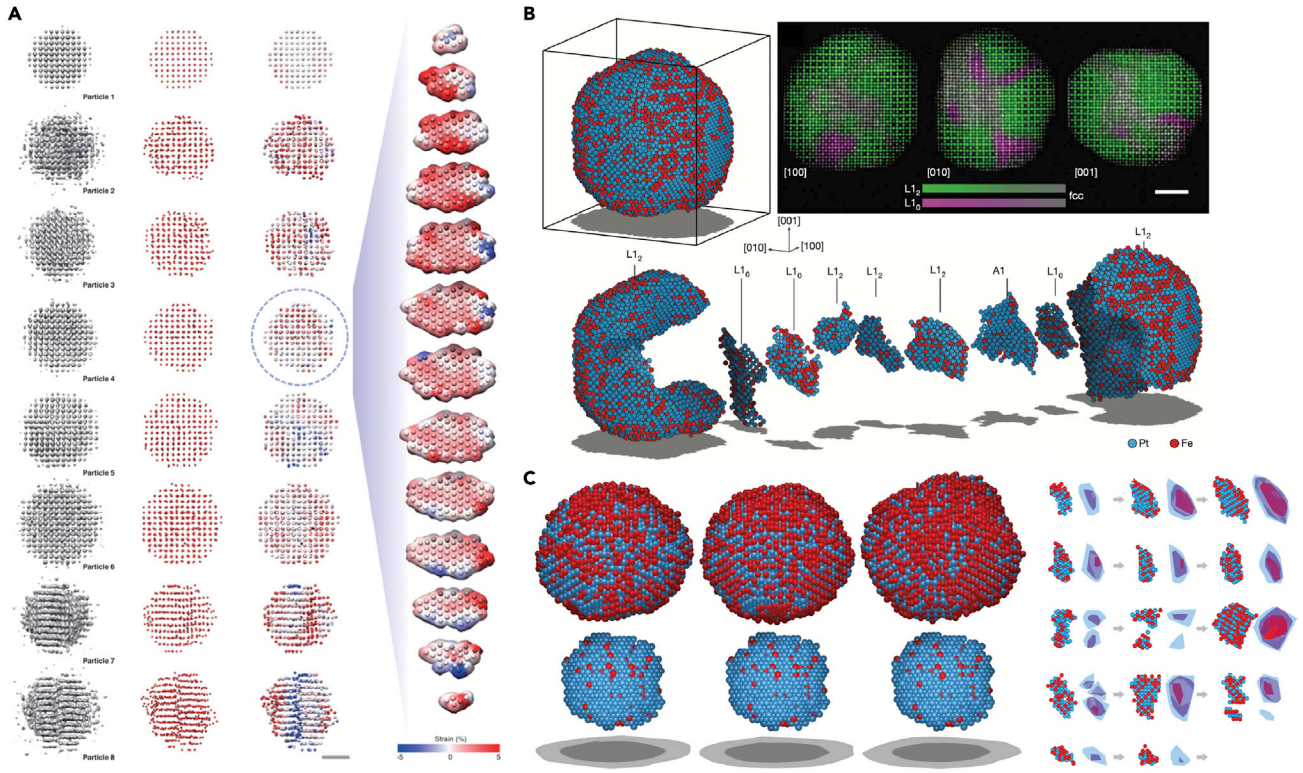

Figure 3. Advanced (S)TEM-based characterization of the 3D atomic structures of synthesized nanoparticles

(A) 3D atomic structure characterization of single Pt nanoparticles based on Brownian one-particle reconstruction.[9] Scale bar, 1 nm.

(B) Characterization of 3D atomic structures of FePt nanoparticles using STEM-based atomic electron tomography.[45] Scale bar, 2 nm.

(C) Tracking crystal nucleation of FePt nanoparticles using sequential STEM-based atomic electron tomography.[46]

focusing and alignment, image data acquisition, to 3D structure reconstruction, is not trivial and is time consuming. There are noticeable technical developments to automate those TEM imaging processes.[47–49] For example, preparing and loading multiple TEM grid samples onto a TEM holder, and an insertion of the TEM holder into a transmission electron microscope are automated by using a robotic manipulator. In addition, a specialized TEM holder for dealing with multiple gird samples, originally developed for cryo-TEM of biological samples, is expanding its applications. Development of automation algorithms for the following processes for data acquisition and downstream structure analysis is not rare in recent TEM practice. Once all steps described above for TEM imaging and 3D atomic structure analysis are fully integrated in automated fashion, it will be possible to provide ample structure information of the ensemble nanoparticles from a single batch, and, thus, to access the structure information in both levels of individual nanoparticles and a population of them. In the meantime, while the needed developments are further pursued on the automated TEM analysis, density-functional theory (DFT) or the molecular dynamics (MD) simulations can be automated[50,51] and be alternatively used to provide the atomistic structure data to be linked to their functions for ML.[52] The atomic arrangements obtained from automated TEM images (when matured) and/or computational data, coupled with their functional properties, will then be an integral part of the multi-modal closed-loop pipeline (spanning different types of data, such as image, texts, and graphs) to optimize the nanoparticle synthesis conditions for desired functions.

MACHINE-LEARNED OPTIMIZATION OF NANOPARTICLE SYNTHESIS

By implementing the robotic synthesis and automated materials characterizations, many of the experimental parts can be automated when exploring the parameter space of the synthesis conditions and optimizing the property of nanoparticles. In exploring this synthesis space, one of the most naive approaches with the robotic system in place is to do a grid search, visiting all possible combinations of experimental conditions, if this ever becomes possible.[53] However, this can be very inefficient, and utilizing an algorithm that takes the existing data or prior visits to suggest the next experiments intelligently would greatly enhance the search efficiency. Therefore, the ML-assisted global optimization comes as a critical component in self-driving laboratories to reduce the number of experiments (i.e., time and cost) and achieve global property optimization more quickly.[53] A practical aspect to consider for the closed-loop approach with multi-modal data emerging from different methods and experiments (e.g., DFT, TEM, process conditions) such as in the present nanoparticle synthesis, is how to integrate the data from different sources in the ML-based optimization tasks in a well-defined manner. One possibility is to construct the encoding schemes for each data type separately (such as the output from the convolutional neural nets for image data and recurrent neural net output for process condition data), and concatenate them to define a global feature to be used for property optimization.

There are roughly three major tasks that ML can offer to autonomously synthesize nanoparticles with optimal properties (Figure 4). One intuitive task is a regression that relates the experimental conditions of the nanoparticle synthesis (as input) and the resulting properties (as output), such as size and optical property. While a number of different traditional ML methods or various modern neural network architectures can be considered, a more critical aspect in constructing a reliable ML model is to collect a sufficient dataset with high-quality experimental data. Given a long history of nanoparticle syntheses, text mining from the literature followed by a careful data curation can be a good starting point to build up a model for the nanoparticle synthesis condition-property relationships.[54–57] Automated robotic and characterization systems described above can also be used to generate the experimental data needed to train this synthesis-property regression model. For experiments whose data are harder to obtain due to the cost and time, active learning algorithms can be implemented to minimize the number of data needed to develop a regression model.[24,25] Once a property prediction model is in place, one can use algorithms to perform an inverse design task to obtain experimental conditions (as output) that would yield the desired property (given as input).[58] This may be possible potentially using a grid search on the experimental parameter space spanning most of the relevant regions of synthesis using a fast regression model, or using a generative model[53,59,60] that learns the distribution of nanoparticle synthesis conditions with a mapping to the property of nanoparticles thus synthesized. While more data can always be added to improve the regression or generative models, these two tasks of regression/prediction or generation are generally performed in a *post hoc* manner after all the necessary data are collected and prepared for training.

Another way to maximally utilize the data to optimize the nanoparticle synthesis conditions for the desired property is to use the data to plan the next synthesis on the fly. This sequential synthesis planning for property optimization can be best practiced with Bayesian optimization (BO) of the experimental parameters based on the current status of experimental data at hand.[61–63] The BO is particularly suited for global optimizations where the data generation is expensive. Gaussian process is

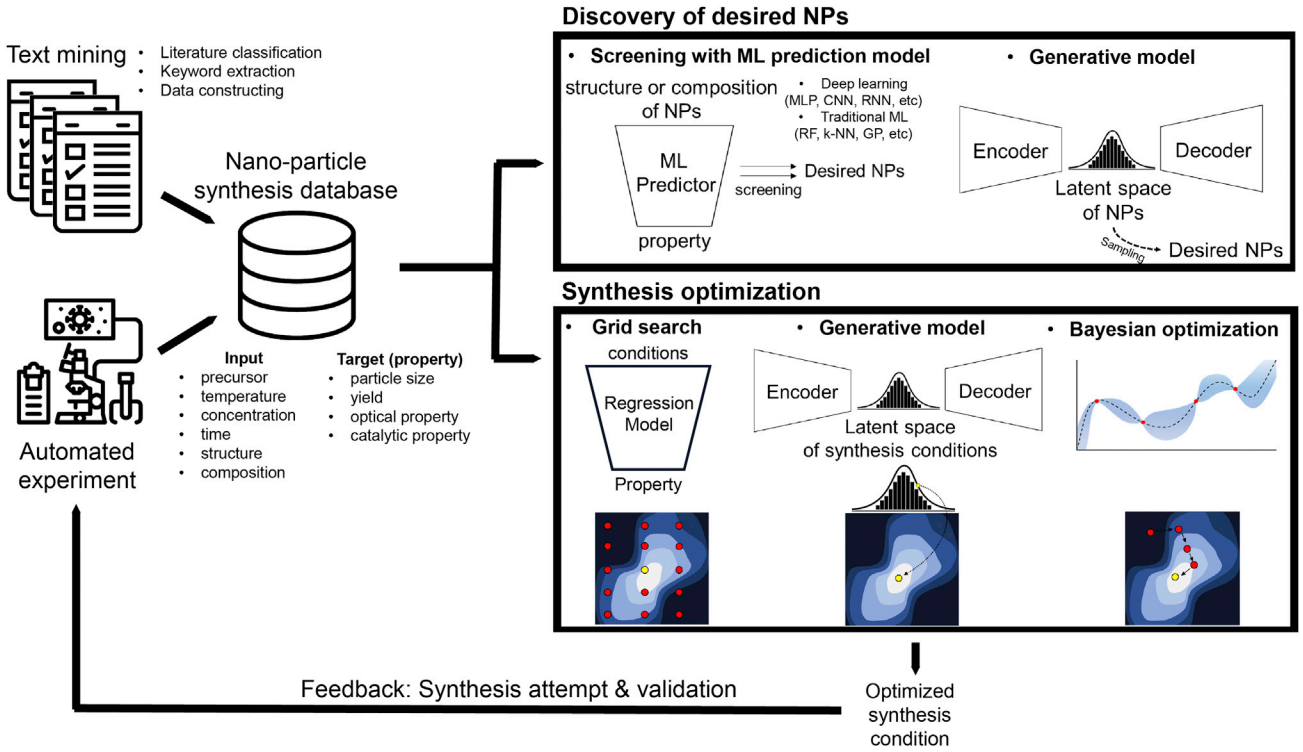

Figure 4. ML-based optimization of nanoparticle synthesis conditions

Synthesis data can be obtained from the literature or can be produced by the high-throughput experiments performed by robotic systems. The collected data are fed into the ML models (regression or generative models), which suggest the optimal recipes for the desired properties of nanoparticles, or plan the next synthesis conditions (BO or reinforcement learning). Experimental synthesis and property evaluation are then performed to validate the prediction. The latter process is repeated until the desired property is achieved.

the popular and widely used BO method due to the built-in uncertainty quantification capability in the formalism,[64] but any other ML models with uncertainty estimation of the predictions can also be used. Genetic algorithm (GA) is another method that can be used in synthesis planning on the fly, with an advantage of using a parallel batch of experiments to plan the next batch of experiments, a characteristic useful for the parallelly implemented robotic systems.[16] Due to the pros and cons of BO and GA, however, the choice of the planning algorithm should be made based on the experimental details and applications. For cases where the parameter space is limited to a handful of conditions by construction, reinforcement learning, albeit generally not very sample efficient, may also be used to optimize experimental conditions in a direction to improve the target property by maximizing the cumulative reward.[65]

SUMMARY AND OUTLOOK

With the ML tools that can predict the properties of nanoparticles based on the synthesis conditions as input or models that can suggest the next experiments to perform by robotic systems, an overall pipeline of self-driving nanoparticle synthesis laboratories can be summarized as in Figure 1. While a full automation of all steps in the loop would be highly desired for fully autonomous developments of nanoparticles without human intervention, the level of difficulty and urgency of automation is not identical for each process, needing a careful consideration of evaluating the priority in the developments. In Table 2, for representative nanoparticle systems, materials development workflows and the current status of process automation

Table 2. Materials development workflows for representative nanoparticle systems and the current status of process automation

Nanoparticle system	Materials discovery workflow	Automation process development
Quantum dot	1. precursor preparation	[a]
Quantum dot	2. synthesis of the QDs	[a]
Quantum dot	3. purification of the QDs	[b]
Quantum dot	4. optical property characterization (absorbance, emission, excitation, quantum yields, time-resolved PL)	[c]
Quantum dot	5. structural characterization (TEM, XRD, EDS, EELS)	[c]
Thermocatalyst	1. precursor solution preparation	[a]
Thermocatalyst	2. synthesis: impregnation and colloidal method	[b]
Thermocatalyst	3. oven dry (vacuum or gas controlled) and calcination	[b]
Thermocatalyst	4. catalytic property characterization (chemisorptions, temperature-programmed analyses, BET)	[c] or [d]
Thermocatalyst	5. chemical and structural characterization (TEM, XRD, FT-IR, CO-DRIFTS, XAS, Raman spectroscopy)	[c]
Thermocatalyst	6. catalyst activity testing and products analysis (conversion, rate, selectivity, stability using GC-TCD, GC-MS, HPLC)	[c] or [d]
Electrocatalyst	1. nanoparticle synthesis and support preparation	[a]
Electrocatalyst	2. loading nanoparticle on the support	[b]
Electrocatalyst	3. preparation of catalyst ink	[b]
Electrocatalyst	4. loading catalyst ink on electrode	[c]
Electrocatalyst	5. chemical and structural characterization (TEM, XRD, FT-IR, CO-DRIFT, XAS, Raman)	[c]
Electrocatalyst	6. catalytic property and activity testing (overpotential, selectivity, stability, ECSA, interfacial properties)	[c] or [d]

QD, quantum dot; TEM, transmission electron microscopy; XRD, X-ray diffraction; EDS, energy-dispersive X-ray spectroscopy; EELS, electron energy loss spectroscopy; BET, Brunauer-Emmett-Teller method; FT-IR, Fourier transform infrared spectroscopy; DRIFTS, diffuse reflectance infrared Fourier transform spectroscopy; XAS, X-ray absorption spectroscopy; GC, gas chromatography; TCD, thermal conductivity detector; MS, mass spectroscopy; HPLC, high-performance liquid chromatography; ECSA, electrochemical surface area.

[a]Source technologies are available. Automation of the process is readily implementable.

[b]Source technologies are under development. Automation of the process requires 3–5 years of engineering.

[c]The process has a tactical complexity. Automation of the process needs development in robotics and algorithms.

[d]The process is highly complicated. Automation of the process requires a long-term research and development plan.

are summarized. Depending on the type of nanoparticles and its target application, the closed-loop synthesis optimization requires different considerations. For example, for the synthesis optimization of quantum dot nanoparticles, incorporation of a system dealing with highly reactive chemicals and heating module for crystallinity-controlled synthesis is desired. In the synthesis optimization of catalysts, both thermal and electrochemical catalysts, mounting synthesized nanoparticles onto the support is critical since catalyst-support interaction is the major knob to control their catalytic activities. Furthermore, a set of characterizations to construct

a property-space database needs to be carefully designed for different types of nanoparticles with a consideration for their target application. Optically active nanoparticles such as quantum dots and plasmonic nanoparticles require high-throughput optical property characterizations, including absorption, emission, fluorescence, and plasmonic scattering, integrated in the closed-loop. Differently, for the catalytic nanoparticles, information from surface activity measurements is an essential part of the property database. An orchestrating software would also need to be implemented to oversee the entire workflow to optimize the user-defined properties and make the pipeline fully autonomous and closed loop.[66]

While the existing literature tends to be biased toward the positive experimental data, negative data also provide important information on the synthesis optimizations.[67,68] Since the fast robotic system can produce both positive and negative results, the data collected from a self-driving laboratory would naturally improve the accuracy of related ML prediction models. In addition, it may also be possible to define the region of positive experimental conditions based on the data, which then allows us to focus on that region to more effectively navigate the synthesis parameter space.

Scale-up is another practical challenge that ML can help. Since the mass transfer behavior in the pilot-scale reactors can differ from the laboratory scale, the mass transfer parameters must be optimized for scale-up. However, the pilot-scale synthesis is substantially more expensive than the laboratory synthesis, by a few orders of magnitude, thus it becomes critical to make the scale-up optimization very efficient. The ML global optimization techniques such as BO and Thompson sampling efficient multi-objective optimization (TSEMO)[69,70] that are suited to optimize a small number of scale-up-related parameters can be used to accelerate the scale-up optimization.

Chemical understanding of the outcomes of a self-driving laboratory would be invaluable to further enhance our insights and use them to design improved materials, in particular with detailed structural information from TEM. In TEM analysis, software and algorithms that aim to scan a large area of the specimen automatically are being developed, enabling the simultaneous acquisition of high-resolution structure data of ensemble nanoparticles.[48] In addition, in several leading companies for TEM equipment, there is intense technical development for the automation of the pre-data-collection steps such as nanoparticle purification, TEM sample preparation, and sample loading into a transmission electron microscope. Once fully integrated, the big image data obtained from automated TEM analysis would be useful resources for computational modeling of the synthesized nanoparticles and their functions.

The closed-loop optimization for nanoparticle synthesis will be readily extended for the materials discovery of different systems, with respect to the type of materials, target applications, and the synthesis batch scale, that need high-speed scans of the synthesis parameters for the synthesis of the desired structures and functionalities.

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AUTHOR CONTRIBUTIONS

All authors contributed to researching and writing this perspective.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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