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Chan, Emory M

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**Automated nanocrystal synthesis:
Lessons from 25 years of robots, microfluidics, and machine learning**

Emory M. Chan^{1*}

¹The Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, California 94720, United States

*Corresponding author: emchan@lbl.gov

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Abstract:

This perspective highlights the evolution of techniques for automating the synthesis of colloidal nanocrystals. Over the past 25 years, microfluidic reactors and robotic workflows have been developed to enhance the reproducibility of nanocrystal synthesis, facilitate rapid screening of reaction conditions, optimize material properties, and perform multi-step syntheses of high-quality nanoparticles with complex heterostructures. Modern automated systems are now valued for their ability to generate robust datasets for validating physical models, supporting chemical mechanisms, training machine learning models, and for directing autonomous experimentation. We discuss the early challenges and limitations of these technologies and present key lessons for effectively utilizing automated and ML-guided tools to accelerate nanocrystal discovery for the next 25 years.

Main Text:

As Nano Letters celebrates its 25th anniversary, I reflect upon my own scientific career, which has grown in parallel with this journal. I started graduate school under the mentorship of Prof. A. Paul Alivisatos and Prof. Richard Mathies in August 2000, around the same time that Alivisatos and fellow co-editors were launching Nano Letters. Little did I know that my first manuscripts as a graduate student and as a postdoc would be published in Nano Letters and would become early examples, respectively, of automating the synthesis of colloidal nanocrystals using microfluidics¹ and robotics.²

Why would one want to automate nanoparticle synthesis? At the start of the millennium, nanocrystal research was producing a steady stream of innovations,³ in areas such as shape control,⁴ heterostructuring,^{5, 6} self-assembly,⁷ for applications in photovoltaics,⁸ biological imaging,⁹ and optoelectronics.¹⁰ But reproducing the nanocrystals in these reports could be challenging, complicated by the large number of synthetic variables, particularly impurities in reagents.^{4, 11} These issues hindered fundamental studies and real-world adoption of colloidal nanocrystals.

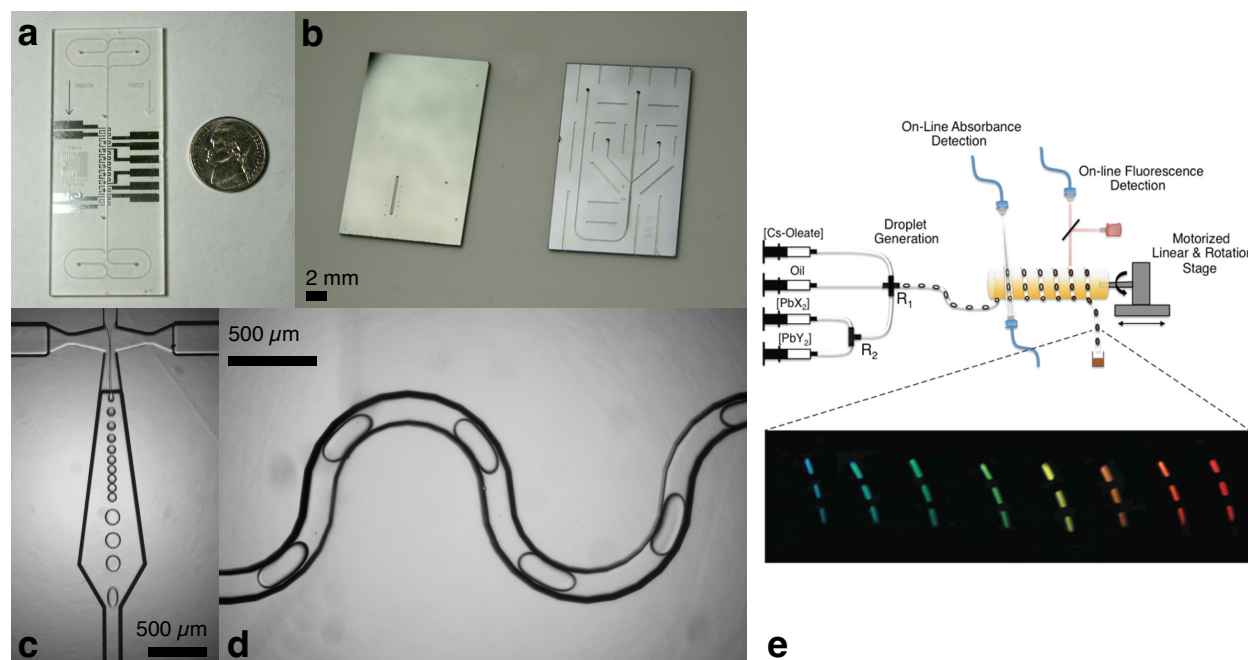


Figure 1. Microfluidic reactors for nanocrystal synthesis. (a) Glass microchip with multi-zone integrated heaters for continuous flow, high temperature synthesis of CdSe nanocrystals.¹² (b) Glass/silicon/SU-8 microchip for measuring millisecond kinetics of CdSe→Ag₂Se with *in situ* X-ray absorption spectroscopy.¹³ X-rays are transmitted through a silicon nitride window on the back side (left) of the chip. Droplet generation (c) and convective mixing microstructures (d) in a glass microchip for high-temperature segmented flow synthesis of CdSe nanocrystals using perfluorinated polyether carrier fluid.¹⁴ (e) Millifluidic, PTFE-tubing-based segmented flow reactor for cesium lead halide nanocrystals. (Inset) Image of generated droplets after exiting the heating zone taken under 405 nm excitation, showing bright luminescence of CsPbX₃ nanocrystals, reproduced from Lignos et al.¹⁵

Tiny reactions for tiny particles. To address these challenges, my advisors and I envisioned a future in which microfluidic reactors¹⁶ would replace the Schlenk lines and three-neck flasks of conventional nanocrystal synthesis. The automated process control and predictable fluid mechanics (e. g., laminar flow) of microfluidic devices would in principle offer greater reproducibility, while controllable mixing and rapid thermal transport in microscopic volumes would enable fine manipulation and even intensification¹⁷ of reactions.¹⁸ Finally, the ease of running multiple reactors in parallel, with small sample volumes and *in situ* characterization, would facilitate high-throughput screening.¹⁸ With a nanocrystal microchip in every fume hood, scientists

would be able to precisely synthesize their desired nanoparticles and quickly optimize their properties.

Twenty-five years later, we still don't have "a chip in every hood," not only due to the technical challenges described below, but also because a single approach rarely addresses every need of a discipline. But, we and others¹⁹ did demonstrate that microfluidics are a viable approach for synthesizing nanocrystals. The first microfluidic reactions, reported in 2002, were room-temperature syntheses of CdS¹⁹ and TiO₂ nanoparticles²⁰ in microfabricated chips, followed by high temperature syntheses of CdSe nanocrystals in fused silica microcapillaries.²¹ In a 2003 *Nano Letters* communication, we reported the high-temperature microchip synthesis of CdSe quantum dots,¹ which reacted and flowed in microchannels etched in glass (Figure 1a) while being characterized in-line spectroscopically. Fine control over nanocrystal size and fluorescence was achieved by varying reaction temperature (180-210 °C), flow rate ratios (1:1 to 5:1 precursor to diluent), and flow rates (1.5-3 µl/min, corresponding to mean residence times of 250-500 s).¹ Subsequent work expanded the utility of these microreactors to a wider range of nanomaterials,^{18, 22} including other semiconductors (e.g., InP²³), metals, (Au,²⁴ Co²⁵), oxides (SiO₂,²⁶ Fe₂O₃,²⁷ and Cu₂O electrocatalysts²⁸), and heterostructures (CuInS₂/ZnS,²⁹ Pt-Pd on Ti₃C₂T_x MXenes³⁰). To characterize rapid reactions such as nanocrystal cation exchange, we used micromachined silicon-based reactors whose narrow, high-aspect-ratio channels facilitated mixing and in situ X-ray absorption spectroscopy on millisecond time scales (Figure 1b).¹³

Lesson #1: Microfluidics do not solve all problems. Early practitioners of microfluidic nanocrystal synthesis discovered their disadvantages: the microreactors produced nanoparticles with lower quality and with properties (e.g., sizes, shapes, compositions, crystal structures) confined to narrower ranges than those accessible to flask syntheses, due to the lower reaction temperatures³¹ and limited reagent compatibility of the devices. Commonly used surfactants like long-chain alkylphosphonic acids were solid at room temperature, making them difficult to flow. Even worse, solids like aggregated nanocrystals often collected on microchannel surfaces, fouling reactions.^{12, 24, 31-33} Short reaction times led to polydisperse nanoparticles, due to the wide residence time distributions³⁴ (>25% standard deviation for a <10 s reaction¹²) arising from the parabolic flow profiles in continuous flow.³¹ Long reaction times, in contrast, required lengthy microchannels³⁵ that resulted in larger dead volumes and high back pressures that could destabilize pumps, resulting in inaccurate and intermittent flow rates and imprecise reaction times.

Lesson #2: Simpler (and segmented) is better. To combat these issues, researchers segmented reaction solutions using multi-phase schemes¹⁷ utilizing gas bubbles^{21, 26, 36, 37} or immiscible carrier fluid,^{14, 15, 26, 32, 38, 39} to separate nanoliter reaction plugs flowing down

microchannels (Figure 1cd). Reagents mixed rapidly within milliseconds inside each plug due to internal convection within the flowing droplets,⁴⁰ while adjacent plugs remained isolated, acting as independent, microscopic batch reactors. In 2005, we developed a high-temperature, liquid-liquid segmented flow microchip reactor in which CdSe nanocrystals grew in droplets of 1-octadecene/oleic acid separated by perfluorinated polyether carrier fluid (Figure 1cd), enabling stable multiphase reactions up to 300 °C.¹⁴ However, segmented flow reactors had their own issues: their fluorinated silane coatings, required to stabilize droplet flow in glass reactors, degraded after hours, and expensive droplet chips still required specialized expertise to fabricate and operate.³³ In addition, multiphase systems can exhibit complex phase diagrams, instability, increased transport, and miscibility at higher temperatures and different pressures.⁴¹

Despite these challenges, the advantages of segmented flow reactors highlighted that microfabricated chips were overengineered for nanocrystal synthesis. Segmenting flow offered the same advantages of microchips – fast mixing, predictable transport, and narrow residence time distributions – but could be achieved without microfabrication. Beginning in 2011, microchips gave way to millifluidic droplet reactors^{33, 42} constructed from off-the-shelf fluoropolymer tubing (e.g., PTFE) with inner diameters of hundreds of microns to millimeters (Figure 1e). The fluorinated material eliminated the need for surface modification and could be easily replaced or cleaned. The simplicity of these polymer tubing reactors has resulted in segmented flow reactors becoming de facto standard in milli/microfluidic nanocrystal synthesis,⁴¹ enabling present-day researchers to construct complex, modular workflows⁴² and perform multi-day reactions of PbS nanocrystals,⁴³ perovskites,^{15, 39} 2D nanomaterials,⁴⁴ doped systems,^{45, 46} gold nanoparticles,^{38, 47} and chiral nanostructures.⁴⁸

Lesson #3: Confining synthetic space confines discovery. The greater problem with nanoparticle microreactors in their first decade was their limited scientific impact on nanocrystal synthesis, with few discoveries of new materials or phenomena. The devices lacked a “killer application” – a use case so compelling that it justified widespread adoption. Microfluidics were not ideal for bleeding-edge nanoparticle research because their restricted reaction conditions could not be used to make the highest quality nanocrystals. Because the devices could be destabilized or permanently disabled by unexpected phenomena like bulk precipitation, they were poorly suited for exploratory research, limiting them to screening well-behaved reaction systems. This was a major disadvantage in the 2000's, when many nanocrystal discoveries (e.g., nano-Kirkendall effect,⁴⁹ nanocrystal cation exchange⁵⁰) were observed serendipitously in experiments gone awry. High-throughput reactions confined in fixed microscale geometries were not conducive to uncovering and investigating such happy accidents, which often required one-off

changes in workflow and new characterization techniques. The problem with early microfluidic reactors was – to paraphrase a movie from that era (2003’s *Finding Nemo*⁵¹) – if you never let anything happen to your microfluidic nanoparticle reaction, then nothing interesting would ever happen to it.

Rise of the robots. As a postdoc at the Molecular Foundry, I postulated that automating nanoparticle synthesis with robots could bypass many of the frustrations of microfluidics. Nanoparticles could be grown in automated batch reactions that closely resembled conventional flask reactions and use identical conditions, facilitating transfer of workflows and knowledge between the modes. Reactions could be isolated in reactor wells such that failed reactions would not disrupt others. Eliminating flow would broaden accessible parameter space by decoupling parameters such as reaction times and mixing rates that were correlated in flow reactors,³⁵ and offline characterization would enable high-quality characterization without sacrificing throughput.

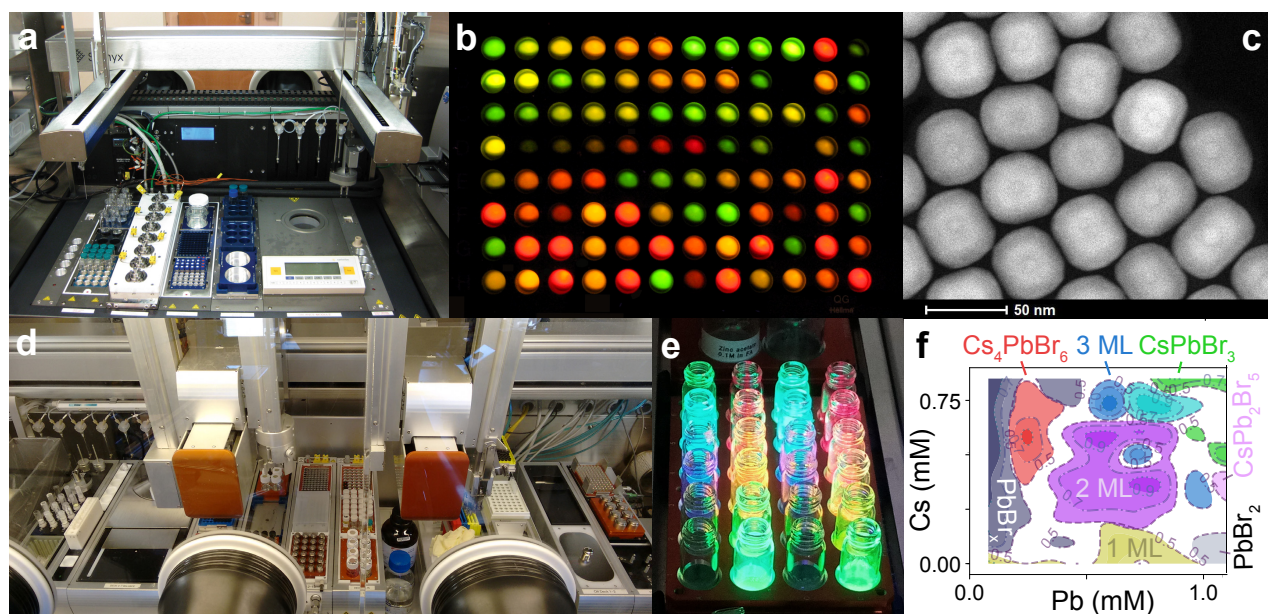


Figure 2. Robotic synthesis of semiconductor nanocrystals. (a) WANDA robot at the Molecular Foundry, Berkeley Lab.² (b) Microplate of CdSe and CdTe nanocrystals synthesized in WANDA. (c) HAADF-STEM image of multi-shell, NaEr_{0.75}Yb_{0.1}Y_{0.15}F₄@NaYF₄@NaGdF₄@NaYF₄@NaGdF₄ nanocrystals synthesized with WANDA using a multi-step, layer-by-layer growth protocol. (d) HERMAN nanocrystal synthesis robot at the Molecular Foundry. (e) Microplate of CsPbX₃ nanocrystals synthesized in HERMAN, where X = Cl, Br, I and their combinations. Image co-credit: Quinten Akkerman. (f) Robotically generated map of dominant species produced by the cesium-lead-bromide system as the concentration of cesium and lead precursors are varied. ML = number of monolayers in a OLA₂Cs_{ML-1}Pb_{ML}Br_{3ML+1} nanoplatelet. Reprinted in part with permission from Dahl et al.⁵² Copyright 2020, American Chemical Society.

In a 2010 *Nano Letters* communication, we introduced a robot called WANDA (Figure 2a) that synthesized high quality nanocrystals such as CdSe (Figure 2b), CdTe, and lanthanide-doped NaYF₄ upconverting nanoparticles (Figure 2c).² WANDA features a custom array of eight, independently controlled, high temperature (350 °C) reactors that could rapidly heat and cool reactions within minutes due to the low thermal mass of the reactors. In contrast to previous high-throughput workflows, WANDA was designed to precisely control a smaller number of flask-scale reactions to prioritize reproducibility and to enable detailed mechanistic studies. Because there were no previously reported robotic reactors for colloidal nanocrystal synthesis, WANDA's reactors took inspiration from parallel reaction arrays developed for polymer synthesis and catalysis by Symyx Technologies,⁵³ the combinatorial materials science pioneer that collaborated in the design of WANDA. Following synthesis, properties of WANDA's nanocrystal products, such as concentration, size, size distribution, and relative quantum yield can be determined rapidly and precisely from absorption and photoluminescence (PL) spectra measured *ex situ* using high-throughput microplate readers.

The benefits of WANDA were immediately apparent: compared to a batch of six manual syntheses, robotically grown CdSe nanocrystals exhibited 10-fold greater reproducibility across and within 8-reactor batches for features like diameter, and they exhibited 25% narrower size distributions (extracted from the full width at half maximum of PL spectra).² WANDA enabled broad screening of nanoparticle reaction conditions, allowing rapid optimization under synthesis conditions relevant to nanocrystal chemists.

Lesson #1 redux: Robots do not solve all problems (but can help isolate them). A significant insight from these reproducibility studies was that only half of the reproducibility gains were achieved through automation of the process control like liquid handling, stirring, and heating. We found that much of the remaining variability in nanocrystal outcomes was introduced before automation started, through impurities in reagents, or via inconsistencies in how precursors were treated during and after preparation. While the robot could not solve all of these issues, the precision of automation allowed us to systematically eliminate errors and quickly isolate external sources of error. Our robotic studies established that, even with automation, reproducibility is a strong function of manual operations like purifying reagents (e.g., recrystallizing trioctylphosphine oxide⁵⁴) and preparing and using large batches of stock solution under consistent conditions, and also subtle adjustments to workflows such as weighing aliquots.²

Lesson #3 redux: Do the right reactions, not the most reactions. As other combinatorial studies have noted,⁵⁵ some reactions have intrinsic variance regardless of experimental rigor.

This fact generalizes Lesson #3 from the Microfluidics section: robots can only optimize reactions or provide insight about them within the chemical space dictated by the reagents. WANDA can screen thousands of combinations of temperature and reagent concentration, but if the nanocrystal precursors (e.g., anionic/cationic precursors for binary semiconductors) are intrinsically irreproducible or do not have the ideal balance of reactivities,^{54, 56, 57} automated methods may not be able to appropriately tune nucleation and growth to achieve the ideal nanocrystal sizes,⁵⁶ size distribution,⁵⁸ alloying,^{57, 59, 60} or heterostructuring.^{57, 61, 62} Expanding experimental space, e.g., performing a single, manual kinetic isotope experiment, often provides more mechanistic insight than sampling 1000 combinations of precursor concentrations within a narrow parameter space. These examples illustrate that even with robots, humans and their experimental designs provide a critical role in determining the effectiveness of automated workflows. In essence, robots are extensions of human effort, acting as force multipliers rather than replacements.

Broadening the library of robotically synthesized materials. Using these lessons, we have expanded the library of nanomaterials produced by WANDA to include semiconductors (PbS, PbSe, LiZnSb,⁶³ CsPbBr₃), metals (Ag, Te), oxides (ZnO^{64, 65}), and doped nanomaterials (NaYF₄:Yb,Er,⁶⁶ KPb₂Cl₅⁶⁷), of various sizes, morphologies (e.g. nanorods^{64, 65, 68, 69} and nanowires), and advanced heterostructures including graded-alloy materials^{57, 61, 62} and rare earth oxychloride nanocrystals with as many as 20 shells.⁷⁰ A key strength of WANDA is the ability to execute complex, multi-step workflows, such as the layer-by-layer, SILAR-like growth of doped oxide nanorods^{64, 65} and multi-shell upconverting nanoparticle heterostructures⁷¹ (Figure 2c) with up to 10 domains,⁷² a process that can take over 12 hours and 100 precursor injections. Beyond WANDA, we and others have developed additional nanoparticle synthesis robots with capabilities including microwave reactors, powder dispensing, and various in-line, in situ, and post-synthetic characterization tools. Our 2nd-generation robot, HERMAN (Figure 2de) integrates a custom high temperature microplate reactor that can heat as many as 96 samples in parallel to 350 °C and purify nanoparticles in an on-deck centrifuge. Other laboratories have developed robots to automate the synthesis of CdSe,⁷³ Cu_{1-x}Ag_xInS_ySe_{1-x},⁷⁴ and metal halide perovskite nanoparticles.^{75, 76} Advanced robotics now automate complex workflows that integrate multiple synthesis and characterization modules, connected by mobile robots⁷⁷ or multi-axis robots.⁷⁸ An outstanding question is whether these robots can deliver scientific innovations that justify their development cost and effort.

Lesson #2 redux: Keep it simple (with robots, too). Our robotic endeavors reinforced previous microfluidic lessons that automated workflows are the most productive when complexity

is kept to the minimum necessary to achieve scientific objectives. While intricate workflows with many degrees of freedom and many steps may seem impressive, each individual operation is an opportunity for failure, and such complexity increases costs and training. Science is accelerated by minimizing steps that can lead to downtime, for example, by using solutions and slurries rather than dispensing powders and by dividing tasks among smaller, more specialized, robots that can operate in parallel. Employing robust, off-the-shelf liquid handling robots allowed us to perform over 25,000 perovskite reactions,⁷⁹ and allowed us to understand the stability of double perovskite nanocrystals,^{80, 81} map cesium lead bromide nanocrystal transformations (Figure 2f),^{52, 82, 83} and elucidate their weakly reversible reaction networks.⁵²

The widespread adoption of inexpensive open-source hardware like Arduino- and Raspberry Pi-based microcontrollers^{84, 85} and OpenTrons liquid handlers^{75, 76} has empowered the construction of nanocrystal synthesis robots by individual labs. 3D printed robots, such as those developed by Cronin et al for the synthesis of gold nanoparticles,^{84, 85} are orders of magnitude less costly, faster to upgrade, and can be controlled with Python frameworks. These robots are less likely to withstand high temperatures and harsh chemistries, but such generality may not be necessary for many nanocrystal reactions with mild conditions.

Lesson #4: Integrate physical models to maximize scientific impact. The most scientifically impactful application of WANDA and other robots has been to produce robust, high-quality datasets for training or validating chemical and physical models. These models have underpinned mechanistic investigations into CdSe QD precursor conversion, nucleation, shell growth,^{54, 86} and size distribution evolution,⁸⁷ gold nanoparticle growth and scattering,⁸⁸ and photophysical modeling of the energy transfer networks within doped upconverting nanoparticles.⁸⁹⁻⁹¹ The importance of interfacing robots with models cannot be overstated: while robots can perform hundreds or thousands of reactions to optimize conditions for properties, computational models can perform millions of calculations in parallel, enabling simultaneous screening of many parameters and generalizing from empirical data into abstract concepts. Compared to traditional combinatorial approaches, these models accelerate discovery by intelligently generating and testing hypotheses for robotic reactions.

A salient example of such synergy between models and robotics is the discovery of photon avalanching nanoparticles.^{92, 93} After training a differential rate equation model⁸⁶ on luminescence spectra of WANDA-synthesized NaYF₄ nanoparticles doped with hundreds of lanthanide ion combinations,⁹⁰ we used it to predict that Tm³⁺-doped nanoparticles exhibit energy looping,⁸⁹ the key energy transfer mechanism behind photon avalanching.⁹⁴ WANDA was used to validate this prediction and further optimize the structure of these nanoparticles, leading to the first

demonstration of photon avalanching in single nanoparticles.⁹⁵ These avalanching nanoparticles (ANPs) exhibit among the highest reported optical nonlinearities -- greater than those of a 30-photon process -- enabling applications such as <70 nm resolution confocal imaging,⁹⁵ super-resolution localization microscopy with 1 Å precision,⁹⁶ and optical switching.^{67, 96} Importantly, while automation was essential to discovering ANPs, it was only one part of a complex, often manual, campaign.

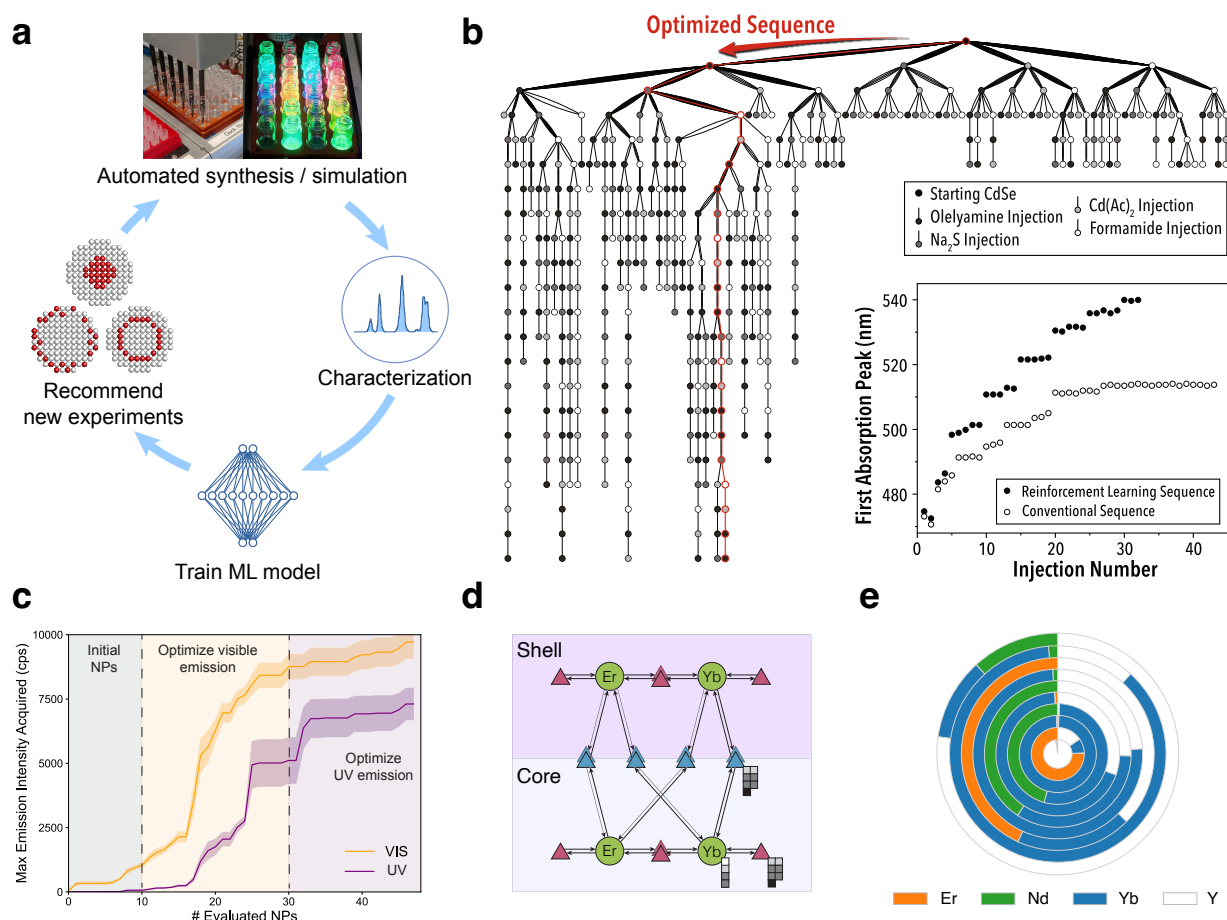


Figure 3. Machine-learning guided synthesis of nanoparticles. (a) General workflow for closed-loop, autonomous nanoparticle synthesis guided by machine learning. (b) Reaction sequences tested and optimal sequence (red trajectory) during the reinforcement learning of the steps (circles) for colloidal atomic layer deposition on CdSe nanoplatelets, reproduced from Volk et al.⁴⁴ Inset: absorption peak wavelength vs injection number for conventional and machine-learned sequences. (c) UV/blue emission intensity vs number of nanoparticles tested during the Bayesian optimization of Yb³⁺, Er³⁺, Tm³⁺-tridoped core-shell NaYF₄ nanoparticles simulated with KMC, resulting in 110-fold enhancement of intensity. Reprinted with permission from Xia et al.⁹⁷ Copyright 2023 American Chemical Society. (d) Heterogeneous graph structure of a core@shell upconverting nanoparticle (UCNP) heterostructure doped with Yb³⁺ and Er³⁺.⁷² (e) 9-shelled Er³⁺, Nd³⁺, and Yb³⁺-doped UCNPs optimized with a heterogeneous graph neural network trained by KMC simulations.⁷²

Machines for machine learning. In the current technological era, microfluidic and robotic workflows have finally found their killer application: feeding the insatiable demand for data by machine learning (ML) models.^{79, 98} High-throughput workflows are now prized for their ability to efficiently generate the “big data” required to train modern ML models.⁹⁹ A major focus is autonomous, “self-driving” labs in which in-line characterization directs subsequent experiments, enabling rapid “closed-loop” optimization of materials and efficient exploration of parameter space (Figure 3a shows an example workflow).s

As early as 2007, pioneers in microfluidic nanocrystal synthesis recognized the value of such reactors for producing large datasets, training neural networks¹⁰² and performing closed-loop statistical optimization of nanocrystal properties.^{103, 104} Such demonstrations were sparse and sporadic, however, until the artificial intelligence (AI) boom of the late 2010’s, when ML-guided nanocrystal research accelerated with the optimization of metal halide perovskite nanoparticle luminescence wavelengths in microfluidic droplet reactors (MARIA¹⁰⁵) and with mobile robots (AIR-Chem¹⁰⁴). By 2020, ML and automation were firmly established in nanocrystal research, with segmented flow reactors utilizing Bayesian and neural network algorithms for optimizing the wavelength,³⁹ doping,⁴⁶ and chirality⁴⁸ of perovskite nanoparticles, and exploring colloidal atomic layer deposition of nanoplatelets (Figure 3b).⁴⁴ Robots have been integrated with genetic algorithms,⁸⁵ literature mining,⁷⁸ large language models^{70, 106} and AI-guided sizing⁸⁸ to synthesize Au nanocrystals, Ag nanorods, CsPbBr₃, and Cs₂AgIn_{1-x}Bi_xCl₆ double perovskite nanoparticles. We used robots to build ML models for ZnCdSSe quantum dots,⁶⁰ and used pairwise difference regression to identify ligands that enhance the luminescence of CsPbBr₃ quantum dots.¹⁰⁷

Lesson #1 revisited: ML does not solve all problems, even with automation. We quickly realized that no robot – regardless of throughput – can fully supply the data demands of ML models. Even active learning approaches^{107, 108} designed for small data struggle to cover the vast synthetic and compositional space of nanocrystals, and even massive experimental campaigns, do not guarantee new discoveries.

A key challenge of training ML models with experimental data is selecting which features to measure – as discussed in Lesson #3, nanocrystal reactions can only be optimized within the confines of the defined feature space. Characterizing and sampling even a fraction of minor but potentially critical features like reagent impurities¹¹ would require immense resources, as would training models in such high-dimensional feature space. Furthermore, while parameters such as temperature and concentration are easily varied, varying critical features like the chemical structure of ligands requires new chemicals to be purchased or synthesized, and properties such

as solubility, chemical compatibility, and toxicity to be determined.¹⁰⁷ These operations become the bottleneck, rather than the trivial steps of synthesis.

Nanoparticles also have complex, hierarchical structures that span disparate length scales – from atomic point defects to microscale super-lattices – that are difficult to represent in models. Unlike organic molecules and bulk crystals, nanoparticles lack a standard digital representation (e.g., string or list of atomic coordinates) because they consist of disparate components, such as dopants, defects, and surface ligands, many of which are not characterized routinely.⁷² Likewise, nanocrystal synthesis can involve multiple steps, including purification, that are not always well documented. We have recently used graph representations to tackle these issues, allowing graph-based models to more efficiently and accurately capture the spatial and conceptual relationships between features, such as energy transfer interactions between dopants in different domains in multi-shelled UCNP heterostructures (Figure 3de).⁷² However, these models are still complex and require large training datasets.

Lesson #4 redux: Statistical models need physical models, too. As with automated synthesis, we have found that nanocrystal applications of ML are most effective when used in conjunction with high-throughput computational screening, which produces well-labeled data that can be generated reproducibly in large quantities. We recently demonstrated the Bayesian optimization of core/shell Yb/Er/Tm-tridoped UCNPs using kinetic Monte Carlo (kMC) simulations achieving over 110-fold increase in ultraviolet luminescence intensity after only 40 iterations (Figure 3c).⁹⁷ For complex heterostructures of 3-10 shells, we used a >6000-element KMC dataset to train heterogeneous graph neural networks (Figure 3d) that exhibited the ability to extrapolate beyond the KMC data and predict structures that had up to 6-fold greater upconverted intensities (Figure 3e).⁷²

Simulations can also be slow, however; some of the aforementioned KMC simulations require more than 60 days.⁷² Computationally trained ML models also need to be validated experimentally. In many cases, further optimization with robots is needed to reconcile discrepancies between experiment and models. Mixed ML models that can learn from both high-throughput experiments and simulation could be developed using fine tuning, transfer learning,¹⁰⁹ multi-fidelity approaches,¹¹⁰ and digital twins.⁴⁶ Such combined approaches will be vital for efficient screening of the high-dimensional parameter spaces of future nanostructures.

Conclusions and outlook. As automated nanochemistry enters its next 25 years, it will be fascinating to see how ML-guided experimentation transforms science. Will there be a robot or AI agent in every hood? My journey through nanocrystal research with microfluidics, robots,

and ML suggests that the most successful applications of AI and automation will be those that focus on the science by keeping the following lessons in mind:

1. Automation and ML should not be treated as magic cure-alls but as tools for augmenting sound scientific strategies. As with any technique, these tools have their strengths and weaknesses and should only be used if they are the most appropriate tools for reaching a conclusion.
2. Keep it simple. Automated workflows are the most effective when they are streamlined and focus on critical bottlenecks, such as initial screening, generating training datasets, and characterizing properties. A key skill is identifying such rate limiting operations as workflows evolve – for some steps, manual experimentation may be most effective and provide the most insight. ML approaches such as digital twins⁴⁴ can be developed to recommend efficient experimental strategies for balancing robotic and manual experiments.
3. Technology should not confine discovery. Automated techniques should be able to adequately sample experimental space and provide opportunities to identify serendipitous phenomena¹¹¹ and make conceptual connections. New ML models, such as those based on foundation and large language models,¹¹² must be trained to make such connections, generate hypotheses¹⁰⁶ from unexpected data, and work around obstacles to testing those hypotheses.
4. Integrate and ground workflows with physical models to maximize fundamental insight and generate useful hypotheses.

The prominence of automated and ML tools will rise and fall as with all technology trends, but their greatest impacts on nanocrystal synthesis will come from accelerating experiments that reveal new materials and scientific insights. Precedent suggests that, like lasers and digital computers, AI and automation will find their role in unexpected and inconspicuous ways, buried in mundane tools and Supporting Information sections, leaving everyday nanocrystal science as their ultimate killer app.

Notes

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References

- (1) Chan, E. M.; Mathies, R. A.; Alivisatos, A. P. Size-Controlled Growth of CdSe Nanocrystals in Microfluidic Reactors. *Nano Lett.* **2003**, *3* (2), 199-201.
- (2) Chan, E. M.; Xu, C.; Mao, A. W.; Han, G.; Owen, J. S.; Cohen, B. E.; Milliron, D. J. Reproducible, High-Throughput Synthesis of Colloidal Nanocrystals for Optimization in Multidimensional Parameter Space. *Nano Lett.* **2010**, *10* (5), 1874-1885.
- (3) Montanarella, F.; Kovalenko, M. V. Three Millennia of Nanocrystals. *ACS Nano* **2022**, *16* (4), 5085-5102.
- (4) Peng, X. G.; Manna, L.; Yang, W. D.; Wickham, J.; Scher, E.; Kadavanich, A.; Alivisatos, A. P. Shape control of CdSe nanocrystals. *Nature* **2000**, *404* (6773), 59-61.
- (5) Hines, M. A.; Guyot-Sionnest, P. Synthesis and Characterization of Strongly Luminescing ZnS-Capped CdSe Nanocrystals. *J. Phys. Chem.* **1996**, *100* (2), 468-471.
- (6) Dabbousi, B. O.; Rodriguez-Viejo, J.; Mikulec, F. V.; Heine, J. R.; Mattoussi, H.; Ober, R.; Jensen, K. F.; Bawendi, M. G. (CdSe)ZnS Core-Shell Quantum Dots: Synthesis and Characterization of a Size Series of Highly Luminescent Nanocrystallites. *J. Phys. Chem. B* **1997**, *101* (46), 9463-9475.
- (7) Sun, S.; Murray, C. B.; Weller, D.; Folks, L.; Moser, A. Monodisperse FePt Nanoparticles and Ferromagnetic FePt Nanocrystal Superlattices. *Science* **2000**, *287* (5460), 1989-1992.
- (8) Huynh, W. U.; Peng, X.; Alivisatos, A. P. CdSe Nanocrystal Rods/Poly(3-hexylthiophene) Composite Photovoltaic Devices. *Adv. Mater.* **1999**, *11* (11), 923-927.
- (9) Bruchez, M.; Moronne, M.; Gin, P.; Weiss, S.; Alivisatos, A. P. Semiconductor Nanocrystals as Fluorescent Biological Labels. *Science* **1998**, *281* (5385), 2013-2016.
- (10) Klimov, V. I.; Mikhailovsky, A. A.; Xu, S.; Malko, A.; Hollingsworth, J. A.; Leatherdale, C. A.; Eisler, H. J.; Bawendi, M. G. Optical Gain and Stimulated Emission in Nanocrystal Quantum Dots. *Science* **2000**, *290* (5490), 314-317.
- (11) Wang, F.; Tang, R.; Buhro, W. E. The Trouble with TOPO; Identification of Adventitious Impurities Beneficial to the Growth of Cadmium Selenide Quantum Dots, Rods, and Wires. *Nano Lett.* **2008**, *8* (10), 3521-3524.
- (12) Chan, E. M.-Y. Synthesis and manipulation of semiconductor nanocrystals in microfluidic reactors. University of California, Berkeley, CA, 2006. <https://escholarship.org/uc/item/82x6m7b2> (accessed 2025/8/22).
- (13) Chan, E. M.; Marcus, M. A.; Fakra, S.; ElNaggar, M.; Mathies, R. A.; Alivisatos, A. P. Millisecond Kinetics of Nanocrystal Cation Exchange Using Microfluidic X-ray Absorption Spectroscopy. *J. Phys. Chem. A* **2007**, *111* (49), 12210-12215.
- (14) Chan, E. M.; Alivisatos, A. P.; Mathies, R. A. High-Temperature Microfluidic Synthesis of CdSe Nanocrystals in Nanoliter Droplets. *Journal of the American Chemical Society* **2005**, *127* (40), 13854-13861.
- (15) Lignos, I.; Stavrakis, S.; Nedelcu, G.; Protesescu, L.; deMello, A. J.; Kovalenko, M. V. Synthesis of Cesium Lead Halide Perovskite Nanocrystals in a Droplet-Based Microfluidic Platform: Fast Parametric Space Mapping. *Nano Lett.* **2016**, *acs.nanolett.5b04981*.
- (16) deMello, J.; deMello, A. Microscale reactors: nanoscale products. *Lab Chip* **2004**, *4* (2), 11N-15N.
- (17) Burns, J. R.; Ramshaw, C. The intensification of rapid reactions in multiphase systems using slug flow in capillaries. *Lab Chip* **2001**, *1* (1), 10-15, 10.1039/B102818A.

- (18) Elvira, K. S.; i Solvas, X. C.; Wootton, R. C. R.; deMello, A. J. The past, present and potential for microfluidic reactor technology in chemical synthesis. *Nature Chemistry* **2013**, 5 (11), 905-915.
- (19) Edel, J. B.; Fortt, R.; deMello, J. C.; deMello, A. J. Microfluidic routes to the controlled production of nanoparticles. *Chem. Commun.* **2002**, (10), 1136-1137, 10.1039/B202998G.
- (20) Wang, H.; Nakamura, H.; Uehara, M.; Miyazaki, M.; Maeda, H. Preparation of titania particles utilizing the insoluble phase interface in a microchannel reactor. *Chem. Commun.* **2002**, 1462-1463.
- (21) Nakamura, H.; Yamaguchi, Y.; Miyazaki, M.; Maeda, H.; Uehara, M.; Mulvaney, P. Preparation of CdSe nanocrystals in a micro-flow-reactor. *Chem. Commun.* **2002**, 2844-2845.
- (22) Negahdary, M.; Mabbott, S. Automated synthesis and processing of functional nanomaterials: Advances and perspectives. *Coord. Chem. Rev.* **2025**, 523, 216249.
- (23) Baek, J.; Allen, P. M.; Bawendi, M. G.; Jensen, K. F. Investigation of Indium Phosphide Nanocrystal Synthesis Using a High-Temperature and High-Pressure Continuous Flow Microreactor. *Angew. Chem. Int. Ed.* **2011**, 50 (3), 627-630.
- (24) Wagner, J.; Köhler, J. M. Continuous Synthesis of Gold Nanoparticles in a Microreactor. *Nano Lett.* **2005**, 5 (4), 685-691.
- (25) Song, Y.; Modrow, H.; Henry, L. L.; Saw, C. K.; Doomes, E. E.; Palshin, V.; Hormes, J.; Kumar, C. S. S. R. Microfluidic Synthesis of Cobalt Nanoparticles. *Chem. Mater.* **2006**, 18 (12), 2817-2827.
- (26) Khan, S. A.; Günther, A.; Schmidt, M. A.; Jensen, K. F. Microfluidic Synthesis of Colloidal Silica. *Langmuir* **2004**, 20 (20), 8604-8611.
- (27) Abou Hassan, A.; Sandre, O.; Cabuil, V.; Tabeling, P. Synthesis of iron oxide nanoparticles in a microfluidic device: preliminary results in a coaxial flow millichannel. *Chem. Commun.* **2008**, (15), 1783-1785, 10.1039/B719550H.
- (28) Jun, M.; Kwak, C.; Lee, S. Y.; Joo, J.; Kim, J. M.; Im, D. J.; Cho, M. K.; Baik, H.; Hwang, Y. J.; Kim, H.; et al. Microfluidics-Assisted Synthesis of Hierarchical Cu₂O Nanocrystal as C₂-Selective CO₂ Reduction Electrocatalyst. *Small Methods* **2022**, 6 (5), 2200074.
- (29) Yashina, A.; Lignos, I.; Stavrakis, S.; Choo, J.; deMello, A. J. Scalable production of CuInS₂/ZnS quantum dots in a two-step droplet-based microfluidic platform. *Journal of Materials Chemistry C* **2016**, 4 (26), 6401-6408, 10.1039/C6TC02057G.
- (30) Liu, B.; Ran, B.; Chen, C.; Shi, L.; Jin, J.; Zhu, Y. High-Throughput Microfluidic Production of Bimetallic Nanoparticles on MXene Nanosheets and Application in Hydrogen Peroxide Detection. *ACS Applied Materials & Interfaces* **2022**, 14 (50), 56298-56309.
- (31) Krishnadasan, S.; Tovilla, J.; Vilar, R.; deMello, A. J.; deMello, J. C. On-line analysis of CdSe nanoparticle formation in a continuous flow chip-based microreactor. *J. Mater. Chem.* **2004**, 14 (17), 2655-2660, 10.1039/B401559B.
- (32) Shestopalov, I.; Tice, J. D.; Ismagilov, R. F. Multi-step synthesis of nanoparticles performed on millisecond time scale in a microfluidic droplet-based system. *Lab Chip* **2004**, 4 (4), 316-321, 10.1039/B403378G.
- (33) Nightingale, A. M.; Krishnadasan, S. H.; Berhanu, D.; Niu, X.; Drury, C.; McIntyre, R.; Valsami-Jones, E.; deMello, J. C. A stable droplet reactor for high temperature nanocrystal synthesis. *Lab Chip* **2011**, 11 (7), 1221-1227, 10.1039/C0LC00507J.
- (34) Trachsel, F.; Günther, A.; Khan, S.; Jensen, K. F. Measurement of residence time distribution in microfluidic systems. *Chem. Eng. Sci.* **2005**, 60 (21), 5729-5737.

- (35) Abolhasani, M.; Coley, C. W.; Xie, L.; Chen, O.; Bawendi, M. G.; Jensen, K. F. Oscillatory Microprocessor for Growth and in Situ Characterization of Semiconductor Nanocrystals. *Chem. Mater.* **2015**, *27* (17), 6131-6138.
- (36) Yen, B. K. H.; Stott, N. E.; Jensen, K. F.; Bawendi, M. G. A Continuous-Flow Microcapillary Reactor for the Preparation of a Size Series of CdSe Nanocrystals. *Adv. Mater.* **2003**, *15* (21), 1858-1862.
- (37) Yen, B. K. H.; Günther, A.; Schmidt, M. A.; Jensen, K. F.; Bawendi, M. G. A Microfabricated Gas-Liquid Segmented Flow Reactor for High-Temperature Synthesis: The Case of CdSe Quantum Dots. *Angew. Chem. Int. Ed.* **2005**, *44* (34), 5447-5451.
- (38) Duraiswamy, S.; Khan, S. A. Droplet-Based Microfluidic Synthesis of Anisotropic Metal Nanocrystals. *Small* **2009**, *5* (24), 2828-2834.
- (39) Epps, R. W.; Bowen, M. S.; Volk, A. A.; Abdel-Latif, K.; Han, S.; Reyes, K. G.; Amassian, A.; Abolhasani, M. Artificial Chemist: An autonomous quantum dot synthesis bot. *Adv. Mater.* **2020**, *32* (30), e2001626.
- (40) Song, H.; Ismagilov, R. F. Millisecond Kinetics on a Microfluidic Chip Using Nanoliters of Reagents. *Journal of the American Chemical Society* **2003**, *125* (47), 14613-14619.
- (41) He, Y.; Kim, K.-J.; Chang, C.-h. Segmented Microfluidic Flow Reactors for Nanomaterial Synthesis. *Nanomaterials* **2020**, *10* (7), 1421.
- (42) Lorber, N.; Sarrazin, F.; Guillot, P.; Panizza, P.; Colin, A.; Pavageau, B.; Hany, C.; Maestro, P.; Marre, S.; Delclos, T.; et al. Some recent advances in the design and the use of miniaturized droplet-based continuous process: Applications in chemistry and high-pressure microflows. *Lab Chip* **2011**, *11* (5), 779-787, 10.1039/C0LC00058B.
- (43) Lignos, I.; Protesescu, L.; Stavakis, S.; Piveteau, L.; Speirs, M. J.; Loi, M. A.; Kovalenko, M. V.; deMello, A. J. Facile Droplet-based Microfluidic Synthesis of Monodisperse IV-VI Semiconductor Nanocrystals with Coupled In-Line NIR Fluorescence Detection. *Chem. Mater.* **2014**, *26* (9), 2975-2982.
- (44) Volk, A. A.; Epps, R. W.; Yonemoto, D. T.; Masters, B. S.; Castellano, F. N.; Reyes, K. G.; Abolhasani, M. AlphaFlow: autonomous discovery and optimization of multi-step chemistry using a self-driven fluidic lab guided by reinforcement learning. *Nat. Commun.* **2023**, *14* (1), 1403.
- (45) Li, S.; Meng, Y.; Guo, Y.; Liu, T.; Stavakis, S.; Howes, P. D.; deMello, A. J. Precision tuning of rare-earth-doped upconversion nanoparticles via droplet-based microfluidic screening. *Journal of Materials Chemistry C* **2021**, *9* (3), 925-933, 10.1039/D0TC04309E.
- (46) Bateni, F.; Sadeghi, S.; Orouji, N.; Bennett, J. A.; Punati, V. S.; Stark, C.; Wang, J.; Rosko, M. C.; Chen, O.; Castellano, F. N.; et al. Smart Dope: A Self-Driving Fluidic Lab for Accelerated Development of Doped Perovskite Quantum Dots. *Advanced Energy Materials* **2024**, *14* (1), 2302303.
- (47) Sebastian Cabeza, V.; Kuhn, S.; Kulkarni, A. A.; Jensen, K. F. Size-Controlled Flow Synthesis of Gold Nanoparticles Using a Segmented Flow Microfluidic Platform. *Langmuir* **2012**, *28* (17), 7007-7013.
- (48) Li, J.; Li, J.; Liu, R.; Tu, Y.; Li, Y.; Cheng, J.; He, T.; Zhu, X. Autonomous discovery of optically active chiral inorganic perovskite nanocrystals through an intelligent cloud lab. *Nat. Commun.* **2020**, *11* (1), 2046.

- (49) Yin, Y.; Rioux, R. M.; Erdonmez, C. K.; Hughes, S.; Somorjai, G. A.; Alivisatos, A. P. Formation of Hollow Nanocrystals Through the Nanoscale Kirkendall Effect. *Science* **2004**, *304* (5671), 711-714.
- (50) Son, D. H.; Hughes, S. M.; Yin, Y.; Paul Alivisatos, A. Cation Exchange Reactions in Ionic Nanocrystals. *Science* **2004**, *306* (5698), 1009-1012.
- (51) Unkrich, L.; Stanton, A. Finding Nemo. Buena Vista Pictures: Burbank, CA, 2003.
- (52) Dahl, J. C.; Wang, X.; Huang, X.; Chan, E. M.; Alivisatos, A. P. Elucidating the Weakly Reversible Cs–Pb–Br Perovskite Nanocrystal Reaction Network with High-Throughput Maps and Transformations. *Journal of the American Chemical Society* **2020**, *142* (27), 11915-11926.
- (53) Murphy, V.; Bei, X.; Boussie, T. R.; Brümmer, O.; Diamond, G. M.; Goh, C.; Hall, K. A.; Lapointe, A. M.; Leclerc, M.; Longmire, J. M.; et al. High-Throughput Approaches for the Discovery and Optimization of New Olefin Polymerization Catalysts. *The Chemical Record* **2002**, *2* (4), 278-289.
- (54) Owen, J. S.; Chan, E. M.; Liu, H. T.; Alivisatos, A. P. Precursor Conversion Kinetics and the Nucleation of Cadmium Selenide Nanocrystals. *Journal of the American Chemical Society* **2010**, *132* (51), 18206-18213.
- (55) Kim, S.; Sohn, K.-S.; Pyo, M. Genetic Algorithm-Assisted Optimization of Nanoporous TiO₂ for Low-Temperature Processable Photoanodes of Dye-Sensitized Solar Cells. *ACS Combinatorial Science* **2011**, *13* (2), 101-106.
- (56) Hendricks, M. P.; Campos, M. P.; Cleveland, G. T.; Jen-La Plante, I.; Owen, J. S. A tunable library of substituted thiourea precursors to metal sulfide nanocrystals. *Science* **2015**, *348* (6240), 1226-1230, 10.1126/science.aaa2951.
- (57) Hamachi, L. S.; Yang, H.; Jen-La Plante, I.; Saenz, N.; Qian, K.; Campos, M. P.; Cleveland, G. T.; Rreza, I.; Oza, A.; Walravens, W.; et al. Precursor reaction kinetics control compositional grading and size of CdSe_{1-x}S_x nanocrystal heterostructures. *Chemical Science* **2019**, *10* (26), 6539-6552, 10.1039/C9SC00989B.
- (58) Campos, M. P.; Hendricks, M. P.; Beecher, A. N.; Walravens, W.; Swain, R. A.; Cleveland, G. T.; Hens, Z.; Sfeir, M. Y.; Owen, J. S. A Library of Selenourea Precursors to PbSe Nanocrystals with Size Distributions near the Homogeneous Limit. *Journal of the American Chemical Society* **2017**, *139* (6), 2296-2305.
- (59) Burks, P. T.; Ostrowski, A. D.; Mikhailovsky, A. A.; Chan, E. M.; Wagenknecht, P. S.; Ford, P. C. Quantum Dot Photoluminescence Quenching by Cr(III) Complexes. Photosensitized Reactions and Evidence for a FRET Mechanism. *Journal of the American Chemical Society* **2012**, *134* (32), 13266-13275.
- (60) Jordan, A. J.; Zhang, Z.; Bennett, E.; Castro, L. G.; Han, D. J.; Rreza, I.; Teitelboim, A.; Theobald, B.; Zekarias, B.; Chan, E. M.; et al. One Pot Synthesis of Cyan Emitting CdZnSSe Quantum Dots for Human Centric Lighting. *J. Phys. Chem. C* **2025**, *129* (1), 993-998.
- (61) Yang, H.; Hamachi, L. S.; Rreza, I.; Wang, W.; Chan, E. M. Design Rules for One-Step Seeded Growth of Nanocrystals: Threading the Needle between Secondary Nucleation and Ripening. *Chem. Mater.* **2019**, *31* (11), 4173-4183.
- (62) Rreza, I.; Yang, H.; Hamachi, L.; Campos, M.; Hull, T.; Treadway, J.; Kurtin, J.; Chan, E. M.; Owen, J. S. Performance of Spherical Quantum Well Down Converters in Solid State Lighting. *ACS Applied Materials & Interfaces* **2021**, *13* (10), 12191-12197.

- (63) White, M. A.; Baumler, K. J.; Chen, Y.; Venkatesh, A.; Medina-Gonzalez, A. M.; Rossini, A. J.; Zaikina, J. V.; Chan, E. M.; Vela, J. Expanding the I–II–V Phase Space: Soft Synthesis of Polytypic Ternary and Binary Zinc Antimonides. *Chem. Mater.* **2018**, *30* (17), 6173-6182.
- (64) Mehra, S.; Chan, E. M.; Salleo, A. Modular synthetic design enables precise control of shape and doping in colloidal zinc oxide nanorods. *Journal of Materials Chemistry C* **2015**, *3* (27), 7172-7179, 10.1039/C5TC01216C.
- (65) Mehra, S.; Bergerud, A.; Milliron, D. J.; Chan, E. M.; Salleo, A. Core/Shell Approach to Dopant Incorporation and Shape Control in Colloidal Zinc Oxide Nanorods. *Chem. Mater.* **2016**, *28* (10), 3454-3461.
- (66) Ostrowski, A. D.; Chan, E. M.; Gargas, D. J.; Katz, E. M.; Han, G.; Schuck, P. J.; Milliron, D. J.; Cohen, B. E. Controlled Synthesis and Single-Particle Imaging of Bright, Sub-10 nm Lanthanide-Doped Upconverting Nanocrystals. *ACS Nano* **2012**, *6* (3), 2686-2692.
- (67) Skripka, A.; Zhang, Z.; Qi, X.; Ursprung, B.; Ercius, P.; Cohen, B. E.; Schuck, P. J.; Jaque, D.; Chan, E. M. Intrinsic optical bistability of photon avalanching nanocrystals. *Nat. Photonics* **2025**, *19* (2), 212-218.
- (68) Kuo, Y.; Li, J.; Michalet, X.; Chizhik, A.; Meir, N.; Bar-Elli, O.; Chan, E.; Oron, D.; Enderlein, J.; Weiss, S. Characterizing the Quantum-Confined Stark Effect in Semiconductor Quantum Dots and Nanorods for Single-Molecule Electrophysiology. *ACS Photonics* **2018**, *5* (12), 4788-4800.
- (69) Park, K.; Kuo, Y.; Shvadchak, V.; Ingargiola, A.; Dai, X.; Hsiung, L.; Kim, W.; Zhou, Z. H.; Zou, P.; Levine, A. J.; et al. Membrane insertion of—and membrane potential sensing by—semiconductor voltage nanosensors: Feasibility demonstration. *Science Advances* **2018**, *4* (1), e1601453.
- (70) Wood, C. H.; Sanchez-Delgado, C. L.; Sternlicht, H.; Soliman, S. S.; Alem, N.; Schaak, R. E. Automated Benchtop Synthesis of a Quadrillion-Plus Member Core@Multishell Nanoparticle Library Using a Massively Generalizable Nanochemical Reaction. *ACS Nano* **2025**.
- (71) Skripka, A.; Lee, M.; Qi, X.; Pan, J.-A.; Yang, H.; Lee, C.; Schuck, P. J.; Cohen, B. E.; Jaque, D.; Chan, E. M. A Generalized Approach to Photon Avalanche Upconversion in Luminescent Nanocrystals. *Nano Lett.* **2023**, *23* (15), 7100-7106.
- (72) Sivonxay, E.; Attia, L.; Spotte-Smith, E. W. C.; Lengeling, B.; Xia, X.; Barter, D.; Chan, E.; Blau, S. Gradient-based optimization of complex nanoparticle heterostructures enabled by deep learning on heterogeneous graphs. *Nature Computational Science* **2025**, DOI: 10.1038/s43588-025-00917-3.
- (73) Salaheldin, A. M.; Walter, J.; Herre, P.; Levchuk, I.; Jabbari, Y.; Kolle, J. M.; Brabec, C. J.; Peukert, W.; Segets, D. Automated synthesis of quantum dot nanocrystals by hot injection: Mixing induced self-focusing. *Chem. Eng. J.* **2017**, *320*, 232-243.
- (74) Stroyuk, O.; Raievska, O.; Langner, S.; Kupfer, C.; Barabash, A.; Solonenko, D.; Azhniuk, Y.; Hauch, J.; Osvet, A.; Batentschuk, M.; et al. High-throughput robotic synthesis and photoluminescence characterization of aqueous multinary copper–silver indium chalcogenide quantum dots. *Part. Part. Syst. Charact.* **2021**, *38* (10), 2100169.
- (75) Sanchez, S. L.; Tang, Y.; Hu, B.; Yang, J.; Ahmadi, M. Understanding the ligand-assisted reprecipitation of CsPbBr₃ nanocrystals via high-throughput robotic synthesis approach. *Matter* **2023**, *6* (9), 2900-2918.

- (76) Xu, J.; Moran, C. H. J.; Ghorai, A.; Bateni, F.; Bennett, J. A.; Mukhin, N.; Latif, K.; Cahn, A.; Jha, P.; Licon, F. D.; et al. Autonomous multi-robot synthesis and optimization of metal halide perovskite nanocrystals. *Nat. Commun.* **2025**, *16* (1), 1-13.
- (77) Li, J.; Lu, Y.; Xu, Y.; Liu, C.; Tu, Y.; Ye, S.; Liu, H.; Xie, Y.; Qian, H.; Zhu, X. AIR-Chem: Authentic Intelligent Robotics for Chemistry. *J. Phys. Chem. A* **2018**, *122* (46), 9142-9148.
- (78) Zhao, H.; Chen, W.; Huang, H.; Sun, Z.; Chen, Z.; Wu, L.; Zhang, B.; Lai, F.; Wang, Z.; Adam, M. L.; et al. A robotic platform for the synthesis of colloidal nanocrystals. *Nature Synthesis* **2023**, *2* (6), 505-514.
- (79) Li, Z.; Najeeb, M. A.; Alves, L.; Sherman, A. Z.; Shekar, V.; Cruz Parrilla, P.; Pendleton, I. M.; Wang, W.; Nega, P. W.; Zeller, M.; et al. Robot-Accelerated Perovskite Investigation and Discovery. *Chem. Mater.* **2020**, *32* (13), 5650-5663.
- (80) Bekenstein, Y.; Dahl, J. C.; Huang, J.; Osowiecki, W. T.; Swabeck, J. K.; Chan, E. M.; Yang, P.; Alivisatos, A. P. The Making and Breaking of Lead-Free Double Perovskite Nanocrystals of Cesium Silver–Bismuth Halide Compositions. *Nano Lett.* **2018**, *18* (6), 3502-3508.
- (81) Dahl, J. C.; Osowiecki, W. T.; Cai, Y.; Swabeck, J. K.; Bekenstein, Y.; Asta, M. D.; Chan, E. M.; Alivisatos, A. P. Probing the stability and bandgaps of Cs₂AgInCl₆ and Cs₂AgSbCl₆ lead-free double perovskite nanocrystals. *Chem. Mater.* **2019**, *31* (9), 3134-3143.
- (82) Dahl, J. C.; Curling, E. B.; Loipersberger, M.; Calvin, J. J.; Head-Gordon, M.; Chan, E. M.; Alivisatos, A. P. Precursor Chemistry of Lead Bromide Perovskite Nanocrystals. *ACS Nano* **2024**, *18* (33), 22208-22219.
- (83) Vurgaft, A.; Strassberg, R.; Shechter, R.; Lifer, R.; Dahl, J. C.; Chan, E. M.; Bekenstein, Y. Inverse size-dependent Stokes shift in strongly quantum confined CsPbBr₃ perovskite nanoplates. *Nanoscale* **2022**, 10.1039/D2NR03275A.
- (84) Jiang, Y.; Salley, D.; Sharma, A.; Keenan, G.; Mullin, M.; Cronin, L. An artificial intelligence enabled chemical synthesis robot for exploration and optimization of nanomaterials. *Sci. Adv.* **2022**, *8* (40), eabo2626.
- (85) Salley, D.; Keenan, G.; Grizou, J.; Sharma, A.; Martín, S.; Cronin, L. A nanomaterials discovery robot for the Darwinian evolution of shape programmable gold nanoparticles. *Nat. Commun.* **2020**, *11* (1), 2771.
- (86) Chan, E. M.; Han, G.; Goldberg, J. D.; Gargas, D. J.; Ostrowski, A. D.; Schuck, P. J.; Cohen, B. E.; Milliron, D. J. Combinatorial Discovery of Lanthanide-Doped Nanocrystals with Spectrally Pure Upconverted Emission. *Nano Lett.* **2012**, *12* (7), 3839-3845.
- (87) Clark, M. D.; Kumar, S. K.; Owen, J. S.; Chan, E. M. Focusing Nanocrystal Size Distributions via Production Control. *Nano Lett.* **2011**, *11* (5), 1976-1980.
- (88) Gleason, S. P.; Dahl, J. C.; Elzouka, M.; Wang, X.; Byrne, D. O.; Cho, H.; Gababa, M.; Prasher, R. S.; Lubner, S.; Chan, E. M.; et al. Automated Gold Nanorod Spectral Morphology Analysis Pipeline. *ACS Nano* **2024**, *18* (51), 34646-34655.
- (89) Levy, E. S.; Tajon, C. A.; Bischof, T. S.; Iafrati, J.; Fernandez-Bravo, A.; Garfield, D. J.; Chamanzar, M.; Maharbiz, M. M.; Sohal, V. S.; Schuck, P. J.; et al. Energy-Looping Nanoparticles: Harnessing Excited-State Absorption for Deep-Tissue Imaging. *ACS Nano* **2016**, *10* (9), 8423-8433.
- (90) Chan, E. M.; Gargas, D. J.; Schuck, P. J.; Milliron, D. J. Concentrating and Recycling Energy in Lanthanide Codopants for Efficient and Spectrally Pure Emission: The Case of NaYF₄:Er³⁺/Tm³⁺ Upconverting Nanocrystals. *J. Phys. Chem. B* **2012**, *116* (35), 10561-10570.

- (91) Teitelboim, A.; Tian, B.; Garfield, D. J.; Fernandez-Bravo, A.; Gotlin, A. C.; Schuck, P. J.; Cohen, B. E.; Chan, E. M. Energy Transfer Networks within Upconverting Nanoparticles Are Complex Systems with Collective, Robust, and History-Dependent Dynamics. *J. Phys. Chem. C* **2019**, *123* (4), 2678-2689.
- (92) Szalkowski, M.; Kotulska, A.; Dudek, M.; Korczak, Z.; Majak, M.; Marciniak, L.; Misiak, M.; Prorok, K.; Skripka, A.; Schuck, P. J.; et al. Advances in the photon avalanche luminescence of inorganic lanthanide-doped nanomaterials. *Chem. Soc. Rev.* **2025**, *54* (2), 983-1026.
- (93) Skripka, A.; Chan, E. M. Unraveling the myths and mysteries of photon avalanching nanoparticles. *Materials Horizons* **2025**, *12* (11), 3575-3597, 10.1039/D4MH01798F.
- (94) Bednarkiewicz, A.; Chan, E. M.; Kotulska, A.; Marciniak, L.; Prorok, K. Photon avalanche in lanthanide doped nanoparticles for biomedical applications: super-resolution imaging. *Nanoscale Horizons* **2019**, *4* (4), 881-889.
- (95) Lee, C.; Xu, E. Z.; Liu, Y.; Teitelboim, A.; Yao, K.; Fernandez-Bravo, A.; Kotulska, A. M.; Nam, S. H.; Suh, Y. D.; Bednarkiewicz, A.; et al. Giant nonlinear optical responses from photon-avalanching nanoparticles. *Nature* **2021**, *589* (7841), 230-235.
- (96) Lee, C.; Xu, E. Z.; Kwock, K. W. C.; Teitelboim, A.; Liu, Y.; Park, H. S.; Ursprung, B.; Ziffer, M. E.; Karube, Y.; Fardian-Melamed, N.; et al. Indefinite and bidirectional near-infrared nanocrystal photoswitching. *Nature* **2023**, *618* (7967), 951-958.
- (97) Xia, X.; Sivonxay, E.; Helms, B. A.; Blau, S. M.; Chan, E. M. Accelerating the Design of Multishell Upconverting Nanoparticles through Bayesian Optimization. *Nano Lett.* **2023**, *23* (23), 11129-11136.
- (98) Epps, R. W.; Abolhasani, M. Modern nanoscience: Convergence of AI, robotics, and colloidal synthesis. *Appl. Phys. Rev.* **2021**, *8* (4), 041316.
- (99) Tao, H.; Wu, T.; Aldeghi, M.; Wu, T. C.; Aspuru-Guzik, A.; Kumacheva, E. Nanoparticle synthesis assisted by machine learning. *Nat. Rev. Mater.* **2021**, *6* (8), 701-716.
- (100) Tom, G.; Schmid, S. P.; Baird, S. G.; Cao, Y.; Darvish, K.; Hao, H.; Lo, S.; Pablo-García, S.; Rajaonson, E. M.; Skreta, M.; et al. Self-Driving Laboratories for Chemistry and Materials Science. *Chem. Rev.* **2024**, *124* (16), 9633-9732.
- (101) Epps, R. W.; Volk, A. A.; Ibrahim, M. Y. S.; Abolhasani, M. Universal self-driving laboratory for accelerated discovery of materials and molecules. *Chem* **2021**, *7* (10), 2541-2545.
- (102) Orimoto, Y.; Watanabe, K.; Yamashita, K.; Uehara, M.; Nakamura, H.; Furuya, T.; Maeda, H. Application of Artificial Neural Networks to Rapid Data Analysis in Combinatorial Nanoparticle Syntheses. *J. Phys. Chem. C* **2012**, *116* (33), 17885-17896.
- (103) Krishnadasan, S.; Brown, R. J. C.; deMello, A. J.; deMello, J. C. Intelligent routes to the controlled synthesis of nanoparticles. *Lab Chip* **2007**, *7* (11), 1434-1441, 10.1039/B711412E.
- (104) Maceiczky, R. M.; deMello, A. J. Fast and Reliable Metamodeling of Complex Reaction Spaces Using Universal Kriging. *J. Phys. Chem. C* **2014**, *118* (34), 20026-20033.
- (105) Bezing, L.; Maceiczky, R. M.; Lignos, I.; Kovalenko, M. V.; deMello, A. J. Pick a Color MARIA: Adaptive Sampling Enables the Rapid Identification of Complex Perovskite Nanocrystal Compositions with Defined Emission Characteristics. *ACS Applied Materials & Interfaces* **2018**, *10* (22), 18869-18878.
- (106) Sanchez, S. L.; Kim, Y.; S. Fuhr, A.; Kanyowa, T.; C. Houston, A.; Mokhtariori, N.; Dubey, A.; Marshall, J.; Poretzky, A.; Duscher, G.; et al. LLM-Guided Ligand Design for Controlling Nanoscopic Morphology of CsPbBr₃ Perovskite Nanocrystals. *ChemRxiv* **2025**.

- (107) Kim, M. A.; Ai, Q.; Norquist, A. J.; Schrier, J.; Chan, E. M. Active Learning of Ligands That Enhance Perovskite Nanocrystal Luminescence. *ACS Nano* **2024**, *18* (22), 14514-14522.
- (108) Li, Z.; Nega, P. W.; Nellikkal, M. A. N.; Dun, C.; Zeller, M.; Urban, J. J.; Saidi, W. A.; Schrier, J.; Norquist, A. J.; Chan, E. M. Dimensional Control over Metal Halide Perovskite Crystallization Guided by Active Learning. *Chem. Mater.* **2022**, *34* (2), 756-767.
- (109) Batra, R.; Pilania, G.; Uberuaga, B. P.; Ramprasad, R. Multifidelity Information Fusion with Machine Learning: A Case Study of Dopant Formation Energies in Hafnia. *ACS Applied Materials & Interfaces* **2019**, *11* (28), 24906-24918.
- (110) Fare, C.; Fenner, P.; Benatan, M.; Varsi, A.; Pyzer-Knapp, E. O. A multi-fidelity machine learning approach to high throughput materials screening. *npj Computational Materials* **2022**, *8* (1), 257.
- (111) Nega, P. W.; Li, Z.; Ghosh, V.; Thapa, J.; Sun, S.; Hartono, N. T. P.; Nellikkal, M. A. N.; Norquist, A. J.; Buonassisi, T.; Chan, E. M.; et al. Using automated serendipity to discover how trace water promotes and inhibits lead halide perovskite crystal formation. *Appl. Phys. Lett.* **2021**, *119* (4), 041903.
- (112) Kim, S.; Schrier, J.; Jung, Y. Explainable Synthesizability Prediction of Inorganic Crystal Polymorphs Using Large Language Models. *Angew. Chem. Int. Ed.* **2025**, *64* (19), e202423950.