Combinatorial materials synthesis: a foundation for AI-driven scientific discovery

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Abstract

Combinatorial synthesis of solid state materials comprises the use of automation or parallelization to systematically vary synthesis parameters. This approach to materials synthesis is a natural fit for accelerated mapping of composition-structure-property relationships, a central tenet of materials research. By viewing combinatorial synthesis not as a panacea but rather as a launching point for holistic design of experimental workflows, we envision a future for accelerated materials science promoted by the co-development of combinatorial synthesis and artificial intelligence techniques. To evaluate the suitability of a synthesis technique in a given experimental workflow, we establish a collection of 10 complementary metrics spanning the speed, scalability, scope, and quality of synthesis. We summarize the state of the field of combinatorial synthesis via a critical review of established techniques in the context of these metrics, which also elucidates opportunities for further development. These opportunities are shaped by the evolution of combinatorial synthesis in research workflows, spanning initial deployments for high throughput experimentation to seminal demonstrations of automated decision making using artificial intelligence. Historical analysis of combinatorial synthesis in the context of the Gartner hype cycle establishes a recent rise in productivity, placing the field on a trajectory for realizing new paradigms in accelerated materials science workflows, built on the foundation of combinatorial synthesis.

Main text

Synthesis is the cornerstone of solid-state materials experimentation. Any synthesis technique will inherently involve the ability to vary some number of synthesis parameters, most commonly composition and annealing temperature. Mapping the relationship between a given synthesis parameter and a property of interest is a core strategy for both discovering and understanding materials. “Combinatorial synthesis” generally refers to automating and/or parallelizing materials synthesis to create a collection of materials with systematic variation of one or more synthesis parameters.[1–3] While this definition does not explicitly address synthesis throughput, the automation and/or parallelization used to achieve the systematic variation typically results in a synthesis throughput exceeding that of traditional, manual techniques. As a result, combinatorial synthesis is often invoked in high throughput experimentation. The role and impact of combinatorial synthesis and high throughput experimentation has substantially evolved over the

past 30 years and is presently being driven by the adoption of artificial intelligence (AI) to automate the decision-making aspects of experimental workflows,[4] which to-date typically involves a one-material-at-a-time implementation of combinatorial synthesis.[5–8] The trajectory of AI-governed experimental workflows places new demands on combinatorial synthesis. Herein we provide an overview of combinatorial synthesis and establish metrics to assess the tradeoffs among different techniques. These metrics also help evaluate the suitability of a technique for a given workflow and illustrate how advancements in combinatorial synthesis will usher in a new era of accelerated materials science.

The original concept of simultaneously synthesizing a series of compositions established *parallelization* as a core strategy for combinatorial synthesis in the middle of the previous century.[9] Despite the ingenuity of this approach, the initial impact was limited due to the throughput mismatch between parallel synthesis and manual, serial metrologies.[1†] By the end of the century, a suite of parallel characterization techniques enabled the construction of end-to-end high throughput experimental workflows, creating a boon for high throughput experimentation in general and combinatorial synthesis in particular.[2,10–13] The vast increase in experiment throughput created anticipation, if not expectation, of a proportional acceleration in discovery of materials for any target technology.

While high throughput experimentation based on combinatorial synthesis has undoubtedly accelerated a broad range of materials research efforts,[1,3,14] the expectations for immediate revolution of materials discovery were misguided, in our opinion, due to three primary factors: 1) There are at least billions of synthesis recipes that may result in materials with unique properties, and when any sizable fraction of these recipes are within scope for a target technology, the search space for materials discovery includes millions to billions of synthesis recipes. Acceleration of experiment throughput as an *isolated* improvement upon traditional experimentation can only be impactful if a substantial fraction of the available search space can be experimentally evaluated. A combinatorial synthesis technique that can achieve throughput on the order of 10-10^4 materials per day only provides a meaningful coverage of the materials search space when operated consistently for years to decades, which generally isn't possible in academic research programs. 2) Most established high throughput workflows rely on a single combinatorial synthesis technique, which inherently limits the materials scope that may be addressed by the workflow. A single synthesis technique cannot typically produce all possible materials that are relevant for optimizing a target property. 3) For most materials discovery efforts, challenges with materials scope are further exacerbated by the hierarchical nature of devices - a material is only one component of a device. Most target technologies of a materials discovery project involve devices whose performance is governed not by a single material but an assembly of materials. Efforts aimed at standalone properties, such as room temperature superconductivity or lightweight structural materials, are exceptions to this issue. For technologies ranging from catalysis to electronics, the properties of materials interfaces are as important or more important than the individual materials properties, and the combinatorial

[1†] We use the term "metrology" to refer to experimental measurement of any property of the synthesized material, spanning the fundamental properties of composition and structure to a broad range of performance-related properties.

synthesis space of all possible materials interfaces is exponentially larger than the search space of individual materials.

By the start of the current century, the hype of high throughput experimentation began to fade in the face of these formidable challenges to accelerating materials discovery, which mirrors the historical evolution of combinatorial synthesis in drug discovery.[15] The entrance into a proverbial "valley of despair" resulted in negative opinions of combinatorial synthesis, however we must recognize that synthesis is only one component of a research workflow. The inability of a given high throughput experiment to vastly accelerate materials discovery is ultimately a failure of the workflow. While limitations of a given combinatorial synthesis technique can contribute to that failure, the responsibility lies in the design of the entire workflow and the associated strategy for its deployment.

To assess the state of combinatorial synthesis and the opportunities for further development, we herein provide a critical review of established techniques in the context of how the synthesis technique may be integrated into experimental workflows. To aid this effort, we establish a set of metrics by which a combinatorial synthesis technique can be evaluated. The metrics expand upon the traditional focus on synthesis throughput to include metrics based on the scope of accessible synthesis recipes, the ability to interface with a breadth of metrologies, and the ability to incorporate different workflow execution strategies. We then compare the performance of different combinatorial synthesis techniques with respect to these metrics and discuss the interplay between advancements in synthesis techniques and the evolution of experimental workflows. This interplay provides a framework in which we can evaluate the trajectory of combinatorial synthesis and the prospects for its continued acceleration of materials science.

Combinatorial Synthesis Metrics

The 10 metrics for evaluating a combinatorial synthesis technique are summarized in Table 1. Starting with the "Speed" category, the most recognizable feature of combinatorial synthesis is the synthesis throughput in terms of i) the number of unique materials that can be produced in some lab-scale time period, for example 1 hour or 1 day. A fixation on increasing instantaneous throughput can lead to shortcomings in 2 other aspects of "speed" that are critical for workflow efficacy. The automation of equipment maintenance increases the up-time of the synthesis and improves its long-term throughput, which can be quantified as ii) the number of automatically synthesized materials per human intervention. For dynamic workflows with on-the-fly design of experiments, a critical parameter is iii) latency, the time between a new synthesis request being made and its delivery to the workflow.

The next category of metrics relates to "Scalability" of the technique, first and foremost in terms of its iv) expense, i.e. the resource intensity per synthesized material, which is a critical consideration for continual operation of a workflow. The next metric considers v) the scalability of a material synthesis to a larger sample or different format to enable follow-up metrologies and validation experiments. Such follow-up experiments are critical to the success of an accelerated screening workflow. For many materials discovery efforts, such follow-up experiments also entail

studying ensembles and/or interfaces of materials, making vi) the ability to combinatorially integrate materials another important metric.

To evaluate the generalizability of a given technique, we also consider the experimental "Scope". A desirably broad scope requires vii) the ability to realize a broad range of composition, phase, and morphology in combinatorially synthesized materials. The ensuing metrology experiments must be compatible with the combinatorially synthesized materials, which is a shared responsibility of the metrology and synthesis techniques. With respect to combinatorial synthesis, this compatibility is facilitated by enabling viii) a breadth of materials formats for integration with electrical, optical, thermal, etc. probes.

The final category pertains to "Quality". While quality requirements must ultimately be determined for a specific project, the most fundamental quality metric is ix) the reproducible purity of the composition, phase, and/or morphology of each synthesized material. For active quality control, the x) incorporation of *in situ* monitoring of synthesis can enable rapid adjustment of synthesis parameters.

Full quantitative evaluation of most to all of these metrics can only be made in the context of a specific experimental workflow. For the present purposes of comparing various techniques and identifying new opportunities, we score techniques on a relative scale of "poor", "moderate", or "good", as summarized in Table 1.

State of the art in combinatorial synthesis

Rather than provide a chronological survey of combinatorial synthesis methods, we highlight here 4 core, complementary synthesis techniques. Since many techniques can be adapted to optimize one metric at the expense of another, our approach is to score a technique based on a small set of representative publications (Table 1, Figure 1) and discuss the key derivatives of the technique that impact the performance against specific metrics.

Sputter deposition

Combinatorial PVD tools provide fine control of synthesis parameters such as growth temperature, deposition atmosphere, film thickness, and deposition geometry, enabling synthesis of thin film composition libraries tailored for a broad range of high-throughput property and performance characterization. The introduction of the "multiple-sample concept" by Hanak[16] used a multi-element target with a single deposition source, planting the seed for further development of vacuum deposition as a parallel synthesis method capable of producing electronic-quality materials.[1,17,18] Over the decades, various PVD techniques have been investigated and adopted for deposition of combinatorial libraries, including magnetron sputtering,[19–25] ion-beam sputtering,[26] evaporation,[27–30] molecular beam epitaxy (MBE),[31] and pulsed laser deposition (PLD).[32–35]

Among these, combinatorial magnetron sputtering was widely used due to its high deposition rate, ease of operation, suitability for a wide range of materials, and process compatibility with industrial applications, which is an asset for translating and scaling discoveries from combinatorial synthesis. While several efforts have combined temperature and composition gradients,[17,36–38] composition libraries have been the workhorse of combinatorial PVD. Due to the temperature-dependence of precursor decomposition, combinatorial heating elements have been more actively developed in chemical vapor deposition.[39,40] Equipped with multiple deposition sources, combinatorial sputtering (Figure 2) is a stalwart of combinatorial synthesis. With respect to Scalability metrics, while sputter deposition is among the least expensive vacuum techniques, the expense per synthesized material is “moderate”. The scalability of thin film synthesis is “good”, and sequential depositions provide “good” interface synthesis capabilities.

Combinatorial sputtering typically produces a thin film library whose composition varies as a function of position across the substrate using either wedge-type multilayer approach [23,24] or co-sputtering technique,[20–22] with state of the art cluster tools combining these techniques.[25] The multilayer approach uses robotically-controlled moving shutters to sequentially deposit overlapping wedge-type thin film layers. The benefits of controlled composition gradients are balanced by a reliance on thermally-driven interdiffusion of the layers and a lowered throughput from sequential vs. concurrent deposition. Co-sputtering utilizes deposition gradients of the different sources to create a continuous composition spread in a single run with intimate mixing of the library constituents in the as-deposited state. The lack of masks increases utilization of sputtered material, shortening deposition time and lowering system maintenance, with limited control of composition gradients obtained through tuning the deposition geometry.[22,41,42] Concerning Speed metrics, the parallel deposition of many compositions makes automation “good”, and with one to several unique composition libraries per day, the throughput is “moderate”. The latency for synthesis is “moderate” since a new request may require changes to the deposition sources.

To gain control of anion composition, recent developments in combinatorial sputtering include control of the partial pressure of reactive gasses such as O_2 at the 0.1 mPa level[43] and use of radio frequency sources to atomize gasses such as N_2, creating more reactive anions than those natively generated in the sputter glow-discharge.[44] With respect to Scope metrics, the combined variation of cations and anions results in a large breadth of accessible materials, with limited control of morphology, resulting in a “moderate” breadth score. The citations in the first paragraph of this section include dozens of metrologies, resulting in a “good” for this metric.

The most common use of *in situ* monitoring in combinatorial sputtering is deposition rate calibration with a quartz-crystal microbalance (QCM),[24,28,29,31] which can be used for spatial profiling of deposition rate[22] and amplified with computational modeling to design deposition parameters for a desired composition gradient.[42] For targeted synthesis of specific structures, scanning reflection high energy electron diffraction (RHEED) equipped in the high-throughput MBE[31] and Combinatorial PLD systems,[32,33] has enabled synthesis with atomic layer control and parallel synthesis of superlattices. A newly developed *in situ* compositional analysis technique,

low-angle x-ray spectroscopy (LAXS) was combined with RHEED during the synthesis of heteroepitaxial $SrTiO_3$ - $SrTi_{0.8}Ru_{0.2}O_{3-\delta}$ continuous composition spread by PLD, further demonstrating the combinatorial synthesis with *in situ* monitoring is a powerful technique for optimizing heteroepitaxy and composition.[45] Other methods to understand and rapidly refine synthesis include integration of PVD vacuum chambers with scanning probe microscopy,[31,46] low energy electron diffraction (LEED), Auger electron spectroscopy (AES),[47] or and Synchrotron beamlines to utilize x-ray based technique such as angle-resolved photoemission spectroscopy (ARPES).[48] With respect to Quality metrics, physical vapor deposition and sputtering in particular provide “good” quality, and the availability of *in situ* monitoring for certain aspects of material quality results in a “moderate” score.

PVD deposition has also served as the initial synthesis step in techniques aimed at broadening the scope of thermal processing space via scanning nanocalorimetry[49] and laser spike annealing.[50,51] These techniques broaden the purview of combinatorial synthesis, provide insight into the evolution of phase behavior in materials synthesis, and provide unprecedented access to metastable materials.

Inkjet printing

For combinatorial synthesis of composition libraries, inkjet printing leverages the speed of industrial printers for ultra-fast deposition of prescribed mixtures of elemental precursors. Subsequent reactive annealing, which can generally be performed in parallel for large libraries of materials, converts the continuum or collection of precursor mixtures into the materials library. The technique was pioneered by Xiang and Schultz for photoluminiscent materials[52] and by Mallouk for electrocatalysts.[53] Application to photoelectrochemical materials was introduced by Woodhouse and Parkinson,[54,55] with subsequent advancements in ink formulations and printing hardware by Fan and Stucky.[56,57]

With this strong foundation of prior art, our high throughput experimentation team built numerous inkjet printing-based materials discovery workflows, commencing with discovery of metal oxide electrocatalysts.[41,58,59] In our implementation of this technique, manual preparation of the inkjet printer enabled, without human intervention, the automed deposition on 1-10 glass plates, each containing in excess of 2000 unique compositions as discrete 1x1 mm^2 samples with sub-1 μm thickness.[60] The collection of glass plates can include different thickness and/or duplicates of the printed metal precursors that become unique materials libraries through variation in thermal processing. Using library designs such as that of Figure 3b and annealing up to 200 library plates per day in large furnaces, the aggregate daily throughput is ca. 400,000 materials per day, placing this synthesis technique at the pinnacle of thin film synthesis throughput. The resulting “good” scores for the throughput and automation aspects of the Speed metrics is balanced by “poor” latency for synthesis using precursors beyond those loaded in the printer.

The printer utilizes small volumes of (inexpensive) precursor ink per synthesized material. Its high deposition speed can be utilized to scale synthesis of a select composition, which can also be achieved by using techniques such as spray or spin coating to deposit a mixed-ink

formulation identified via combinatorial synthesis. Regarding Scalability metrics, these considerations result in a “good” performance with respect to expense and “moderate” for synthesis scale-up. The ability to synthesis interfaces is also “moderate”, as demonstrated by integration of catalysts with light absorbers to prepare libraries of photoanode[61,62] or photocathode[63] assemblies (Figure 3), a combinatorial materials integration strategy that requires light absorber compatibility with the reactive annealing conditions for precursor conversion.

The strategy of parallel reactive annealing of many mixtures of mixed elemental precursors is most suited to preparation of metal oxide materials. Metals (via H_2 annealing) or sulfides (via H_2S annealing) can also be made if a mutually compatible annealing condition can be identified for all precursors. The reactive annealing requirements also limit the ability to control material morphology, especially using state-of-the-art ink formulations that are optimized for ensuring intimate mixing of elemental precursors.[56,57] Expanding the scope of materials that may be synthesized by this approach requires development of ink formulations and printer settings for their robust deposition. Combinatorial inkjet printing has been applied to the deposition of polymer microarrays,[64] gas phase catalyst discovery and optimization,[65] and compositional optimization in lead halide perovskite photovoltaic devices.[66] Regarding Scope metrics, inkjet printing is thus “moderate” with respect to breadth and metrology metrics.

The massive synthesis throughput has traditionally limited *in situ* monitoring, and the propensity for asynchronous precipitation of precursors poses challenges for controlling phase purity, leading to “poor” scores for these Quality metrics. These shortcomings may be well addressed by emerging techniques, such as the accelerated development of printing parameters through integration of machine vision and Bayesian optimization.[67]

Beyond inkjet printing, other printing methods are being implemented to deliver controlled stoichiometries of precursor inks to defined substrate locations, most notably for the synthesis of well-defined nanoparticles through the use of dip pen lithography.[68,69] This approach combines the parallelization of inkjet printing with precision nanoparticle synthesis via block copolymer nano-reactors deposited and patterned by scanning probe dip pen lithography. The desirable combination of throughput and precision synthesis are balanced by the challenges for coupling synthesis and metrology, a challenge in nanoparticle synthesis that has been addressed for some metrologies using microfluidic systems, as discussed in the following section.

Microfluidic nanoparticle synthesis

Automated microfluidic synthesis of nanoparticles occurs in microfluidic channels, where reaction conditions such as reactant droplet size (in segmented flows), temperature profiles, residence time, and reactant mixing can be finely controlled. The technique has been developed for a wide range of materials, most notably chalcogenide quantum dots, but also metal halide perovskite nanocrystals, metal and alloy nanoparticles, oxides, salts, polymer nanoparticles, and carbon nanoparticles, as recently reviewed.[70–72] Regarding Scope metrics, these demonstrations result in a “good” score for materials breadth. The low quantity of synthesized

material limits the metrologies that can be employed for combinatorial characterization, resulting in a “moderate” score for the metrology-based metric.

Automated control of the combinatorial process parameters can be integrated with in-line characterization such as photoluminescence and absorption spectroscopies,[73] enabling real-time characterization of the impact of synthesis parameters on optical properties, from which nanoparticle composition, size, and size distribution may be inferred.[74,75] Consequently, this synthesis technique is most exemplary in its Quality metrics, earning a “good” bor both purity and monitoring aspects.

Controlled delivery in multi-stage reactors enable initial nucleation of quantum dots, followed by subsequent reactant injection to produce continued controlled growth of the quantum dot core, or deposition of shell materials to form core/shell nanoparticles.[76,77] This fine control of interfaces is unique among combinatorial synthesis techniques but is limited to synthetically compatible materials systems. The balance of uniqueness and limitations result in a “moderate” score for the interfaces-based metric. Regarding the other Scalability metrics, the expense per synthesis is “good” since thousands of experimental conditions can be explored using only microliters of precursor solutions. For a select recipe, synthesis scale-up may be achieved via parallel microchannel reactors,[70] although this scaling strategy is challenging compared to other synthesis techniques, resulting in a “moderate” score.

Compared to inkjet printing, the throughput of microfluidic nanoparticle synthesis is lower, while the latency for responding to new synthesis requests is better, resulting in “moderate” scores for these Speed metrics. The automated control of many process parameters enables many syntheses to be performed without human intervention, earning a “good” score for the automation-based metric.

This synthesis platform is particularly amenable to incorporation of data science for reaction planning and control. The detailed information on reaction, nucleation, and growth kinetics obtained from combinatorial experiments can be used to design batch synthesis of target nanoparticles.[75,78] Since synthesis duration can be as low as 3-5 seconds and on-line optical characterization provides real-time monitoring, this synthesis platform is ripe for machine learning-based navigation of the synthesis space,[73,79,80] which relates to the autonomous workflows discussed in the following section.

Solution-based synthesis in autonomous workflows

The integration of combinatorial synthesis into autonomous experimental workflows has included exploration of thermal processing space via laser annealing,[81,82] although benchtop solution-based synthesis instruments comprise the core combinatorial synthesis approach due to relative ease for robotically coupling synthesis and metrology.[5,6,83] The original demonstration of the Ada platform was based on synthesis of organic transport layers for solar cells via robotic pipetting of organic hole transport material, dopants, and plasticizers followed by aspiration and spin coating onto microscope slides with subsequent annealing in a forced convection furnace.[6] In the robot-accelerated perovskite investigation and discovery (RAPID) platform, halide

perovskite crystals were grown using a robotic micropipettor with 4 independent channels to aspirate reagent stock solutions into a glass vial in which the crystals were grown under programmed heating, shaking, and vortexing.[83] In the materials acceleration operating system in cloud (MAOSIC) platform, perovskite nanoscrystals were synthesized via syringe pump-based mixing of precursors with subsequent injection into a heated tube.[5]

The scope of synthesis in each of these platforms is dictated by the several degrees of freedom in precursor mixing and subsequent processing, and their operation as autonomous workflows were demonstrated via identification of local maxima of a performance metric in a 2 or 3-dimensional search space. Given these similarities, these techniques share the same scoring against the combinatorial synthesis metrics, with “moderate” performance with respect to the Speed metrics for throughput and materials per human intervention, which is on the order of 10-10^3 materials. Per the purpose of enabling autonomous experimentation, these techniques feature “good”, very-low latency.

The miniaturization of serial synthesis provides low resource intensity, and while the methods should be amenable to scale-up, that capability was not practiced in these initial demonstrations. While the spin coating technique can nominally be extended to multiple layers of materials for integration studies, largely these techniques produce isolated samples to-date. The resulting expense-based and scale-up-based Scalability scores are “good”. The interface synthesis score is “poor”, as this remains an active area for development.

Each workflow includes metrology but the coupling of many metrologies to these synthesis platforms remains an area under active development. The resulting “moderate” score for metrology-based Scope metric. Similarly, each synthesis platform is tailored for a specific type of material morphology and chemistry, but requires reconfiguration to support different morphologies, resulting in a “poor” score for materials breadth. We anticipate that these metrics will be substantially improved in the coming years as the scope of individual autonomous workflows expands.

Regarding material quality and the real-time monitoring thereof, the performance for any single synthesis recipe can vary substantially, resulting in a “moderate” score for the purity-based Quality metric. The virtue of autonomous synthesis is that the recipe can be optimized without human intervention, creating a new paradigm of quasi-real-time monitoring that earns a “good” score for the monitoring-based metric.

Evolution of workflows

To conceptualize how the advancement in synthesis may enable new modes of experimentation, we consider the evolution of combinatorial synthesis in the context of experimental workflows. Figure 6a-d illustrates this evolution with a series of implementations of the three fundamental steps of i) materials synthesis, ii) metrology to measure any number of materials properties, and iii) learning from prior data to design the next generation of experiments. This series of workflows provide a high-level view of the evolution of combinatorial synthesis, and to further visualize this evolution, Figure 6e provides the publication history for

combinatorial synthesis-related research. Figure 6f also provides the approximate chronology of the field in terms of the Gartner hype cycle,[21] which provides a high level description of the development of a technology from an “initial trigger” to “lasting productivity” and was recently applied to materials research in the context of machine learning.[85]

Compared to the traditional workflow of manual, serial iterations through the steps (Figure 6a), parallel and/or automated combinatorial synthesis enables efficient preparation of materials, which upon coupling to parallel and/or automated metrologies enables high throughput experimentation (Figure 6b). The acceleration to knowledge generation for such a workflow is not commensurate with the acceleration of experiments because the marginal knowledge gain per experiment cannot compete with the manual, hypothesis-driven design of experiments in traditional workflows (Figure 6a). The establishment of combinatorial synthesis and metrology techniques provided the “technology trigger”, and initial demonstrations of high throughput workflows created considerable hype and inflated expectations. These expectations could not be met with the inherent mismatch between the rate of data generation and knowledge generation, leading to the onset of the “valley of despair” at the turn of the century.

Figure 6b is not meant to imply that high throughput experiments cannot be hypothesis-driven, but rather that many initial implementations of high throughput experiments had a primary focus of demonstrating fantastic experimental throughput, which is natural for the “technology trigger” phase of the field. Advancement of the field through the “valley of despair” has proceeded with 2 complementary implementations of combinatorial synthesis. By removing the throughput-focus of workflow design, high throughput experimental workflows (Figure 6b) have been effectively deployed to answer specific research questions.

In the past decade, the mismatch between high throughput experiments and learning-based design of experiments has also been addressed through incorporation of AI to automated decisions. Combined with full synthesis-metrology automation, the resulting so-called “autonomous”, “closed-loop”, or “self-driving” workflows (Figure 6c) use machine learning-based identification of experiments with optimal expected value by updating a predictive model with every iteration through the workflow.[6,8,86] This single-material-per-iteration workflow does not inherently benefit from much of the parallelization in materials synthesis, although one exemplar adaption of the autonomous strategy combines parallel synthesis with AI-driven selection of metrology experiments that have relatively high resource intensity.[87]

Collectively, these modern implementations of combinatorial synthesis have enabled the field to enter the “slope of enlightenment” phase of the Gartner hype cycle. The corresponding increase in research productivity is reflected by the recent up-tick in publication rate (Figure 6e). We describe below the steps required to establish next-generation workflows (Figure 6d) wherein accelerated experiments more substantially generate knowledge and enable the continued growth in productivity.

Outlook

The principled implementation of combinatorial synthesis is poised to accelerate materials discovery via continued co-development with the other components of an automated experimental workflow. The throughput of combinatorial synthesis, which has traditionally been measured as the acceleration with respect to traditional methods, should be considered in the context of both the relative throughput of the pertinent metrologies and the fraction of the search space that can be accessed. Quantifying the accessible synthesis space, both globally and with each existing synthesis method, will be a great asset for designing future workflows. Synthesis recipes are typically documented as a sequence of steps, each annotated with parameters and observables. This type of data is naturally represented by a directed graph with a node for each step.[88–90] By establishing the set of relevant permutations of synthesis steps and the pertinent granularity of the process parameters, for example what change in temperature or composition is sufficient to constitute a new material, the size of the materials synthesis space could be estimated.

For machine learning-guided experiments, the community must map out the tradeoffs between low latency and breadth of synthesis space that can be accessed without human intervention. The Pareto front of these metrics will not only facilitate judicious choice of a synthesis method for a given project but also help guide the development of new synthesis tools that are more amenable to integration in highly automated workflows. In conjunction, development on the AI-guided design of synthesis recipes will be critical, for which progress is rapidly being made, for example with generative models based on recipes mined from the scientific literature.[91]

While workflows that integrate combinatorial synthesis with a single metrology can provide effective and rapid exploration of the synthesis search space, such approaches are inherently limited in aiding materials discovery efforts wherein performance evaluation requires multiple metrologies, for example because the target technology requires multiple functionalities from a component material. To leverage the power of combinatorial synthesis for such materials discovery efforts, workflow development should focus on automated integration of multiple techniques to increase the fluidity of workflows.[92] The mechanics of multi-technique integration have important consequences for operational resource intensity and the ability of the workflow to adapt to generated knowledge. Combinatorial synthesis techniques often efficiently utilize resources via miniaturization of synthesis, although some workflows may be more amenable to automation via humanoid robotics that can leverage the breadth of metrologies that have been developed for human operators.[33] Regardless of the mechanics, increasing the purview of automated workflows will require development of modular, adaptive instrument control software[94,95] to enable hierarchical decision making,[82] thereby increasing the flexibility of robotic experimentation.

While decision-making is central to automation of workflows, advances in AI methods are also needed for other processes, from quality control and anomaly detection to data interpretation and communication. While the autonomous workflows to-date perform optimization within a given search space, ultimately we want a higher grade of scientific knowledge, which may take

the form of symbolic composition-processing-property relationships[96] or simultaneous machine-learning of the appropriate physical model along with its parameters.[97]

As we continue making advancements in combinatorial methods, we must also remain humbled by the vast combinatorial space of all possible materials and all properties of interest. Consider the purview of any single workflow to-date, which may address 0.1% of the materials and 0.1% of the properties, collectively covering 1 part per million of the global material-property space. A recent survey highlighted that that span between when a material is discovered and when it is deployed can be multiple decades, often because the most superlative performance attributes of the material were not evaluated at the time of discovery.[98] Negative results have been shown to carry value in the context of machine learning,[99] a value proposition for universal materials data management[4] that is amplified by the notion that one technology's trash materials may be another technology's treasure. Expert human scientists build chemical intuition to formulate hypotheses and recognize the potential in previously-overlooked regions of the material-property space. A new generation of AI for science [100] may produce the analogy of these skills in machines, which will enable workflows to more effectively capitalize on the power of combinatorial synthesis.

Tables

Table 1: The description of 10 synthesis metrics and respective evaluation of 4 combinatorial synthesis platforms. Sputter deposition is a physical vapor deposition technique and has been a mainstay in combinatorial materials synthesis. The 3 other techniques are related through their use of wet chemistry but are complementary in the format of synthesized materials and their focus on parallelization-based throughput enhancement vs. on-the-fly adaptation of the synthesis recipe.

Combinatorial synthesis metric	Sputter Deposition	Inkjet Printing	Microfluidic Nanoparticle Synthesis	Autonomous Solution Synthesis
Speed / throughput: Number of unique materials per day	moderate	good	moderate	moderate
Speed / automation: Number of synthesized materials per human intervention	good	good	good	moderate
Speed / latency: Low latency for new synthesis requests	moderate	poor	moderate	good
Scalability / expense: Low resource intensity per synthesized material	moderate	good	good	good
Scalability / scale-up: Transferability of synthesis recipe to create larger replicates for detailed and/or device testing	good	moderate	moderate	good
Scalability / interfaces: Ability to integrate multiple materials to study interfacial properties	good	moderate	moderate	poor
Scope / breadth: Breadth of accessible composition, phase, and morphology within a single instrument configuration	moderate	moderate	good	poor
Scope / metrology: Compatibility of synthesized materials with a breadth of metrologies	good	moderate	moderate	moderate
Quality / purity: Purity of synthesized materials with respect to composition, phase, and/or morphology	good	poor	good	moderate
Quality / monitoring: Ability for *in situ* monitoring of the material to actively control synthesis	moderate	poor	good	good

Figures

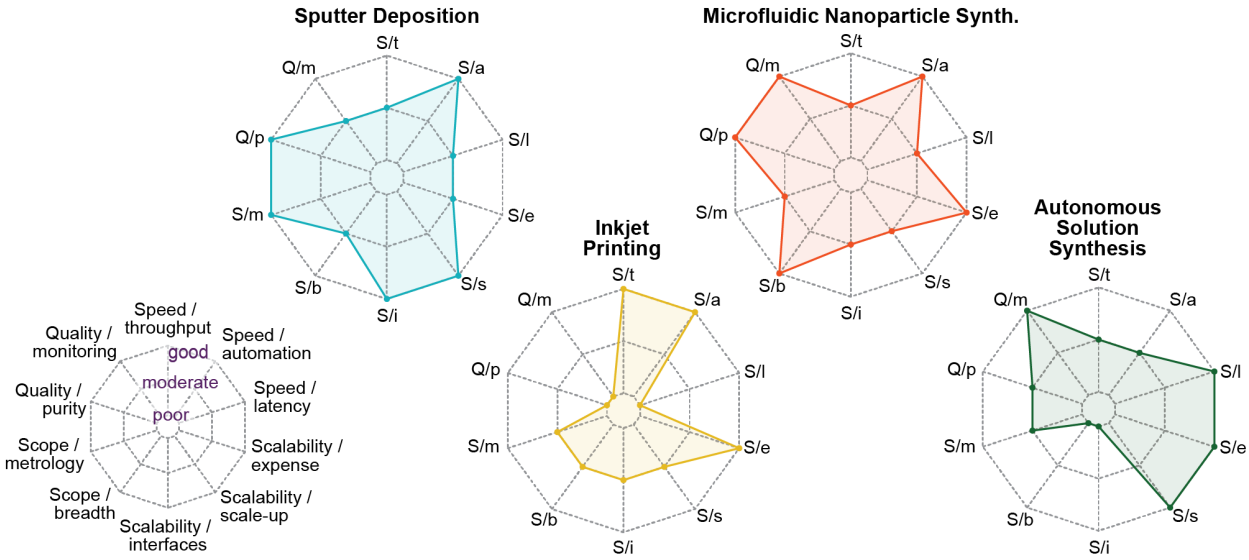

Figure 1: The performance of combinatorial synthesis techniques with respect to 10 metrics. The metrics and categorical scores are noted in the legend (bottom left). For each of 3 combinatorial synthesis platforms, the 10 axes are labeled with abbreviations of the metrics. Sputter deposition and microfluidic nanoparticle synthesis are “moderate” to “good” in all categories, making them broadly-applicable synthesis platforms for materials of their respective thin-film and nanoparticle format. Inkjet printing offers an unrivaled combination of synthesis throughput and low resource intensity per material but is not amenable to real-time quality monitoring. The priority of solution-based synthesis in autonomous workflows is low latency, which to-date has been achieved with a limited scope of materials available at low latency.

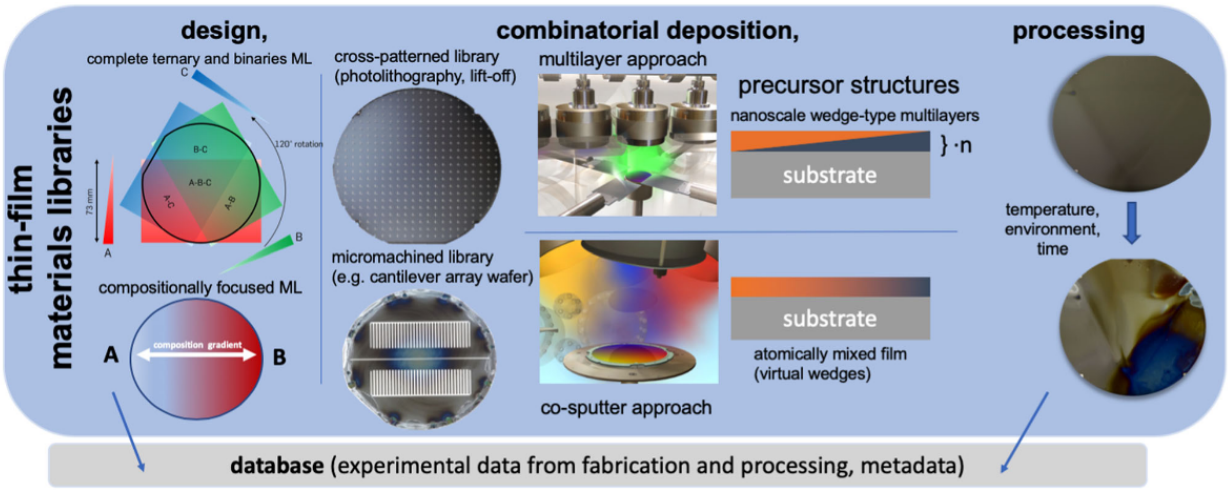

Figure 2: Overview of sputter deposition in combinatorial materials discovery workflows, reproduced from Ref. [1]. The deposition strategy is designed to produce the desired range of compositions (left). The deposition technique may involve lithographically-defined samples/sensors, deposition masks, and co-sputtering to achieve the composition library in a format suitable for metrology (middle). After deposition, parallel processing of the entire library completes the synthesis (right). The throughput and breadth of the resulting materials produce rich datasets for data-driven discovery (bottom). Each circular outline of a materials library is nominally a 75 or 100 mm-diameter wafer.

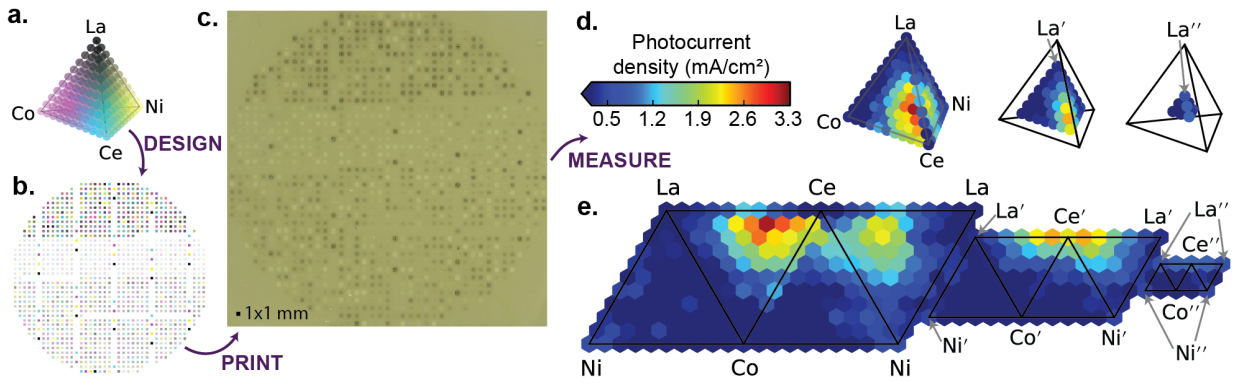

Figure 3: Example implementation of inkjet printing for combinatorial synthesis of catalyst-semiconductor interfaces. a. The composition library is designed based on all mixtures of 4 elements with 10% intervals in elemental concentrations. The composition points are colored using the cyan, magenta, yellow, and black color scheme. b. The printing instructions are encoded as color images where each discrete sample is colored according to composition with saturation indicating the catalyst thickness. c. A photograph of the material library synthesized atop a uniform semiconductor layer. d. Metrology includes the performance of the semiconductor-catalyst interface, whose compositional variation is shown in the composition tetrahedron (top) and a flattened representation (bottom).

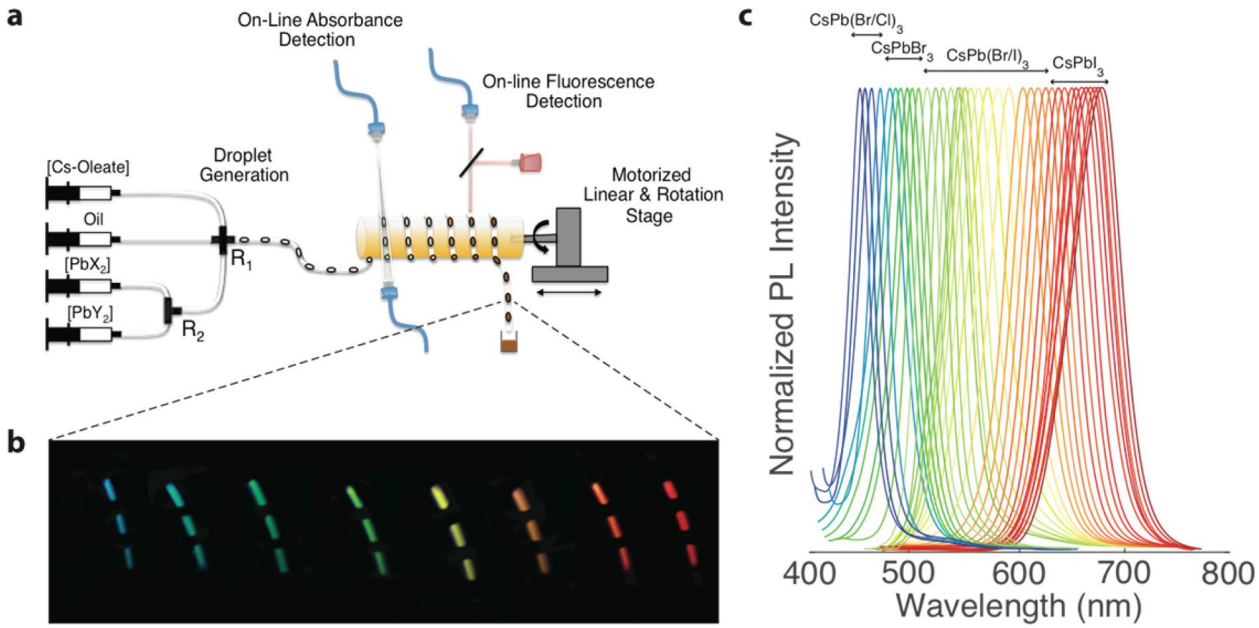

Figure 4: Example microfluidic synthesis of compositionally varied CsPbX nanocrystals (X: Cl, Br, I and Cl/Br and Br/I mixed hilides). (a) schematic representation of the robotically controlled syringes generating segmented droplets containing varying stoichiometry of reactants to the heated zone, with in-line absorbance and fluorescence detection. (b) photographs of the produced nanoparticles after photoexcitation. (C) Representative PL spectra as a function of halide composition, collected in-line during synthesis.[78]

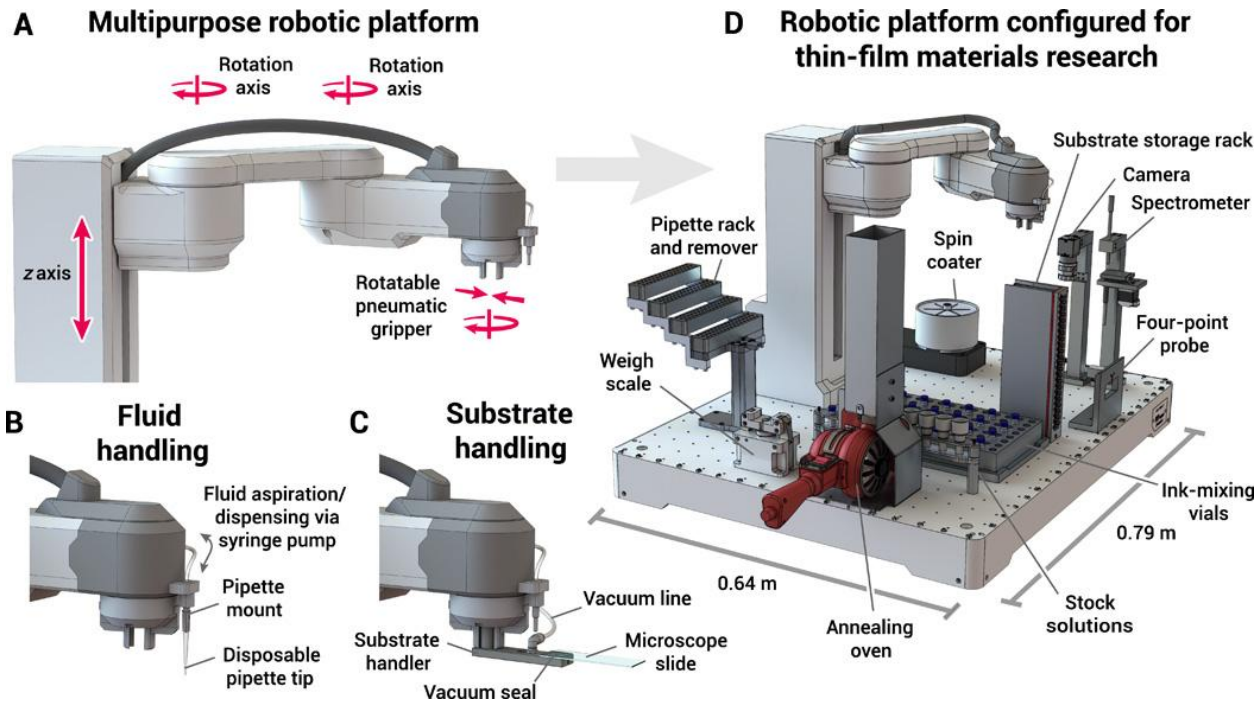

Figure 5: Implementation of solution-based synthesis in an autonomous workflow. The robotic execution of thin film synthesis provides exceptionally low latency for new synthesis requests, which are made automatically upon updating a decision algorithm based on the previous material's measured performance. Reproduced from Ref. [6].

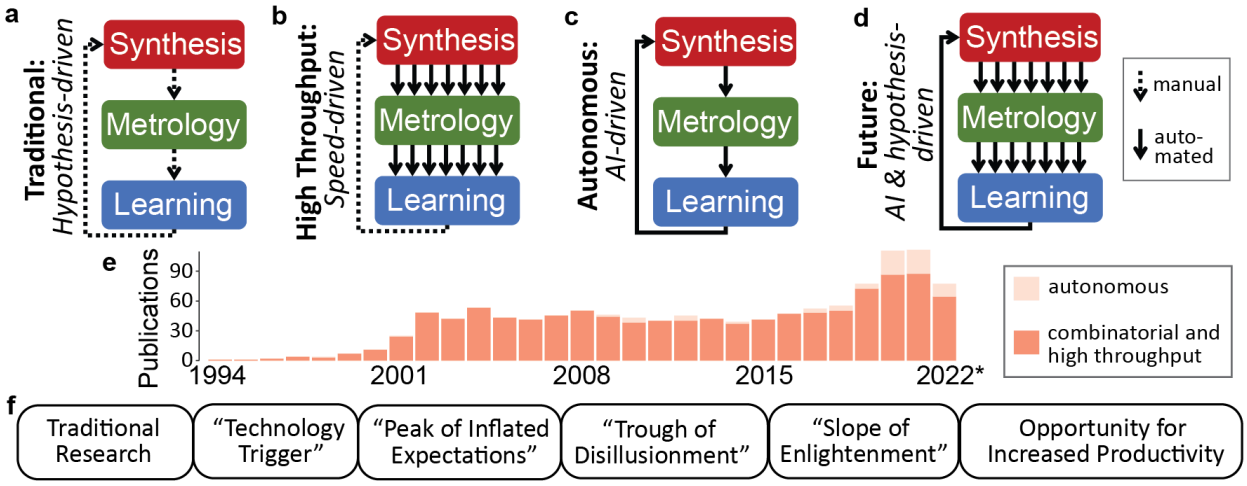

Figure 6: The trajectory of combinatorial synthesis. a. The high level schematic of a traditional materials experiment workflow. Implementations of combinatorial synthesis include b. massive parallelization and/or automation in workflows focused on high throughput experimentation; c. one-at-a-time synthesis enabling sequential learning, typically via AI-based selection of the next experiment; and d. a combination of these approaches coupled with hypothesis-based design of experiments, which is envisioned as the future of combinatorial synthesis. e. On 6 August 2022, Web of Science searches were performed to provide the annual publication count. The "autonomous" publications contain "autonomous materials" or the combination of "materials" and "autonomous synthesis". The "combinatorial and high throughput" publications contain "combinatorial materials" or a combination of "materials" and "combinatorial synthesis", "high throughput experimentation", or "high throughput synthesis". f. Approximately aligned with the publication timeline, the phases of the maturity of combinatorial synthesis are indicated, where the phrases in quotation marks refer to the the first 4 phases of the technology life cycle in the Gartner hype cycle model.[21] The quasi-steady-state phase of "Plateau of Productivity" is not shown as productivity from combinatorial synthesis has yet to plateau.

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