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Perspective

Scanning probes as a materials automation platform with extremely miniaturized samples

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SUMMARY

New materials that meet mounting societal challenges are urgently needed, but current strategies are too slow to meet this need because of the vast variety of potential compositions and processing conditions. One approach to increase the speed and efficiency of materials research is the use of materials acceleration platforms (MAPs) or systems in which experiments are iteratively selected by artificial intelligence and performed by robots. An important aspect of increasing the efficiency and sustainability of this approach is miniaturizing the size of the samples in MAPs. Here, we explore the fundamental and practical limits of miniaturizing material samples in MAPs and propose scanning probes as a platform technology for preparing and characterizing samples at the femtoliter scale and below. In addition, we identify three technological challenges that must be overcome, along with three material systems that are ideally suited for exploration using a scanning-probe-based MAP.

INTRODUCTION

The need for advanced materials that can meet pressing societal challenges has led to the development of materials acceleration platforms (MAPs) that can iteratively select interesting materials or processing conditions and then perform physical experiments on these systems with little to no human interaction.[1–4] Compared with manual experimentation, MAPs enjoy the dual benefits of automation, which generally leads to faster and more reliable experiments with a rich generation of metadata, and sequential selection of experiments using all available knowledge in a manner that collectively allows for more rapid progress toward the chosen goal. Interest in MAPs is evident from the many materials systems and form factors that have been explored.[5–9] The impact of these emerging systems begs the question of how they can be most rapidly adopted and utilized by the broader materials community in a manner that produces convergent advances across the materials spectrum.[10]

In an effort to identify promising directions for future MAPs, we look for inspiration to other technologies that have revolutionized the research enterprise. In particular, the semiconductor industry has powered advances in computing, communication, and analysis that have defined new fields of computational and data-driven research.[11] Examining the features that have made computation so successful, perhaps the most immediately apparent is the trend known as Moore's law,[12,13] or the shrinking of transistors from the macroscale to the nanoscale through the concerted work of the semiconductor industry and related researchers in both industry, the academy, and national laboratories. The ability to have billions of devices working in perfect concert in a tiny area is a flagship capability of modern

PROGRESS AND POTENTIAL

Many major challenges facing society require new materials, but there are effectively innumerable candidate material formulations and processing conditions. A powerful strategy to combat this challenge is the use of materials acceleration platforms (MAPs), which combine automation to rapidly perform experiments with machine learning to iteratively select the most impactful experimental conditions. Here, we explore the fundamental and practical limitations of how small material samples can be as a means of making the process more efficient and sustainable. We propose that scanning probes provide a unique opportunity for developing MAPs with samples at the femtoliter scale and below, as they can both prepare and characterize samples at this scale. Such a system has the potential to drastically lower the barrier to studying the multifunctional properties of highly specialized formulations in fields such as structural polymers, organic optoelectronic materials, and biomaterials.

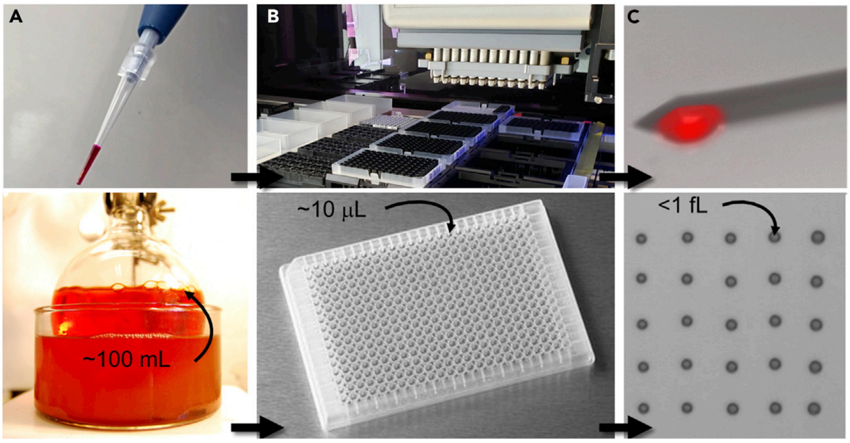

Figure 1. Vision for extreme miniaturization of samples for materials analysis

(A) Conventional sample handling is done at the macroscale using tools such as pipettes and benchtop sample preparation that typically involves samples that are milliliter scale.

(B) High-throughput experimentation has enabled robotic preparation of numerous samples at the several microliter scale.

(C) Fluid handling with scanning probe lithography is used to deposit sub-femtoliter-scale fluid samples.

semiconductors. Thus, it is fascinating to consider whether it is possible to miniaturize materials experiments to the same degree, and if so, what the implications would be.

Before performing billions of miniaturized materials experiments, it is first important to consider whether materials research can or should be miniaturized to this degree. To address the question, one can consider whether there are enough unique formulations of matter to justify this scale of experimentation. This question can be answered with an unequivocal yes. Studies that have tried to enumerate possible materials systems conclude that there are more possible structures or materials than atoms in the observable universe.[14,15] No matter how small we make each experiment, it is impossible to consider exhaustively studying them all, even without considering how processing conditions might provide a further set of variables that balloon the space of possible experiments. This vast scope has led to the fields of combinatorial materials science and the use of high-throughput experimentation (HTE).[16–19] Even if it were not possible to increase the rate at which experiments are performed by miniaturizing them, each experiment being smaller would mean that the quantity of reagents needed to prepare each sample would vastly decrease, enhancing the sustainability of the process and making it easier for chemists to prepare specialty reagents for use. That said, it is important to consider that not all experiments can be miniaturized and not all material properties are consistent across scales.[20,21] For instance, size-dependent phenomena can lead to properties that vary with scale due to, for example, internal length scales such as grain size in metals.[22]

In this white paper, we explore the fundamental constraints, practical implementation, and potential applications of extreme miniaturization of MAPs (Figure 1). We begin by establishing criteria for the smallest scale that is reasonable for materials experiments in terms of fundamental considerations. Next, we address the practical considerations of how such samples can be prepared and interrogated. Finally, we discuss strategies for performing nanoscale experiments in massively parallel

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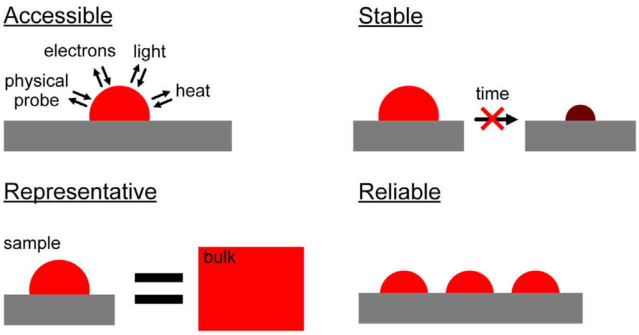

Figure 2. Four fundamental requirements that must be achieved to enable the extreme miniaturization of samples in a materials acceleration platform (MAP)

arrangements and how such systems can fit into the broader MAP ecosystem. While there are many potential strategies for realizing materials experiments at extremely small scales, we center our discussion on scanning-probe-based systems, as these provide the capability to both manipulate and interrogate samples in a litany of possible ways.[23,24] Additionally, scanning probe systems are common in research institutes across the globe, meaning that if we could learn how to transition them into MAPs, there is the potential for widespread adoption. We conclude with an outlook for extreme miniaturization of MAPs.

DISCUSSION

To begin the discussion of an extremely miniaturized format for materials experiments in MAPs, it is important to introduce the fundamental and practical constraints at play. We propose that these can be divided into four major categories that represent requirements for the samples, namely that they are (1) accessible, (2) stable, (3) representative, and (4) reliable (Figure 2).

Accessible

Samples must be positioned and encapsulated such that they can be found and interrogated using various avenues of multimodal characterization. To be compatible with electron microscopy, scanning probe techniques, or most types of optical characterization, this means that they should be arranged in two dimensions. Further, it is important that the samples are not encapsulated within containers that would prevent or complicate analysis. Envisioning a platform where characterization is largely performed by physical scanning probes, this means that samples should either not be encapsulated or that they should feature an extremely thin and functionally inert encapsulation strategy.

Stable

Samples need to maintain their properties for at least as long as it takes to complete the sample preparation and characterization cycle. It would be further advantageous if samples would remain functional long term so that samples of interest can be revisited later for further characterization if desired. When considering extremely miniaturized samples compared with larger samples, some facets of stability become critical due to the higher surface area to volume ratio of smaller samples. For instance, if aqueous samples or solutions of volatile solvents are to be studied, evaporation will occur too quickly to allow adequate time for sample preparation. Thus, extreme miniaturization is most appropriate for solid-state materials. However, fabrication is often much easier to perform in a liquid state. Thus, robust strategies for transitioning samples from a liquid state to a solid state after preparation are extremely important. Common strategies for achieving stability include working with hygroscopic materials in a high-relative-humidity environment, utilizing non-volatile fluids, or studying resins that can be cured into a solid form with light or heat. In particular, prior work has realized patterning and chemistry using materials in aqueous conditions by performing the work with a hygroscopic material, often poly(ethylene glycol), which retains water when the relative humidity is above ∼70%.[25] This process could allow aqueous reactions to be undertaken in a hydrogel by controlling the relative humidity.

Representative

The goal of experiments in a MAP is generally to provide fundamental information about the material system under study, which means that artifacts that emerge due to the nanoscale size of the sample may obfuscate properties of interest. Further, there will be a discrete number of components (e.g., molecules, grains, crosslinks) in a given sample, which might lead to discretization effects. Practically, this imposes a minimum volume for a given type of sample. For instance, for soluble species at different concentrations, the minimum size can be estimated as the volume at which a set number of species are present in a given sample (Figure 3). Once this number crosses ∼100, fluctuations about the mean will amount to less than 10% of the total. Similar analysis can be used to approximate the average number of discrete polymer chains in a sample based on their molecular weight. While it is likely best to perform experiments well above these limits, MAPs that can prepare samples on this scale present a unique opportunity to study size effects by preparing samples at a variety of scales and observing how properties change with sample size.

Reliable

Ultimately, the limit for sample size will likely be determined by how reliably samples can be prepared and tested at a given scale. Thus, the selection of the sample preparation technique and partner analytical approaches will dictate the working scale. Here, we consider reliability to include the precision with which sample size, composition, and processing conditions can be chosen. However, it is worth noting that an alternative to preparing samples with a high degree of precision is additional characterization. For instance, if sample size cannot be tightly controlled, it can at least be measured as part of the characterization process. That said, reliance on such in-loop characterization would likely come with a substantial reduction in throughput.

We propose a class of MAP that uses scanning probes to both prepare and interrogate material samples. This is motivated by two complementary capabilities exhibited by scanning probes that have been developed over the past decades. Scanning probes were originally developed as imaging tools, and there is a rich library of techniques available for functionally characterizing the material at the tip of a probe.[24,26] Such techniques involve applying electric, magnetic, mechanical, electrochemical, thermal, or optical stimuli and measuring the response through, for example, the motion of the probe. The spatial resolution of scanning probe microscopy depends on the imaging mode in question but is often commensurate with the radius of the probe, which is itself on the nanoscale. Thus, one could easily obtain many dozens of independent measurements on a single attoliter-scale material sample. To complement scanning probe microscopy, scanning probe lithography comprises a vast set of techniques for defining patterns on surfaces.[23] Of these, our main interest centers on techniques that directly write materials onto a surface, namely dip-pen nanolithography (DPN), as this family of techniques allows one to deposit material onto surfaces with extremely high resolution and has been shown to function with a vast array of materials from polymers to

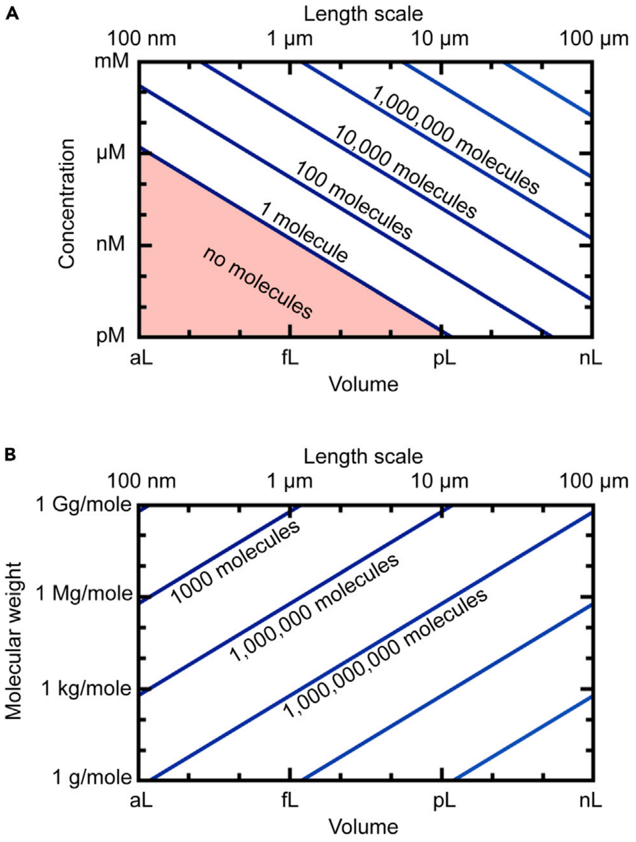

Figure 3. Fundamental considerations about the degree to which miniaturized solution and polymer samples are representative of bulk samples

(A) The number of molecules that would be present in different volumes at various concentrations. 100 molecules represent a reasonable lower limit to mitigate statistical effects from variations about the average number.

(B) The number of polymers that would be present if the volume was completely occupied by a polymer with a specified molecular weight. Here, the solid is assumed to have a density of 1 g/cm^3.

biomolecules.[27,28] While our main interest is lithographic techniques that additively combine multiple materials, scanning probes can also locally alter and detect the state of materials in a manner that has enabled, for example, the study of ferroelectric behavior in a single closed-loop system.[29]

Our proposed vision for materials discovery using this MAP would entail three steps (Figure 4). First, a human experimenter would initialize the system in the materials space of interest by providing stock materials (e.g., polymer resins, dissolved reagents). A major virtue of this system is that very little material would be required; even a few micrograms would be enough for millions of experiments. Next, the samples would be jet printed into reservoirs with set ratios on a flat sample to serve as a canvas. Subsequently, a scanning probe system will acquire aliquots from these local reservoirs and then pattern a set of samples with known composition, size, and location. At this stage, any processing such as local photocuring or heating can be performed *in situ*. Finally, a separate probe would be used to functionally characterize the material samples using scanning probe microscopy. The results of this characterization can be interpreted automatically and used to inform the next cycle. This envisioned MAP would empower the efficient study of a number of important material systems, but there remain several open questions and unsolved technical challenges

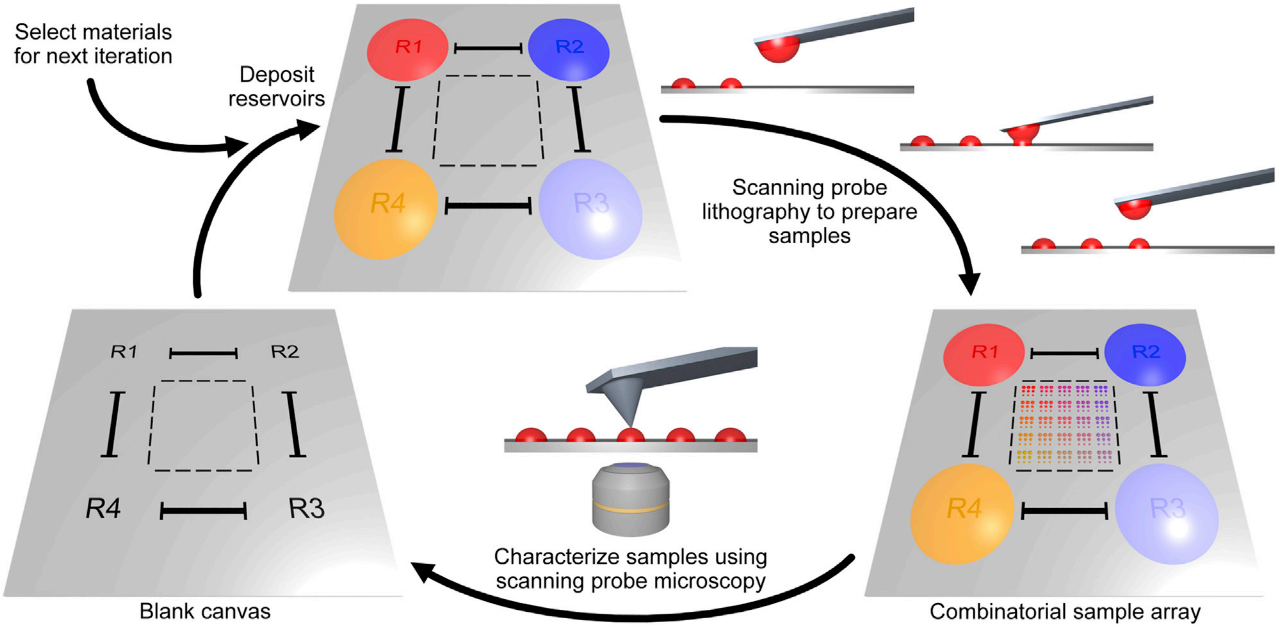

Figure 4. Proposed MAP based on scanning probes to both prepare and interrogate samples
An experimental cycle begins with a set of materials being deposited onto a blank canvas at the nanoliter scale using jet printing. Subsequently, a scanning probe is used to prepare mixtures at the femtoliter or attoliter scale. Finally, another scanning probe system is used to characterize samples along with complementary characterization methods such as optical microscopy. The results of these experiments are used to select the materials for the next experimental cycle.

that have yet to be overcome. To explore these, we formulate a series of opportunities and challenges.

Opportunity 1

Screening photocurable resins for advanced and multifunctional additive manufacturing represents a major opporutnity for scanning-probe-based MAPs. Additive manufacturing approaches such as vat polymerization or stereolithography rely on photocurable polymers that solidify upon exposure to UV light.[30,31] A major synthetic challenge in this field is identifying compositions or blends that (1) have desired mechanical properties, (2) cure rapidly and completely upon exposure to UV light, and (3) exhibit multifunctional properties such as the ability to move in response to stimuli. The proposed scanning-probe-based MAP would be ideal for screening for blends of photocrosslinkers, additives, and base polymers to find those that co-optimize these properties. Since UV light can be directed locally using a coaxial microscope, this process can also be used to study the effects of processing conditions such as illumination dose or processing temperature.

Opportunity 2

Organic materials are prime candidates for sustainable optoelectronic energy conversion applications such as photovoltaics or light-emitting diodes.[32,33] The coordination of electrical stimuli from a probe and light collected by a coaxial optical microscope could allow such properties to be measured *in situ*. In order for a system based around this concept to screen a meaningfully large spectrum of different materials, it should be paired with a versatile synthetic strategy that enables combinations of different polymers and polymer blocks to be tested from a set of feedstock solutions.[34] Additionally, such a MAP could mix different ratios of monomers and then utilize radical polymerization or grafting to synthesize materials *in situ*.

Opportunity 3

Synthetic biology provides a set of tools for producing functional materials that are inherently sustainable by virtue of being biologically derived and biodegradable.[35] One could imagine using nanoscale bioreactors as a path to performing cell-free synthesis and producing biopolymers with highly controlled properties.[36] Here, a goal could be to identify reaction conditions that result in the fastest synthesis of polypeptides. Alternatively, such a system could identify blends of mRNA that result in the synthesis of heterogeneous materials with superlative mechanical properties. In addition to the usual suite of scanning probe tools that can be used to study the mechanics and structure of the synthesized material, the open nature of the reactors mean that the typical array of optical imaging methods used in synthetic biology could be employed to study the result of synthesis in nanoreactors.

While the identified opportunities are meant to highlight the strengths of scanning-probe-based MAPs, there are many other promising material systems that deserve mention. For example, perovskites are a promising fit for scanning-probe-based MAPs as they have recently been synthesized in a combinatorial fashion using scanning probe techniques[37] and are most often characterized using optical approaches. Throughout these examples, it is important to keep in mind what process parameters can easily be controlled and which would be challenging to control. For instance, environmental control systems make it straightforward to control deposition temperature and relative humidity. As for the samples themselves, closed-loop control over feature size has been demonstrated with resolution as good as 20 aL and maximum feature sizes as large as several nL.[38] Controlling the composition of mixtures could be achieved by mixing several samples together, which implies that compositional control would be limited by the ratio of sensing resolution to the sample size, which implies that for 1 fL samples, composition could be controlled to within a few percentage points. There are process parameters associated with scanning probe lithography that can be controlled, such as dwell time and approach speed, although it is unclear what role they would play on nanoreactor composition, so these variables would likely require dedicated study. Finally, post-deposition processing such as illumination or heating can be controlled either in batch or locally. Importantly, the state of the art in scanning probe lithography is advancing steadily, so interactions between MAP users and scanning probe developers has the potential to fruitfully push the envelope in terms of process control.

Challenge 1

While there have been major advances made in the preparation of samples using scanning probes, controlling the composition of samples remains a challenge. For instance, conventional DPN is an open-loop process where the amount of material transferred is only determined after the experiment using other means.[28] Recently, we found that it was possible to use inertial sensing and to measure the quantity of material on a tipless probe and that this feedback could be used to adjust processing conditions to affect closed-loop patterning of fluids.[38,39] While this is a major step forward in controlling the volume of samples, the ability to mix multiple fluids together with a single probe is an open challenge, as efforts to date to control the composition of inks mixed *in situ* do not provide quantitative control.[40,41] Given the evidence that fluid transfer from an atomic force microscope (AFM) to a surface behaves analogously to bulk fluid transport processes,[38,42] it stands to reason that techniques like those used at the macroscale for bulk mixing could be brought to bear, but these require further experimentation.

Challenge 2

While AFMs are themselves robotic systems in that the position and state of the probe are guided electronically using sophisticated software, adapting these to function as part of an integrated system in which samples move both macroscopically and microscopically is an open challenge. From a hardware side, multiprobe systems and motorized sample positioning provide examples of how integration may be achieved.[43] In parallel, there have been recent efforts to control microscopes using open-source and easily integrated programming languages, such as Python.[44] For wide adoption of a MAP based on these ideas, it is important that inexpensive and modular AFM systems are available and that they allow for scripting and advanced instrument control using common programming languages. Beyond this, there is development work that needs to occur to efficiently couple the microscale canvases accessible to an external system to deposit material reservoirs.

Challenge 3

While it is possible to construct statistical arguments to justify the use of extremely miniaturized material samples, there remains the possibility that size effects will manifest in such small volumes. Perhaps the situation where this is most important is when trying to direct chemical reactions in such miniscule volumes, a situation that has been termed a nanoreactor.[45] At these scales, interactions with surfaces could impact reaction kinetics, and concentration gradients could lead to unexpected diffusiophoretic behavior. While this presents a barrier to rapid adoption of chemistries that are well known at the bulk scale, it also presents tremendous scientific opportunities to use scale as a variable to guide and understand chemical reactions and material properties. As an example, scanning probe-produced fluid nanoreactors have been used to produce single inorganic nanoparticles through a sintering process.[46] Here, the discrete nature and small size of such nanoreactors allow for the tailoring of nanoparticle size. In this way, deliberately changing sample size could provide a facile avenue for identifying scale-dependent phenomena.

In addition to the challenges and opportunities described herein, there are several unique opportunities embodied by this type of MAP. For example, there has been a rapid expansion of modular fluid-flow-based MAPs for synthesizing organic reagents and nanoparticles.[47,48] While the volumes in question in such systems are typically thousands if not millions of times bigger than those in consideration here, this indicates that they could be ideal for generating feedstocks for further combinatorial analysis at the attoliter scale. Indeed, the scanning-probe-based MAP described here could be used as a final step of a system in which reagents are synthesized in an as-needed fashion by a robot chemist. Such a system would be empowered to explore open-ended chemical hypotheses that concern far more than simple combinations of known reagents. Indeed, depending on the throughput and efficiency of the synthetic system, it may be of great interest to directly functionally characterize macroscopic samples made from these feedstocks.

It is important to mention that there are commercially available technologies that allow one to reliably print reagents at the picoliter scale, such as the microplotters produced by Sonoplot.[49] These can interact with scanning-probe-based MAPs in several interesting ways. Comparing the two as platforms for mixing reagents for combinatorial experiments, scanning probes have three key advantages: first, there are a tremendous number of scanning probe systems that already exist in materials laboratories that could be converted into MAPs, whereas jet printing systems are presently less common in materials laboratories. Second, a scanning probe system can functionally characterize the features that are created, meaning that a partner analytical system is not required. And finally, the ability to prepare samples using three to six orders of magnitude less volume is expected to translate to a vast increase in the volume of data that is available without increasing the environmental or economic burden of the system. Certainly, the picoliter scales accessible to jet printing systems are an improvement over the conventional approaches used today, but in light of the innumerable varieties of materials and processing conditions, researchers will need every advantage that is possible. Finally, it is worth emphasizing that jet printing technologies partner quite well with scanning-probe-based MAPs. In particular, such a system could present an ideal method for preparing reservoirs that are then mixed at much finer scales using the scanning probe. With the advent of open-source fluid-dispensing hardware, it is easy to envision that such systems could be widely adopted.[50]

One point to make clear is that miniaturizing material samples does not necessarily make it faster to prepare and analyze them. Here, the process of preparing, locating, and characterizing samples could still take on the order of a minute per sample, perhaps longer depending on the processing and characterization required. One common path to higher throughput used widely in the nanotechnology community is parallelization. In scanning probes, cantilever-free scanning probe systems have taken the processes of DPN and performed it with millions of probes in parallel.[51] Such systems can even employ combinatorial inking processes that allow gradients in size and composition to be prepared in a single process.[41] While these approaches are generally less mature than their cantilever-based counterparts, they are unmatched in their ability to generate raw numbers of samples. If these could be combined with equivalently paced analytical tools, it would present a transformative opportunity for a MAP. In a recent report, we found that cantilever-free scanning probes can be used to generate topographical images even though they lack the cantilever typically used in AFM.[52] This example shows the potential for future technological developments to lead to MAPs in which millions of samples are prepared and characterized per minute.

Conclusion

In this white paper, we have discussed the motivation, opportunities, and challenges associated with extreme miniaturization of samples for MAPs. Our conclusion is that scanning probes represent a unique centerpiece technology for this goal as they can prepare and functionally characterize materials samples at extremely fine scales. There are remaining technological needs including the ability to control the composition of samples as they are prepared, robotic integration with external systems both in terms of sample handling and software control of AFMs, and understanding the reaction chemistries in ultra-small volumes. If addressed, this system could have an immediate impact on, for example, the development of resins for additive manufacturing and organic optoelectronic devices and the discovery of novel biomaterials. While there are notable successes in terms of materials synthesis performed in nanoreactors, there are open questions as to what chemistries can be performed at this scale. Interactions with the surface, the need to manage volatility, and the discrete nature of compounds at low concentrations all need to be considered. Thus, there is need for work to establish general principles for understanding what chemistries are compatible with extreme miniaturization, and, as a potentially virtuous cycle, such studies could be enabled by scanning-probe-based MAPs. While there are open questions as to what chemistry can be performed in scanning-probe-patterned nanoreactors, other types of aqueous nanoreactors, such as hollow polymer nanoparticles,[53] have been used extensively for performing synthesis, for example of metallic nanoparticles, increasing confidence in the idea that advances from other fields can be readily translated to scanning-probe-based systems. It is worth emphasizing that AFM systems are commonplace across industry, the national laboratories, and the academy, so if the understanding and techniques required to transform AFMs into MAPs are realized, we anticipate that many researchers can make this transition with minimal effort. For this reason, we expect that industrial partners are strongly incentivized to evolve their existing AFM systems to provide these features. The scanning probe has already been termed a "lab on a tip,"[54] so transforming a scanning probe into a MAP has the potential to shrink by a dozen orders of magnitude the scale at which materials experiments take place.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information should be directed to and will be fulfilled by the lead contact, Keith A. Brown (brownka@bu.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

This study did not generate new data and code.

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AUTHOR CONTRIBUTIONS

Conceptualization, writing, review, and editing: K.A.B.

DECLARATION OF INTERESTS

K.A.B. has a financial stake in TERA-Print, LLC, a company that sells cantilever-free scanning probe instruments. K.A.B. is a co-inventor on patents related to cantilever-free scanning probe lithography (US10203598B2, US9971239B2, and US9766551B2) and cantilever-free scanning probe microscopy (US10989736).

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