Nanosensor Manufacturing Workshop: Finding Better Paths to Products

June 13-14, 2017

About the National Nanotechnology Initiative

The National Nanotechnology Initiative (NNI) is a U.S. Government research and development (R&D) initiative involving 20 Federal departments, independent agencies, and independent commissions working together toward the shared and challenging vision of a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry that benefits society. The combined, coordinated efforts of these agencies have accelerated discovery, development, and deployment of nanotechnology to benefit agency missions in service of the broader national interest. More information can be found at www.nano.gov.

About the Nanotechnology Signature Initiatives

The Federal agencies participating in the NNI have identified focused areas of national importance that may be more rapidly advanced through enhanced coordination and collaboration of agency research and development efforts. These Nanotechnology Signature Initiatives (NSIs) provide a spotlight on critical areas and define the shared vision of the participating agencies for accelerating the advancement of nanoscale science and technology to address needs and exploit opportunities from research through commercialization. They are intended to be dynamic, with topical areas rotating and evolving over time. More information about the NSIs can be found at www.nano.gov/signatureinitiatives.

About this document

This is the report of the NNI Nanosensor Manufacturing Workshop: Finding Better Paths to Products, held on June 13-14, 2017, in Arlington, VA, organized by the National Nanotechnology Coordination Office (NNCO) in support of the Nanotechnology for Sensors and Sensors for Nanotechnology Signature Initiative (Sensors NSI). The workshop report was developed through the contributions of the workshop participants, including representatives from U.S.-based companies producing nanotechnology-enabled products and from NNI agencies participating in the Sensors NSI. Any opinions, findings, conclusions, or recommendations expressed in this report are those of the meeting participants and do not necessarily reflect the views of the United States Government or the meeting participants' parent institutions. This report is not a consensus document but rather is intended to reflect the diverse views, expertise, and deliberations of the meeting participants.

About the cover

Researchers at Iowa State University have exploited a versatile, high-resolution method to pattern and transfer graphene-based sensors onto flexible tape substrates. Using this method, a plant tattoo sensor was created, and real-time measurements of water use were obtained. This low-cost, versatile, and flexible method can be applied in the development of other wearable sensors.

Photo courtesy of Liang Dong/Iowa State University. See *Advanced Materials Technologies*, 2017; 2 (12): 1770055 for details (https://onlinelibrary.wiley.com/doi/epdf/10.1002/admt.201770055).

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Key Takeaways

The National Nanotechnology Initiative (NNI) hosted the Nanosensor Manufacturing Workshop: Finding Better Paths to Products, in support of the Nanotechnology for Sensors and Sensors for Nanotechnology signature initiative (Sensors NSI), on June 13–14, 2017, in Arlington, Virginia. Participants, including Federal, private, and academic stakeholders, surveyed the ecosystem for taking a nanotechnology-enabled sensor from the research lab to production. Important issues related to manufacturing such as fabrication, testing, and product performance were examined. Key findings included the following:

- Performance and materials specifications play a critical role in guiding product development and can facilitate communication of technical requirements between sensors developers and their suppliers, manufacturers, and customers.
- The availability and reliability of commercially sourced nanomaterials may be uncertain, posing a unique challenge for developers of nanotechnology-enabled sensors. These uncertainties will likely diminish as nanomaterial production processes mature.
- Sensor testing can be improved by proactively creating a tiered testing strategy that spans the entire development process and by ensuring access to appropriate testbeds, either by building the testbeds in-house or working with an outside organization. While sensor arrays often provide powerful analytic capabilities, the inclusion of multiple sensor types can vastly complicate the testing process.
- Attaining reproducible performance can reduce the need to fully test and calibrate every sensor in a large batch. Reproducibility depends on many factors such as fabrication tolerances, failure modes, and materials reliability.

Background

The demand for sensors continues to grow across sectors and applications ranging from homeland security and defense to healthcare and precision agriculture. Many technical challenges—such as power supply, lifetime, and size—must be addressed before this demand can be met and widespread adoption occurs. Recognizing the opportunity for nanotechnology-enabled sensors to provide unique solutions to many of these challenges, the Sensors NSI was established under the National Nanotechnology Initiative to facilitate interagency communication and coordination of research and development of both nanotechnology-enabled sensors and sensors to detect and quantify the presence of nanomaterials.

Critical aspects of nanosensor manufacturing include components related to technical performance (e.g., specificity and sensitivity), usability factors (e.g., sampling readout and integration), and fabrication considerations (e.g., scale-up and reproducibility). This workshop, focused primarily on technical manufacturing issues, was organized as part of a suite of activities that the Sensors NSI has undertaken to build community, bolster the commercialization ecosystem, and address the scientific challenges related to the development and commercialization of nanotechnology-enabled sensors. The event consisted of plenary presentations, a speaker panel, and an interactive activity in which participants discussed the scale-up of a hypothetical sensor technology to explore themes from the plenary sessions in a more tangible manner. This document provides a summary of the workshop conversations and does not represent the views of the Federal Government. More information about the event is available on the workshop webpage: https://www.nano.gov/nanosensormanufacturing. Future updates from the Sensors NSI will be available at www.nano.gov/SensorsNSIPortal.

Standards and Specifications

Conversations at the workshop explored how issues such as market fragmentation may impede the development of new standards. Comparisons were made to previous attempts to develop standards for microelectromechanical systems (MEMS) and microfluidic devices. The wide range of potential applications for MEMS and microfluidic devices creates a broad and fragmented market, with many small companies implementing different approaches. When large companies with multiple suppliers identify specifications, the market can begin driving toward standardization. The markets are still too small and fragmented to facilitate standardization for MEMs and microfluidic devices, and the markets for nanotechnology-enabled sensors may also face the same challenges.

Speakers discussed the need for performance and materials specifications at length and in technical detail during the workshop. When companies consider incorporating a new material into a product, the lifetime and stability of the material are key parameters. For example, one presentation described a company's interest in conformal, flexible substrates built with printable nanomaterials for use as ion or electron sources in smoke detectors. Because smoke detectors must last a decade, researchers are specifically looking for materials that are not only stable under room and elevated temperatures, but also have a long lifetime. This comment sparked a discussion on the important role that performance and materials specifications play, both in guiding product development and in facilitating a common understanding between sensors developers and their suppliers and customers.

Federal Resources for Sensors Developers

During a plenary panel, speakers identified Federal programs and facilities that they had utilized while developing and commercializing their technologies. Resources mentioned included single-investigator and research center awards, Small Business Innovation Research (SBIR) awards, public-private partnerships, business training programs, and research infrastructure such as characterization and fabrication tools and equipment that are too expensive for companies to purchase on their own. Specific examples cited included the NextFlex Manufacturing Institute (a Department of Defense-supported public-private partnership), the National Science Foundation's Innovation Corps, the Small Business Administration-supported SCORE mentorship program, the Center for Nanoscale Science and Technology (CNST) NanoFab at the National Institute of Standards and Technology (NIST), and the Army Research Lab's Open Campus initiative.

Figure 1. A clean room at the CNST NanoFab at NIST. This facility provides users with access to state-of-the-art characterization and fabrication tools in addition to technical expertise. Image credit: J. Garcia, NIST.

Product development can be greatly impacted by application-dependent specifications. For example, sensors for the automotive and smartphone sectors have different requirements for parameters such as lifetime, packaging size, and form factor. By engaging with potential customers as early as possible, sensors developers can better understand the customer and market specifications. These application-specific requirements can help the developer evaluate which markets to pursue and, once a target market is chosen, can also guide product development.

The product development process is often iterative, and it can be helpful to group performance specifications into categories of "drop-dead," "must-have," and "nice-to-have." For instance, in the smoke detector example given above, a ten-year lifetime would be a drop-dead requirement. It is important for developers and their customers to have an honest conversation about what specifications are attainable in a given time frame for a given cost. Once the developer builds a sensor based on these specifications, the customer and developer collaboratively evaluate the prototype and its performance and revise the specifications as necessary. Materials specifications can include parameters such as purity, size, and stability. Materials can greatly impact key sensor performance specifications such as lifetime and reliability. With clear materials specifications, the developer communicates requirements to nanomaterials suppliers, and if the product is not consistent, defective materials can be returned more easily.

Materials Selection and Supply Chain

The importance and complexity of supply chain management was a recurring topic of conversation throughout the workshop. Fabricating a product often requires many material inputs and a variety of chemical and/or physical processes. For example, one speaker noted that 35 to 40 different processes may be used to make a given sensor, with many different material inputs from a number of different vendors. Qualifying material inputs and managing suppliers is essential. In addition to testing upon receipt, materials need to be properly stored to minimize changes (e.g., degradation, aging) over time.

While supply chain issues can impact all sensors developers, supply chain management is particularly important for small businesses and can make or break a startup company. For example, one speaker recounted the need to find an alternative supplier for carbon nanotubes (CNTs) when an existing vendor went out of business. Not only did the company have to qualify the nanotubes from the new supplier, which was time consuming and expensive, but it also had to modify its production process because the new nanotubes had different bulk densities and hydrophobicities than the previous nanotubes. Another panelist described challenges with batch-to-batch variability in zinc selenide nanoparticles. At one point, the supplier was providing nanoparticles that were about four times larger than what had been ordered, and it took six months for the vendor to provide nanoparticles that matched the order specifications. These anecdotes illustrate both the importance of developing clear materials specifications and of qualifying materials from multiple vendors.

Many companies may eventually decide to use contract manufacturers to scale up their production processes. Materials and supply chain issues remain a key consideration for transferring production to contract manufacturers. For instance, some contract manufacturers will only use a predefined set of materials in their workhorse tools to avoid contamination. Proactively working with both suppliers and manufacturers to understand what materials and processes will be compatible can ease the transition to a contract manufacturer.

Interactive Nanoscrimmage

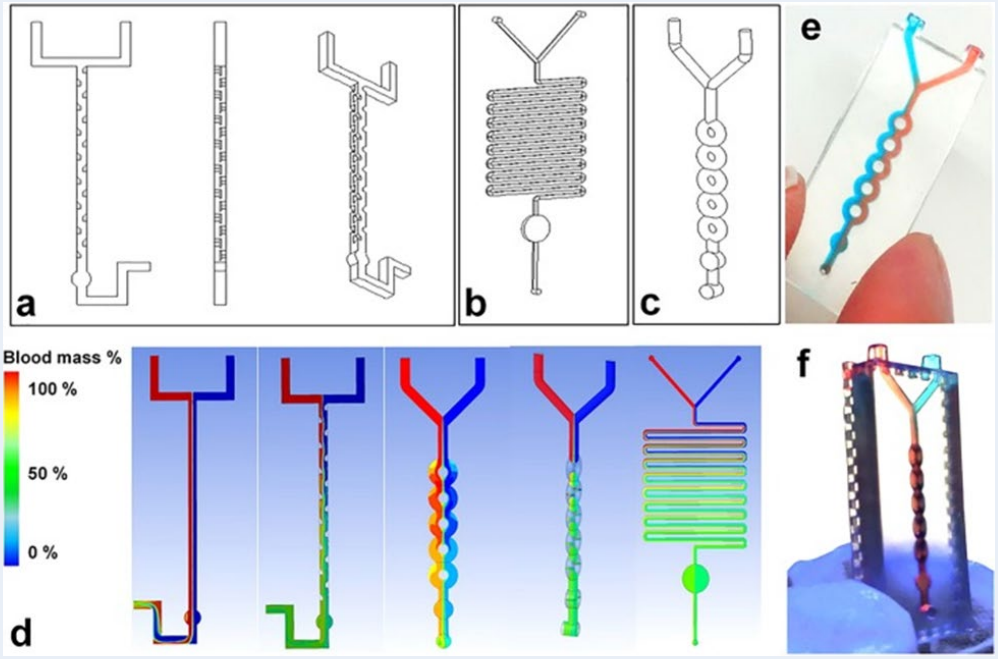

Figure 3. CAD design (a-c), simulation (d), and photos of microfluidic channel and photo (e, f) of 3D-printed microfluidic mixer & sensor, which served as one of two scenarios during the interactive "scrimmage" at the workshop. Image adapted from Biomicrofluidics *10, 054113 (2016) with the permission of AIP Publishing (https://doi.org/10.1063/1.4964499).*

The workshop included an interactive "scrimmage," in which participants walked through a hypothetical scenario of planning the scale-up or migration of a technology platform. Workshop participants were divided among four teams, and each team addressed one of two hypothetical technologies (a 3D-printed microfluidic sensor or a conventionally fabricated CNT gas sensor) and one of two application areas (environmental monitoring or biomedical). The teams discussing the microfluidic sensors considered either the measurement of arsenic in water (environmental monitoring scenario) or the detection of a biomarker for pancreatic cancer in blood (biomedical scenario). The teams working with the hypothetical CNT gas sensors discussed either the measurement of nitrogen dioxide in air (environmental monitoring scenario) or the measurement of a biomarker for lung cancer in breath (biomedical scenario). Specific details about the technologies and application areas are available on the workshop website. Each group was asked to address technical topics related to manufacturing quality control and scale-up. Conversations during the activity provided concrete illustrations of many of the themes and challenges that were discussed elsewhere during the event. Specific highlights related to materials selection, testing, and reproducibility are summarized below.

Participants in the nanoscrimmage discussed, among other topics, issues related to material selection, functionalization, stability, supply, and safety. The gold nanoparticles used in both hypothetical microfluidic devices are readily and cheaply available for purchase. The lifetime of the device would depend on the stability of the gold nanoparticles. Based on a preliminary analysis with the Nano Guidance for Risk Informed Deployment (NanoGrid) tool developed at the U.S. Army Engineer Research and Development Center, neither the gold nor the silica nanoparticles would present significant safety concerns. The plastic that is chosen for the microfluidic devices would need to be carefully chosen and/or functionalized to impart the desired stability and hydrophilicity.

For both hypothetical gas sensors, the manufacture and functionalization of the CNTs was noted as a critical technical challenge to address. A reliable supplier would need to be identified with appropriate quality control processes, including the removal of surfactants, metal impurities, and other contaminants. The CNTs would also need to be functionalized with the molecule of interest, and the functionalization of nanotubes on a large scale could be a significant challenge for manufacturing.

With regards to testing, the protocols for the biomedical sensors are subject to review and approval by the Food and Drug Administration. For the hypothetical CNT-based breath sensor, testing would be simplified by the fact that breath is consistent in temperature and humidity. The hypothetical CNT-based environmental sensor might be deployed in a wide range of settings that could introduce potential interferences (particulate or chemical) that would need to be addressed during testing. Based on previous experience with failed sensors in the field, several participants suggested thorough field tests for the CNT-based environmental sensor to avoid complications from wildlife infestations. For both hypothetical microfluidic devices, participants suggested tests to determine detection limits, sensitivity, false positives, and durability. The water tested with the microfluidic arsenic sensor could vary widely from site to site (e.g., differing levels of salinity, various microbial and chemical contaminants), and the sensor developer would need to consider whether the other chemicals or microbes in the water might inhibit the signal or provide a false positive.

On the topic of reproducibility, it was noted that the design of the microfluidic devices would need to account for fluid properties such as viscosity through modifications to, for example, the surface chemistry, shape, and size of the channel to ensure reproducible mixing of solutions. While the prototype microfluidic sensors may be made via 3D printing, injection molding or stamping may be more efficient and reproducible methods for mass production. For many, if not all, of the hypothetical technologies, an array of sensors could assure better reproducibility and allow for multiple test channels, including a control. The use of a sensor array might be particularly helpful for the CNT-based sensors to accommodate any to batch-to-batch variability in CNT quality as well as variability in the drop-cast films. Averaging results across multiple sensors can help minimize batch effects. Large clinical samples could help ensure reliable statistical results for the CNT breath sensor. Multiple CNT sources may be needed for different functionalizations in the array, and the degree of functionalization in each individual sensor would need to be quantified because small changes in properties like packing density can have a large impact on performance. For the CNT breath sensors, the device designer needs to control for external factors such as what the test subject had for lunch. For the CNT NO_2 sensor, it might help to keep the array at a slightly elevated temperature to reduce drift and to eliminate temperature-dependent results.

Testing

Thorough and appropriate testing is required to develop sensors that will be reliable in the field. Developers often postpone this critical step until late in the product development cycle and devote too few resources to testing. Further complicating testing is that widely accepted testing and characterization protocols may not be available; each company might need to develop its own testing schemes. A well-executed tiered testing strategy can provide vital information to guide and inform product development at key steps along the way. For example, during early-stage research, tests that yield data on performance parameters such as humidity interference and response stability can guide sensor design, while later-stage product development requires more quantitative information. Even then, later-stage testing can be done in multiple tiers, with initial tests furnishing information quickly. Final adjustments can be made based on those results before the most complex and expensive measurements, such as the characterization of reliability and drift, are made.

A sensor testing strategy may need to provide information on the following performance parameters: response and recovery times; sensitivity; selectivity; receiver operating characteristic curve; sensor-to-sensor reproducibility; sensor repeatability; relative humidity effects; temperature effects; dynamic range; drift; and lifetime. Of these parameters, sensor-to-sensor reproducibility and relative humidity effects were mentioned as particularly important. Relative humidity effects tend to dominate in gas sensors because water is present in higher concentrations than the analyte of interest in real-world environments. Sensor-to-sensor reproducibility is critical because it is not practical to test every sensor that is produced. When the sensors are reproducibly made, testing and calibration results can be transferred from one sensor to an entire batch. Some sensors are poisoned during use, and an extensive calibration would impact the sensors' lifetimes. In this case, it would be very useful to make limited tests per lot. Many biomedical devices are designed with a built-in test to verify that the sensor is working. One well-known example of such a "double run" is the control line on a pregnancy test.

There are many practical issues to be addressed when designing testing systems. A primary factor, particularly for startup companies, is cost, which can impact the decision of whether to buy or to custom build the testbed. Ideally, the testbed is versatile enough to reproduce most conceivable use conditions. This versatility should also include the ability to test sensors, packages, modules, and systems because fully packaged devices contain many potential failure points (e.g., membranes, encapsulants, and dyes) and the test results for an unpackaged sensor may not translate to the fully packaged device. Minimizing testbed downtime is also a key consideration. For example, a robust system will minimize downtime for maintenance and repair, and a well-designed testbed will be able to switch between testing conditions with relative ease and speed. As a company scales up production, rapid, high-throughput testing becomes important. Another useful testbed feature is the ability to upgrade the system for future testing programs or products.

In addition to the practical challenges outlined above, there are also many technical requirements for accurate and reliable tests. For instance, in a testbed for gas sensors, the vapor generation needs to be reproducible and stable. Vapor sources—including calibrated gas standards, which can degrade over time—need to be regularly tested. Temperature and relative humidity stability are also key. Different volumes of gases will be mixed when testing sensor performance over a range of concentrations, and efficient mixing across all concentrations is vital. Analyte-specific characteristics also need to be addressed. For example, hydrazine requires additional considerations in testbeds because it is highly reactive and very "sticky," which can lead to non-uniform delivery or to carryover effects in subsequent tests from hydrazine that remained in the chamber. The integration of the sensor with the testbed is also important. It can be helpful to specify a standard sensor format and to design for side-by-side testing, which can shed light on how multiple sensors from the same batch or across several batches perform under identical conditions. Testbed measurements need to be validated to verify that no unexpected contamination occurred and that the correct concentration of analyte was delivered. For example, gas chromatography-mass spectrometry could be used to validate a gas testbed. Tests need to be repeated enough times to generate statistically significant data.

The topic of testing sensor arrays was discussed extensively. A sensor array can be a powerful tool, particularly when it combines multimodal sensors that measure different parameters. For example, a flame has signatures in the visible, infrared, and ultraviolet ranges. If a sensor is only measuring ultraviolet light, it might give a false positive for sunlight. Integrating sensors for visible, infrared, and ultraviolet on one platform may reduce the false positive rate. Sensor arrays also present many unique challenges, such as different sensor response times or signal strengths, sensor-sensor interactions, and noise. Further, adding additional sensors to an array does not always make a better product; it may just increase the number of false alarms without increasing recognition. Another issue is that each sensor in a heterogeneous array will drift independently. Calibrating and compensating for this drift across multiple sensors can be quite complex. Often the greatest challenge is developing the probabilistic models that relate the data from multiple sensors to the specific application and range of potential conditions. It has been shown that one type of sensor array, the electronic nose, works best in a closed and controlled environment. It is more challenging to use the electronic nose in an open environment where the developer cannot test for every potential variation.

Naval Research Lab Sensor Testing Resources

The U.S. Naval Research Laboratory (NRL) has a variety of testing resources and facilities that are available for sensors developers. Researchers at NRL have developed the Trace Explosive Sensor Testbed (TESTbed), as well as TV-Gen, a smaller, portable system. The TESTbed features six identical sample ports, four vapor generation sources, humidity control between 0 and 85%, and an online validation system. The system can be used to test sensors with a variety of explosive chemicals. For example, TESTbed can test trinitrotoluene (TNT) concentrations between 10 parts per trillion and 10 parts per billion. The TV-Gen system features two easily exchangeable manifolds—one for the control and one for the analyte—and a single sensor port. The vapor system is contained in an oven set to 130°C to prevent adsorption.

NRL also has a number of specialized high bays that can be used for sensor testing. The high bays recreate key environments and bridge the gap between bench science and field experiments. The tropical high bay simulates a Southeast Asian rainforest, with live plants, a stream, pond, and appropriate terrain. The temperature is held at 80°F with 80% humidity, and the high bay can generate up to six inches of rain per hour. The desert high bay provides sand and rock, and includes a wind generator to create blowing sand conditions. Three water tanks are available in the littoral high bay (which recreates conditions close to the shore in a sea, lake, or river) for evaluating sensors. Finally, the sensor lab is available to test and calibrate a variety of individual chemical and biological sensors or complete sensor systems. This fully equipped laboratory is designed to serve as a test platform for sensor prototypes prior to full-scale field demonstrations. The sensor lab includes an ambient air test facility and several environmental chambers.

Figure 4. Image of the desert and tropical high bays at the Naval Research Laboratory. Image credit: U.S. Naval Research Laboratory.

Reproducibility

Reproducibility was a common theme woven throughout the workshop conversations, with extensive discussions of technical issues related to device design, fabrication, and performance. Creative design approaches to ensure repeatable performance were discussed. For instance, in a CNT junction, a single nanotube across the gap may not provide sufficiently reproducible results. However, if the device is designed with several CNTs across the gap, the average response across many nanotubes is more likely to give a statistically significant and repeatable result. In another device design example, one speaker described an ink that was not printing uniformly at the ends of a line. To compensate for this limitation, the line was made longer so the variation occurred outside of the interconnect attachment to give reproducible performance.

Potential failure modes are an important consideration during device design. Redundant design may not be effective if all the sensors fail via the same mechanism (e.g., poisoning by the same gas). However, designers can take a range of approaches, such as waiting to expose or turn on a redundant sensor until after the initial sensor has failed, to address this challenge.

During device fabrication a number of issues, such as materials variability and fabrication tolerances, can greatly impact reproducibility. It is important for device designers to take device physics into account when determining acceptable fabrication tolerances because the physical processes can have linear or higher-order effects depending on phenomena of interest.

Summary

On June 13–14, 2017, the National Nanotechnology Initiative hosted the Nanosensor Manufacturing Workshop: Finding Better Paths to Products. Federal, private, and academic stakeholders participated in discussions that explored technical issues associated with the manufacture of nanotechnology-enabled sensors. Conversations covered topics ranging from fabrication to testing to product performance. The importance of performance and materials specifications was a key theme during the event. These specifications can help guide sensor development and enable communication among developers, suppliers, manufacturers, and end users. The use of commercially sourced nanomaterials can pose unique challenges related to material availability and reliability. These challenges reflect the early stages of nanomaterial production and will likely dissipate as production processes mature. It was noted that testing is a crucial aspect of sensor development and can be improved through the proactive use of a tiered testing approach that spans the development process. The need to test and calibrate every sensor in a batch can be minimized when sensor performance is reproducible. However, device and performance reproducibility depend on a multitude of factors, including fabrication tolerances, failure modes, and materials reliability.

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