Process Principles for Large-Scale Nanomanufacturing

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Abstract

Nanomanufacturing—the fabrication of macroscopic products from well-defined nanoscale building blocks—in a truly scalable and versatile manner is still far from our current reality. Here, we describe the barriers to large-scale nanomanufacturing and identify routes to overcome them. We argue for nanomanufacturing systems consisting of an iterative sequence of synthesis/assembly and separation/sorting unit operations, analogous to those used in chemicals manufacturing. In addition to performance and economic considerations, phenomena unique to the nanoscale must guide the design of each unit operation and the overall process flow. We identify and discuss four key nanomanufacturing process design needs: (a) appropriately selected process break points, (b) synthesis techniques appropriate for large-scale manufacturing, (c) new structure- and property-based separations, and (d) advances in stabilization and packaging.

Keywords

nanotechnology, nanomanufacturing, process design, scale-up
INTRODUCTION

Rapid progress in nanomaterials synthesis over the past few decades has generated high expectations for industrial nanomanufacturing and a significant investment in its development. Carbon nanotubes, perhaps the most well-known nanomaterial, are commercially used in products ranging from rechargeable batteries to lubricants (1). These products contain and can tolerate heterogeneous nanotube mixtures, where there is variability in the structure of individual carbon nanotubes. Homogeneous mixtures of semiconductor nanocrystals, however, now find application in flat-panel displays (2), but the quantity of nanocrystals needed for the entire flat-panel display market is relatively small. These two examples highlight the dichotomy of present-day nanomaterials manufacturing. It is possible to achieve heterogeneous nanomaterials at large scales or homogeneous nanomaterials at small scales. However, there are large classes of applications for which both homogeneity and large scales are required. Consider the production of solar cells based on semiconductor nanowires (3). Nanowires with carefully controlled morphologies and dopant profiles must be manufactured at the thousands-of-kilograms level to impact the power generation market. Such capabilities remain largely off-limits. This article identifies obstacles to successful nanomanufacturing technologies and outlines a roadmap to overcome them.

The term nanomanufacturing means different things to different people. Here, we are interested specifically in the manufacture of products that derive crucial benefits from building blocks with a characteristic length scale in the nanometer range. By analogy to macroscopic manufacturing, we refer to these building blocks as nanoparts. Standard nomenclature constrains the characteristic length scale of a nanopart to between 1 nm and 100 nm (4) because this is the regime in which nanoscale structure most impacts nanopart properties. Because the physiochemical processes that govern nanomanufacturing are active both below and above 100 nm, however, we include nanoparts with characteristic length scales up to a micrometer. Correspondingly, we also refer to microscale (or macroscale) assemblies of nanoparts as microparts (or macroparts).

We focus on nanoparts that derive their functionality from well-defined nanoscale structure. Semiconductor nanocrystals with diameter-dependent optical properties, as used in flat-panel displays (2), are a prime example of such high-definition, functional nanoparts. Nanowire-based transistors would also be included because their device characteristics depend heavily on the nanometer dimensions of the source, channel, and drain regions. However, titanium dioxide nanoparticles, produced with little control over the nanoscale structure for applications in sunscreens and cosmetics, would not fall into this category. Nanoparts may themselves be marketable products (e.g., quantum dots) or assembled into macroparts. An antireflective coating consisting of aligned nanotubes (5), a thermoelectric material composed of composition-modulated nanowires (6), an integrated circuit (IC) composed of nanowire-based transistors (7), and a nanocrystal solar cell (8) would all qualify as macroparts.

We are interested in nanopart manufacturing at the kilogram-per-day scale and above. Although this threshold is somewhat arbitrary and technology dependent, it defines a scale at which engineering considerations such as cost, throughput, purity, and yield are as important as raw performance metrics. One does not have to look further than the electronics or solar industries to appreciate the importance of these factors. Silicon is the dominant material in both industries, even though it exhibits neither the fastest charge transport nor the strongest absorption of sunlight. Silicon owes its preeminence in these markets to a well-established processing knowledge base and supply chain, which have been fine-tuned through decades of use.

Nanomanufacturing at the kilogram scale favors the use of bottom-up syntheses and continuous processes. Bottom-up syntheses create parts of any size (e.g., nanoparts, microparts) by additively combining smaller parts. Nanopart fabrication from molecular precursors containing the nanopart’s constituent elements and the assembly of a micropart from an ensemble of nanoparts are
both examples of bottom-up syntheses. Top-down processes, however, start with larger parts (e.g., semiconductor wafers) and remove material to fabricate smaller parts (e.g., nanowires). The waste associated with material removal generally makes top-down processes untenable at large scale, especially for expensive starting materials or when recycling and repurposing are not viable. Continuous processing, where feed and product materials are constantly delivered to and removed from a process unit (e.g., reactor or separator), respectively, also becomes advantageous at these scales.

Few large-scale commercial nanomanufacturing processes exist despite $24 billion in funding for research and development from the US government alone (9). There are several contributing factors. Processes on the nanometer length scale exhibit physicochemical phenomena that introduce unique challenges. Methods used for laboratory exploration or small-scale manufacturing are often incompatible with the needs of large-scale manufacturing. For example, heat and mass transport become increasingly difficult to control in large-scale processes, which reduces product uniformity and creates the need for separation techniques to remove undesired components. Nanomanufacturing processes have also been developed in a largely compartmentalized fashion when a holistic approach is needed, similar to classical manufacturing processes. The function of individual parts as well as their interactions with other parts of the system must be considered. An automotive alternator, for example, is designed to simultaneously operate at a target efficiency, interface with the engine and electrical system, be mounted inside the engine compartment, and be produced at a rate of tens of millions per year. Similarly, it is not sufficient for nanoparticles to exhibit desired material properties. They must also be produced in sufficient quantity, assembled into structures with higher-order complexity, and interfaced with neighboring nanoparticles or other auxiliary components (e.g., electrodes).

Meeting these manufacturing demands is a worthy goal not only because of the obvious technological rewards. Indirect benefits can be expected from the coupling of nanomanufacturing and nanoscience. Improved nanomanufacturing methods will feed back into nanoscience: Wider availability of highly purified nanoparticles at low cost will simplify many aspects of nanoscience, thus shortening the time between scientific breakthroughs that in turn can stimulate manufacturing progress.

Here, we examine reasons why nanomanufacturing has yet to deliver on its promise and discuss a way forward that leverages the strengths of classical chemical engineering strategies that are not commonly applied in the context of modern nanotechnology. Our discussion is predicated on the conventional notion of process scale-up, where larger processing units are used to process larger quantities of material. This approach to scale-up is based on conventional engineering cost principles (10). Traditionally, operating one large-scale process unit required less labor and capital investment per unit of material produced than operating multiple smaller units. In recent years, improved manufacturing and automation capabilities have driven interest in scale-up via parallel operation of large numbers of small-scale, modular process units. Of relevance for the present discussion, some attempts at nanomanufacturing fall into this category, including microreactors (11, 12) and droplet reactors (13). We refer the reader to this work but do not consider it further here.

We begin our discussion by reviewing the concepts of modular and integrated manufacturing as well as the spectrum that exists in between. An overview of the physicochemical phenomena that govern the processing of nanoparticles is presented next. The central tenets of large-scale chemicals manufacturing, primarily the combination of synthesis/assembly and separation/sorting steps, are subsequently introduced. We then describe four critical nanomanufacturing needs. Along the way, we mention several exemplary nanotechnologies but make no attempt to be exhaustive. Excellent summative reviews are available on many of the topics discussed herein, including nanosyntheses (14–17), nanoseparations (18, 19), self-assembly (20, 21), nanopatterning (22–24), and nanodevices (25–27). Notably, throughout this review, we include introductory content.
for both chemical engineers and nanotechnologists (e.g., materials scientists, physicists) so that each discipline may better understand the other’s approaches and, in doing so, engage in a more productive interdisciplinary dialogue.

**COMPARISON OF MANUFACTURING PARADIGMS**

All products and devices with advanced functionality require multiple production and assembly steps to achieve hierarchical structural complexity. This applies to macroscale products like buildings, airplanes, and computers, as well as to devices that are more commonly associated with nanomanufacturing, such as electronics and batteries. Even advanced molecular-level products like multi-block copolymers, pharmaceutical active ingredients, and nanocomposite materials require multistep manufacturing processes.

When assessing such processes, it is valuable to distinguish between two paradigms: integrated and modular manufacturing. In a completely integrated manufacturing process, the input consists of raw materials without advanced functionality (e.g., concrete, steel, or silicon wafers), whereas the output of the process is a fully functional final product (e.g., a building, car, or IC). A completely modular manufacturing process, by contrast, relies on distinct subprocesses to produce intermediate modular parts that can either serve as feedstock for subsequent assembly steps or be sold for use in other, external processes (28). Integrated paradigms do not involve breaks in the manufacturing process during which the assessment, separation/sorting, and reassignment (e.g., recycling, disposal) of intermediate parts takes place, whereas modular manufacturing paradigms rely heavily on such breaks to screen parts before transfer to subsequent process steps.

Successful manufacturing processes generally exhibit aspects of both integrated and modular paradigms, but examples of commercial processes toward either extreme do exist. The semiconductor industry, on the one hand, employs highly integrated manufacturing processes. ICs are produced in a sophisticated, multistep process, where sorting based on functionality occurs predominantly at the final product level, when entire ICs are tested. On the other hand, computers and cell phones are good examples of modular manufacturing: Functional products are assembled from modules (e.g., power supply, memory, processor, graphics card, display) that already possess inherent complexity and functionality themselves. These modules can be either produced in house or obtained from separate suppliers.

These examples illustrate that it is crucial to make decisions about trade-offs between integrated and modular manufacturing for specific products based on available technology. A main disadvantage of integrated manufacturing is that a sequence of many processing steps without quality control and sorting/purging of defective modules can adversely affect the yield and productivity of the overall process, unless each individual step is extremely reliable. The production of ICs at economically acceptable yields, for example, imposes extreme quality demands on individual processing steps, because yields in a multistep process are multiplicative. In a 100-step process, even 99% yield for each step leads to an overall process yield of only 37%; a 10-step process could achieve the same overall yield with a much less demanding 90% yield per step. **Figure 1** quantitatively illustrates the accumulative effect of the yield of each step on overall process yield. Balancing the number of processing steps and efficiency of each step should be a major consideration during process design.

**QUIRKS AND PERKS OF THE NANOSCALE**

Whereas the examples mentioned above may serve as illustrations from everyday life, applying these concepts to nanomanufacturing requires a better understanding of the phenomena that operate at the nanoscale. A variety of factors that are important for manufacturing processes depend
Figure 1
Overall yield for a multistep process as a function of the number of processing steps and yield per step. The overall yield is strongly affected when the per-step yield drops even slightly and forces an optimization between the number of processing steps and the efficiency of each step.

systematically on the length scale of the parts that must be assembled. Figure 2 illustrates some of these factors, which conspire to make the demands and potential rewards of nanomanufacturing different from those of manufacturing smaller molecular parts and larger macroparts.

Surface-to-Volume Ratio
Nanoparts exhibit large surface area-to-volume ratios. Every atom in a nanopart is close to an interface, with a significant fraction located directly at an interface. Thus, surface and interfacial phenomena play a much bigger role for nanoparticles than they do for larger parts. Unfortunately, in many applications, it is precisely the interfaces that constitute the dominant source of performance loss. Photovoltaic devices and light-emitting diodes composed of nanoparticles (e.g., nanocrystals or nanowires), where recombination of charge carriers at interfaces limits efficiency, are cases in point (29). Interfacial problems can arise from poor passivation (i.e., dangling bonds) and/or imperfect contact between nanoparticles. The number of ways to achieve a perfect interface is small (i.e., low entropy), whereas the number of ways to achieve a poor interface is large (i.e., high entropy). The 3D nature of nanoparticles often leads to the contacting of different facets, which leads to the equivalent of a grain boundary even when the nanoparticles are composed of the same material. The interfacial challenge is exacerbated when nanoparticles composed of different materials, and often different crystal structures, must be interconnected.

Nonetheless, the ubiquitous proximity of interfaces and the strong confinement of phonons, photons, and/or electrons also offer distinct advantages. Thermoelectric materials are an excellent example. These materials generate an electric voltage in response to a temperature difference across the material and can thus be used to convert (waste) heat into (valuable) electric energy. Doing so efficiently requires materials that are capable of maintaining large temperature gradients while simultaneously facilitating electric energy transport (i.e., high electrical and low thermal conductivities). This is a tall order, because electrical and thermal conductivity usually go hand in hand, making it difficult to raise one without the other (7). Nanoparts offer a solution to this problem: The closely spaced interfaces of semiconductor nanowires, for instance, strongly scatter phonons, while still permitting efficient charge carrier transport, thus enhancing the ratio of electrical to thermal conductivity (30–32).
Figure 2

The nanoscale occupies a regime intermediate to the molecular scale and macroscale. Thermal motion, interaction specificity/selectivity, and van der Waals forces combine to make nanomanufacturing challenging. Thermal motion, which helps nanoparticles and assemblies access different configurations, is larger at the nanoscale compared with the microscale, though less pronounced than at the molecular scale. Interactions at the molecular scale (i.e., chemical bonding) or at the macroscale (i.e., locks and keys) are or can be specific and selective. At the nanoscale, unless designed into a nanopart, there usually is no inherent specificity or selectivity. Finally, the strength of van der Waals forces relative to other forces becomes maximal at the nanoscale and promotes irreversible agglomeration.

The short length scales between interfaces in nanomaterials also mean that heat, light, or charge can travel fast across an entire nanopart volume, and that transport limitations familiar from larger structures can often be avoided. This behavior is central to the scaling of transistors and the associated improvements in IC performance over the past several decades (33). The transit time of electrons decreases as the transistor channel length decreases, enabling faster switching and lower power requirements. Strain relaxation promoted by interfaces also tends to enhance structural pliability relative to the bulk. Heterogeneous nanoparticles with defect-free heterointerfaces are commonplace even for lattice mismatches exceeding 10% (34). Compositions and crystal structures absent on larger length scales are also possible in nanoparticles (35). These differences, which can result from thermodynamics or kinetics, greatly expand the available property space.
Thermal Motion

Large stochastic fluctuations owing to thermal forces are another characteristic feature of nanoparticles, and these, too, introduce both challenges and benefits (Figure 2). At the micro- and macroscale, parts can be manipulated in the deterministic fashion familiar from the macroscopic world: via handling, sorting, and positioning objects mechanically, sometimes with the help of fluid flow [as in inkjet printing (36) and 3D printing (37)] or with external fields [as in the manufacturing of electrophoretic displays (38, 39)]. For nanoparticles, however, thermal forces can no longer be neglected. Thermal fluctuations make synthesis and assembly processes a matter of statistics, which inherently reduces the achievable fidelity. At the same time, the randomizing action of thermal motion facilitates collective reorganization and an efficient exploration (fast sampling) of configurational phase space without the need for mixing. Although fluctuations around the thermodynamically optimal configurations can be strong, the risk of missing target states during self-assembly by becoming kinetically trapped in nonoptimal, metastable configurations is significantly reduced (40). In summary, strong thermal motion at the nanoscale severely hampers external manipulation while simultaneously facilitating self-assembly.

Direction and Selectivity of Interactions

Interactions between nanoparticles are quite distinct from the interactions of their molecular and macroscopic counterparts (Figure 2). At the molecular (and atomic) level, quantum mechanical constraints lead to interactions that can be highly directed and selective. For this reason, atomic assembly results in products (i.e., molecules) with extreme structural uniformity. Similarly, specific intra- and intermolecular interactions can produce well-defined, higher-order structures, such as protein-folding states and supramolecular complexes. On the other end of the size spectrum, precise deterministic manipulation and positioning of macroparts can be achieved with tools and fasteners (e.g., nuts and bolts). Assembly at intermediate length scales, by contrast, typically lacks the same degree of precision. For nanoparticles, the directed and selective interactions of their constituent atoms or molecules typically combine into a more smeared-out net interaction. The force between two nanoparticles or microparticles can often be described, to a reasonable approximation, by a perfectly unstructured isotropic force (41) that simplifies mathematical descriptions but offers little help in directing the self-assembly of complex objects. Some progress has been made in designing nano- and microsized colloidal particles that display directed or selective interactions in the absence of external fields. Examples include the use of complementary DNA grafts for surface-selective binding (42, 43), schemes to produce particle shapes with geometric fits for shape-selective binding via depletion attraction (44, 45), or strategies to pattern particle surfaces for directed interactions (46–48). In most cases, the complexity and fidelity of the currently achievable assembly structures are limited, although DNA nanotechnology in particular has made significant strides toward programmable self-assembly (49–51), with some of the most impressive demonstrations involving complexes of pure DNA as building blocks (52, 53). The production of nanoparticles with an interaction sophisticated enough to produce complex, self-assembled structures remains, by and large, quite challenging—even at the laboratory scale.

Van der Waals Interactions

Van der Waals attraction plays a prominent role on the nanoscale and deserves special mention. Although the van der Waals force can be repulsive between dissimilar materials interacting across a liquid medium (41, 54), attractive van der Waals interactions are much more common. For
nanoparts, the relative strength of this attraction compared with other interaction forces tends to be higher than it is for smaller or larger objects (Figure 2). This behavior obviously cannot be rationalized simply by the surface-to-volume ratio, which decreases monotonically with increasing object size. In principle, the strength of the van der Waals interaction between two parts is closely related to the number and excess polarizability of atoms/molecules in each of the interacting parts, and should therefore increase rapidly with the part size. For instance, two spherical nanoparticles of 10 nm in diameter experience a much stronger van der Waals interaction than two spheres of half that size with otherwise identical properties. To appreciate why the relative importance of van der Waals interaction does not simply grow with part size, but in fact peaks for nanoparticles, one must consider two more parameters: the range of interaction and surface roughness. The van der Waals force decays almost completely within a few tens of nanometers (55). Therefore, the resulting adhesion between contacting parts is determined by their mass in a contact zone of nanoscale thickness (Figure 2). For contacting micro- or macroparts, only a small fraction of the mass lies in the contact zone where it contributes to the van der Waals interaction, whereas a larger fraction of each part can contribute to longer-range body forces (e.g., gravity) that act on the entire part. The surfaces of micro- and macroparts tend to exhibit nanoscale roughness, which introduces void spaces in the all-important contact zone with similar dimensions as the zone itself. These features combine to reduce adhesion as part size increases above the nanometer scale. For nanoparticles, by contrast, their entire volume can contribute to the van der Waals attraction and produce an adhesion force comparable to that of larger, locally rough particles, whereas all other forces are generally scaled down with decreasing part size. As a consequence, nanoparticles are much more prone to aggregation and agglomeration than larger parts. This problem is especially acute in gaseous media, where the Hamaker constant (the key material parameter in van der Waals force expressions) for interacting solids is largest.

THE WHY AND HOW OF CHEMICALS MANUFACTURING

In searching for strategies to overcome the technical challenges of manufacturing at the nanoscale, we might be well advised to take a closer look at an existing industry that has successfully developed processes for the adjacent molecular regime: chemicals manufacturing. Chemicals are produced through a sequence of unit operations that include reactions and separations. Reaction steps convert lower-value feedstocks into higher-value products, whereas separation steps purify the product to maximize its value.

Only in rare cases does the reactor output contain only the target product. For example, the reaction of hydrogen (H₂) and chlorine (Cl₂) forms only hydrogen chloride (HCl), and it does so with 100% yield:

\[
\text{H}_2 + \text{Cl}_2 \to 2\text{HCl}
\]

However, more commonly, the reactor output is a mixture of desired target and undesired by-product species. This situation results from two key reasons: (a) Reactions do not always go to completion, which means that reactant species are present in the reactor output, and (b) multiple reactions often occur in the same reactor and can produce both target and by-product species. For example, the chlorination of ethane (C₂H₆) produces monochloroethane (C₂H₅Cl), which is used to manufacture polyvinylchloride (PVC). However, a second reaction also produces a by-product species, dichloroethane (C₂H₄Cl₂):

\[
\text{C}_2\text{H}_6 + \text{Cl}_2 \to \text{C}_2\text{H}_5\text{Cl} + \text{HCl}
\]
and
\[ \text{C}_2\text{H}_3\text{Cl} + \text{Cl}_2 \rightarrow \text{C}_2\text{H}_4\text{Cl}_2 + \text{HCl}. \]

Separation processes are therefore essential to purify the product stream by leveraging differences in physical and chemical properties (e.g., density, volatility, freezing point) of components in a molecular mixture. For example, distillation exploits differences in the volatility of different components. Final product purification is a goal of many separation processes; however, the separation and recycle of unused feedstock species are also common and greatly influence process economics.

The economic viability of a chemical manufacturing process depends on the relative value of the input and output streams, up-front capital costs, and ongoing operational costs. The cost of feedstocks and waste disposal must be minimized, whereas the value of all product species—target products and by-products—must be maximized. Thus, no refinery is built to produce only gasoline. Refineries produce a range of valuable products, including gasoline, fuel oil, and a variety of gases, that result from the cracking of crude oil (i.e., reaction) and the subsequent fractionation (i.e., separation) of the resulting product mixture. Very few output species are disposed of as waste. Capital and operating costs per quantity of product decrease as productivity increases, which is the main incentive for process scale-up. However, scale-up also poses challenges: In-reactor concentration and temperature variations tend to increase with reactor size, which also enhances the nonuniformity of product mixtures and further drives the need for separations.

This approach to chemicals manufacturing has proved remarkably successful. Today, the chemicals supply chain is largely taken for granted. There exists a highly branched family tree of chemicals that begins with commodities such as ethylene and terminates with highly specialized derivatives such as Kevlar (56). The extreme modularity of the chemicals supply chain provides manufacturers, both large and small, with a range of feedstocks for any given process. Recent efforts to establish a chemicals supply chain based on bioderived feedstocks (e.g., cellulose) underscore the value of this paradigm (57, 58). This model is also equivalent to the personal computer industry, where manufacturers have access to an array of modular components (e.g., microprocessors, graphics cards, hard drives, displays) from which to build computers. Notably, each new commercial process defines additional branch points in the chemicals family tree, which further increases the modularity of the supply chain. The commercial availability of new modular feedstocks often eliminates the need for in-house manufacturing, thereby accelerating new process development and chemical discovery.

**NANOMANUFACTURING AS CHEMICALS MANUFACTURING**

A versatile nanomanufacturing industry would benefit from many of the characteristics of the chemicals manufacturing industry. Here, we propose a conceptual blueprint, which adapts and extends the central tenets of chemicals manufacturing, to guide the development of future nanomanufacturing processes. We define four key process design needs and discuss each in detail below: (a) selection and optimization of process break points, (b) synthesis techniques appropriate for large-scale manufacturing, (c) new structure- and property-based separations, and (d) advances in nanopart stabilization and packaging.

**Selection and Optimization of Process Break Points**

A nanomanufacturing process, which consists of multiple synthesis/assemble and separation/selection steps and produces a range of intermediate nanoparts, must maximize the quality
Comparison of nanomanufacturing processes to produce doped Si nanowires for a thermoelectric device with different levels of modularity. Process A is the most modular, but poor control of interfaces may limit the thermoelectric performance. Process B is more integrated than process A, because nanowires are directly fabricated. Process C, which combines nanowire synthesis and doping into a single step, is the most integrated.

and minimize the cost of the final nanopart. This objective raises important process design questions: What level of nanopart complexity should a single synthesis step achieve? When should separation processes be performed to purge defective nanoparts? At what stage and via what means can nanoparts be assembled into larger-scale micro- or macroparts?

Consider, for example, the manufacturing of Si nanowires (16). These nanoparts hold promise in a range of electronic, photonic, and energy conversion applications (26). In the case of thermoelectrics (59, 60), nanowire diameter, length, and dopant concentration all influence the thermoelectric figure of merit, known as ZT. Surface roughness is also an important structural parameter (61) but is omitted here for simplicity. Among the selection of possible processing routes illustrated in Figure 3, which is most appropriate for thermoelectrics? Process A is based on the synthesis of nanoparticles followed by assembly and sintering into wirelike structures and consists of the following steps:

1. Synthesis of doped Si nanoparticles
2. Separation based on nanoparticle diameter
3. Separation based on nanoparticle carrier density
4. Assembly of nanoparticle chains
5. Nanoparticle chain sintering (to enhance electrical conductivity)
6. Separation based on nanoparticle chain length and morphology

Process B uses fewer processing steps but requires a more challenging initial synthesis step and final separation step:

1. Growth of undoped Si nanowires
2. Separation based on nanowire length and diameter
3. Doping of nanowires
4. Separation based on nanowire carrier density
Process C has the fewest process steps but increases the complexity of each even further:
1. Growth of doped Si nanowires
2. Separation based on nanowire length and diameter
3. Separation based on nanowire carrier density

The above processes range from highly modular (process A) to highly integrated (process C). There are advantages and disadvantages for each process, but it is not a priori obvious which can be implemented most effectively. Process A, the most modular, leverages the existing commercial availability of Si nanoparticles with well-defined diameters. However, the quasi-spherical symmetry of nanoparticles makes it difficult to assemble nanoparticles into straight, linear chains without branching. As a result, separating mixtures of linear and branched assemblies may be needed, which is generally complicated, because overall mass is not a suitable property for selection in this scenario (see the section titled Synthesis Techniques Appropriate for Large-Scale Manufacturing). Moreover, ZT values for nanostructured Si remain inferior to those for directly synthesized nanowires (32). Process B first synthesizes nanowires, which offer a better combination of thermal and electrical transport, but the postsynthesis doping process may result in unwanted radial dopant gradients (62) and/or morphological changes that may be difficult to detect in separation steps. Finally, process C offers the highest degree of integration and, potentially, nanoparts with the best thermoelectric performance. However, the simultaneous growth and doping of nanowires in the synthesis step may be prohibitively difficult (63–66), especially at the production rates and yields required for large-scale nanomanufacturing. The details that must be considered when partitioning an overall nanomanufacturing process into individual synthesis/assembly and separation/selection steps will ultimately depend on the desired material properties or device function; however, there are several recurring themes that one should consider.

Interface management. When interfaces are critical to material properties or device function, synthesis must be performed in an integrated manner to the extent necessary for high-quality interface formation, rather than relying on postsynthesis assembly of modular nanoparts. Electronic, photonic, and phononic transport at and/or across interfaces are important for devices as diverse as transistors, lasers, light-emitting diodes, thermoelectrics, and catalysts. Semiconductor nanowire growth via the vapor-liquid-solid mechanism, for example, permits the formation of axial or core-shell heterostructures (67, 68), often with compositionally abrupt interfaces (65, 69–71). These capabilities have enabled the fabrication of a range of high-performance electronic (72, 73), photonic (74), and optoelectronic (3, 75) devices. Analogous capabilities and opportunities exist for colloidal nanoparticle syntheses (76). Although the assembly of compositionally homogeneous nanowires or nanoparticles could in principle be used to produce the same devices (Figure 3), performance would likely suffer as a result of poor interface quality.

Multifunctional nanoparts. Significant progress has been made in the fabrication of high-performance nanoparts and the programming of their self-assembly, but the two have yet to be combined in a meaningful way. The utility of nanoparts with exotic properties but that cannot be successfully assembled is limited. Nanoparts that can be assembled but have few useful properties also offer limited utility. The fabrication of nanoparts that combine functional and assembly-directing components, even at the laboratory scale, will be critical moving forward.

Hierarchical assembly. It is impractical to assemble a macropart simply by combining nanoparts in a single process step. Figure 4 shows how, in the case of nanoparts, the growth rate of assembled structures via sequential addition becomes restrictively slow even before reaching
Hierarchical part assembly

Continuous addition of nanoparts

Figure 4

Illustration of the hierarchical assembly required to bridge the nanometer and larger length scales of micro- and macroparts. Solid black line: nanoparts with a volume of 1 nm³ are combined by adding on one nanopart at a time (constant growth rate of 1 nm³ per time step). This type of assembly quickly becomes an inefficient route to increase the size (characteristic length) of the assembled part. Dashed red line: the assembled part grows orders of magnitude more quickly by hierarchical assembly where assemblies after reaching a critical volume (here 1,000 times the previous part volume) are combined at the addition rate of one part per time step. The present example is meant to be illustrative. Different processes would likely carry out part assembly at different length scales. Although this would result in different assembly rates as well as pauses between assembly processes, these differences do not change the conclusion that hierarchical assembly will be orders of magnitude faster than sequential addition.

Decoupling manufacturing rates. Nanomanufacturing processes must also accommodate differences in component design requirements and tolerances. Consider, for example, the manufacturing of large-area, flexible ICs (77, 78). At present, analogous to conventional Si-wafer processing, the manufacturing process is entirely integrated. Top-down patterning techniques are used to define the smallest transistors as well as the largest interconnects. High-throughput patterning techniques (e.g., inkjet printing, nanoimprint lithography) are able to generate the relatively large dimensions of interconnects at reasonable rates (substrate linear velocities of several m/s) (24). These techniques cannot, however, achieve nanoscale channel lengths at similar rates. This long-standing technological challenge continues to constrain the switching speed and energy efficiency of transistors produced in this manner. One solution, which exemplifies the thinking required in nanomanufacturing, is to decouple transistor and interconnect fabrication. Processes for fabrication of modular transistor nanoparts can be selected based on their ability to provide nanometer-scale channel lengths. The vapor-liquid-solid growth of nanowires, which makes it
possible to integrate source, channel, and drain along a single-crystalline semiconductor, is a prime example (79). The resulting transistor nanoparts can then be positioned and interconnected in a separate assembly process, perhaps leveraging the advantageous production rates of the above-mentioned patterning techniques (24).

Synthesis Techniques Appropriate for Large-Scale Manufacturing

Synthesis methods and reactor designs that are appropriate at the laboratory scale are often incompatible with process scale-up owing to heat and mass transport limitations (80). These considerations are well-known in chemicals manufacturing, where fundamental and heuristic strategies have been developed to achieve scale-up from milligrams per batch in the lab to tens of tons per day in commercial processes. Nanomanufacturing is no different, requiring a rethinking of synthesis methods and reactor design. Characteristics of nanoparticle synthesis that deserve specific attention during development of scalable techniques are discussed below.

2D versus 3D. Nanoparticle synthesis scale-up requires, wherever possible, bulk (i.e., in 3D) processes to meet productivity needs. Although this need is readily met by methods, such as colloidal (81, 82) and plasma-based (83) syntheses, many techniques still occur on substrates (i.e., in 2D). Surface-based carbon nanotube (1, 84) and semiconductor nanowire (16, 26) growth, Janus particle fabrication via metal evaporation onto particle films (85), and molding of polymer nanoparticles into complex shapes by embedding them in deformable polymer sheets that are stretched (86) are prime examples of nanoparticle syntheses in 2D. Although syntheses confined to flat substrates are useful for initial demonstrations in the laboratory, areal or 2D scaling cannot offer economically competitive scale-up. The floating catalyst method for carbon nanotube synthesis is exemplary of the 3D approaches that are necessary (87); it enables kilogram-level production of carbon nanotubes by entraining catalyst nanoparticles in the gaseous flow of a tubular reactor. As shown in Figure 5, an analogous approach, dubbed Aerotaxy, is now possible for semiconductor nanowire production (88, 89). For semiconductor nanowires, however, 3D synthesis has yet to match the exquisite structural control offered by 2D substrate-based growth. Circumventing the van der Waals force–driven irreversible agglomeration of nanoparticles and preventing perturbations to synthesis from nanoparticle collisions are key challenges, especially at the high-nanopart densities required for large-scale manufacturing.

Condensed versus gas phase. Condensed (i.e., liquid)-phase syntheses are regularly promoted as simple and scalable relative to gas-phase syntheses. This argument largely stems from the mild reaction conditions of many such methods, which allow simple glass flasks to serve as reaction vessels. The plethora of coordinating ligands available in the condensed phase also allow for tremendous shape and crystal structure control (82). Relative to the gas phase, liquids also reduce the magnitude of nanoparticle-nanoparticle van der Waals forces and sedimentation rates owing to the greater density of the surrounding medium (i.e., solvent). At the same time, condensed-phase methods must contend with solvent waste and, for high-end applications, such as electronics, precursor and solvent purity. Although heat and mass transport are sufficiently fast in liquids in small, laboratory-scale reaction vessels, mixing becomes increasingly challenging upon scale-up. Cross-reactor heat and mass gradients increase product heterogeneity and require additional separation steps to maintain product quality.

Gas-phase syntheses, in contrast, are often argued to be excessively complicated and/or not scalable, especially when high temperatures and low pressure are required. However, there are many examples of successful large-scale gas-phase processes. Nanoparticle (83) and carbon
Figure 5

Large-scale nanowire synthesis via the Aerotaxy process. (a) Metal nanoparticles, which catalyze nanowire growth, are produced, size-selected, and injected into a tubular reactor. Nanowire growth precursors are co-flowed and decompose in the metal nanoparticles as they are transported along the length of the tube. (b) Scanning electron microscope image of collected nanowires, many of which have agglomerated, after the Aerotaxy process. (c) The morphology and crystal structure (not shown) of individual nanowires are on par with state-of-the-art substrate-based growth procedures. Adapted from References 88 and 89 with permission from Nature Publishing Group and the American Chemical Society, respectively.

nanotube (87) syntheses are widely practiced in large-scale bulk chemical vapor deposition systems, and both processes can be used to produce materials at the kilogram level and beyond. No solvent is required, and gases, when necessary, can be purified to extreme levels.

Rapid mass transport, a defining feature of gas-phase methods, minimizes heat and mass transport limitations but also offers benefits for synthesizing nanoparticles with well-defined structural nanoscale heterogeneity. Importantly, the majority of methods to produce heterogeneous nanoparticles are serial. Consider the synthesis of semiconductor nanowires, each containing a source, channel, and drain region (i.e., an ABA structure). After growing the A domain, precursors for the A domain are removed, and precursors for the B domain are added. The reverse process must occur when transitioning from growing the B domain to growing the second A domain. The rates at which precursors A and B can be removed or added, respectively, may influence domain dimensions and/or limit the sharpness of transitions between domains. Such processing steps are easier to carry out in gas-phase reactors because of the three to four orders of magnitude–greater mass transfer rates for gases compared with liquids.

Reactor design. The flow behavior in a chemical reactor will influence nanopart synthesis and, in many cases, limit product homogeneity (90). In chemicals manufacturing, residence time distributions (RTDs) and mixing models are common tools to characterize reactor behavior and predict product quality. RTDs describe the variability in times that individual fluid elements and, by extension, individual nanoparticles spend in the reactor. Mixing models describe the exchange, or lack thereof, of material between different regions of the reactor. An ideal RTD would be
Figure 6
Comparison of reactor behavior for continuous tubes and stirred tanks, and its impact on the distribution of nanopart structure. These residence time distribution plots schematically illustrate the probabilities that nanoparts will exit a reactor after a certain period of time (i.e., residence time). (a) All nanoparts would exit an ideal continuous tubular reactor (i.e., plug flow) after the same amount of time, which would yield a narrow distribution of structures and thus properties. Even in nonideal tubular reactors, the distribution of residence times and thus nanopart structures is relatively narrow. (b) Continuous stirred tanks reactors, owing to the increased mixing, likely yield nanoparts with a broader range of structures.

narrow and easy to manipulate: All nanoparts would then spend the same amount of time in the reactor. Real reactors approach this limiting behavior only rarely. Consider the RTDs depicted in Figure 6, which are representative of common tubular and stirred tank reactors. In nonideal tubular reactors, nanoparts with shorter residence times may form incompletely, whereas those with longer residence times may grow beyond design specifications (Figure 6a). Stirred tank reactors that are common for continuous liquid-phase processes exhibit RTDs that decay exponentially (Figure 6b). Some nanoparts will be ejected almost immediately, whereas others spend a much longer time in the reactor.
Although tubular reactors exhibit narrow RTDs, particularly as compared with stirred tanks, the concentration gradient of reactants decreases significantly between reactor entrance and exit; in the case of a first-order reaction, for example, the decay is exponential. The resulting variations in reaction environment are very likely to affect nanoparticle synthesis. For example, the growth of semiconductor nanowires via the vapor-liquid-solid mechanism is highly sensitive to gas-phase partial pressure, which is known to influence nucleation (91), sidewall termination (and thus tapering of the wire) (92), and catalyst phase (solid versus liquid) (93). As a result, the morphology of semiconductor nanowires synthesized via Aerotaxy in a tubular reactor (Figure 5) (88) is likely to degrade as nanoparticles are being transported through the reactor tube. Continuous injection of precursor along the tube length could stabilize reactant concentration and/or new growth chemistries could suppress the above deleterious effects; however, this complicates reactor design. Balancing the advantages and disadvantages of various reactor types is a critical process design need, for which lessons from chemicals manufacturing can be applied directly.

New Structure- and Property-Based Separation Processes

Synthesis/assembly of nanoparticles has received the lion’s share of attention and investment, but robust separation/sorting methods are also required. The fact that separations of all types account for as much as 15% of global energy consumption underscores their general importance. For nanomanufacturing, high-purity and high-yield separations are needed for nanoparticles as well as assemblies of nanoparticles. The degree to which separations are needed will depend on the ultimate application. Moderate heterogeneity may be acceptable for carbon nanotube applications in fabrics but cannot be tolerated in electronics (1). In some cases, a sequence of multiple separation processes may be required to achieve an acceptable level of nanoparticle performance. For high-value products, purity is usually of utmost importance. Lower-value products often require high-yield separations in which the majority of fractions are subsequently usable. Although improvements to synthesis can sometimes mitigate separation demands, as exemplified by the narrow diameter distributions of nanocrystals synthesized via the hot-injection method (17), some degree of variability should always be expected.

The chemical and structural heterogeneity of nanoparticle ensembles can result from both fundamental and engineering considerations. The stochastic nature of nucleation, for example, will fundamentally limit the uniformity of nanoparticle ensembles. Engineering constraints, such as the spatial and temporal variability of reactor conditions, will also increase nanoparticle heterogeneity. For example, carbon nanotubes synthesized via the floating catalyst method are highly entangled and structurally heterogeneous, exhibiting a distribution of lengths, diameters, and chiralities (87).

Structure-based separations. Separation techniques commonly leverage differences in nanoparticle structure, such as size, mass, and shape, to affect a separation (19). Precipitation (94, 95), (di)electrophoresis (96, 97), chromatography (98), and density gradient ultracentrifugation (DGU) (99) are well-documented approaches. As shown in Figure 7, DGU enables the kilogram-scale production of diameter-purified (99) and chirality-purified (100) single-walled carbon nanotubes. More recent studies have extended DGU to inorganic nanomaterials (101, 102) and to transition metal dichalcogenides (103). These purified materials enable high-performance electronic and photonic devices that were previously off-limits (78), exemplifying how advances in nanomanufacturing process engineering feed back into fundamental science by providing new materials as the basis for further research. Notably, DGU uses surfactants that bind selectively to structurally distinct nanoparticles to improve the separation. This amplification of structural differences is likely a general need for nanoparticle separations, even though implementation details will vary from system...
Figure 7

Two scalable nanopart separation techniques. (a) Density gradient ultracentrifugation can separate carbon nanotubes (shown), inorganic nanoparticles, and 2D materials. It uses surfactants that bind selectively to nanoparticles of different structures. Clusters of carbon nanotubes are initially separated from single carbon nanotubes. Each fraction exhibits distinct optical properties. (b) Separations of semiconducting and metallic carbon nanotubes, which exhibit different diameters and chiralities, can also be achieved and (c) exhibit distinct absorption behavior. (d) Gas-expanded liquids leverage tunable nanopart-CO$_2$ interactions to drive separations and use less solvent than most methods. A sequence of pressure changes drives nanoparticles of increasingly smaller diameter to precipitate. (e) Different absorption spectra are observed for nanoparticles from different fractions. Panels a–c adapted from Reference 18 with permission from the Nature Publishing Group. Panels d and e adapted from Reference 104 with permission from the American Chemical Society.

to system. Solvent usage is an important consideration in separations as well as synthesis processes (see the section titled Synthesis Techniques Appropriate for Large-Scale Manufacturing). Although the medium used for the DGU of carbon nanotubes is recycled, and nanoparticle seed catalysts are collected, opportunities exist to further decrease solvent consumption. For example, as shown in Figure 7, gas-expanded liquids leverage tunable nanopart-CO$_2$ interactions to drive separations (95, 104).

Property-based separations. Significant property changes can result from seemingly minute structural differences in some classes of materials, which necessitates the development of property-based separations to complement structure-based methods. Consider the separation of semiconductor nanoparticles based on their carrier density. A single substitutional P atom in a Si nanocrystal with a diameter of 10 nm (~50,000 atoms) yields a rather large carrier density of $10^{18}$ cm$^{-3}$ (assuming perfectly passivated surfaces). For this situation, mass-based separations...
will be exceedingly challenging. The mass difference between nanocrystals containing one or two phosphorus atoms is only \( \sim 2 \times 10^{-4}\% \). For comparison, the percent mass difference between \( ^{238}\text{U} \) (i.e., the most abundant isotope) and \( ^{235}\text{U} \) (i.e., usable for fission) is \( \sim 1\% \). Even for nanocrystals of identical composition, carrier density will still depend on the dopant atom’s proximity to the surface (105). Separation methods based on nanopart properties are likely necessary in these situations, as is often practiced in chemicals manufacturing. For example, distillation relies on differences in volatility, which can be large even for isomers. Many nanopart properties are desirable targets for separations—e.g., carrier density, emission wavelength, thermal conductivity—but very few techniques are currently available.

The separation methods described above can be categorized as fractionation techniques, where an ensemble of nanoparts is separated into a gradient of nanopart structures or properties from which subsets can then be collected in a bulk mode. For instance, fractions of the original nanopart ensemble with different sedimentation rates can be collected from DGU. In some cases, however, interrogation and binning of individual nanoparts may also prove useful. Electro-orientation spectroscopy-based separation (106, 107) is an excellent example of such a process. An initial determination of carrier density for single nanowires is used as the basis of a subsequent sorting step. An automated version of the technique allows nanowire conductivity distributions, which are quite broad, to be determined orders of magnitude faster than by conventional electrical probe-based techniques. The route to large-scale separations is not initially obvious for this specific example, but analogous interrogation and binning methods exist in other fields. For example, state-of-the-art cell sorters can process tens of thousands of cells per second and bin them according to biophysical characteristics (108).

**Heterogeneous part separations.** The separation of heterogeneous nanoparts, their hierarchical assemblies, and even complete devices will be a key challenge going forward. DGU has been applied to nanocrystal assemblies (109, 110) where there are large mass differences between assemblies of one, two, or more nanoparts. In many situations, it will be critical to distinguish between the properties of individual nanoparts and nanopart assemblies. Consider, for example, a solar cell consisting of semiconductor nanowires. Because the p/n junction is central to device performance, an integrated synthesis process, where junction formation is completed during synthesis, is preferred. A large-scale growth process will inevitably yield a distribution of nanopart properties (e.g., short-circuit current, open-circuit voltage) and, when assembled in parallel to create the final macropart (i.e., solar cell), will degrade performance. Techniques that separate nanoparts based on the properties of the interface, such as the built-in voltage, would be quite useful but do not currently exist. In many cases, a sequence of orthogonal separations will be necessary. The manufacturing of nanoparts containing both functional and assembly-directing domains (see the section titled Selection and Optimization of Process Break Points) will require different methods to perform separations based on the structure and properties of either.

**Advances in Nanopart Stabilization and Packaging**

A flexible nanomanufacturing supply chain requires that the functionality of nanoparts and nanopart assemblies (i.e., microparts) be guaranteed throughout the supply chain. Reliable methods for nanopart storage, transportation, and postprocessing are needed. The chemicals manufacturing industry has developed standard protocols to effectively package and transport chemical intermediates. The entire discipline of product formulation is dedicated to the task of ensuring that products are passed on in a form that simultaneously meets all performance, stability, and processability requirements. Successful formulations often require additives to stabilize chemicals.
against various types of chemical or physical degradation. Fortunately, the low reactivity of many molecules at room temperature permits their long-term storage and transportation without special care. If molecules have a tendency to degrade, for example via self-reaction or oxidation, methods exist to circumvent and suppress these effects.

A nanomanufacturing industry will be subject to similar stabilization requirements for its nanopart products throughout the supply chain. Although chemical degradation can likely be prevented via similar methods as for chemicals, the unique size range of nanoparticles imposes additional demands. In particular, agglomeration is a major concern. Van der Waals forces between nanoscale objects are relatively strong in comparison with other interparticle forces (see the section titled Quirks and Perks of the Nanoscale), making agglomeration difficult to control and often irreversible, unless stabilizing measures are taken. Surface modification is typically used to add stabilization in the form of electrostatic or steric forces (111). Surfactant species with long alkyl chains prevent agglomeration during liquid-phase syntheses. Gas-phase processes are likely to require postsynthetic surface modifications of nanoparts prior to dispersion in an appropriate solvent. In both cases, the design of swappable surfactants, where specific chemistries are designed to handle the conditions in different processing steps, may be needed (112). The exchange or removal of ligands on nanocrystals after processing, often to enhance internanocrystal charge transport, is one example of such a capability.

The transport of dilute suspensions of nanoparts becomes economically unfavorable at large scales. Dry powders are likely to be preferred in such cases because they eliminate the liquid, which would account for a significant fraction of the product’s mass. However, new stabilization strategies will be necessary to circumvent van der Waals forces upon redispersion while maintaining functionality when nanoparts reach their next destination.

Illustrative Example

Many of the issues described above can be illustrated with the example depicted in Figure 8. Imagine that two types of nanopart monomers, A and B, are available that must be assembled into the target nanopart tetramer, ABAB. Depending on the properties of the monomers, such superstructures could be useful in thermoelectrics (6) or light-emitting diodes (113), among other applications. For this simple example, we assume perfect control of assembly length is possible, such that only nanopart tetramers form. Although this is not realistic for many assembly processes (e.g., polymerization), assembly in a nearly ideal tubular reactor could get close (see RTD in Figure 6). Even with the simplifying assumption of homogeneous nanopart lengths, multiple manufacturing strategies exist to achieve the goal. With no selectivity toward A/B interconnectivity, nine nanopart by-products, such as AAAA, AAAB, AABA, and AABB, will be created in addition to the target product, if the tetramer is created in a one-step process (Figure 8a). In this case, it becomes necessary to purify the compositionally complex product mixture to obtain the target product. If the A and B nanopart monomers have different masses, a mass-based separation could remove nanopart tetramers with different numbers of A and B blocks than the target product (e.g., ABAB versus AAAB). However, nanopart tetramers with the same number of A and B blocks as the target product (e.g., ABAB versus AABB) would remain intermixed. Removal of these isomers would require a different, likely more challenging separation (100).

A two-step assembly process provides a powerful alternative (Figure 8b). First, nanopart dimers are synthesized (76) and separated into an intermediate target nanopart, AB, and by-product nanoparts, AA and BB. This separation can easily be achieved through a mass-based technique with excellent selectivity to create pure nanopart dimer product streams. The AB nanopart dimers can then be assembled into tetramers of three types: the target nanopart, ABAB, and two by-products,
Comparison of different assembly pathways toward a targeted nanopart tetramer with monomer sequence ABAB. (a) One-step assembly can yield up to nine different by-products and requires a potentially challenging separation. (b) Two-step assembly with separation steps at the dimer and tetramer level can provide numerous advantages described in the text, including higher-value by-products, improved yield, and simplified purification steps. (c) In the case of highly selective monomer interaction, self-assembly in a single step can ideally yield the target product without the need for purification.

ABBA and BAAB. Although a second separation is still necessary to remove these tetrameric by-products, the number of species in the product stream is reduced from 10 in the one-step assembly (Figure 8a) to 3 in the two-step assembly (Figure 8b), which should aid the separation. It must be noted that mass-based separation of the nanopart tetramer mixture would not work for this case, and alternatives would still have to be found.

Although the number of processing steps is twice as large in the two-step assembly, it takes advantage of several of the manufacturing features explained above. First, the nanopart dimer separation step is relatively easy and can yield highly pure intermediate by-product nanoparticles, AA and BB. The potential use of these nanoparticles as feedstock in other processes greatly improves the process economics. The by-product nanopart tetramers, ABBA and BAAB, are also more regular than some by-products of the one-step assembly (Figure 8a) and potentially valuable as feedstock for other products. Even if all by-products had to be discarded as waste, the two-step assembly (Figure 8b) would still provide significant advantages, with respect both to the selectivity required in the separations and to the overall yield. Whereas the single separation of the one-step assembly requires selecting one of ten different species formed (Figure 8a), the dimer and tetramer
separations in the two-step assembly require selectivity for only one of three different species (Figure 8b). The dimer separation is further facilitated by the stoichiometric difference between the target dimer and all dimer by-products. To appreciate the yield benefit of the two-step assembly, consider the oversimplified case where all assembly steps yield each possible outcome with equal probability, and conversion is perfect. In this case the yield for the one-step assembly would be \(\frac{2}{16} = 12.5\%\), because the number of possible tetramers formed from the two building blocks is \(2^4 = 16\), with only two of them (ABAB and, its equivalent, BABA) representing the target product. By the same token, each separation in the two-step assembly would have a yield of \(\frac{2}{4} = 50\%\), and thus the overall yield would be 25%, twice that of the one-step assembly.

As the comparison of the processes in Figure 8a,b shows, it can sometimes be advantageous to increase the number of separation steps, but this is not always the best strategy. If the assembly process is perfectly selective with regard to the A/B linkage, a one-step assembly of nanoparticle monomers into nanoparticle tetramers suffices and yields only the targeted ABAB tetramers (assuming synthesis stops upon reaching tetramers) without the need for any purification steps (Figure 8c). Such highly selective interactions are readily available on the molecular level and are used to manufacture alternating copolymers with great sequence precision (114). Semiconductor nanowire growth, which operates at the atomic level, can exhibit similar characteristics (26). However, such selectivity is rare for nanoparticle assembly (see the section titled Quirks and Perks of the Nanoscale), and in most cases this manufacturing pathway is therefore not (currently) accessible.

**SUMMARY**

Manufacturing of materials and devices composed of high-definition, functional nanoparticles holds tremendous technological promise. In spite of the opportunities and associated funding support for research and development, successful large-scale industrial nanomanufacturing remains elusive. Formidable challenges must still be overcome, which arise partly from the unique properties of nanoscale materials and partly from the need to reconcile nanoscale processing methods with principles that have been proven critical for other manufacturing processes.

Chemicals manufacturing in particular offers useful lessons and guidelines. The chemicals supply chain, which consists of a large and branched family tree of standard chemicals, enables manufacturers to use chemicals as modular components in their processes and provides flexibility and stability to the entire industry. This kind of infrastructure development is also desirable for nanomanufacturing, and likely necessary for it to be commercially viable. As with chemicals, it will be important to develop robust separations, recycle unconverted feedstock, and efficiently use all product streams. Environmental and health concerns must also be taken into consideration.

We have identified several nanomanufacturing process design needs that must be addressed to make the necessary transition:

1. Process break points need to be selected with great care. Judicious choices are required on how the overall manufacturing process is partitioned into synthesis/assembly and separation/sorting steps, which can profoundly impact the overall productivity and efficiency. During laboratory-scale development work, such issues generally do not receive much attention, but they are critical for the viability of commercial processes.

2. Synthesis techniques must be appropriate for large-scale manufacturing. Both bulk gas-phase and condensed-phase processes can be attractive options depending on specific process needs. The behavior of different reactor types should be considered to ensure the necessary level of control during nanoparticle synthesis.
3. New and improved techniques for separations and characterization of nanoparticles are needed. Because the performance of nanoparticles can depend on minute structural differences, it is likely to be necessary to pursue amplification of structural differences prior to separation and to complement structure-based separations with property-based separations.

4. Industry-wide protocols for nanoparticle stabilization and packaging are necessary to enable facile product exchange between manufacturers and their customers.

Success will require overcoming a type of chicken-and-egg problem that is characteristic of new markets: To profitably generate multiple nanoparticle product streams with economical value, a market demand for these diverse nanoparticles must exist. This demand, however, requires an established infrastructure ready to receive and further process those product streams—which again presses the need for a concerted, modular manufacturing approach, akin to chemicals manufacturing.

In closing, the chemicals industry and its supply chain did not emerge overnight. Decades of process optimization at the individual and overall process level, in addition to continual reductions in waste and energy inefficiencies, were required to reach a mature state. The same is likely to be true for nanomanufacturing. However, our analysis does not indicate any fundamental obstacles. We are optimistic that the remaining roadblocks for large-scale nanomanufacturing outlined above can be overcome, especially if nanotechnologists, process engineers, and industrial decision makers work in concert and if the effort is guided by chemical engineering principles.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED


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The Annual Review of Cancer Biology reviews a range of subjects representing important and emerging areas in the field of cancer research. The Annual Review of Cancer Biology includes three broad themes: Cancer Cell Biology, Tumorigenesis and Cancer Progression, and Translational Cancer Science.

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