Nanoparticle Manufacturing – Heterogeneity through Processes to Products

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ABSTRACT: Commercial products are now making use of the unique properties of nanoscale particles. However, common challenges of making nanoparticles into products still limit their impact. In this article, we review recent advances in nanoparticle manufacturing in liquids, clarifying the similarities between different processes and products at a system level. Our integrative survey emphasizes the fundamental challenge of heterogeneity, which propagates through manufacturing processes and increases the cost of



quality control. We also consider the central constraint of production scale, external costs of safety and sustainability, and technology transfer from the laboratory to the market. We review applications of nanoparticles in nanocomposite materials, healthcare and medicine, electronics and photonics, and energy and the environment, and conclude with a summary of the critical issues.

KEYWORDS: synthesis, stabilization, functionalization, purification, characterization, integration

1. INTRODUCTION

Nanoparticles are now enabling commercial products¹ but manufacturing challenges² still limit their impact. These challenges have become more urgent as early efforts³ have led to a second era of nanotechnology⁴, in which the initiative is refocusing from research to commerce, and nanoscale parts are undergoing development into complex systems. To better understand this emerging enterprise, we review recent advances in nanoparticle manufacturing at a system level and in the context of quality and profit. From this broad perspective, and in contrast to detailed reviews of specific subtopics of nanoparticle science and technology, we aim to clarify some general challenges of making nanoparticles into products, as we illustrate in Figure 1. In particular, many studies have noted that quality control is a critical issue in nanoparticle manufacturing, but none has systematically investigated the propagation of heterogeneity through processes to products. The commercial production and market introduction of nanoparticles also require new analysis of profitability,⁵ as the state of the art has changed considerably since the publication of early perspectives on such topics.⁶⁻⁷



Figure 1. Processes of making nanoparticles into products.

Nanoparticle manufacturing is a broad topic with a vast literature. We focus our review on processes that use liquids and apply to nanoparticles of diverse materials and morphologies. For processes and products in which a specific material or morphology is critical, such as the separation of metallic from semiconducting single-wall carbon nanotubes, or the effect of gold nanocrystal facets on a chemical property, we tend to identify the specific subpopulations. For issues that are broadly applicable to many populations of nanoparticles, we use generic terminology. We focus on the liquid phase as many synthesis reactions occur in liquids, and even nanoparticles that form in other phases often require downstream processing in liquids. Such processes can dominate products initially form and eventually disintegrate in a liquid. Even within this focus, nanoparticle manufacturing is still a broad topic, ranging from designing synthetic viruses to tracking single particles to assembling nanocomposite materials. These processes and products seem to be disparate, but we can describe them in a common framework at a system level. Accordingly, we review only the essential results of a selection of recent advances to discuss their underlying similarities within this common framework and to illustrate our main ideas.

One such idea is that nanoparticle manufacturing is an inherently holistic venture, involving everything from the initial details of synthesis processes to market forces on consumer products. Through our integrative survey of recent advances, we encourage researchers to consider prior knowledge from different disciplines, the current challenges facing others working upstream and downstream from them, and the future potential for commercial ventures. This broad perspective will enable researchers to accelerate the practical application of nanoparticle technologies. We also hope that administrators appreciate our identification of organizational issues, entrepreneurs value our discussion of technology transfer, and manufacturers appreciate our focus on quality and profit. Each group is a part of a system that is necessary for society to benefit from nanoparticles.

This article has the following structure.

In Section 2, we begin with an overview of nanoparticle manufacturing, including a general model to guide our review, definitions of heterogeneity, and analyses of its propagation through processes to products. We then survey recent advances that minimize this fundamental challenge of heterogeneity or mitigate its consequences, while simultaneously addressing the central constraint of scalable production and external costs of safety and sustainability. To order our survey, we consider advances in six primary processes of synthesis, stabilization, functionalization, purification, characterization, and integration, as well as the overlap of these processes.

In Section 3, we review the transfer of nanoparticle technologies from the laboratory to the market, focusing on manufacturing issues that cause losses of capital in the valley of death. We emphasize the challenge of knowledge transfer, due to the variable origin and reliability of information that is critical to new ventures.

In Section 4, we survey manufacturing issues across overlapping categories of nanocomposite materials, healthcare and medicine, electronics and photonics, and energy and the environment. We consider how a broad range of manufacturing costs and product prices, and private and public interests, affect the development of nanoparticle technologies for these applications.

In Section 5, we conclude by summarizing the critical challenges and opportunities of advancing nanoparticle manufacturing.

2. MANUFACTURING PROCESSES

2.1 Overview. The principle of factor sparsity states that 80% of the effects come from 20% of the causes. We apply this fundamental concept in nonstatistical quality control⁸ to identify the few vital ideas without describing the many useful details of nanoparticle manufacturing. This perspective limits the granularity of our review but provides insight into dependences between different processes and products at a system level.

2.1.1. General model of nanoparticle manufacturing. We present a general model to guide our review of the propagation of heterogeneity through six primary processes in a manufacturing operation. For clarity of presentation, we illustrate the processes in Figure 2 as being discrete and occurring in a certain order. However, the processes can overlap and occur in a different order, and all of them are not always necessary, which is of interest in our integrative survey. The scale of production is always of central importance in manufacturing and varies from grams to tonnes, depending on the specific application. Safety and sustainability are usually externalities that require testing standards and quantitative analysis to assess hazards,⁹⁻¹⁰ workplace exposure,¹¹ and cost metrics.¹² These factors set the respective locations of scale and externalities in this model. External costs also arise after manufacturing, as we revisit.



Figure 2. General model of nanoparticle manufacturing. Six processes occur in an operation starting at (A) and proceeding clockwise to (F). The production scale is of central importance, and safety and sustainability are externalities. (A) Synthesis reactions form nanoparticles with useful properties. (B) Stabilization of nanoparticles allows storage in and transfer between liquids. (C) Functionalization of nanoparticle surfaces tunes interfacial interactions. (D) Purification of nanoparticles reduces heterogeneity and facilitates inspection of properties. (E) Characterization of nanoparticle structures and test of properties provide information for quality control. (F) Integration of nanoparticles into devices or materials results in products. Knowledge enables design of the operation for minimum cost.

2.1.2. Definitions of Heterogeneity. Heterogeneity is a fundamental challenge of nanoparticle manufacturing. Therefore, the specific manifestations of this general term require precise definition. The primary manifestation of nanoparticle heterogeneity is a distribution of nanoparticle properties, typically beginning with initial distributions of material and dimensional properties, and propagating to dependent distributions of physical, chemical, and biological properties. The term polydisperse is often used to describe variation in nanoparticle size, with the coefficient of variation relating the standard deviation and mean of a size distribution. However, such metrics do not fully describe asymmetric or multimodal property distributions, which are common. Moreover, the term monodisperse, defined strictly as a size

distribution with a coefficient of variation of less than approximately 3%,¹³ is often used imprecisely. Considering the limiting precision of these two terms, we do not use them further. The secondary manifestation of heterogeneity is the variation of a distribution moment from population to population, often from batch to batch. The term reproducibility is commonly used to describe this. Whereas nanoparticle property distributions are inevitable at some scale, irreproducibility of a manufacturing process can be slow and costly to research¹⁴⁻¹⁶ and ruinous in commerce.

2.1.3. Qualitative Propagation of a Property Distribution. In Figure 3, we introduce the propagation of a property distribution through the six primary processes in a manufacturing operation. Variable conditions in a synthesis reaction form an inadvertent distribution of nanoparticle core size. A larger and broader distribution of hydrodynamic size emerges from the instability of smaller nanoparticles and their loss or growth into larger nanoparticles, as well as the adsorption of stabilizing ligands. Functionalizing ligands similarly affect hydrodynamic size and introduce interfacial nonuniformity. Hydrodynamic size separation narrows this size distribution but reduces yield and generates waste. Characterization aims to quantify the resulting distribution, which itself causes inaccuracies in the apparent distribution in an ensemble measurement. The operation concludes with assembly of nanoparticles into an array with a spacing distribution that limits its order and resulting function. We subsequently review specific examples that often but not always follow these general trends, and that address these issues.



Figure 3. Illustrative histograms introducing the propagation of a property distribution. Nanoparticle counts are to scale to show loss in some processes, and are offset on the vertical axis for clarity. Different dimensional properties share a horizontal axis. Open circles indicate the preceding property distribution. (A) Core size from a synthesis reaction with variable conditions. (B) Core size from the instability of smaller particles and the addition of stabilizing ligands. (C) Hydrodynamic size from the addition of functionalizing ligands. (D) Hydrodynamic size from size separation and purification. (E) Apparent size from an ensemble measurement with biases from larger nanoparticle signals. (F) Nanoparticle spacing in an array from assembly to form a device.

2.1.4. Quantitative Propagation of a Property Distribution. Various properties of nanoparticles and forces relevant to manufacturing exhibit varying dependences on nanoparticle dimensions. Table 1 shows several dimensional dependences of essential properties and forces for isotropic spherical nanoparticles, representing the simplest example of diverse morphologies. Analogous dependences exist for other morphologies, and the properties and forces in Table 1 also depend on other parameters, as we describe in Note S1. We quantitatively simulate the multiplicative propagation of a property distribution. For a lognormal distribution¹⁷⁻¹⁸ of core radius *r* with a coefficient of variation of 10%, which is representative of many nanoparticles, properties or forces that depend on *r* to the powers of x=2, 3, or 6 have increasingly

broad and asymmetric distributions, as Figure 4 shows. The coefficient of variation of r^x increases superlinearly with x, and skew and kurtosis increase dramatically as outlier values of r^x emerge. Further details are in Note S2 and Table S1. A normal distribution of r produces similar results, as Figure S1 and Table S2 show. This exemplary analysis informs our subsequent review of some salient dependences of processes and products on distributions of nanoparticle properties.

Table 1. Dimensional Dependence of Nanoparticle Properties and Manufacturing Forces

	<u>1</u>	0
dimensional	nanoparticle	manufacturing
dependence	property	force
r	core radius	
t	shell thickness	
R=r+t	hydrodynamic radius	viscous drag, depletion
R^{-1}	diffusion coefficient	
r^2	core surface area, net surface charge, ligand attachment sites	electrostatic
R^2	sedimentation coefficient	
$exp(-r^2)$	small-angle X-ray scattering	
r^3	core volume, core mass, magnetic moment, electromagnetic absorbance	magnetostatic, dielectrophoretic, inertial
r ⁶	electromagnetic scattering	



Figure 4. Histograms quantifying the multiplicative propagation of a property distribution. Normalization of r^x values facilitates graphical comparison of histograms. Further details are in Note S2. (A) Histogram from a standard lognormal distribution of core radius with a coefficient of variation of 10%. (B-D) Histograms of properties or forces that depend on core radius to the power of (B) two, (C) three, and (D) six. The coefficient of variation increases superlinearly with the power, and skew and kurtosis increase dramatically as outlier values of property or force emerge, as Table S1 shows.

2.1.5. Illustrative Examples of Manufacturing Operations. To introduce how the propagation of property distributions affects costs, we compare and contrast two operations for making gold nanoparticles into sensors, and carbon nanotubes into logic devices. Quantifying the cost of even one process requires accounting for labor, materials, equipment, energy, and production scale,¹⁹ before considering external costs. Few research reports provide any of these costs, and evaluating all of them in a comparison of these two operations with six processes each is beyond the scope of this article. Rather, we aim to qualitatively describe the complexity and cost of these operations, and their diversity of materials and methods with respect to standard operations for electronics manufacturing. We base these representative examples on specific reports that we review subsequently, and we also revisit the important issue of manufacturing costs from the perspective of product prices and profitability.

In Figure 5A, we illustrate the costs of producing a sensor from gold nanoparticles, for which a manufacturer can profit from prior knowledge of a synthesis process that results in similar core sizes. These resist ripening and present similar surfaces for functionalization, reducing purification to only the removal of excess reagents, and shifting characterization from measuring property distributions to monitoring process parameters. Similar nanoparticles assemble into larger arrays with fewer defects. This operation has a simple cost function and a low total cost. In contrast, in Figure 5B, we illustrate the costs of making a logic device from single-wall carbon nanotubes, for which the diverse species that result from current synthesis processes require costly downstream processing in liquids. After dispersion of the crude product into a stable suspension, nanotubes with similar morphologies but different electronic properties require selective separation. An electronic purity specification of one part per billion requires comprehensive characterization of this property distribution. The pure product then requires integration into specific locations at the wafer scale. This operation has a complex cost function and a high total cost. For either operation, the product value must eventually justify the process costs.



Figure 5. Illustrative process cost functions for manufacturing operations. (A) Synthesis of gold nanoparticles with similar properties decreases downstream costs in a simple operation to produce a sensor. Nanoparticles of similar size resist ripening and present similar surfaces for functionalization. This reduces the need for purification, shifts characterization to process monitoring, and reduces defects in the assembly of an array. (B) Synthesis of single-wall carbon nanotubes of diverse species increases downstream costs in a complex operation to produce a logic device. After dispersion, purification is necessary to separate nanotubes by electronic properties. Comprehensive characterization is necessary to quantify this property distribution, and precise integration of nanotubes is necessary at the wafer scale.

These examples emphasize the importance of considering overall operations rather than fixating on single processes, imply the requirement for processes that are compatible, as well as scalable and reproducible, and illustrate the significance of the complexity of the cost function. A simple function with a readily identifiable minimum is more amenable to empirical optimization, whereas a complex function requires a deeper understanding to optimize. For context, processes to manufacture electronic devices from silicon build on decades of standardization. Processes to make nanoparticles into products are much more diverse, as we review presently.

2.2. Synthesis. The synthesis of urea in 1828 precipitated a phase change in chemistry²⁰ and the Bakerian Lecture of 1857 drew attention to processes of forming gold colloids and their resulting optical properties.²¹ The advent of modern pharmaceuticals a century later established process chemistry,²² with

the goal of synthesizing useful molecules. Nanoparticle synthesis often extends this paradigm of production²³ and relies on similar methods and devices, such as mixing and heating chemical reagents in a flask or a vat to nucleate and grow useful particles. However, variation of chemical and physical parameters in synthesis reactions often causes an inadvertent distribution of nanoparticle properties. Identification and elimination of process variation is a fundamental concept in statistical quality control,²⁴ motivating various strategies to improve control of synthesis processes, from bulk solution to fine scales, for a wide range of materials and applications.

2.2.1. Chemical Contaminants. Synthesis at any scale involves a reactor vessel and chemical reagents. Either can be a source of chemical contaminants, which can result in a broad distribution of nanoparticle properties, as well as reaction irreproducibility or misunderstanding.²⁵ In pharmaceutical manufacturing, the cost and environmental impact of cleaning reactor vessels has led to the use of disposable polymer bags,²⁶ although these can also leach chemical contaminants. Beyond using pristine and inert reactor vessels, and pure chemical reagents,²⁷ an efficient solution is to develop processes that are robust against chemical contaminants. A basic principle of engineering design is that simple processes²⁸⁻³⁰ are more robust against faults than complex processes. Economical and versatile reagents for nanoparticle synthesis and stabilization such as oleylamine are of interest for such processes.³¹

2.2.2. Bulk Synthesis. There are various approaches to understand and improve bulk synthesis. Developing a fundamental understanding of the details of a synthesis reaction, such as by in situ characterization of gold nanoparticle formation by the citrate method, allows better control of product properties.³² Conversely, in an empirical approach, design of experiments can identify optimal synthesis parameters, such as for zinc oxide nanoparticles³³ and nanorods.³⁴ Analogously, theoretical computations predict the mixing and heating of reagents at large scales,³⁵ while pilot plants allow empirical tests of scale up.³⁶⁻³⁷ Microwave heating can reduce thermal variation,³⁸ improve process control,³⁹ accelerate reaction rates,⁴⁰ and facilitate scale up.⁴¹⁻⁴² Theoretical and empirical studies are ongoing to discriminate between the effects of microwaves, temperature, and pressure on the reaction pathway, and the resulting compromise between rate and yield.⁴³ Empirical study of different processes to form the same nanoparticles, such as precipitation, salting-out, and emulsification-diffusion of polymeric carriers of ibuprofen, elucidates the process scalabilities and product properties.⁴⁴ Such advances are leading to synthesis processes that are reproducible at large scales, 45-47 and that reduce the distributions of dimensional properties. In particular, continuous addition of iron oleate precursor extends the LaMer mechanism to form iron oxide nanoparticles with a low coefficient of variation in size.⁴⁸ Equilibration in the first step of the Brust method⁴⁹ and selection of thiol type and ratio produces gold nanoparticles with a low coefficient of variation in size.⁵⁰ As well, there are other approaches to improve control of synthesis at fine scales, as we review in following sections, closing the gap between the bulk manipulation of mass and heat transport, and the nanoscale formation of particles.⁵¹

2.2.3. Fluidic Devices. Small fluidic devices can improve control of synthesis. Millifluidic and microfluidic devices control mass and heat transport at the microscale,⁵²⁻⁵³ while microfluidic control of shear force forms emulsions at the nanoscale.⁵⁴⁻⁵⁵ Integration of microfluidic devices and microwave heating further improves temporal control of nanoparticle synthesis in microdroplets.⁵⁶ Fouling of small fluidic devices can be a challenge, motivating the isolation of synthesis reactions from solid–liquid interfaces, such as in microdroplets of an inert carrier liquid.⁵⁷ In addition to improving control of transport and force, microfluidic systems can facilitate the study of synthesis for applications from healthcare⁵⁸ to electronics,⁵⁹ and enable combinatorial synthesis⁶⁰ and integration of synthesis and characterization.⁶¹ Small fluidic devices are easy to fabricate and replicate in elastomers⁶²⁻⁶³ to form disposable microreactors, but these soft materials can be incompatible with harsh solvents⁶⁴ and high vacuum.⁶⁵ The main challenge of small fluidic devices is that their small volumes restrict the production scale, which is sufficient for some applications such as pharmaceuticals⁶⁶ but insufficient for many other applications. Volumetric flow rate can increase through scale out of parallel devices without loss of flow control,⁶⁷ as well as scale up of device dimensions and flow rates⁶⁸⁻⁶⁹ with potential loss of flow control.

2.2.4. *Microstructures and Nanostructures*. A variety of other artificial microstructures and nanostructures can improve control of synthesis at fine scales. Membrane structures ranging from microchannels to nanopores enable multiple modes of synthesizing nanoparticles with opportunities for scale up, but also present challenges of fouling.⁷⁰⁻⁷¹ Nanopores can function as templates to form anisotropic nanoparticles.⁷²⁻⁷⁴ Emulsions and micelles can improve control of chemical reactions⁷⁵ that are compatible with their soft matter properties,⁷⁶ and membranes and microfluidics can reduce emulsion heterogeneity.⁷⁷ Soft lithography enables the patterning of organic nanoparticles with direct control of property distributions.⁷⁸ Seeds provide a mechanism internal to a synthesis reaction to reduce distributions of nanoparticle size and shape by decoupling the processes of nucleation and growth.⁷⁹⁻⁸¹ Microfluidic devices produce seeds with high throughput.⁸² Seeds and micelles in combination can improve control of nanoparticle shape.⁸³ These artificial structures invite consideration of natural systems that can provide control of synthesis reactions at corresponding scales.

2.2.5. Biological Processes. Biological systems have evolved processes from the cellular scale⁸⁴ down to the macromolecular scale⁸⁵ that synthesize diverse nanoparticles. Reaction conditions vary broadly. For example, extremophiles survive harsh reactions to form inorganic nanoparticles,⁸⁶ whereas humans synthesize organic vesicles under mild conditions.⁸⁷ Production scales also vary broadly and extend up to large scales. For example, bacteria can synthesize semiconductor nanocrystals at the scale of a pilot plant,⁸⁸ and trees naturally grow nanocrystalline cellulose at forest scales. While such biological synthesis may seem to be environmentally benign, the extraction of nanocrystalline cellulose from lignocellulosic biomass still requires significant amounts of energy and chemicals,⁸⁹ illustrating a challenge in developing green processes of nanoparticle synthesis.

2.2.6. External Costs. The motivation to reduce the use, and external costs, of energy and chemicals extends throughout nanoparticle manufacturing. Diverse approaches such as deriving chemical reagents from plant extracts⁹⁰ or electronic waste,⁹¹ and replacing organic solvents with supercritical water,⁹² are increasing the human safety⁹³ and environmental sustainability⁹⁴ of synthesis and downstream processes.⁹⁵⁻⁹⁷

2.3. Stabilization. During and following synthesis, the tendency to reduce surface energy often causes nanoparticles to aggregate, dissolve, react, or otherwise cease to be nanoparticles at time scales that are inconsistent with applications.⁹⁸ These effects can be irreversible and often require nanoparticle stabilization. This challenge is complex. For example, measurements of silicon dioxide nanoparticles in aqueous electrolytes, a relatively simple system in comparison to many products and application environments, show simultaneous dependences of stability on pH, electrolyte type, ionic strength, and temperature.⁹⁹

2.3.1. Initial Stability. Nanoparticle property distributions resulting from synthesis propagate forward to affect nanoparticle stability, which feeds back to affect the nanoparticle property distributions. Ostwald ripening is a classic example.¹⁰⁰ This spontaneous process reduces nanoparticle surface energy and determines the core size distribution of gold nanoparticles, for example, during synthesis as smaller nanoparticles dissolve and feed the growth of larger nanoparticles.¹⁰¹ More recent studies show how distributions of size and charge affect the rates of destabilizing processes such as aggregation.¹⁰² Conversely, aggregation feeds back to the dimensional distribution, potentially narrowing it.¹⁰³

2.3.2. Surface Ligands. Synthesis and stabilization frequently conjoin through ligands, which attach to nanoparticle surfaces and influence size distribution,¹⁰⁴ determine the growth rates of crystal facets to form anisotropic nanoparticles,¹⁰⁵⁻¹⁰⁷ and prepare nanoparticle surfaces for functionalization.¹⁰⁸ Ligands that stabilize nanoparticles do not always attach irreversibly to them, and can exchange between nanoparticle surfaces in dynamic equilibrium.¹⁰⁹ Generally, ligands stabilize nanoparticles by electrostatic repulsion or steric exclusion, or both, depending on the surface and liquid properties. Steric exclusion is less sensitive to liquid properties such as ionic strength.¹¹⁰ Carboxylic acids stabilize nanoparticles in aqueous suspensions by electrostatic repulsion.¹¹¹ Amphiphilic polymers such as poly(ethylene glycol) (PEG) provide stability¹¹² in both aqueous electrolytes and organic solvents by steric exclusion. Multiple

ligands are often available to stabilize the same nanoparticle,¹¹³ and their selection requires knowledge of downstream processes and product functions. For example, a stable suspension can inhibit an intermediate assembly process but be necessary for final product stability. This implies the benefit of multifunctional ligands.¹¹⁴ Ligands cannot always stabilize nanoparticles, as in the dissolution of silver nanoparticles, which can still depend on their surface area.¹¹⁵ The distribution of this property and its effect on stability limit applications of silver nanoparticles, as we review subsequently.

2.3.3. Liquid Transfer. Nanoparticles often must be stable in different liquids, for example, beginning with synthesis in an organic solvent and transitioning to storage in an aqueous electrolyte. Nanoparticle transfer between liquids often requires an exchange, modification, or addition of ligands on the nanoparticle surfaces to provide stability, as well as a strategy for the physical process of liquid transfer.¹¹⁶ Ionic liquids¹¹⁷ and centrifugation¹¹⁸ facilitate the stable transfer of metal nanoparticles from an aqueous electrolyte to an organic solvent. Scalable processes are emerging to rapidly evaporate organic solvents from suspensions of hydrophobic nanoparticles, increasing nanoparticle stability against Ostwald ripening and reducing the toxicological consequences of the remaining liquid.¹¹⁹

2.3.4. Storage Conditions. For nanoparticles that remain in a liquid until or during application, nanoparticle instability is a function of temperature and time, so that storage and use conditions can affect expiration date or cause product failure.¹²⁰⁻¹²¹ This is of particular concern for medicines.¹²² Coating gold nanoparticles with polymer shells that are either sensitive or insensitive to temperature enables discrimination between thermal and temporal factors in nanoparticle aggregation.¹²³ Stable suspensions with high concentrations, which are necessary for many applications, require particular control over ligand chemistry and length.¹²⁴ Nanoparticles of soft matter, such as lipids and polymers, can require lyophilization for stable storage over a long duration between synthesis and application.¹²⁵ Spray freezedrying of nanoparticle suspensions into nanocomposite microparticles can improve the ability to reconstitute the nanoparticles.¹²⁶ Combinatorial tests of stabilizing ligands and lyophilization cryoprotectants can optimize the stability and bioavailability of nanoparticle medicines.¹²⁷

2.3.5. Complex Media. Applications of nanoparticles in complex media result in congruently complex challenges of stability. Physiological liquids contain various biological molecules which can cause nanoparticles, particularly those that rely on electrostatic repulsion for stabilization, to aggregate.¹²⁸⁻¹³¹ PEG avoids this and is generally recognized as safe for internal medicines.¹³² Protein adsorption and resulting cellular interaction of nanoparticles are topics of ongoing study.¹³³ Conversely, organic matter in aqueous media such as humic substances can adsorb to nanoparticles and stabilize them against aggregation.¹³⁴ Variable results motivate ongoing study of this topic,¹³⁵ in particular the effects of different ligands on the environmental fate of nanoparticles.

2.4. Functionalization. In addition to causing instability, nanoparticle surfaces dominate their interaction with liquid environments in subsequent processes and products. Functionalizing ligands bind to nanoparticle surfaces by exchanging with, modifying, or adding to ligands that are often already present from stabilization. Such processes can be independent of the underlying core material, so the same processes can apply to different nanoparticles.¹³⁶ Conversely, the same nanoparticles can have different functional groups, depending on the application.¹³⁷⁻¹³⁸

2.4.1. Ligand Distribution. Heterogeneity of functionalization is a significant challenge, as nanoparticle property distributions propagate and often broaden from synthesis to stabilization and functionalization. Multiple functionalization reactions can also decrease process reproducibility.¹³⁹ In common processes of chemical conjugation, if the number of attachment sites on a nanoparticle surface exceeds the number of conjugate ligands, then experimental distributions of ligands can become much broader than theoretical models assume.¹³⁹ All of this can impede production by requiring extensive purification and characterization to control functionalization. For example, gel electrophoresis enables separation of conjugates of nanoparticles with one, two, and three PEG molecules, with potential for preparatory sorting.¹⁴⁰ Reverse-phase high-performance liquid chromatography reveals complex distributions of ligands on nanoparticles that other characterization methods do not resolve.¹⁴¹ Resistive pulse sensing

resolves single nanoparticles with different surface densities of DNA, with broad distributions of charge that indicate the propagation of the property distribution from the underlying coating of streptavidin protein.¹⁴²

2.4.2. Anisotropic Functionalization. Anisotropic nanoparticles and mixtures of different ligands present further challenges and opportunities. Different facets of nanocrystals can have different chemical reactivities, resulting in spatially variable functionalization.¹⁴³ This complicates control and characterization of the number and location of ligands, but also enables anisotropic assembly of nanoparticles.¹⁴⁴ Ligand mixtures can potentially assemble into spatial patterns on nanoparticle surfaces with useful functions, but the presence¹⁴⁵⁻¹⁴⁶ or absence¹⁴⁷⁻¹⁴⁸ of artifacts in electron micrographs of the ligand patterns remains controversial. Simulations also indicate the presence¹⁴⁹ or absence¹⁵⁰ of such patterns at equilibrium, further emphasizing the challenge of characterizing nanoparticle functionalization.¹⁵¹

2.4.3. Click Chemistry. After starting with the most homogenous nanoparticle surfaces that are possible, one approach to reducing the distribution of functionalization at its source is to improve control of chemical reactions. For example, click chemistry¹⁵² enables potentially quantitative functionalization of nanoparticles with high efficiency at low temperatures,¹⁵³ reducing energy consumption. Such reactions can apply to both inorganic and organic nanoparticles and can facilitate subsequent assembly processes, for example of nanoparticles on DNA templates.¹⁵⁴ In a multifunctional process, a mesofluidic reactor enables the synthesis of gold nanoparticles with azide functional groups, producing clickable nanoparticles that are also dispersible and stable in an aqueous suspension.¹⁵⁵

2.3.4. Carbon Nanotubes. Chemical functionalization is particularly important in the processing of carbon nanotubes for products which apply their mechanical properties. Covalent chemistry is often necessary to disperse nanotubes into liquids, make nanotubes compatible with material matrices, and produce hybrid structures.¹⁵⁶ Processes are emerging to reduce energy and chemical use and preserve nanotube quality. Microwave radiation can functionalize multi-wall nanotubes with various terminal groups and derivatize nanotubes with nanoparticles in one process without the use of harsh oxidants or ultrasonication.¹⁵⁷ A photochemical process using mild chemicals functionalizes multi-wall nanotubes for attaching DNA and gold nanoparticles.¹⁵⁸ Noncovalent chemistry allows for dispersion of pristine nanotubes, but the functional molecules are generally in dynamic equilibrium with a bulk concentration, which constrains downstream processes are advancing to address this issue in the production. Noncovalent functionalization processes are advancing to address this issue in the production of nanocomposite materials,¹⁵⁹ which we revisit.

2.4.5. Liquid Processing. The method of liquid processing can improve control of functionalization processes. For example, layer-by-layer deposition forms multiple shells on nanoparticles with core diameters of tens of nanometers and shell thicknesses of several nanometers.¹⁶⁰ This allows multiple functionalities without degrading nanoparticle size distribution or stability.¹⁶¹ Layer-by-layer deposition commonly involves the use of polyelectrolytes with opposite charges, which can respond dynamically to liquid environments.¹⁶² The number of materials that are suitable for this type of functionalization process is growing.¹⁶³ Spray coating can increase the efficiency and throughput of such processes.¹⁶⁴

2.4.6. Biological Functionalization. Biological molecules are of interest as functional groups for purification and integration processes, as well as medical applications,¹⁶⁵⁻¹⁶⁶ of nanoparticles. In particular, the information content and interaction specificity of DNA¹⁶⁷ enables downstream processes ranging from purification of single-wall carbon nanotubes¹⁶⁸ to integration of nanoparticles into superstructures.¹⁶⁹ But stabilization and functionalization of nanoparticles with DNA can be in competition. Depending on liquid properties, steric and electrostatic interactions between DNA on gold nanoparticles can stabilize the nanoparticles but limit the availability of the DNA to recognize targets, and *vice versa*.¹⁷⁰⁻¹⁷¹

2.5. Purification. Processes to synthesize, stabilize, and functionalize nanoparticles often result in residual reagents such as excess ligands, contaminants such as inadvertent aggregates, and products with property distributions that are overly broad for applications. Purification can address these issues, and

often one purification process can simultaneously address multiple issues.¹⁷²⁻¹⁷³ However, purification of a crude product can also require a combination of processes,¹⁷⁴ which must then be compatible and scalable. Residual reagents can significantly affect nanoparticle structures and properties,¹⁷⁵ requiring processes to purify nanoparticles from molecular reagents in solution. However, to maintain our focus on nanoparticle heterogeneity, we primarily consider selective separation processes to narrow the property distributions of nanoparticles. We consider such processes, which exploit dependences of separation forces on nanoparticle structures and properties to achieve selectivity, on a spectrum from chemical to physical methods. Despite the motivation to improve upstream processes and obviate purification, which reduces yield and generates waste, separation is critical for nanoparticles with characteristic property distributions, and separation and characterization processes often overlap, as we discuss subsequently.

2.5.1. Precipitation and Extraction. Separation processes that rely primarily on differences between the chemical properties of nanoparticle surfaces or interfaces can be both highly selective and scalable. These processes depend on surface area distributions and lead to different interactions with the liquid environment, which often includes two liquid phases. The second liquid phase retains the nanoparticles, or not, for subsequent release, enabling nanoparticle separation by the properties of the bulk liquids. For example, precipitation and resuspension is a traditional method¹⁷⁶ of removing residual reactants and refining nanoparticle size distribution,¹⁷⁷ but has finite selectivity for reactants¹⁷⁸ and can cause irreversible aggregation of nanoparticles.¹⁷⁹ Liquid–liquid extraction can be more selective and gentler than precipitation, with examples ranging from extraction of semiconductor nanocrystals using organic solvents¹⁸⁰ to extraction of single-wall carbon nanotubes using aqueous solutions of polymers.¹⁸¹ The latter is a textbook example of the use of prior knowledge to solve a current problem. The classic Chemical Engineers' Handbook,¹⁸² in print since 1934, identifies equipment for continuous separation of biomolecules that is applicable to nanotubes. Not all separation methods are equally scalable, so developing methods that are compatible with modern industrial equipment for liquid processing of small particles is good practice, ensuring the availability of contract manufacturers for pilot production.

2.5.2. Centrifugation. Centrifugation separates nanoparticles by size, shape, area, density, and aggregation, as these properties result in differences in hydrodynamic transport.¹⁸³⁻¹⁸⁸ In a remarkable example of the development of this classic process, density-gradient ultracentrifugation can separate single-wall carbon nanotubes, by surfactant selection of different nanotube species and the resulting variation in buoyant density,¹⁸⁹ and by nonlinear gradients of media density.¹⁹⁰ Optical spectroscopy of nanotubes after separation inside centrifugation tubes¹⁹⁰ and after recovery¹⁹¹ allows characterization of the products. In an approach to design for nanomanufacturing, microcentrifugation separates nanoparticle assemblies on DNA origami, exploiting multiple functions of gold nanoparticles as product parts, hydrodynamic separators, and optical indicators.¹⁹² In addition to improving separation resolution, a general motivation for the ongoing development of preparatory centrifugation is to increase throughput and facilitate recovery of nanoparticles for subsequent processing.

2.5.3. Chromatography. Various chromatographic processes separate nanoparticles by a combination of their physical and chemical properties, and can be scalable. For example, gel chromatography can separate single-wall carbon nanotubes¹⁹³⁻¹⁹⁴ and purify semiconductor nanocrystals.¹⁹⁵ Size exclusion chromatography with recycling can separate nanoparticles with diameters of several nanometers with subnanometer resolution.¹⁹⁶ Nanoparticle adsorption to the stationary phase is a suspension instability that reduces yield and can limit such methods. Characterization of yield is not a universal practice¹⁹⁷ but is necessary for optimization of chromatographic purification processes.

2.5.4. *Electrophoresis*. Electrophoretic processes combine physical and chemical manipulation of nanoparticles to separate them by size, shape, and charge, with potential for quality control.¹⁹⁸ Agarose gel electrophoresis can separate nanoparticles with subnanometer resolution.¹⁹⁹ Functionalization can affect both nanoparticle charge and size, and so influence such processes.²⁰⁰ Free-flow electrophoresis separates nanoparticles by their charge-to-size ratio, and is more scalable than other electrophoretic methods due to the potential for continuous operation²⁰¹ in microfluidic²⁰² and millifluidic²⁰³ devices.

2.5.5. Fluidic Devices. Microfluidic and nanofluidic devices are emerging technologies for nanoparticle separation. For example, deterministic lateral displacement²⁰⁴ continuously separates small particles by size, and recent advances to the method through nanofabrication provide better resolution and range.²⁰⁵⁻²⁰⁶ The device dimensions enable novel functionality through microscale and nanoscale control of nanoparticles, while presenting a similar challenge of production scale as microfluidic synthesis. However, the devices can be ideal for analytical rather than preparatory separation, as well as other approaches to nanoparticle characterization, as we discuss subsequently.

2.5.6. *Filtration*. There are a variety of methods to physically filter nanoparticles by size, from diafiltration of nanoparticles with diameters of several nanometers²⁰⁷ to direct filtration of larger nanoparticles by nanofiber membranes.²⁰⁸ Processes of forming nanofibers for filters, ranging from electrospinning to hydrothermal carbonization, are advancing to improve control of the size distributions of nanofiber networks and resulting nanopores.²⁰⁹ Processes of filtering and assembling nanoparticles overlap, as we revisit.

2.5.7 Overlap with Characterization. Purification and characterization processes overlap extensively, for several reasons. As preceding examples indicate, inspection of nanoparticle separation facilitates characterization of a purification process. Moreover, nanoparticle dimensional distributions not only limit control of critical properties in applications, they are also a challenge in many characterization processes. Analytical separation is often essential to such processes, while characterization of dimensional and property distributions is necessary to determine nanoparticle purity.²¹⁰

2.6. Characterization. Characterization is a challenge throughout nanoparticle manufacturing.²¹¹ This is due in large part to nanoparticle property distributions, which present distinct challenges in processes to characterize nanoparticles in ensembles or as single objects. There are other challenges. Different nanoparticle properties require different measurements, and the availability of standards for comparisons is lagging.²¹² Sample contaminants, in particular from complex media, can produce artifacts that result in erroneous measurement results.²¹³ Even homogeneous nanoparticles have apparent property distributions that arise from measurement uncertainty, which requires evaluation in quantitative measurements²¹⁴ and propagation in the conversion of distributions from one metric to another.²¹⁵

2.6.1. Knowledge and Cost. A critical issue, in the context of quality and profit, is that characterization must provide the requisite knowledge at a tolerable cost. Measurements that provide a fundamental understanding of nanoparticles are often slow and complex, requiring expert operation of expensive instruments, multiple methods for comprehensive characterization, and models to interpret the results.²¹⁶ Such measurements can be profitable for valuable products, such as reference materials,²¹⁷ but all other things being equal, higher costs result in lower profits. In contrast, routine measurements to ensure quality are often less demanding and lower in cost, as their function is to yield only the information that is necessary to know that a product meets its specification. Direct measurement of a nanoparticle property may be unnecessary, and precision may be more important than accuracy. For example, if a relation between a product performance metric and a manufacturing process parameter is identifiable and measurable, then only that measurement may be necessary. In this context, we review methods to characterize nanoparticle structures in liquids.

2.6.2. *Nanoparticle Ensembles*. Nanoparticles generally exist in large ensembles and have small signals as single objects. This motivates ensemble measurements that sum these small signals, introducing the challenge of accurately measuring the nanoparticle property distributions.

2.6.2.1 Scattering Methods. Scattering methods vary over wide ranges of measurement cost and resulting knowledge. Neutron scattering is a costly method of characterizing nanoparticles in liquids,²¹⁸ requiring access to a nuclear reactor, typically at a user facility, and providing particular insight into magnetic nanoparticles.²¹⁹ X-ray scattering is more widely available and applicable but requires access to a synchrotron for the best precision.²²⁰ Dynamic light scattering is a routine method of inferring hydrodynamic size from nanoparticle diffusivity, with many uses from online characterization in a manufacturing context²²¹ to sensitive measurements of subnanometer particles.²²² But large outliers bias

this ensemble measurement, due to the high dimensional dependence of scattering intensity,²²³ as Table 1 shows.

2.6.2.2. Separation and Spectroscopy. Various methods of nanoparticle separation and spectroscopy mitigate the confounding effects of property distributions on ensemble measurements. For example, field flow fractionation²²⁴ separates nanoparticles by diffusivity prior to characterization by light scattering. Adsorption of nanoparticles to the fractionation membrane limits the method, motivating its functionalization to improve separation and recovery.²²⁵ Analytical ultracentrifugation, which has a long history in the study of biomolecules,²²⁶ occurs in free solution and more directly measures nanoparticle properties, as sedimentation rate depends on nanoparticle size, shape, and functionalization.²²⁷⁻²²⁸ Such methods are costly and some require low concentrations or offline characterization of nanoparticles, often leading to correlation of spectroscopic properties such as optical absorbance²²⁹⁻²³⁰ or fluorescence emission²³¹ as proxy parameters for nanoparticle size. A fundamental understanding of absorbance and emission transitions will ultimately facilitate characterization of bulk ensembles of carbon nanotubes by optical spectroscopy.²³² This motivates the separation of single-wall carbon nanotubes by gel chromatography for elucidation of band structure by circular dichroism spectroscopy.²³³ Similarly, dimensional variation can obscure the properties of gold nanoparticles²³⁴ and semiconductor nanocrystals²³⁵ in ensembles, motivating the development of methods to measure single nanoparticles.

2.6.3. Single Nanoparticles. The ability to measure single particles reduces artifacts of property distributions in ensemble measurements, but introduces competing requirements for high sensitivity to detect small signals, and high throughput to sample the population with statistical validity.

2.6.3.1. High Resolution. Microscopy methods with high resolution enable direct imaging of single nanoparticles. Electron microscopy is common but the enabling interaction between electrons and materials perturbs soft nanoparticles and functional molecules in liquids. Cryogenic electron microscopy mitigates these problems but sample preparation is challenging.²³⁶ Similar comments apply to *in situ* electron microscopy, which can elucidate nanoparticle formation mechanisms,²³⁷ but requires care to avoid electrolysis artifacts.²³⁸⁻²³⁹ Nanofluidic devices that facilitate electron microscopy of soft nanoparticles in liquids are emerging.²⁴⁰ Automation of electron micrograph analysis²⁴¹ reduces user intervention and facilitates quantitative measurements.²⁴² Similarly, elimination of user subjectivity improves the accuracy of atomic force microscopy of nanoparticles under non-ideal conditions.²⁴³⁻²⁴⁴

2.6.3.2. Low Resolution and Measurement Devices. Various methods and devices extract useful information from micrographs with low resolution, or otherwise measure single nanoparticles. Optical tracking can extract hydrodynamic size from nanoparticle transport in liquid media,²⁴⁵⁻²⁴⁸ although the accuracy depends on many subtleties.²⁴⁹ Optical microscopy and spectroscopy can directly measure some structural properties of static nanoparticles. ²⁵⁰⁻²⁵¹ In combination with synthesis arrest, such measurements reveal the morphological evolution of anisotropic gold nanoparticles.²⁵² Magneto-optical films indicate the magnetic properties and interactions of single nanoparticles,²⁵³⁻²⁵⁴ which are otherwise difficult to discern. Nanofluidic devices manipulate nanoparticles for optical imaging²⁵⁵ or electronic detection,²⁵⁶ enabling size and charge measurements.²⁵⁷⁻²⁵⁸ Nanofluidic size exclusion can achieve subnanometer accuracy and elucidate optical properties of nanoparticles,²⁵⁹ but measurement devices must be sufficiently reliable and economical to produce to have broad impact.²⁶⁰

2.7 Integration. The integration of nanoparticles into materials or devices implies a general need for spatial control, with the scale and complexity of integration processes varying by product. Processes for single-wall carbon nanotubes, for example, range from dispersion into an epoxy matrix,²⁶¹ to assembly into macroscopic fibers,²⁶² to alignment in electronic devices.²⁶³⁻²⁶⁴ Importantly, achieving spatial control of nanoparticles in an integration process is often necessary but not sufficient for product function. For example, colloidal nanocrystals can require processing after assembly to achieve high electronic mobilities,²⁶⁵ and carbon nanotubes require interconnects with low contact resistance to exploit their outstanding properties in electronic devices.²⁶⁶

2.7.1. Dimensional Dependence. Integration processes rely on various interparticle and external forces,²⁶⁷⁻²⁶⁸ with varying dimensional dependences that affect the design of a manufacturing operation. In particular, forces with low dimensional dependence such as depletion are less sensitive to a distribution of nanoparticle dimensions, although that distribution can still limit the order of an assembly.²⁷ In contrast, forces with high dimensional dependence such as dielectrophoresis are sensitive to dimensional distributions and enable selection of nanoparticles from a complex distribution, effectively combining aspects of purification and integration processes.

2.7.2. Bulk Liquids and Evaporating Interfaces. Scalability is also critical in integration processes, favoring the use of forces that occur spontaneously in bulk liquids and at evaporating interfaces to assemble nanoparticles from the bottom up.²⁶⁹ Whereas stabilization prevents unintentional aggregation of a suspension, depletion forces, which depend on the presence of molecular additives in solvents, can order anisotropic nanoparticles into hexagonal assemblies that form microscale sheets in suspension.²⁷⁰ Nanoparticle diffusivity limits the rate of this process. Evaporation of a suspension of isotropic²⁷¹ and anisotropic²⁷² nanoparticles drives a faster, nonequilibrium assembly process at a liquid–gas interface,²⁷³ forming binary and ternary superlattices. Entropic and hydrophobic forces between ligands order nanoparticles at the wafer scale, while their size and shape influence packing. Vacuum filtration of a suspension of single-wall carbon nanotubes aligns them into monodomain films at the centimeter scale.²⁷⁴ Hydrodynamic and electrostatic forces affect this assembly process. Wet spinning forms fibers of carbon nanotubes of any morphology by injecting a nanotube suspension into a coagulating solution.²⁷⁵⁻²⁷⁶ Such processes are advancing to enable assembly with milder chemicals and higher purity at larger scales.²⁷⁷ Similar to synthesis, there are various strategies to improve control of integration processes at finer scales.

2.7.3. Surface Patterns. Surface patterns provide additional spatial control of liquid and interfacial forces from the top down. Dewetting of a suspension across a template assembles nanoparticles into patterns, depending on template geometry, meniscus curvature, and nanoparticle charge and concentration.²⁷⁸ Such methods provide control of particles with diameters of several nanometers.²⁷⁹ Inorganic templates using electrostatic forces to assemble nanoparticles are reusable.²⁸⁰ Nanoparticle assemblies can themselves generate surface patterns for subsequent manufacturing applications by the method of colloidal lithography.²⁸¹

2.7.4. Electric Fields. Electric fields provide further control of nanoparticles in liquids. Field application during solvent evaporation vertically aligns and assembles semiconductor nanorods in two and three dimensions.²⁸² Electrophoresis of metal nanoparticles in an organic solvent forms a nanoparticle monolayer at the wafer scale.²⁸³ Dielectrophoresis and impedance spectroscopy allow simultaneous selection and assembly of semiconducting silicon nanowires from a crude feedstock.²⁸⁴ Simulations indicate the possibility of using an atomic force microscope for dielectrophoretic manipulation of single nanoparticles.²⁸⁵ The small scale of this process indicates that it would be most profitable for the production of devices with high complexity and price. Electrospinning integrates nanoparticles into nanofibers, with simple processes operating at ambient conditions and without organic solvents.²⁸⁶ Such nanocomposite materials have many applications, as we review subsequently.

2.7.5. *Printing Processes.* Printing combines many of the preceding forces and integration processes. Piezoelectric actuation and inkjet printing of nanoparticle suspensions enables the direct fabrication of devices from nanoparticles. Material properties similar to bulk are possible at low sintering temperatures due to the rapid coalescence of nanoparticles.²⁸⁷⁻²⁸⁸ Printing processes extend beyond piezoelectric actuation of nanoparticle inks. For example, surface patterns can improve printing resolution into the submicrometer scale by meniscus dewetting or ligand binding.²⁸⁹⁻²⁹⁰ Aerosol jetting of nanoparticle suspensions enables printing of complex structures with microscale resolution in three dimensions.²⁹¹

2.7.6. *Biological Assembly*. Biological molecules can assemble nanoparticles into complex structures, subject to control of interfacial interactions. Functionalization of nanoparticles with DNA oligomers enables their recognition and organization.²⁹² DNA origami provides a scaffold for the hierarchical assembly of nanoparticles,²⁹³ as well as the formation of superlattices of nanoparticles,²⁹⁴ potentially

independent of nanoparticle size and shape.²⁹⁵ DNA origami can selectively fold only in the presence of gold nanoparticles, mediating their interaction and assembly.²⁹⁶ DNA can form dynamic assemblies of nanoparticles,²⁹⁷ with applications to cellular interaction.²⁹⁸ Proteins can also direct the hierarchical assembly of nanoparticles into complex structures with dynamic responses to liquid environments.²⁹⁹

2.7.7. *Disintegration*. The integration of nanoparticles into products leads to their eventual disintegration during use or after disposal,³⁰⁰ presenting safety and environmental hazards which can differ from those that are present during production.³⁰¹ Understanding such hazards and quantifying their costs are complex challenges. The potential toxicity of metal nanoparticles, for example, depends not only on their composition, size, shape, and surface functionalization but also on the environmental media and exposure route.³⁰²

3. TECHNOLOGY TRANSFER

3.1. Valley of Death. Transferring nanoparticle technologies from the laboratory to the market requires consideration of the costs to do so, which the public and private sectors share. Public funding generally supports precompetitive research, creating knowledge but not profit. However, some of this knowledge leads to commercial ventures that contribute to economic growth. Private funding for product development is generally competitive, and commercial entities dedicate this funding to making money. Therefore, private industry is typically reluctant to fund research that is not proprietary and does not generate profit. In this context, Figure 6 shows a funding trajectory with a critical feature, the valley of death,³⁰³ between the laboratory and the market. This funding gap is a general issue for advanced technologies, and measures to determine when public funding should end and private funding should begin are themselves a topic of research.³⁰⁴ Nanotechnology commercialization presents further challenges³⁰⁵ due to the diversity of disciplines and organizations with roles to play in this enterprise,³⁰⁶ inhibiting the transfer of useful knowledge and coordination of action.³⁰⁷ In addition to technical innovation in nanoparticle manufacturing, we consider approaches toward meeting these challenges and improving the funding trajectory, which we illustrate as filling the valley of death, mitigating the descent into loss and accelerating the rise into profit.



Figure 6. Illustrative funding trajectory from the laboratory to the market. Red circles indicate loss. Black circles indicate profit. Open circles indicate a trajectory with greater loss or lesser profit. Closed circles indicate the opposite. Milestones include discovering the existence of a nanoparticle technology, proposing applications that meet market needs, testing prototypes of manufacturing processes and commercial products, refining manufacturing processes, beginning production, and controlling the quality

of final products. Without committing resources to technical innovation in nanoparticle manufacturing, transferring knowledge, coordinating action, and sharing resources can mitigate the descent into loss and accelerate the rise into profit.

3.1.1. From the Laboratory. In the beginning, grand challenges can inspire the study and discovery of nanoparticle technologies to solve societal problems that capture the imagination³⁰⁸ and have potential for commercial application. The following stages of proposing specific applications and testing prototypes typically benefit from the participation of inventors, who are often researchers from academic or national laboratories. There can be institutional impediments to such participation, which the different sectors are generally aware of, as they are to the benefits of coordination.³⁰⁹ During initial stages of research and development, multidisciplinary user facilities,³¹⁰ often at national laboratories, can reduce capital losses of new ventures. This can occur both directly by sharing the costs of expensive instruments for nanoparticle characterization, and indirectly by developing economical processes for nanoparticle manufacturing.

3.1.2. Through the Valley. The valley of death seems to be an uninviting location for a costly reinvention of the wheel. Therefore, before committing resources to technical innovation in nanoparticle manufacturing, researchers would be wise to make use of prior knowledge of process scalability and compatibility from chemical engineering and contract manufacturing,³¹¹ among other prior knowledge of nanoparticle technologies, to refine existing processes and begin production. However, there are at least three significant challenges to the application of this prior knowledge. First, nanoparticle technologies and manufacturing operations are often multidisciplinary,³¹² and knowledge transfer between disciplines can be inefficient.³¹³ This motivates an inherently multidisciplinary approach to process selection and refinement. Second, the relevant scientific literature is vast, due to the significant interest in nanoparticle technologies across disciplines. In particular, the broadest of four common databases of scientific literature³¹⁴ currently returns more than 1.2×10^6 publications for a search topic of nanoparticle or nanoparticles. This scale is a significant impediment to identifying essential knowledge.³¹⁵ Third, there is an increasing understanding of the significant incidence of errors in the literature.³¹⁶ Unidentified chemical contaminants are but one source of process irreproducibility or misunderstanding. Such errors can preclude profitable integration of new processes into manufacturing operations. These three challenges motivate rigor on the part of individual investigators to ensure the reliability of their results, and attention on the part of multidisciplinary organizations to validate the utility of knowledge and standardize and aggregate useful knowledge.

3.1.3. To the Market. Quality control is a critical challenge near the end of the valley of death. For example, reproducibility of the synthesis and functionalization of semiconductor nanocrystals impedes their application to biological analysis.³¹⁷ Optimizing manufacturing operations for quality presents further challenges in knowledge transfer. Without a fundamental understanding of an overall operation, many manufacturers empirically identify and optimize process parameters that correlate to product performance. However, different applications of similar nanoparticles can have different sets of functional properties, and process parameters that are measurable often provide an incomplete understanding of such properties. This can lead to costly and redundant optimization efforts by multiple companies.³¹⁸ In such situations, industrial consortia and standards organizations can reduce manufacturing costs for multiple companies.

4. COMMERCIAL APPLICATIONS

4.1. Nanoparticle Commerce. Across the valley of death is an open landscape of diverse applications, making use of the unique properties that result from nanoparticle composition, size, shape, functionalization, assembly, and interaction with radiation.³¹⁹ However, such properties add value to products only if the properties confer novelty, by solving an unsolved problem, or economy, by displacing an existing solution to reduce cost. The need for profit presents several basic questions of commercial

viability. Do entrenched interests in incumbent technologies increase the probability of nanoparticle products creating new markets, rather than disrupting old markets?³²⁰ How rapid is progress along a learning curve to reduce the manufacturing cost of a product below its sale price?³²¹ What are the prices of competing products? How do market factors influence these costs and prices? How do public and private interests affect the markets? The answers to these questions inform a broad perspective on nanoparticle manufacturing. To begin to summarize the results of these issues, Figure 7 shows manufacturing costs and product prices across different markets.



Figure 7. Commercial applications of nanoparticles. Red indicates loss. Black indicates profit. Open circles indicate initial loss. Closed circles indicate final profit. Manufacturing costs vary with product complexity, production scale, material scarcity, and regulatory requirements. Product prices range over orders of magnitude in different market categories. The eventual success of a commercial product relies on being above the dashed line along which product price and manufacturing costs are equal. Particularly for a consumer product with a maximum price, reducing manufacturing costs is essential to profit. We show this for a television display making use of semiconductor nanocrystals and recently selling at a loss.³²² Unit costs and prices are approximate and dynamic.

4.1.1. Application Categories. To order our survey, we group applications of nanoparticles into four categories of nanocomposite materials, healthcare and medicine, electronics and photonics, and energy and the environment. We note that applications of nanoparticles commonly extend across categories, and that materials, structures, and devices are not always clearly distinct. Indeed, such overlaps motivate our integrative survey. Within each category, we first discuss general issues and then survey specific applications in approximate order from the low end toward the high end of the market.

4.1.2. Commercial Status. Commercial viability is dynamic as products enter and exit the market regularly, and our aim is to review applications in the context of manufacturing issues rather than to inventory products.¹ Therefore, in our survey, we do not discriminate absolutely between nanoparticle technologies that have emerged, that are emerging, and that have yet to emerge in commercial products. Although we review only reported applications of nanoparticles, we also note the possibility of commercial products that include nanoparticles implicitly. As such applications become explicit, market demand for the useful properties of nanoparticles may increase.

4.1.3. Application Specificity. The manufacturing cost of nanoparticle heterogeneity is highly dependent on the specific application. For example, even for a single nanocomposite material, multiple physical properties of the material can have different dependences on nanoparticle structure, functionalization, and dispersion.³²³ Therefore, implicit in each application is the need for a statistical analysis of the specific effects of heterogeneity through manufacturing processes to product performance. **4.2.** Nanocomposite Materials. We begin our survey with nanocomposite materials, which have applications that extend across market categories and commercial scales. Various nanoparticles, carbon nanotubes in particular,³²⁴ enable nanocomposite materials with high performance. Currently, such materials are most profitable when they provide new capabilities, or support critical applications that tolerate high cost to achieve high performance. As enabling knowledge emerges and aggregates, quality increases, and cost decreases, the design space will continue to extend toward the low end of the market.

4.2.1. *Materials Design*. Design is an initial challenge for many nanocomposite materials. Models enable prediction of some aspects of material performance and reliability from the properties of the constituent particles and polymers.³²⁵⁻³²⁷ The many possible combinations thereof motivate a materials genome approach to curate research data and integrate predictive models to facilitate knowledge transfer and reduce costly trial and error in materials design.³²⁸

4.2.2. Quantity and Quality. Depending on the application, both the quantity and the quality of nanoparticle feedstock can limit nanocomposite materials. For structural materials, production of a sufficient quantity of nanoparticles, potentially at the scale of many tonnes, can be a primary challenge. Relative to quality requirements for critical applications such as logic devices, a broad distribution of nanoparticle properties may be tolerable for a structural material. However, the nanoparticle properties must still be quantifiable within engineering tolerance at the production scale. Nonuniform nanoparticle properties can limit performance and reliability in critical applications. In particular, functionalization determines nanoparticle interaction with a polymer matrix.³²⁹⁻³³¹ In this way, ligands affect the assembly and order of semiconductor nanorods and block copolymers for electronic devices,³³² and the functionalization of silicon dioxide nanoparticles affects the stability of polycyanurate nanocomposite in aerospace applications.³³³ As well, integration processes can depend on feedstock nonuniformity in the form of chemical or morphological impurities. Measurements of multi-wall carbon nanotubes from multiple vendors reveal different metal nanoparticle contaminants and nanotube agglomerate structures, and show how wet processing restructures them to optimize their dispersion.³³⁴

4.2.3. *Metal–Organic Frameworks*. Metal–organic frameworks have potential applications from healthcare to energy, and consumer products are emerging at the low end of commercial markets,³³⁵ such as in gas storage to control the ripening of climacteric fruit.³³⁶ There are different approaches to integrating nanoparticles into such nanocomposite materials. Solution infiltration fills the nanopores of existing frameworks by capillary forces to synthesize and template nanoparticles.³³⁷ Synthesis and encapsulation of nanoparticles into a framework allows more control of nanoparticle properties such as shape.³³⁸ In either approach, challenges include stabilizing nanoparticles and controlling their order within the framework to achieve the functional property. Simple methods are emerging to form frameworks integrating metal nanoparticles for energy applications.³³⁹

4.2.4. Textile Garments. Nanocomposite materials are emerging in other consumer products, such as textiles comprising organic microfibers and inorganic nanoparticles that provide antibiotic and antistatic properties, block sunlight, and repel water. There are different approaches to producing these materials, such as the initial synthesis of zinc oxide nanoparticles and their subsequent application to cellulose and keratin microfibers by soaking.³⁴⁰ Another approach is to synthesize nanoparticles directly onto textile microfibers. The reduction of silver ions in the presence of keratin microfibers forms silver nanoparticles to form a silver–wool nanocomposite.³⁴¹ Similarly, growth seeds form silver nanocrystals on the polysaccharide surfaces of cellulose microfibers to form a silver–cotton nanocomposite.³⁴² Challenges include stabilizing the adhesion of inorganic nanoparticles to organic microfibers so that the resulting garments are rubfast and washfast.³⁴³

4.2.5. Optical Materials. Optical applications of nanocomposite materials extend from consumer products to critical infrastructure. For example, lights and displays require the synthesis at large scales of ceramic nanoparticles, such as zirconia, and their functionalization and dispersion into polymer matrices to form nanocomposites with precise control of properties such as refractive index.³⁴⁴⁻³⁴⁵ In a potential application of optical materials at a large scale, ultrasonic dispersion of carbon nanotubes in a polyurethane

varnish forms a nanocomposite film which can function as a fluorescent sensor of mechanical strain on critical structures such as bridges to prevent collapses.³⁴⁶

4.2.6. Cement and Concrete. Cement and concrete are complex nanocomposite materials³⁴⁷ with large production scales, commercial markets, and environmental impacts. Carbon nanotubes and silicon dioxide nanoparticles can reduce the energy input for their production,³⁴⁸ decrease the porosity and increase the strength of self-compacting high-performance concrete,³⁴⁹ reduce the leaching of calcium and increase the stability of cement in water,³⁵⁰ and enable electrical monitoring of cement behavior in critical structures such as oil wells to prevent spills.³⁵¹ Challenges include rational design of the matrix nanostructure, economical production of a large quantity of nanoparticles, and control of their dispersion from agglomerates into liquid cements.³⁵²

4.3. Healthcare and Medicine. Applications of nanoparticles to improve health range from everyday lotions that prevent disease to experimental medicines that aim to cure it. Sunblocks, antibiotics, and diagnostics compete with existing products at the low end of the market. Internal medicines extend to the high end of the market, but profits can vary even within this category on the basis of novelty and competition. Safety regulations are of critical importance at the high end of the market. Nanoparticle medicines must pass strict tests before receiving approval from regulatory agencies.³⁵³ Few have³⁵⁴⁻³⁵⁵ due to the challenge of making nanoparticles that meet the requirements of safety and efficacy.³⁵⁶ For example, control of functionalization is necessary to maintain stability,³⁵⁷ prevent cytotoxicity,³⁵⁸ optimize immunoreactivity,³⁵⁹ and achieve efficacy.³⁶⁰⁻³⁶¹ Safety also limits material selection and requires good manufacturing practices, sterility, and quality control.³⁶² In contrast, topical lotions have lower regulatory costs and can sustain lower returns. The production scale for such commodities at the low end of the market is also much larger than internal medicines for infrequent use.

4.3.1. Sunblocks. Skin cancer is the most common of all cancers, and sunblocks with both physical and chemical mechanisms of protecting the skin from ultraviolet radiation are commercially available. Titanium dioxide and zinc oxide particles are common components of physical sunblocks.³⁶³ Reducing the size of these particles from the microscale to the nanoscale can result in a transparent coating that absorbs and scatters light. These interactions have high dimensional dependences, as Table 1 shows, and the resulting sensitivity to dimensional distributions extends across healthcare and medical applications. Aggregation of nanoparticles changes these optical properties, requiring a stable suspension.³⁶⁴ Dispersion of nanoparticles into emulsions or lipid carriers can improve stability and delivery. The encapsulation of chemical sunblocks in polymeric nanoparticles enables dispersion into aqueous suspension, reduces biological exposure to the chemicals, and increases water resistance of the product.³⁶⁵

4.3.2. Antibiotics. Nanoparticles have other applications to prevent disease, such as in antibiotic materials.³⁶⁶ The stability and efficacy of silver nanoparticles as commercial antibiotics³⁶⁷ depend on their surface area distribution ³⁶⁸ and electrolyte type.³⁶⁹ Manufacturing innovations range from improving classical processes to inventing new ones. Study of the synthesis parameters in a semi-batch reactor and the resulting antibacterial properties of silver nanoparticles enables scale up.³⁷⁰ Genetic engineering of microbial systems has the potential to synthesize homogeneous silver nanoparticles with antimicrobial properties.³⁷¹ The infusion of silver ions into lignin nanoparticles and their functionalization with polyelectrolytes results in antibiotic nanoparticles that do not persist in the environment,³⁷² simultaneously achieving functional properties and reducing environmental impact.

4.3.3. Diagnostics. Nanoparticles enable routine diagnostic tests in commercial products. Immunoassays use gold nanoparticles³⁷³ to increase the sensitivity of test strips for visual detection of low concentrations of hormones indicating pregnancy,³⁷⁴ and potentially of biomarkers for sexually transmitted diseases.³⁷⁵ Manufacturing challenges include stabilizing nanoparticles against aggregation upon exposure to physiological liquids, and functionalizing nanoparticles for detection of specific biomarkers.³⁷⁶ The use of clinical samples in the development of sensors may accelerate their commercialization.³⁷⁷ Nanoparticle printing has the potential for the economical manufacturing of diagnostic devices with complex functions.³⁷⁸⁻³⁷⁹

4.3.4. Vaccines. Vaccines prevent over three million deaths per year, and viruslike nanoparticles are emerging in new vaccines.³⁸⁰ For example, norovirus causes acute gastroenteritis and lacks a vaccine, motivating the development of novel processes of biological synthesis.³⁸¹ These involve isolating norovirus genotypes and identifying antigenic proteins. Synthetic DNA combines those sequences with a norovirus scaffold and replicates in cells, generating proteins that assemble into homogenous nanoparticles resembling the virus. This process occurs at a large scale in a standard recombinant protein facility and requires purification of the vaccine nanoparticles from other proteins in the reactor output.³⁸²

4.3.5. Cancer. Finally, cancer is a valuable market for nanoparticle products. Multiple properties of nanoparticles are potentially useful to evade the immune system, target tumors, interact with radiation for imaging and heating, and release drugs.³⁸³ Size and functionalization affect immune response, while shape affects cellular interaction,³⁸⁴ motivating processes to improve shape control.³⁸⁵ Interactions with radiation span the electromagnetic spectrum. Gold nanoparticles enable photothermal imaging and heating,³⁸⁶ iron oxide nanoparticles have similar functions for magnetic resonance imaging and hyperthermia,³⁸⁷⁻³⁸⁹ and various metal nanoparticles provide X-ray contrast.³⁹⁰ Innovations are reducing the heterogeneity, cost, and environmental impact of manufacturing nanoparticles for such applications. A microemulsion method and sol-gel reaction synthesize and functionalize tantalum oxide nanoparticles with low cost.³⁹⁰ Aqueous processes synthesize magnetic nanoparticles at large scales with complete conversion of reactants,³⁹¹ tuneable functionality, and high reproducibility.³⁹² Gold nanoshells, often around silicon dioxide cores, reduce the amount of precious metal, relative to solid nanoparticles, that is necessary to achieve a plasmonic property.³⁹³ However, this comes at the cost of more complex synthesis processes with more critical dimensions to control. Genetic engineering of diatoms can lower the cost of forming silicon dioxide nanoparticles for drug delivery.³⁹⁴ Microfluidic devices can simplify processes to synthesize and functionalize gold nanoshells.³⁹⁵

4.4. Electronics and Photonics. Applications of nanoparticles in electronics and photonics range from sensors at the low end of the market to logic devices at the high end. Whereas safety regulations are the critical barrier to new internal medicines, complementary metal–oxide–semiconductor (CMOS) technology is the critical barrier to new logic devices. The complexity of CMOS manufacturing requires reengineering many processes to replace silicon nanostructures with single-wall carbon nanotubes, for example. In particular, the technology to assemble nanoparticles with precision and yield equivalent to conventional CMOS devices does not yet exist. Therefore, researchers often consider niche applications of carbon nanotubes in logic devices.³⁹⁶ Photonic devices present similar challenges of quality control for single-wall carbon nanotubes, while presenting new application opportunities. Various sensors have lesser constraints for quality control and present new application opportunities for consumer products.

4.4.1. Arrays. The assembly of nanoparticle arrays with order over a long range enables a variety of electronic and photonic materials and devices. Arrays of zinc oxide nanorods can form field-effect transistors³⁹⁷ and photovoltaic devices,³⁹⁸ metal–dielectric nanoparticles can form optical metamaterials,³⁹⁹ and indium tin oxide nanorods can form plasmonic materials.⁴⁰⁰ An application opportunity for such arrays, in comparison to silicon crystals, is the production of flexible devices.⁴⁰¹ Single-wall carbon nanotube arrays with high density⁴⁰² have emerging applications in terahertz detection.⁴⁰³ This application relies on precise control of nanotube structure to specify properties such as electronic or photonic band gap, contact resistance, and thermal and mechanical properties. For applications such as magnetic recording media, which require precise control of array spacing, nanopore templates can impose order by combining the synthesis and integration of ferromagnetic nanorods.⁴⁰⁴

4.4.2. Networks. The formation of networks of anisotropic nanoparticles can result in electronic and photonic properties of potential value for commercial applications. In particular, metallic nanowires and carbon nanotubes are possible replacements for indium tin oxide in transparent electrodes.⁴⁰⁵ For silver nanowires, the diameter distribution critically affects the transmission and scattering of light by the network.⁴⁰⁶ Rod coating of silver nanowires⁴⁰⁷ and dip coating of carbon nanotubes⁴⁰⁸ forms random networks for touch screens and flexible electronics. Dip coating avoids the potentially detrimental effects

of ultrasonication and functionalization to preserve nanotube quality, and is scalable. Deposition of carbon nanotubes on a solid poly(dimethylsiloxane) (PDMS) film and immersion in liquid PDMS forms a capacitive sensor for wearable electronics.⁴⁰⁹ Elastomeric nanocomposites of silver nanowires have similar potential applications.⁴¹⁰

4.4.3. Fibers. The integration of anisotropic nanoparticles such as carbon nanotubes into macroscopic fibers can produce an advantageous combination of electrical conductivity, mechanical flexibility, biological compatibility, and weight reduction in comparison to existing technologies.⁴¹¹ Single nanotubes can have remarkably high values of current carrying capacity.⁴¹² While assembly into macroscopic fibers reduces this value, it can still remain significantly higher than copper to produce lightweight cables.⁴¹³ Electronic and photonic applications of fibers of single-wall carbon nanotubes are emerging, including terahertz polarizers⁴¹⁴ and detectors.⁴¹⁵

4.4.4. Interconnects. Beyond the challenge of controlling the location of nanoparticles, another challenge in electronic devices is tuning the conductivity between nanoparticles.⁴¹⁶ For conducting metals such as gold, the subnanometer tunnelling distance limits electronic transport. Ligands that tune the gaps between nanoparticles can result in metallic conductivities. However, ligands for synthesis and stabilization of nanoparticles can result in gaps between nanoparticles that are too large for effective tunnelling, resulting in the need for ligand exchange. The functionalization of gold nanoparticles and assembly into layers with opposite charges that rectify current enables the fabrication of chemoelectronic circuits which sense chemical signals and process electronic information.⁴¹⁷

4.4.5. Chemical Sensors. Nanoparticles have various electronic and photonic properties that change in response to molecular adsorption.⁴¹⁸ Gold nanoparticles, in particular, have diverse functional properties and potential applications.⁴¹⁹ For example, the plasmon resonance frequency of a nanoparticle array can indicate small concentrations of a target chemical in a gas.⁴²⁰ Detection using surface-enhanced Raman spectroscopy (SERS) promises high sensitivity to hazardous chemicals.⁴²¹ Despite this apparent value, commercial products remain elusive. Evidently, gas sensors are sufficiently sensitive and inexpensive at the state of the art to resist displacement. Manufacturing innovations can reduce this gap in performance and cost. Assembly of silver nanoparticles at a liquid-liquid interface forms a dense array with low order at the centimeter scale, resulting in a relative standard deviation of SERS intensity of more than 10%.⁴²² Evaporation of a suspension of gold nanoparticles with poly(vinylpyrrolidone) (PVP) surfactant forms a nanoparticle monolayer with hexagonal close packing at the centimeter scale, resulting in SERS intensity variation of less than 10%.⁴²³ A hydrothermal process to synthesize arrays of zinc oxide nanorods on a silica film at low temperatures has the potential for manufacturing gas sensors with low cost and high performance.⁴²⁴ A Langmuir–Blodgett technique to pack iron oxide nanoparticles into multilayers with variable density can tune the performance of sensors for carbon monoxide gas.⁴²⁵ For chemical sensing in liquids, convective assembly of polystyrene nanoparticles, replica molding with PDMS, and molecular imprinting enables herbicide detection in aqueous solution.⁴²⁶

4.4.6. Logic Devices. Per our illustrative examples, logic devices have high value relative to sensors, and require further consideration of quality control. There is motivation to do so. Despite the challenges of reengineering CMOS fabrication, CMOS scaling will eventually end, and fundamental limits of heat dissipation and quantum mechanical leakage within conventional semiconductor materials will halt further progress at some point.⁴²⁷ To continue improving performance, manufacturers are developing prototypes of field-effect transistors using semiconducting single-wall carbon nanotubes.²⁶⁶ The contamination specification for this application is very low, with approximately one part per billion of metallic single-wall nanotubes allowable among semiconducting nanotubes for digital logic. Purification and characterization of property distributions to achieve such impurity levels requires intrinsic codevelopment of these manufacturing processes. Advancing to very-large-scale integration (VLSI) then requires precise positioning of many nanotubes over trenches with widths of tens of nanometers. Scaling up this form of epitaxy is a challenge. Possible methods include electrophoretic deposition of the nanotubes onto vias⁴²⁸ or DNA assembly using templates.⁴²⁹

4.5. Energy and the Environment. Applications of nanoparticles in this category range from storing, conserving, and producing energy to purifying air, soil, and water, extending from consumer products to the utility scale. Energy production and electronic devices have an economic similarity, in that an incumbent technology reduces the availability of private funding. For energy, the incumbent technology is fossil fuels, with fluctuating prices. Public funding for alternative technologies also fluctuates. Energy storage and conservation depend less on fossil fuel prices, while nanoparticles for environmental purification present the opportunity to reduce the use of precious metals with fluctuating prices. Many technologies for energy and the environment exploit the high surface-to-volume ratios of nanoparticles in liquids, resulting in the general challenge of heterogeneity of stabilization and functionalization. As well, some technologies have intrinsic dependences on nanoparticle structures that result in specific sensitivities to property distributions, as we review subsequently.

4.5.1. Batteries. Lithium–ion batteries, in particular, power a wide range of consumer products from mobile devices to electric vehicles, and are driving manufacturing innovation involving nanoparticles.⁴³⁰ The assembly of lithium manganese nanoparticles on carbon nanotubes to form a cathode increases surface area and improves the diffusion kinetics of lithium, producing higher rates of charging and discharging and improving tolerance to structural distortion.⁴³¹ Coating silicon nanoparticles with conducting hydrogels forms a network that improves anode tolerance to structural distortion.⁴³² Electrospinning silicon nanoparticles into carbon shell fibers forms robust anodes by a scalable process.⁴³³ Crosslinking nanoparticles into a polymer web improves electrolyte stability by reducing nanoparticle aggregation and dendrite formation.⁴³⁴

4.5.2. Lubricants. In systems with interacting surfaces in relative motion, nanoparticles can improve lubricants to conserve energy by reducing friction and waste heat. Inorganic nanotubes and fullerene nanoparticles can form solid lubricants,⁴³⁵ but production at a large scale is a challenge.⁴³⁶ Inorganic nanoparticles in liquid lubricants, which are commercially available, have the additional challenge of remaining stable in a suspension under variable operating conditions.⁴³⁷ Functionalization of nanoparticles with polymer brushes improves their stability and performance.⁴³⁸ X-ray tomography and tracking of nanoparticles in a liquid lubricant enables *in situ* characterization of its performance, showing nanoparticle dispersion and load bearing under shear.⁴³⁹

4.5.3. Thermoelectrics. Given the generation of waste heat, thermoelectric devices can capture it to produce electricity⁴⁴⁰ or cool other devices.⁴⁴¹ Nanoparticle assemblies with sufficient order can produce high values of thermoelectric figure of merit, and nanocomposite materials integrating nanoparticles can be more economical.⁴⁴² Single-wall carbon nanotubes in both random networks and in nanocomposite materials have the potential to displace the incumbent technology of bismuth telluride, but require advances in purification, functionalization, and integration to form practical devices.⁴⁴³

4.5.4. Photovoltaics. Nanoparticles have other applications in energy production, such as converting sunlight into electricity. Photovoltaic devices are exemplary of a specific dependence of product performance on a nanoparticle property distribution.⁴⁴⁴ In particular, the inclusion of semiconductor nanocrystals with large particle diameters and small band gaps results in defects, and their concentration affects the open-circuit voltage of the device.⁴⁴⁵ Nanoparticles are also useful in dye-sensitized solar cells, in which dye molecules absorb sunlight and excite electrons onto titanium dioxide nanoparticles. Arrays of single-wall carbon nanotubes improve the efficiency of such cells,⁴⁴⁶ which can be comparable to silicon photovoltaics,⁴⁴⁷ but they degrade faster and cost more. Gold nanoparticles with silicon dioxide shells can improve the stability and efficiency of such cells.⁴⁴⁸

4.5.5. *Photosynthesis*. In another approach to converting sunlight into another form of energy, artificial photosynthesis splits water into hydrogen fuel, but organic dyes are insufficiently stable for this application. Functionalization of hydrophobic nanocrystals of cadmium selenide with dihydrolipoic acid allows their dispersion into aqueous suspension. In combination with a nickel catalyst and ascorbic acid as an electron donor, the result is a robust chromophore system without using organic solvents or precious metals.⁴⁴⁹ Nanoparticle structure and stability affect the performance of suspension reactors for

photocatalytic water splitting,⁴⁵⁰ as well as other catalytic applications of nanoparticles for energy conversion and environmental purification.

4.5.6. Catalysis. Nanoparticles, in particular of metals and alloys,⁴⁵¹ are useful as catalysts with diverse applications from fuel cells to environmental purification. For example, platinum nanoparticles are commercially available in catalytic converters for automotive applications.⁴⁵² Stabilizing the nanoparticles against agglomeration during operation is a challenge.⁴⁵³ For some metals such as gold, nanocrystal faceting affects catalytic function.⁴⁵⁴ This motivates the use of seeds and ligands to improve shape uniformity, but ligands to synthesize and stabilize nanoparticles can inhibit catalysis. For example, green processes of synthesizing palladium nanoparticles can produce biogenic adsorbates that degrade catalysis.⁴⁵⁵ This requires chemical⁴⁵⁶ and thermal⁴⁵⁷ processes to remove such ligands without degrading nanoparticles. Conversely, surface functionalization tunes gold nanoparticles for carbon dioxide reduction.⁴⁵⁸ Synthesis processes are emerging to reduce the use of precious metals in catalytic nanoparticles. A reverse microemulsion and temperature ramp forms atomically thin shells of platinum on carbide cores,⁴⁵⁹ while carbon nanotubes encapsulating iron nanoparticles can outperform platinum electrocatalysts for oxygen reduction.⁴⁶⁰ Processes are emerging to control and characterize the morphological and electrocatalytic properties of nanoparticles with iron oxide cores and nickel shells.⁴⁶¹ Nanoparticles have further applications, catalytic and otherwise, to environmental purification.

4.5.7. Environmental Remediation. Environmental contamination presents application opportunities for nanoparticles. Iron nanoparticles can break down pesticides and chemicals⁴⁶² but the extent of soil and groundwater contamination requires production at a large scale. Iron oxide nanoparticles are economical to produce for cleanup of oil spills, although the mechanism of magnetic recovery remains uncertain.⁴⁶³⁴⁶⁴ Stability and functionalization are critical for this application,⁴⁶⁵ which can also exploit assembly processes. A core of multiple iron oxide nanoparticles can increase magnetic response and swell during adsorption of oil, while an organic shell enables stable dispersion into water.⁴⁶⁶

4.5.8. Water Purification. Finally, about a billion people do not have access to clean water, motivating the application of nanoparticles to purify water.⁴⁶⁷ Superhydrophobic nanoparticles generate osmotic pressure in forward osmosis–ultrafiltration systems for water reuse and desalination.⁴⁶⁸ The nanoparticles are magnetic for separation and recycling, but ultrasonication to reduce aggregation degrades the nanoparticles. Stable integration of nanoparticles into nanocomposite membranes for water purification is also a challenge.⁴⁶⁷ Hierarchical integration of silver nanoparticles into electrospun fibers and woven filters for wastewater treatment improves antibiotic efficiency.⁴⁶⁹ However, nanoparticle washout from purification systems results in counterproductive contamination of the environment,⁴⁷⁰⁻⁴⁷¹ reemphasizing the importance of the environmental fate and external costs of nanoparticle products.

5. CONCLUSIONS

We have reviewed recent advances in nanoparticle manufacturing in liquids. To organize our review at a system level, we have introduced a paradigm that is sufficiently general to encompass many materials and applications, but is also specific enough to identify the primary processes and essential dependences that make up the complete enterprise. Our integrative survey has emphasized the propagation of heterogeneity through processes to products as a fundamental challenge of nanoparticle manufacturing, between the central constraint of production scale and external costs of safety and sustainability. We hope that this broad perspective encourages researchers to consider prior knowledge from different disciplines, current challenges of others working upstream and downstream, and future potential for commercial ventures.

The most profitable innovations in nanoparticle manufacturing minimize heterogeneity in upstream processes of synthesis, stabilization, and functionalization, rather than by mitigating it in downstream processes. This reduces the need for purification that decreases yield and generates waste, shifts characterization from comprehensive measurement for quality control to process monitoring for quality assurance, and improves the precision of integration into devices and materials. Nonetheless, the intrinsic distribution of some nanoparticle properties requires advances in these downstream processes. Models of

the dimensional dependence of nanoparticle properties and manufacturing processes, and statistical analysis of the propagation of property distributions, can facilitate the design of efficient operations that limit variability within engineering tolerance for specific applications.

There is a nonrecurring engineering cost either to obtain a fundamental understanding of manufacturing processes and the resulting properties of nanoparticle products, or to optimize an overall operation empirically. Which of these approaches is more profitable depends on the complexity of the cost function, with simple functions amenable to empirical approaches, and complex functions requiring deeper knowledge. Conducting research and development in consideration of this context is likely to shorten the time from development to manufacturing.

To avoid reinvention of the wheel in the valley of death, new ventures would be wise to make use of prior knowledge that is relevant to nanoparticle manufacturing. However, knowledge transfer between multiple disciplines can be inefficient, and the literature is vast and includes errors that can be costly to discover. These challenges motivate individual rigor to ensure reliability, and organizational attention to curate knowledge and facilitate its transfer. Even then, gaps remain between public and private funding for technology transfer. Industry, government, and academia recognize these challenges and aim to meet them through coordination.

The commercial viability of a nanoparticle product depends on many factors. Product prices and manufacturing costs vary over orders of magnitude by market and application. Private funding depends not only on the resulting profit margins but also on the existence of incumbent technologies that affect the investment risk. Public interests of human safety and environmental impact create both challenges and opportunities for nanoparticle products.

Nanoparticle manufacturing is advancing. Challenges remain but the motivation to proceed is overwhelming, and as companies bring more products to market, the possibility of breakthroughs and rapid growth becomes more probable.

ASSOCIATED CONTENT

Supporting Information, including details of dimensional dependences, methods of Monte Carlo simulations, and additional simulation results, is available below.

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Notes

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Supporting Information for

Nanoparticle Manufacturing – Heterogeneity through Processes to Products

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Note S1

We describe other parameters determining the nanoparticle properties and manufacturing forces in Table 1. We restrict the following descriptions to spherical nanoparticles and note simplifying approximations. It is possible to apply such analysis to other nanoparticle morphologies, properties, and forces.

A nanoparticle has a core radius r. A shell of ligands around the core has a thickness t, resulting in a hydrodynamic radius R=r+t.

The viscous drag on a nanoparticle is $6\pi\eta vR$. η is the dynamic viscosity of the suspending liquid and v is its relative speed.

The diffusion coefficient *D* of a nanoparticle is $k_{\rm B}T/6\pi\eta R$. $k_{\rm B}$ is the Boltzmann constant and *T* is the absolute temperature of the suspending liquid.

The depletion force between two nanoparticles, in the Derjaguin approximation, is $2\pi \int f(z) dz (R_1R_2)/(R_1+R_2)$. f(z) is the normal force per unit area between two flat surfaces a distance z apart. The integral extends from the nanoparticle separation distance to infinity.

The net surface charge of a nanoparticle is $4\pi\sigma r^2$. σ is the net surface charge density from surface groups that may ionize, ionic species that may adsorb, and ligands that may attach.

The small-angle X-ray scattering intensity of a nanoparticle, in the Guinier approximation, is $I_0 \exp(-q^2 r^2/5)$. I_0 is an intensity coefficient that is independent of nanoparticle size and q is the modulus of the scattering vector.

The electrophoretic mobility of a nanoparticle is $\varepsilon_1 \varepsilon_0 \zeta / \eta$ in the Smoluchowski approximation of $r\kappa >>1$, and $2\varepsilon_1 \varepsilon_0 \zeta / 3\eta$ in the Hückel approximation of $r\kappa <1$. ε_0 is the permittivity of free space, ε_1 is the permittivity of the suspending liquid, κ is the Debye length of the electric double layer, and ζ is the zeta potential of the slipping plane in the electric double layer.

The sedimentation coefficient of a nanoparticle is $2((\rho_p - \rho_l)/9\eta)R^2$. ρ_p is the mean density of the nanoparticle core and shell and ρ_l is the density of the suspending liquid.

The dielectrophoretic force on a nanoparticle core is $4\pi\varepsilon_0\varepsilon_1 \text{Re}|(\varepsilon_{p^*}-\varepsilon_{l^*})/(\varepsilon_{p^*}+2\varepsilon_{l^*})|E\cdot\nabla Er^3$. ε_{p^*} is the complex printivity of the core, and ε_{l^*} is the complex permittivity of the suspending liquid, and *E* is the electric field.

The magnetic moment of a nanoparticle core is $m = (4/3)\pi\mu_0 Mr^3$. μ_0 is the permeability of free space and M is a constant and spatially homogenous magnetization of the material.

The electromagnetic absorbance cross-section of a spherical nanoparticle core is $4\pi k \text{Im}|((\varepsilon_{p^*}-\varepsilon_{l^*})/(\varepsilon_{p^*}+2\varepsilon_{l^*}))|r^3$. *k* is the wave number of the electric field.

The electromagnetic scattering cross-section of a nanoparticle core is $(8/3)\pi k^4 |((\varepsilon_{p^*}-\varepsilon_{l^*})/(\varepsilon_{p^*}+2\varepsilon_{l^*}))|^2 r^6$.

Note S2

We consider a standard lognormal distribution of nanoparticle core radius r with a coefficient of variation of 10 %. Lognormal distributions of nanoparticle size are common, and 10 % is a representative coefficient of variation for many nanoparticle products. We simulate 10⁶ values of r from this distribution to achieve relative standard errors of the mean and standard deviation of 0.1 %. We include a third digit in the tables to avoid significant rounding errors. We calculate values of r^2 , r^3 , and r^6 . To facilitate graphical comparison of the histograms of these values in Figures 4 and S1, we normalize each value of r^x by subtracting the corresponding mean value μ_{rx} and dividing by the corresponding standard deviation σ_{rx} . This normalization results in false negative values for distributions on the plots, but does not affect the tabular statistics. After normalizing the histograms, we plot a subset of 10⁴ values of r^x to illustrate the emergence of outlier values of properties and forces for a large count of nanoparticles from the

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perspective of measuring single nanoparticles. Statistics from all 10^6 values of r^x without normalization are in Table S1.

We repeat this analysis for a standard normal distribution of nanoparticle core radius with a coefficient of variation of 10 %. We normalize and compare these histograms in Figure S1. Statistics from all 10^6 values of r^x without normalization are in Table S2.

The multiplicative propagation of heterogeneity compounds as the initial distribution broadens, and many nanoparticle size distributions have coefficients of variation exceeding 10 %. A similar analysis applies to the additive propagation of nanoparticle heterogeneity, as well as dependences of nanoparticle properties and manufacturing forces on nanoparticle composition, morphology, and functionalization.

Table S1. Statistics of Figure 4

dimensional dependence	coefficient of variation	skew	kurtosis
r^1	0.100	0.301	0.171
r^2	0.202	0.615	0.689
r^3	0.307	0.951	1.65
r^6	0.658	2.25	9.73



Figure S1. Histograms quantifying the multiplicative propagation of a property distribution. Normalization facilitates graphical comparison. (A) Histogram from a standard normal distribution of nanoparticle core radius with a coefficient of variation of 10 %. (B-D) Histograms of properties or forces that depend on core radius to the power of (B) two, (C) three, and (D) six. The coefficient of variation increases linearly with the exponent, and skew and kurtosis increase as outlying properties and forces emerge, as Table S2 shows.

Table S2. Statistics of Figure S1

dimensional dependence	coefficient of variation	skew	kurtosis
r^1	0.100	0.001	-0.009
r^2	0.199	0.298	0.108
r^3	0.297	0.594	0.533
r^6	0.606	1.56	4.17