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Nanoparticle puzzles and research opportunities that go beyond state of the art

Ah-Young Jee,[a] Kai Lou,[a] Hyun-Sook Jang,[a] K. Hima Nagamanasa[a] and Steve Granick*[ab]

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We present an overview of current progress and research challenges in the field of nanoparticle assembly, touching on the following topics: (1) historical perspective; (2) consideration of what is a nanoparticle; (3) contrast between nanoparticle self-assembly and top-down construction; (4) opportunities for nanoparticles with more intelligent sub-structures; (5) opportunities for nanoparticle systems cued to interact subtly in space and time. In this personal and subjective account, certain holy grails for nanoparticle science and technology are identified.

Introduction

Recent magnificent progress in nanoparticle science and nanotechnology, stimulated especially by pioneering government initiatives,[1] is accompanied nowadays by a sense of topicality and optimistic excitement that is shared internationally. Nanoparticles have become an interdisciplinary subject that transcends all conventional disciplines and provides opportunities both scientific and career related for many chemists, physicists, and engineers, not to speak of those interested in biology, drugs, and medicine. A quarter of a century since the first initiatives at the U.S. National Science Foundation,[1] it is fitting and proper to step back and reflect on where we have come from; where we are now; and where we as a field should set our sights to be going.

Where we come from

We stand on the shoulders of giants whose names it is well to remember as without their seminal contributions, the science-based approach to nanoparticles that we presently enjoy would be unthinkable. In our opinions expressed in this

[a]Center for Soft and Living Matter, Institute for Basic Science (IBS), Ulsan 44919, Republic of Korea. E-mail: sgranick@ibs.re.kr

[b]Department of Chemistry, UNIST, Ulsan 44919, Republic of Korea

highly personal account, four great scientists are worth remembering especially. One is P.-G. de Gennes, the "Newton of our times";[2] by brilliance and force of personality, he convinced a generation of physicists that it is possible to do honest, rigorous, penetrating physics on problems that, in prior years, had been considered too messy, unclean, and tainted by too much association with applications and technology. P.-G. de Gennes made an essential contribution culturally: he helped to make our discipline respectable.

If we did not understand surface forces, we could not understand how nanoparticles interact with their environments. Nanoscientists working today have probably almost all learned about this from the beautiful monograph of Jacob Israelachvili.[3] It is a gem: beautifully written and presented with a point of view and humor that give it personal character in addition to great scientific content. Thanks to it, we as a community are comfortable with analyzing nanoparticle stability and instability; we understand van der Waals forces, double layer forces, hydration and hydrophobic forces, and more; we know the limits of these concepts; and we are sensitive to how to deepen understanding of these concepts. Tending to take this knowledge for granted as part of the tools of our trade, we forget that there was a day when these ideas were known only in smaller niche communities, and also when the concepts had not yet been validated. Much of the scientific work to perform the experimental validation was performed by Israelachvili and the field of surface forces and AFM research that he helped to spawn.[3]

Perhaps equally as important, much related research was performed by a scientific titan in the former Soviet Union: Boris Derjaguin and the scientific community around him.[4] It is fascinating to survey the development of nanoscience in retrospect and to reflect on how ideas were developed and pursued independently in different corners of the world, back in the days when the scientific world was less networked than it is today. The source materials to which we just referred[2,3] contain numerous original references to the many other scientists, living and dead, who also contributed in essential ways.

Forces are just part of the story, however. We call especial attention to the intellectual contributions of Ludwig Boltzmann, whose shadow continues to be cast into the 21st century though he lived so long ago. Battles fought long ago by Boltzmann taught the world that nanoparticles and atoms exist. Nanoparticles are buffeted by thermal energy; enthalpic forces of interaction between them are countervailed by entropy; sometimes paradoxically so.[5] The essential role played by entropy in understanding nanoparticle order has been preached eloquently.[5]

In making these few references to specific scientists, we apologize to the numerous other scientists who deserve to be cited, if this were a history of the subject. But instead this is a short and personal essay, so we hope our brevity with citations can be forgiven.

What is a nanoparticle?

Like great art, we recognize nanoparticles but to agree on what they are, this is more difficult. We mean something more subtle than simply a material that is nm in dimension, as macromolecules are also nm in dimension: not only in the synthetic world of polymers and microgels but also in the biological world of proteins, RNA, and DNA. So: we cannot discriminate on the basis of size alone. However, it is helpful, in organizing our thinking, to exclude large objects the size of soccer balls, even though it is true that a Devil's Disciple might argue that a soccer ball is nm-sized relative to the size of a sun. For soccer balls, thermal energy = 0, but not so for nanoparticles.

Quantum mechanics is at the heart of the matter, when understanding a molecule. One needs to understand covalent bonding, aromaticity, molecular structure, and much more; and the whole is *not* the sum of its parts. Consider the caffeine molecule, for example. Information about its atomic composition, $C_8H_{10}N_4O_2$, is relatively uninformative as the organization of those atoms in space with quantum mechanical interactions between them is so relevant and interesting. But from the nanoparticle perspective, nanoparticle and colloidal "molecules" are a metaphor[6] for systems where often we are content to know the structural makeup: that the "molecule" is a dimer, trimer, or some other cluster. To a useful approximation, such clusters indeed are the sum of their parts. In the current understanding of nanoparticles, quantum mechanics is often secondary and the classical language of enthalpy and entropy are sufficient to describe the interactions between them.

Exceptions matter

The burgeoning field of plasmonic assemblies does rely on quantum mechanical interactions between nanoparticles, especially when the nanoparticle is a metal.[7] Furthermore, understanding of active matter is developing rapidly, but active matter does not involve a significant contribution from thermal energy.[8] An intriguing challenge for the future is that the importance of biological nanomachines ("molecular motors") is clear[9] but synthetic active nanomachines are at an early stage of development.

If the nanoparticle is sufficiently large, beyond roughly 20 nm in linear dimension, the span of surface forces is smaller than this, and hence interactions can be decomposed pairwise. But smaller nanoparticles often obey force interactions whose distance span actually exceeds the particle size. In those cases, numerous nanoparticles are mutually influenced by the same force interactions, and simplifications such as DLVO cease to be helpful to the point of becoming an oversimplification. It is not widely enough appreciated that the ratio of nanoparticle size to span of surface force interactions is so essential.

Nanoparticle self-assembly *versus* macroscopic top-down construction

Most of the attendees at this meeting arrived by automobile or airplane. Modern airliners are marvelous machines with millions of parts going into their construction; their cost is enormous, their size is enormous, they employ hundreds of thousands of workers for their construction and maintenance, and they contain millions of parts. It is fascinating to contrast such mega-machines with living cells: living cells reproduce themselves, they are tiny, their cost is low, and yet they too contain millions of parts, parts which we know by the name of "protein". We can find from company literature that a commercial airplane contains on the order of 2 million parts, while a living cell contains on the order of 2 million proteins per cubic micron. The airplane is created by a careful and deliberate top-down construction, but living cells just grow.

Nanoscience and nanotechnology are a long way from knowing how to achieve this synthetically but nature shows us, by example, that the concept is possible. A holy grail for our community is to learn how to assemble complex machines from the bottom-up and with nm-sized interacting parts. Whatever progress we make in this direction, it could become a step towards implementing one of the goals of this meeting: to understand how a fundamental understanding of the rapidly evolving field of nanoparticle self- and driven assembly can be translated into design principles useful for applications.

Nanoparticles with more intelligent substructures

In this exciting age of discovery, nanoscientists have contributed to understanding biology; as an example, a lovely recent work shows some principles of protein assembly and reveals a figurative "periodic table of protein complexes".[10] Conversely, we nanoscientists have much to learn from the example of nm-sized proteins, not just from their role as nanomachines[9] but even more generally so.

A limitation is that our nanoparticles often consist of frozen structures: for example, a gold or silver or silica nanoparticle, or a quantum dot, or some other construct whose size and structure is known. For these frozen structures, their size and surface chemical makeup are most of the information needed to understand the nanoparticle's physical behavior. This has carried the field a long way but increasingly the field is looking towards new functions that cannot be thus achieved. Might it be possible to design new nanoparticles whose function changes by binding to a function that is far away? If we could learn to do this, it would be the "allostery" effect known for proteins. In fact, proteins present, by their existence, proof that there can be a dynamic continuum of allosteric phenomena, with rigid-body motions of protein sub-elements on one extreme of relatively little disorder, and local unfolding or even intrinsically disordered nanoparticle structures on the other extreme of high disorder.[11] There is the possibility to engineer new kinds of synthetic nanoparticles whose structure will respond to the environment in a more subtle fashion than in conventional ways. Responses to pH changes, temperature changes and the like are already known and well understood[1] but there is scope for allosteric responses that would be significantly more subtle and complex, not with the goal of reproducing what nature has already achieved, but to find ways to learn from it by analogy and metaphor. To achieve such goals, our nanoscience community will need to invent fundamentally new ways to design nanoparticles with intelligent substructures.

Nanoparticle systems cued to interact subtly in space and time

Upon a survey of the literature, it is striking to notice that the interactions between nanoparticles are built so much on the classical forces of colloid science[3,4] without the specificity that nature displays in any living cell.

To a nanoscientist, one of the most gloriously surprising aspects of living cells is that the nm-sized proteins manage to coexist without too much interference with one another; they interact as needed, and also they *fail to interact*, as needed. This allows the presence of systems in which nm-sized proteins of many sorts coexist while allowing each to perform its function.[12] They follow rules of network interactions, consisting of "subnets" within larger networks, in which interacting elements are orthogonal in space and time, thus enabling functions which go magnificently beyond what can be designed using concepts of classical nanoscience and nanotechnology.[12] Nanoscience can learn thematically from this proof of concept too. Presently we know too little about how to signal interactions between selected nanoparticles, too little about how to switch interactions on and off, too little about how to design the structure of one spatio–temporal element of a nanoparticle assembly while leaving other portions of the sample unaffected. This should be possible to achieve in the synthetic nanoparticle world but our community does not know well enough how to design it. This could become a holy grail for nanotechnology of the future.

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