CHALLENGES AND OPPORTUNITIES FOR NANOSCIENCE AND TECHNOLOGY

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Last year I testified before the science subcommittee of the US Senate on the subject of the reauthorization of the National Nanotechnology Initiative (NNI).[1] When this initiative was launched by President Bill Clinton in 2001, the number of researchers working on nanotechnology was relatively small and the field was not even fully defined. That soon changed as the NNI started to invest more than $1billion per year in nanoscience and technology at universities, national laboratories and elsewhere. Other governments soon followed suit, and nanotechnology institutes began to spring up around the globe. Although the field was extremely long on promise, it fell equally short on delivery. Almost any idea that could even be partially defended could garner some sort of grant funding.

Around that time, which coincided with the dot.com boom, I was at a party near the heart of Silicon Valley, and venture capitalists were offering to fund nanotechnology start-up companies that had, as their basis, perhaps one refereed journal article and some notes on a cocktail napkin. The wild landscape that surrounded nanotechnology at that time is now much tamer, and the number of researchers (and papers and journals) in the field has grown dramatically. Moreover, funding agencies, companies, venture capitalists and so forth now demand that any proposals in nanoscience and technology they are going to fund must have a significant scientific foundation. Perhaps the biggest sign of how the field has matured, however, is that lawyers and legislators have now become interested in regulating nanotechnology, as I witnessed during my visit to the senate. The need to regulate nanotechnology was the main theme of the hearing I took part in. It felt a bit like the taming of the American west.

In the early 1990s when nanoscience was first coming into its own, there were two basic drivers for the field. The first was the goal of developing a bottom-up, or biologically inspired, manufacturing approach. Such an approach, in principle, would integrate organic, inorganic and biomaterials to yield novel nanosystems with properties that arose from the collective interactions of the components. The second goal was to develop advanced-performance electronic and photonic devices through the integration of extreme scaling (that is, making everything smaller) with non-traditional, high-performance electronic components. The value proposition for each of these two goals was that the pathway towards achieving either one would result in capabilities that would enable many applications. Work over the past several years has begun to establish the scientific fundamentals of nanotechnology more firmly, and the nanotechnology application space is becoming increasingly better defined. The reviews contained within this book provide a marvellous view of that progress, and give evidence that the promise of the field is now beginning to be balanced with a significant amount of delivery.

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For those of us who have worked in the field for a long time, nanotechnology still seems young and filled with remarkable potential. In this article I attempt to project where nanotechnology is headed over the next decade or two. New technologies evolve exponentially (an example is the rapidly dropping cost of DNA sequencing), with the result that enabled applications can emerge in unpredictable and often disruptive ways (consider how extremely inexpensive transistors enabled the internet, iPods and cellular phones). Thus, application-specific predictions regarding the future of emerging technologies almost always miss the mark. Nevertheless, there are some major scientific and technological challenges that will certainly drive a large fraction of nanotechnology research for the next several years, and those problems provide a more reliable framework for a future-of-nanotechnology discussion.

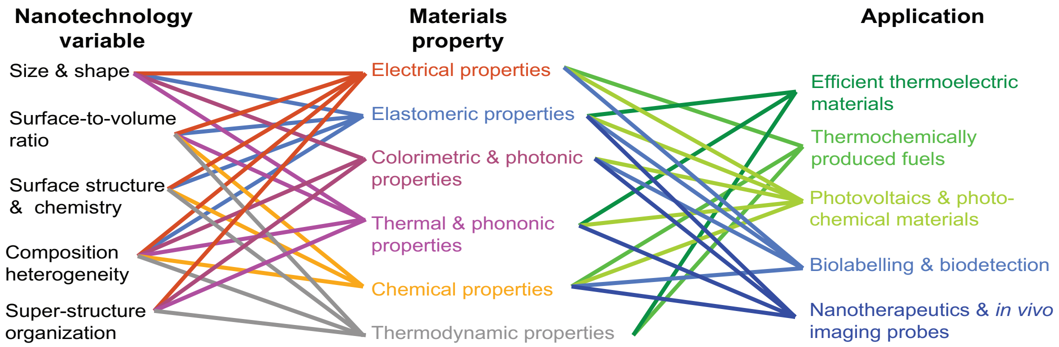

Figure 1. The left column of this figure shows what I call the nanotechnology variables (parameters that can be controlled in experiments). The middle column shows the various materials properties that can be controlled by some or all of the nanotechnology variables. The right column lists five selected applications in the fields of energy and health that depend on some or all of the materials properties.

I will begin by summarizing the value of nanotechnology, which can be framed within a discussion of what I call nanotechnology variables — that is, experimentally controllable parameters (such as size and surface-area-to-volume ratio; Fig. 1) that serve to distinguish nanotechnologies from more traditional technologies. I will then turn to the current state-of-the-art in nanotechnology within the context of the original goals of the field. The bulk of this article will then be devoted to covering two of the newer challenges. The more important of these involves the development of inexpensive, clean and renewable energy. A second major challenge is to provide broadly available and cost-effective healthcare in the developed and developing worlds. Finding solutions to these problems will require coordinated international efforts involving scientists, politicians, an informed public and the corporate world. However, if the science that provides the foundation for solving these problems is not correct, then not much else matters. For these problems, nanotechnologies will have important supporting roles in improving the performance of existing products and processes. First, however, let's turn to some of the reasons that make nanotechnologies attractive for a broad range of problems.

The value proposition of nanotechnology

For bulk materials, certain fundamental properties — such as electrical and thermal conductivity, colour, melting point, elasticity, electronic structure and so on — are intrinsic to the material structure and composition. A unique hallmark of nanomaterials is that each of these fundamental properties has one or more associated length scales and, as a consequence, the properties may themselves be controlled by experimentally tuning one or more of the nanotechnology variables (Fig. 1). This adds a tremendous flexibility to nanomaterials, in ways that are only partially understood. It can also make the optimization of a given physical property challenging, as so many variables can influence that property. Whatever the challenges, these variables set nanotechnologies apart, and give them significant and unique value for a host of applications. Some potential and existing applications are presented in the right-hand column of Fig. 1, and these are representative of nanotechnologies only in that they span the range from existing commercial products to avenues that are still evolving at the basic science level. They also relate to the two problems at hand — energy and healthcare — and at least some important proof-of-concept demonstrations exist for all the applications listed.

The early goal of building advanced electronic and photonic technologies using a combination of novel materials integrated into near molecular- or macromolecular-scale devices has resulted in some impressive scientific demonstrations. A partial list includes molecular electronic memories,[2] circuits based on nanowires[3,4] and carbon nanotubes,[5] novel circuit architectures, new photonic materials,[6] and new patterning approaches.[7] Photonics is a younger technology, and so nanotechnology advances in that field are likely to have a shorter-term impact. For information technology, there will certainly be some niche applications that directly arise from this work, perhaps through patterning methods and new materials. In addition, the nanotechnology-based metrology tools already have important roles in commercial manufacturing. It is even possible that a disruptive technology in the form of a new switching device that can replace the silicon transistor will yet emerge. Nevertheless, the semiconductor industry has successfully continued its focus on pushing silicon-based (top-down) manufacturing towards higher performance and lower-cost devices. This, in itself, is increasingly a form of nanotechnology, but nanowires, nanotubes and molecular electronic devices do not have major roles in this push at present.

Instead, the real value of the nanoscience effort has been threefold. First, a whole new set of nanomaterials (quantum dots, molecular machines, nanowires and so on) is now broadly available. Second, manufacturing approaches that include the programmed formation and assembly of nanostructures, the integration of disparate materials types, and novel patterning and pattern-replication approaches, are now established. Third, an accompanying knowledge is emerging of how the nanotechnology variables of Fig. 1 may be controlled to influence a given set of physical properties for a given nanosystem, and this is having a profound influence on a whole new set of challenges, some of which are discussed below.

A full discussion of the graph in Fig. 1 is beyond the scope of this article, and so I will limit the discussion to the few applications listed, connecting those opportunities back to the nanotechnology variables, and I will attempt to elucidate the fundamental limits of the applications, and how nanotechnology can be harnessed to help approach those limits. The top three applications in Fig. 1 (green font) are all related to the problem of clean energy, whereas the last two applications are related to disease diagnostics and therapeutics.

Selected energy applications

Compelling arguments can be made that the Sun will provide our eventual, primary source of clean and renewable energy,[8] and so the scientific challenges are to find cost-effective ways to harvest, store, convert and transport this energy. The most important of these challenges are energy harvesting and conversion. If solar energy can be efficiently captured and converted into transportable fuels, then existing infrastructure can go a long way towards providing a solution for the rest of the energy problem. The three energy applications listed in Fig. 1 are for energy capture and conversion — the first two (thermoelectric materials and thermochemically produced fuels) treat the Sun as a source of heat, whereas the third (photovoltaic devices and photoelectrochemical cells) treats it as a source of photons. Between them these three applications illustrate emerging new science and also serve as examples of how the nanotechnology variables can be harnessed for specific applications.

Thermoelectric materials convert thermal gradients into electric fields for power generation (or convert electricity into thermal gradients for refrigeration). Thermoelectric nanomaterials are promising because the thermoelectric efficiency of a material depends on its electronic, thermal, phononic and thermodynamic properties, which, in turn, are connected to virtually every nanotechnology variable listed in Fig. 1.

A thermoelectric device is effectively a heat engine with no moving parts, with an efficiency that is somewhat analogous to a Carnot engine, so that maximizing the temperature difference between the hot and cold sides, and minimizing entropic losses, will lead to higher efficiencies.[9] Formally, the efficiency of a thermoelectric material is defined by a dimensionless parameter $ZT = \sigma S^2 T/\kappa$, where T is temperature, σ is electrical conductivity, S is the thermopower (which correlates with entropy), and κ is the thermal conductivity. For bulk materials, maximizing ZT is challenging because optimizing one physical parameter often adversely affects another. However, at the nanoscale, some of these co-dependencies can be separated. For example, in a semimetal or highly doped semiconductor, the thermopower is proportional to the energy derivative of the density of electronic states. In a nanostructured semiconductor or semimetal, the density of electronic states can have sharp peaks, and this can, in theory, produce a high thermopower.[10] Harnessing this effect to produce high-ZT materials has had only limited success, possibly because lattice distortions can provide energetically favourable routes for lifting electronic-state degeneracies.

A promising avenue for developing better thermoelectric materials is to exploit size-dependent thermal and phononic affects. The thermal conductivity in nanoscale semiconductor wires (and particle composites[11]) may be dramatically lowered without significantly influencing the electrical conductivity or the thermopower.[12,13] Much (but not all) of this effect can be attributed to large surface-to-volume ratios, which increase phonon scattering rates.[14,15] Also, long-wavelength acoustic phonons in nanostructures can sometimes be partially defined by the overall size and shape of the structure. In a nanowire, this means that the length rather than the cross-section of the nanowire limits the phonon mean free path. A charge carrier injected into a nanowire can relax by giving off heat to the lattice (this is the origin of electrical resistance), and the first step in this relaxation process is a collision between the electron and a long-wavelength phonon that conserves momentum (that is, is non-dissipative). The long-wavelength phonon can carry the heat to the other end of the nanowire, thus increasing the thermopower. As the thermal conductivity, κ, is averaged over all phonon modes, it is possible to dramatically reduce the thermal conductivity and increase the thermopower at the same time.[12]

Heat transport in nanostructures has recently emerged as an exciting new area for study. New physics is being reported,[16,17] but quantitative models that capture this physics and provide guidance for materials design are still lacking. One challenge is that any real thermocooling or thermopower application requires both hole and electron (p- and n-type) thermoelectric materials, as well as high values of ZT, which may be difficult to achieve.

Thermochemically produced fuels treat the Sun as a source of heat, with solar concentrators providing the energy necessary to drive the endothermic part of a thermochemical cycle. The cycle converts the kinetic energy of heat into the potential energy of chemical bonds. Such a cycle can, for example, use CO_2 or H_2O as feedstocks and generate H_2, CO or hydrocarbon fuels.[18] An example of a thermochemical cycle designed to split water via the reduction and subsequent oxidation of a metal oxide is:

$$\begin{array}{ll} T_{\text{HIGH}} & \text{MO}_x \rightarrow \text{MO}_{x-\delta} + \frac{\delta}{2}\text{O}_2 \\ T_{\text{LOW}} & \delta\text{H}_2\text{O} + \text{MO}_{x-\delta} \rightarrow \delta\text{H}_2 + \text{MO}_x \\ \hline \text{Net} & \text{H}_2\text{O} \rightarrow \frac{1}{2}\text{O}_2 + \text{H}_2 \end{array}$$

If the efficiency of this process is defined as the power stored in the free energy of the products divided by the solar power from the concentrator, then the Carnot efficiency limit applies, so that a bigger temperature difference $(T_{\text{HIGH}} - T_{\text{LOW}})$ translates into a higher efficiency. This is distinct from approaches that treat the Sun as a light source, which are designed for lower-temperature operation.

The solar thermal harvester itself is a decidedly macroscopic system — large mirrors concentrate solar heat onto collectors, which then often drive steam or Stirling (compressed gas) engines — and the electricity produced with this approach can cost as little as 10–15 cents per kilowatt hour. Although there are likely to be a number of opportunities for nanomaterials for the more efficient capture and storage of solar heat, the clearest opportunities lie within the relatively new use of solar–thermal technology to produce transportable fuels. As would be expected, most mature thermochemical processes do not rely on nanomaterials.[19] Nevertheless, nanostructured materials hold significant promise as the base materials (the MO_x in the equations above) for promoting thermochemical cycles. The nanotechnology variable of surface-to-volume ratio can be harnessed to increase the rate of a heterogeneous chemical process, such as the reduction or oxidation of the metal oxide at the gas/solid interface. Moreover, high surface-to-volume ratio materials can exhibit relatively high rates of oxygen diffusion — thus potentially accelerating the thermochemical cycle. In fact, similar arguments can be made for nanostructured lightweight battery materials.[20] Compositional heterogeneity at the nanoscale (for example, doping or catalyst addition) can be harnessed to increase the melting point of the oxide, thus permitting higher-temperature operation, or potentially generating different product fuels. However, trade-offs can include reduced melting points that are characteristic of finite-sized materials, or the appearance of new (and perhaps undesired) catalytic processes that occur at surface structures that are more common at the nanoscale than for bulk surfaces.

Developing a quantitative understanding of the surface science of nanomaterials will be a central theme of fundamental nanoscience research for years to come. It will require the development of new analytical tools and chemical approaches, and it will probably have the same profound influence on nanotechnologies that traditional surface (and interface) science has had on the semiconductor industry. Surface science is central to all of the applications discussed in this article.

Photovoltaic devices convert light into electrical power, and **photoelectrochemical cells** add an additional energy-conversion step by electrochemically generating transportable fuels, such as H_2, by the electrochemical splitting of H_2O.

For photovoltaics, the major challenge is to efficiently capture the incident solar photon flux and convert it into electrical power while minimizing resistive losses. Economic considerations are very important: about \$100 m^{-2} is a viable target for an array of 10%-efficient solar cells — this cost per unit area is more expensive than paint[8] but less than a good carpet. Although the thermodynamic limit of the efficiency of a solar cell can exceed 90% (Ref. 21), the Shockley limit is more realistic, and is around 30% for a conventional p–n junction silicon solar cell.[22,23] The Shockley limit assumes a p–n homojunction solar cell, with an energy bandgap. In such a junction, a photo-excited electron–hole pair is separated at the junction, with the hole and the electron travelling through the p-doped and n-doped regions of the junction, respectively, to be collected as current at the contacts to the semiconductor. The solar spectrum spans many wavelengths, but photons with energy less than the bandgap are not used, and photo-excited carriers with energies greater than the bandgap quickly relax to the band edges, giving off their excess energy as heat to the lattice. This relaxation mechanism alone limits the achievable sunlight-conversion efficiency within single-crystal silicon photocells to 44%.

Finding ways to match, or even beat, the Shockley limit leads naturally to an exploration of nanotechnologies. For example, minimizing the time between when a photon is absorbed, and the electron–hole pair is separated, implies the need for very small junctions in which the area of the interface between the p- and n-type regions is large — such as might be achieved by making interpenetrating super-structures comprising both p- and n-type conductors. The discussion on phonon physics in the section on thermoelectric materials above is also relevant, as designing systems in which the relaxation rate of photo-excited carriers is reduced is another promising avenue of study, but one that has received only slight attention so far.[24,25] The surface structure of nanoscale photoconductors is of key importance, as a roughened or charged surface can have an adverse effect on performance by scattering charge carriers, reducing carrier mobilities and enhancing non-radiative recombination rates. Certain chemical passivation strategies have provided encouraging results,[26] but no clear strategies have yet emerged. One approach that has proved promising, but is currently too expensive for most applications, is to build a thin-film superlattice with layers characterized by graded bandgaps, so that the lowest-energy bandgap material is at the bottom, and the largest is at the top.[27] This allows, within the restrictions of the Shockley limit, a more efficient absorption and use of solar light, as each layer within the stack absorbs light near the bandgap of the material in that layer, thus limiting losses caused by non-radiative processes.

For photoelectrochemically generated fuels, the photogenerated and separated electron and hole pairs are used to drive multi-electron electrochemical processes, such as the splitting of water or reduction of CO_2 (Ref. 8). Although photoelectrochemical cells operate at moderate temperatures, many of the challenges associated with thermochemical fuel production remain, such as the integration of catalysts, and the use of high surface-to-volume materials to efficiently drive heterogeneous chemical processes. The development of high-efficiency nanotechnology-based photovoltaics and photoelectrochemical fuel generators is significantly more complex than what is required for photothermal fuels production, largely because the demands on the quality of the surfaces, interfaces and superstructure are more extreme, and these are coupled with the need to fabricate that platform at very low cost. Nevertheless, this is an area where even incremental advances can translate into huge economic benefits, and that incentive will provide a pathway for the incorporation of nanotechnologies over the next decade or so.

Selected health applications

Over the next 10–20 (or more) years, healthcare will evolve from reactive medicine (disease is detected and treated in late stages) to a personalized, proactive and preventative medicine (presymptomatic disease is detected and treated on an individual basis). At the heart of this transformation will be a host of new, miniaturized technologies that permit biological information to be acquired and analysed quickly and cheaply.

Consider how cancer is detected and treated today. An initial diagnosis typically occurs through imaging (for example, mammography), physical inspection or an endoscopic procedure that is carried out on a patient who presents with certain complaints. If a potential cancer is found, it is biopsied and analysed. If cancerous, a major surgery is often performed, followed by radiation and chemotherapies — both of which have serious, detrimental side effects. For many cancers, multiple treatment options are possible, and so a patient is first placed on one treatment, followed by a watch-and-wait period. If the patient does not respond within a couple of months, then a second treatment is prescribed, and so on.

As genomic sequencing becomes more affordable, patients will have at least some information relevant to their probabilistic health future, which can be used to schedule physician visits before the development of symptoms. Given advances in the knowledge of disease biomarkers such as proteins, circulating tumour cells[28] and microRNAs,[29] it is likely that, for a given disease, a panel of blood-based biomarkers will be assessed to provide presymptomatic information relevant to the onset and progression of the disease. Therapies that are targeted to attack just the diseased cells will be administered, and a second set of biomarker measurements will be carried out to identify potential positive and adverse responses, or to rapidly adjust or alter the therapy. Following therapy, the patient will continue to be monitored using a panel of biomarkers that are indicative of disease recurrence.

Nanotechnology will have several roles in this evolution of healthcare.

Biolabelling and biodetection are major components of *in vitro* disease diagnostics, and nanotechnology already has a minor role in these areas. In fact, quantum dot biolabels are the prototypes that illustrate how the optimization of multiple nanotechnology variables (size and shape, surface structure and chemistry, composition heterogeneity) can lead to a robust commercial product.[30] Given the richness of the human blood proteome,[31] it is likely blood-based proteins (and potentially microRNAs) will eventually provide the major window for monitoring a patient's evolving health and disease, so I will focus on this area. Genome sequencing, which is rapidly becoming cost-effective, will provide the window into predictive medicine. For the case of proteins, the appropriate question is: "what additional technology advances are needed to drop protein biomarker measurements down to a penny (or less) per protein?". Answering this question can provide a guide for determining which technologies might and might not have roles in future healthcare.

For *in vitro* diagnostics, lab-on-a-chip microtechnologies[32] will have a more important role than nanotechnologies. Compared with existing assay techniques, microtechnologies can allow similar measurements, but from greatly reduced sample sizes. Small sample sizes have benefits that range from rapid assays to assays that can resolve information at the single-cell level — both of which will be important in future healthcare. A less mature, but extremely valuable advantage, is that microtechnologies can potentially integrate the steps of biospecimen handling, purification and so on, with the actual assay.[33] Looking slightly further ahead, the development of miniaturized platforms designed for the measurement of large panels of biomarkers, from sample sizes as small as a single cell (for example, circulating tumour cells[34] or stem cells[35]) will become increasingly important.

Nanotechnologies that find use in amplifying signals from existing protein assay technologies will probably have roles in increasing the sensitivity of *in vitro* diagnostics measurements.[36] However, many biomolecular detection nanotechnologies, such as nanowire[37] or nanocantilever[38] biosensors, are simply too expensive for wide-scale use.

Such nanosensors, when entrained within microfluidic channels, can rapidly detect specific biomolecules from small quantities of serum or other tissues. However, conventional assays can do the same,[39] and for less cost. For a highly multiplexed conventional (antibody-based) protein assay, the major costs are the antibodies that are used to capture and detect specific proteins. Alternative protein capture agents[40,41] that show the selectivity and sensitivity of antibodies, but also exhibit chemical, biochemical and physical stability, would provide a transformative technology that would influence all assay platforms, from conventional to nanotechnology-based.

Nanotherapeutics and *in vivo* imaging probes are nanoparticles that represent a significant step beyond quantum dot biolabels, and will be a very high-impact nanotechnology. I will focus my discussion on nanotherapeutics because nanotechnology-based *in vivo* imaging probes, although important, possess only a subset of the requirements that are needed for an effective nanotherapeutic.

Although some nanotherapeutics are plasmonic particles that act on tumours via physical effects (infrared heating to induce cell death),[42] most nanotherapeutics are organic nanoparticles that contain, within their core, $\sim 10^3$ copies of a known drug, which can range from a traditional small-molecule drug to a siRNA oligomer.[43] The shell of the particle is engineered for a host of possible functions that are independent of the payload. These functions can include controlled circulation times (up to days), evasion of the immune system, controlled targeting and delivery, controlled release, and controlled decomposition and clearance. To achieve these functions, virtually every physical and chemical property of the particle — including its size and shape, elastic modulus, surface charge, composition, the way in which the drug is released and so on — must be carefully engineered through control of the nanotechnology variables. However, the demonstrated and potential benefits are tremendous compared with standard therapeutics.[44]

To appreciate the potential value of a nanotherapeutic, first consider the limitations of a small-molecule chemotherapy. Chemotherapeutics have very short circulation times, which means that high-frequency dosing is often required. Small molecules can also leak out of the circulatory system and damage healthy tissues. In addition, resistance to chemotherapies can develop when certain cell surface proteins become over-expressed so that they pump the drugs out of diseased cells as soon as they are internalized. Although antibody therapeutics and antibody–drug conjugates can avoid some of these limitations, only nanoparticles have the potential to avoid all of them. For some emerging drug concepts, such as siRNA therapeutics, delivery is a huge challenge, and nanoparticles provide one of the most promising avenues for solving that problem.

This field is evolving so rapidly that almost any review is out of date by the time it is published. Nevertheless, I'll make some predictions. First, it is likely that, over the next decade, nanoparticle-encapsulated chemotherapies will go a long way towards removing the toxic side effects, and perhaps some of the acquired drug resistances, that are associated with traditional chemotherapies. In addition, nanoparticles that adopt new functions that include accurate targeting of diseased tissues, the ability to penetrate deep into tissues, avoidance of the liver (a common issue with nanoparticles) or enzymatically triggered drug release (to increase release specificity) are also likely to emerge. In the more distant future we will likely see nanotherapeutics with release mechanisms that are customized for precisely controlled release rates, dependent upon the mechanism of the therapeutic to be delivered. It is also likely that nanotherapeutics will appear that have their size, shape[45] and elastic modulus optimized to permit passage across the blood/brain barrier.

Conclusions

Over the past 10–15 years, nanotechnology has advanced beyond the stage of an infant scientific field to now provide a toolkit that is poised to help solve a number of pressing problems. For even the small number of applications that I have described here, the relevant nanotechnologies span the range from inorganic to organic to biologically derived nanomaterials. A common hallmark that sets these various nanomaterials apart from more traditional bulk or molecular materials are the experimental handles, or the nanotechnology variables, that give scientists and engineers a whole new design space for optimization of properties.

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