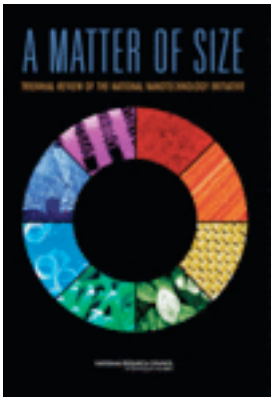

A Matter of Size: Triennial Review of the National Nanotechnology Initiative

Committee to Review the National Nanotechnology Initiative, National Research Council

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composites. For example, nanoporous materials can be specifically tailored to accommodate individual protein catalysts. Such materials could simultaneously protect the bulk protein molecule from destructive physical forces while retaining a channel to the catalytic site. The ability to synthesize biological macromolecules with novel materials components creates both the opportunity to build enzymes that function outside the normal cellular environment and the opportunity to modify the cellular environment by filling it with hybrid biomolecular-materials composites. The synthesis of DNA molecules containing metallo-base pairs creates a molecular structure that can transfer both biological information and anelectrical signal. Methodology has recently been developed to genetically encode novel amino acids. This has already been used to create heavy-atom-containing amino acids to facilitate x-ray crystallographic studies; amino acids with novel steric/packing and electronic properties; photocrosslinking amino acids that can be used to probe protein-protein interactions in vitro or in vivo; and keto- and acetylene-containing amino acids that can be used to selectively introduce a large number of biophysical probes, tags, and novel chemical functions.[15]

As the examples above make clear, the lines between nanotechnology and biotechnology are becoming blurred. Indeed, at the molecular level of structure, the border between living and nonliving materials is also rapidly fading. This reality begins to redefine commonly used definitions and confounds accepted paradigms.

Technical Feasibility of Site-Specific Chemistry for Large-Scale Manufacturing

Prudent extrapolation of the current research results presented above suggests an amazing future for nanotechnology. Indeed, many scientists foresee a long-term future in which a variety of strategies, tools, and processes allow nearly any stable chemical structure to be built atom by atom or molecule by molecule from the bottom up. However, there is still a gulf between this vision and popular images of nanotechnology in which the bottom-up approach is routinely used to manufacture complex, large-scale industrial objects such as computers or buildings at very low cost. The feasibility of such developments would depend on the attainable *efficiency* of the manufacturing processes. The proposed manufacturing systems[16–19] can be viewed as highly miniaturized, highly articulated versions of today's scanning probe systems, or perhaps as engineered ribosome-like systems designed to assemble a wide range of molecular building blocks in two or three dimensions rather than the linear assembly of amino acids by the ribosome. In this approach, reactions are described with both reagent and product as part of extended "handle" structures, which can be moved mechanically.[20] To be practical for the manufacture

of large-scale objects, such mechanisms would have to operate at a very low error rate, a very high speed, and near-perfect thermodynamic efficiency. Technical arguments for the eventual attainability of these attributes have been provided.[21] Design strategies have been outlined that, it is maintained, would allow such systems to greatly exceed the error rates, speed, and average thermodynamic efficiency of naturally evolved biological systems. Proponents of these design and manufacturing strategies foresee the exploitation of exquisitely controlled site-specific chemistry on a vast industrial scale. While scanning probe systems have demonstrated the feasibility of some site-specific reactions, scale-up to manufacturing systems is still a daunting task, and the majority of nanoscale scientists and engineers believe it is too early to try to predict the ultimate capabilities of such systems.

The committee found the evaluation of the feasibility of these ideas to be difficult because of the lack of experimental demonstrations of many of the key underlying concepts. The technical arguments make use of accepted scientific knowledge but constitute a "theoretical analysis demonstrating the possibility of a class of as-yet *unrealizable* devices."[22] Thus, this work is currently outside the mainstream of both conventional science (designed to seek new knowledge) and conventional engineering (usually concerned with the design of things that can be built more or less immediately). Rather, it may be in the tradition of visionary engineering analysis exemplified by Konstantin Tsiolkovski's 1903 publication, "The Exploration of Cosmic Space by Means of Reaction Devices,"[23] and today's studies of "space elevators" based on hypothetical carbon nanotube composite materials.[24]

Construction of extended structures with three-dimensional covalent bonding may be easy to conceive and might be readily accomplished, but only by using tools that do not yet exist.[25] In other words, the tool structures and other components cannot yet be built, but they can be computationally modeled. Modeling the thermodynamic stability of a structure (showing that it can, in principle, exist) does not tell one how to build it, and these arguments do not yet constitute a research strategy or a research plan.

To bring this field forward, meaningful connections are needed between the relevant scientific communities. Examples include:

- Delineating desirable research directions not already being pursued by the biochemistry community;
- Defining and focusing on some basic experimental steps that are critical to advancing long-term goals; and
- Outlining some "proof-of-principle" studies that, if successful, would provide knowledge or engineering demonstrations of key principles or components with immediate value.

CONCLUSIONS

Materials and devices of moderate complexity can be designed and manufactured by molecular self-assembly. Although self-assembly operates on simple and well-understood scientific principles, understanding of the details is far from complete. The ultimate potential of self-assembly processes in nature and in engineered manufacturing systems remains to be explored.

Proceeding beyond simple self-assembly, there is experimental evidence that biological systems can be modified to operate in conditions far outside those of the living cell, and therefore, many biotechnologists believe that these systems will form the basis for many future manufacturing processes.[26] Manufacturing trends and research directions in information technology and related fields also suggest the eventual development of manufacturing processes with some capability to pattern structures with atomic precision.[27]

Although theoretical calculations can be made today, the eventually attainable range of chemical reaction cycles, error rates, speed of operation, and thermodynamic efficiencies of such bottom-up manufacturing systems cannot be reliably predicted at this time. Thus, the eventually attainable perfection and complexity of manufactured products, while they can be calculated in theory, cannot be predicted with confidence. Finally, the optimum research paths that might lead to systems which greatly exceed the thermodynamic efficiencies and other capabilities of biological systems cannot be reliably predicted at this time. Research funding that is based on the ability of investigators to produce experimental demonstrations that link to abstract models and guide long-term vision is most appropriate to achieve this goal.

NOTES

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