Building molecular machine systems

K. Eric Drexler

Compared with conventional technologies, many natural molecular machines systems display tremendous abilities. The molecular machinery of green plants, for example, converts more energy and synthesizes a greater tonnage of organic compounds than does humanity's entire chemical industry, and does so cleanly and by using cheap raw materials. At a conservative megabyte or so per genome, the digital storage capacity of the millions of bacteria in the dirt on a typical computer far exceeds that of the advertised components. Although we spend billions of dollars on dense digital storage systems, nature places far denser systems in the same boxes free of charge, but unintended and unusable.

From megaton-per-year product streams to megabyte-per-cubic-micron storage systems, natural molecular machinery has outperformed anything we currently know how to build. Perhaps, then, we should learn to build molecular machine systems ourselves, aiming to make a wider range of products, including computer components. This is the first in a series of articles organized around the theme of nanotechnology. Other authors will describe a range of micro- and nanoscale systems – some useful today, others demonstrating components and techniques with promise for the future. I will outline how these trends can build toward a molecular machine technology delivering (and even exceeding) the technological promise demonstrated by the molecular machinery of nature.

What are molecular machine systems?

Speaking of molecular machines is not a metaphor. If something has moving parts and does useful work, we call it a machine. If something is nanometers in scale and has a precise arrangement of bonded atoms, we call it a molecule, or a molecular assembly. If something matches both these descriptions, we can properly call it a molecular machine; if it comprises many parts, each worthy of the name 'machine', it may be better described as a molecular machine system.

Such descriptions don't define sharp boundaries. Although it seems hard not to view the bacterial flagellar motor as a molecular machine, somewhere on the path towards simplicity – from ribosome to enzyme, organometallic catalyst or solvated ion – the term 'machine' loses its utility. The very fuzziness of the boundary, however, emphasizes that no barrier separates the simpler systems we can design and build from the more intricate and capable systems we can as yet only sketch and analyse. Development can proceed by increments rather than by breakthroughs.

As is so often the case in technology, engineering design and analysis can describe at least some of the possibilities. As one might expect, however, the easiest systems to analyse are not the easiest to synthesize. Biological systems and modern synthetic techniques can most easily make polymeric structures, but these must fold appropriately if they are to form compact, stable molecular objects. Designing and modeling polymers that fold and function in solution, however, presents severe challenges. Flexibility multiplies the possible configurations beyond any hope of an exhaustive analysis, and (with help from the solvent) ensures that the driving forces for molecular interactions depend strongly on the entropic components of the free energy. Accordingly, theoretical studies of molecular machine systems[1–3] have focused on inflexible covalent structures – graphitic and diamondoid materials – working in the simplest possible medium, a vacuum. Among the devices analysed are gears, bearings, motors and logic gates, and systems using them, including nanoscale separators, conveyors and assemblers for manipulating molecules, and sensors, signal channels and computers for manipulating bits.

A straightforward analysis based on well-established physical principles shows that these advanced devices can process matter, energy, and information precisely, efficiently and with high productivity[1]. Theoretical studies have explored synthetic strategies for such structures, guiding reactions by the atomically precise positioning of highly reactive species[3]. These synthetic strategies, however, themselves rely on preexisting molecular machinery to do the positioning – a good way to build on an initial success, perhaps, but not a good way to start. Diamondoid nanomachines seem an appealing goal for the long term (and they make a fine theoretician's playground today), but they can't be synthesized using current or next-generation laboratory techiques.

Concrete progress must build on existing technologies. As the most attractive approaches involve solvated, self-assembled systems of folded macromolecules, it should come as no surprise that biotechnology and its allied fields are well positioned to exploit the early opportunities. Both current developments and future possibilities have been explored in a series of conferences sponsored by the Foresight Institute[4–6].

Molecular design and fiddling

The most complex molecular machine systems yet shaped by human ingenuity are proteins. But, although current biotechnology modifies and shuffles natural proteins, it makes little use of *de novo* designs. This limitation stems in part from real difficulties, but bolder design efforts may also be inhibited by a tacit misconception of the nature of the design problems.

For classic example, 'the protein-folding problem,' is better thought of as two quite different problems, those of fold prediction and fold design. The first is scientific: given the primary structure of a natural protein, can we infer the tertiary structure (without help from knowledge of a homologous protein)? The second is technological: given a desired tertiary structure, can

K. E. Drexler is at the Institute for Molecular Manufacturing, 123 Fremont Ave., Los Altos, CA 94022, USA.

 0167-7799/99/$ – see front matter PII: S0167-7799(98)01278-5

'It's obvious you don't fully understand the company's approach to scale-up!'

we design a primary structure that will fold to produce it (with help from whatever choices of objective and approach prove most useful)? Because evolution – unlike human design – doesn't aim to develop humanly predictable folds, it seemed clear early on that the technological problem should prove easier[7]. Indeed, despite an early consensus that nature must be understood before engineering could succeed, fold design has advanced more quickly than fold prediction.

The lesson here is that technologists can cheat. In a technological context, the right approach to a difficult scientific question is often to go around it, to learn the basics from nature and then do something different. In protein design, for example, the numerous ~1 kcal mole^{-1} uncertainties in the stabilizing or destabilizing effect of residue-level choices can be buried by incorporating an unnaturally high density of interactions, each of which is expected (although not known) to be stabilizing. The individual uncertainties aren't eliminated, but are instead accommodated by allowing an overall margin for error.

Another escape from the paralysis-inducing contemplation of our scientific limitations is to exploit evolutionary methods. Nature, after all, has developed complex molecular machine systems without using graduate students or any other mechanism for designing and modeling proposed structures. *In vitro* evolutionary systems for peptides and nucleic acids show the value of large-scale trial and error, as does the recent explosion of combinatorial chemistry. Knowledge and clever design can shape experimental objectives and techniques while still relying on brute-force searches to find molecular solutions to a particular problem of binding or catalysis. With further ingenuity, these search techniques might be extended to aid the development of components for molecular machine systems.

Yet another way around problems is to work with more tractable biological materials. Protein folds are, in part, difficult to design because individual amino acids have no strong, natural complementarity. Designing self-assembling sticky-ended DNA structures, by contrast, is utterly routine. Elaborating this principle in more difficult directions has led to the design and synthesis of branched, three-dimensional structures (including a cube-like framework containing eight Y junctions) and a growing range of successors[8]. This work indicates that nucleic acids can be engineered to serve as scaffolds for complex molecular systems.

Biomimetic systems

Nature relies chiefly on proteins and nucleic acids for molecular machine components, but evolution has responded to incentives that differ from ours and has been locked into the same basic chemistry for billions of years. By learning from nature and then applying the tools of organic synthesis to realize quite different designs, we can gain still more freedom to avoid problems and implement solutions.

When building protein-like molecular objects, adding amino acids from outside the genetically encoded set can allow better core packings, complementary interactions, novel modes of cross linking, and a wider range of surface moieties[9]. Adding stabilizing interactions enables stable folds in shorter chains,

reducing the synthetic challenges. Entirely replacing the standard peptide backbone can also make synthesis easier; some choices also facilitate the formation of helical segments, producing so-called 'foldamers'. Like peptide chains, nonbiological foldamers can presumably serve as building blocks for tertiary and quaternary assemblies of the complexity necessary to implement molecular machine systems.

Fully synthetic nonbiological structures may seem far from the concerns of biotechnologists, but the actual overlap is quite broad. At the outset, good technological objectives will often stem from a biological inspiration. Then, after an excursion through nonbiological techniques to forge covalent structures, many of the key problems and techniques tend to reconverge. The purification, characterization and manipulation of solvated macromolecules and macromolecular assemblies will be as important here as in molecular biology; many of the same instruments and intellectual tools will be essential to the enterprise.

Tools

Regardless of whether specifically biological molecules remain the preferred choice for implementing design concepts, ongoing advances in tools for biotechnology will boost molecular machine research. The growth of combinatorial chemistry has strengthened the drive towards high-throughput, automated systems for chemical synthesis and analysis. Improved microfluidic systems – 'labs on a chip' – will make experiments faster and cheaper, expanding the utility of trial and error in overcoming limited predictive knowledge and design methods. Micromechanical systems in the form of scanning-probe microscopes now enable the direct visualization and manipulation of individual macromolecules.

Powered by the exponential explosion in microprocessor performance, advances in molecular modeling software have expanded the range of systems that can be effectively simulated. Here again, the distinction between scientific and technological questions makes a difference. For example, no molecular modeling system can correctly predict the equilibrium crystal structure of every organic molecule, if only because the choice between structures of different symmetry may depend on arbitrarily small differences in free energy. If modeling is viewed as a scientific effort to develop a comprehensive, predictive theory, this is a grave shortcoming. If modeling is seen as a means of searching for extraordinarily stable structures, however, substantial errors in energy calculations may be acceptable. In many areas of molecular engineering, designs for which modeling gives ambiguous results will be those lacking overall robustness. Better, then, to fix the design than perfect the model.

Toward biomimetic machinery

With computational modeling to aid rational design, and faster, cheaper cycles of synthesis and analysis to correct mistakes, it seems that emerging technologies will eventually enable the routine fabrication of diverse macromolecular objects comparable in function to proteins. As proteins in nature form molecular machine systems, it seems worth considering what analogous systems could do for us.

Current technological approaches have shaped plans to spend billions of dollars in a worldwide, multi-year effort to read the human genome. The scale of this effort seems odd, because every person working in it has a body with trillions of cells, each containing a human genome and a set of molecular machines able to read and copy it in a matter of hours. These DNA readers transfer genetic information to other molecules, rather than to a conventional database, but this reflects evolutionary, not physical constraints. Many techniques (optical, mechanical and electrical) are now known for sensing changes in single molecules. Thus, an early product of a molecular machine technology could be a DNA reader using arrays of devices comparable to a bacterial DNA polymerase in size (~6 nm) and throughput (~10 bases s^{-1}) but bound to a solid surface and interfaced to microelectronics. At the current cost of sequence data, even molecular complexes laboriously nudged together and monitored using scanning-probe systems could prove to be economical.

Of more direct use to molecular machine technology itself would be a device with ribosome-like utility, able to piece together sequences of nonbiological monomers that fold to make stable, functional products. Like the DNA polymerases, natural ribosomes transfer information from one molecular medium to another, and here again, a direct link to the macroscopic world would be useful. Biology makes little use of a mechanism ubiquitous in chemical technology: building structures by exposure to a sequence of chemical environments with differing temperature, pressure, pH, reagents and so forth; solid-phase synthesis schemes provide good examples. Temporal sequencing could likewise be used to control the sequence of monomers added by a simple machine. Ideally, of course, a sequence-builder would comprise a set of self-assembling molecules of the sort that it itself can build.

There is no great technological divide between adding monomers to a chain or to a dendrimer, a sheet or a sturdy cross-linked block. External signals can drive complex sequences of actions in simple nanoscale systems[1], allowing them to place monomers in patterns that form systems that are larger and more intricate. The interactions between small molecular parts are as simple as the interactions between transistors, but microprocessors show that patterns of simple interactions can enable microscopic systems to perform complex, programmable behaviors. It will be similar with molecular machine systems, and the limits are hard to see.

References

1 Drexler, K. E. (1992) *Nanosystems: Molecular Machinery, Manufacturing, and Computation*, Wiley–Interscience
2 Tuzun, R. E., Noid, D. W. and Sumpter, B. G. (1995) *Nanotechnology* 6, 64–74
3 Merkle, R. C. (1997) *Nanotechnology* 8, 149–162
4 Whole issue (1991) *Nanotechnology* 2, 111–219
5 Crandall, B. C. and Lewis, J., eds (1992) *Nanotechnology: Research and Perspectives*, MIT Press
6 Whole issue (1998) *Nanotechnology* 9, 143–304
7 Drexler, K. E. (1981) *Proc. Natl. Acad. Sci. U. S. A.* 78, 5275–5278
8 Seeman, N. C. *et al.* (1998) *Nanotechnology* 9, 257–273
9 Drexler, K. E. (1994) *Annu. Rev. Biophys. Biomol. Struct.* 23, 377–405