



## CHAPTER ONE

# Engines of Construction<sup>[1]</sup>

*“Protein engineering ... represents the first major step toward a more general capability for molecular engineering which would allow us to structure matter atom by atom.”*

—KEVIN ULMER<sup>[2]</sup>  
Director of Exploratory Research  
Genex Corporation

COAL AND DIAMONDS, sand and computer chips, cancer and healthy tissue: throughout history, variations in the arrangement of atoms have distinguished the cheap from the cherished, the diseased from the healthy. Arranged one way, atoms make up soil, air, and water; arranged another, they make up ripe strawberries. Arranged one way, they make up homes and fresh air; arranged another, they make up ash and smoke.

Our ability to arrange atoms lies at the foundation of technology. We have come far in our atom arranging, from chipping flint for arrowheads to machining aluminum for spaceships. We take pride in our technology, with our lifesaving drugs and desktop computers. Yet our spacecraft are still crude, our computers are still stupid, and the molecules in our tissues still slide into disorder,

first destroying health, then life itself. For all our advances in arranging atoms, we still use primitive methods. With our present technology, we are still forced to handle atoms in unruly herds.

But the laws of nature leave plenty of room for progress, and the pressures of world competition are even now pushing us forward. For better or for worse, the greatest technological breakthrough in history is still to come.

## **Two Styles Of Technology**

Our modern technology builds on an ancient tradition. Thirty thousand years ago, chipping flint was the high technology of the day. Our ancestors grasped stones containing trillions of trillions of atoms and removed chips containing billions of trillions of atoms to make their axheads; they made fine work with skills difficult to imitate today. They also made patterns on cave walls in France with sprayed paint, using their hands as stencils. Later they made pots by baking clay, then bronze by cooking rocks. They shaped bronze by pounding it. They made iron, then steel, and shaped it by heating, pounding, and removing chips.

We now cook up pure ceramics and stronger steels, but we still shape them by pounding, chipping, and so forth. We cook up pure silicon, saw it into slices, and make patterns on its surface using tiny stencils and sprays of light. We call the products “chips” and we consider them exquisitely small, at least in comparison to axheads.

Our microelectronic technology has managed to stuff machines as powerful as the room-sized computers of the early 1950s onto a few silicon chips in a pocket-sized computer. Engineers are now making ever smaller devices, slinging herds of atoms at a crystal surface to build up wires and components one tenth the width of a fine hair.

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These microcircuits may be small by the standards of flint chippers, but each transistor still holds trillions of atoms, and so-called “microcomputers” are still visible to the naked eye. By the standards of a newer, more powerful technology they will seem gargantuan.

The ancient style of technology that led from flint chips to silicon chips handles atoms and molecules in bulk; call it *bulk technology*. The new technology will handle individual atoms and molecules with control and precision; call it *molecular technology*. It will change our world in more ways than we can imagine.

*Microcircuits* have parts measured in *micrometers*—that is, in millionths of a meter—but molecules are measured in *nanometers* (a thousand

times smaller). We can use the terms “nanotechnology” and “molecular technology” interchangeably to describe the new style of technology. The engineers of the new technology will build both nanocircuits and nanomachines.

## **Molecular Technology Today**

One dictionary<sup>[3]</sup> definition of a machine is “any system, usually of rigid bodies, formed and connected to alter, transmit, and direct applied forces in a predetermined manner to accomplish a specific objective, such as the performance of useful work.” Molecular machines fit this definition quite well.

To imagine these machines, one must first picture molecules. We can picture atoms as beads and molecules as clumps of beads, like a child’s beads linked by snaps. In fact, chemists do sometimes visualize molecules by building models from plastic beads (some of which link in several directions, like the hubs in a Tinkertoy set). Atoms are rounded like beads, and although molecular bonds are not snaps, our picture at least captures the essential notion that bonds can be broken and reformed.

If an atom were the size of a small marble, a fairly complex molecule would be the size of your fist. This makes a useful mental image, but atoms are really about 1/10,000 the size of bacteria, and bacteria are about 1/10,000 the size of mosquitoes. (An atomic nucleus, however, is about 1/100,000 the size of the atom itself;

the difference between an atom and its nucleus is the difference between a fire and a nuclear reaction.)

The things around us act as they do because of the way their molecules behave. Air holds neither its shape nor its volume because its molecules move freely, bumping and ricocheting through open space. Water molecules stick together as they move about, so water holds a constant volume as it changes shape. Copper holds its shape because its atoms stick together in regular patterns; we can bend it and hammer it because its atoms can slip over one another while remaining bound together. Glass shatters when we hammer it because its atoms separate before they slip. Rubber consists of networks of kinked molecules, like a tangle of springs. When stretched and released, its molecules straighten and then coil again. These simple molecular patterns make up passive substances. More complex patterns make up the active nanomachines of living cells.

Biochemists already work with these machines, which are chiefly made of protein, the main engineering material of living cells. These molecular machines have relatively few atoms, and so they have lumpy surfaces, like objects made by gluing together a handful of small marbles. Also, many pairs of atoms are linked by bonds that can bend or rotate, and so protein machines are unusually flexible. But like all machines, they have parts of different shapes and sizes that do useful work. All machines use clumps of atoms as parts. Protein machines simply use very small clumps.



Biochemists dream of designing and building such devices, but there are difficulties to be overcome. Engineers use beams of light to project patterns onto silicon chips, but chemists must build much more indirectly than that. When they combine molecules in various sequences, they have only limited control over how the molecules join. When biochemists need complex molecular machines, they still have to borrow them from cells. Nevertheless, advanced molecular machines will eventually let them build nanocircuits and nanomachines as easily and directly as engineers now build microcircuits or washing machines. Then progress will become swift and dramatic.

Genetic engineers are already showing the way. Ordinarily, when chemists make molecular chains—called “polymers”—they dump molecules into a vessel where they bump and snap together haphazardly in a liquid. The resulting chains have varying lengths, and the molecules are strung together in no particular order.

But in modern gene synthesis machines<sup>[4]</sup> genetic engineers build more orderly polymers—specific DNA molecules—by combining molecules in a particular order. These molecules are the nucleotides of DNA (the letters of the genetic alphabet) and genetic engineers don’t dump them all in together. Instead, they direct the machine to add different nucleotides in a particular sequence to spell out a particular message. They first bond one kind of nucleotide to the chain ends, then wash away the leftover material and add chemicals to

prepare the chain ends to bond the next nucleotide. They grow chains as they bond on nucleotides, one at a time, in a programmed sequence. They anchor the very first nucleotide in each chain to a solid surface to keep the chain from washing away with its chemical bathwater. In this way, they have a big clumsy machine in a cabinet assemble specific molecular structures from parts a hundred million times smaller than itself.

But this blind assembly process accidentally omits nucleotides from some chains. The likelihood of mistakes grows as chains grow longer. Like workers discarding bad parts before assembling a car, genetic engineers reduce errors by discarding bad chains. Then, to join these short chains into working genes (typically thousands of nucleotides long), they turn to molecular machines found in bacteria.

These protein machines, called restriction enzymes, “read” certain DNA sequences as “cut here.” They read these genetic patterns by touch, by sticking to them, and they cut the chain by rearranging a few atoms. Other enzymes splice pieces together, reading matching parts as “glue here” — likewise “reading” chains by selective stickiness and splicing chains by rearranging a few atoms. By using gene machines to write, and restriction enzymes to cut and paste, genetic engineers can write and edit whatever DNA messages they choose.

But by itself, DNA is a fairly worthless molecule. It is neither strong like Kevlar, nor colorful like a dye, nor active like an enzyme, yet it has something that industry is prepared to spend millions of dollars to use: the ability



to direct molecular machines called ribosomes. In cells, molecular machines first transcribe DNA, copying its information to make RNA “tapes.” Then, much as old numerically controlled machines shape metal based on instructions stored on tape, ribosomes build proteins based on instructions stored on RNA strands. And proteins are useful.

**“ ... much as old numerically controlled machines shape metal based on instructions stored on tape, ribosomes build proteins based on instructions stored on RNA strands.”**

Proteins, like DNA, resemble strings of lumpy beads. But unlike DNA, protein molecules fold up to form small objects able to do things. Some are enzymes, machines that build up and tear down molecules (and copy DNA, transcribe it, and build other proteins in the cycle of life). Other proteins are hormones, binding to yet other proteins to signal cells to change their behavior. Genetic engineers can produce these objects cheaply by directing the cheap and efficient molecular machinery inside living organisms to do the work. Whereas engineers running a chemical plant must work with vats of reacting chemicals (which often misarrange atoms and make noxious byproducts), engineers working with bacteria can make them absorb chemicals, carefully

rearrange the atoms, and store a product or release it into the fluid around them.

Genetic engineers have now programmed bacteria to make proteins ranging from human growth hormone to rennin, an enzyme used in making cheese. The pharmaceutical company Eli Lilly (Indianapolis) is now marketing Humulin, human insulin molecules made by bacteria.

### **Existing Protein Machines**

These protein hormones and enzymes selectively stick to other molecules. An enzyme changes its target's structure, then moves on; a hormone affects its target's behavior only so long as both remain stuck together. Enzymes and hormones can be described in mechanical terms, but their behavior is more often described in chemical terms.

But other proteins serve basic mechanical functions <sup>[5]</sup>. Some push and pull, some act as cords or struts, and parts of some molecules make excellent bearings. The machinery of muscle, for instance, has gangs of proteins that reach, grab a "rope" (also made of protein), pull it, then reach out again for a fresh grip; whenever you move, you use these machines. Amoebas and human cells move and change shape by using fibers and rods that act as molecular muscles and bones. A reversible, variable-speed motor drives bacteria through water by turning a corkscrew-shaped propeller. If a hobbyist could build tiny cars around

such motors, several billions of billions would fit in a pocket, and 150-lane freeways could be built through your finest capillaries.

**“Ribosomes are proof that nanomachines built of protein and RNA can be programmed to build complex molecules.”**

Simple molecular devices combine to form systems resembling industrial machines. In the 1950s engineers developed machine tools that cut metal under the control of a punched paper tape. A century and a half earlier, Joseph-Marie Jacquard had built a loom that wove complex patterns under the control of a chain of punched cards. Yet over three billion years before Jacquard, cells had developed the machinery of the ribosome. Ribosomes are proof that nanomachines built of protein and RNA can be programmed to build complex molecules.

Then consider viruses. One kind, the T<sub>4</sub> phage, acts like a spring-loaded syringe and looks like something out of an industrial parts catalog. It can stick to a bacterium, punch a hole, and inject viral DNA (yes, even bacteria suffer infections). Like a conqueror seizing factories to build more tanks, this DNA then directs the cell's machines to build more viral DNA and syringes. Like all

organisms, these viruses exist because they are fairly stable and are good at getting copies of themselves made.

Whether in cells or not, nanomachines obey the universal laws of nature. Ordinary chemical bonds hold their atoms together, and ordinary chemical reactions (guided by other nanomachines) assemble them. Protein molecules can even join to form machines without special help, driven only by thermal agitation and chemical forces. By mixing viral proteins (and the DNA they serve) in a test tube, molecular biologists have assembled working T<sub>4</sub> viruses. This ability is surprising: imagine putting automotive parts in a large box, shaking it, and finding an assembled car when you look inside! Yet the T<sub>4</sub> virus is but one of many self-assembling structures<sup>[6]</sup>. Molecular biologists have taken the machinery of the ribosome apart into over fifty separate protein and RNA molecules, and then combined them in test tubes to form working ribosomes again.

To see how this happens, imagine different T<sub>4</sub> protein chains floating around in water. Each kind folds up to form a lump with distinctive bumps and hollows, covered by distinctive patterns of oiliness, wetness, and electric charge. Picture them wandering and tumbling, jostled by the thermal vibrations of the surrounding water molecules. From time to time two bounce together, then bounce apart. Sometimes, though, two bounce together and fit, bumps in hollows, with sticky patches matching; they then pull together and stick. In this way protein adds to protein to make sections of the virus, and sections assemble to form the whole.

Protein engineers will not need nanoarms and nanohands to assemble complex nanomachines. Still, tiny manipulators will be useful and they will be built. Just as today's engineers build machinery as complex as player pianos and robot arms from ordinary motors, bearings, and moving parts, so tomorrow's biochemists will be able to use protein molecules as motors, bearings, and moving parts to build robot arms which will themselves be able to handle individual molecules.

### **Designing With Protein<sup>[7]</sup>**

How far off is such an ability? Steps have been taken, but much work remains to be done. Biochemists have already mapped the structures of many proteins. With gene machines to help write DNA tapes, they can direct cells to build any protein they can design<sup>[8]</sup>. But they still don't know how to design chains that will fold up to make proteins of the right shape and function. The forces that fold proteins are weak, and the number of plausible ways a protein might fold is astronomical, so designing a large protein from scratch isn't easy.

The forces that stick proteins together to form complex machines are the same ones that fold the protein chains in the first place. The differing shapes and kinds of stickiness of amino acids—the lumpy molecular “beads” forming protein chains—make each protein chain fold up in a specific way to form an object of a particular shape. Biochemists have learned rules that suggest how an amino acid chain might fold,

but the rules aren't very firm. Trying to predict how a chain will fold is like trying to work a jigsaw puzzle, but a puzzle with no pattern printed on its pieces to show when the fit is correct, and with pieces that seem to fit together about as well (or as badly) in many different ways, all but one of them wrong. False starts could consume many lifetimes, and a correct answer might not even be recognized. Biochemists using the best computer programs now available still cannot predict how a long, natural protein chain will actually fold, and some of them have despaired of designing protein molecules soon.

Yet most biochemists work as scientists, not as engineers. They work at predicting how natural proteins will fold, not at *designing* proteins that will fold predictably. These tasks may sound similar<sup>[9]</sup>, but they differ greatly: the first is a scientific challenge, the second is an engineering challenge. Why should natural proteins fold in a way that scientists will find easy to predict? All that nature requires is that they in fact fold correctly, not that they fold in a way obvious to people.

Proteins *could* be designed from the start with the goal of making their folding more predictable. Carl Pabo, writing in the journal *Nature*<sup>[10]</sup>, has suggested a design strategy based on this insight, and some biochemical engineers have designed and built short chains of a few dozen pieces<sup>[11]</sup> that fold and nestle onto the surfaces of other molecules as planned. They have designed from scratch a protein<sup>[12]</sup> with properties like those of melittin, a toxin in bee venom. They have modified existing

enzymes, changing their behaviors in predictable ways<sup>[13]</sup>. Our understanding of proteins is growing daily.

**“In 1959 ... some geneticists called genetic engineering impossible; today, it is an industry.”**

In 1959, according to biologist Garrett Hardin<sup>[14]</sup>, some geneticists called genetic engineering impossible; today, it is an industry. Biochemistry and computer-aided design are now exploding fields, and as Frederick Blattner wrote in the journal *Science*<sup>[15]</sup>, “computer chess programs have already reached the level below the grand master. Perhaps the solution to the protein-folding problem is nearer than we think.” William Rastetter of Genentech, writing in *Applied Biochemistry and Biotechnology*<sup>[16]</sup> asks, “How far off is *de novo* enzyme design and synthesis? Ten, fifteen years?” He answers, “Perhaps not that long.”

Forrest Carter of the U.S. Naval Research Laboratory, Ari Aviram and Philip Seiden of IBM, Kevin Ulmer of Genex Corporation, and other researchers in university and industrial laboratories around the globe have already begun theoretical work and experiments aimed at developing molecular switches, memory devices, and other structures that could be incorporated into a protein-based computer. The U.S. Naval Research Laboratory has held two international workshops on molecular electronic devices<sup>[17]</sup>, and a meeting



sponsored by the U.S. National Science Foundation has recommended support for basic research [18] aimed at developing molecular computers. Japan has reportedly begun a multimillion-dollar program aimed at developing self-assembling molecular motors and computers, and VLSI Research Inc., of San Jose, reports [19] that “It looks like the race to bio-chips [another term for molecular electronic systems] has already started. NEC, Hitachi, Toshiba, Matsushita, Fujitsu, Sanyo-Denki, and Sharp have commenced full-scale research efforts on bio-chips for bio-computers.”

Biochemists have other reasons to want to learn the art of protein design. New enzymes promise to perform dirty, expensive chemical processes more cheaply and cleanly, and novel proteins will offer a whole new spectrum of tools to biotechnologists. We are already on the road to protein engineering, and as Kevin Ulmer notes in the quote from *Science* that heads this chapter, this road leads “toward a more general capability for molecular engineering which would allow us to structure matter atom by atom.”

## **Second-Generation Nanotechnology**

Despite its versatility, protein has shortcomings as an engineering material. Protein machines quit when dried, freeze when chilled, and cook when heated. We do not build machines of flesh, hair, and gelatin; over the centuries, we have learned to use our hands of flesh and bone to build machines of wood, ceramic, steel,

and plastic. We will do likewise in the future. We will use protein machines to build nanomachines of tougher stuff than protein.

As nanotechnology moves beyond reliance on proteins, it will grow more ordinary from an engineer's point of view. Molecules will be assembled like the components of an erector set, and well-bonded parts will stay put. Just as ordinary tools can build ordinary machines from parts, so molecular tools will bond molecules together to make tiny gears, motors, levers, and casings, and assemble them to make complex machines.

Parts containing only a few atoms will be lumpy, but engineers can work with lumpy parts if they have smooth bearings to support them. Conveniently enough, some bonds between atoms make fine bearings; a part can be mounted by means of a single chemical bond<sup>[20]</sup> that will let it turn freely and smoothly. Since a bearing can be made using only two atoms (and since moving parts need have only a few atoms), nanomachines can indeed have mechanical components of molecular size.

How will these better machines be built? Over the years, engineers have used technology to improve technology. They have used metal tools to shape metal into better tools, and computers to design and program better computers. They will likewise use protein nanomachines to build better nanomachines. Enzymes show the way: they assemble large molecules by "grabbing" small molecules from the water around them, then holding them together so that a bond forms. Enzymes assemble DNA, RNA, proteins, fats, hormones,

and chlorophyll in this way—indeed, virtually the whole range of molecules found in living things.

Biochemical engineers, then, will construct new enzymes to assemble new patterns of atoms. For example, they might make an enzyme-like machine which will add carbon atoms to a small spot, layer on layer. If bonded correctly, the atoms will build up to form a fine, flexible diamond fiber<sup>[21]</sup> having over fifty times as much strength as the same weight of aluminum. Aerospace companies will line up to buy such fibers by the ton to make advanced composites. (This shows one small reason why military competition will drive molecular technology forward, as it has driven so many fields in the past.)

**“... the great advance will come when protein machines are able to make structures more complex than mere fibers.”**

But the great advance will come when protein machines are able to make structures more complex than mere fibers. These programmable protein machines will resemble ribosomes programmed by RNA, or the older generation of automated machine tools programmed by punched tapes. They will open a new world of possibilities, letting engineers escape

the limitations of proteins to build rugged, compact machines with straightforward designs.

Engineered proteins will split and join molecules as enzymes do. Existing proteins bind a variety of smaller molecules, using them as chemical tools; newly engineered proteins will use all these tools and more.

Further, organic chemists have shown that chemical reactions can produce remarkable results even without nanomachines to guide the molecules. Chemists have no direct control over the tumbling motions of molecules in a liquid, and so the molecules are free to react in any way they can, depending on how they bump together. Yet chemists nonetheless coax reacting molecules <sup>[22]</sup> to form regular structures such as cubic and dodecahedral molecules, and to form unlikely-seeming structures such as molecular rings with highly strained bonds. Molecular machines will have still greater versatility in bondmaking, because they can use similar molecular motions to make bonds, but can guide these motions in ways that chemists cannot.

Indeed, because chemists cannot yet direct molecular motions, they can seldom assemble complex molecules according to specific plans. The largest molecules they can make with specific, complex patterns are all linear chains. Chemists form these patterns (as in gene machines) by adding molecules in sequence, one at a time, to a growing chain. With only one possible bonding site per chain, they can be sure to add the next piece in the right place.

But if a rounded, lumpy molecule has (say) a hundred hydrogen atoms on its surface, how can chemists split off just one *particular* atom (the one five up and three across from the bump on the front) to add something in its place? Stirring simple chemicals together will seldom do the job, because small molecules can seldom select specific places to react with a large molecule. But protein machines will be more choosy.

A flexible, programmable protein machine will grasp a large molecule (the workpiece) while bringing a small molecule up against it in just the right place. Like an enzyme, it will then bond the molecules together. By bonding molecule after molecule to the workpiece, the machine will assemble a larger and larger structure while keeping complete control of how its atoms are arranged. This is the key ability that chemists have lacked.

Like ribosomes, such nanomachines can work under the direction of molecular tapes. Unlike ribosomes, they will handle a wide variety of small molecules (not just amino acids) and will join them to the workpiece anywhere desired, not just to the end of a chain. Protein machines will thus combine the splitting and joining abilities of enzymes with the programmability of ribosomes. But whereas ribosomes can build only the loose folds of a protein, these protein machines will build small, solid objects of metal, ceramic, or diamond—invisibly small, but rugged.

Where our fingers of flesh are likely to bruise or burn, we turn to steel tongs. Where protein machines are likely

to crush or disintegrate, we will turn to nanomachines made of tougher stuff.

## Universal Assemblers

These second-generation nanomachines — built of more than just proteins — will do all that proteins can do, and more [23]. In particular, some will serve as improved devices for assembling molecular structures. Able to tolerate acid or vacuum, freezing or baking, depending on design, enzyme-like second-generation machines will be able to use as “tools” almost any of the reactive molecules used by chemists — but they will wield them with the precision of programmed machines. They will be able to bond atoms together in virtually any stable pattern, adding a few at a time to the surface of a workpiece until a complex structure is complete. Think of such nanomachines as *assemblers* [24].

Because assemblers will let us place atoms in almost any reasonable arrangement (as discussed in the Notes) [25], they will let us build almost anything that the laws of nature allow to exist. In particular, they will let us build almost anything we can design — including more assemblers. The consequences of this will be profound, because our crude tools have let us explore only a small part of the range of possibilities that natural law permits. Assemblers will open a world of new technologies.

Advances in the technologies of medicine, space, computation, and production — and warfare — all depend on our ability to arrange atoms. With assemblers, we will be able to remake our world or

destroy it. So at this point it seems wise to step back and look at the prospect as clearly as we can, so we can be sure that assemblers and nanotechnology are not a mere futurological mirage.

## **Nailing Down Conclusions**

In everything I have been describing, I have stuck closely to the demonstrated facts of chemistry and molecular biology. Still, people regularly raise certain questions rooted in physics and biology. These deserve more direct answers.

**Will the uncertainty principle of quantum physics make molecular machines unworkable?**

This principle states (among other things) that particles can't be pinned down in an exact location for any length of time. It limits what molecular machines can do, just as it limits what anything else can do. Nonetheless, calculations show that the uncertainty principle places few important limits on how well atoms can be held in place, at least for the purposes outlined here. The uncertainty principle makes electron positions quite fuzzy, and in fact this fuzziness determines the very size and structure of atoms. An atom as a whole, however, has a comparatively definite position set by its comparatively massive nucleus. If atoms didn't stay put fairly well, molecules would not exist. One needn't study quantum



mechanics to trust these conclusions, because molecular machines in the cell demonstrate that molecular machines work.

Will the molecular vibrations of heat make molecular machines unworkable or too unreliable for use?

Thermal vibrations will cause greater problems than will the uncertainty principle, yet here again existing molecular machines directly demonstrate that molecular machines can work at ordinary temperatures. Despite thermal vibrations, the DNA-copying machinery in some cells [26] makes less than one error in 100,000,000,000 operations. To achieve this accuracy, however, cells use machines (such as the enzyme DNA polymerase I) that proofread the copy and correct errors. Assemblers may well need similar error-checking and error-correcting abilities, if they are to produce reliable results.

Will radiation disrupt molecular machines and render them unusable?

High-energy radiation can break chemical bonds and disrupt molecular machines. Living cells once again show that solutions exist: they operate for years by repairing and replacing radiation-damaged parts [27]. Because individual machines are so tiny, however, they present small targets for radiation and are seldom hit. Still, if a system of nanomachines must be reliable, then it will

have to tolerate a certain amount of damage, and damaged parts must regularly be repaired or replaced. This approach to reliability is well known to designers of aircraft and spacecraft.

Since evolution has failed to produce assemblers, does this show that they are either impossible or useless?

The earlier questions were answered in part by pointing to the working molecular machinery of cells. This makes a simple and powerful case that natural law permits small clusters of atoms to behave as controlled machines, able to build other nanomachines. Yet despite their basic resemblance to ribosomes, assemblers will differ from anything found in cells; the things they do—while consisting of ordinary molecular motions and reactions—will have novel results. No cell, for example, makes diamond fiber.

The idea that new kinds of nanomachinery will bring new, useful abilities may seem startling: in all its billions of years of evolution, life has never abandoned its basic reliance on protein machines<sup>[28]</sup>. Does this suggest that improvements are impossible, though? Evolution progresses through small changes, and evolution of DNA cannot easily *replace* DNA. Since the DNA/RNA/ribosome system is specialized to make proteins, life has had no real opportunity to evolve an alternative. Any production manager can well appreciate the reasons; even more

than a factory, life cannot afford to shut down to replace its old systems.

Improved molecular machinery should no more surprise us than alloy steel being ten times stronger than bone, or copper wires transmitting signals a million times faster than nerves. Cars outspeed cheetahs, jets outfly falcons, and computers already outcalculate head-scratching humans. The future will bring further examples of improvements on biological evolution, of which second-generation nanomachines will be but one.

In physical terms, it is clear enough why advanced assemblers will be able to do more than existing protein machines. They will be programmable like ribosomes, but they will be able to use a wider range of tools than all the enzymes in a cell put together. Because they will be made of materials far more strong, stiff, and stable than proteins, they will be able to exert greater forces, move with greater precision, and endure harsher conditions. Like an industrial robot arm—but unlike anything in a living cell—they will be able to rotate and move molecules in three dimensions under programmed control, making possible the precise assembly of complex objects. These advantages will enable them to assemble a far wider range of molecular structures than living cells have done.

Is there some special magic about life, essential to making molecular machinery work?

One might doubt that artificial nanomachines could even equal the abilities of nanomachines in the cell, if there were reason to think that cells contained some special magic that makes them work. This idea is called “vitalism.” Biologists have abandoned it because they have found chemical and physical explanations for every aspect of living cells yet studied, including their motion, growth, and reproduction. Indeed, this knowledge is the very foundation of biotechnology.

Nanomachines floating in sterile test tubes, free of cells, have been made to perform all the basic sorts of activities that they perform inside living cells. Starting with chemicals that can be made from smoggy air, biochemists have built working protein machines without help from cells. R. B. Merrifield, for example, used chemical techniques <sup>[29]</sup> to assemble simple amino acids to make bovine pancreatic ribonuclease, an enzymatic device that disassembles RNA molecules. Life is special in structure, in behavior, and in what it feels like from the inside to be alive, yet the laws of nature that govern the machinery of life also govern the rest of the universe.

The case for the feasibility of assemblers and other nanomachines may sound firm, but why not just wait and see whether they can be developed?

Sheer curiosity seems reason enough to examine the possibilities opened by nanotechnology, but there are stronger reasons. These developments will sweep the world within ten to fifty years—that is, within the expected lifetimes of ourselves or our families. What is more, the conclusions of the following chapters suggest that a wait-and-see policy would be very expensive—that it would cost many millions of lives, and perhaps end life on Earth.

Is the case for the feasibility of nanotechnology and assemblers firm enough that they should be taken seriously? It seems so, because the heart of the case rests on two well-established facts of science and engineering. These are (1) that existing molecular machines serve a range of basic functions, and (2) that parts serving these basic functions can be combined to build complex machines. Since chemical reactions can bond atoms together in diverse ways, and since molecular machines can direct chemical reactions according to programmed instructions, assemblers definitely are feasible.

## **Nanocomputers**

Assemblers will bring one breakthrough of obvious and basic importance: engineers will use them to shrink the size and cost of computer circuits and speed their operation by enormous factors.

With today's bulk technology, engineers make patterns on silicon chips by throwing atoms and photons at them, but the patterns remain flat and molecular-scale flaws are unavoidable. With assemblers, however, engineers will build circuits in three dimensions, and build to atomic precision. The exact limits of electronic technology today remain uncertain because the quantum behavior of electrons in complex networks of tiny structures presents complex problems, some of them resulting directly from the uncertainty principle. Whatever the limits are, though, they will be reached with the help of assemblers.

**“With assemblers, however, engineers will build circuits in three dimensions, and build to atomic precision.”**

The fastest computers will use electronic effects, but the smallest may not. This may seem odd, yet the essence of computation has nothing to do with electronics. A digital computer is a collection of switches able to turn one another on and off. Its switches start in one pattern (perhaps representing  $2 + 2$ ), then switch

one another into a new pattern (representing 4), and so on. Such patterns can represent almost anything. Engineers build computers from tiny electrical switches connected by wires simply because mechanical switches connected by rods or strings would be big, slow, unreliable, and expensive, today.

The idea of a purely mechanical computer is scarcely new. In England during the mid-1800s, Charles Babbage invented a mechanical computer built of brass gears <sup>[30]</sup>; his co-worker Augusta Ada, the Countess of Lovelace, invented computer programming. Babbage's endless redesigning of the machine, problems with accurate manufacturing, and opposition from budget-watching critics (some doubting the usefulness of computers!), combined to prevent its completion.

In this tradition, Danny Hillis and Brian Silverman of the MIT Artificial Intelligence Laboratory built a special-purpose mechanical computer able to play tic-tac-toe. Yards on a side, full of rotating shafts and movable frames that represent the state of the board and the strategy of the game, it now stands in the Computer Museum in Boston. It looks much like a large ball-and-stick molecular model, for it is built of Tinkertoys.

Brass gears and Tinkertoys make for big, slow computers. With components a few atoms wide, though, a simple mechanical computer would fit within 1/100 of a cubic micron, many billions of times more compact than today's so-called microelectronics. Even with a billion bytes of storage, a nanomechanical computer could fit in a box a micron wide <sup>[31]</sup>, about the size of a



bacterium. And it would be fast. Although mechanical signals<sup>[32]</sup> move about 100,000 times slower than the electrical signals in today's machines, they will need to travel only 1/1,000,000 as far, and thus will face less delay. So a mere mechanical computer will work faster than the electronic whirl-winds of today.

*Electronic* nanocomputers will likely be thousands of times faster than electronic microcomputers—perhaps hundreds of thousands of times faster, if a scheme proposed by Nobel Prize-winning physicist Richard Feynman<sup>[33]</sup> works out. Increased speed through decreased size is an old story in electronics.

## **Disassemblers**

Molecular computers will control molecular assemblers, providing the swift flow of instructions needed to direct the placement of vast numbers of atoms. Nanocomputers with molecular memory devices will also store data generated by a process that is the opposite of assembly.

Assemblers will help engineers synthesize things; their relatives, disassemblers, will help scientists and engineers analyze things. The case for assemblers rests on the ability of enzymes and chemical reactions to form bonds, and of machines to control the process. The case for disassemblers rests on the ability of enzymes and chemical reactions to break bonds, and of machines to control the process. Enzymes, acids, oxidizers, alkali metals, ions, and reactive groups of atoms called free

radicals—all can break bonds and remove groups of atoms. Because nothing is absolutely immune to corrosion, it seems that molecular tools will be able to take anything apart, a few atoms at a time. What is more, a nanomachine could (at need or convenience) apply mechanical force as well, in effect prying groups of atoms free.

A nanomachine able to do this, while recording what it removes layer by layer, is a disassembler. Assemblers, disassemblers, and nanocomputers will work together. For example, a nanocomputer system will be able to direct the disassembly of an object, record its structure, and then direct the assembly of perfect copies. And this gives some hint of the power of nanotechnology.

## **The World Made New**

Assemblers will take years to emerge, but their emergence seems almost inevitable. Though the path to assemblers has many steps, each step will bring the next in reach, and each will bring immediate rewards. The first steps have already been taken, under the names of “genetic engineering” and “biotechnology.” Other paths to assemblers seem possible. Barring worldwide destruction or worldwide controls, the technology race will continue whether we wish it or not. And as advances in computer-aided design speed the development of molecular tools, the advance toward assemblers will quicken.

To have any hope of understanding our future, we must understand the consequences of assemblers, disassemblers, and nanocomputers. They promise to bring changes as profound as the industrial revolution, antibiotics, and nuclear weapons all rolled up in one massive breakthrough. To understand a future of such profound change, it makes sense to seek principles of change that have survived the greatest upheavals of the past. They will prove a useful guide.