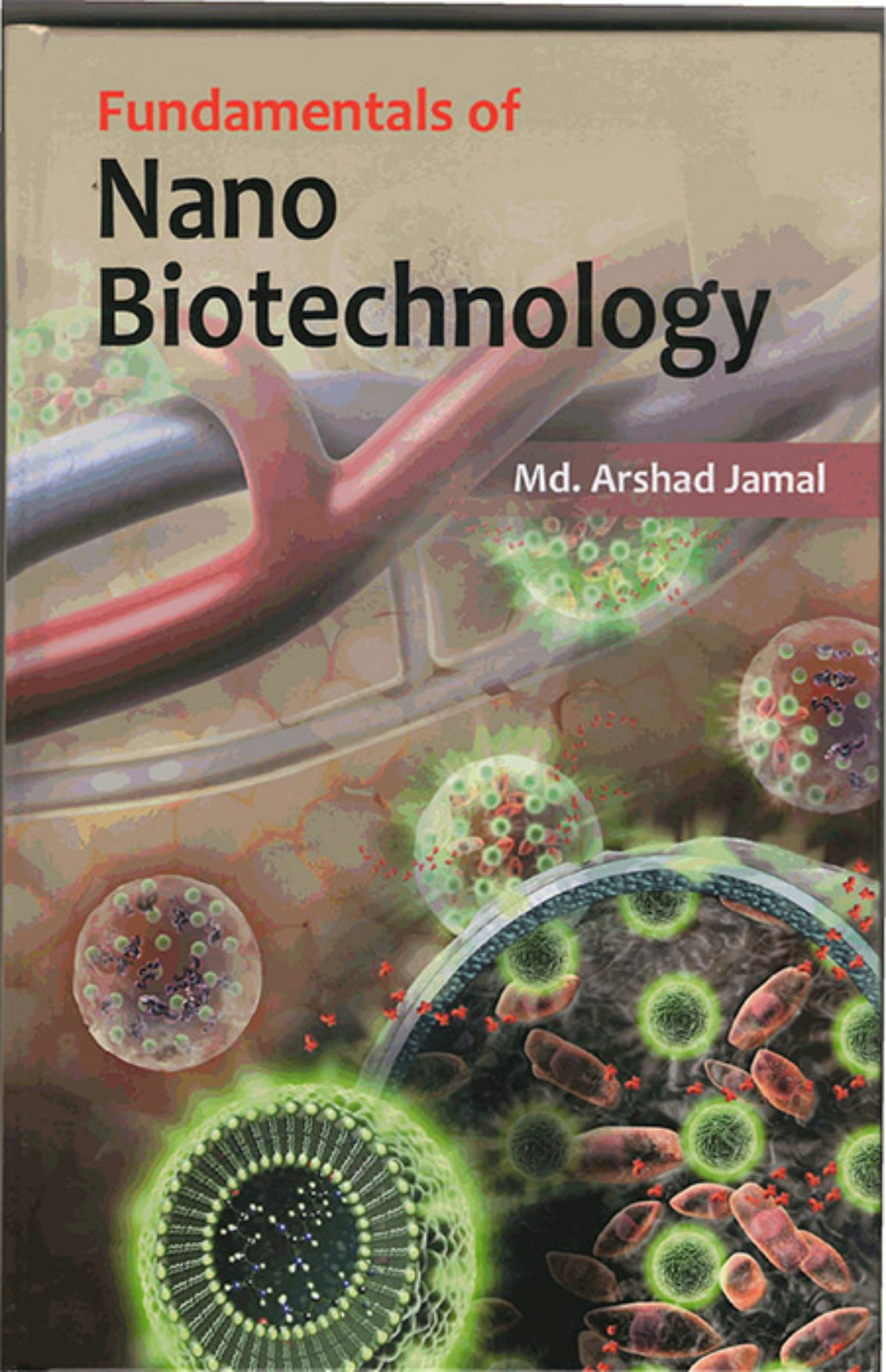
Fundamentals of Nano Biotechnology

Md. Arshad Jamal



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Preface

Nanotechnology is the key technology of the 21st century. The possibility to exploit the structures and processes of biomolecules for novel functional materials, biosensors, bioelectronics and medical applications has created the rapidly growing field of nanobiotechnology. Nanotechnology is the manipulation of matter on an atomic, molecular, and supramolecular scale. The earliest, widespread description of nanotechnology referred to the particular technological goal of precisely manipulating atoms and molecules for fabrication of macroscale products, also now referred to as molecular nanotechnology. A more generalized description of nanotechnology was subsequently established by the National Nanotechnology Initiative, which defines nanotechnology as the manipulation of matter with at least one dimension sized from 1 to 100 nanometers. This definition reflects the fact that quantum mechanical effects are important at this quantum-realm scale, and so the definition shifted from a particular technological goal to a research category inclusive of all types of research and technologies that deal with the special properties of matter that occur below the given size threshold. It is therefore common to see the plural form "nanotechnologies" as well as "nanoscale technologies" to refer to the broad range of research and applications whose common trait is size. Because of the variety of potential applications, governments have invested billions of dollars in nanotechnology research. Through its National Nanotechnology Initiative, the USA has invested 3.7 billion dollars. The European Union has invested 1.2 billion and Japan 750 million dollars.

Nanotechnology as defined by size is naturally very broad, including fields of science as diverse as surface science, organic chemistry, molecular biology, semiconductor physics, microfabrication, etc. The associated research and applications are equally diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing

new materials with dimensions on the nanoscale to direct control of matter on the atomic scale. Scientists currently debate the future implications of nanotechnology. Nanotechnology may be able to create many new materials and devices with a vast range of applications, such as in medicine, electronics, biomaterials and energy production. On the other hand, nanotechnology raises many of the same issues as any new technology, including concerns about the toxicity and environmental impact of nanomaterials, and their potential effects on global economics, as well as speculation about various doomsday scenarios. These concerns have led to a debate among advocacy groups and governments on whether special regulation of nanotechnology is warranted. Molecular nanotechnology, sometimes called molecular manufacturing, describes engineered nanosystems operating on the molecular scale. Molecular nanotechnology is especially associated with the molecular assembler, a machine that can produce a desired structure or device atom-by-atom using the principles of mechanosynthesis. Manufacturing in the context of productive nanosystems is not related to, and should be clearly distinguished from, the conventional technologies used to manufacture nanomaterials such as carbon nanotubes and nanoparticles. The combination of biology and nanotechnology has led to a new generation of nanodevices that make it possible to characterize the chemical, mechanical, and other molecular properties, as well as discover novel phenomena and biological processes occurring at the molecular level. These advances provide science with a wide range of tools for biomedical applications in therapeutic, diagnostic, and preventive medicine.

The present book 'Fundamentals of Nano Biotechnology' integrates interdisciplinary research and recent advances in instrumentation and methods for applying nanotechnology to various areas in biology and medicine. Pioneers in the field describe the design and use of nanobiosensors with various analytical techniques for the detection and monitoring of specific biomolecules. The textbook focuses on the design of novel bio-inspired materials, particularly for tissue engineering applications. Each chapter provides introductory material including a description of methods, protocols, instrumentation, and applications, as well as a collection of published data with an extensive list of references.

—Editor

Chapter 1

Nanotechnology Applications

Microtechnology and Nanotechnology

Can bulldozers can be used to make wristwatches? At most, they can help to build factories in which watches are made. Though there could be surprises, the relevance of microtechnology to molecular nanotechnology seems similar. Instead, a bottom-up approach is needed to accomplish engineering goals on the molecular scale.

Tools used for Molecular Engineering

Almost by definition, the path to molecular nanotechnology must lead through molecular engineering. Working in different disciplines, driven by different goals, researchers are making progress in this field. Chemists are developing techniques able to build precise molecular structures of sorts never before seen. Biochemists are learning to build structures of familiar kinds, such as proteins, to make new molecular objects.

In a visible sense, most of the tools used by chemists and biochemists are rather unimpressive. They work on countertops cluttered with dishes, bottles, tubes, and the like, mixing, stirring, heating, and pouring liquids-in biochemistry, the liquid is usually water with a trace of material dissolved in it. Periodically, a bit of liquid is put into a larger machine and a strip of paper comes out with a graph printed on it. As one might guess from this description, research in the molecular sciences is usually much less expensive than research in high-energy physics (with its multibillion-dollar particle accelerators) or research in space (with its multibillion-dollar spacecraft). Chemistry has been called "small science," and not because of the size of the molecules.

Chemists and biochemists advance their field chiefly by developing new molecules that can serve as tools, helping to build or study other molecules.

Further advances come from new instrumentation, new ways to examine molecules and determine their structures and behaviors. Yet more advances come from new software tools, new computer-based techniques for predicting how a molecule with a particular structure will behave.

Many of these software tools let researchers peer through a screen into simulated molecular worlds much like those toured in the last two chapters.

Of these fields, it is biomolecular science that is most obviously developing tools that can build nanotechnology, because biomolecules already form molecular machines, including devices resembling crude assemblers.

This path is easiest to picture, and can surely work, yet there is no guarantee that it will be fastest: research groups following another path may well win. Each of these paths is being pursued worldwide, and on each, progress is accelerating.

Physicists have recently contributed new tools of great promise for molecular engineering. These are the proximal probes, including the scanning tunneling microscope (STM) and the atomic force microscope (AFM).

A proximal-probe device places a sharp tip in proximity to a surface and uses it to probe (and sometimes modify) the surface and any molecules that may be stuck to it.

The scanning tunneling microscope (STM, on the left) images surfaces well enough to show individual atoms, sensing surface contours by monitoring the current jumping the gap between tip and surface.

The atomic force microscope (AFM, on the right) senses surface contours by mechanical contact, drawing a tip over the surface and optically sensing its motion as it passes over single-atom bumps.

Functionong of STM

An STM brings a sharp, electrically conducting needle up to an electrically-conducting surface, almost touching it. The needle and surface are electrically connected, so that a current will flow if they touch, like closing a switch. But at just what point do soft, fuzzy atoms "touch"?

It turns out that a detectable current flows when just two atoms are in tenuous contact-fuzzy fringes barely overlapping-one on the surface and one on the tip of the needle.

By delicately maneuvering the needle around over the surface, keeping the current flowing at a tiny, constant rate, the STM can map shape of the surface with great precision. Indeed, to keep the current constant, the needle has to go up and down as it passes over individual atoms.

The STM was invented by Gerd Binnig and Heinrich Rohrer, research physicists studying surface phenomena at IBM's research labs in Zurich, Switzerland. After working through the 1970s, Rohrer and Binnig submitted their first patent disclosure on an STM in mid-1979. In 1982, they produced images of a silicon surface, showing individual atoms.

Ironically, the importance of their work was not immediately recognized: Rohrer and Binnig's first scientific paper on the new tool was rejected for publication on the grounds that it was "not interesting enough." Today, STM conferences draw interested researchers by the hundreds from around the world.

In 1986-quite promptly as these things go-Binnig and Rohrer were awarded a Nobel Prize. The Swedish Academy explained its reasoning: "The scanning tunneling microscope is completely new and we have so far seen only the beginning of its development.

It is, however, clear that entirely new fields are opening up for the study of matter." STMs are no longer exotic: Digital Instruments of Santa Barbara, California, sells its system (the Nanoscope) by mail with an atomic-resolution-or-your-money-back guarantee.

Within three years of their commercial introduction, hundreds of STMs had been purchased.

Working of an AFM

The related atomic force microscope is even simpler in concept: A sharp probe is dragged over the surface, pressed down gently by a straight spring. The instrument senses motions in the spring (usually optically), and the spring moves up and down whenever the tip is dragged over an atom on the surface.

The tip "feels" the surface just like a fingertip in the simulated molecular world. The AFM was invented by Binnig, Quate, and Gerber at Stanford University and IBM San Jose in 1985.

After the success of the STM, the importance of the AFM was immediately recognized. Among other advantages, it works with nonconducting materials.

The next chapter will describe how AFM-based devices might be used as molecular manipulators in developing molecular nanotechnology. As this is written, AFMs have just become commercially available.

(Note that that AFMs and STMs are not quite as easy to use as these descriptions might suggest. For example, a bad tip or a bad surface can prevent atomic resolution, and pounding on the table is not recommended when such sensitive instruments are in operation. Further, scientists often have trouble deciding just what they're seeing, even when they get a good image.)

Can Proximal Probes Move Atoms?

To those thinking in terms of nanotechnology, STMs immediately looked promising not only for seeing atoms and molecules but for manipulating them. This idea soon became widespread among physicists.

As Calvin Quate stated in Physics Today in 1986, "Some of us believe that the scanning tunneling microscope will evolve... that one day [it] will be used to write and read patterns of molecular size." This approach was suggested as a path to molecular nanotechnology in Engines of Creation, again in 1986.

By now, whole stacks of scientific papers document the use of STM and AFM tips to scratch, melt, erode, indent, and otherwise modify surfaces on a nanometer scale. These operations move atoms around, but with little control. They amount to bulk operations on a tiny scale-one fine scratch a few dozen atoms wide, instead of the billions that result from conventional polishing operations.

In 1987, R. S. Becker, J. A. Golovchenko, and B. S. Swartzentruber at AT&T Bell Laboratories announced that they had used an STM to deposit small blobs on a germanium surface.

Each blob was thought to consist of one or a few germanium atoms. Shortly thereafter, IBM Almaden researchers John Foster, Jane Frommer, and Patrick Arnett achieved a milestone in STM-based molecular manipulation.

Of this team, Foster and Arnett attended the First Foresight Conference on Nanotechnology, where they told us the motivations behind their work.

Foster came to IBM from Stanford University, where he had completed a doctorate in physics and taught at graduate school. The STM work was one of his first projects in the corporate world.

He describes his colleague Arnett as a former "semiconductor jock" involved in chip creation at IBM's Burlington and Yorktown locations. Besides his doctorate in physics, Arnett brought mechanical-engineering training to the effort.

Arnett explains what they were trying to do: "We wanted to see if you could do something on an atomic scale, to create a mechanism for storing information and getting it back reliably." The answer was yes.

In January 1988, the journal Nature carried their letter reporting success in pinning an organic molecule to a particular location on a surface, using an STM to form a chemical bond by applying an electrical pulse through the tip.

They found that having created and sensed the feature, they could go back and use another voltage pulse from the tip to change the feature again: enlarging it, partly erasing it, or completely removing it.

IBM quickly saw a commercial use, as explained by Paul M. Horn, acting director of physical sciences at the Thomas J. Watson Research Center: "This means you can create a storage element the size of an atom. Ultimately, the ability to do that could lead to storage that is ten million times more dense than anything we have today." A broader vision was given by another researcher, J. B. Pethica, in the issue of Nature in which the work appeared: "The partial erasure reported by Foster et al. implies that molecules may have pieces deliberately removed, and in principle be atomically 'edited,' thereby demonstrating one of the ideals of nanotechnology."

Foster's group succeeded in pinning single molecules to a surface, but they couldn't control the results-the position and orientation-precisely. In April 1990, however, another group at the same laboratory carried the manipulation of atoms even further, bringing a splash of publicity. Admittedly, the story must have been hard to resist: it was accompanied by an STM picture of the name IBM," spelled out with thirty-five precisely placed atoms. The precision here is complete, like the precision of molecular assembly: each atom sits in a dimple on the surface of a nickel crystal; it can rest either in one dimple or in another, but never somewhere between.

Donald Eigler, the lead author on the Nature paper describing this work, sees clearly where all this is leading: "For decades, the electronics industry has been facing the challenge of how to build smaller and smaller structures. For those of us who will now be using individual atoms as building blocks, the challenge will be how to build up structures atom by atom."

How far can Proximal Probes take Us?

Proximal probes have advantages as a tool for developing nanotechnology, but also weaknesses. Today, their working tips are rough and irregular. To make stable bonds form, John Foster's group used a pulse of electricity, but the results proved hard to control. The "IBM" spelled out by Donald Eigler's group was precise, but stable only at temperatures near absolute zero-such patterns vanish at room temperature because they are not based on stable chemical bonds. Building structures that are both stable and precise is still a challenge. To form stable bonds in precise patterns is the next big challenge.

John Foster says, "We're exploring a concept which we call 'molecular herding,' using the STM to 'herd' molecules the way my Shetland sheep dog would herd sheep... Our ultimate goal with molecular herding is to make one particular molecule move to another particular one, and then essentially force them together. If you could put two molecules that might be small parts of a nanomachine on the surface, then this kind of herding would allow you to haul one of them up to the other.

Instead of requiring random motion of a liquid and specific chemical lock-and-key interactions to give you exactly what you want in bringing two molecules together [as in chemical and biochemical approaches], you could drive that reaction on a local level with the STM.

You could use the STM to put things where you want them to be." The next chapter will discuss additional ideas for using proximal probes in early nanotechnology.

Proximal-probe instruments may be a big help in building the first generation of nanomachines, but they have a basic limit: Each instrument is huge on a molecular scale, and each could bond only one molecular piece at a time.

To make anything large-say, large enough to see with the naked eye-would take an absurdly long time. A device of this sort could add one piece per second, but even a pinhead contains more atoms than

the number of seconds since the formation of Earth. Building a Pocket Library this way would be a long-term project.

How can such Slow Systems Ever Build Anything Big?

Rabbits and dandelions contain structures put together one molecular piece at a time, yet they grow and reproduce quickly. How? They build in parallel, with many billions of molecular machines working at once. To gain the benefits of such enormous parallelism, researchers can either (1) use proximal probes to build a better, next-generation technology, or (2) use a different approach from the start.

The techniques of chemistry and biomolecular engineering already have enormous parallelism, and already build precise molecular structures. Their methods, however, are less direct than the still hypothetical proximal probe-based molecule-positioners. They use molecular building blocks shaped to fit together spontaneously, in a process of self-assembly. David Biegelsen, a physicist who works with STMs at the Xerox Palo Alto Research Center, put it this way at the nanotechnology conference: "Clearly, assembly using STMs and other variants will have to be tried.

But biological systems are an existence proof that assembly and self-assembly can be done. I don't see why one should try to deviate from something that already exists.

Advantages

A huge technology base for molecular construction already exists. Tools originally developed by biochemists and biotechnologists to deal with molecular machines found in nature can be redirected to make new molecular machines. The expertise built up by chemists in more than a century of steady progress will be crucial in molecular design and construction.

Both disciplines routinely handle molecules by the billions and get them to form patterns by self-assembly. Biochemists, in particular, can begin by copying designs from nature. Molecular building-block strategies could work together with proximal probe strategies, or could replace them, jumping directly to the construction of large numbers of molecular machines. Either way, protein molecules are likely to play a central role, as they do in nature.

Protein Engineering and Molecular Machines

Proteins can self assemble into working molecular machines, objects that do something, such as cutting and splicing other molecules

or making muscles contract. They also join with other molecules to form huge assemblies like the ribosome (about the size of a washing machine, in our simulation view). Ribosomes-programmable machines for manufacturing proteins-are nature's closest approach to a molecular assembler.

The genetic-engineering industry is chiefly in the business of reprogramming natural nanomachines, the ribosomes, to make new proteins or to make familiar proteins more cheaply.

Designing new proteins is termed protein engineering. Since biomolecules already form such complex devices, it's easy to see that advanced protein engineering could be used to build first-generation nanomachines.

Making proteins is easier than designing them. Protein chemists began by studying proteins found in nature, but have only recently moved on to the problem of engineering new ones. These are called de novo proteins, meaning completely new, made from scratch. Designing proteins is difficult because of the way they are constructed.

As Bill DeGrado, a protein chemist at Du Pont, explains: "A characteristic of proteins is that their activities depend on their three-dimensional structures. These activities may range from hormonal action to a function in digestion or in metabolism. Whatever their function, it's always essential to have a definite three-dimensional shape or structure."

This three-dimensional structure forms when a chain folds to form a compact molecular object. To get a feel for how tough it is to predict the natural folding of a protein chain, picture a straight piece of cord with hundreds of magnets and sticky knots along its length.

In this state, it's easy to make and easy to understand. Now pick it up, put it in a glass jar, and shake it for a long time. Could you predict its final shape? Certainly not: it's a tangled mess. One might call this effort at prediction "the sticky-cord-folding problem"; protein chemists call theirs "the protein-folding problem."

Given the correct conditions, a protein chain always folds into one special shape, but that shape is hard to predict from just the straightened structure. Protein designers, though, face the different job of first determining a desired final shape, and then figuring out what linear sequence of amino acids to use to make that shape. Without solving the classic protein-folding problem, they have begun to solve the protein-design problem.

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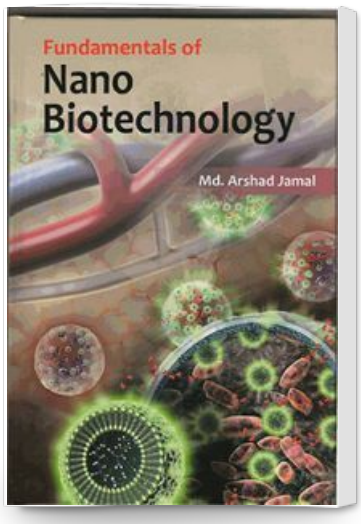

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