Biologically Inspired Nanotechnology

Zhan Huan Zhou, *Member, IEEE*
Institute of Biomaterials and Biomedical Engineering
Edward S. Rogers Sr. Department of Electrical and Computer Engineering
University of Toronto, CANADA

***Abstract*—Cellular processes operate directly on atoms and molecules in an orderly fashion. Nanotechnology also aspires to have such precise control. With biology as a guide, nanoscale devices should be able to take advantage of positional assembly and self-assembly to create complex systems. Artificial and inorganic modifications can be made to these systems to enhance the robustness and functionality of existing biological structures. Design principles based on biological process does not require a full understanding of the underlying mechanisms.**

***Index Terms*—molecular assembly nanotechnology, proteins, systems biology**

I. Introduction

The cell is often referred to as a molecular factory [1]. Even simple prokaryotic cells are incredibly complex systems containing molecular machinery for such tasks as manufacturing, signalling systems, and gene regulatory networks. Systems biology aims to uncover the underlying mechanisms of cellular process so that accurate and detailed models can be created thereby allowing computer simulations to be developed [2].

Nanotechnology has been intricately linked with biological systems since its inception by Richard Feynman in his famous 1959 speech, "There's Plenty of Room at the Bottom." In reference to the complexity and smallness of the cell, Feynman challenged the scientific community to "make a thing very small which does what we want" [3]. In 1981, Eric Drexler's landmark paper was published on molecular engineering and manipulation on the atomic scale. Drexler focused on protein synthesis as a pathway for creating nanoscale devices [4].

Both Feynman and Drexler's propositions have been met with much skepticism and proclamations that accurate manipulation at the nanoscale is impossible [5]. These proponents need a lesson in systems biology. It comes as no surprise that cellular mechanisms are often cited as proof to the viability of nanotechnology devices with atomic precision [1].

Discoveries in systems biology can be applied to biological approaches to nanotechnology. Conversely, biological advances in nanotechnology may shed more light on problems within systems biology. It is evident that systems biology and nanotechnology are complementary.

A view of realising nanotechnology inspired by biological systems is presented in this paper.

II. Approaches To Manufacturing Nanodevices

A. Inorganic Methods

Nanotechnology is a nascent field and as such, there are many unexplored areas and opportunities. The "biomimetic" approach proposed by Feynman and Drexler is not the only method of manufacturing nanosystems. Feynman also mentioned the possibility of "shrinking hands" in which a set of hands would control a set of smaller hands until the last set of hands could directly manipulate atoms and molecules. This may have been regarded as a science-fiction dream in the days of Feynman, but it is now a reality. The atomic force microscope (AFM) and scanning tunnelling microscope (STM) have allowed us to both detect and manipulate individual atoms [1]. Nanomechanical devices have also been fabricated in hard, inorganic materials using conventional photolithography [6]. These and alternative methods of inorganic nanofabrication are currently being explored by various groups.

B. The Biomimetic Approach

Perhaps the greatest advantage of the biomimetic approach is that nature has already proven that it is possible to make complex machines on the nanoscale. There is an existing framework of working components manufactured by nature than can be used as a guide to develop our own nanodevices (Table I). Furthermore, the molecular machinery outperforms anything that can be artificially manufactured by many orders of magnitude [7].

However, with the advent of systems biology, the biomimetic approach may be more feasible than ever. Drexler speculated that computer simulation of protein molecules in solution shows promise [4]. With the goal of systems biology to build models of cellular processes intended for computer simulation, it seems systems biology may spearhead growth in biomimetic nanotechnology. Drexler's vision of gaining new insight into protein behaviour through simulation to permit designers to modify molecules quickly and to observe their behaviour directly [4] may be realized very shortly due to advances in systems biology.

TABLE I
COMPARISON OF MACROSCALE AND NANOSCALE COMPONENTS

Technology	Function	Biomolecular Examples
Struts, beams, casings	Transmit force, hold positions	Microtubules, cellulose, mineral structures
Fasteners	Connect parts	Collagen
Solenoids, actuators	Move things	Actin/myosin
Motors	Turn shafts	Flagellar Motor
Numerical Control Systems	Store and read programs	DNA, RNA

Molecular analogies to macroscale phenomena demonstrating the feasibility of biomimetic nanodevices [4].

III. THE PROTEIN FOLDING PROBLEM

A fundamental difference between systems biology and nanotechnology is the ultimate goal. Systems biology aims to uncover the fundamental operation of the cell in an effort to predict the exact response to specific stimuli and genetic variations. Nanotechnology does not aspire to be so precise nor is it required; nanotechnology is chiefly concerned with useful design. Systems biology is a scientific discovery problem whereas nanotechnology is an engineering design problem.

Consider the classic example of the protein folding problem presented by Drexler [4]. The genome is often likened to a computer program and for good reason. Reading the genetic code to predict protein folding is like deciphering a program written by someone else without documentation – it doesn't make much sense. The naturally occurring genetic sequence found in an organism is not necessarily optimized since it was generated by the trial and error process of evolution. A protein generated from a non-optimized genetic sequence may or may not adopt a conformation corresponding to a global energy minimum [4]. Furthermore, the folding process may be guided by chaperones which cannot be predicted from the genetic sequence. In general, predicting protein folding is a very arduous task.

In contrast, designing a protein to fold predictably is a much less formidable task. For a polypeptide chain of 1000 amino acids, there are 10^{1300} possible different chains. However, even if only one in 10^{1000} of these sequences yield a predictable conformation, it still represents a vast number of proteins. These predictable conformations may be part of a "design toolbox" from which an engineer can design a protein with a specific conformation. It is well known that it is not the chemical composition of the protein that dictates its function, but rather the final conformation. In fact, nature has shown us that two proteins can evolve into the same three-dimensional conformation performing the same task yet not have any matching amino acids in the primary sequence [8]. If the prediction problem is akin to reading undocumented code, the protein design problem is like to writing a program with well-characterized functions or objects.

Although systems biology cannot yet predict the folding for all polypeptide chains, engineers can capitalize on the sequences that are predictable for designing custom proteins.

Moreover, there is nothing restricting the design of polypeptides to only 20 amino acids. It is possible to insert unnatural amino acids into proteins [9] giving rise to an entirely new range of possibilities not seen in nature. At an even more fundamental level, an artificial Watson-Crick base pair has been inserted into DNA and RNA, expanding the genetic alphabet from 4 to 6 letters [9]. The consequences of artificial amino acids and bases are far reaching. Naturally occurring amino acids that produce unpredictable folding patterns can be completely replaced with a synthetic system based on artificial amino acids with well behaved folding characteristics. This can lead to applications yet undreamt of. Imagine artificial amino acids containing pre-made machine parts. The possibilities are endless.

IV. ASSEMBLY OF NANODEVICES

A. Positional Assembly

Traditionally, machinery in the macroworld is assembled by physically bringing components together and then fastening them in a process referred to as positional assembly. In the nanoscale, the idea of bringing atoms together and fastening them becomes slightly fuzzy. Instead of a screw to hold the pieces in place, atoms are fastened with a covalent bond. There are two problems associated with positional assembly on the atomic scale described by Richard Smalley as the "fat fingers problem" and "sticky fingers problem" [5]. Smalley argues that since the "fat fingers" of a nanoassembler will itself consist of a few atoms, it is impossible to position molecules with atomic precision. Furthermore, Smalley goes on to describe the "sticky finger" problem stating that even if a molecule can be positioned with atomic precision, it would have no method of releasing the molecule due to attractive forces. Although Smalley's conjectures may be correct in certain circumstances, it seems he neglected to look at the workings of the cell. The cell contains countless examples of positional assembly processes at work, for example, protein synthesis at the ribosome. New amino acids brought to the ribosome are lined up exactly with the growing polypeptide chain where it chemically binds with atomic precision to form an exact sequence of amino acids. The problem of fat and sticky fingers has been solved by nature aeons ago. The scientific community has also solved this problem; recently, a CO molecule was successfully bound to an iron atom on a silver substrate using a scanning tunnelling microscope [5]. This is experimental proof that we currently have technology to circumvent both the fat fingers and sticky fingers problems with artificial means. There appear to be no fundamental barrier for using positional assembly to create nanodevices; however, we have yet to match the efficiency and precision of biological positional assemblers.

B. Self-Assembly

The major drawback of the positional assembly method currently is its low throughput and cost. Even though we can

bind a CO molecule to an iron atom with an STM, it is not economically feasible and perhaps not even possible to construct complex nanostructures on a large scale using this method. We must find an efficient method of manipulating molecules on a large scale if nanotechnology is to be economically feasible. Once again, we look at biological systems for inspiration, specifically self-assembly. Both Drexler [10] and George Whitesides [11] agree that self-assembly should be exploited. Self-assembly relies on weak atomic and molecular interactions to hold the macromolecule together and is very efficient at building complex molecules [6].

Molecular self-assembly is a process in which molecules spontaneously form ordered aggregates and involves no human intervention; the interactions involved usually are noncovalent [11]. Molecular self-assembly is ubiquitous in biology, examples include protein folding, formation of nucleic acid structures and macromolecules such as the ribosome [11]. Self-assembly offers several key advantages over positional assembly. As stated earlier, self-assembly is an efficient method for building nanostructures on the nanoscale. Secondly, we already routinely take advantage of self-assembly when designing sticky-ended DNA structures [10]. Finally, perhaps most enticing is that self-assembly seems to offer one of the most general strategies now available for generating nanostructures [11].

C. *Universal Assemblers*

There is a wildly different approach to assembly advocated by Eric Drexler. He proposes that before nanotechnology emerges as an industrial force, a universal assembler must first be built [12]. In principle, the universal assembler will have the ability to build almost anything that the laws of nature allow to exist, including more assemblers [12]. His train of though is clear. The assemblers can build more assemblers until there are enough assemblers that it is feasible to construct a macroscale object, such as a book, in a matter of seconds. The problem with this scheme is that a universal assembler must be built in the first place and no one is quite sure how to do this, but Drexler proposes a solution to this as well.

The universal assembler will be made as a "second generation" nanotechnology device. First generation nanotechnology will involve engineering of proteins for specialized tasks and catalyzing specific reactions. Using these relatively crude tools and taking advantage of both positional and self-assembly, more complex devices can be built until it becomes possible to manufacture a universal assembler. The rationale for an assembler to be "second generation" lies in the inherent instability of proteins. A protein assembler is not "universal" because it is not rugged. Protein machines can only work in a very limited temperature and pH range. In contrast, just as machines in the macroworld are not built of flesh and bone, neither will the universal assemblers.

It is in my opinion that a universal assembler can be built as a first generation device. It has already been argued protein engineers will be able make designer proteins, perhaps with synthetic nucleic acids and amino acids containing pre-fabricated components. Taking advantage of self-assembly, it will be possible to construct a universal assembler directly, bypassing the intermediate stage described by Drexler.

V. Powering Nanomachines

So far this paper has been concerned itself with the manufacturing of nanoscale machines. The assembler discussed in the previous section is like Henry Ford's assembly line, but there is still the fundamental problem of power. Without fuel, Ford's cars, as much of a technological marvel as they were, would be useless. So too is the problem with nanomachines. We may be able to manufacture marvellous devices to perform a multitude of tasks, but without power, they would sit idle and useless.

Once again, biology serves as inspiration. Adenosine triphosphate (ATP) powers most cellular processes. ATP in the cell is usually synthesized in the mitochondrion or the chloroplast. The mitochondrion uses glucose to generate ATP while the chloroplast converts light energy into ATP. It is the latter method which artificial techniques have successfully mimicked.

Devens Gust has successfully synthesized a liposome sphere which absorbs light, exciting an electron [13]. The excited electron helps to transport protons from the outside to the inside of the liposome. By incorporating ATP synthase in the liposome, Gust demonstrated that it was possible to synthesize ATP and transport it out of the liposome. Once outside of the liposome, the ATP can be used to power the appropriate process.

VI. The Nanochopper

One of the most impressive results of nanoengineering to date is the "nanochopper" developed at Cornell [14]. The nanochopper consists of a biomolecular motor with an inorganic blade powered by ATP (Figure 1). This hybrid device may enable the creation of a new class of sensors, mechanical force transducers, and actuators [14]. Initially the device was powered by infusing a solution with ATP where it

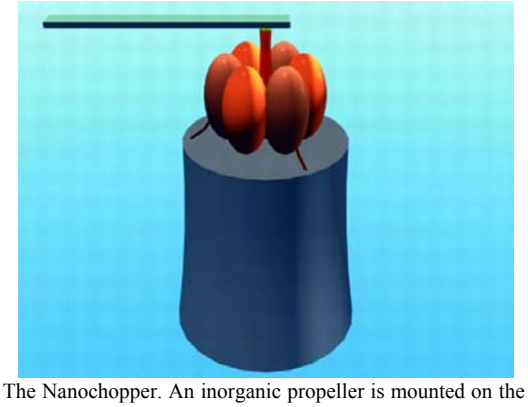

Fig. 1. The Nanochopper. An inorganic propeller is mounted on the shaft of a biomolecular motor [14].

simply covered the device. However, later trials employed Gust's light activated liposomes. The propeller blade spun when shone with light. The results of this experiment are significant. Specifically, the nanochopper is a method for driving nanoelectromechanical devices. On a more grand scale, it perfectly encapsulates biologically inspired nanotechnology. The basis is a self-assembling biomolecular motor. The inorganic modification of the motor by positional assembly was a useful addition to allow detection of rotation. Its power source was ATP generated by chloroplast inspired liposomes. The nanochopper has been hailed to as "a first step to a purely engineered systems" of nanomachines that can work without human intervention [13]. The nanochopper may quite literally be the engine that drives nanotechnology.

VII. Conclusion

This paper has focused on mimicking biology for designing nanotechnology devices. More research is required to understand the molecular cell processes. This knowledge will aid in the design of molecular devices. Nature can teach us many lessons in designing nanoscale machines, but ultimately, we will have to modify naturally occurring phenomena to meet our design needs.

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