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Final Paper

Hey y'all, another final paper for my class that I want to share on this blog. Enjoy☺

DNA Nanotechnology

Introduction

Nanotechnology comprises of research done at the nanometer scale. In this field, we want control over the smallest unit of measurement as possible. A challenge like this may call for a bottom-up approach as opposed to a top-down one. Immediately, biological systems come to mind. Deoxyribonucleic acid, or DNA, is the genetic code of life. It is made up of four bases, adenine, thymine, cytosine, and guanine (ATCG). These bases are each about 0.33 nanometers (nm) long. The bases are governed by the Watson-Crick base pairing rule: adenine binds complementarily to thymine, while cytosine binds to guanine. This is the reason for the canonical DNA double helix structure, shown in Figure 1. Already, in nature, there exists incredibly small scale units that we can use to code and hold information. DNA is the most programmable natural molecule. Others realized this phenomena could be exploited, thus resulting in a field called DNA nanotechnology.

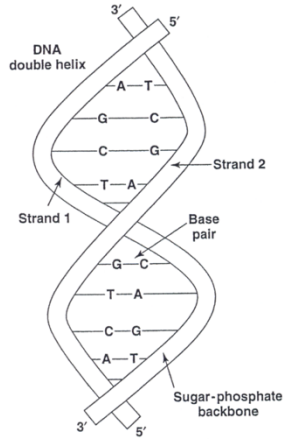
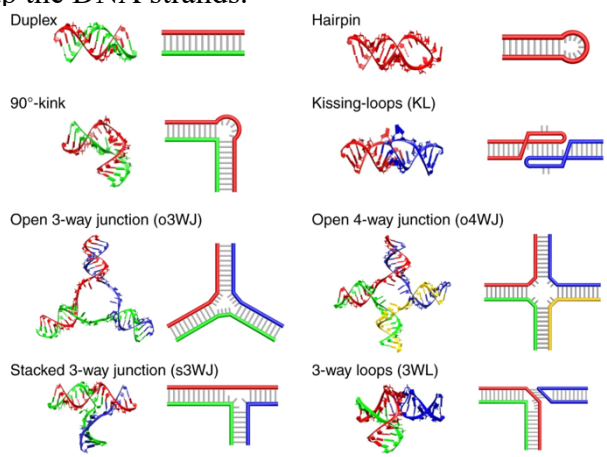


Figure 1 The canonical structure and fold of DNA. Notice the Watson-Crick base pairs align, A is with T, and G binds to C. This allows for the attachment of two complementary DNA strands. Image from ResearchGate[1].

Scientists began thinking about exploiting DNA in 1982. Then, Nadrian Seeman stated "It is possible to generate sequences of oligomeric nucleic acids which will preferentially associate to form migrationally immobile junctions, rather than linear duplexes, as they usually do" (Yan, 2007[3]). This opened eyes to a plethora of possible structures that DNA could take. In Figure 2, we see the duplex, or the DNA structure most people consider, alongside seven other possible structures DNA can take. These structures can all be created, simply by manipulating the code that makes up the DNA strands.



One of the most notable and influential discoveries in this field was the development of DNA scaffolds to create nanoscale patterns. This was released in a paper in 2006 written by

Figure 2 Various possible structures DNA can make. Alongside simple shapes such as duplexes or hairpins, we can also create open 4-way junctions. The different colors represent the backbones. Watson-Crick base pairing is assumed. Image from Mao et al., 2018[2]).

detailed images. This results in a stable structure that can make almost any desired shape, such as a Mona Lisa painting seen on the cover of a Nature journal in 2017 developed by Caltech's Prof. Lulu Qian (Figure 3)[8]. Developed structures can be visualized by using atomic force microscopy, as seen in Figure 4.

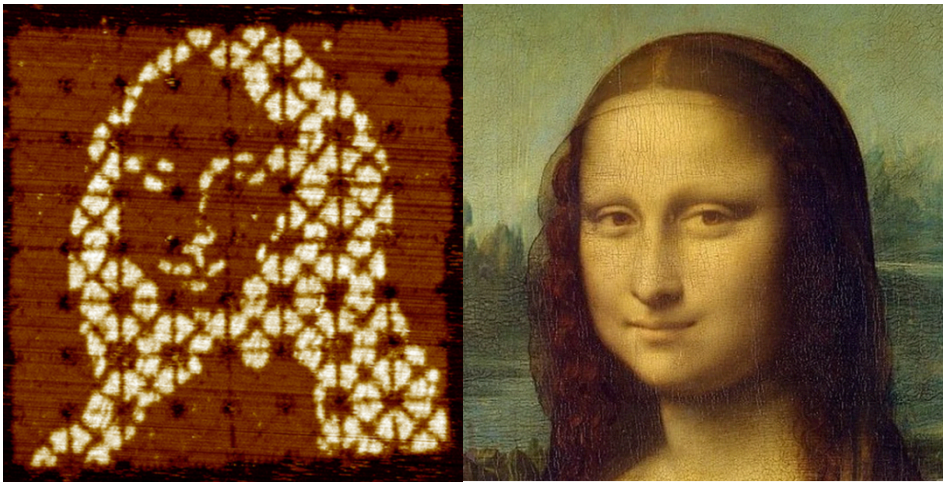


Figure 3 Mona Lisa sculpted from DNA on the left. Leonardo Da Vinci's original painting on the right.[8]

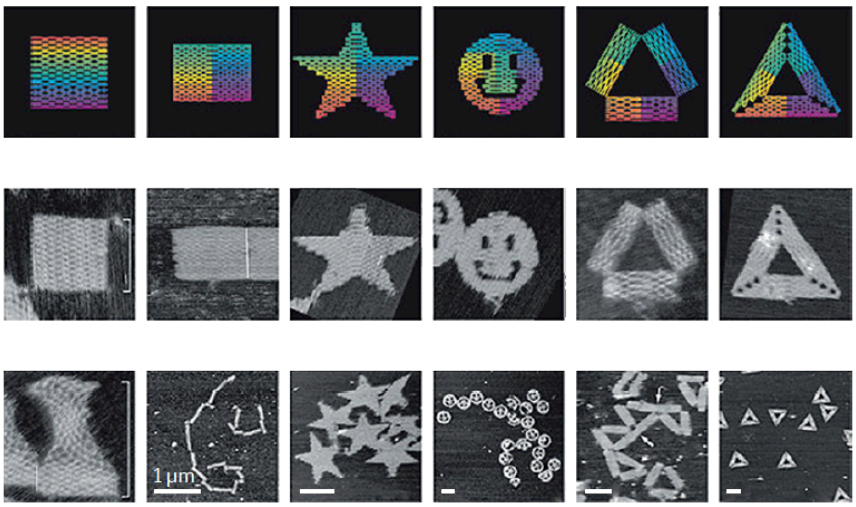


Figure 4 Images taken with Atomic Force Microscopy of various structures made using DNA nanotechnology[4].

Current Applications

Today, DNA nanotechnology is used for DNA-mediated assembly of gold nanoparticle crystals, to create synthetic lipid membrane channels from DNA, for drug delivery, for gene silencing, with semiconductor technology, and much more [4].

Researchers have been able to implement dynamic motion of these DNA structures. DNA cages (Fig 5a) were created and, with the addition of designed DNA strands, these cages could expand or contract to a different desired shape. To test this idea, researchers entrapped a gold nanoparticle in a DNA cage and added DNA 'eraser' strands. Since these 'eraser' strands are complementary to DNA strands that make up the DNA cage, the strands in the cage get pulled out. Thus, any particles trapped inside the cages are released. We can see a schematic of this in Figure 5b. This has incredible use potentials as a mechanism for targeted drug delivery. DNA is a natural substance, so we are aware of any side effects that may arise. We can also have programmed and targeted release by the simple addition of or presence near a triggering 'eraser' strand.

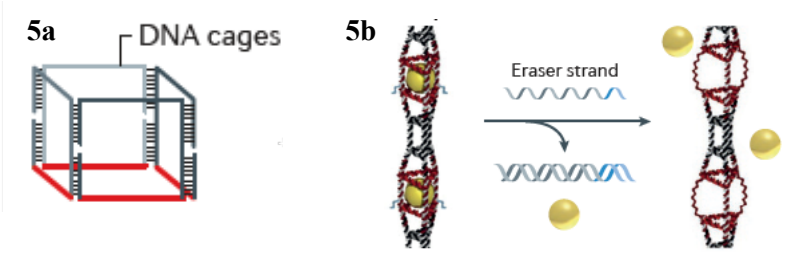


Figure 5a, Structure of a DNA cage. Figure 4b, Addition of an eraser strand can trigger shape change and release gold nanoparticles.

DNA nanotechnology can also be used for diagnostic advances. MicroRNA are integral to the regulation of gene expression. Because they have a diverse set of functions, many believe they have the potential to be developed for therapeutics and used as biomarkers for diseases, including cancer and schizophrenia[10]. Current methods to sense microRNA's have many drawbacks, thereby calling for a new type of technology. DNA nanostructures have functioned to relieve many of these limitations. This includes the use of DNA tetrahedra, DNA origami, as well as DNA devices [10]. With DNA origami for example, 2D DNA tiles were made that had single stranded DNA (ssDNA) probes that were complementary to the target microRNA. These ssDNA would be tagged with a fluorophore, effectively tagging the microRNA. Super-resolution fluorescence microscopy can be used as the detection method [10]. Many more technologies exist, highlighting the diverse applications of DNA nanotechnology.

Research by Professor Erik Winfree at Caltech published in 2009 has shown that carbon nanotubes can self-assemble in 2D geometries using DNA origami, which is folded into a predetermined shape [11]. Single-walled carbon nanotubes (SWNTs) have unique electronic properties. Arranging these SWNTs into complex geometries at the nanoscale has been a challenge thus far. By using the binding specificity and predictable structural formation of DNA, templates can be made which could organize SWNTs into complicated architectures. They were

able to show that the SWNT + DNA systems can transfer from solution to dry SiO_2 while maintaining their geometry and electronic properties, indicating this process could work with other standardized microfabrication techniques [11]. They were also able to integrate other materials, like gold nanocrystals, indicating that complex structures with unique electronic, electrochemical, or optical properties could be developed. Thus, DNA nanotechnology has the opportunity to advance fields orthogonal to bioengineering as well.

To continue, the merging of DNA nanotechnology and semiconductors reveals unprecedented technologies. One of the goals includes using DNA nanotechnology to organize nano electronic components into 3D arrays. In 2017, members of Seeman Lab at NYU were able to organize such an organic semiconductor by using a 3D DNA array. An octameric aniline (or octaniline) molecule was used. By using protonic doping, they were able to get the conductive form of polyaniline. They used redox cycling, which was visualized with color changes and Raman microscopy [5]. This technology can be extended to other electroactive compounds or materials. With this, we can "study the spectra of isolated single molecules whose signals are amplified by incorporation into a macroscopic object" [5]. This can also theoretically be done with more than one type of molecule using more involved DNA scaffolds and construction. This could possibly allow for the creation of more complicated electronic systems, like photovoltaic devices.

The Future

In my opinion, we are at the beginning of the biological revolution. Whether in regards to DNA nanotechnology, gene therapies, or DNA computers, we are at a point in our biological knowledge where we can begin to apply engineering principles. Instead of discovery, we can focus on creation with the concepts and tools we have already figured out.

I think DNA nanotechnology has the potential to become integral in many types of technologies and experimental methods in the future. Mainly because it employs a bottom-up approach and starts with inherently small parts – a goal central to nanotechnology.

The main disadvantages of DNA technologies include the cost of sequencing DNA, the cost of making synthetic DNA, and the high error-rate that can accompany self-assembly. However, it seems that Moore's law can be applied to the price of DNA sequencing. Its cost has approximately halved every two years, as shown in Figure 6. This has promise for the future. Further, a typical scaffold strand is about 7,429 nucleotides long[7]. As of 2011, prices for making this length of scaffold strand was about $0.10 per base or around $700 total. Although, with the development of new technologies and mass production of these types of sequences, prices could drop to $0.0001 per base[7]. The question of high-error rates needs to be answered via more research that studies kinetic components of DNA assembly. There are not yet competent quantitative tools that can allow us to analyze defects in DNA nanostructures. Technologies such as NuPack, developed by Professor Niles Pierce and Dr. Justin Bois at Caltech, can potentially help solve this problem.

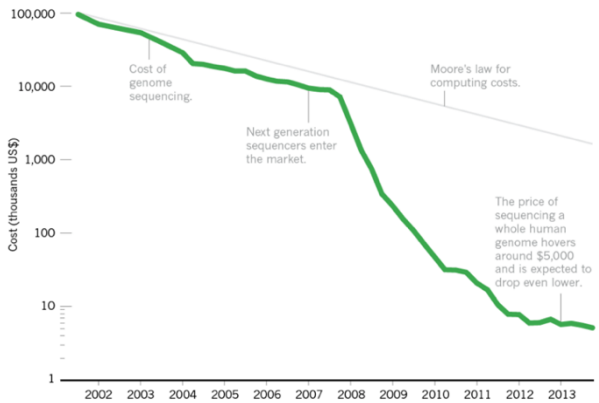


Figure 6 Moore's Law for DNA sequencing cost. Figure from Hayden, Technology: The $1,000 genome[6].

Some may be concerned about the limited degrees of freedom with DNA. We only have four bases, which are paired. However, DNA can make complex bonds with organic, inorganic, and polymeric molecules, thereby expanding the alphabet. Although these interactions are not thoroughly documented, it could open up an avenue for many more types of structures and functionalities.

As some of these issues are overcome, I believe DNA nanotechnology will begin to have increasing influence, including with semiconductor technology, biophysics, drug delivery, and scientific understanding. We can use DNA nanostructures as 'motherboards' for various applications as we start to understand how nanoparticles and oligonucleotides collaborate [7]. DNA nanoboxes for targeted drug delivery could be a revolutionary technology. Since we can have phenomenal control of shape, size, and flexibility, it may be the best technology for more natural uses. Furthermore, the surfaces of DNA structures can be addressable. Adding tags and ligands can allow for more specific imaging, delivery, and communication. For example, these DNA structures can be programmed to recognize specific cancer or viral antibodies, and can then trigger the release of some chemical held inside or the execution of another function. With specific programmability, we can better guarantee accurate release of drugs which could allow us freedom to use remedies that are more harmful but more effective.

The phenomenal modular design, small scale, and biological compatibility of DNA nanotechnology can allow for many different applications, the majority of which have yet to be invented.

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