Computer-Aided Design for DNA Self-Assembly: Process and Applications

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Abstract— **CAD plays a fundamental role in both top-down and bottom-up system fabrication. This paper presents a bottom-up circuit patterning process based on DNA self-assembly in terms of the design tool requirements and the new opportunities self-assembly creates for circuit designers. The paper also connects recent demonstrations of addressable self-assembly to applications in computer architecture and system design.**

I. INTRODUCTION

Since the introduction of the idea that nucleic acids could be used to synthesize nanoscale grids and lattice structures the development of DNA self-assembly into a practical method for creating nanoscale circuit patterns has garnered increasing support [1-3]. However, the exotic nature of DNA self-assembly as compared to conventional photolithography introduces new challenges for system designers and CAD tool makers.

Rudimentary tools exist for DNA sequence and structure design and are routinely used in the development of high yield and robust DNA self-assembly processes [4-10]. However, there is no shortage of future work and the next generation of tools must incorporate higher level awareness of the system task, such as a computing function or target fabrication yield, for DNA self-assembly to gain wider support in the circuits and systems design community.

This task is challenging because it requires a wide audience from sub-fields with experience in system and circuit design to solve new problems in CAD for self-assembly. In that context this paper will serve as a focused tutorial on DNA self-assembly and feature a few of the potential applications of the method.

Section II discusses the DNA self-assembly process and the fabrication of nanoscale patterns. Section III discusses the new capabilities self-assembly introduces to the circuit design challenge and section IV describes some of the benefits and challenges DNA self-assembly presents to system design. Final remarks and conclusions are in section V.

II. DNA SELF-ASSEMBLY

Nucleotide basics— The study of DNA has a rich and extensive past owing to its many decades as an important part of the central theme in molecular genetics. This tutorial will not be a summary of that work but instead will narrowly focus on DNA as a substrate for the fabrication of nanostructures.

DNA is an acronym that stands for a class of chemicals known as *deoxyribonucleic acids* which have a basic block called a nucleotide. Nucleotides are composed of a phosphodiester covalently bound to a *nucleoside* or a derivative of a deoxyribose sugar and either a purine or pyrimidine nucleobase. The nucleobases commonly used in DNA self-assembly are the purines: adenine (A) and guanine (G), and the pyrimidines: thymine (T) and cytosine (C). The nucleotides can be bound to each other to form a linear chain (or strand) through their phosphodiester bonds that must terminate or begin at either the 5' or 3' carbon of the adjacent nucleotide (i.e., the 5^{th} or 3^{rd} carbon in the deoxyribose sugar). This arrangement imparts a direction to the chain because of an exposed 3' or 5' site at opposite ends (each end is capped with either an –OH or phosphate group). The sequence of nucleotides (also called bases) in the strand can be arbitrary and by convention is written as a sequence from the 5' end to the 3' end (e.g., 5'-AGGTC-3'). This represents a so-called single-stranded DNA molecule.

The geometry of the phosphodiester bond and shape of the nucleosides create the potential for single strands of DNA to wrap around one another in anti-parallel directions. That is, any two strands are geometrically compatible if oriented in an anti-parallel fashion and can form a helical structure, or double stranded DNA molecule. In fact, a single strand can wrap around on itself to form a self-pairing double stranded structure.

The double stranded DNA structure is most stable when the pairwise nucleobase interactions are "complementary" i.e., if A pairs with T and G pairs with C. Under these conditions each base pair is approximately 2 nm wide (diameter of the helix) and on average 0.34 nm long (along

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the strand per base). The helical twist of the two strands (in the common B-form) is such that a full turn occurs between every 10^{th} and 11^{th} base. Further, the stability of this interaction is only approximately linear per base and depends on neighboring mismatch or complementary interactions [11]. The stability and exact dimensions, orientation, and form of the interaction depends on a basket of microenvironmental factors including salinity and pH of the solution and local properties of the DNA including local strain.

Thermodynamics— The central theme in the use of static self-assembly for nanoscale fabrication is the application of an external control over an otherwise spontaneous reaction to control its outcome [12]. This control directs the assembly of materials into structures that are interesting and relevant to a target design problem. In the context of computer system fabrication the self-assembly is used to direct the formation of switching devices (e.g., transistors and wires) to create logic circuitry, memory, and I/O interfaces.

The temperature of the reaction volume (i.e., the solution) is a simple control in DNA self-assembly. This follows from the experimental evidence that demonstrates the formation of double helices from single strands of complementary DNA as the solution temperature is changed from high to low. The melting temperature (T_m) of a DNA strand is the temperature at which the transition from single strands to double strands has reached 50%. That is, half of the single strands in solution are bound to their complementary strand when the solution temperature is exactly the melting temperature of the strand. The T_m of two strands is dependent on their sequence and the degree to which they are complementary. Clearly this simple picture is complicated by the introduction of multiple sequences and hence multiple types of single stranded DNA in solution. Further, the time evolving dynamics of these interactions are still under study [13-15]. It is the richness of this interaction that is at the root of why DNA can be used to form complex nanostructures. A thorough and precise definition of the control mechanisms for self-assembly is beyond the scope of this tutorial and can be found in more comprehensive reviews [12].

Sequence design— A strand of DNA obeys certain thermodynamic behavior, most importantly that double strands form at temperatures below the T_m of the constituent single strands, and this interaction can be complex if multiple unique (sequences) DNA strands are in solution at the same time. Specification of the strand sequences provides external control over the self-assembly process (through temperature control) and determines the formation of structures. Good sequence design leads to a minimization of sequence mismatches, or unintentional interaction between strands of similar but not perfectly complementary sequence, at a given temperature and therefore high yield fabrication of the target structures.

It is important for designers to have access to tools that are capable of modeling self-assembled structures, within a framework, for complex DNA nanostructure fabrication. The next section describes some of the aspects that DNA self-assembly CAD tools will encounter as the process finds greater application to computer system fabrication.

A. CAD for DNA self-assembly

The discussion so far has covered some of the basics behind DNA self-assembly and highlighted the important aspects that make it possible to fabricate nanostructures with DNA. The open problems that present the greatest opportunity for improvement are related to design optimization and awareness of three key factors in DNA self-assembly: thermodynamics, geometry, and yield.

Thermodynamic-aware design— Control over the thermodynamic interaction of single strands of DNA directs the self-assembly process to form intentional structures. New CAD tools must incorporate sufficiently accurate models of this interaction to predict and optimize against the formation of unintentional structures.

However, severely constrained sequence spaces (to prevent mismatches) will limit the complexity of potential structures. An example of this can be found in the use of the Hamming distance metric to evaluate the potential for two sequences (or sub-sequences) to form an unintentional structure. The intuition is correct that maximally distant sequences are less likely to form mismatches but this can overly constrain the sequence space by neglecting nearest-neighbor interactions (both stabilizing and destabilizing). A more accurate model should include the nearest-neighbor interactions and evaluate mismatches based on thermodynamic behavior rather by pure sequence analysis [11].

Geometry-aware design— An important topic missing from this discussion is how exactly sequence matching and double strand formation can lead to nanostructure formation. The key is in the use of geometric constraints made on otherwise flexible DNA strands to form structures. Figure 1 illustrates a simple example of three distinct strands (attached to spherical particles) assembling into a triad structure when the temperature of the solution drops below the T_m of each strand [16].

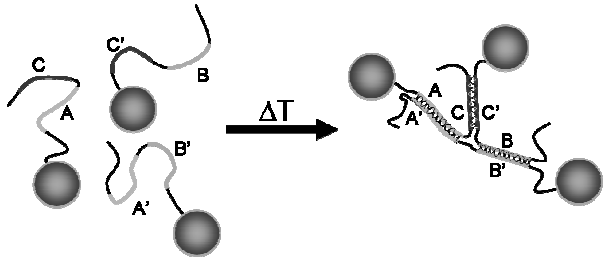

Figure 1. Three distinct DNA-functionalized particles will assemble into a triad structure if the indicated sub-sequence complementarity exists.

The constraint is thermodynamic in that the strands are more stable if they form duplex structures (e.g., B with B',

C' with C, and so forth). This requires the particles to come together and given the relationship between sub-sequence regions on each strand the particles will form a triad.

This concept can be extended to more complex structures including grids or lattices [7, 17, 18] and is limited only by the availability of distinct sequences (if no re-use strategy is applied) and compatible geometries.

Yield-aware design— As with any fabrication process, the yield of the DNA self-assembly process is less than 100%. Estimates for DNA grid fabrication yield approach 60% - 80% for some systems [8]. The challenge for future CAD tools will be to optimize the yield by ordering the geometric constraints to minimize the number of potential side products (or malformed structures). This requires an understanding of the assembly process, which is an open topic of research, but relies on sequence choice and therefore a schedule for the assembly steps.

This brief primer on DNA self-assembly certainly leaves many more questions than answers. However, the goal is to develop a reasonable understanding that will serve as a platform for describing how DNA self-assembly can be applied to the fabrication of nanoscale circuitry for computing systems.

The formation of double helix structures from single strands of DNA can be thermodynamically favorable and can drive the formation of structures. The process requires the optimization of sequence choice for high structure yield and this creates an opportunity for CAD tool design and process refinement.

A geometric framework based on a grid will be used to explain how DNA self-assembly can be used to make nanostructures that are relevant to circuit fabrication. As with conventional integrated circuit design, layout tools can be applied to the device placement and routing problem [6] for later refinement by thermodynamic-aware, geometry-aware, and yield-aware CAD tools.

B. Patterning with DNA grids

DNA strands can be designed to form a grid structure by constraining their interaction along orthogonal directions [8, 19]. This enables a grid structure like the one illustrated in figure 2. In this figure, each unique site where a nanoscale component can be attached is numbered.

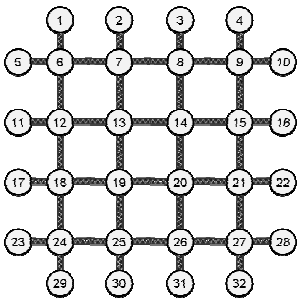

Figure 2. The 32 available binding sites on the grid is indicated by a number. Each site can be independently functionalized.

The spherical particles from figure 1 are examples of components that can be attached to each site but many other nanoscale materials can be attached, or functionalized, at each site [20-22]. Figure 3 shows three atomic force microscope (AFM) images of three independent experiments where a protein (*streptavidin*) is patterned to form the letters 'C', 'A', and 'D'. The pattern was defined by selectively attaching the protein to specific sites as described by figure 2.

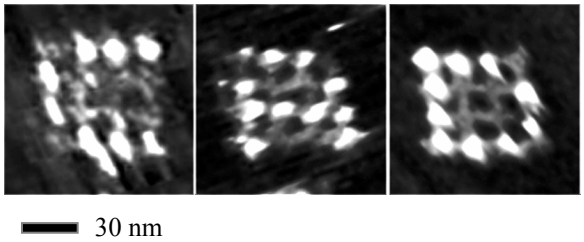

Figure 3. Atomic force microscope images of three patterned grids. Each grid is ~60 nm on a side and the highlights are created by height differences due to selectively bound protein.

Such "stunt" experiments are interesting because they demonstrate that arbitrary patterns on the grids are possible. Further, these patterns can be used to form templates for the nucleation of conducting and semiconducting materials with better than 20 nm pitch [23-25]. The ultimate limit in pattern resolution is unknown but from these preliminary results the minimum pitch may be as small as 1.5 – 2.0 nm with this system.

The self-assembled grids are capable of forming patterns that are relevant to logic circuitry and can serve as templates for metals and semiconductors [24]. This new capability makes self-assembly an interesting alternative to ever more expensive silicon-based circuit fabrication processes if only as a stop-gap solution as future photolithographic lines are amortized. Progress toward wider adoption of self-assembly is partly limited by the challenges in circuit and system design that must be overcome by advances in CAD tool work for this emerging technology.

C. Challenges in self-assembly

Many of the challenges to the wide spread adoption of DNA self-assembly hinge upon the apparent costs and yield associated with self-assembly. This should be put into perspective since many of the costs associated with any fabrication process (conventional or exotic) are design related rather than material related. However, even as the exponential increase in silicon-based fabrication costs per technology node change the cost model, for the time being design and verification will remain as paramount factors in the cost equation [26].

The material costs for the experiments shown in figure 3 were less than $40 USD and given the estimated number of structures that were formed (10^{12} – 10^{14}) and a yield of ~60%, the final material cost was less than $\$10^{-11}$ USD per grid. An increased yield will further reduce this cost and make the method even more appealing as costs in

conventional technologies continue to increase due the stringent requirements of an ultra clean environment and decreasing feature pitch.

Another important challenge in self-assembly is to increase the size of the largest feasible structure that has complete addressability. Addressability enables the unique and independent functionalization (as in the grids shown in figure 3) of arbitrary patterns and will always be a limiting constraint for computer systems. The stepwise and incremental growth of the grids makes the yield of larger structures drop off exponentially. This may be overcome by a purification process that selects good structures from bad structures but methods for increasing yield in this way remain as open challenges.

Despite obstacles to yield enhancement, the DNA self-assembly process is quickly becoming viable for circuit fabrication. Advances in CAD support for the thermodynamic, geometric, and yield constraints of this process will enable new applications in computer system fabrication. An important step toward self-assembled computer systems is the demonstration of grid structures with nanoscale feature pitch and high yield fabrication. The grids shown in figure 3 exhibit a minimum pitch that approaches 1.5 nm – 2.0 nm with a fabrication yield between 60% - 80%. With the potential that these nanostructures can serve as templates for the growth of metallic and semiconducting materials they will be relevant to future computer systems built by self-assembly.

III. Opportunities for Circuit Design

Self-assembly presents many interesting new opportunities for circuit designers. One such opportunity is the use of algorithmic assembly during the fabrication process [27-30]. That is, as with DNA computing, DNA self-assembly can algorithmically generate patterns to be included as pieces of a larger system or even correct errors during the assembly [31]. Indeed, the addressability concerns mentioned in section II remain, but this capability is remarkable when compared to the static patterns required by photolithography. However, the application of algorithmically defined patterns to a useful problem still remains an open challenge in DNA self-assembly.

The thermodynamics that drive DNA to form helical structures is fundamentally a stochastic process. As such, DNA self-assembly can incorporate random events into the fabrication process. In some regard this is a degenerate case of algorithmic self-assembly but can be used to randomly seed growing structures. For example, random seeds are often used in global optimization problems to probabilistically spread parallel processing elements over a search space. DNA self-assembly can incorporate this random seed generation as part of the system fabrication and in-so-doing create distinct elements from an otherwise uniform assembly process [29].

IV. Benefits and Challenges

There are several benefits DNA self-assembly can bring to computer architectures and systems. The minimum pitch exhibited in the DNA nanostructures is un-obtainable except by electron beam, extreme UV, or X-ray lithography. This implies that the ultimate circuit density with DNA self-assembly can be comparable to that of an end-of-the-roadmap silicon process [26].

The synthesis scale of DNA self-assembly has the potential to far exceed current silicon process capacity. For example, a foundry producing 50,000 wafers per month at a functional density of $1x10^{11}$ transistors per wafer would take approximately one day to create as many nanoscale structures as are formed in a single self-assembly reaction (in a 60 μL reaction volume nonetheless) like the ones shown in figure 3. This will become a more meaningful comparison as templating methods are developed to integrate active devices onto the grids.

Challenges for systems— Since self-assembly relies on thermodynamics to create structures there is an inherent element of randomness in the process. This randomness can manifest itself in many ways the most prominent of which is low structure yields that degrade the nanoscale precision obtainable with the grids. This requires system designers to mitigate errors through the use of redundancy or other defect-tolerant methods.

Further, the small length scales over which DNA self-assembly can form structures (< ~10 μm) makes the I/O problem particularly difficult. Therefore, the development of design methods that can map arbitrary network topologies onto randomly interconnected graphs will be important to harnessing the potential of DNA self-assembly for large-scale system fabrication.

This problem has been addressed within the context of other technologies through reconfigurable computing and *n*-modular redundancy to demonstrate that it is possible to construct a general-purpose computer architecture from many identical components under the presence of defects [32-37]. Several alternative approaches leverage the probabilistic nature of signals through defective networks with feedback and either Markov fields or neural networks to structure the flow of logic signals through otherwise noise-saturated or missing channels [38, 39].

Similar to other nanotechnologies, DNA self-assembly will introduce a range of design constraints and fabrication defects that must be handled by a system or architecture. Systems that overcome these challenges will benefit from the density and synthesis scale of self-assembly.

V. Conclusions

The chemical structure and thermodynamic behavior of DNA create the potential for complementary sequences to bind in well defined ways. Through the concatenation of sequences and minimization of potential mismatches between strands specific geometric constraints can be placed

on the strand interactions to enforce the formation of intentional geometric structures.

A framework for the design and fabrication of networks enables the fabrication of structures with lattice or grid geometries that are suitable as templates for metallic and semiconducting materials. This process will enable the fabrication of active switching elements on self-assembled circuits for use in computer architectures and systems. The CAD tool support required to design within this context is beginning to emerge and future work should include fabrication and process models that are thermodynamic, geometry, and yield aware.

The opportunities that DNA self-assembly offers to computer fabrication stem from the nanometer pitch and large ($10^{12} - 10^{14}$) synthesis scale of the self-assembled grid structures. However, the randomness introduced during the self-assembly process presents a challenge to system designers. Functional systems will need to mitigate such errors through the use of redundancy, reconfigurability, or other defect-tolerant methods. Future CAD tool development that places importance on integrating accurate models of the assembly process and system-level constraints will enable the fabrication of useful systems from this technology.

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