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Designing ordered nucleic acid self-assembly processes

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A major goal of self-assembly research is the synthesis of biomolecular structures with diverse, intricate features across multiple length scales. Designing self-assembly processes becomes more difficult as the number of species or target structure size increases. Just as the ordered assembly of a machine or device makes complex manufacturing possible, ordered (or 'algorithmic') biomolecular self-assembly processes could enable the self-assembly of more complex structures. We discuss the design of ordered assembly processes with particular attention to DNA and RNA. The assembly of complexes can be ordered using selective, multivalent interactions or active components that change shape after assembly. The self-assembly of spatial gradients driven by reaction-diffusion can also be ordered. We conclude by considering topics for future research.

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Introduction

While significant progress has been made toward the self-assembly of complex, synthetic biomolecular structures [1–3], the complexity and functionality of these structures are still dwarfed by the complexity and functionality of the structures assembled by organisms. For example, animals can have billions or more ordered features across 12 orders of magnitude in size: Fundamental advances are needed to design and synthesize structures whose complexity compares to those of living things. One potential route to self-assembling structures of significantly greater complexity than is possible currently is to design self-assembly processes by modeling them after the way macroscale machinery is designed and built. Typically, cars or computers are assembled using well-defined, sequential processes. Considered generally, this notion of a set of well-defined sequential steps can be applied not only to building, but also to process design or information processing. In each case, such a well-defined recipe is referred to as an *algorithm*. Importantly, this usage of the word 'algorithm' does not refer to software run on an electronic computer to help design self-assembling systems. This algorithm is the set of steps *biomolecules themselves* follow to assemble a given structure. The idea that biomolecules could execute an algorithm to self-assemble complex structures is supported by recent studies of self-assembly processes in biology: one of their hallmarks is the control of assembly kinetics over multiple assembly steps [4••,5,6].

To design an algorithm for the self-assembly of a biomolecular structure, it is necessary to design both the structure of what is to be assembled and the *sequence of self-assembly steps* expected to produce the desired structure. We will refer to a self-assembly process designed in this way as an ordered self-assembly process. In contrast to designing a set of components that stably form a desired structure at equilibrium, designing an ordered assembly process means that the kinetics of assembly must be understood and optimally, explicitly designed. In practice, characterization and determination of assembly kinetics is more difficult than equilibrium analysis and design because the latter requires only characterizing the minimum energy states of the systems, whereas the former requires characterizing all possible states of the system, and the transition rates between them. Experimental characterization of rapid kinetic transitions can also be technically challenging. Yet despite these potential obstacles, it is become increasingly possible to approach these problems and to do so with an eye to scaling the complexity and functionality of the structures being assembled. Further, the scaling and design of ordered assembly processes can be addressed by considering assembly processes as algorithmic and applying powerful tools for algorithm design from computer science.

This article describes progress toward designing ordered self-assembly processes for DNA and RNA components that assemble via Watson–Crick hybridization, with an emphasis on the application of algorithmic ideas from computer science to enable processes to be scaled. By scaling, we refer to scaling both the size of the assembly (so that it extends across multiple length scales) and the complexity with which the components are arranged (which may be measured in a variety of ways). An increase in either of these metrics may also require that the

number of different types of components (species) used to self-assemble a structure also increase.

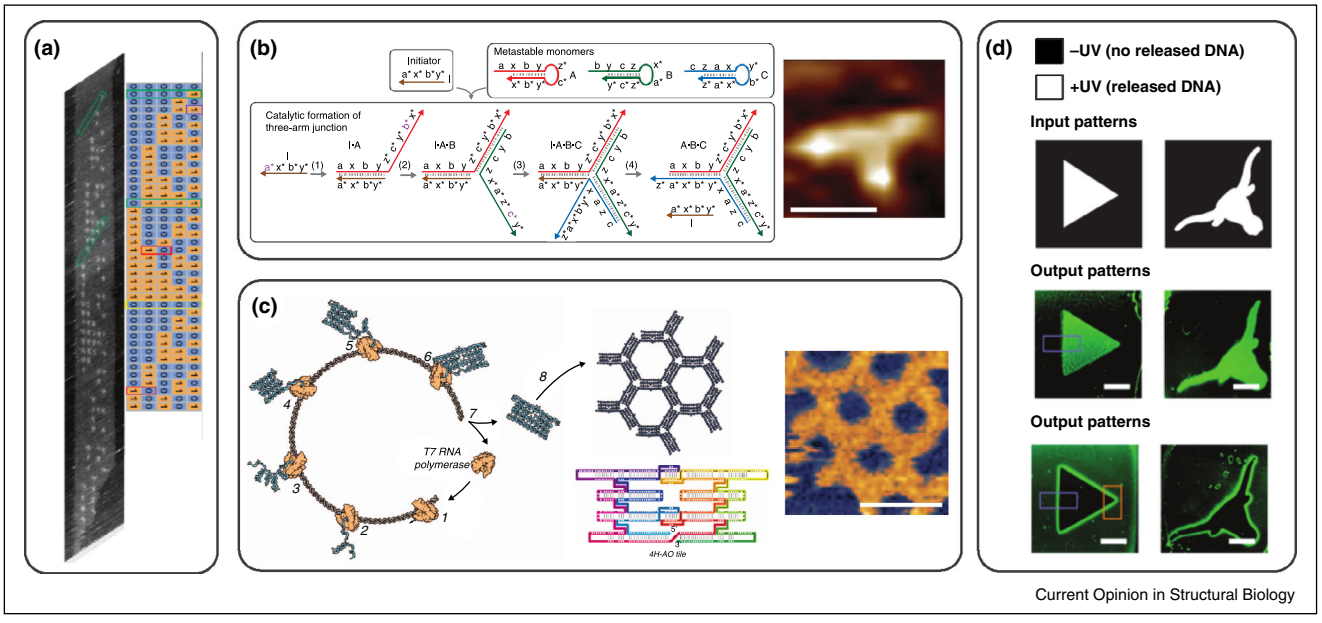
Watson–Crick hybridization processes are particularly amenable to scalable design because base pairing interactions are relatively easy to model and predict computationally [7]. It is also often possible to scale the number of components in a process by using many different components with similar or identical architectures but different sets of complementary subsequences. Because these different subsequence pairs assemble specifically and can have almost identical structures, it is feasible to design large structures in which the order of interactions between the components of the assembled structure are controlled. Examples are shown in Figure 1. In this article we describe two of these examples — algorithmic tile self-assembly and reaction diffusion systems — in detail and touch on related work.

Algorithmic tile self-assembly

Algorithmic tile self-assembly was first described by Winfree [13] as a mechanism for assembling aperiodic crystals from different types of DNA monomers that could cocrystallize [8]. Winfree showed that the assembly of these crystals could be viewed as analogous to the execution of a type of computer program, called a cellular automaton [14]. This view of the assembly process is powerful because it makes it possible to assemble large, complex structures with only a few types of components in a one pot reaction. Algorithmic tile self-assembly processes have been used to assemble fractal structures [15,16] and nanoscale circuit diagrams [17], to design self-replication processes [18] and could in principle be extended to assemble structures of arbitrary complexity and size in one pot reactions.

The ordered execution of programmatic steps during assembly is made possible by experimental conditions in which a monomer attaches favorably to two or more binding sites on a crystal but unfavorably to only a single binding site. In algorithmic assembly literature, the term *cooperative binding* is used to describe this effect. The biochemistry literature sometimes uses the term *avidity* to describe this effect, and reserves 'cooperative binding' for a different usage (to describe how binding affinity of a ligand to a substrate increases nonlinearly with ligand concentration).

Figure 1



DNA/RNA structures produced using processes in which the order of assembly is designed and controlled. (Figures taken from respective citations.) **(a)** Algorithmic tile self-assembly of double-crossover DNA tiles [8]. Here, monomers assemble into an aperiodic crystal structure. The example shown is a 'binary counter' in which the dots in each row encode incrementing numbers in binary [9]. (Width of structure ≈100 nm.) The structure is assembled from bottom to top, such that each tile that attaches matches two binding sites in the structure, effectively integrating information about the structure's current assembly state (Figure 2). In other words, assembly steps perform simple computations. **(b)** Catalytically triggered self-assembly of a three-arm junction from DNA hairpin components [10]. (Scale bar: 10 nm.) Although a three-arm junction is the thermodynamically most stable state, a large energetic barrier prevents the formation of the structure until a catalyst strand triggers its assembly. A cascade of trigger and release steps can be used to order an assembly process. **(c)** Co-transcriptional folding of an RNA structure. Secondary structure formation occurs more quickly than transcription so that existing complementary domains will hybridize first and will not interact with domains transcribed later. The order of transcription therefore controls the order of self-assembly. Tile components subsequently assembly into a hexagonal lattice [11••]. (Scale bar: 100 nm.) **(d)** A transformation of a concentration pattern of DNA components, driven by a designed reaction diffusion process [12•]. While multiple reactions and diffusion processes are occurring at once, a separation of time-scales of reaction and diffusion processes produces a well-defined pattern of chemical concentrations. (Scale bar: 3 mm.)

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