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Original Article

A Simple Tool for the Design of Polyhedral DNA Nanostructures

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Abstract

DNA nanostructures are a class of self-assembling nanomaterials with a wide range of potential applications in biomedicine and nanotechnology. DNA nanotechnology originated in the 1980s with the construction of simple DNA polyhedra guided by human intuition or basic algorithmic approaches, which later evolved into platforms for applications such as molecular diagnostics and drug delivery. Today, the field is dominated by DNA origami constructs, to such an extent that the original algorithms used to design non-origami nanostructures have been lost. In this work, we describe Arktos: an algorithm developed to design simple DNA polyhedra without the use of DNA origami. Arktos designs DNA sequences predicted to fold into a desired structure, using simulated annealing to optimize strand binding energies and minimize misfolded configurations. As a proof-of-concept, we used Arktos to design a simple DNA tetrahedron. The generated oligonucleotide sequences were synthesized and experimentally validated via PAGE, indicating that they fold into the desired structure. These results demonstrate the feasibility of using Arktos to design simple DNA polyhedra, providing a foundation for future extensions.

Categories: Biotechnology and Engineering, Nanotechnology, Polymer Science and Engineering

Keywords: dna nanostructures, algorithm, bio-nano-process, dna, dna molecules

Introduction

DNA nanocages and nanostructures are a class of self-assembling nanomaterials that have been developed over the past several decades. These structures are formed by the hybridization of complementary DNA strands, and they can be designed to have a variety of shapes and sizes. DNA nanocages and nanostructures have a wide range of potential applications in biomedicine and nanotechnology, including drug delivery, biosensing, and tissue engineering [1].

The history of DNA nanotechnology can be traced back to the 1980s, when Ned Seeman and his colleagues developed the first DNA nanostructures [2]. Seeman's early work focused on the design of DNA junctions, which are the basic building blocks of DNA nanostructures. Early DNA nanotechnology involved the design of nanostructures using self-assembling DNA oligonucleotides. Early accomplishments using this approach include the design of a simple DNA cube [3], a truncated octahedron [4], a tetrahedron [5], a truncated bipyramid, and a wide array of prisms [6].

In the early 1990s, Paul Rothemund developed the DNA origami technique, which allows for the creation of complex DNA nanostructures with arbitrary shapes [1]. DNA origami uses short DNA oligonucleotides, or "staples," that bind to and fold a long single-stranded "scaffold" into any desired shape. Currently, it is possible to create any arbitrary 2-dimensional or

3-dimensional shape using DNA origami. Examples include its use to create a 2D "smiley face" [1], a polyhedral mesh resembling the Stanford bunny [7], and nanocages possessing an assortment of sizes, shapes, and functions [8-16].

Despite its advantages, DNA origami requires the synthesis of hundreds of staples, making it an expensive approach. Furthermore, the requirement for a scaffold and staples makes the synthesis and assembly of a DNA origami-based nanostructure very difficult in vivo. Simple oligonucleotide-based DNA nanostructures would be preferable under such restraints.

There exists a plethora of software used for the creation of DNA nanostructures, such as caDNAno [17], Tiamat [18], CanDo [19-21], VHelix [7], and OxDNA [22]. However, most of these tools are optimized for the design of DNA origami-based nanostructures. Furthermore, all of the tools mentioned rely on graphical user interfaces, making the high-throughput programmatic design of DNA nanostructures difficult. Early DNA oligomer-based nanostructures were either designed by hand or using tools that are no longer available.

In this work, we describe Arktos: a simple tool optimized for the design of DNA oligomer-based nanostructures. Arktos (Algorithm for the Rational Konstruction of Topological Oligonucleotide Structures) reduces DNA nanostructures to simple graphical abstractions containing nodes and edges. Arktos performs both positive and negative design via simulated annealing while designing sequences to fit the inputted nanostructure topologies. We computationally validated Arktos by benchmarking it against sequences designed to fold into tetrahedra [5]. We experimentally validated Arktos by designing a simple DNA tetrahedron containing four strands that were observed to assemble on a PAGE gel. Furthermore, Arktos can be run on a Linux terminal, making the programmatic generation of a large variety of DNA nanostructures possible. We have made Arktos freely available through this work (Supplementary Protocol S1) as a GitHub repository (https://github.com/1337deepesh/Arktos). We hope Arktos will be of use to the research community.

Materials And Methods

Oligomer synthesis

The sequences of our four designed DNA oligomers (Table *2*) were synthesized by Biotech Desk Pvt. Ltd. (Bangalore, India).

Oligomer annealing

All DNA oligomers were dissolved in TE buffer at a stock concentration of 170 µM. Oligomers were diluted in folding buffer containing 50 mM Tris-Cl (Tris-Base [Sigma, Cat. No. 77861]; HCl [Fisher Scientific, Cat. No. 29507]), pH 8.0, 12.5 mM $MgCl_2$ [EMPLURA, Cat. No. 105833], and 0.2 mM EDTA [SRL, Cat. No. 35888] to give a final concentration of 10 µM, which was then subjected to the annealing process and used in further steps [16]. Oligomers were heated to 90 °C for 5 minutes and subsequently cooled to 4 °C in steps of 0.1 °C every 5 seconds using a thermocycler [Eppendorf Mastercycler X50, Cat. No. 6311000015]. In this protocol, nanostructure assembly does not rely on a single sequence-specific annealing temperature; instead, gradual cooling enables progressive hybridization of complementary regions, promoting correct 3-dimensional folding to allow the DNA strands to anneal. The assembled structures were stored at −20 °C for short-term preservation and thawed once immediately prior to analysis; under these conditions, no loss of structural integrity was observed.

Nanostructure electrophoresis

Before loading the samples onto the gel, they were thawed at room temperature for 20 minutes. An 8% polyacrylamide gel (29:1) was prepared in 1× TAE/Mg^{2+} buffer and used to analyze the formation of the self-assembled nanostructures. A total of 20 µL of each sample was loaded into a well on the gel, along with 5 µL of loading dye containing 0.003% bromophenol blue and 60% glycerol in 1× TAE/Mg^{2+} buffer. A 100 bp DNA ladder [Invitrogen™, Cat. No. 15628019] was used as a molecular weight marker in the first lane.

The gel was run at a constant voltage of 100 V for 80 minutes in a cold room at 4 °C. The cold temperature helps to prevent the DNA sequences from denaturing. The gel was then stained with GelRed [Biotium, Cat. No. 41003], diluted to 3× in 0.1 M NaCl solution, for 30 minutes on a gel rocker [Benchmark Scientific, Cat. No. BR2000]. GelRed is a fluorescent dye that binds to DNA. The gel was then visualized using BioRad Image Lab software [Bio-Rad, Version 6.1, Cat. No. 1709690].

Results And Discussion

We describe the Arktos algorithm, its computational validation, and its experimental validation via the creation of a simple DNA tetrahedron in the sections below.

Algorithm design

Arktos attempts to design simple DNA polyhedra using both positive and negative design principles. DNA polyhedra are reduced to graphical abstractions for input (Figure *2B* and C). ssDNA-ssDNA interactions that form dsDNA are represented as edges or connections.

Positive design involves creating on-target matches (base-pair complementarity) for every intended strand pairing. Negative design ensures that off-target matches, which may arise by chance in unpaired strands, are minimized. Arktos achieves this using a scoring function defined below.

Let:

LM = Length of a single off-target match (length ≥ 4) between a pair of strands (including self-pairings).

M = Total number of off-target matches (length ≥ 4) between a pair of strands (including self-pairings).

n = Total number of nucleotides in all strands.

N = Total number of strands.

The ArkScore is then given by:

$$ArkScore = \sum_{N+{}^{N}C_2}^{0} \sum_{M}^{0} LM^2$$

A normalized ArkScore can be defined as:

$$ArkScore/nucleotide = \frac{ArkScore}{n} = \frac{\sum_{N+{}^{N}C_2}^{0} \sum_{M}^{0} LM^2}{n}$$

For a system of N strands, there are $N + \binom{N}{2}$ total strand pairings (including self-pairings at off-target regions). A summation of the squares of all off-target matches of sequence length ≥ 4 across all $N + \binom{N}{2}$ strands constitutes the ArkScore (Equation 1). A sequence length of ≥ 4 was chosen as the mismatch threshold since shorter mismatches (≤ 3 nucleotides) bind only transiently and do not significantly affect foldability of the designed polyhedron. The square term disproportionately penalizes longer off-target matches.

The ArkScore is always non-negative, with lower values indicating fewer off-target matches. To optimize sequence design, Arktos employs a simulated annealing algorithm [23] to minimize the ArkScore, thereby maximizing the likelihood of correct folding into the target polyhedral structure. The normalized ArkScore (Equation 2) allows comparisons across DNA polyhedra with different strand numbers and sequence lengths.

Designed sequences are output in FASTA format, with vertical bars ("|") marking breaks between complementary regions (nodes) within a strand. The Arktos script, along with full details on input and output formats, is available in Supplementary Protocol S1 and at our GitHub repository (https://github.com/1337deepesh/Arktos).

Algorithm validation

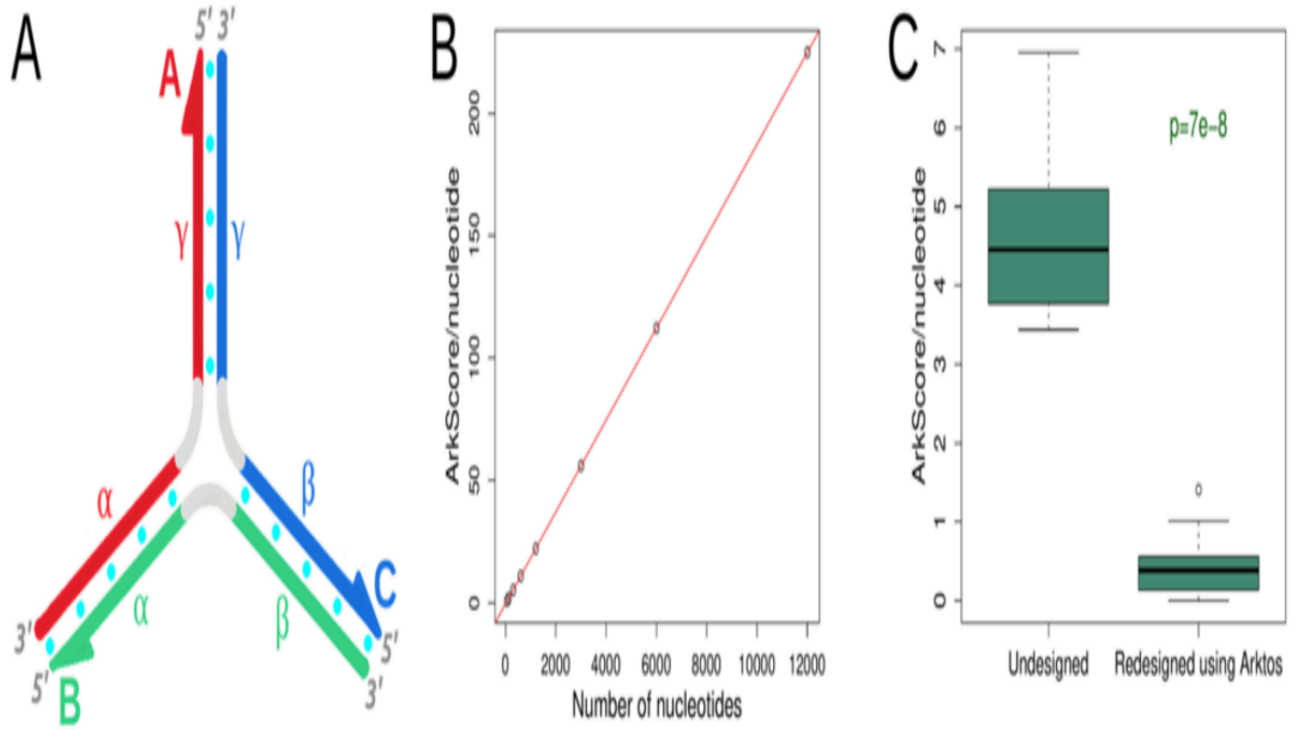

FIGURE 1: Computational evaluation of Arktos

(A) A DNA trimer containing strands A, B, and C was used for testing design scalability. Each strand can be subdivided into nodes; for example, strand A possesses nodes α, hinge, and γ. Hinges are single unpaired adenine residues and are shown in gray. Inter-strand base pairing is represented with cyan dots. The DNA trimer depicted here possesses 5 base pairs per complementary region (10 base pairs per strand). However, complementary regions containing 10, 20, 50, 100, 200, 500, 1000, and 2000 base pairs were also used for evaluation.

(B) ArkScore/nucleotide (Equations 1 and 2) increases linearly with an increasing number of nucleotides (summed across all three strands). ArkScore/nucleotide increases by 0.01877 units per nucleotide. A normalized score (ArkScore/nucleotide^2 × 100) can be used when comparing DNA nanostructures across different orders of magnitude in size. However, ArkScore/nucleotide alone is sufficient for comparing nanostructures of the same order of magnitude with negligible error.

(C) Benchmarking of Arktos against previously designed DNA tetrahedra [5]. First, the existing tetrahedra were scored using Arktos. Second, their sequences were redesigned using Arktos while keeping the overall topology intact. The ArkScore values of redesigned tetrahedra were significantly lower lower ($p = 7 \times 10^{-8}$, Welch 2-sample T-test) compared to previously designed tetrahedra merely scored using Arktos. A detailed score breakdown is provided in Table 1.

We performed two exercises to computationally validate Arktos. First, we evaluated the scalability of Arktos. Here, "scalability" denotes the ability of Arktos to output consistent scores irrespective of the size of the DNA nanostructure under design. We evaluated scalability using a simple DNA trimer with extendable strands (Figure *1A*). Strands A, B, and C form interactions through "nodes," or short complementary DNA stretches. DNA trimers containing 10-2000 nucleotide nodes were chosen for scalability evaluation (Figure *1B*). We observed that the ArkScore per nucleotide remains fairly constant for designed DNA nanostructures within the same order of magnitude in size, increasing by only 0.01877 units per nucleotide. This increase is expected, as larger DNA nanostructures inherently possess a greater number of off-target strand permutations. When comparing DNA nanostructures across different orders of magnitude in size, a normalized score (ArkScoreOM_\text{OM}OM, Equation 3) can be used to compensate for this increase.

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$$\mathbf{ArkScore_{OM}} = \frac{\mathbf{ArkScore}}{n^2} \times 100 = \frac{\sum LM^2}{n^2 \cdot \left(N + \binom{N}{2}\right) M} \times 100$$

Second, we benchmarked Arktos against experimentally validated DNA tetrahedra designed by Goodman et al. [5]. In a preliminary communication [24], Goodman et al. mentioned that the sequences were designed to "minimize the strength of undesirable interactions," but did not describe any specific method. We scored DNA tetrahedra designed by Goodman et al. using Arktos. Further, we used Arktos to redesign the sequences of Goodman et al. tetrahedra, while keeping their overall topology intact. We found a statistically significant difference between these undesigned and redesigned scores (Table *1*, Figure *1C*). Redesigned tetrahedra possessed significantly lower ArkScore per nucleotide values compared to the undesigned Goodman et al. tetrahedra.

These results indicate that while Goodman et al. tetrahedra were experimentally observed to rapidly fold into their desired structure, the methods used by Goodman et al. [5] may not be scalable for larger DNA polyhedra. Larger polyhedra require longer DNA sequences, which inherently possess a greater number of off-target strand permutations. This makes the design of larger DNA polyhedra or nanostructures from DNA oligonucleotides inherently more difficult. Therefore, Arktos is expected to outperform the method used by Goodman et al. for larger DNA nanostructures, although further experimental validation via the synthesis and characterization of such structures is required to confirm this expectation.

Tetrahedron	Total N	Undesigned	Redesigned
		AS/N	AS/N
4 × 20, 2 × 10	112	5.01	0.00
4 × 20, 1 × 10, 1 × 15	117	5.63	0.14
5 × 20, 1 × 10	122	3.74	0.13
4 × 20, 1 × 10, 1 × 25	127	4.61	0.38
5 × 20, 1 × 15	127	4.29	0.25
4 × 20, 1 × 10, 1 × 30	132	5.22	0.39
6 × 20	132	3.77	1.41
5 × 20, 1 × 25	137	3.44	0.53
5 × 20, 1 × 30	142	4.27	0.56
3 × 20, 3 × 30	162	6.96	1.01

TABLE 1: A comparison of ArkScore/nucleotide (AS/N) for previously designed DNA tetrahedra [5] redesigned using Arktos vs. previously designed DNA tetra simply scored using Arktos (undesigned)

The tetrahedral architecture is provided in the first column. 4 × 20, 2 × 10, for example means the designed tetrahedron contained 4 edges (ds DNA strand pairings) of 20 nucleotides and 2 edges of 10 nucleotides (6 edges total, see Figure 2B). "Total N" refers to the total number of nucleotides in all DNA strands of a given tetrahedron. This value includes both paired edges and unpaired hinges. The ArkScore/nucleotide of redesigned DNA tetrahedra is significantly lower than the ArkScore/nucleotide of undesigned tetrahedra.

Experimental validation

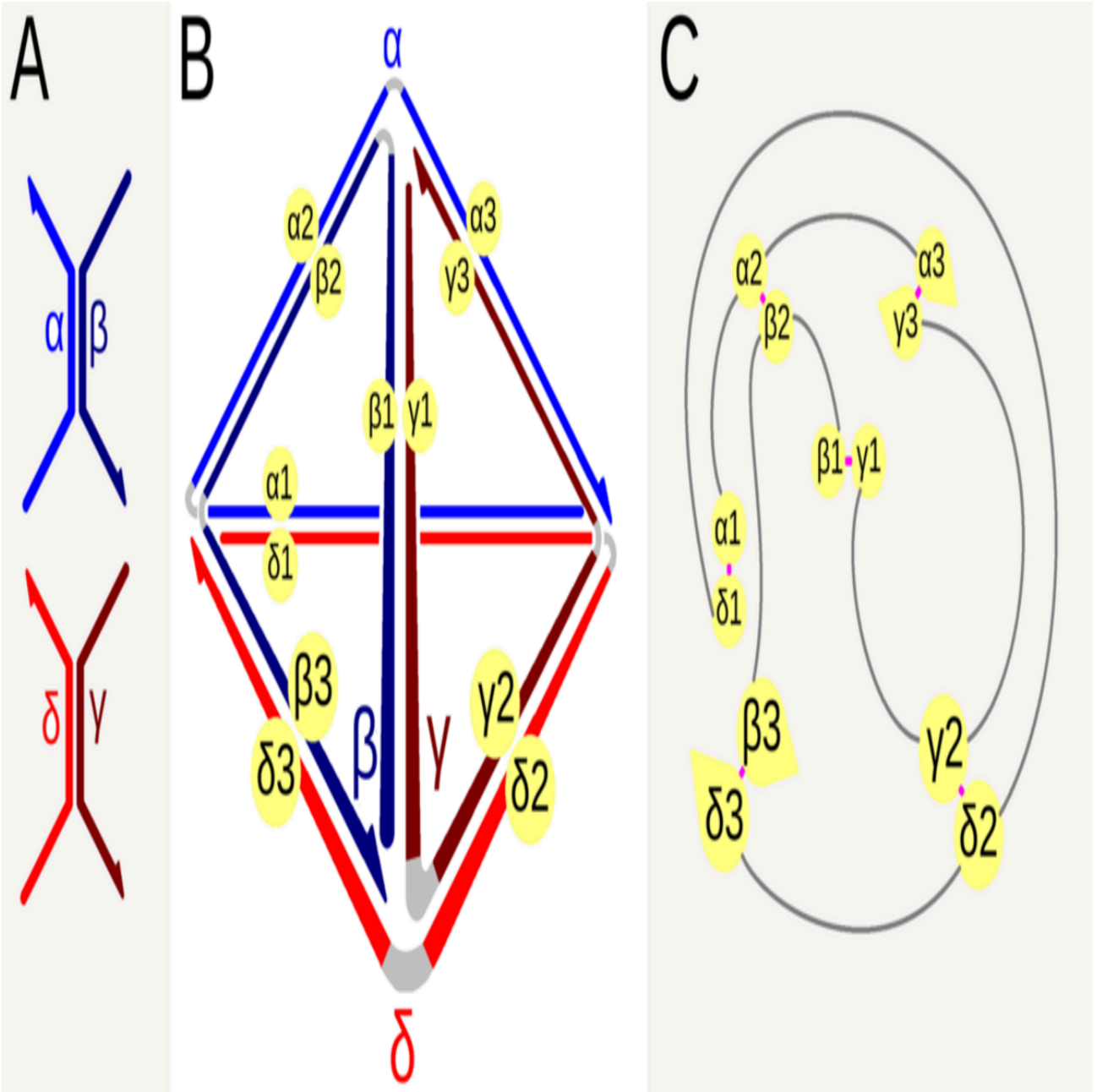

FIGURE 2: Design of a simple DNA tetrahedron to validate Arktos

Four DNA oligomers named α, β, γ, δ were designed using Arktos and synthesized. Their sequences are provided in Table 2.
(A) Strand-pairings in isolation. DNA oligomers α –β and γ –δ are shown as pairs to help the reader understand their placement in the full DNA assembly.
(B) Strand-pairings within the DNA tetrahedron. Individual strands are divided into "nodes" based on their strand-pairings. Strand α, for example, is divided into nodes α1, hinge1, α2, hinge2, and α3. Gray regions indicate hinges. All hinges are composed of lone unpaired adenine nucleotides.
(C) Reducing the DNA tetrahedron to a graphical representation for input into Arktos. Individual nodes are now represented as points with "edges" connecting to other nodes. Magenta edges represent designed complementary strand pairings. Gray edges represent hinges that are always connected to 2 nodes on either end. Any arbitrary polyhedral shape is reducible to a graphical representation.

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Oligomer	Nodes	Sequence (5′ → 3′)
Strand α	α1 | hinge1 | α2 | hinge2 | α3	CCGACTCACAGTGCCGGCCCCTCGTGAGGG|A| CCCGCTGATCAAGCCTTAGCGATGTCGCGG|A| GCAGCATAGCTCTACCTAGTAGAGTCATCC
Strand β	β 1 | hinge1 | β 1 | hinge2 | β 3	CCCATGGGGCGTATACTTCGGTGTTACAAC|A| CCGCGACATCGCTAAGGCTTGATCAGCGGG|A| GATATTTTGGTTAAATTGCAACCAATAATC
Strand γ	γ1 | hinge1 | γ1 | hinge2 | γ3	GTTGTAACACCGAAGTATACGCCCCATGGG|A| CCTGTGGCATTCTTCCACGCCAGAAACGTC|A| GGATGACTCTACTAGGTAGAGCTATGCTGC
Strand δ	δ 1 | hinge1 | δ 1 | hinge2 | δ 3	CCCTCACGAGGGGCCGGCACTGTGAGTCGG|A| GACGTTTCTGGCGTGGAAGAATGCCACAGG|A| GATTATTGGTTGCAATTTAACCAAAATATC

TABLE 2: Nucleotide sequences for all four DNA strands designed using Arktos

These strands were designed to form a tetrahedral nanostructure upon assembly. "|" breaks between sequences represent the starts/ends of nodes (including hinges).

Using Arktos, we designed a simple DNA tetrahedron possessing an edge length of 31 nucleotides with mono-adenyl hinges. The entire structure consists of 4 strands, each containing 92 nucleotides (Table *2*), for a total of 368 nucleotides. The topological design of this structure, showing the 4 DNA strands α, β, γ, and δ and their expected sub-assemblies, is provided in Figure *2*. For example, the central regions of strands α and β are designed to be complementary, while the 5′ and 3′ regions are designed to be complementary to the 5′ and 3′ regions of strands γ and δ. The entire assembly is provided in Figure *2B*. Each strand is subdivided into "nodes" designed to be complementary to nodes on other strands. This assembly is reduced to a graphical abstraction (Figure *2C*) containing only nodes and edges for input into Arktos.

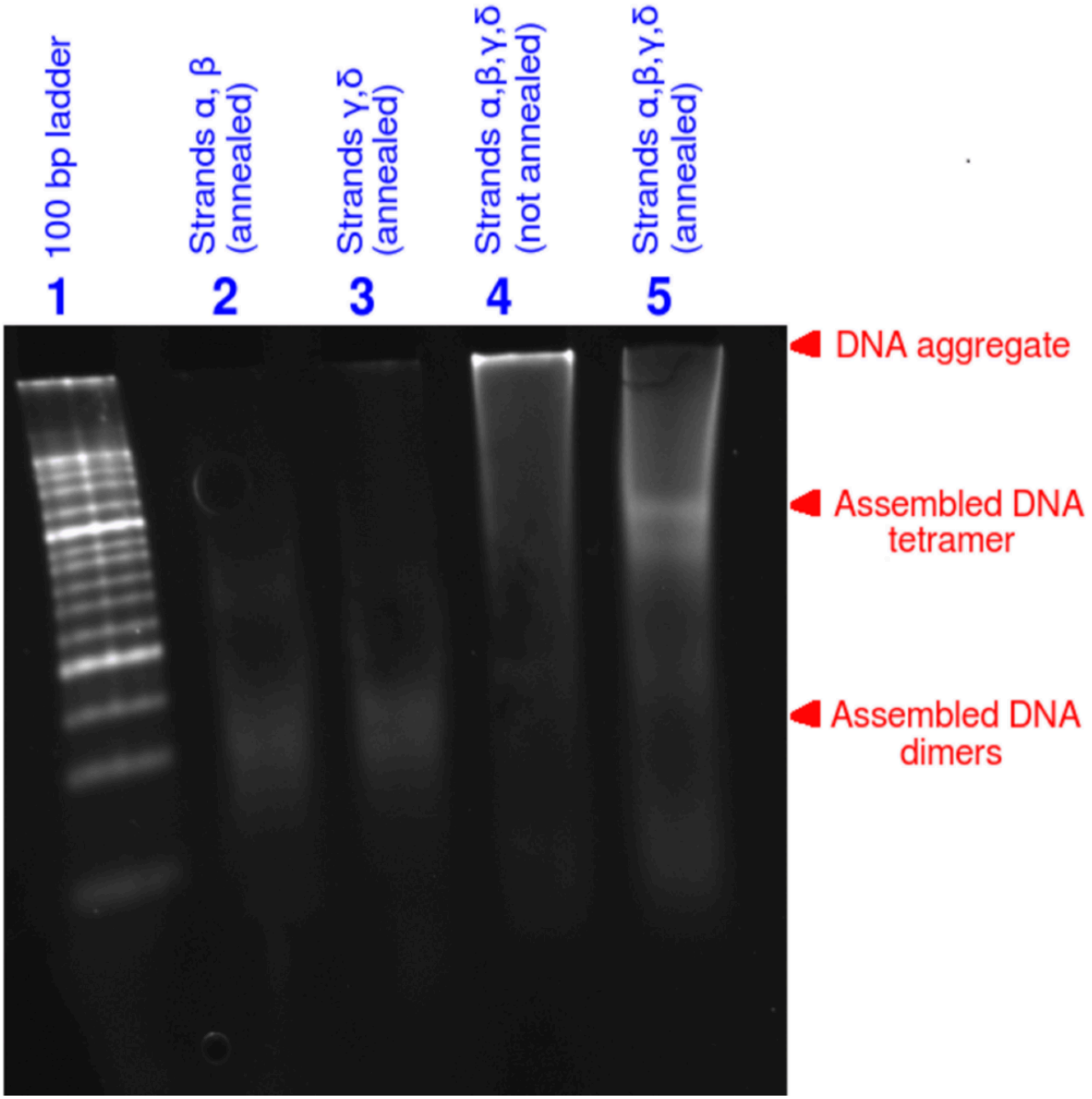

FIGURE 3: Polyacrylamide gel electrophoresis confirms that DNA strands α, β, γ, and δ assemble into ordered structures

Lane 1: 100 bp ladder. Lane 2: Strands α and β annealed together. They form a dimer as expected. Lane 3: Strands γ and δ annealed together. They form a dimer as expected. Lane 4: Strands α, β, γ, and δ run without annealing. The strands aggregate, showing that annealing is necessary to form an ordered structure. Lane 5: Strands α, β, γ, and δ run after annealing. The strands display an ordered assembly expected to be tetrahedral. However, further experiments are required to confirm its structure.

Arktos uses simulated annealing [23] to optimize designed sequences to minimize off-target matches. As simulated annealing is a stochastic heuristic process, it can generate different outputs in close approximation to the global minima. Arktos was therefore run 1000 times using the same input graph, and the output sequences possessing the lowest ArkScore were selected for oligomer synthesis.

The four designed oligomers were mixed in 1:1 or 1:1:1:1 stoichiometric ratios and annealed as described in the Methods section. The annealed products were visualized on a PAGE gel (Figure *3*). We observed single bands for the annealed products of strands α and β (lane 2) as well as strands γ and δ (lane 3). This indicates that these strand-pairs dimerize, as depicted in Figure *2A*. Strands α, β, γ, and δ were also annealed in a one-pot approach, with the annealed product also displaying a single band (lane 5) higher along the gel than the α-β (lane 2) and γ-δ (lane 3) bands, indicating the assembly of an ordered nanostructure. Finally, strands α, β, γ, and δ display aggregation when run on the gel without annealing (lane 4), indicating that annealing is required to form an ordered nanostructure.

These results strongly indicate that strands α, β, γ, and δ folded into the desired DNA tetrahedron. However, further experimentation using cryo-electron microscopy, atomic force microscopy, or X-ray diffraction are required to confirm its shape.

Conclusions

In conclusion, we have developed Arktos, a simulated annealing-based algorithm to design DNA nanostructures from DNA oligomers. We have computationally validated the algorithm against existing DNA tetrahedra designed by Goodman et al. We have also experimentally validated Arktos by using it to design a simple DNA tetrahedron. We have made Arktos freely available and hope it will find applications within the research community. Beyond tetrahedral structures, Arktos can be adapted to design more complex polyhedral DNA assemblies, offering flexibility in tailoring nanostructures for diverse applications. The algorithm's stochastic nature also ensures that a wide design space is sampled, thereby increasing the probability of generating highly optimized sequences. With continued improvements and integration with downstream experimental workflows, Arktos has the potential to accelerate the rational design of DNA-based nanodevices in fields ranging from drug delivery to molecular computation and synthetic biology.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Deepesh Nagarajan, Pushya Pradeep

Acquisition, analysis, or interpretation of data: Deepesh Nagarajan, Harshitha Balaji, Anish Hemanth Samprathi, Rakshita Sukruth Kolipakala

Drafting of the manuscript: Deepesh Nagarajan, Harshitha Balaji, Anish Hemanth Samprathi

Critical review of the manuscript for important intellectual content: Deepesh Nagarajan, Pushya Pradeep, Rakshita Sukruth Kolipakala

Supervision: Deepesh Nagarajan

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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