The Biophysicist

Modular, Articulated Models of DNA and Peptide Nucleic Acids for Nanotechnology Education

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ABSTRACT Dynamic and flexible nucleic acid models can provide current and future scientists with physical intuition for the structure of DNA and the ways that DNA and its synthetic mimics can be used to build self-assembling structures and advanced nanomachines. As more research labs and classrooms dive into the field of structural nucleic acid nanotechnology, students and researchers need access to interactive, dynamic, handheld models. Here, we present a 3D-printable kit for the construction of DNA and peptide nucleic acid (PNA). We have engineered a previous modular DNA kit to reduce costs while improving ease of assembly, flexibility, and robustness. We have also expanded the scope of available snap-together models by creating the first 3D-printable models of γPNA, an emerging material for nuclease- and protease-resistance nanotechnology. Building on previous research, representative nucleic acid duplexes were split into logical monomer segments, and atomic coordinates were used to create solid models for 3D printing. We used a human factors approach to customize 3 types of articulated snap-together connectors that allow for physically relevant motion characteristic of each interface in the model. Modules are easy to connect and separate manually but stay together when the model is manipulated. To greatly reduce cost, we bundled these segments for printing, and we created a miniaturized version that uses less than half the printing material to build. Our novel 3D-printed articulated snap-together models capture the flexibility and robustness of DNA and γPNA nanostructures. Resulting handheld helical models replicate the geometries in published structures and can now flex to form crossovers and allow biologically relevant zipping and unzipping to allow complex demonstrations of nanomachines undergoing strand displacement reactions. Finally, the same tools used to create these models can be readily applied to other types of backbones and nucleobases for endless research and education possibilities.

KEY WORDS Structural DNA nanotechnology; DNA origami; manipulable; 3D printing; models; peptide nucleic acids

I. INTRODUCTION

Structural DNA nanotechnology is a versatile technique for the self-assembly of structures and dynamic machines with versatile chemical functionality. This field first arose from the work of Nadrian Seeman, who recognized that DNA could form lattices and junctions to form ordered structures for the arrangement of material at the nanoscale (1). DNA-templated assembly was shown to enable the patterning of proteins and create conductive nanowires (2), and the complexity of these systems increased with landmark demonstration of structures

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like the DNA octahedron folded from 1.7-kb single-stranded (ss)DNA (3). The technique called DNA origami, invented in 2006 by Paul Rothemund (4), demonstrated a computationally simple way to build multiple kilobase–scale structures from a large ssDNA "scaffold" and hundreds of small ssDNA "staples." Since that development, both scaffolded and scaffold-free or tile-based DNA nanostructures, like DNA bricks (5), have demonstrated the unmatched addressability and feature resolution of DNA nanostructures. These advances have driven their application in a broad range of biophysics domains (6) including membrane biophysics (7–9), mechanosensing (10–12), and even the creation of synthetic biological systems such as external mesh networks (13, 14) and membrane-embedding nanopores (15).

The shape, mechanics, and thermodynamics of these structures result from their complex internal architecture, and given the extraordinary utility of structural DNA nanotechnology for advancing the field of biophysics, educational tools are needed for teaching key structural concepts fundamental to the design of DNA-based nanostructures. Additionally, the emerging field of peptide nucleic acid (PNA) nanotechnology presents new challenges and requires new design rules for the construction of complex nanostructures (16). To support the next generation of nanotechnology students and researchers, here we present 2 types of articulated, snap-together nucleic acid models for enabling hands-on nanotechnology training: DNA models and PNA models.

A. Scientific and pedagogical background

Numerous educational kits exist for modeling 2 to 3 turns of a DNA double helix, introducing key concepts such as antiparallel binding, base complementarity, and the emergence of major and minor grooves in the resulting duplex. However, the small number of nucleobases in these static models coupled with their lack of flexibility can make it difficult to model complex DNA nanostructures like DNA origami that can consist of hundreds to thousands of base pairs, with individual duplex segments functioning as elastic rods with crossover domains linking those rods together. To understand how DNA nanostructures are constructed, students first need a large number of monomer units for building flexible and sequence-customizable ssDNA oligomers. Next, these models must be able to hybridize or reconfigurably "zip" together and flex to accommodate helix-spanning Holliday junctions or "crossovers."

The 2015 "Folding DNA model" by Michael Kuiper (mkuiper) on the National Institutes of Health (NIH) 3D Print Exchange (17) and Thingiverse (18) provides an excellent starting point for such a tool. This existing model consists of individual 3D-printable components for the bases and DNA backbone. Backbone segments are connected with a split-pin or duckbill connector, and nucleobase hydrogen bonds are represented by peg and hole mechanisms. We have utilized this kit to teach the fundamentals of the DNA structure in our Carnegie Mellon University course "24-684/42-692 Special Topics: Nanoscale Manufacturing Using Structural DNA Nanotechnology." However, the need to create more complex structures with larger conformational flexibility and robustness drove our interest in developing a nanotechnology-focused variation.

B. Re-mixing the folding DNA model

We are not the first team to re-mix the Folding DNA model, and the magnetic variation created by James Tyrwhitt Drake aims to increase the degrees of freedom for both the backbone–backbone and backbone–nucleobase bonds while providing magnetic connections that represent the hydrogen bonds between the nucleobases (19). Our variation similarly increases the robustness of the snap connections while supporting increased degrees of freedom for articulated motion, but it is fully 3D printed and ready to use out of the box. Our cost-aware design (Fig 1) bundles pieces together for ease of printing and can also be 3D printed at 75% scale to greatly reduce cost without sacrificing connection performance.

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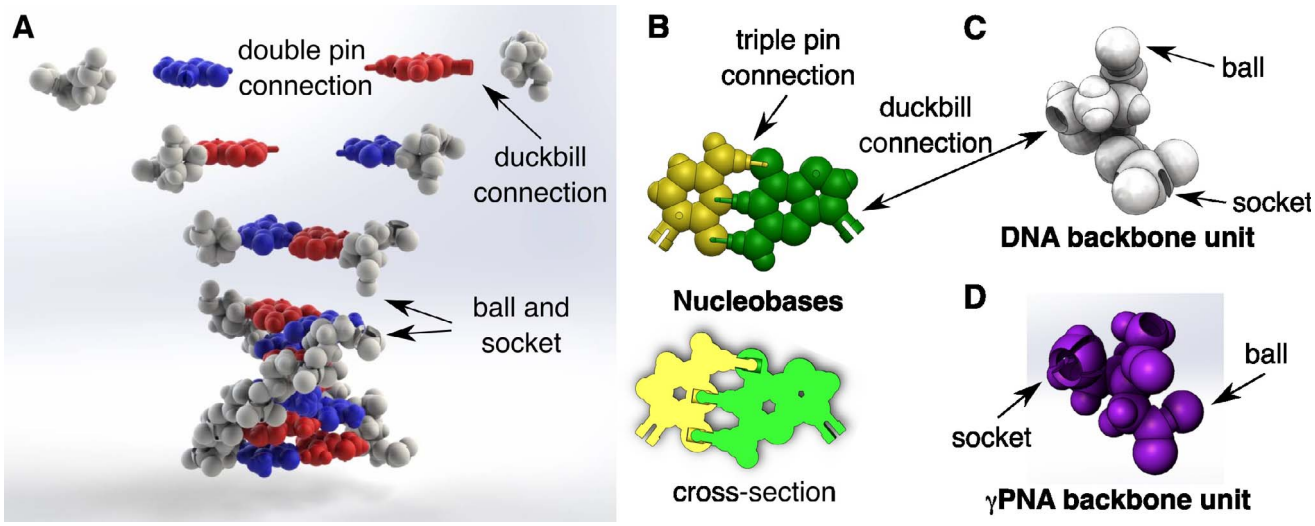

Fig 1. Assembly of single strands, duplexes, and more complex nanostructures from modular backbone and nucleobase pieces. (A) Exploded rendering shows how individual nucleotides are built by first connecting nucleobases and backbone segments with the duckbill connections. Nucleotides can be used to build single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA). (B) Nucleobases can be connected with double-pin and triple-pin connectors that represent hydrogen bonds, and (C) backbone segments can be connected with ball-and-socket connections. (D) This is the first model kit to provide a backbone segment for peptide nucleic acid (PNA). The color scheme used in these models is as follows: adenine = red, thymine = blue, cytosine = yellow, guanine = green, DNA backbone = white, and γPNA backbone = purple.

Additionally, to our knowledge, no model kits available to date provide the ability to create models of synthetic nucleic acid mimics (PNAs) for the construction of larger PNA nanostructures. PNA synthetic nucleic acid mimics are more enzyme-resistant than natural nucleic acids but can still bind to DNA and RNA with high affinity (20, 21). In this kit, we have created backbone pieces for uncharged gamma-modified PNA (γPNA) (22–24). PNA oligomers are built with the PNA backbones, along with the existing nucleobase pieces. Taken together, our low-cost system allows for the construction of flexible and complex nanostructures made from DNA and from PNA oligomers, whose distinct helicity (approximately 18 bases per turn for PNA instead of 10.5 bases per turn for DNA) is enabling new architectural approaches for structural nucleic acid nanotechnology (16, 25).

II. MATERIALS AND METHODS

A. Engineering of flexible and robust connectors

When teaching the structure of DNA to a multidisciplinary audience of biophysics and engineering students, we have used 3D-printed models (17, 18) to facilitate student learning and promote exploration of the architectures of structural DNA nanotechnology. However, despite the overwhelmingly positive student feedback for this learning tool, students also reported that it was discouraging when the fragile models would sometimes fall apart in their hands.

We were therefore motivated to engineer improved connectors that provided more robust connections and physically relevant degrees of freedom while still maintaining ease of disconnection. In this work we present our nucleic acid model system, from which flexible single-stranded nucleic acids can be constructed. Unlike existing static nucleic acid models, our system can easily form flexible single-stranded nucleic acids and allow their hybridization to form duplexes. This model is a "remix" or variation on the approach used by Michael Kuiper (17, 18).

The Kuiper approach utilized scripted solid modeling of nucleobases and backbones by the programmable computer-aided design tool OpenSCAD (26), building spheres at known atom positions and implementing connectors

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as well as part bundles to facilitate 3D printing. We built on this approach, reimplementing the nucleobase and DNA backbone parts with the commercial computer-aided design tool SolidWorks (Dassault Systèmes), which afforded greater control in the design and fine-tuning of the connector features. The need for improved human factors motivated these changes. Depending on hand size, strength, and coordination, people assembling these models may struggle to orient modules perfectly to each other when connecting them together. Thus, all our connectors feature curvature at the interface between the plug and socket parts to help guide them into position (Fig 2). We then ensured that the pieces will not easily separate when models are manipulated. With the use of simulation software and a prototyping process, we developed connectors that elastically deform during manual insertion and removal, then snap back to their original state. We optimized these connectors to handle many repeated insertions and removals, without requiring excessive hand strength.

To address the different types of bonds and range of motion expected between backbone segments and bases and between backbones and bases, we used 3 different connectors with movement characteristic of those bonds. Like the previous model, we used a split-pin or duckbill connection with one degree of rotational freedom to connect nucleobases to the backbone pieces (Fig 2A,B). Hybridization of nucleobases is achieved with our modified double-pin and triple-pin connections that represent the hydrogen bonds formed between adenine/thymine and cytosine/guanine, respectively (Figs 1B, 2C,D). We developed custom-optimized pin-receiving features to facilitate ease of pin connection and prevent accidental disassembly, while maintaining rigidity with zero degrees of rotational freedom.

Finally, to provide 3 rotational degrees of freedom between the backbone pieces, we developed custom ball-and-socket connectors (Figs 1C,D, 2E,F), which increased backbone flexibility and capture strength of the ball-and-socket joint, effectively increasing the robustness of the backbone connections. The additional degrees of freedom also improve ease of assembly, because backbone chains can now flex and rotate when neighboring modules are attached, instead of falling apart. The combination of these connectors align modules so that, when nucleic acid models are fully assembled, their orientations match published geometry (Fig 1A).

B. Engineering a low-cost model kit

The next challenge we aimed to address was that of affordability. Our initial implementation that we call the 100% scale model cost about $45 for an 8-base duplex, which is a high price for a single student kit. The high price also greatly limited the complexity of what could be built, putting more complex nanostructures (like kilobase-size DNA origami) firmly out of reach. As a first step toward low-cost models, we recreated our modules at 75% scale (see Fig 3). By reducing length dimensions to 75% we achieve parts that use $0.75 \times 0.75 \times 0.75 = 42\%$ the material of the 100% models. To date with our 75% scale models we have created nanostructure models with hundreds of nucleobases, and in future iterations we hope to continue to increase the complexity of what can be built.

Directly scaling the connector to 75% led to a direct reduction in the robustness of the interfaces, so connector features on the reduced scale parts were rescaled and reoptimized to achieve desired properties. As a result of these efforts, we have been able to verify the successful performance of this 3D-printed model system at both 100% and 75% scales. We used a widely available print-on-demand service, Shapeways Inc (https://www.shapeways.com/), to print our parts in sintered nylon that is sold under the name "Versatile Plastic."

In Table 1 we provide the part dimensions, part volumes, machine space, and cost of these parts as quoted by Shapeways at the time of publication of this article. The 75% natural parts are approximately half the cost of the 100% natural parts, but the costs for processing and dyeing parts substantially raise costs. Therefore, for students and educators looking

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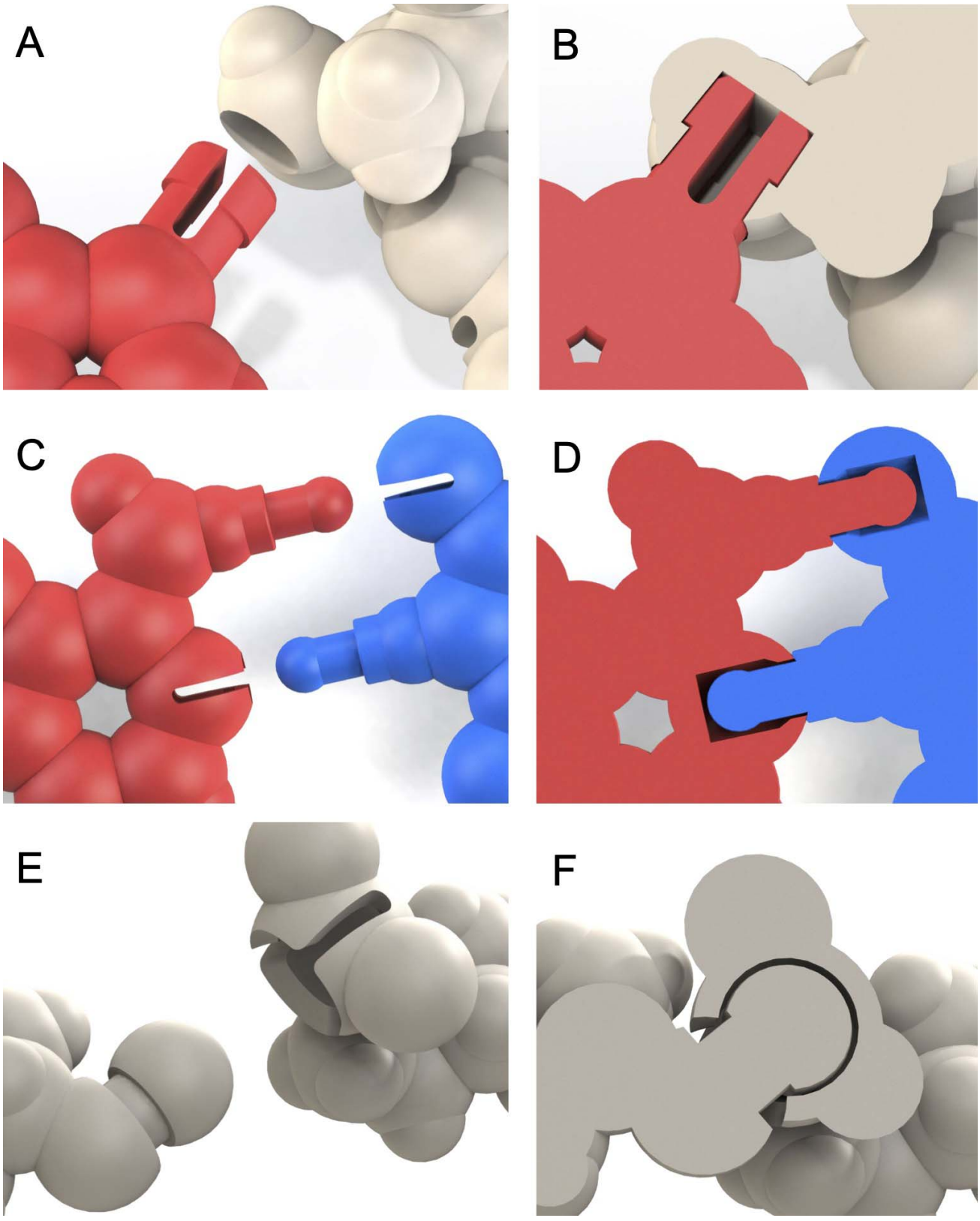

Fig 2. Self-aligning snap connectors created in SolidWorks. Their geometry allows for human error on insertion and greater freedom of motion to ease assembly. When the models are fully assembled, fidelity to true orientations is achieved. Duckbill-style connectors are used to join backbones to nucleobases; (A) disconnected and (B) connected segments highlight how these pieces fit together. Double-pin–style connectors are used to connect nucleobases with other nucleobases: (C) disconnected and (D) connected. Ball-and-socket–style connectors are used to connect backbone segments: (E) disconnected and (F) connected.

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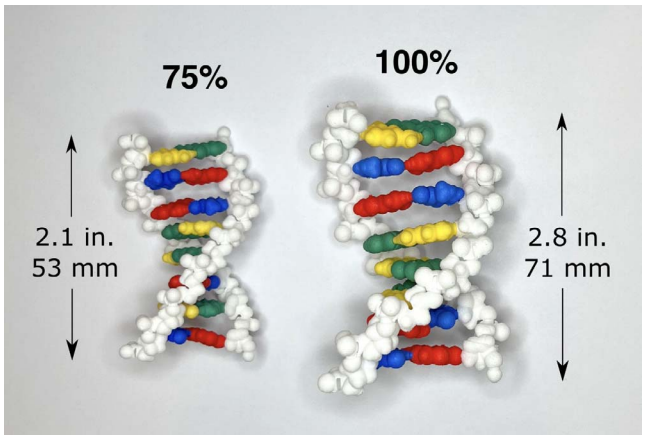

Fig 3. Model variations have been optimized for printing at 2 scales. For unfinished and undyed parts, the smaller 75% scale models cost approximately half as much as the larger 100% models, while maintaining flexibility, ease of attachment, and robust connections.

for cost savings, we recommend natural 75% parts. At 75% scale an 8-base duplex can be built for less than $20. In our Supplemental Material we provide 4 lesson plans, and Lesson Plan 1 describes a classroom activity for constructing a simple low-cost 8-base duplex with 16 DNA backbone pieces, 8 adenines, and 8 thymines. For those looking to hand dye sintered nylon parts, the Shapeways blog contains a useful tutorial (27).

C. Creating backbone segments for peptide nucleic acids

To create backbone segments for PNA, we wrote a Python script to extract atomic positions from the atomic model (PDB 2KVJ) for a γPNA duplex by He *et al*. (24). Our script then isolated the relevant atoms for a backbone segment and scaled the atomic positions into usable coordinates for computer-aided design modeling. This information was output as a comma-separated value (CSV) file for easy readability. These coordinates were created as single points in space in a SolidWorks part file. Additionally, coordinates of adjacent atoms in the backbone and nucleobases were added as reference points, to help orient connectors.

To transfer custom shapes from the DNA backbone model, we used sketch blocks, which are 2D sketches with a fixed geometry. These blocks included semicircles sized to represent different atomic radii and all the shapes required to create snap connectors. The blocks were inserted and aligned with the coordinate points. As with the DNA models, the γPNA backbone piece accepts a split-pin or duckbill connector from a nucleobase piece, and the ball-and-socket connections enable robust connections between backbone segments (see Fig 1D).

III. RESULTS AND DISCUSSION

To demonstrate the fidelity of 3D models to published atomic structures, we built 3 duplexes: a DNA duplex, a PNA–DNA duplex, and a PNA duplex. In Figure 4 we present a comparison between those structures and the following atomic structures: a B-form DNA duplex (28), a PNA–DNA duplex (29), and a γPNA

Table 1. Part dimensions, model volume, machine space, and cost information for unfinished and finished and dyed part bundles. Costs are based on estimates from Shapeways Inc. as of August 2022.

Part name	Parts per bundle	*X* (mm)	*Y* (mm)	*Z* (mm)	Model volume (cm^3)	Machine space (cm^3)	Natural (US$)	Processed and dyed (US$)
Thymine 100%	16	19.3	86.9	18.5	8.5	25.8	10.63	17.23
Thymine 75%	16	14.5	65.2	13.9	3.6	12.0	5.69	12.29
Adenine 100%	16	22.4	86.4	17.4	9.3	24.8	10.61	17.21
Adenine 75%	16	16.8	64.8	13.1	3.9	11.4	5.66	12.26
Cytosine 100%	16	15.3	86.4	21.1	7.4	22.4	9.42	16.02
Cytosine 75%	16	11.5	64.8	15.8	3.1	10.4	5.16	11.76
Guanine 100%	16	18.8	86.4	23.0	10.5	29.8	12.20	18.80
Guanine 75%	16	14.1	64.8	17.3	4.4	13.7	6.37	12.97
PNA backbone 100%	16	51.8	27.0	101.5	11.0	41.3	15.17	21.77
PNA backbone 75%	16	39.0	20.2	76.1	4.7	19.3	7.81	14.41
DNA backbone 100%	16	36.7	20.2	99.1	9.7	36.5	13.55	20.15
DNA backbone 75%	16	27.5	15.2	74.4	4.1	16.8	7.03	13.63

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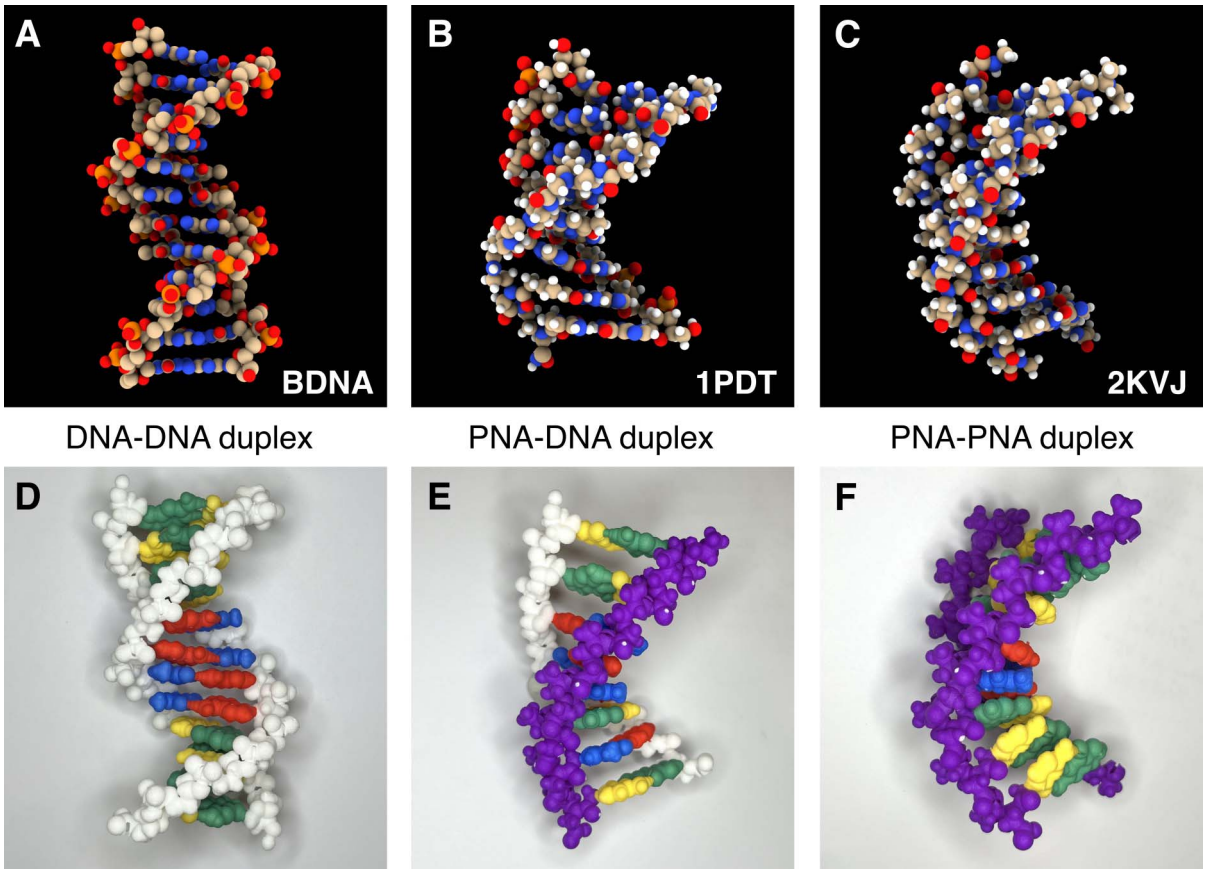

Fig 4. Our 3D-printed models are able to reproduce the geometry of DNA and γPNA duplexes. (A) The B-form DNA duplexes undergo one full turn approximately every 10.5 bases (29). PNA-containing duplexes are less twisted with (B) DNA–PNA duplexes undergoing approximately 13 base/turn (30) and (C) γPNA duplexes adopt an 18 base/turn configuration (24). (D–F) Our DNA- and PNA-containing duplex models can match the geometries shown in their corresponding Protein Data Bank (PDB) files shown in panels (A, B, and C).

duplex (24). These images (Fig 4D–F) show that our 3D-printed models are able to recapitulate the helical geometry of DNA and γPNA duplexes. In particular, these models clearly show that DNA duplexes are more tightly wound than γPNA duplexes, whereas hybrid PNA–DNA duplexes adopt an intermediate configuration. This nucleic acid model is the first that we are aware of that is able to capture the altered helicity of DNA- and PNA-based structures, and therefore these 3D-printed models represent a powerful tool for the design of novel PNA-containing nanostructures.

Although this kit enables the construction of simple DNA and PNA duplexes, it can also be used to build nanostructures and nanomachines containing hundreds of nucleotides. To provide guided learning experiences for novices to experts and to recruit the next generation of DNA nanotechnology researchers, we include 4 lesson plans in order of increasing complexity. The following activities highlight the capabilities of the model kit and introduce concepts that are fundamental in bioengineering and nanotechnology (Fig 5).

- Classroom Activity 1: A Simple 8-Base Pair Duplex—introduces students to the structure of DNA and guides them in the antiparallel hybridization of a simple duplex.
- Classroom Activity 2: DNA Polymerase Action—introduces a key step in the process of polymerase chain reaction. This activity guides students through the construction of a template ssDNA strand and a primer ssDNA strand that they hybridize together. Next, mimicking the action of a polymerase, they sequentially add complementary nucleotides in the 5′–3′ direction until the duplex is complete.

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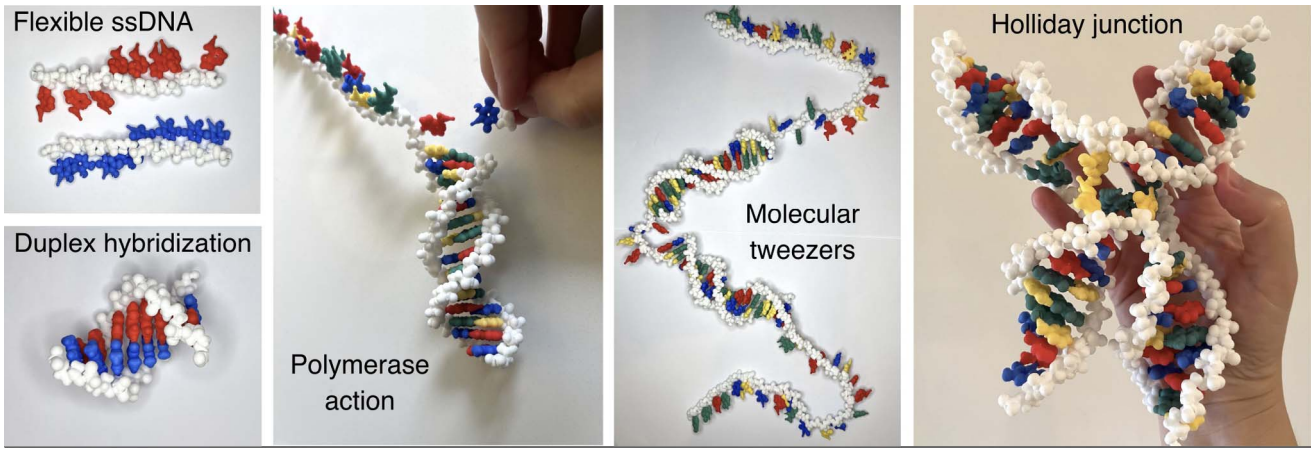

Fig 5. Lesson plans and a cost worksheet are provided in the Supplemental Material, and these resources support teaching activities that lead students through the construction of the following nanostructures: (left to right) a simple DNA duplex built by hybridizing flexible ssDNA, a simulation of polymerase activity, construction of a dynamic molecular tweezers system, and a Holliday junction.

- Classroom Activity 3: Molecular Tweezers—introduces the dynamic tweezers system introduced by Yurke *et al*. (30) in 2000. The steps in this activity guide a team of students (preferably 5 per team) through the construction of a 5-stranded molecular tweezer system that can be locked closed and then dynamically reopened by a strand displacement reaction. Stepwise assembly and strand displacement elucidate the mechanism of dynamic tweezer actuation.
- Classroom Activity 4: Holliday Junction Investigation—teaches the students how double-crossover junctions can be formed from 4 neighboring strands. Students will learn about the sequence complementarity required to form Holliday junctions. They will also gain physical insights into why some of the central nucleobases can become unpaired in a Holliday junction.

Each activity lists the pieces that are needed, and Table 1 can be used to estimate the cost for a class to employ these activities. There are ways to obtain 3D printed models of these parts. First, all of the models have been deposited in the NIH 3D print exchange (jrbexbox, https://3dprint.nih.gov/discover/3dpx-017650 and https://3dprint.nih.gov/discover/3dpx-018017). As a ''remix'' of mkuiper's original Folding DNA model, our system is freely available under the Creative Commons Attribution license. Users can download our part files and choose how to print them. Second, for those looking for a simpler ordering and printing process, we have made these parts available for purchase on our Shapeways store (jrbexbox, https://www.shapeways.com/shops/bexshop), and to keep costs down, we are not taking a fee on these DNA and PNA models printed through Shapeways.

Because of the success and usefulness of the γPNA models, we believe labs and classrooms would benefit from the ability to generate articulated models of other nucleic acid structures. We therefore provide a flowchart of our straightforward workflow (Fig 6). Future users can follow the steps to generate other backbone segments, such as an RNA backbone, and other nucleobases, such as Uracil. End caps for DNA and γPNA models could also be generated to increase the biological accuracy of large-scale models.

IV. CONCLUSION

DNA is an engineering material and a data storage platform and comprises critical machinery for life. Our goal is for interested users from the K12 to graduate school level to dig into playing with this toy to better understand its structure, mechanics, and dynamic capabilities. We hope that by assisting students to build DNA-based structures, we can excite their curiosity and recruit the next generation of nanotechnologists.

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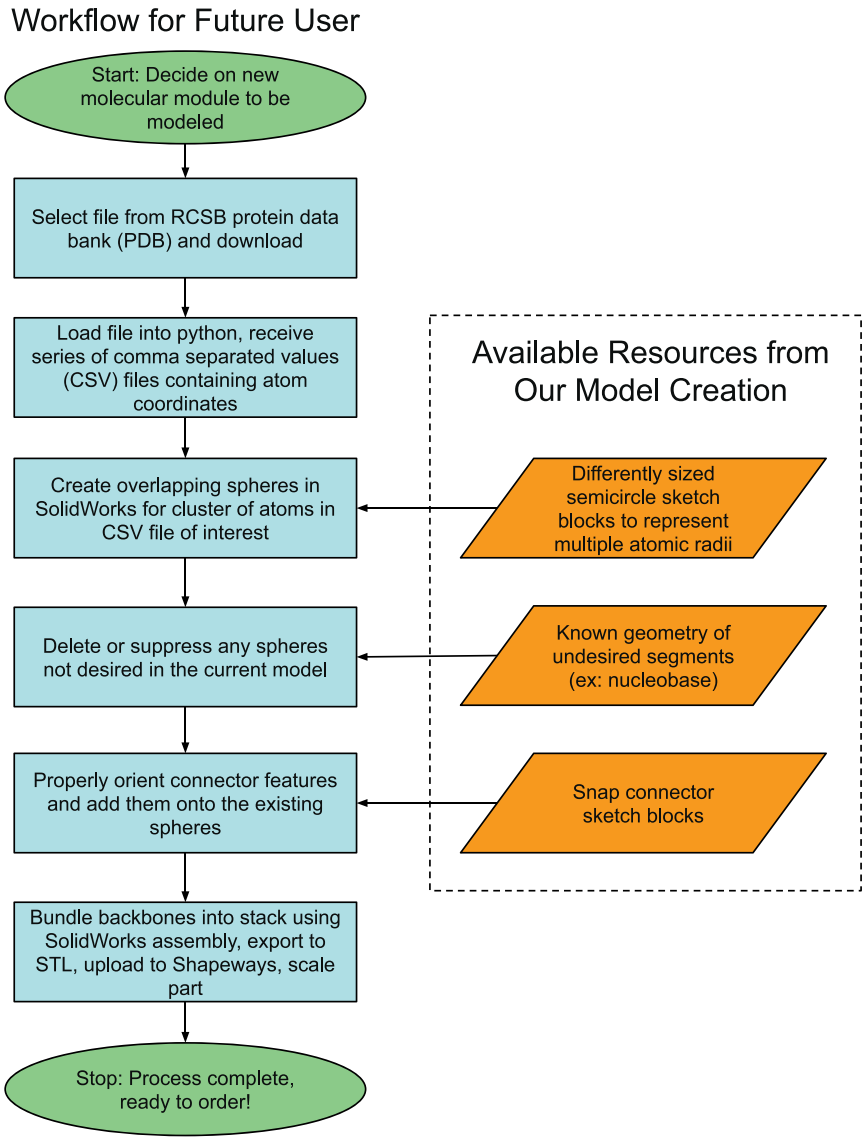

Fig 6. Flowchart detailing the steps a future user would take to create modular 3D-printed snap-together pieces from molecules available in the Research Collaboratory for Structural Bioinformatics Protein Data Bank. Many of the steps are automated, including extracting coordinates from a PDB file by a python program and inserting connector geometry with SolidWorks.

We also would love help from the community in the design of novel structural motifs for holding PNA nanostructures together. We recently faced the challenges of designing for PNA when we realized that no existing nucleic acid software design package natively supported designing with altered helicities. Although we have shown one motif to building with PNA (16, 25), we invite the community to use these PNA models to develop new structural motifs for this emerging material. We encourage readers to reach out to us to tell us about your DNA and PNA nanotechnology inventions.

Going forward we recognize there is still much to do on the model. We are interested in implementing RNA and xeno nucleic acids other than PNA. We hope to refine the DNA model by experimentally evaluating the persistence length, which for a simple semiflexible rod model of a DNA duplex is equal to the mechanical bending stiffness (K_B) divided by the Boltzmann constant times temperature (k_BT) (31). These studies could inform changes to the backbone connections to help the model better replicate the bending stiffness of double-stranded DNA. Finally, cost and limited

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complexity remain a challenge, so we will continue to develop approaches to reduce the size and cost of the model further with the future goal of creating affordable kits for creating DNA nanostructures with thousands of nucleotides like DNA origami.

SUPPLEMENTAL MATERIAL

All Supplemental Material is available at: https://doi.org/10.35459/tbp.2022.000225.s1.

AUTHOR CONTRIBUTIONS

CMG created the SolidWorks models of the individual backbone segments and nucleobases. CMG and RET conceptualized the project, created nanotechnologic demonstrations, and wrote the paper.

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