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Design Approaches and Computational Tools for DNA Nanostructures

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ABSTRACT Designing a structure in nanoscale with desired shape and properties has been enabled by structural DNA nanotechnology. Design strategies in this research field have evolved to interpret various aspects of increasingly more complex nanoscale assembly and to realize molecular-level functionality by exploring static to dynamic characteristics of the target structure. Computational tools have naturally been of significant interest as they are essential to achieve a fine control over both shape and physicochemical properties of the structure. Here, we review the basic design principles of structural DNA nanotechnology together with its computational analysis and design tools.

INDEX TERMS DNA, nanotechnology, design principle, computational tools.

I. INTRODUCTION

The deoxyribonucleic acid (DNA) molecule offers the essence of genetic information through combinations of four types of chemical groups, i.e., nucleotides. Its structure is paired in a given way determined by nature, known as Watson-Crick base pairing rule. Structural DNA nanotechnology, pioneered by Seeman [1] in 1982, is the sequence-based assembly of nucleotides into various structures in scales of nanometer to micrometer in the solution [2], [3]. The fundamental design methodologies and governing rules enabling single strands of DNA to be transformed into a 2D plate or simple tubes [4], [5] have been expanded to a variety of systems, including tubes with different lengths and cross-sections [6], [7] alongside structures with controlled bending [8] and torsion angles [9]. Additionally, there are techniques developed to vary the structure's functionality as seen in the dynamic linkage system [10], DNA walkers [11], [12], folding actuators [13], element-wise self-assembly system [14], [15] or even wire-framed shapes in 2D and 3D [16], [17]. The key underlying component enabling the versatility in designing shapes and structures is the ability to arrange the sequences of DNA to be held by short 'staple' strands, which then can be combined as the designated pairs to be structured as designed. In this methodology, the role of short DNA strands is similar to how RNA or synthesis of amino acids is dependent on the information given by the sequence in nature. In addition, the modular self-assembly of finite-sized, discrete, and complex DNA nanostructures at all scales was demonstrated through 3D helical twisting in a stereospecific fashion [18], [19]. Using thousands of short preprogrammed synthetic DNA strands, one-step annealing completes the reactions that result in self-assembly of various prescribed 3D shapes with

sophisticated surface features and intricate interior cavities and tunnels, demonstrating a simple, robust, modular, and versatile framework for constructing complex 3D nanostructures. The artificially arranged molecular structure from these simple techniques has been explored for numerous aspects of engineering to empower biotechnological approaches including exploring unprecedented strategies in bioimaging [20]–[22], therapeutic functionality [23] and as proof of concept for advanced biophysics [24] like artificial self-replication [25], [26] as well as enhancing the capability of intelligent drug delivery [27], [28], and photonic and electronic applications [18], [29].

The amount of sequence information translates into the size of the design, which ranges from thousands to millions of base pairs per structure. The computational analysis and design tools have been adapted not only to prepare the sequence of the structure, which is assembled as arranged pairs, but also to make a desired shape as a result of relaxation from the pre-strained double helix assembly with precision [30]. Especially, for the usage of DNA nanostructures in therapeutic applications and nanoscale robots, designing the dynamics of the structure to be able to respond to stimuli like pH changes and light has been regarded as a critical design feature [23], [25]–[28], [31], [32]. To develop new design rules for a dynamic and responsive system [33]–[35], more precise prediction of the functionality of the system with thermal fluctuation [36], [37] is required. It is, however, a demanding task to estimate computationally using atomic [38], [39] or coarse-grained (CG) molecular dynamics [36], [37], [40] and the finite-element-based approach [41]–[43] as each method has its limitations in accessible time scale or resolution.

In this review, the computational tools for sequence arrangement and predictive models utilized to design and analyze the DNA nanostructures are considered. First, the general technique for structure preparation of basic components like nanotubes and junctions is introduced alongside the most recent design choices and underlying rules. Then, the computational tools and analytic approaches for various design strategies are reviewed. Finally, suggestions for computational approaches to improve the current knowledge of DNA nanostructures are introduced.

II. DESIGN APPROACH FOR DNA NANOSTRUCTURES

A. BASIC DESIGN PRINCIPLES

The design and preparation process for DNA origami self-assembly, as introduced in [41] and [44], has six steps in general (Fig. 1A): 1) conceive the target shape, 2) design the layout, evaluate the design, and determine staple sequences, 3) prepare scaffold DNA and synthesize staples, 4) pool subsets of concentration normalized oligonucleotides, 5) run molecular self-assembly reactions, and 6) analyze folding quality and purify objects. Different design strategies serve as good reasons to modify the preparation steps. For example, Wang *et al*. showed the details regarding the design and preparation process for a dynamically responding knitting structure [45]. In the case of Tikhomirov *et al.* [14], restricted and controlled pooling orders were proposed to expedite self-assembly. Likewise, the process can be varied with more steps and preparations adjusted for advanced design strategies, for example, when the target system has decorated staples with nanoparticles [46]–[48], is hybridized with polymers [13], [49]–[52], functions as actuators [53]–[55] or has additional design complexities [45], [56], [57].

Whereas various design strategies have been considered [3], [7], [56]–[58], one of the main concerns has been to expand the versatility of DNA nanostructure design using motif [59]–[61] and modular-based concepts [14], [62]. The most basic motif, i.e., the repeated element in which the folded DNA scaffold is shaped into, is the Holliday Junction consisting of two different staples, which combine two different parts of scaffolds, as shown in Fig 1B. According to the review of Pfeifer and Saccá [3] alongside recent works for various junction designs [60], [61] that consist of multiple arms and combination of intentionally arranged nicks [9], [43], [63] and gaps [8], different types of motifs and their subsequent arrangements provide the versatility in the design and properties of the structure.

A modular-based strategy is similar to the motif since the module is a basic element of the origami structure as well. The key distinction is that it is regarded as a larger chunk of the core element compared to a junction or crossover. The module can work as a conceptual LEGO block that is placed in the designing stage. It can be prepared as a certain range of sequences to form an identically-shaped unit along the scaffold [62]–[64] as shown in Fig. 1C. The concept of modular design was further expanded through the emerging assembly technique leveraging nanoparticles [58] and sticky ends for hierarchical structures [14], [65].

Furthermore, many shorter (e.g., 32 nucleotides) synthetic DNA strands can be utilized as LEGO-like blocks to form a robust, modular, and versatile framework, known as DNA bricks, for self-assembling more complex 3D nanostructures [18], [66]. DNA bricks additionally remove the need for a longer scaffold strand as required in origami strategies thereby enabling a straightforward motif with modular design capacity. Modular-based design is known for its rapid structuring in solution. It allows the structure to be realized in a programmed manner with ensured versatility [62], [66].

In most recent research of DNA origami, the second step of preparation process, i.e., designing the layout, evaluating that design, and determining staple sequences as shown in Fig. 1A, is assisted by computational tools. These are developed to compose the sequence arrangement for motifs and modules to ultimately assemble the DNA scaffolds and staples into the designated shape and to confirm the final shape of the design in experiments. The predictive computational analysis can demonstrate the possible shape of the DNA origami structure in the solution. Due to the recent advances on the DNA origami technique and efforts to utilize the end result of this methodology as functional bio-materials, many more diverse DNA origami systems that go beyond the capability of the traditional design approach have begun to emerge, demanding

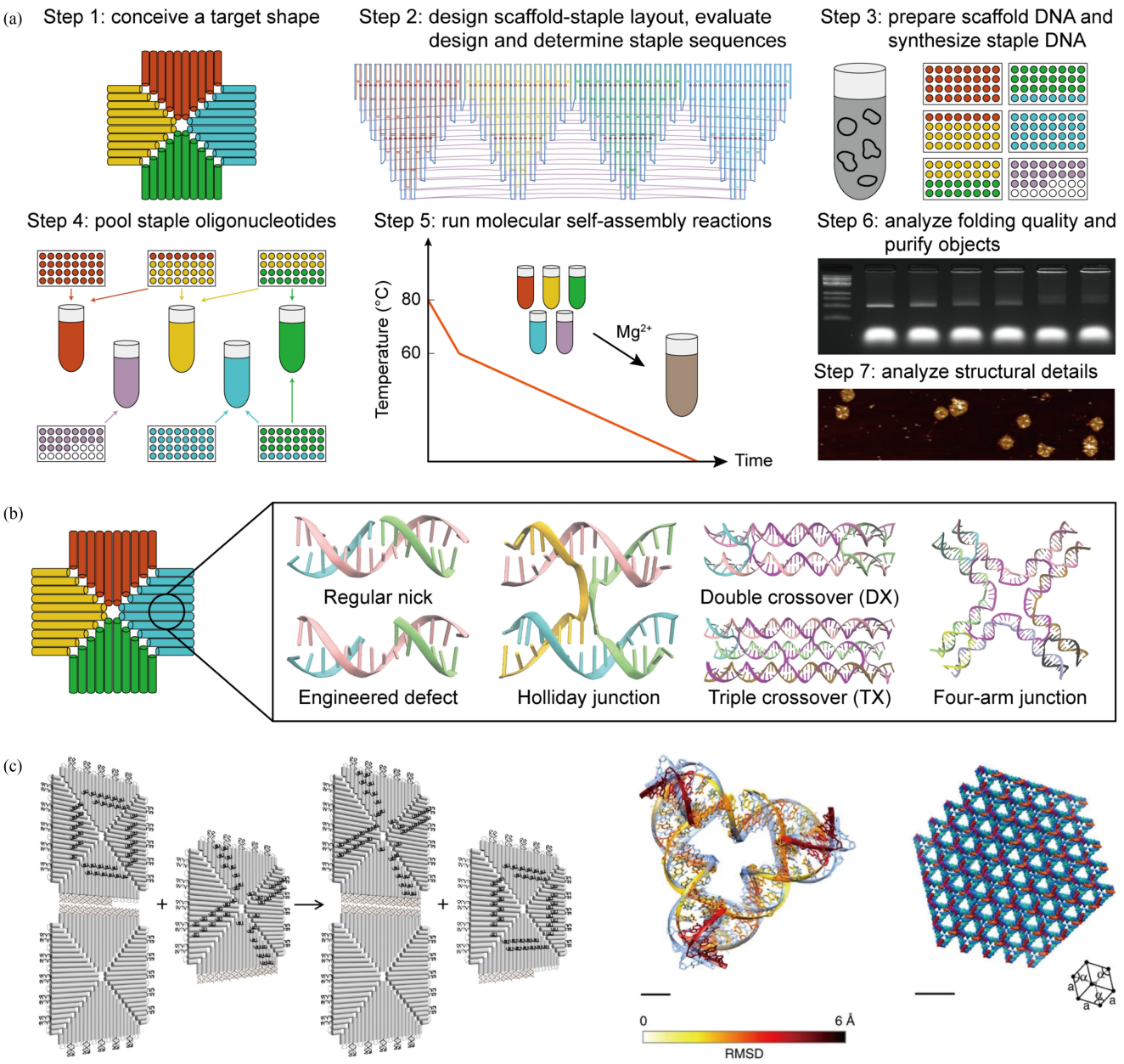

FIGURE 1. **Example of DNA origami structure: (A) General process to complete origami from design stage to realize the structure in solution, (B) Examples of motifs in DNA nanostructure, (C) Examples of modules. Left, displacement reaction of DNA tile designed as modules [83]. Right, examples of motif design [59]. Crystal cell aligned with the crystallographic structure PDB ID: 3GBI (light blue) and overall crystal structure of PDB ID: 3GBI, respectively. Scale bars are 1 nm (left) and 10 nm (right). Both figures are distributed in terms of the Creative Commons CC BY license.**

consequent progress on the level of sophistication offered by computational tools for analysis and design.

One example is hierarchical assembly [14], [15], which has increased the size of structures achievable by combining separate pieces of modules into one larger structure. In the case of hierarchical structuring [3], [54], the nucleation of modules and the formation of secondary structures are important issues to be resolved where the complexity of design deteriorates the productivity in the annealing speed and the folding yield. Thus, the assembly quality depends on the type of sticky-ends among other factors. The predictive computational design tools considering such effects have not been developed yet.

Free energy analysis is another area where current computation tools and design strategies lack effective execution. The approaches to dynamic structure design as seen in the DNA origami mechanism (DOM) have been emerging for their potential usage to create responsive, functional nanomachines including linkage or crank-like systems [10], [33], [67]–[69], molecular actuators [70]–[72], and intelligence models [73]–[78]. For instance, DNA nanotubes (DNTs) can be connected

by ssDNA linkers as a linkage system, which has multiple stable configurations [34], [36]. Since DNTs and ssDNA linkers are the basic segments of the system, the knowledge on their properties in solution is essential to apply them in design as an element of nanomachinery [10], [37], [79], which is hardly measurable experimentally. Hence, computational tools considering the dynamics of DNA structures are in high demand. In addition, since dynamic DNA structures would eventually be working in response to external stimuli, developing computational models for the interaction of DNA with various chemical, biological agents would be necessary.

B. MULTISCALE CHARACTERISTICS OF THE MECHANICAL PROPERTIES IN DNA NANOSTRUCTURES

One of the essential properties related to the integrity of structured DNA assemblies is the rigidity. The rigidity is the stiffness proportional to its characteristic length and shares the same definition as 'rigidity' within the continuum scale framework. However, it is distinguished from bulk materials particularly in the case of DNA origami structures in that they are formed by a long single elastic string bonded by short connecting strands to fold into an intended shape. As a result, the structure may exhibit various rigidities depending on how exactly the string-like DNA is folded into a structure. Sequence-dependent mechanical properties of base-pairs add another layer of complexity. Most DNA structures integrate various structural parts so that different levels of rigidity are unevenly distributed on the structure. This complexity makes the estimation of the final shape and mechanical properties of the structure in the solution difficult, but, at the same time, it can be attractive for some applications that require a structure with versatile shape and properties. When structured DNA assemblies are modeled, different levels of rigidity need to be considered in a hierarchical manner. The stiffness of the DNA nanostructure can be organized in 3 different levels.

It starts from the tendency of atoms to be in the most optimized distance in an equilibrium state of DNA nanostructures. This tendency originates from the strength of bonds and the affinity between chemical species. They can be changed by chemical decoration or reactivity, which in turn influences and varies the shape and properties. Conformational changes by the interaction with surrounding molecules [80], [81] and artificially binding chemicals on the helix are good examples [53]–[55]. On the other hands, interaction between structures controlled with sticky ends [82]–[84], shape-complimentary stacking interfaces, and ion density or species in solution affects the nucleation and affinity characteristics of DNA nanostructures [66], [80]. The quantitative analysis and modeling of nucleation are active areas of research in determining scaffold assembly characteristics, which are supposed to be sequence-dependent [62], [85].

The next level of stiffness comes from a small portion of the folded strand forming structural motifs or modules. For example, the distribution and density of junctions or defects can alter the structural rigidity as well as the shape [8], [9], [28], [59]. Arranging these motifs and modules significantly expands the design space of the 3D structure with precision [86], [87].

Lastly, there is the rigidity of the entire structure. Construction of DNTs with varying crossover and helical packing densities show that the nanotube rigidity can be controlled by various design strategies [6], [7], [79], [88]. To further extend the programmability of the overall rigidity of the structure, it is essential to have computational analysis and design tools that can predict the force equilibrium state and its accompanying rigidity from the sequence information.

The stiffness of the structure is also related to the stability, which governs the structural life under environmental conditions like pH, temperature, and surrounding chemicals [89]. It is especially important for therapeutic applications such as DNA-based drug delivery systems; hence, building a stable structure has been a target property in design [90], [91]. Yet, it is hard to find a proper design strategy against this problem other than decorating with other molecules to prevent digestion or bolstering the rigidity of the overall structure since there are various uncertainties in factors affecting the stability [24], [27], [92]. As a result, computational models that consider this issue in the design phase are hardly found.

III. COMPUTATIONAL TOOLS

In case of sequence arrangement for structured DNA assemblies, approximately a dozen computational tools as shown in Table I have been developed for automatic sequence prototyping of a specified target structure such as arbitrary 2D/3D or polyhedral wireframe shapes. Predictive models are mostly based on a couple of traditional analysis methods such as atomistic or coarse-grained molecular dynamics and the finite element method.

A. PROTOTYPING AND SEQUENCE DESIGN

1) GIDEON

Birac *et al.* [93] launched the first sequence arrangement tool for DNA origami on 3D domain structure, GIDEON (Graphical Integrated Development Environment for Oligonucleotides). It is a graphical user interface with relaxation algorithm for the rearrangement of the base pair coordinates in GUI (Graphical User Interface) to prevent steric clashes. Length, planar and torsional angle segments of double helix on the designed structure with small oscillations are supposed to reduce the internal strain using Proportional Integral Differential algorithm. No energy-based calculation is adapted, but the error defined on helix structure is considered to be minimized. Nicks, crossovers, and vertices can be manipulated on the interface using a simple point and click with iterative relaxation steps including the rearrangement of nucleotides number in junctions or connectivity of the strands. A simple 3D structure with sticky ends designed by GIDEON is shown in Fig. 2A.

TABLE I Computational Tools for Prototyping and Sequence Design

	Author/ year	Type	Target	Sequence preparation	Algorithm/limits rules
GIDEON	Birac et al.,2006 [93]	Manual sequence arrangement	Any design under consideration	Readjustment of base pairs	Proportional integral differential algorithm
SARSE	Anderson et al., 2008 [94]			T loop and T extension editor	1.5 helical turn for crossovers
TIAMAT	Williams et al., 2009 [95]			Random sequence generator with 3 rules	1) Unique sequence limit 2) Repetition limit to prevent the same letter in series 3) Manual modification of GC portion
caDNAno	Douglas et al., 2009 [96]			Arbitral connecting between helices	- Every 21 base pairs with 2 helical turns - Antiparallel staple crossovers
V-Helix BSCOR 2D/3D	Benson et al., 2015 [16] 2016 [17]	Automatic sequence arrangement	3D polyhedral mesh	Desired scaffold strand sequence	A-trail search algorithm with heuristically designed rules
DAEDAL US	Veneziano et al., 2016 [102]		3D polyhedron	No under or over-winding condition	Prim's algorithm
TALOS	Jun et al., 2019 [103]			Edges of six-helix bundles	Vertices of honeycomb-rod edges "mitered vertex" (MV) motif arrangement
PERDIX	Jun et al., 2019 [104]		2D wireframe	Manually adjustable poly T loop	Prim's algorithm, nonmember's spanning tree algorithm
tacoxDNA	Suma et al., 2019 [106]	Web service	Data file type conversion	Given data file	Input/output file conversion between oxDNA, caDNAno, TIAMAT, CanDo, PDB, xyz, LAMMPS input files
ATHENA	Jun et al., 2020 [107]	Integrated design processing	Any design under consideration	Same as TALOS and PERDIX	Algorithm used in TALOS, PERDIX
ADENITA	Llano et al., 2020 [109]			Semi-manually defined strand or structure	Algorithm in Daedalus and semi-manual modification from GUI into the sequence information

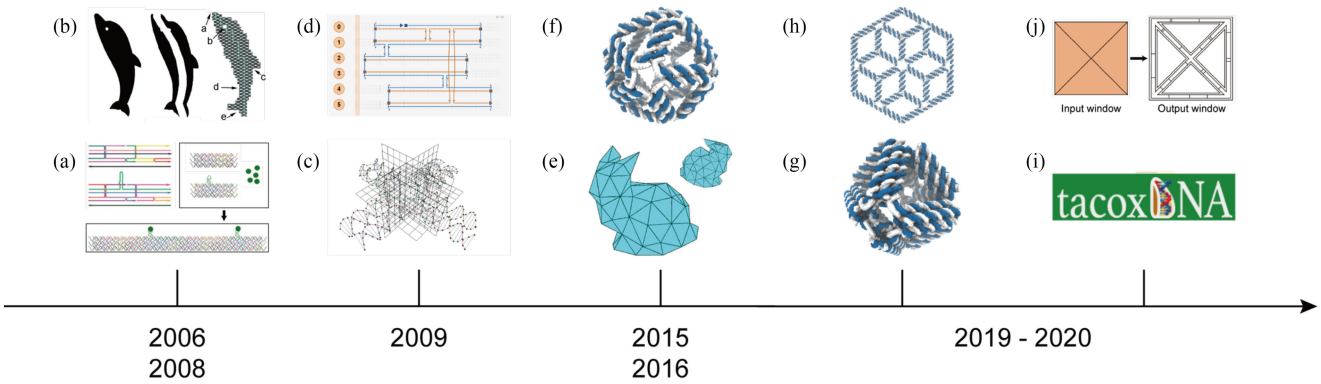

FIGURE 2. Development of DNA origami computational tools. (A) Blunt end using 3-helix motif design using GIDEON. Reproduced from [105] with permission from The Royal Society of Chemistry. (B) SARSE [94]. Reprinted with permission. Copyright 2008, American Chemical Society. (C) Screenshot from TIAMAT [95]. (D) Screenshot from caDNAno [96]. (E) Stanford bunny made with v-Helix [87]. (F) Wire-framed polyhedron by DAEDALUS [102]. (G) Vertex connectivity designed by TALOS[103]. (H) 2D wire-framed structure by PERDIX [104]. (I) Banner of the webservice for tacoxDNA [106] from http://tacoxdna.sissa.it/. (J) ATHENA [107].

2) SARSE

In 2008, Andersen *et al.* [94] renewed the package SARSE (Semiautomated RNA Sequence Editor) for DNA origami developers. For example, the list of oligonucleotide sequences is arranged on a bitmap image of a dolphin separated into two parts as in Fig. 2B. The SARSE editor also adds T-loops and T-extensions on the edges to hinder the unwanted additional structure on the boundary. The 1.5 helical turns are used for staple strand crossovers.

3) TIAMAT

Williams *et al.* [95] suggested "TIAMAT" to compensate a couple of limits of computer-aid design tools by enhancing the visualization technique as shown in Fig. 2C. With base centric representation, it offers random sequence generation, which prevents secondary structure with the following rules: 1) A unique sequence limit to allow the short sequence to only appear once, 2) a repetition limit to prevent the same letter in series with certain number of repetitions, and 3) manual modification of GC portion in the entire sequence.

4) CADNANO

caDNAno is one of the most commonly used sequence preparation package offered by Douglas *et al.* [96] It can create antiparallel staple crossovers automatically based on the default rule (i.e., every 21 base pairs or 2 helical turns). No staple

crossovers are allowed near the scaffold crossover. However, it allows the user to enforce the link between helices violating the default rule. Three different panels in GUI show raster style presentation as illustrated in Fig. 2D with scaffold and staple routing map, helix arrangement on a cross-section, and 3D shape. As several default sequences for the scaffold are provided and the users can input their own alternatively, it can reduce the time to prepare the sequence assignments.

5) V-HELIX

V-Helix BSCOR 2D/3D [16], [17] is an Autodesk Maya plug-in for DNA sequence design of polyhedral meshes (Fig. 2E). It has its own design schemes to manage the largest degree of freedom of versatility in automated manner. Continuous development has made this tool engaged with other design software, including a multi-resolution simulation (mrDNA) [97] and coarse-grained molecular dynamics (oxDNA) [98]–[101] software.

6) DAEDALUS

DAEDALUS (DNA Origami Sequence Design Algorithm for User-defined Structures) [102] is an automated inverse design procedure for wireframe DNA nanostructures. Various polyhedral and non-spherical topologies as illustrated in Fig. 2F can be modeled as two-helix bundles joined with antiparallel double crossovers comprising the edges of polyhedrons. Once the target shape in 3D is projected in 2D within the design criteria, it guarantees the projected 2D structure to be in Euler circuit, which can be expressed using scaffold routing by Prim's algorithm finding the minimum number of edges to include every given element to complete the form. The edges have 10.5 base pairs to be constrained to nearest nucleotide. Using B-form DNA, no under or over-winding condition is considered. No limit in sequence length exists.

7) TALOS

TALOS (Three-dimensional, Algorithmically-generated Library of DNA Origami Shapes) [103] is the design tool, which prepares the sequence especially for 3D wireframe polyhedrons with the edges of six-helix bundles. For the vertices of honeycomb-rod edges, a three-way vertex crossover or "mitered vertex" (MV) motif where every duplex on it can be connected is used for better stability as shown in Fig. 2G.

8) PERDIX

PERDIX (Programmed Eulerian Routing for DNA Design using X-overs) [104] is an autonomous sequence design of free-form 2D wireframe assemblies for DNA origami. Autonomous process for long scaffold strand folding to target geometry has an arbitrary network of edge lengths and vertex angles unlike the top-down approach with discrete edge lengths as shown in Fig. 2H. Same as DAEDALUS, Prim's algorithm and nonmember's spanning tree algorithm in graph theory in dual space offer the information where the crossover will include unpaired poly(T) loop on in vertexes. The limit of this poly(T) loop is determined in an empirical but manually adjustable manner with a fully automated process for a design procedure.

9) TACOXDNA

For the general data type conversion in DNA origami structure, there is tacoxDNA (Fig. 2I), which is a web server written as multiple open source codes in Python. TacoxDNA, developed by Suma *et al.* [106], provides various input coordinates of DNA and RNA for different computational tools. The input files of widely used design tools, such as caDNAno, Tiamat, vHelix, and CanDo, can be transformed into one for oxDNA, which is one of the most popular coarse-grained models. The coordinates in oxDNA format are also interchangeable to other simulation coordinate file formats such as xyz, LAMMPS input file, and PDB coordinates. This web-based service also provides a relaxation process prior to being used in other software, enhancing the convergence of analysis in predictive simulations.

10) ATHENA

The graphical user interface for wireframe DNA origami, ATHENA (Fig. 2J) [107], offers integrated processing of other tools, such as DAEDALUS and TALOS. It is the first developing tool for meshed truss structure [108] including the data conversion to oxDNA and PDB.

11) ADENITA

Adenita developped by Llano *et al.* [109] has a well-arranged GUI process which can define a desired shape or part of DNA origami hierarchically from nucleotide to whole structure level. It is intended to manage the algorithms from Daedalus [103] so that semi-automatic sequence arrangement may become possible with positioning of protein or aptamer structures. The editor offers various visualization options from atomic-scale representation to simplified wireframes, including the deletion, creation and connection of small portions of strands.

B. PREDICTIVE MODELS AND STRUCTURAL ANALYSIS

1) ATOMISTIC MOLECULAR DYNAMICS SIMULATION

Atomistic molecular dynamics simulation has been employed [8], [38], [43]. However, due to its computational cost [38], [66], [110], [111], it is mainly used for the parametric study of small motifs including crossovers, nicks, and short DNA strands alongside the analysis of the structures with reduced size as shown in Fig. 3.

As an alternative, there is a lattice-based modeling of DNA based on the atomic-scale Monte Carlo algorithm [112]. Also, it is shown that Brownian dynamics, which ignores the influence of inertia, can provide a similar degree of precision with all-atom molecular dynamic simulation in the analysis of short DNA strands [113].

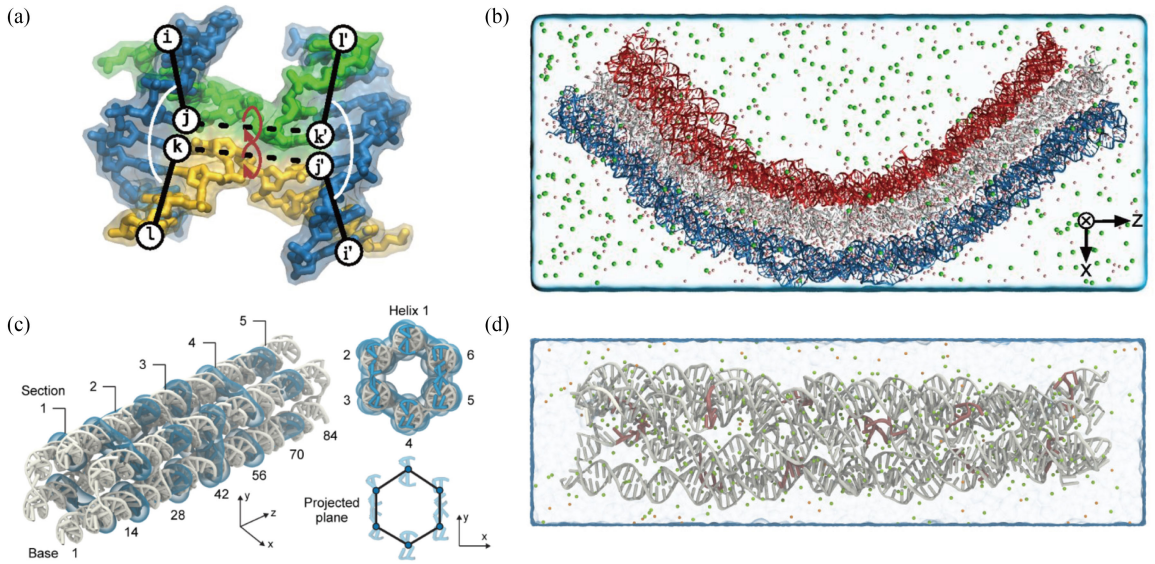

FIGURE 3. Atomistic molecular dynamics simulation. (A) Holliday junction in atomic simulation [38]. Copyright 2016 National Academy of Science. (B) Conformation of honeycomb structure [38]. Copyright 2016 National Academy of Science. (C) Schematic representation of a six-helix bundle. Reprinted from [8] with the permission. Copyright 2019 American Chemical Society. (D) Snapshot showing an equilibrated configuration of the six-helix bundle with gaps. Red-colored regions indicate the gap positions. Reprinted from [8] with the permission. Copyright 2019 American Chemical Society.

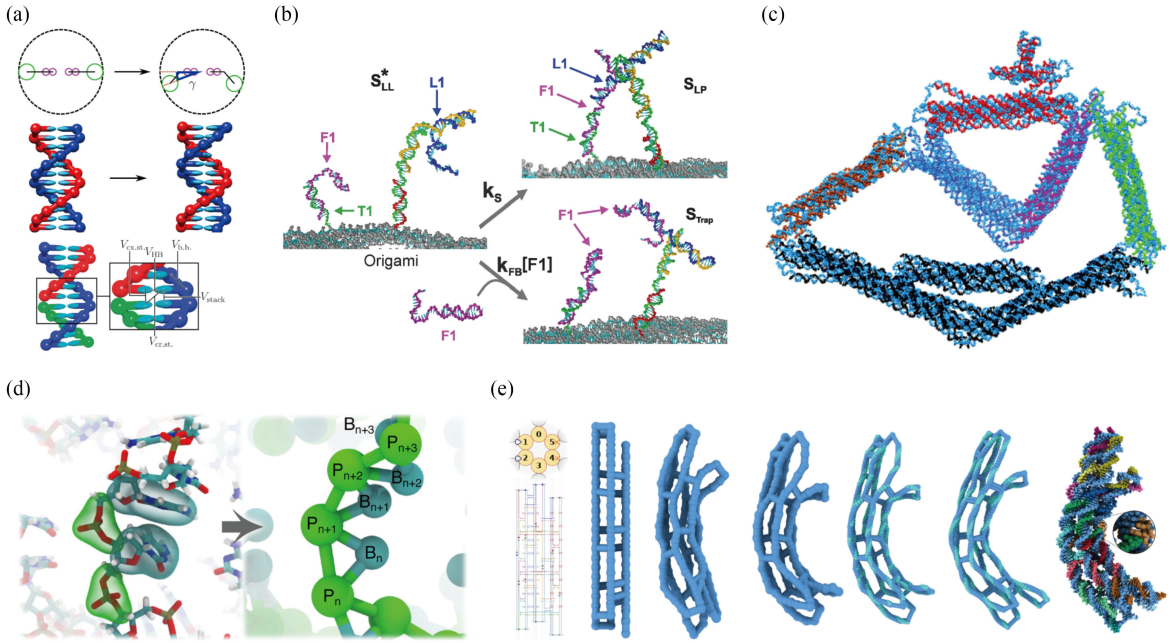

FIGURE 4. Coarse-grained (CG) molecular dynamics simulation. (A) Configuration change from oxDNA to oxDNA2 for major-minor groove (top). Reprinted from [122] with the permission of AIP Publishing. Specific potential energy modeling for dsDNA (bottom). Reproduced from [99] with the permission from the PCCP Owner Societies. (B) DNA walker simulated by oxDNA [40]. Copyright 2017, Oxford University Press. (C) Linkage system in oxDNA simulation. Reproduced from [37] with the permission from the Royal Society of Chemistry. (D) Schematic representation of CG particles [116]. Copyright 2014, American Chemical Society. (E) Multiscale prediction using MrDNA [97]. Copyright 2020, Oxford University Press.

2) COARSE-GRAINED MOLECULAR DYNAMICS SIMULATION

Among the coarse-grained modeling approaches for DNA origami [39], [98], [114]–[116], oxDNA (Fig. 4), developed by Ouldridge *et al.* [98], [99], [117]–[120] with parameterization from SantaLucia's nearest-neighbor [121], [122], has been widely adopted for analysis of DNA molecules and nanostructures. Its utility has been shown for simulation of the DNA walker [40], [123], force sensor [124], and self-assembly [125], [126]. It is also used to develop the design

strategies for better yielding efficiency [118] and force propagation along the scaffold [127]. The stability of the nanostructure is also considered in oxDNA [36], [69], [79], [128], [129]

Structured DNA assemblies are heavily affected by thermal energy and the coarse-grained model offers justifiable and accessible thermal-energy analysis to determine valid design factors. Kinematic variance [36], [37] change of the strain-line linkage (SLL) made of DNT is a decent example. As shown in Fig. 4C, kinematic variance analysis using oxDNA enables the understanding of the motion pathways and the uncertainty of performance in SLL caused by deviation of the component by thermal fluctuation in a quantitative manner. The effect of thermal fluctuation, which changes the linkage length and the joint angle, is then summarized as possible conformational states of the system.

3) FINITE-ELEMENT-BASED STRUCTURAL ANALYSIS

CanDo (Computer-aided Engineering for DNA Origami) is a structural analysis program for DNA origami nanostructures based on the finite element method (FEM) as shown in Fig. 5A and 5B [41]. This computational tool helps users confirm the validity of their designs in minutes to hours before staple oligonucleotide synthesis. Each DNA base pair is modeled as a finite element node with 6 distinct translational and rotational degrees of freedom. Two-node beam element describes the mechanical properties of base-pair-level interactions. The interhelical crossovers are modeled as rigid constraints. The program uses sequence arrangement from caDNAno files directly as the input and the designed configuration, which is supposed to be the nanoscale shape after the relaxation in the solution, is predicted by nonlinear finite element analysis. Within this initial framework, Kim *et al.* [42] enhanced the parameterization of CanDo. The effect of nick is considered to have reduced bending and torsional stiffness values, and ssDNA connected to dsDNA is regarded as entropic spring. Sedeh *et al.* [130] have shown that the finite-element-based structural model employed in Brownian Dynamics simulation can predict the origami structure with efficiency and precision. It assumes an over-damped system in solution so that the inertia effect can be ignored.

Pan *et al.* [59] have expanded it for analysis of lattice-free structures. In this study, crossovers are no longer considered as rigid constraints. Their equilibrium configuration and mechanical properties are characterized by atomistic molecular dynamics simulation and incorporated into the finite element model.

Recently, Lee *et al.* [43] made a thorough investigation of the sequence-dependent mechanical properties. Geometric and mechanical parameters of base pairs with or without nicks (i.e., strand breaks) are characterized using the all-atom molecular dynamics simulation and used to develop a finite element model. These parameters are calculated statistically using the stiffness and covariance matrix. It is revealed that the sequence-dependent properties can indeed be used to control the torsional deformation of DNA origami bundles.

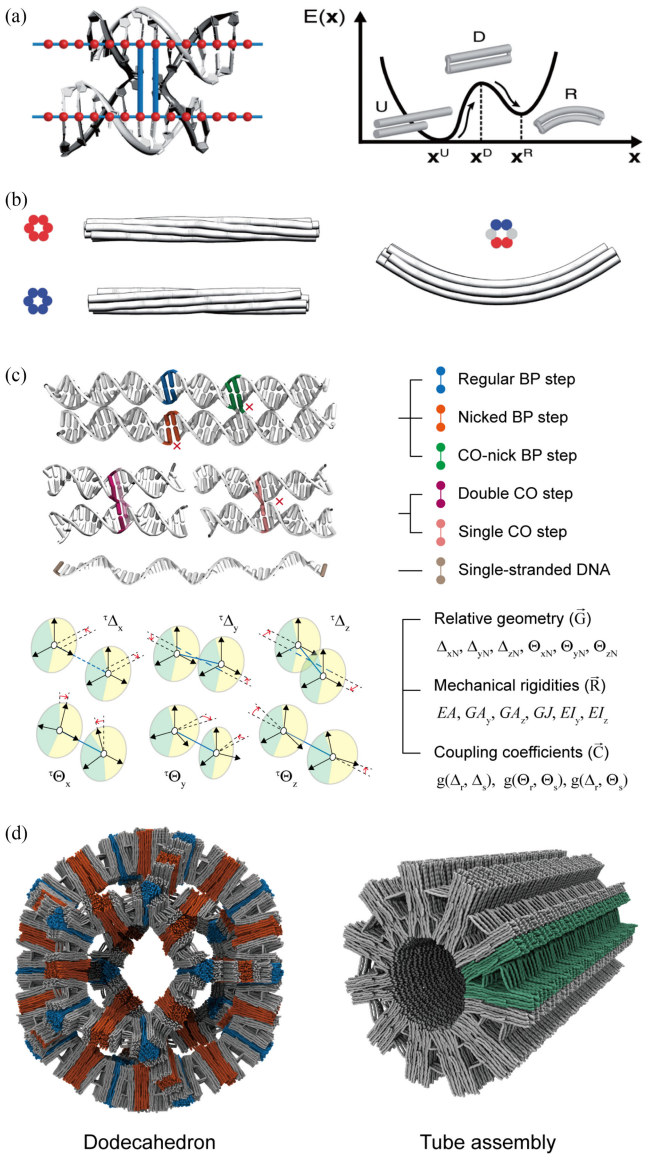

FIGURE 5. Finite-element-based structural analysis. (A) DNA double helices as isotropic elastic rods with rigid crossovers. Reproduced with permission, Copyright 2011, Oxford University Press [42]. (B) Example deformations induced by the mismatch between neighboring DNA helices by (red) insertions and (blue) deletions for a honeycomb lattice bundle [42]. Copyright 2011, Oxford University Press. (C) Classification and characterization of structural motifs in DNA nanostructures. Reproduced with permission, Copyright 2011, Oxford University Press [43], Copyright 2021, American Chemical Society [131]. (D) Prediction results of giga-dalton scale hierarchical assemblies of dodecahedron and tube, Copyright 2021, American Chemical Society [131].

4) MULTI-SCALE SIMULATION

The multiscale simulation is a key approach to linking various computational methods or tools to overcome the limits that each method possesses. MrDNA is such a multi-resolution model developed by Maffeo *et al.* [97] for predicting the

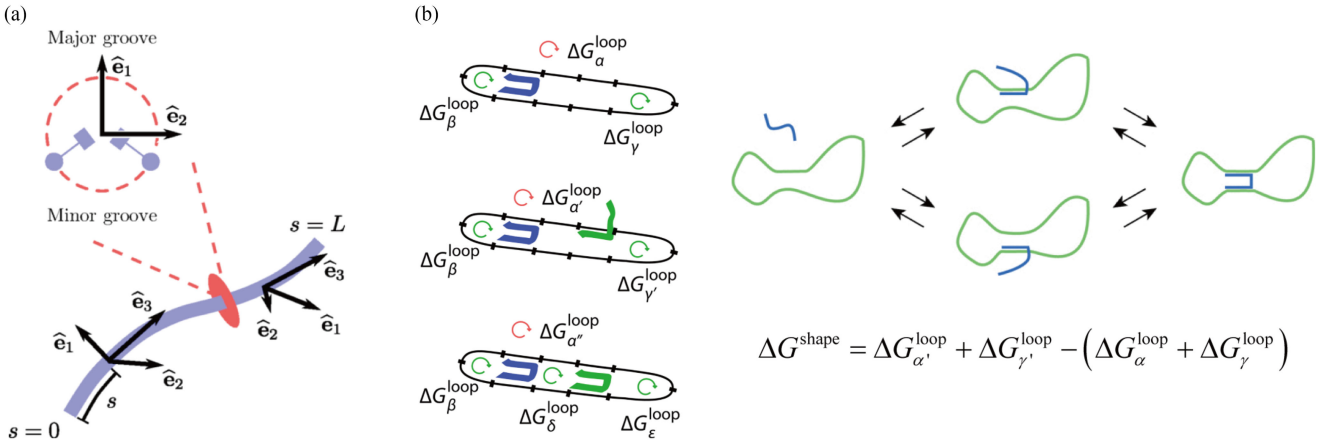

FIGURE 6. **Theoretical models. (A) Orthogonal set of vectors defined at each point of a rod (grey-purple). *s* is the arc-length of the rod, and the subset with red dashed line indicates the unit vector definition based on the groove condition so that the unit vector set has twist angle along the double helix [135]. Different conditions of unit vector set along the rod causes the perturbation on the strain energy to consider the unique strain energy condition of double helix. Reprinted from [133] with the permission. Copyright 2019, by the American Physical Society. (B) Schematic cartoons for topological changes due to the difference in entropic cost. Reprinted from [125] with the permission of AIP Publishing.**

structure and dynamics of nanoscale DNA objects. It provides the DNA configuration in 3D with user-specified resolution from atomistic to coarse-grained levels as shown in Fig. 4E. Configuration is checked through in-house GPU accelerated CG simulation and Atomic Resolution Brownian Dynamics (ARBD) [113] with the accuracy of cryo-EM reconstruction in 30 minutes.

Most recently, SNUPI (Structured NUcleic acids Programming Interface) has been proposed based on the multiscale framework [131]. It integrates the intrinsic properties of DNA at the atomic level to the finite element description to achieve both the accuracy in atomic simulations and the efficiency of structural models as shown in Fig. 5C. The sequence-dependent intrinsic properties characterized through all-atom simulations and the electrostatic interaction between helices in DNA structures are incorporated into the finite-element-based model to calculate the structural shape, the equilibrated dynamic properties, and the mechanical rigidities accurately and rapidly. SNUPI performs the structural analysis at the continuum level without significant loss of atomic information, enabling analysis of hierarchical supramolecular assemblies as shown in Fig. 5D.

C. THEORETICAL MODELS

Theoretical modeling by developing analytical expressions regarding the DNA double helix or structural modules can be a powerful tool especially given the ability to return an analytical solution quickly and the intuitive understanding of underlying physics. The nanoscale modeling using continuum frameworks or statistical mechanics has been validated by comparing its results with experimental observations or results from computational methods. In case of DNA or semi-flexible polymers with chirality, there is a theoretical approach started from the elastic modeling for strain energy caused by chirality or bundling [132]–[137]. The deformation of dsDNA is defined along the backbone of the helix following its rotational symmetry expressed with a unit vector at a local point as shown in Fig. 6A. Entangled unit vector definition makes a perturbation term in arbitrary deformation, so that it can be added as the part of the strain along the helix and derive the free energy of the deformation. As Marko and Shiggia [138] have guided such expression in the case of dsDNA, various conditions, such as dsDNA-like loops [139] and overtwist in minicircle [140], [141], have been modeled and compared with full atomistic or coarse-grained molecular dynamics simulations. The same approach can be pursued for DNA origami designs to investigate the nonlinear dynamic characteristics and their response to the environment.

Quantifying the energy landscape is a primary theoretical approach for analyzing the formation of structural motifs or modules in DNA origami in solution using statistical mechanics modeling. Fern *et al.* [142] have verified the energy landscape of self-assembly between DNA tile monomers excavated out of weaker interactions compared to biomolecular complex. Parallel pathways are demonstrated from the experiments showing the preferential binding tendency between four segments of DNA tile attached with different sticky ends. Kosinski *et al.* [143] has used tiles with different aspect ratios to impose more topological constraints with various sequence arrangements at the boundary of the tile. By doing so, they can validate the sequence-dependent forces.

Energy landscape modeling is not only for predicting the self-assembly efficiency and nucleation of DNA origami in a quantitative way [125], [126] as shown in Fig. 6B, but also for obtaining the necessary understanding on the system to extend its scope of applications. Zhou *et al.* [67] has proved the DNA origami nanostructure with two local energy minima by the compliant DOM. It is supposed to be dependent on the tunable stiffness and deformation of a linkage joint. The suggested design rule for linkage system [144]–[147] and its analysis

[34], [37] have pointed out that module's rigidity and the effect of thermal fluctuation on the rigidity are required to be quantified in another level such as in topological engineering model [148] for a simple parallel pathway from the artificially altered stiffness of the linkage system.

IV. SUGGESTIONS AND PERSPECTIVES

Nanotechnology is the research field where multiscale simulation and modeling are highly useful. Further improvement of computational tools for DNA nanostructures is still necessary to advance the field of structural DNA nanotechnology and related research areas. Considering the uniqueness of structured DNA assemblies, where a structure is formed by folding a long strand into motifs and modules at multiple scales, their sequence-dependent information and energy landscape should be thoroughly studied both computationally and experimentally. Several previous review publications have dealt with this examination by introducing the most recent experimental and computational results, addressing valuable perspectives on the future of the technology.

For instance, Pfeifer and Saccá [3] have explained the detailed progress within the DNA origami and self-assembly technique. The modeling of tile rigidity and forcing motifs between tiles is regarded as one of the main targets to be explored when modeling the energy landscape. Zhang *et al.* [149] have mentioned that the new strategy to control the relaxation time of molecular intelligent systems is necessary. This is only possible when the dynamical mechanism within the DNA origami structure is fully known and we have precise understanding of the energy landscape at the molecular level, both in vitro and in vivo.

Ramezani *et al.* [150] have suggested that mimicry on the dynamical characteristic, which the DNA molecule already has in nature, could be another approach rather than suppressing it into its current form as DNA origami with many staple strands. They also specifically mentioned the need for improvement of the computational method in that effective energy landscape modeling would be inherently more essential. Indeed, the dynamic characteristics of ssDNA in DNA walkers have shown the capability of controlling the response time in experiment [151]. There seems to be plenty of room to improve the functionality of such a molecular system by understanding the fundamental underlying mechanism.

Jabbari *et al.* [152] have summarized computational tools and models for DNA nanostructures and suggested proper parameterization. Frederix *et al.* [153] have mentioned the improvement of computational models from quantum mechanics with more usage of steering pathways as a future algorithm for atomic-level simulation for biomaterials. In addition, DeLuca *et al.* [70] have suggested the importance of mesoscopic scale of simulation with statistical mechanics.

In this review, we summarize the computational tools essential for the design and preparation of DNA nanostructure as introduced in section II. We emphasize the importance of both prototyping tools and predictive models in considering the multiscale features of DNA nanostructures. From this viewpoint, we provide our suggestions and perspectives to advance the design process of DNA nanostructures and thereby structural DNA nanotechnology.

A. MULTISCALE COMPUTATIONAL MODEL AND ITS PARAMETERIZATION

The stiffness of DNA nanostructures is hierarchically determined as described in section II. Computational and experimental research has shown that designing stiffness at multiscale structural levels can manipulate essential properties of the structure including rigidity, stability, and shape. It is also crucial for structures with dynamic mechanisms to properly consider their structural stability and their response to various external stimuli. However, molecular-level simulations are limited by the accessible time scale due to their extremely high computational cost to run. Also, structural models require model parametrization, which is often determined arbitrarily. Hence, to analyze and design DNA nanostructures efficiently and accurately, developing a multiscale model and systematic parameterization is desirable, considering the unique nature of DNA folding. This becomes more and more important as the size of DNA nanostructures to be folded continues to grow via hierarchical assembly strategies.

For example, the nonlinear dynamic behaviors of the double helix itself complicate the prediction of mechanical and dynamical properties of structured DNA assemblies in a single simulation task. While the coarse-grained model [117], [154] has shown the capability of dealing with such nonlinear dynamics in an origami structure to some extent [118], [123], [124], [155], [156], the necessity of much longer time integration for much larger assemblies has increasingly emerged [36], [37], [69], [79]

MrDNA [97] proposed a parameterization algorithm to traverse different scales of simulation by iterative design-try-design runs. This hierarchical approach in parameterization might be a solution to enable the modeling and analysis of mesoscale structures in designing stage with efficiency. Molecular dynamics simulation at multiple scales would be useful particularly for the design of dynamic structures or nanomachines if their model parameters could be identified systematically with reasonable prediction accuracy, although it is still limited by the size of structure that can be simulated.

The FEM-based simulation provides an opportunity to analyze supramolecular DNA structures with reasonable computational expenses when combined with multiscale parameterization. While it is mainly used for estimating the mean structure and properties in equilibrium via static analysis, dynamic analyses for structured DNA assemblies can be realized within Brownian Dynamics formalism. However, in order to obtain more comprehensive dynamic properties in response to environmental stimuli, such as nonlinearity and the memory effect [157], more general dynamic analysis methods should be incorporated in the FEM-based structural analysis.

B. THEORETICAL MODELING

Developing computational tools for DNA nanostructures requires ground-breaking theoretical modeling as well. In particular, theoretical expression for energy landscape would be essential to understand and devise a design strategy for dynamic structures with precision and efficacy. Recent strategies using the crease dynamics [148], [158], the role of each part of dynamical systems in statistical mechanics [125], and intuition on nonlinearity [136] are representative cases in points.

Thermodynamic properties predicted by oxDNA have been compared with trials that have shown quantitative theoretical approximation of the double helix and origami structures [127], [159], [160]. A more systematic analysis of the general system and theoretically linked modeling could be conducted alongside the experiments and the quantitative thermodynamic modeling [37]. To incorporate nonlinear dynamic characteristics as well as chemical responses with various nanomaterials, more general theoretical modeling for the energy landscape and parameterization would be necessary [132].

Advanced free-energy-based design strategy would be also crucial to prolong the expected life of the structure in vivo, particularly when it is designed to be used for targeted delivery of certain chemicals into a living cell. Free energy modeling would enhance the understanding of the dynamic characteristics of the DNA strand and origami structure as it relates to the overall stability and its affinity to a target biosystem. It might provide a solution to overcome the current obstruction in developing precise and functional DNA nanostructures and to broaden their application in biotechnology.

C. EXPANSION INTO MODULAR SELF-ASSEMBLY OF NANOPARTICLES

DNA-guided self-assembly of various nanoparticles (NPs) with desirable functionalities has received much attention as an emerging approach for a new generation of multifunctional nanomaterials with tailored properties and functions [40], [58], [161]–[163]. The ability to converge many discrete NPs into a single nanoscale ensemble with predefined physical, chemical, or biological characteristics has enormous potential to transform many fields of research, ranging from optoelectronics and nanophotonics to nanomedicine [40], [161], [164]. DNA with superior flexibility, affinity, and programmability continues to be a promising material to build nanostructures with NPs, especially those based on the DNA origami and tile techniques [40], [58], [165], [166]. Despite great advances in the past two decades, the controlled fabrication of multiple NPs into designed nanostructures with specific shapes and functions still remains a formidable challenge because of the inherent randomness in the experimental environment and the complexity of design and analysis. The methodology so far has mostly been trial and error, and it is difficult to achieve optimal designs of functional structures with arbitrary size and shape that incorporate diverse NPs. Thus, there is much room for better design methods to guide experimental NP assembly and make it more efficient and effective.

There are two foundational challenges for the controllable and scalable self-assembly of nanostructures with NPs. First, the creation of a basic building block to be used to create anisotropic nanostructures across a diverse range of NP compositions and geometries has been difficult. While DNA-constructed scaffolds have demonstrated their own merits as templates to construct complex NP ensembles, the direct incorporation of NPs into the fundamental building block would enable the potential to construct structures with arbitrary geometries, which produce desired functions depending on the features of constituent NPs and their overall composition [58], [147], [148], [161], [167]–[169]. Through precise control over the number, location, and relative orientation of DNA, nanoparticle building blocks could be leveraged to increase control both the shape and functionality of the final self-assembled structures [161], [169]. Nonetheless, despite progress in self-assembly research alongside progress in NP synthesis, approaches, which effectively solve this challenge, have been limited in success. Specifically, there is a great demand for manipulation of building blocks by controlling their precise placement and orientation at desired locations to allow for favored assembly. Such advancement would dramatically improve the performance and stability of synthesizing NP building blocks with desired features as a programmable material, which is defined as 'a distributed system of agents that can act cooperatively to configure themselves into arbitrary shapes with arbitrary functions' [161]. The second challenge is successfully designing both the structure and function of self-assembled nanostructures utilizing NPs. There needs to be greater development of practical design methods for self-assembly wielding NP building blocks, which effectively incorporate functional responses into the process and deconstruct the difficulty of the design task. The inherent randomness and potential for disorder in complex systems serve as hurdles for successful design methodologies; however, they also serve the necessity to innovate with new models and approaches. Specifically, adaptations and expansions of the computational toolkits for DNA nanotechnology to NP building block assembly could serve as a viable method to overcome hurdles by providing an efficient and effective means to self-organization of multifunctional nano-architectures that have intelligent functionalities in their 'programmable' and 'customizable' natures [169].

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