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REVIEW

Towards Active Self-Assembly Through DNA Nanotechnology

Jinyi Dong[1,2] · **Chao Zhou**[1] · **Qiangbin Wang**[1]

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Abstract

Self-assembly, which is ubiquitous in living systems, also stimulates countless synthetic molecular self-assembling systems. Most synthetic self-assemblies are realized by passive processes, going from high-energy states to thermodynamic equilibrium. Conversely, living systems work out of equilibrium, meaning they are energy-consuming, dissipative and active. In recently years, chemists have made extensive efforts to design artificial active self-assembly systems, which will be pivotal to emulating and understanding life. Among various strategies, emerging approaches based on DNA nanotechnology have attracted a lot of attention. Structural- as well as dynamic-DNA-nanotechnology offer diverse tools with which to design building blocks and to shape their assembly behaviors. To achieve active self-assembly, a synergy of diverse DNA techniques is essential, including structural design, controllable assembly–disassembly, autonomous assembly, molecular circuits, biochemical oscillators, and so on. In this review, we introduce progress towards, or related to, active assembly via DNA nanotechnology. Dynamic DNA assembly systems ranging from passive assembly–disassembly systems, to autonomous assembly systems to sophisticated artificial metabolism and time-clocking oscillation systems will be discussed. We catalogue these systems from the perspective of free energy change with the reaction process. We end the review with a brief outlook and discussion.

Keywords DNA nanotechnology · DNA origami · Self-assembly · Out-of-equilibrium assembly · Active assembly

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✉ Chao Zhou
czhou2018@sinano.ac.cn

✉ Qiangbin Wang
qbwang2008@sinano.ac.cn

Extended author information available on the last page of the article

1 Introduction

Fascinated by the mystery of life, scientists are currently busy looking for extraterrestrial life and trying to create artificial life in the laboratory [1, 2]. One of the most amazing aspects of life is that all living things are formed by self-assembly, which is a fundamental biological design process through which an organized structure seems to be constructed from a disordered collection of smaller parts. Self-assembly can be classified into two types. One is passive and obeys an equilibrium thermodynamic: the system starts from a relatively higher free energy state and reaches a thermodynamic equilibrium state by minimizing free energy. Most artificial self-assembly systems follow this framework. The other type works out of equilibrium, meaning it is energy-consuming and dissipative; in other words, active. Life adopts the latter strategy to organize numerous molecules into the filaments, membranes and organelles that make up cells and carry out myriad complex biochemical reactions [3–5]. By continually consuming energy in endless assembly and disassembly cycles, life continually responds and adapts to the environment via complex biochemical reaction networks. To realize active self-assembly working like living systems could be seen as the Holy Grail in this field, since it is extremely important for understanding and emulating life. Although a formidable challenge, extensive efforts have been made towards this goal in recent years [6–11].

Among various strategies for designing self-assembly systems, DNA nanotechnology is particularly impressive. DNA molecules, as sequenced polymers and nanoscale materials, could be programmed to form nanoscale motifs as building blocks for self-assembly simply by exploiting Watson–Crick base pairs. Since Seeman proposed this concept in the 1980s [12], the field has seen dramatic progress in recent decades. Self-assembled DNA architectures, like DNA tiles [13], DNA origami [14], DNA bricks [15], wireframe structures [16] and even crystals [17, 18], have been prepared readily and successfully by manipulating the hybridization of DNA strands. One the other hand, dynamic DNA nanotechnology offers a toolbox for designing reconfigurable structures, controlling kinetics of assembly, building DNA-based chemical reaction networks [19–21], etc. All these achievements indicate that DNA nanotechnology could be a promising approach towards the goal of life-like self-assembly, or, at least, to mimic some aspects of living systems. Thanks to its high programmability and simplicity, active DNA assembly has been introduced recently in a few exciting successful demonstrations [9–11]. We believe this offers great encouragement to the fields of both DNA nanotechnology and self-assembly. Therefore, we decided to write this review to introduce what DNA nanotechnology has achieved so far towards this goal.

In this review, we would like to talk about active self-assembly systems using DNA nanotechnology. To achieve this goal, a synergy of diverse DNA techniques is essential, including structural design, controllable assembly–disassembly, autonomous assembly, molecular circuits, biochemical oscillators, and so on. Here, we focus mainly on dynamic DNA self-assembly. From the perspective of

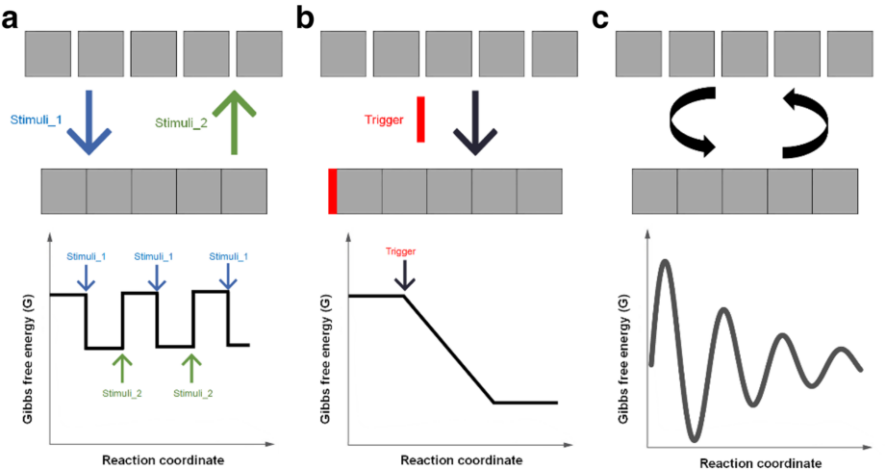

Fig. 1 Three models of dynamic self-assembly and their Gibbs free energy change during the process. **a** Passive assembly–disassembly. **b** Trigger-initiated autonomous assembly. **c** Energy-dissipative oscillating assembly

energy change with the reaction process, such systems can be divided into three major types (Fig. 1). We start from the most fundamental passive assembly–disassembly systems, which were realized by switching between two equilibrium states (Fig. 1a), and subsequently introduce autonomous assembly systems that rely on triggers to initiate the system and, therefore, direct the system from a high energy state to an equilibrium state (Fig. 1b). Finally, we discuss several successful demonstrations of active assembly systems developed very recently, mainly including an assembly system with a cascade of transformations [9], a time-clocking oscillation system [10] (Fig. 1c) and a mesoscale artificial metabolism system [11]. We end the review with a brief discussion and outlook. It should be noted that the term of 'active assembly' has been used for various connotations under different circumstances. In a broad sense, it can be used for self-assembly systems that can respond to external stimuli, more like 'dynamic'. Here, we use the term in its narrowest sense, meaning that self-assembly is energy-consuming and dissipative, like the self-assembly in living organisms.

2 Passive Assembly–Disassembly of DNA

Switchable assembly–disassembly is the simplest dynamic DNA assembly system, as well as the most fundamental component for constructing complicated active assembly systems. In this section, we introduce DNA-based passive assembly–disassembly systems. The energy change of a passive assembly–disassembly system is normally as follows: in the initial state, the system remains at equilibrium; upon some external energy input or environmental change, the equilibrium is disturbed and the system reaches a new equilibrium state under the new circumstance; by

retrieving the input or switching back the environment, the system goes back to its initial equilibrium state (Fig. 1a).

One critical factor for determining the thermodynamic equilibrium state of a system is temperature. Walther et al. [22] reported the thermally controlled assembly–disassembly of a DNA origami filament system. The building block is a cuboid made of DNA origami that is pre-assembled via a thermal annealing process. Such DNA origami cuboids could further assemble into micrometer filaments via the hybridization of connecting DNA strands (blue ends in Fig. 2) at the sides of cuboids. The ligation based on DNA hybridization could be denatured at a relatively higher temperature, which induces disassembly of the filaments. Therefore, this assembly and disassembly process could be controlled by tuning the temperature. The temperature window could be tuned by adjusting the affinities of the DNA connectors. It should be noted that this temperature dependent assembly–disassembly process does not destroy the DNA origami building blocks due to the high thermal stability of DNA origami (melting temperature normally higher than 50 °C). Dietz et al. [23] introduced a non-base-pairing, shape-complementary strategy for engineering the interface of DNA origami. This provides a robust means of higher-order assembly as well as allowing dynamic control. The interface affinity is affected by both temperature and cation concentrations, thus both factors could be used to control the dynamic assembly–disassembly of high-order DNA origami assemblies.

DNA can also sense other environmental factors for designing assembly–disassembly system, for example, pH. To this end, a pH-sensitive connection between DNA building blocks is necessary. A DNA duplex based on Watson–Crick base-pairing can interact with a single-stranded DNA through pH-sensitive parallel Hoogsteen base-pairing to form a triplex. This duplex–triplex transition is highly

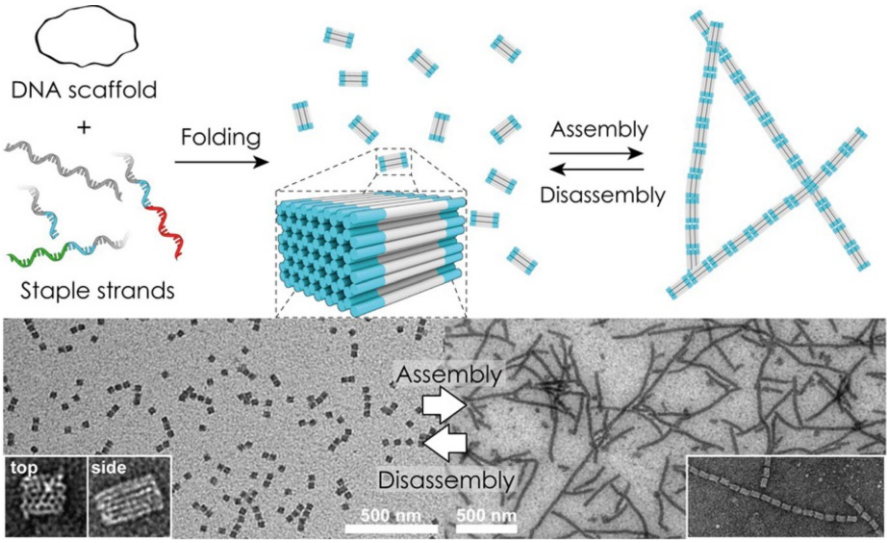

Fig. 2 Temperature controlled assembly–disassembly of DNA origami filaments Reproduced with permission from Ref. [22]. Copyright © 2016, American Chemical Society

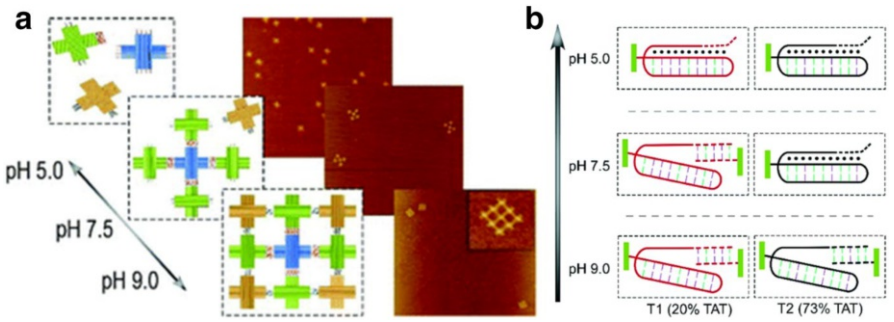

Fig. 3 pH-controlled stepwise assembly–disassembly of DNA origami nanostructures. **a** The reversible stepwise assembly–disassembly of DNA origami at different pH values. **b** Linkers that work at different pH based on duplex–triplex transition Reproduced with permission from Ref. [24]. Copyright © 2019, the Royal Chemical Society

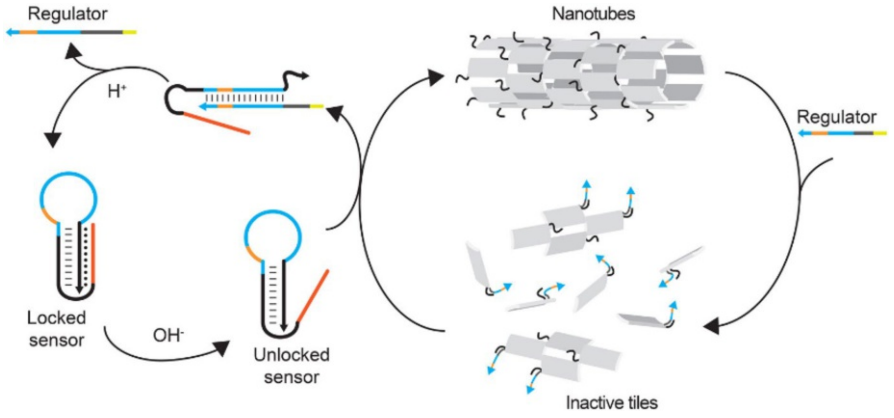

Fig. 4 Reversible self-assembly of DNA nanotubes through intermediate DNA regulator strands. Left side pH sensing device that can release and sequester regulator strands. Right part Regulator intervened assembly–disassembly of DNA tiles Reproduced with permission from Ref. [28]. Copyright © 2017, American Chemical Society

pH-dependent and could be regulated to sense different pH by tuning the ratio of C–G·C to T–A·T. Employing this strategy, Wang et al. [24] reported the pH-controlled, stepwise assembly–disassembly system of DNA origami (Fig. 3). The DNA triplex connection between DNA structures could be programmed to form and break at certain pH values, enabling stepwise assembly and disassembly of up to nine DNA origami pieces. Similarly, other responsive DNA motifs, e.g., pH-sensitive i-motif [25], K^+ responsive G-quadruplex [26], cation-dependent DNAzyme [27], etc., have also been used as the bridge between DNA nanostructures for constructing assembly–disassembly systems.

This pH manipulation can also work in an indirect manner. Franco et al. [28] introduced a system that employ the duplex–triplex transition as a pH sensor that can

release or sequester regulator DNA strands (Fig. 4). Here, these authors employed DNA double crossover tile assembly as the model. This DNA double crossover tile assembly, which was developed by Rothemund et al. [29], has been used widely for investigating dynamic self-assembly. The regulator DNA strands can activate or deactivate tile-based DNA nanotube assembly by interacting with the sticky ends through toehold-mediated strand-displacement reactions. At high pH, the pH sensor sequesters the regulator strands and enables the assembly of DNA tiles into micrometer nanotubes. At low pH, the pH sensor releases the regulator strands. The regulator strands disrupt the connection among DNA tiles via strand-displacement and the nanotubes then disassemble into small tiles. This idea of bridging an upstream regulatory unit and downstream DNA assembly through intermediate DNA strands gives more possibility and flexibility to the design of complex DNA assembly. A similar strategy is also employed for achieving active self-assembly system, which we will introduce below in the section on "Active DNA Self-Assembly System".

DNA nanostructures could be placed on lipid membranes by conjugated cholesterol moieties. The lipid membranes confine the DNA structures to the surfaces while also providing fluidity. The thermodynamic behavior of DNA nanostructures on fluid soft lipid bilayers will differ from those in solution. The assembly–disassembly process of DNA can be performed on artificial lipid membranes as well as on cell surfaces. These dynamic processes could be directly monitored with various tools, such as high-speed atomic force microscopy (AFM). Endo et al. [30] reported a light-controlled DNA origami assembly–disassembly system on supported lipid bilayers (Fig. 5a). They used pseudo-complementary photo-responsive DNA modified by azobenzene molecules as the linkers of two DNA origami units. Under visible light, the trans-form azobenzene moieties help maintain DNA hybridization and thus bring two DNA origami units together to form dimers. With UV light irradiation, the trans-azobenzene moieties switch to the cis-form and thus dissociate the

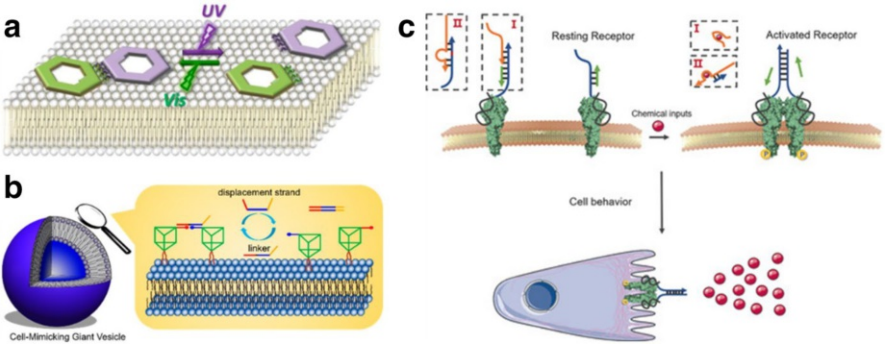

Fig. 5 Dynamic DNA assembly on artificial and cell membranes. **a** Photo-controlled DNA origami association–disassociation on supported lipid bilayer. **b** DNA nanoprisms assembly–disassembly on the surface of cell-mimicking giant vesicles. **c** Dynamic DNA association for controlling the cell membrane receptor dimerization and cell behaviors **a** Reproduced with permission from Ref. [30]. Copyright © 2014, American Chemical Society; **b** reproduced with permission from Ref. [31]. Copyright © 2017, American Chemical Society; **c** reproduced with permission from ref [32]. Copyright © 2018, John Wiley and Sons

DNA origami dimers. The supported lipid bilayer offers a platform to visualize the process by high-speed AFM. Tan et al. [31] reported the assembly–disassembly of DNA nanoprisms driven by strand-displacement reactions on cell-mimicking giant vesicles, and visualized the process by fluorescence microscopy (Fig. 5b). DNA strands can also be attached to specific cell membrane receptors. Thereby, assembly and disassembly could be used for inducing cell membrane receptor dimerization or clustering, thus regulating downstream signalling to control cell behaviors (Fig. 5c) [32].

3 Trigger-Initiated Autonomous DNA Self-Assembly

Active assembly is always autonomous although autonomous assembly is not necessarily active. To some extent, designing autonomous assembly could be regarded as a preliminary to achieving active assembly. In the previous section, we focused on the switch between the assembled state and the disassembled state, which requires alternative external interference to change thermodynamic equilibrium states. In this section, we pay attention to the process of assembling individual units into higher-order assemblies, and how to make this process proceed autonomously. In principle, the autonomous assembly system starts from a meta-stable non-equilibrium state. Upon a trigger that disturbs this meta-stable state, the system reaches its equilibrium state in an autonomous manner. Once the process is initiated by a trigger, no further external intervention is needed (Fig. 1b).

3.1 Hybridization Chain Reaction-Based self-Assembly

One classical demonstration of autonomous DNA assembly is the hybridization chain reaction (HCR) that was first developed by Dirks and Pierce (Fig. 6) [33]. HCR is based on the toehold-mediated strand invasion of stable hairpin structures with long stem duplexes. The HCR system consists of two types of DNA hairpins, H1 and H2, with single-stranded toehold extensions at the 5′ and 3′ ends of the hairpins, respectively (Fig. 6a). Ingeniously, the loop region of H1 contains the complement of H2 toehold, while the H2 loop is complementary to H1 toehold, and the double-strand stems of H1 and H2 are identical. Due to the long double-strand stem region, the two hairpins coexist metastably. When a trigger molecule with the appropriate sequence is added (complementary to the toehold and adjacent stem sequence), one of the hairpins is opened by toehold-mediated strand displacement, allowing the loop sequence to become freely accessible. This loop sequence can now be attached to the toehold of another hairpin, triggering a chain reaction in which multiple H1 and H2 molecules bind to each other to form long double-stranded polymers.

The initiator of HCR could be encoded as other signals as long as they can interact with strands to open the H1 hairpin. For example, encoding an ATP aptamer to the toehold could initiate the HCR with ATP molecules. The HCR is particular useful for biological imaging since it could work as a molecular

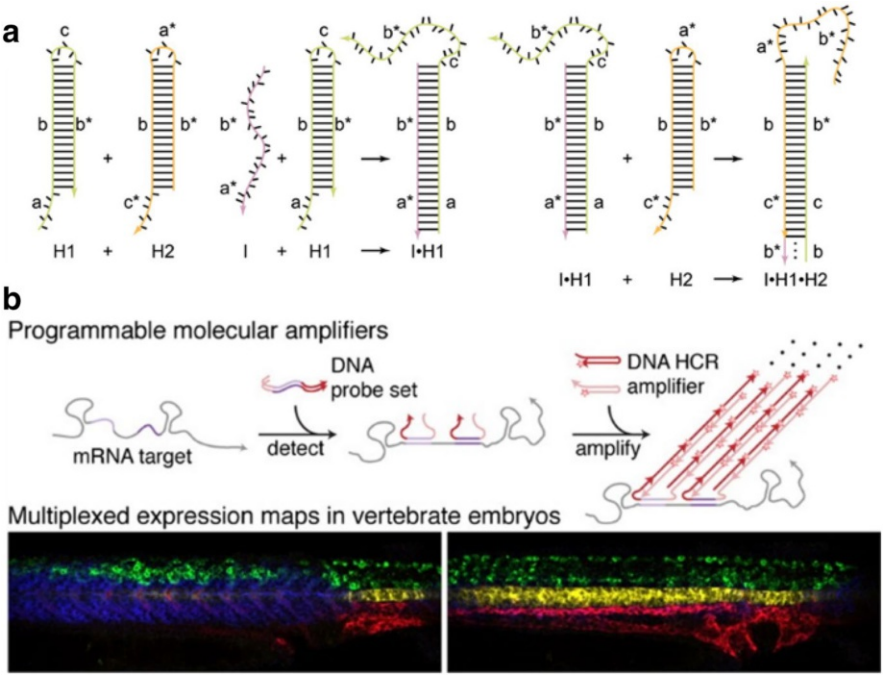

Fig. 6 The hybridization chain reaction (HCR). **a** Principle of HCR. **b** In-situ HCR for multiplexed imaging of mRNA in zebrafish embryos **a** Reproduced with permission from Ref. [33]. Copyright © 2004, National Academy of Sciences; **b** reproduced with permission from Ref. [34]. Copyright © 2010, Springer Nature

amplifier in diverse settings. With three generations of development, Pierce et al. [34] presented in situ HCR as a powerful tool for multiplexed and quantitative bioimaging with high sensitivity and low background (Fig. 6b). Tan et al. [35] developed aptamer-tethered DNA nanotrains with fluorescence as carriers; drug fluorescence quenching, real-time signaling of behaviors of drugs and nanotrains at target cells can be performed.

A variant of HCR uses four-way branch migration for the construction of hybridization polymerization systems (Fig. 7) [36]. In this case, the reaction between H1 and H2 is initiated by the introduction of the DNA duplex with three toeholds. The overhangs *a** and *x* of the complex hybrid with the complementary overhangs *a* and *x** of the hairpin H1 to produce a movable Holliday junction (state 1 in Fig. 7). By four-way branch migration, this structure transforms into state 2, and the hairpin H1 unfolds to expose the toehold domain, c. The toeholds c and y are available for hairpin loop H2 to bind to, creating another Holliday junction intermediate (state 3). The configuration relaxes to that of state 4, with two new domains, *x* and *a**, being used for loop H1 binding. The sequence of the hybridization is repeated cyclically, resulting in a long-nicked duplex strand. Incorporating this autonomous polymerization into DNA-cross-linked

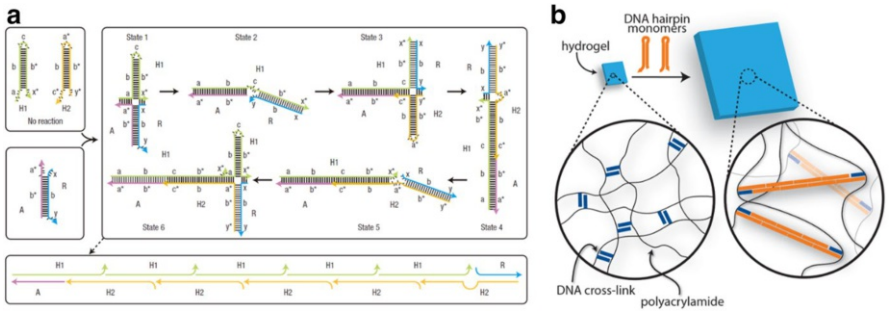

Fig. 7 Autonomous polymerization powered by four-way junction branch migration. **a** Principle of polymerization. **b** Swelling of DNA-cross-linked polyacrylamide hydrogels by the autonomous polymerizations **a** Reproduced with permission from Ref. [36]. Copyright © 2007, Springer Nature; **b** reproduced with permission from Ref. [37]. Copyright © 2017, American Association for the Advancement of Science

polyacrylamide hydrogels, Schulman et al. [37] realized up to 100-fold volumetric hydrogel swelling by successively extending DNA cross-links by autonomous polymerizations.

The principle of HCR could be applied for more complicated autonomous DNA assembly. Fan et al. [38] adapted the concept of HCR in high-order DNA assembly systems (Fig. 8). They designed DNA hairpin tiles (DHTs) that could be opened by initiator strands. Unlike single-stranded hairpin strands, DHTs can be encoded with structural information and therefore endow the system with much more designability and hierarchical complexity. The DHT motif is a double-crossover structure, in which two double helices are arranged in parallel and ligated by a pair of crossover junctions. Fan and colleagues first showed the DHTs could be polymerized into long filaments of low dispersity in a chain-growth way. They then programmed this chain-growth copolymerization to form two-dimensional nanoplatelets. To this end, they changed the distance of two crossover junctions between two associated DHT monomers. In the one-dimensional polymerization, the distance of two intermolecular crossover junctions is about 2.5 helical turns, whereas it was increased to 3 helical turns in 2D chain-growth assembly. This subtle adjustment changed the angle of the two associated DHT monomers. Specifically, the DHT monomers bind to opposite sides of the chain-growth strands. Combining this altered chain-growth copolymerization with DNA overhang associations, the DHTs can assemble into 2D nanoplatelets. Nie et al. [39] showed that two HCRs could be synchronized for assembling nanoladders. With one HCR plus one T-junction cohesion, they also prepared closed nanorings.

3.2 DNA Catalytic Self-Assembly

Another widely explored way of directing meta-stable non-equilibrium systems to equilibrium is catalysis. The first DNA catalytic system was developed by Zhang et al. [40]. As illustrated in Fig. 9a, substrate complex S and fuel strand F react to form waste product W and release oligomers SB and OB as signals and/

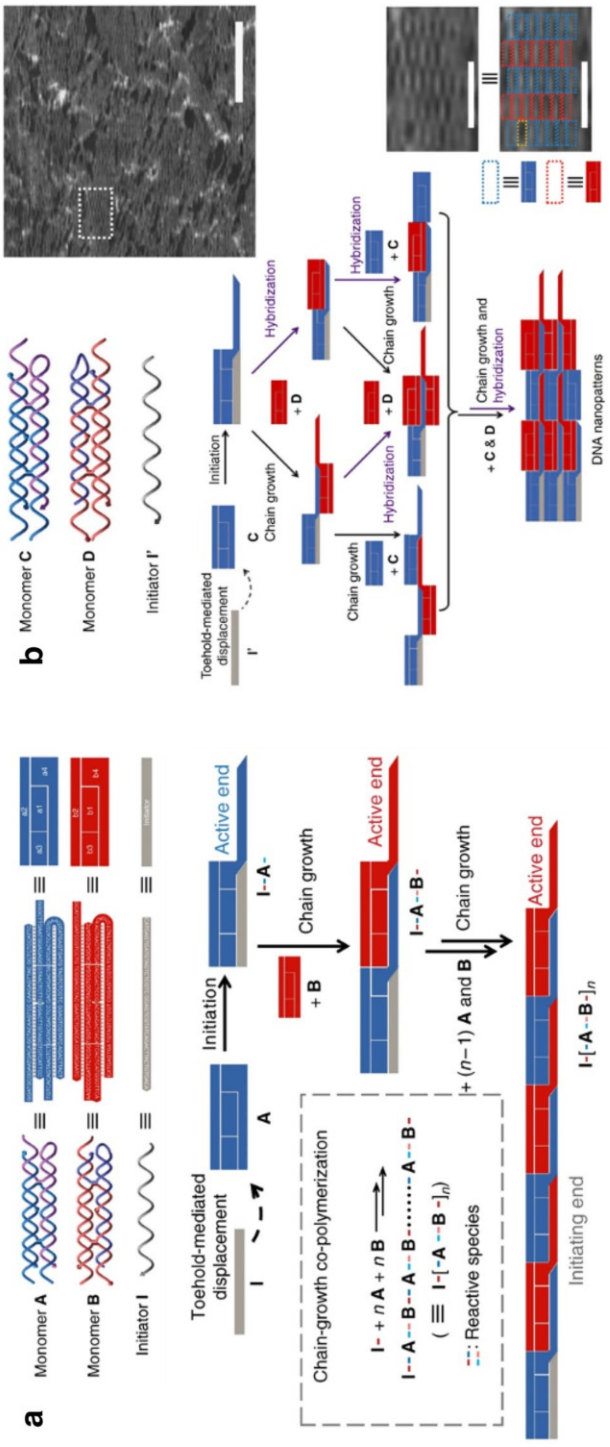

Fig. 8 **a** One- and **b** two-dimensional chain-growth copolymerization of DNA hairpin tiles (DHTs). Bar 50 nm Reproduced with permission from Ref. [38]. Copyright © 2019, Springer Nature

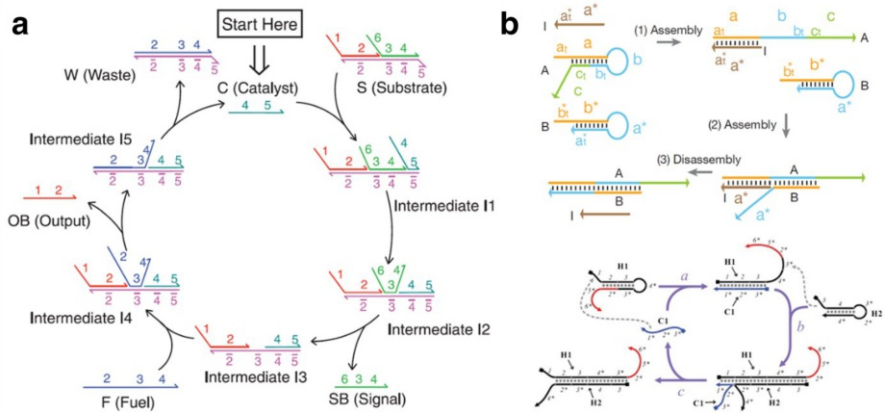

Fig. 9 DNA catalysis system. **a** The first entropy-driven DNA catalysis system that can output two single strands as outputs or downstream signals. **b** The catalytic hairpin assembly that directs the hybridization of two hairpin strands **a** Reproduced with permission from Ref. [40]. Copyright © 2007, American Association for the Advancement of Science; **b** reproduced with permission from Ref. [41]. Copyright © 2008, Springer Nature and Ref. [42] Copyright © 2011, Oxford University Press

or outputs. The reaction is driven by entropy due to the increase in the number of components from two to three. With addition of the catalyst C, SB can be released from intermediate I2 and the hidden toehold becomes exposed. This toehold provides an attachment site for F, which then drives the reaction to completion by toehold-initiated strand invasion. The concept of DNA catalysis has been further adapted to a system termed 'chain hybridization assembly (CHA)' (Fig. 9b) [41, 42]. Like HCR, CHA starts from two pre-formed hairpin strands that have complementary strands. The hybridization of these two hairpins is initiated by a short strand to open the first hairpin and therefore disclose the toehold. Different from HCR, CHA stops after hybridization of the two hairpins and releases the initiator strand. Therefore, the initiator strand here functions only as a catalyst.

An entropy-driven DNA catalysis system could be utilized to initiate autonomous DNA tile self-assembly as upstream molecular circuits (Fig. 10) [43]. Here, the DNA double crossover precursor tiles are deactivated by replacing one of the long single-stranded regions with two strands that cover the sticky ends and protect the tiles from hierarchical assembly. These two protecting strands could be displaced by deprotector strands via strand-displacement reactions, while the deprotector strands are stored in the DNA catalysis circuits. Upon addition of DNA catalyst, the upstream control circuit is turned on, and starts to release deprotector strands successively (Fig. 10a), thereby the double crossover tiles are activated and assembled into micrometer filaments autonomously (Fig. 10b). There are many challenges in coupling a DNA catalytic circuit with downstream self-assembly. One such challenge is leakage of the DNA catalytic circuit, meaning a small number of deprotector strands could leak from the substrates. To solve this, DNA sink complexes could be introduced as a competitive threshold for the deprotectors (Fig. 10c).

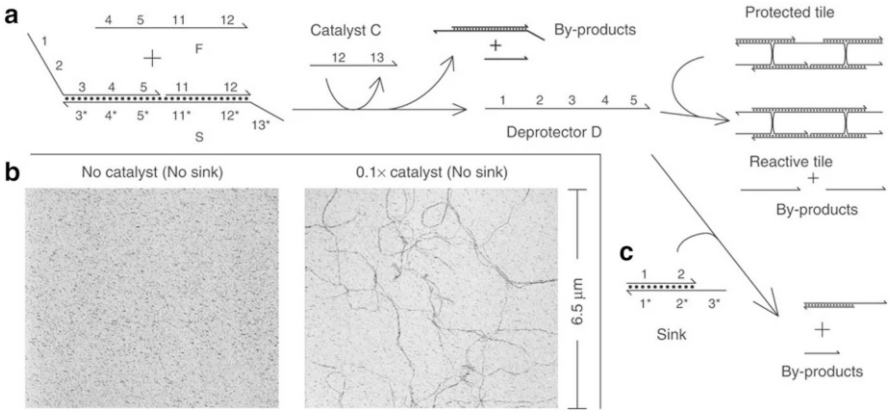

Fig. 10 DNA catalytic circuit controlling autonomous DNA tile self-assembly. **a** The entropy-driven DNA catalysis system that produces the deprotector strands. **b** Atomic force microscopy (AFM) results from the integrated reaction network. DNA nanotubes can assemble in the presence of catalyst. **c** The sink complex acts as a competition threshold for the deprotector to prevent the release of a small amount of deprotector, which will result in DNA nanotube assembly Reproduced with permission from Ref. [43]. Copyright © 2013, Springer Nature

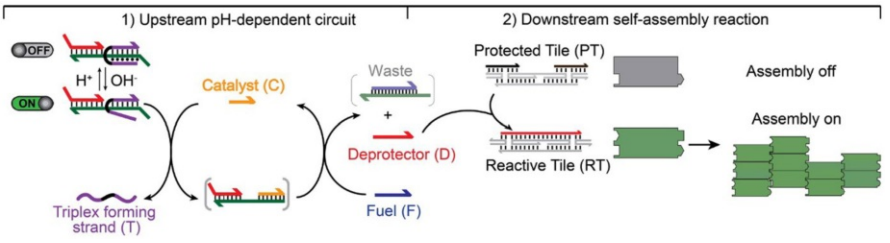

Fig. 11 pH-controlled assembly of DNA tiles. The upstream circuit (*1*) is a pH-dependent DNA catalytic module, and the downstream self-assembly reaction (*2*) the self-assembly of DNA double crossover tiles Reproduced with permission from Ref. [44]. Copyright © 2014, American Chemical Society

The modularity of integrating upstream DNA circuit and downstream self-assembly offers the possibility of designing versatile autonomous self-assembly. Ricci et al. [44] developed a pH-dependent circuit for controlling self-assembly of the same DNA double crossover tiles (Fig. 11). These latter authors re-engineered the three-strand substrate to be responsive to pH by introducing a triplex based on Hoogsteen interactions. The substrate was only accessible to the DNA catalyst at basic pH. Therefore, the generation of deprotector strands could be turned on and off by pH. Ultimately, downstream tile assembly is controlled successfully by the upstream pH-dependent circuit.

CHA may provide an alternative means of catalyzing autonomous assembly. Yang et al. [45] made pioneering efforts in this regard. Unlike DNA catalytic circuits, the CHA does not export a single strand as output. Instead, it simply recombines two individual hairpin strands into one hybridized duplex. Therefore, the

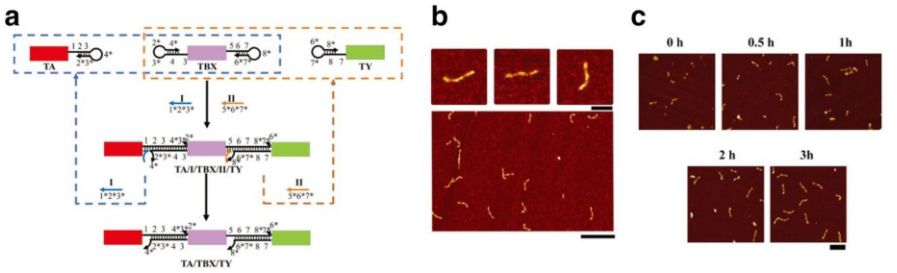

Fig. 12 Chain hybridization assembly (CHA)-driven DNA self-assembly. **a** Self-assembly process of the DNA tile trimer. **b** AFM image of the three-tile assembly product. **c** Kinetic evaluation of the formation of trimer tiles by AFM at different reaction times (0, 0.5, 1, 2, and 3 h). Bars **b** 50 and 100 nm, **c** 100 nm Reproduced with permission from Ref. [45]. Copyright © 2019, John Wiley and Sons

hairpin strands could be employed directly as linkers of DNA building blocks, and CHA could then be used to control assembly. Yang et al. [45] integrated the CHA reactions with DNA tiles and explored them as a means of assembling nanostructures dynamically (Fig. 12). They used DNA tiles (double crossover tiles as well as DNA origami) as artificial "carriages", hairpin structures modified on DNA tiles as "couplers", and initiators as "wrenches" to initiate the CHA to actively self-assemble train-shaped DNA nanostructures of controlled length.

3.3 Seed-Guided Self-Assembly

The HCR and DNA catalysis provide tools for solving the problem of how to initiate self-assembly. Another import aspect of controlling self-assembly is to determine when and where to initiate self-assembly. Winfree et al. [46] demonstrated the concept of using pre-assembly DNA origami to efficiently seed and nucleate the growth of DNA tiles (Fig. 13). They used a rectangular DNA origami, which can present up to 32 DNA tile adapters at one side. The tile adapters could recruit desired DNA tiles using sequence-specific sticky ends. Under certain circumstances, DNA double crossover tiles assemble only when the seeds are present, and the growth of DNA tiles started from the tile adapters of DNA origami seeds.

Schulman et al. [47] further developed the seed-directed self-assembly system, designing nanotube origami as the seed to nucleate the assembly of DNA tiles (Fig. 14). Under a thermal annealing process, DNA origami seeds and tiles first formed. DNA tiles would then grow from the nucleated seeds following an isothermal self-assembly pathway (Fig. 14a). In their subsequent work, Schulman and colleagues demonstrated that this growth process could be terminated by rigid or flexible caps that block the growth interfaces (Fig. 14b); based on this, they demonstrated that DNA nanotubes can grow to connect pairs of molecular landmarks with micrometer separation distances and relative orientations [48]. With DNA origami seeds as molecular landmarks, DNA tile nanotubes grow and then join end to end to form stable connections. This process relies simply on diffusion of the free ends and does not need external guidance.

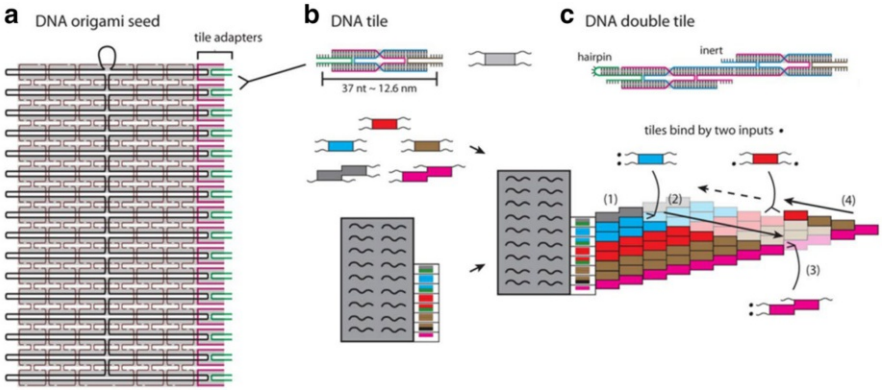

Fig. 13 Molecular design and self-assembly scheme. **a** The DNA origami seed consists of 32 tile adapter strands (*pink* and *green*) that bind at specific locations. **b** Each DNA tile consists of four strands that self-assemble into a molecule with a double-stranded core and four single-stranded 5-nt sticky ends. **c** Each DNA double tile, structurally equivalent to two fused tiles, consists of six strands that display four active sticky ends; two helix arms end either with a hairpin or with an inactive (inert) sticky end whose sequence matches no other sticky end Reproduced with permission from Ref. [46]. Copyright © 2009, National Academy of Sciences

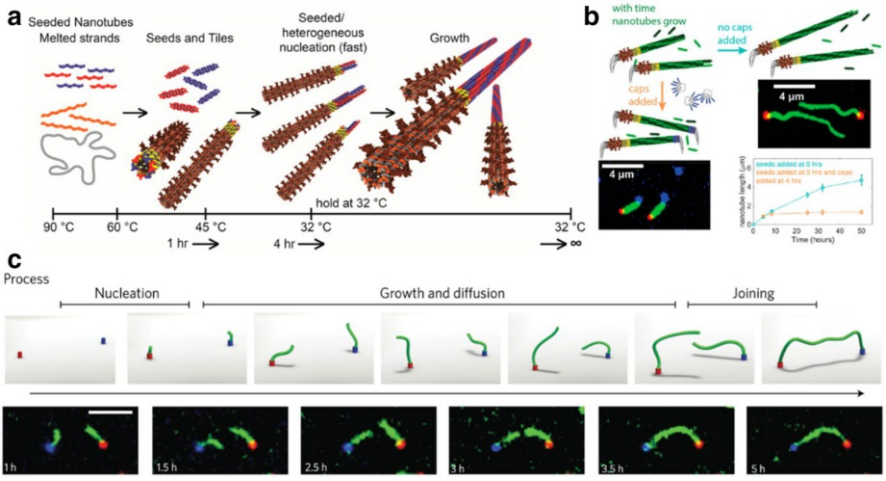

Fig. 14 Seed-mediated growth of DNA nanotubes. **a** Illustration of nucleation-growth process. **b** Termination of nanotube growth. **c** Connection of molecular landmarks by seed-mediated DNA nanotube growth. Bar 5 μm **a**, **b** Reproduced with permission from Ref. [47]. Copyright © 2017, American Chemical Society; **c** reproduced with permission from Ref. [48]. Copyright © 2017, Springer Nature

It should be noted that nucleation and growth would happen even without the origami seeds. However, nucleation from tiles would be much slower since it requires overcoming a significant energy barrier. From this viewpoint, the seeds not only provide spatiotemporal starting points for self-assembly but also play a role as initiators to lower energy barrier and guide the system to equilibrium.

4 Active DNA Self-Assembly System

The above-mentioned systems all follow the equilibrium thermodynamic framework. In this section we talk about active self-assembly systems with much more complexity. To date, there have been only a few successful demonstrations, most of which were published very recently. Here, we introduce three kinds of system: (1) a self-assembled nanoarray with a cascade of transformations for information-relay systems; (2) a biochemical oscillator controlled dynamic assembly system; and (3) an artificial metabolism system. Each has its own characteristics and could be seen as an out-of-equilibrium active assembly from some aspects. Each can also be regarded as a demonstration of active assembly at different scales, from nanoscale to micrometer and mesoscale.

4.1 Self-Assembled Information-Relay System

The ability to faithfully deliver information in a cascaded and controlled fashion has worked wonders for civilization and biology. Researchers are eager to control the flow of information within a network at nanometer-to-micrometer scale. Song et al. [9] used a DNA "antijunction" as a basic unit to construct limited-size nanoarrays that transmit information from one side to the other in the form of structural transformation (Fig. 15). In a typical diamond-shaped unit, its four adjacent elements share a joint, so that all cells are connected to each other by a four-armed connection, which is a branched DNA motif that can be opened and closed like scissors. In principle, when one antijunction unit changes conformation, the scissor joints communicate this motion to the adjacent units, which then also undergo the same conformational change. This change can be passed to the neighbors' neighbors and so on, until the entire array adopts the new conformation. Thus, Song and colleagues demonstrated the dynamic reconfiguration of DNA relay arrays. By adding and removing trigger strands, they can switch pre-assembled nanoarrays between different conformations and monitor the process in real time. In addition, they also showed that the conversion path was highly programmable. First, the starting point of transformation depends on where the trigger strands invade and lock the joints. Second, continuous transformation can be stopped and resumed by removing and replacing or locking and unlocking internal units. Finally, the transformation pathway can be controlled by designing odd-shaped nanoarrays with tight corners and adding trigger strands in a stepwise manner.

From the viewpoint of energy change, this self-assembled array is quite interesting. If we focus only on the start and the end states, it seems to be a trigger-initiated system. However, if we look into the landscape change during the relay process, it is very different. The system undergoes an energy oscillating process from the start state to the end state (Fig. 15e) given the alternate generation and disappearance of high-energy antijunction motifs (orange box in the figures).

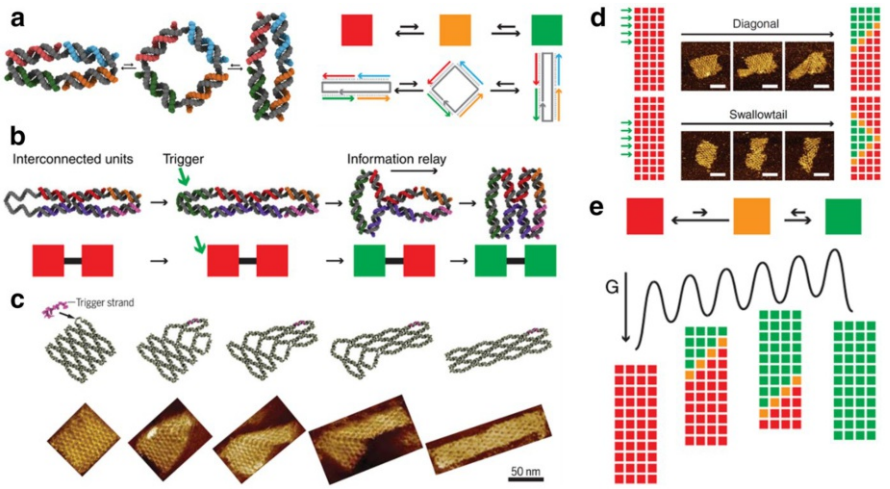

Fig. 15 Molecular information-relay arrays assembled by DNA. **a** A dynamic DNA antijunction that can switch between two stable conformations, through an unstable open conformation. Diagrams for a DNA antijunction: stable conformations red and green, and unstable conformation orange. **b** Transformation of an antijunction unit can be induced by addition of a trigger strand. The information is passed from the converted unit to its closest neighbors, causing them to undergo subsequent transformation. **c** Information relay in DNA "domino" nanoarrays. The molecular DNA nanoarray transforms in a step-by-step relay process, initiated by the hybridization of a trigger strand to a single unit. **d** Control of initiation of transformation via selection addition o green triggers. **e** Free energy landscape during the domino-like cascade transformations Reproduced with permission from Ref. [9]. Copyright © 2017, American Association for the Advancement of Science

4.2 Biochemical Oscillator Controlled Dynamic Assembly System

The cytoskeleton consists of three major unbalanced supramolecular assemblies that continuously polymerize and depolymerize: microtubules [49], actin filaments [50] and intermediate filaments [51]. The microtubules—the largest of these structures—are mechanically stiff, highly dynamic, and alternate between stable growth and rapid depolymerization. The active assembly of microtubules represents advanced spatiotemporal control. In living organisms, high spatiotemporal ordering is realized by regulatory networks that are prototypes of chemical fuels, energy-dissipating self-assembly with dynamic and adaptive properties.

One of the most important elements of the regulatory network is called the biochemical oscillator, which controls the timing of cellular processes and provide circadian rhythms. Such chemical oscillation could be produced in non-living systems. The BZ reaction is the first example of a chemical oscillator that exhibits imbalances, such as bistability, as well as macroscopic oscillations and synchronization [52, 53]. When appropriate negative feedback is introduced, the well-stirred setup becomes susceptible to stimulation (that is, an input above a certain threshold will cause the output to peak before returning to the initial steady state) or to become oscillating. However, the susceptibility of the chemical oscillator makes it extremely difficult to make it compatible with other systems.

In organisms, long-duration time control is heavily dependent on gene expression. Instead of building pure chemical oscillators, Kim and Winfree [54] built an in vitro transcriptional oscillator by employing biological enzymes (Fig. 16a). They devised a 'two-switch negative-feedback oscillator'. The biological oscillator is composed of nucleic acid strands (RNA and DNA) and enzymes (T7 RNA polymerase and RNase H). As depicted in Fig. 16, there are two switches (SW21 and SW12) in the oscillator as RNA 'genelets', each of which could produce single-stranded RNAs (rI2 and rA1) transcribed by T7 RNA polymerase. The activation and inhibition of these genelets could be regulated by DNA reaction networks involving the produced RNAs (Fig. 16b). In short, the produced RNAs can remove DNA strands from the promoter region by forming RNA–DNA hybrids. As a result, with the production and increasing concentration of RNAs, the generation of RNAs is inhibited. At the same time, the RNase H in the system continuously digests the RNAs and releases the DNA strands of the promoter, inducing re-activation of the genelets. The synergy of two such genelets enables the 'two-switch negative-feedback oscillator,' which exhibits sustained RNA concentration oscillations. This biochemical oscillator is programmable and compatible with the self-assembled DNA system. Simmel et al. [55] investigated and compared the effect on the oscillators of different strategies of load tweezer-like DNA nanomachines (Fig. 16c). One optimized strategy involved an extra transcription circuit as an insulator genelet. The insulators make the system more robust by isolating the oscillators and the loads, amplifying signals from the oscillators and thus allowing relatively high loads.

Integrating the structural DNA nanotechnology, the dynamic DNA nanotechnology as well as the biochemical oscillator, Franco et al. [10] demonstrated the active oscillating self-assembly of DNA tubular structures, a preliminary analogue to the dynamic growing and shrinking of microtubules (Fig. 17). They chose the DNA double crossover tile self-assembly we introduced earlier in this review. DNA tiles with sticky ends can self-assemble isothermally into nanotube filaments with diameters ranging from 7 to 20 nm. In their system, they added short segments to the sticky ends as toeholds, which could mediate the RNA invaders to break the intertile connections by strand-displacement reactions. The generation of RNA invaders is controlled by the biochemical oscillator and the insulator. In addition to playing the role of toehold, the intrusion of a single sticky end region weakens the interaction between the tiles, causing the nanostructures to collapse. Tiles bound to the RNA invader become 'inactive'. Meanwhile, the RNase H sustainedly digests the RNA invader and converts the inactive tiles to become active. The active tiles reassemble into nanotubes autonomously. Therefore, the concentration oscillating of RNA invaders actually controls the active assembly and disassembly of nanotubes by the interplay of digestion and generation. They observed the time clocking growth and shrinking of filaments over a time scale of hours.

Integrating these elements to make them work synergistically is not easy. One of the challenges is to match the kinetics of different elements. The oscillating period should match the rate of tile assembly, which is relatively slow. Since enzyme activities are hard to control, the oscillator can be modulated only by tuning the concentrations of oligonucleotides and enzymes. In addition, the oscillator operates in a closed system, so the system faces reduced enzymatic activity, accumulation of

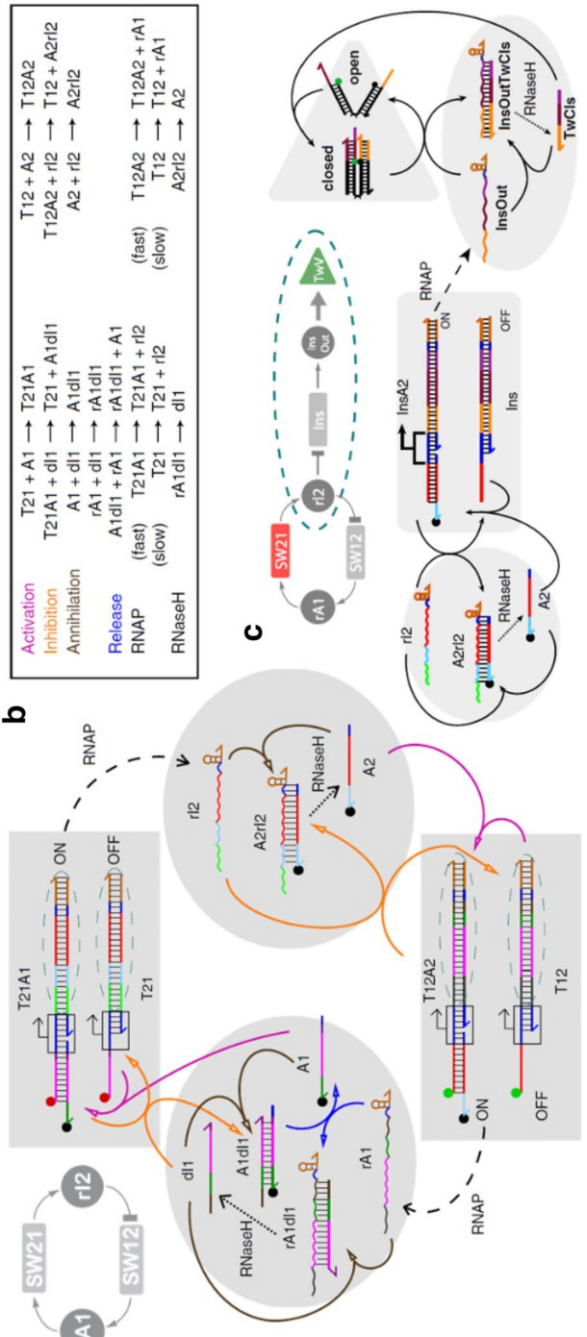

Fig. 16 Schematics of a biological oscillator system that can be coupled to high loads. **a** Topology of the oscillator and its biochemical reactions. **b** List of interactions between oscillator-component species. **c** Driving DNA tweezers with the Oscillator. Transcription of Ins releases InsOut which opens DNA tweezers previously closed by TwCls **a**, **b** Reproduced with permission from Ref. [54]. Copyright © 2011, John Wiley and Sons; **c** Reproduced with permission from Ref. [55]. Copyright © 2011, National Academy of Sciences

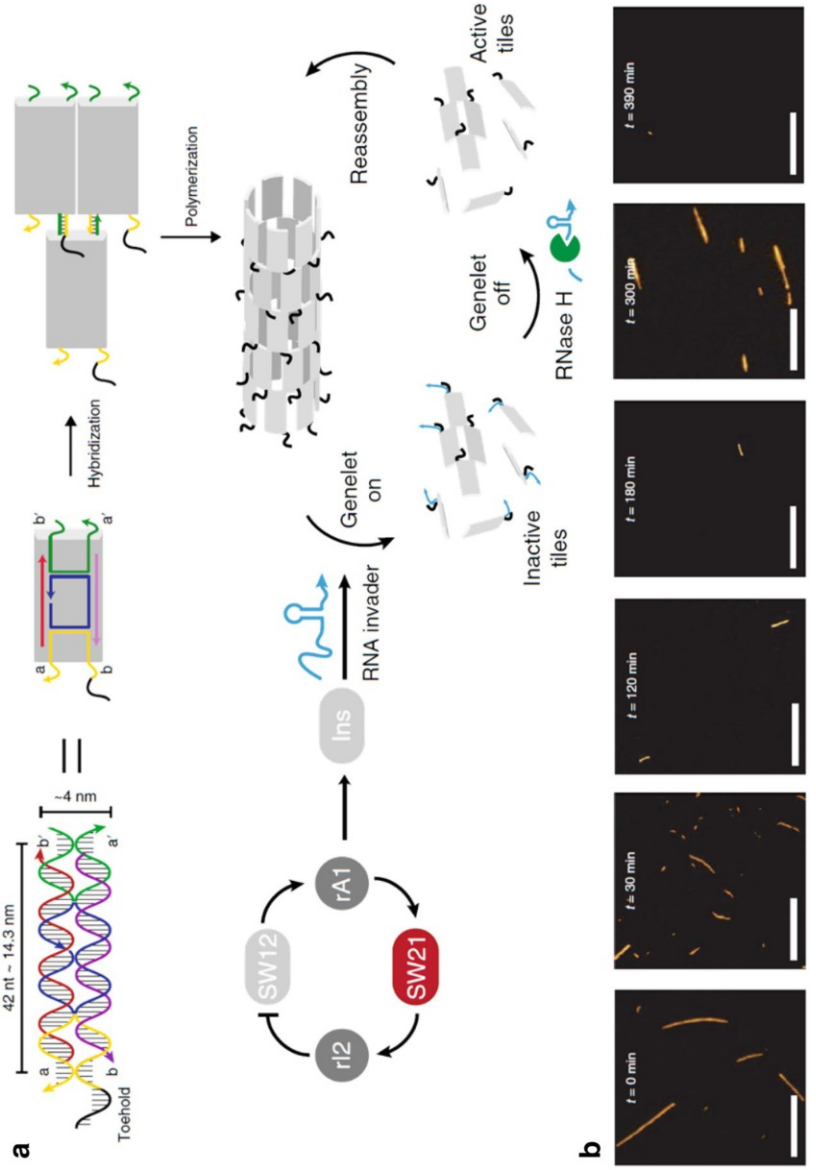

Fig. 17 Biochemical oscillator controlled dynamic assembly of DNA nanotubes. **a** DNA tiles self-assemble into DNA nanotubes that can collapse and reassemble with the driving of a biological oscillator system. **b** Representative fluorescence microscopy images of nanotube samples at different points in time. Bar 10 μm Reproduced with permission from Ref. [10]. Copyright © 2019, Springer Nature

incompletely degraded RNA, and consumption of NTPs. With all these challenges in mind, Franco et al. [10] achieved a system in which nanotube assembly can be controlled by the oscillator to exhibit one or two large-amplitude oscillations.

4.3 Artificial Metabolism System

The above-mentioned dynamic DNA assembly systems work at the molecular or supramolecular level, and rely on the careful design of building blocks and their precise interactions. Conversely, Luo et al. [11] created a DNA-based dissipative assembly system that works at the mesoscale. Instead of using DNA for the assembly of DNA motifs or nanostructures, they employed DNA as source material for the generation of a hydrogel. By manipulation of the sequential generation and degradation of the DNA hydrogel with a built-in spatiotemporal feedback, they realized an artificial metabolism system. To realize this concept, they engineered a mechanism termed DASH (DNA-based Assembly and Synthesis of Hierarchical materials) that mimics how nature uses metabolism to build structural hierarchy materials through biochemical synthesis and dissipative assembly processes (Fig. 18).

The anabolic generation pathway of DASH (Fig. 18a) consists of two processes: biochemical synthesis of DNA with the help of an enzyme-based rolling circle amplification (RCA) reaction and the assembly of DNA into pre-defined patterns by gelation in a microfluidic device. With this pathway, the continuously generated DNA molecules flow into the microfluidic chamber and form programmed patterns with DNA gelation (Fig. 18b–d) in a dissipative manner. The catabolic degeneration process happens simultaneously along with the anabolic pathway. This is achieved by the enzymatic DNA-hydrolyzing reactions. These two pathways are executed synchronously without any external manipulation. In a three-inlet microfluidic device, the growth and decay of DASH patterns could be controlled by a spatiotemporal feedback mechanism (Fig. 18e). With this artificial metabolism system, Luo et al. [11] further realized emergent locomotion and racing behaviors (Fig. 18f).

5 Discussion and Perspective

Biological cells typically reconfigure their shapes using dynamic signals and regulatory networks that direct the self-assembly process in time and space by sensing, processing, and transmitting information from the environment through molecular components. Bio-inspired out-of-equilibrium systems will set the scene for the next generation of molecular materials with active, adaptive, autonomous, emergent and intelligent behavior. Indeed, life provides the best demonstrations of complex and functional out-of-equilibrium systems: cells keep track of time, communicate, move, adapt, evolve and replicate continuously. Stirred by the understanding of biological principles, artificial out-of-equilibrium systems are emerging in many fields of soft matter science.

Through the route of DNA nanotechnology, much compelling effort has been made towards life-mimicking active assembly. The dynamic control of DNA assembly has been realized by different means with spatial and temporal programmability. However,

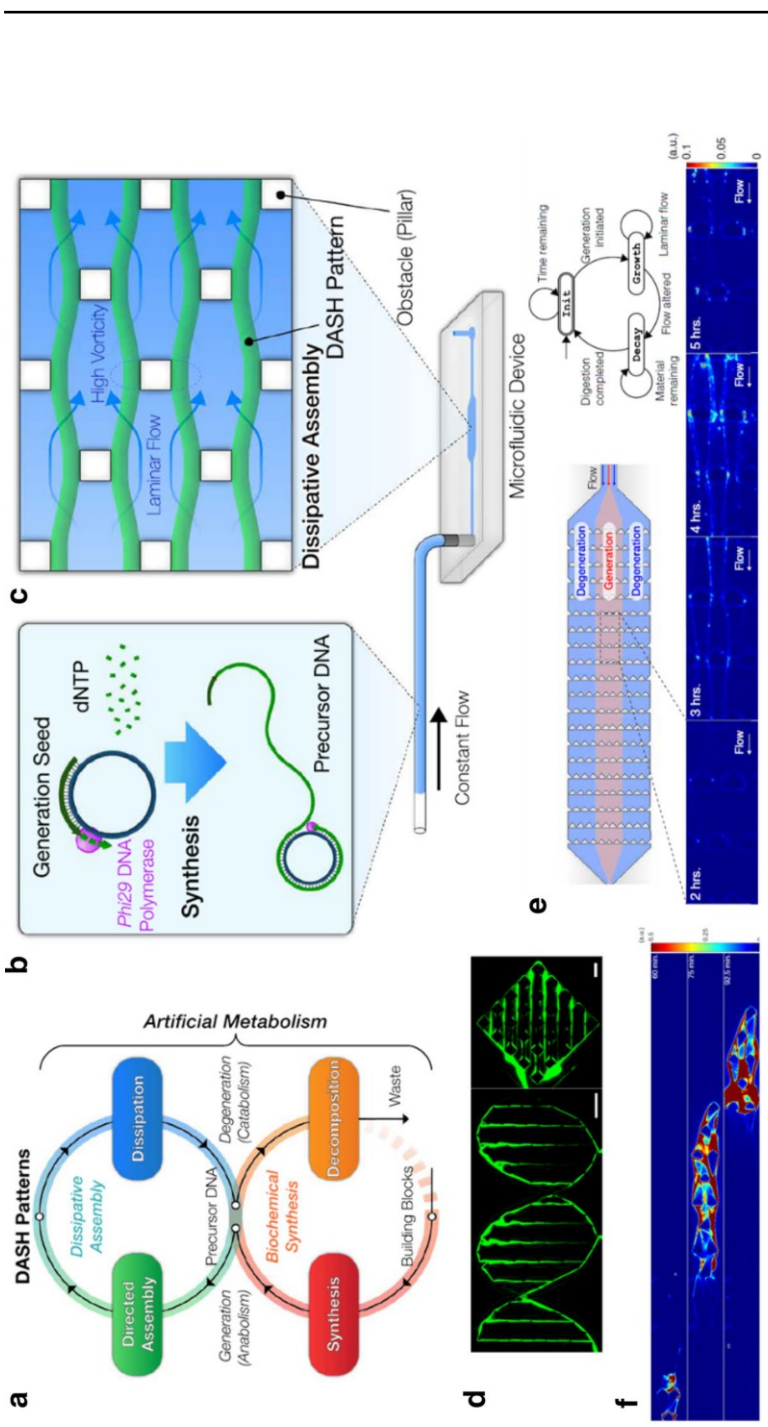

Fig. 18 DNA-based assembly and synthesis of hierarchical materials. **a** Scheme of the artificial metabolism system. **b** Synthesis of precursor DNA by rolling circle amplification (RCA). **c** Formation of DASH (DNA-based Assembly and Synthesis of Hierarchical materials) patterns by dissipative assembly using the flow with obstacles in microfluidic devices. **d** Exemplary DASH patterns formed by DNA hydrogel. **e** Dynamic DASH patterns formed by sequential generation and degeneration of DNA hydrogels. **f** Emergent locomotion and racing behavior powered by dynamic DASH patterns Reproduced with permission from Ref. [11]. Copyright © 2019, American Association for the Advancement of Science

compared with what happens in living organisms, the development of artificial out-of-equilibrium active systems are still at a very early stage.

The most important and obvious gap is complexity. In addition, the response time of current DNA dynamic systems is significantly slower than the inherent fluctuation time of dynamic biological events, indicating that the response speed of the dynamic DNA structure has large room for improvement. Moreover, the ability to achieve gradual and continuous control over a wide range of states remains a huge challenge. The simplicity and programmability of DNA nanotechnology give us a feasible means to emulate and, in turn, better understand life. While combining these techniques with other materials, and applying design guidelines from DNA systems to other systems may bring more opportunities to achieve bigger successes.

Living organisms decay towards a thermodynamic equilibrium state only when they die. In contrast, the sustainability of artificial out-of-equilibrium systems is still far from satisfactory. There are many thorny issues to be solved to make artificial systems more sustainable. In living systems, energy and precursor materials are supplied continuously at regulated rates, and molecular wastes are recycled or cleaned effectively. In contrast, in an artificial system, energy and precursor materials are normally added at the beginning of the reaction and are consumed irreversibly while wastes accumulate. A possible direction may be to perform artificial systems in vivo. Establishing the interfaces between cellular signals and artificial active assembly may solve some of these problems. On the other hand, the coupling of these two systems may provide the means of applying external regulation to life.

To date, the most successful demonstrations have been based on biological enzymes and the use of ATP as fuel. ATP is the molecular unit of currency for energy transfer in life, driving numerous biological motors in a cell by the universal chemical reactions of converting ATP to ADP or AMP. A human-made molecule that can play similar roles, and a set of molecular machines driven by such molecules would be extremely exciting.

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Compliance with Ethical Standards

Conflict of interest On behalf of all authors, Chao Zhou and Qiangbin Wang states that there is no conflict of interest.

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Affiliations

Jinyi Dong[1,2] · Chao Zhou[1] · Qiangbin Wang[1]

[1] CAS Key Laboratory of Nano-Bio Interfaces, Division of Nanobiomedicine and i-Lab, Suzhou Institute of Nano-Tech and Nano-Bionics, Chinese Academy of Sciences, Suzhou 215123, People's Republic of China

[2] School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, People's Republic of China