Analytica Chimica Acta xxx (xxxx) xxx

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Review

Recent advances in DNA walker machines and their applications coupled with signal amplification strategies: A critical review

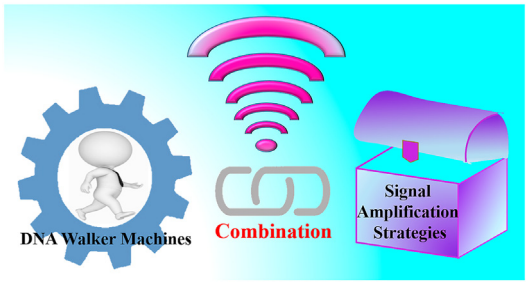
Mingdi Xu [a, b, **], Dianping Tang [b, *]

[a] College of Ecological Environment and Urban Construction, Fujian University of Technology, Fuzhou 350108, People's Republic of China
[b] Key Laboratory of Analytical Science for Food Safety and Biology (MOE & Fujian Province), Department of Chemistry, Fuzhou University, Fuzhou 350108, People's Republic of China

HIGHLIGHTS

- We critically review recent advances in DNA walkers for bioanalytical application.
- Different DNA walkers based on three characteristic driving forces are discussed.
- DNA walkers based on multiple dimensional tracks are assessed for amplified sensing signal.
- DNA walkers coupled with diverse signal amplification strategies are sorted and evaluated.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 December 2020
Received in revised form
13 April 2021
Accepted 13 April 2021
Available online xxx

Keywords:
DNA walker
Biosensors
Multiple dimensional tracks
Signal amplification strategies
Hyphenated techniques

ABSTRACT

DNA walkers, a type of dynamic nanomachines, have become the subject of burgeoning research in the field of biology. These walkers are powered by driving forces based on strand displacement reactions, protein enzyme/DNAzyme reactions and conformational transitions. With the unique properties of high directionality, flexibility and efficiency, DNA walkers move progressively and autonomously along multiple dimensional tracks, offering abundant and promising applications in biosensing, material assembly and synthesis, and early cancer diagnosis. Notably, DNA walkers identified as signal amplifiers can be combined with various amplification approaches to enhance signal transduction and amplify biosensor sensing signals. Herein, we systematically and comprehensively review the walking principles of various DNA walkers and the recent progress on multiple dimensional tracks by presenting representative examples and an insightful discussion. We also summarized and categorized the diverse signal amplification strategies with which DNA walkers have coupled. Finally, we outline the challenges and future trends of DNA walker machines in emerging analytical fields.

Contents

* Corresponding author.
** Corresponding author. College of Ecological Environment and Urban Construction, Fujian University of Technology, Fuzhou 350108, People's Republic of China.
E-mail addresses: mingdixu@fjut.edu.cn (M. Xu), dianping.tang@fzu.edu.cn (D. Tang).

https://doi.org/10.1016/j.aca.2021.338523
0003-2670/

1. Introduction

Because of the structural and functional characteristics of DNA, on the foundation of rigorous Watson-Crick base pairing, DNA has emerged as a notable building material for designing programmable and versatile nanostructures. In the biomedical field, DNA nanotechnology [1–6] has become a popular method for guiding the precise manipulation of artificial systems at microscopic molecular levels. Various machines, including DNA switches [7–9], DNA robots [10,11], DNA logic gates [12,13], DNA tweezers [14,15] and DNA motors [16,17], have been exploited for bioanalytical application and exhibit the properties of high flexibility, precision, efficiency, sensitivity and specificity. Remarkably, DNA walkers that imitate the natural kinesin movements through which cargo is directionally transported along microtubules have been shown to perform controllable mechanical motion along predetermined tracks on a unique nanoscale. These DNA walker machines, which constantly traverse progressively and autonomously along one-dimensional linear tracks, two-dimensional origamis and three-dimensional nanoparticles, have great application prospects in biosensing and bioimaging, material assembly and synthesis, and monitoring living processes [18–27]. Moreover, prominent sensitivity and detection limits can be obtained because of the superior design schemes and advantageous properties of DNA walkers. Herein, we intend to highlight the biosensing application of DNA walkers as emerging dynamic molecular machines.

Structurally, DNA walkers mainly rely on the driving forces of enzymatic reactions, strand displacements or conformational transitions and walking bodies migrating along different dimensional tracks. This paper summarizes the mechanisms of DNA walker machines in detail and discusses representative examples of relative biosensors based on multiple dimensional tracks. Importantly, DNA walkers have been essentially tested as signal amplifiers, which are capable of recycling mechanical behaviors without reversing the original operations. Recently, vast efforts have been made towards engineering DNA walkers that can strengthen signal transduction in biosensors by integrating diverse signal amplification strategies. Although several previous reviews have summarized the analytical applications of DNA walkers [28–31], we first summarize and evaluate the hyphenated techniques in which DNA walkers are coupled with various amplification methods. Finally, in this paper we also define the challenges and anticipate the development prospects for DNA walkers in this inspiring field.

2. Principles of DNA walker machines

The representative DNA walker machine comprises three essential ingredients, including the driving force, walking foot and track. From a dynamic perspective, biased walking is realized by breaking the initial balance through external driving forces, which promotes the conversion of light or chemical energy into mechanical energy. Then, a fuel molecule is supplied to restore the equilibrium system, thereby yielding the signal substance. Through the cyclic process of damaging and repairing this equilibrium, the energy cascade promotes spontaneous walking that occurs progressively and autonomously along the track to amplify the biosensing signal.

2.1. Strand displacement reaction

The strand displacement reaction is a vital driving approach that enables DNA walkers to control strand hybridization through Watson-Crick hydrogen bonds [32–36]. This process is initiated by toeholds and displaces the prehybridized strands towards branch migration. Given the capability of the kinetic process to alter the sequence length and toehold complementarity regions, the reaction is advantageous for engineering synthetic DNA machines and is independent of the enzymatic process.

The DNA walker was first exploited by Pierce's group, who mimicked kinesin motion to perform molecular transport driven by strand displacement reactions (Fig. 1A) [20]. Supplemented by complementary single-stranded hinges (A1 and A2), the two feet of the synthetic walker were fixed to the branches of the track (green and purple). When fuel strand D1 nucleated with strand A1 at the exposed toehold, the walking leg was released and reattached to the other track after the addition of new fuel strands. A persistent walking mode can be achieved by providing energy through the abovementioned strand displacement reaction without the participation of enzymes. Directional motion can be achieved by precisely controlling the walking steps through the addition of specific fuel strands. However, an increased fuel concentration reduced the efficiency of the leg-placing process, resulting from the formation of a stable "trap state" that binds one fuel strand to the foothold and another to the leg. Thus, a metastable hairpin structure has been extensively introduced as a fuel strand for these nanomachines that prevents the formation of trap states. Tomov et al. [37] developed a bipedal motor that employed hairpin fuel strands to increase the timed walker stepping speed, and over 32

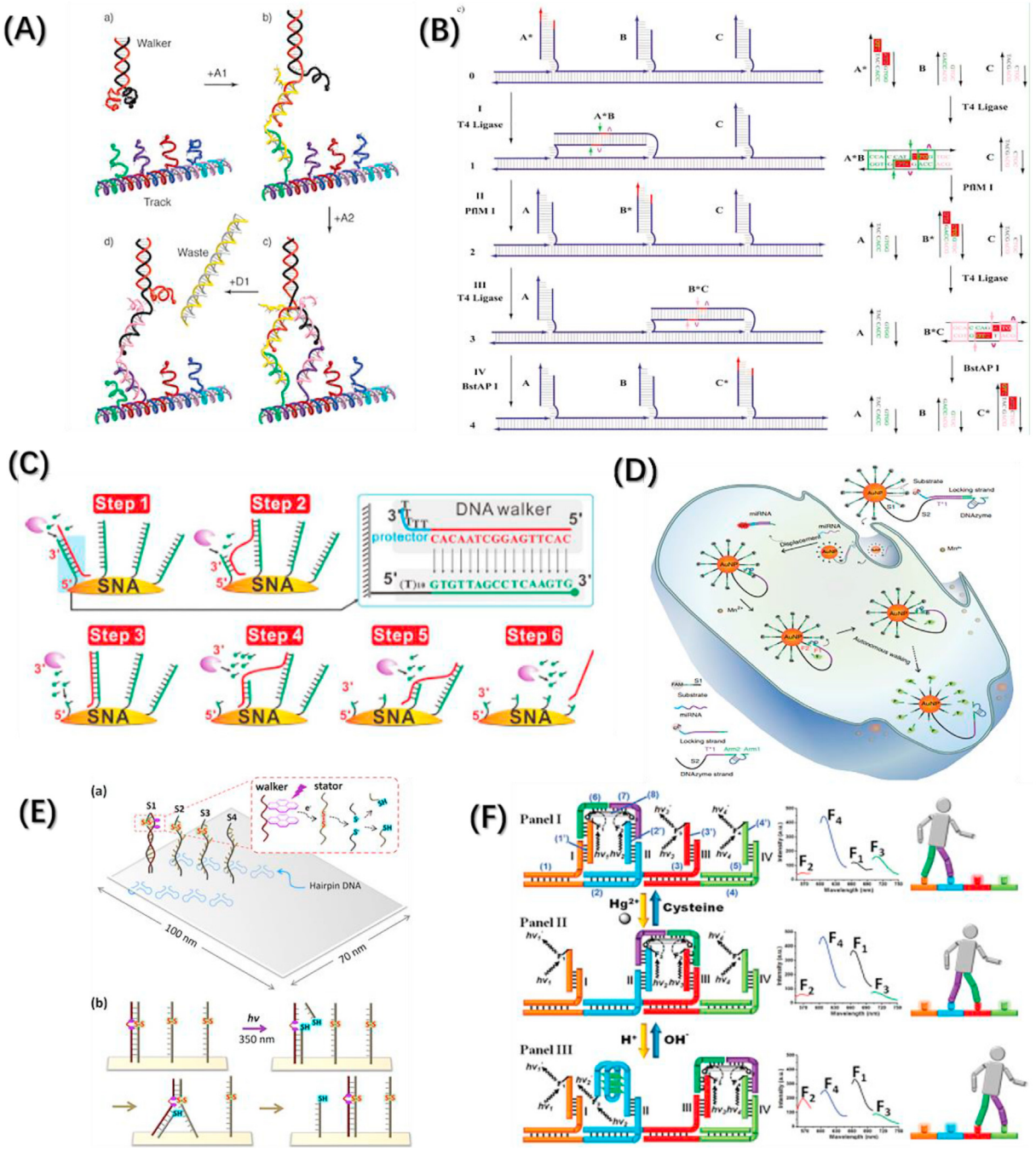


Fig. 1. Walkers powered by different driving forces. (A) Strand displacement reaction [20], (B) ligase and restriction endonuclease [42], (C) exonuclease [47], (D) DNAzyme [52], (E) UV/vis light source-induced conformational transition [56] and (F) pH or ions-activated conformational change [57].

high-efficiency steps that represented movement along the origami track could be obtained using a microfluidic device. Specifically, the approach presented in this study enabled a distinct increase in the operation yield and processivity without eliminating command strands. In addition, Ellington's group [38] adapted a catalytic hairpin assembly to construct a stochastic DNA walker that activated the interaction of H1 (hairpin)-like substrates with hairpin fuel strands to traverse the microparticle surface. The robust walking behavior led to walker motion that continuously exceeded 30 steps.

2.2. Protein enzyme/DNAzyme reaction

Protein enzyme or deoxyribozyme (DNAzyme) reactions tend to balance nucleic acid chemistry. There exists a class of DNA walkers that are propelled by enzymatic reactions caused by covalent bond hydrolysis of DNA substrates along the tracks. The operation efficiency of these walking systems relies on competent enzyme/DNAzyme-induced strand shearing and is approximately three orders of magnitude quicker than traditional machines based on hybridization reactions.

Endonucleases that catalyze the breakage of polynucleotide

chains in the middle can nick single or double strands by recognizing particular nucleotide sequences [32,39–41]. Yin's team [42] established the first enzyme-driven walker machines for transporting DNA fragments, as achieved by scission and ligation actions (Fig. 1B). A walking fragment of six nucleotides could be bound to three anchor strands; the walker was ligated to the next anchor strand by the T4 ligase and was regenerated upon cutting from the previous anchorage by the restriction endonucleases of PflM I and BstAP I. Repetition of the recognition site destruction and new site creation processes allowed the walker to move autonomously and unidirectionally along the DNA track. A similar walker scheme driven by a simple nicking enzyme (N. BbvC IB) was presented for transporting DNA cargo. The free-running molecular motor operated directionally, locating the desired position with an easy modified track, and moved on the nanometer scale at a speed of 0.1 nm s^{-1} [43].

Endonuclease-induced walking machines still rely on the specific recognition units of nucleic acid sequences, so the emergence of exonucleases perfectly circumvents this requirement. This exonuclease degrades the polynucleotide chain in sequence from the end to produce a single nucleotide [44–46] and has been employed for various DNA walker devices. Fan et al. [47] reported an exonuclease III (Exo III)-powered DNA walker that moved autonomously along a three-dimensional (3D) track (Fig. 1C). For a single-foot DNA walker hybridized with a nucleic acid track, Exo III catalyzed the hydrolysis of the track from the blunt 3′ termini. The released walker binded to the adjacent track for a new Exo III cleavage. The Exo III-propelled walking movement displayed high processivity because the hydrolysis efficiency of Exo III was hundreds of times higher than those of endonucleases and DNAzymes.

Although DNA walkers based on protein enzymes exhibit fantastic operation efficiency, introducing bioenzymes into living cells is difficult. This bottleneck is overcome through the utilization of DNAzyme as a driving force for DNA walker design. DNAzymes are a category of artificial enzymes with catalytic properties [48–51]. Among them, RNA-cleaving DNAzymes with easy synthesis and favorable stability can trigger the autonomous movement of DNA walkers with the aid of metal ions. Le et al. [52] exploited a DNAzyme motor by controlling the autonomous and directional miRNA motion response, which is driven by Mn^{2+}-dependent DNAzyme-catalyzed cleavage in living cells (Fig. 1D). This motor, which avoided the necessity for bioenzymes and DNA fuel strands, showed practical significance regarding live cells. In addition, DNAzyme-induced dissociation has been used to extend the applications of such motors in cell imaging, drug delivery and gene diagnosis.

2.3. Conformational transition

The energy generated by DNA conformational transitions [53–55] comprises an emerging power source for walker devices. The representative design, powered by an ultraviolet/visible (UV/vis) light source, employs photosensitive molecules modified to oligonucleotides to mediate walker conformation. Yang et al. [56] incorporated pyrene molecules into oligonucleotides and maintained the composite stability to constitute a DNA walker strand via a coupling reaction. The photosensitizer of the pyrene-modified DNA walker was successfully constructed to promote cleavage of the disulfide bond-connected stator on a DNA tile under 350 nm photoirradiation (Fig. 1E); when the pyrene absorbed light energy to transfer electrons to disulfide bonds, the stator strand was cleaved, and the short fragment was released from the track. The partially metastable walker strand stepped up to the adjacent stator due to strand displacement. The stepwise migration along the track facilitated autonomous unidirectional movement driven by the sustainable optical source. The real-time mechanical motion of each forward walking strand was first observed upon utilization of a high-speed atomic force microscope. This walking nanomachine can be remotely controlled through photochemical reactions, broadening its application in mesoscopic systems.

In addition to light power, driving forces activated by pH or ions can also act as critical factors in walker machines. A bipedal walker engineered by Willner's group [57], traversing on a DNA template track composed of four footholds, was driven by Hg^{2+} ions/cysteine or H^+/OH^- ions (Fig. 1F). Initially, the two walker feet were positioned on footholds I and II because of prior hybridization. The use of Hg^{2+} in the system gave rise to a forward walking motion of one foot from foothold I to foothold III, yielding an elevated stable thymine-Hg^{2+}-thymine (T) complex. Subsequently, adjusting the pH of the system to acidic conditions led to strand rearrangement to the i-motif structure (panel II) and locomotion of the other foot from foothold II to foothold IV. Interestingly, due to the OH^- ion and cysteine activators, backward walking can be driven to dissociate the i-motif or T-Hg^{2+}-T complex. Generally, this study presented the development of a reversible DNA machine that enabled both forward and backward walking, as triggered by Hg^{2+}/cysteine and H^+/OH^- ions, respectively. Moreover, this approach introduced external trigger signals that were applied to monitor pH changes or pernicious ions in cells.

3. DNA walker machines based on multiple dimensional tracks

The walking track plays a vital role in the operation of the DNA walker machine, as the fundamental platform for transducing and amplifying signals. The track is designed through the arrangement and positioning of rigid substrate molecules (e.g., common DNA). The anchor strand must be steadily fixed on the track to bind the walking strand to the track, and various nanoparticle-based tracks have been used to embrace the electrochemical or fluorescence properties attributed to well-designed DNA walker machines with advantageous controllability, mobility and transport efficiency. In accordance with the walking manner and region, we classified the machines into three categories of one-dimensional, two-dimensional and three-dimensional DNA walkers.

3.1. One-dimensional (1D) DNA walker

Pierce's group of pioneers devoted to DNA walkers exploited a strand displacement reaction to drive a biped walking device in striding along a one-dimensional (1D) track [20]. To track walker motion, the four protruding branches of the walker track were labelled with fluorescence dyes, and the legs of the walker strand were labelled with quenchers. The use of walker movement for molecular transport could be monitored in real time by the variation in the fluorescence signal in response to homologous fuel strands, demonstrating high fidelity in controlling walking movement at the nanoscale. The track scaffold found on rigid double-stranded DNA can be easily designed and rationally adjusted, allowing the device to progressively and autonomously mimic motor protein locomotion.

Many DNA walkers built in strand-displacement regimes have been used to make considerable advances in bioanalysis, whereas additional fuel strands for hybridization render the byproducts of double strand accumulation and dilute the system. The excellent impetus in which light energy offers a high degree of precise controllability overcomes the necessity of invasive changes to the system. Famulok's team [58] reported an orthogonal light-driven DNA walker that traversed the back-and-forth directions along a 1D path (Fig. 2A). Two azobenzene derivatives corresponding to

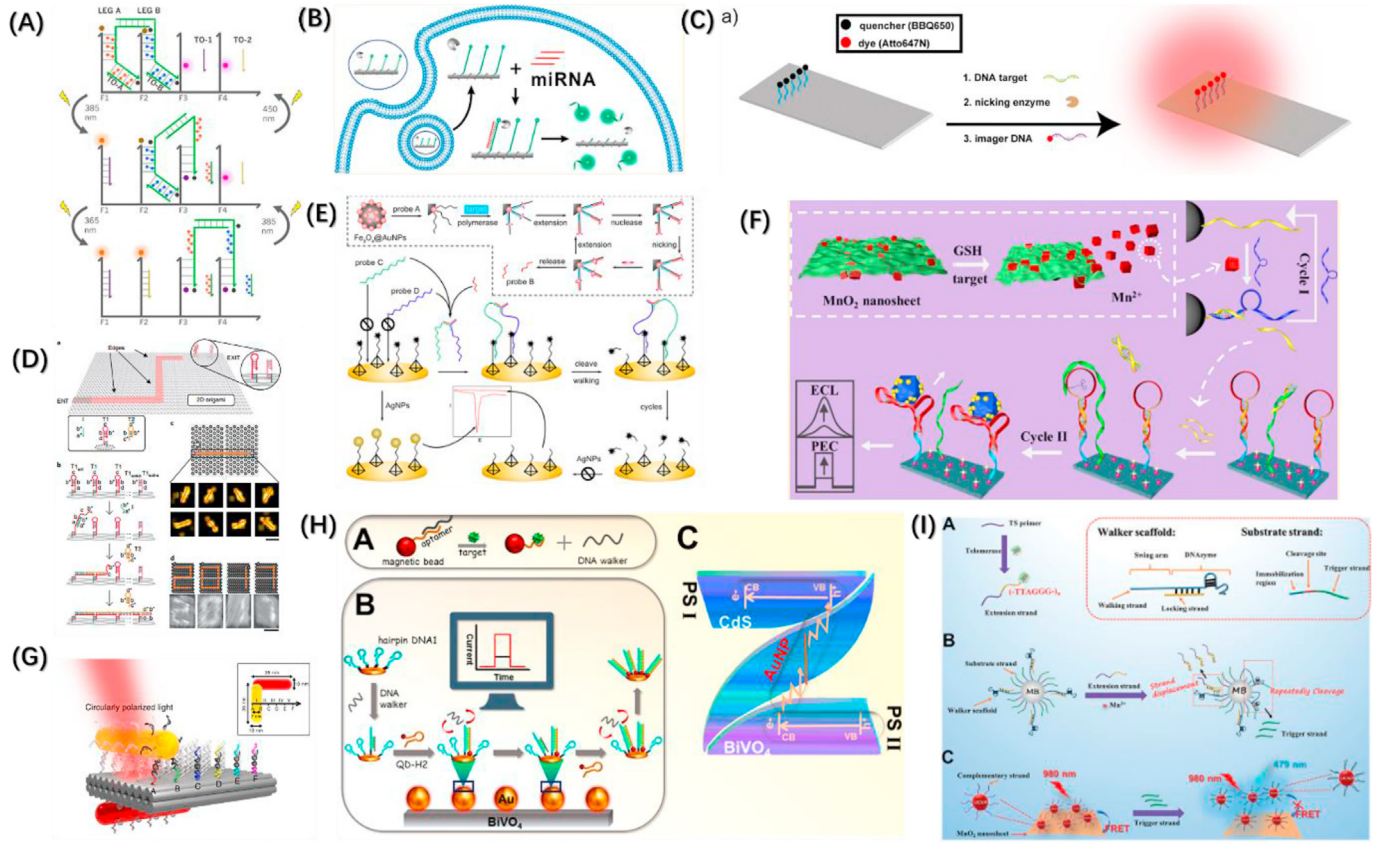


Fig. 2. DNA walker supported by multiple dimensional tracks. (A) 1D double helix path [58], (B) a 1D single wall carbon nanotube track [59], (C) and (D) 2D rectangular DNA origamis [60,64], (E) gold electrode [65], (F) ITO electrode [66], (G) 3D DNA origami [68], (H) 3D gold nanoparticles (AuNPs) [70] and (I) 3D magnetic beads (MBs) [49]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

different optical wavelengths were implemented to coordinate the strand displacement courses via cis/trans isomerization. By means of four photocontrolled strand displacement processes, the DNA walker was flexibly regulated in a reversible walking pattern under the appropriate light irradiation. This orthogonal photocontrol system addressed the necessity of two or more photoactuators and implemented greater spatiotemporal control. It could be expanded to employ another orthogonal wavelength for guiding directional walking. This highly accurate control over walker motion, based on the power provided by light, paves a new road for designing noninvasive progressive walking machines on the nanoscale.

Although these walker machines that employ DNA hybridization control exhibit delicate sensitivity and specificity, the efficiency of target-triggered hybridization declines consistently between the target and probes, hindering low-abundance detection in living cells due to slow target-recycling kinetics. To overcome this limitation, Xiao et al. [59] presented enzyme-powered stochastic RNA walkers that move along a 1D single-wall carbon nanotube (SWCNT) track (Fig. 2B). Duplex-specific nucleases (DSNs) can selectively recognize and digest the DNA of DNA/RNA heteroduplexes without specific splice sites and exhibit no activity against single-stranded DNA or RNA; in the reaction system, they effectively reduced DNA contamination from DNA/RNA heteroduplexes. The DSN-mediated cleavage of FAM-labelled DNA from DNA/RNA heteroduplexes promoted autonomous and progressive locomotion, allowing the transduction and amplification of biorecognition fluorescence signals for miRNA detection. The high target-recycling kinetics enabled amplified signal outputs and an excellent detection limit of 1.67 fM. The use of DSNs in the RNA walker, provided excellent selectivity that distinctly discriminated one-base mismatched miRNA from perfectly matched miRNA. In particular, the DSN can be effectively transported into HeLa cells by a transfection agent, and this approach provides a new perspective for extending the application of RNA walkers to living cells.

3.2. Two-dimensional (2D) DNA walker

Inheriting the advantages of a 1D DNA walker, a two-dimensional (2D) DNA walker with a planar structure offers a higher degree of freedom for movement on the DNA track. The 2D platform is preferable for fixing substrate molecules and effectively controlling locomotion to improve processivity. Tinnefeld and his partners [60] advanced a 2D walker machine that served as a fluorescence signal amplifier for elevated sensitivity of target molecular detection (Fig. 2C). A 2D track of 100 nm in length and 70 nm in width was instituted upon folding the M13 mp18-derived scaffold strand into a rectangular DNA origami using 192 staple strands. The DNA target acted as a walker bound to the track, yielding a specific duplex involving the recognition sequence. Propelled by the enzymatic nicking reaction, autonomous walking proceeded continuously along the origami track accompanied by the release of quenchers. After adding dye-labelled imaging strands, the brightness distribution could be characterized to visualize the effect of walking behavior. The DNA walker was successfully converted into a linear fluorescence amplifier to obtain single nucleotide sensitivity. Monte Carlo simulations [61–63] were used to prove the high processivity for the above walking movement, and the rate constant of the perfectly matched sequence was

2-fold larger than that of a single mismatch. The DNA walker was also integrated into plasmonic fluorescence enhancement, demonstrating that the unification of various amplification techniques amplified the sensing signals. Moreover, DNA origami has an information-bearing capacity with a precise geometry and an excellent addressability and is successfully employed for the implementation of intelligent nanorobotics. Fan's research group [64] developed a DNA navigator system based on a hybridization chain reaction that implemented a parallel depth-first search on DNA origami (Fig. 2D). The application of these solved mazes defeated the complexity and scalability limitations of DNA computing systems in solution, enabling the single DNA navigator to explore possible paths randomly through a surface-based DNA computational approach performed at the single-molecule level.

Even though DNA origami is addressable, flexible and functions computationally, the nanoassembly cost is high, and the operation environment in vacuum or at low temperature is relatively harsh. Fortunately, electrodes have been discovered as prominent 2D tracks for improving the walking surface area and working condition. Such electrodes enable the modification of biomolecules and can be innovatively combined with DNA walkers to develop electrochemical biosensors, resulting in the transduction and amplification of electrochemical signals to obtain high sensitivity in bioanalysis. Miao and his coworker [65] developed an electrochemical genosensing approach by coupling a bipedal DNA walker with a strand displacement reaction on magnetic nanomaterials (Fig. 2E). The implementation of this walking track, which was supported by the tetrahedral DNA scaffold, improved the molecular recognition efficiency and removed space molecules on the surface of the gold electrode. In this assay, target DNA was enriched by magnetic nanomaterials, inducing strand displacement amplification to generate the trigger for subsequent DNA walking. The application of silver nanoparticles (AgNPs) as signal sources modified on the electrode surface generated sharp stripping peaks due to the highly characteristic solid-state Ag/AgCl reaction. In the presence of the target DNA, Pb^{2+}-dependent DNAzyme cleavage led to the removal of single-stranded DNA segments with amino groups, disabling the adsorption of AgNP signaling molecules. The electrochemical signals were analyzed to quantitatively identify the target DNA. In this nanomachine, the nanomaterials of Fe_3O_4@AuNPs were beneficial for enriching target DNA through magnetic separation in practical application. In addition to target enrichment, two more amplification processes, namely, strand displacement amplification and DNAzyme-induced walking contributed to triply amplification of the sensing signal, enhancing the sensitivity. In addition, in contrast to traditional walker machines, the bipedal DNA walker was driven by proximity-dependent DNA hybridization, leading to high selectivity for the target DNA. Indium tin oxide (ITO) electrodes with fantastic light absorption and favorable electron transference have also been used to establish 2D tracks. Jie's group [66] reported a versatile electrochemiluminescence (ECL) and photoelectrochemical (PEC) biosensor for ultrasensitive glutathione (GSH) detection by combining a DNAzyme-powered amplification strategy with DNA walker-mediated allosteric modulation (Fig. 2F). As CdS:Mn-SA signal probes were linked to the 2D ITO electrode, both the ECL and PEC signals were dramatically enhanced for ultrasensitive GSH determination. By combining Mn^{2+}-powered DNAzyme amplification and DNA walker-mediated conformation transformation, this work offered an efficient new strategy for the determination of non-nucleic acid target and presented bright application prospects in human serum samples.

In addition, glass slides have emerged as a favorable 2D planar material for building DNA walker tracks. Zhu et al. [67] designed a 2D DNA walker-based pixel-counting strategy for the sensitive determination of target nucleic acids on glass slide surfaces. With the synergistic amplification of the DNA walker and a digital counting program, the fluorescence spot representing the target on glass slides was analyzed with a low detection limit down to the femtomole level based on this approach.

3.3. Three-dimensional (3D) DNA walker

A class of DNA walkers that travel along 1D tracks or 2D tracks demonstrate advantageous signal transformation and amplification for biosensing systems. In contrast, the 3D DNA walkers that have been found by researchers have superior amplification performance, and the corresponding tracks possess strong DNA enrichment capacities because of the abundant surface area of 3D nanoparticles. The origami technique can therefore be extended to a 3D scale; for instance, a plasmonic system presented by Zhou et al. [68] was used to realize a gold nanorod that implemented progressive nanoscale walking on 3D DNA origami (Fig. 2G).

In addition to 3D origami, gold nanoparticles (AuNPs), as universal 3D materials, have generated tremendous attention upon being used to establish tracks for diverse walking machines. These spherical nucleic acid-based 3D tracks are continuously prepared by functionalizing AuNPs with thiolated DNA via Au—S bonds, providing a higher cargo loading capacity and faster mobility on the spherical surface than possible with 2D tracks. In particular, the DNA components can be sequentially arranged on the surface of AuNPs, and these high local concentrations on the nanoparticle surfaces strengthen the catalytic efficiency and output signal. The pioneering work by the Le laboratory [69] took advantage of AuNPs to introduce a binding-induced DNA nanomachine for the sensitive detection of proteins and nucleic acids. The merits of this scheme can be summarized as follows: i) the 3D tracks provides high loading density to promote the conjugation of DNA components on the well-defined AuNPs to accelerate the walking efficiency; ii) the binding-induced assembly of separate DNA components improved the specificity of target recognition; iii) the DNA walker achieved high sensitivity powered by the enzymatic cleavage of releasing hundreds of fluorescently-labelled oligonucleotides. Accordingly, the Li laboratory [18] also reported an enzyme-powered 3D DNA nanomachine built on a DNA-AuNP track. DNA walking was also confirmed to work based on a well-defined space of a single AuNP co-conjugated with all DNA components. It was advantageous that various components could be integrated on a single nanoparticle to expand the functionality of the nanomachine. Furthermore, Lv et al. [70] presented a photoelectrochemical sensing platform for disease biomarker determination based on 'Z-scheme' double photosystems coupled with 3D DNA walkers (Fig. 2H). The AuNPs not only functioned as building blocks for the DNA walking track but also acted as electron mediators to facilitate electron transfer between the two photosystems containing CdS quantum dots (QDs) and $BiVO_4$ materials. The target-triggered DNA walker induced the progressive assembly of numerous CdS QDs on the surface of AuNP@$BiVO_4$, resulting in the formation of 'Z-scheme' photosystems that remarkably amplified the photocurrent signal. The all-solid-state artificial 'Z-scheme' system could effectively impede electron-hole recombination to increase photocurrent density. This DNA walker-based photoelectrochemical strategy with a detection limit of 1.5 pg mL^{-1} could screen small molecules by altering the sequence of the aptamer and thus expand the horizons of in vitro diagnostic applications.

Magnetic nanoparticles with high loading capacity are also used for constructing 3D tracks for DNA walkers. Xu et al. [49] developed an original fluorescence scheme for telomerase activity detection based on a 3D DNA walker that was amplified by a fluorescence resonance energy-transfer (FRET) system employing DNA-

functionalized magnetic beads (MBs) as the track (Fig. 2I). The effective DNA concentrations and experimental efficiencies were improved as nucleic acids were immobilized on the high-density surface of the MBs, thereby promoting progressive walking along the MBs. The magnetic separation of DNA-functionalized MBs also induced a low background signal for the 3D DNA walker. Due to the dual-amplification strategies within the DNA walker and MnO_2 nanosheet-upconversion nanoparticle FRET system, a highly sensitive detection method was realized with a detection limit of 23 HeLa cells (based on the telomerase extracted from HeLa cells).

Moreover, an artificial DNA probe, reported by Tan's group [71], was constructed to monitor molecular encounters via walking locomotion through a strand-displacement reaction. This study of a DNA walker, using live cell membranes as a track, verified the occurrence of rapid encounters within the same lipid domains.

4. DNA walker machines coupled with signal amplification strategies

Abundant signal amplification strategies, including catalytic hairpin assembly [72,73], roll circle amplification [74–77], hybridization chain reaction [48,78–80], nanomaterial-based amplification methods [81–92] and so on, have been uncovered that amplify biorecognition signals to obtain excellent detection sensitivity in biosensors. Remarkably, the DNA walker machine, a famous fourth-generation biosensor, is also regarded as an intelligent amplifier for analytical applications; the sensing signal can be effectively amplified through walking locomotion, powered by driving forces, moving progressively and autonomously along engineered tracks. To enhance biosensor sensitivity, selectivity and specificity, researchers have reported numerous biosensing approaches based on the organic coupling of DNA walkers with diverse amplification tactics. We review the combined techniques and sort them based on the different amplification strategies to which DNA walkers are coupled. Relevant, insightful discussions are also put forth in this section. Table 1 lists the techniques coupling DNA walker machines with diverse types of signal amplification strategies.

4.1. DNA walkers coupled with enzyme-free amplification strategies

Enzyme-free amplification strategies include a variety of widespread approaches for amplifying the sensing signals in bioanalysis; common examples include catalytic hairpin assembly, hybridization chain reaction, and entropy-driven amplification. Given the amplified capabilities of enzyme-free amplification methods and DNA walkers, these two methods have been innovatively combined to construct DNA nanomachines with excellent performance properties.

Catalytic hairpin assembly (CHA), a nonenzymatic isothermal amplification reaction, is activated by a specific single-stranded initiator to catalyze the self-assembly of two customized hairpins, and abundant stable duplex signal readouts are yielded for the amplified detection of target molecules. Due to the high signal-to-noise ratio and remarkable catalytic amplification effects of the CHA recycling reaction, it has been successfully combined with a DNA walker machine for protein or nucleic acid determination. Xiong et al. [93] developed a 3D-bipedal DNA walker coupled with a CHA strategy for the cascade signal amplification determination of thrombin (Fig. 3A). Taking advantage of the high local concentration of track DNA and the wide walking region, while in the presence of thrombin, a 3D DNA walker with two freely walking feet demonstrated a surprising amplification effect on the production of plentiful trigger DNA (T-DNA) for the following CHA reaction. After magnetic separation, the T-DNA initiated the generation of copious H1/H2 complexes in the CHA system that were used to activate the signal reporters and yield amplified signal readouts. Eventually, the ultrasensitive fluorescence biosensor was triple amplified by the synergistic effect of a DNA walker, magnetic enrichment and CHA reaction, giving rise to excellent selectivity, specificity and a detection limit of 23 fM. Compared with traditional unipedal DNA walking machines with the foot DNA and track DNA fixed on same sensing interface, this walker with the two free feet anchored on different sensing interfaces increased the local concentration of track DNA, thereby improving the walking efficiency and expanding the range of the walker. Moreover, the enzyme-free biosensing platform enabled the issues of tedious and costly thermal cycling processes to be avoided and demonstrated promising applications in biomedical research. Yao et al. [94] designed a four-legged DNA walker by embedding CG-C^+ triplex DNA into CHA circuitry (Fig. 3B). In this project, cleavage of the hairpin substrates for the CHA-based walker was not required, so the walkers shared with "spiders" features could therefore yield DNA outputs for further work on a 3D microparticle surface. In addition, walking of the proton-controlled walker powered by toehold exchange reactions could be dynamically caused to start and stop on highly organized DNA tracks. Thus, the programmable walker exhibited prospective applicability in large nanomachines.

A hybridization chain reaction (HCR) is another familiar enzyme-free amplification technique that enables sensitive nucleic acid detection. HCR also consists of two designed hairpins and a trigger strand. In contrast to CHA, the trigger strand activates the two hairpins to alternately unfold and form long nicked double-helix structures. Although HCR has an intrinsic property of amplifying sensing signals, the method may encounter problems including high background noise and cumbersome labelling processes, decreasing its detection accuracy in biosensing. To

Table 1
Comparison of DNA walker machines coupled with signal amplification strategies.

Design principles of DNA walker	Signal amplification strategies	Analytes	Linear range	LOD	Ref.
DNAzyme reaction	CHA	Thrombin	0.1–5 × 10^3 pM	23 fM	[93]
Protein enzyme reaction	HCR	miRNA-141	1.0 × 10^{-3}- 1.0 × 10^6 fM	1.1 × 10^{-4} fM	[95]
DNAzyme reaction	HCR	let-7a	10–1.0 × 10^6 fM	7.9 fM	[96]
Strand displacement reaction	EDA	miRNA-21	20–10 × 10^3 pM	8 pM	[101]
DNAzyme reaction	EDA	Target DNA	0.3–500 fM	0.29 fM	[102]
Strand displacement reaction	RCA	HIV	5.0–1.67 × 10^3 fM	1.46 fM	[104]
DNAzyme reaction	RCA	16S rRNA;	10-10^6 fM	10 fM	[105]
		P. aeruginosa	10–1.0 × 10^8 CFU/mL	10 CFU/mL	
Strand displacement reaction	ERA	Carcinoembryonic antigen (CEA)	0.01–100 ng mL^{-1}.	1.2 pg mL^{-1}	[106]
Protein enzyme reaction	MOF nanoparticles	Target DNA	1.0 × 10^{-4}-100 nM	33.6 fM	[114]
DNAzyme reaction	UCNPs	Telomerase	50 to 2000 cells	23 HeLa cells	[49]
Protein enzyme reaction	MOF and UCNPs	CEA	0.1–300 ng mL^{-1}.	0.032 ng mL^{-1}	[107]
DNAzyme reaction	AgNPs	Target DNA	1.0–100 fM	0.22 fM	[65]

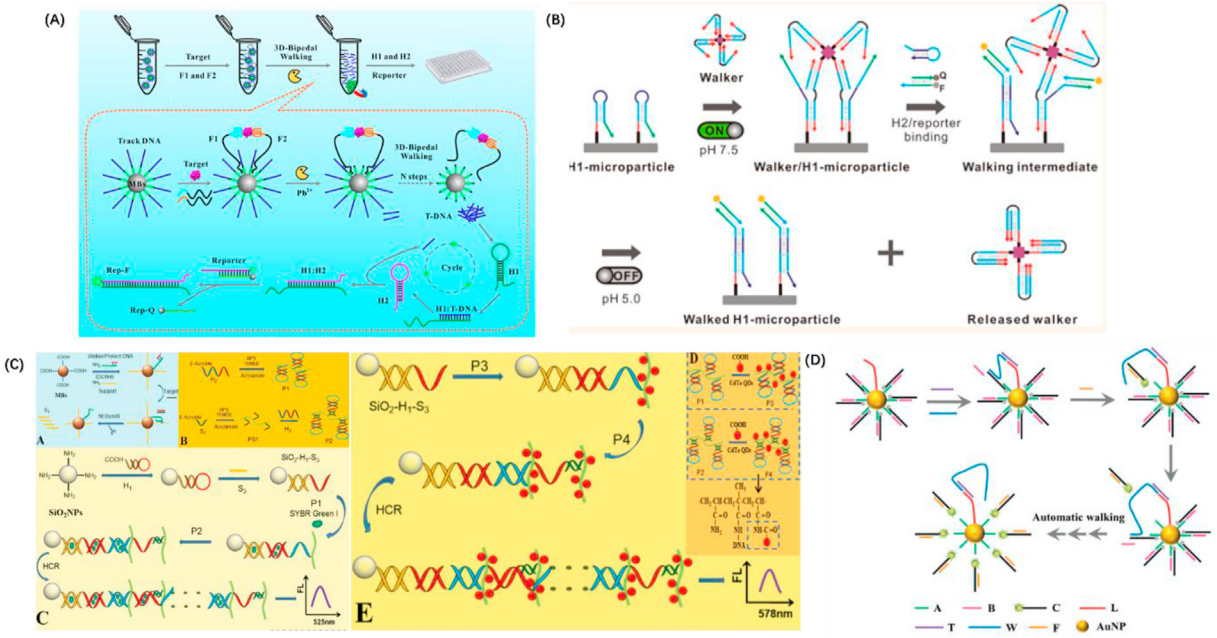


Fig. 3. DNA walker machines coupled with enzyme-free amplification strategies. (A) and (B) catalytic hairpin assemblies [93,94], (C) hybridization chain reaction [95], (D) entropy-driven amplification [101].

overcome these drawbacks, Li et al. [95] developed a versatile DNA hydrogel-based fluorescence platform by combining a 3D DNA walker with an HCR strategy for the ultrasensitive monitoring of miRNA (Fig. 3C). With the introduction of target miRNA into the system, the walking machine was initiated and yielded large amounts of DNA S3 for the subsequent HCR process. Upon linking S3 to H1, P1 and P2 were, in turn, opened to hybridize and assemble a cross-linked DNA hydrogel on SiO_2 microspheres. Ultimately, dye or QD-based fluorescence indicators were imbedded into the hydrogel; thus, the fluorescence signal was significantly multi-amplified by a DNA walker machine and HCR-induced DNA hydrogel, demonstrating an ultralow detection limit and satisfactory precision for miRNA-141 detection in prostate cancer diagnosis. Wang et al. [96] constructed an enzyme-free and label-free cascade amplification platform by coupling a 3D DNA walker with the HCR technique, which dramatically amplified the fluorescence response signal to obtain high sensitivity and admirable specificity towards let-7a. These coupling approaches used a single target to induce continuous walking motion, and thus a mass of trigger DNA was released to initiate the HCR process for amplified fluorescence signals, achieving highly sensitive detection of a single target corresponding to multiple signal probes.

In contrast to CHA and HCR, which are both powered by base-pair formation-induced changes in the negative free energy, the entropy-driven amplification (EDA) reaction discovered by Zhang et al. [97] in 2007 enabled the engineering of a range of rational single-stranded DNAs for the construction of a catalytic circuit through toehold-mediated strand displacement, which played a crucial role in developing highly effective biological approaches. The design of this EDA strategy is simpler and more stable than that based on hairpin assemblies and prevents false-positive signals generated by nonspecific hybridization between metastable hairpin structures generated from CHA or HCR [98–100]. Recently, Liang and teammates [101] customized the EDA strategy into a 3D walker machine for intracellular miRNA imaging. Activated by target miRNA, the walking foot was attached to the surface of AuNPs loaded with high-density DNA substrates (Fig. 3D). This intelligent machine could autonomously and progressively walk on the 3D tracks through EDA-induced strand migration, resulting in a persistent fluorescence signal generated by the continuous release of dye-labelled substrate strands. The superior sensitivity and kinetics of this nanomachine were achieved by the accelerated effective DNA component that was co-anchored onto individual AuNPs through a proximity-induced intramolecular reaction. Moreover, the analytical results of this method also exhibited a high signal-to-noise ratio on account of the unique design of the walking leg for walking motion. Wang et al. [102] reported the development of an electrochemical biosensor that was fabricated by integrating EDA with a DNA walker for cascade-amplified detection of nucleic acids. Biorecognition and EDA reactions could be realized in homogeneous solutions that improved amplification efficiencies. Benefiting from the cascade amplification assay, abundant electroactive probes were released from the gold electrode, giving rise to satisfactory reproducibility and reliability and a low detection limit of 0.29 fM.

4.2. DNA walkers coupled with enzyme-assisted amplification strategies

Although enzyme-free amplification technologies have shown favorable amplification performance, this performance is still lower than that of enzyme-assisted amplification reactions in terms of response efficiency, amplification power and design flexibility. Thus, enzyme-assisted amplification approaches, including Exo III-assisted target recycling amplification [44,75,103] and rolling circle amplification, exhibit faster and more effective analytical performances for low abundance target detection due to the beneficial catalytic activity of nucleases. The incorporation of DNA walkers with enzyme-assisted amplification approaches has been applied to enable ultrasensitive bioanalysis.

Rolling circle amplification (RCA) is frequently utilized to construct a biosensing platform for amplified sensing signals. RCA is an effective isothermal enzymatic amplification method powered by DNA polymerase, producing long single-stranded DNA on

circular Padlock probes using DNA or RNA primers. DNA walkers with negligible background signals and facile operation capabilities have been efficiently integrated with the RCA method for nucleic acid analytes. Zheng et al. [104] developed a DNA nanomachine based on the DNA walker amplification reaction and RCA procedure for human immunodeficiency virus (HIV) biomarker detection (Fig. 4A). HIV nucleic acid was identified as a primer hybridized with Padlock DNA assisted by T4 DNA ligase, and the RCA reaction was driven by phi29 DNA polymerase. The generated long single-stranded DNA derived from RCA was nicked by enzyme Nb. BtsI. The catalysts hybridized with H1 and then H2 could be prompted to displace the catalysts for forming the H1/H2 duplex on the AuNP surface, thereby turning on the fluorescence signals of the 5-carboxyfluorescein (FAM) labelled on H1. As the RCA reaction propelled the DNA walker machine, the evidently amplified fluorescence signal of the target DNA validated the excellent sensitivity and selectivity of the proposed strategy. In summary, the DNA nanomachine powered by the RCA product provided the high hybridization efficiency of the target DNA, and high local effective concentrations of H1 could be accumulated on the AuNP surface to produce an obvious sensing signal due to DNA walker cascade amplification. Zhou et al. [105] also introduced a multipedal DNA walker coupled with an RCA reaction to build a cascade signal amplification platform (Fig. 4B). Once the target 16S rRNA was captured by CP, the RCA reaction was activated to produce repeated sequences that were partially complementary with walker probes (WP). Pb^{2+}-dependent DNAzymes were constructed by hybridizing WP with signal probes and upon the addition of Pb^{2+}, methylene blue (MB)-modified signal probes were cleaved to release MB from the Au electrode surface, dramatically reducing the peak current of MB. The proposed cascade amplification approach displayed an outstanding detection limit of 10 CFU/mL. The notable merits of this integrated technology were as follows: (i) supplying large number of binding sites due to the long RCA products that bind to walking DNA legs and (ii) forming a multipedal DNA walker driven by multiple DNAzymes to accelerate walking efficiency. This protocol provided the desirable amplification ability for ultrasensitive *Pseudomonas aeruginosa* detection.

By means of template-dependent extension procedures, the RCA reaction strongly facilitates biosensor signal transduction and amplification. However, the preparation and purification steps for circular templates are tedious and complicated. Exo III-assisted target recycling amplification (ERA) is a delicate alternative method for constructing sensitive biosensors without the application of customized templates. Once exonuclease digests the recessed 3′ terminus of mononucleotides or the blunt double-stranded DNA, the ERA approach promotes target recycling accompanied by the generation of substantial repeated units. The

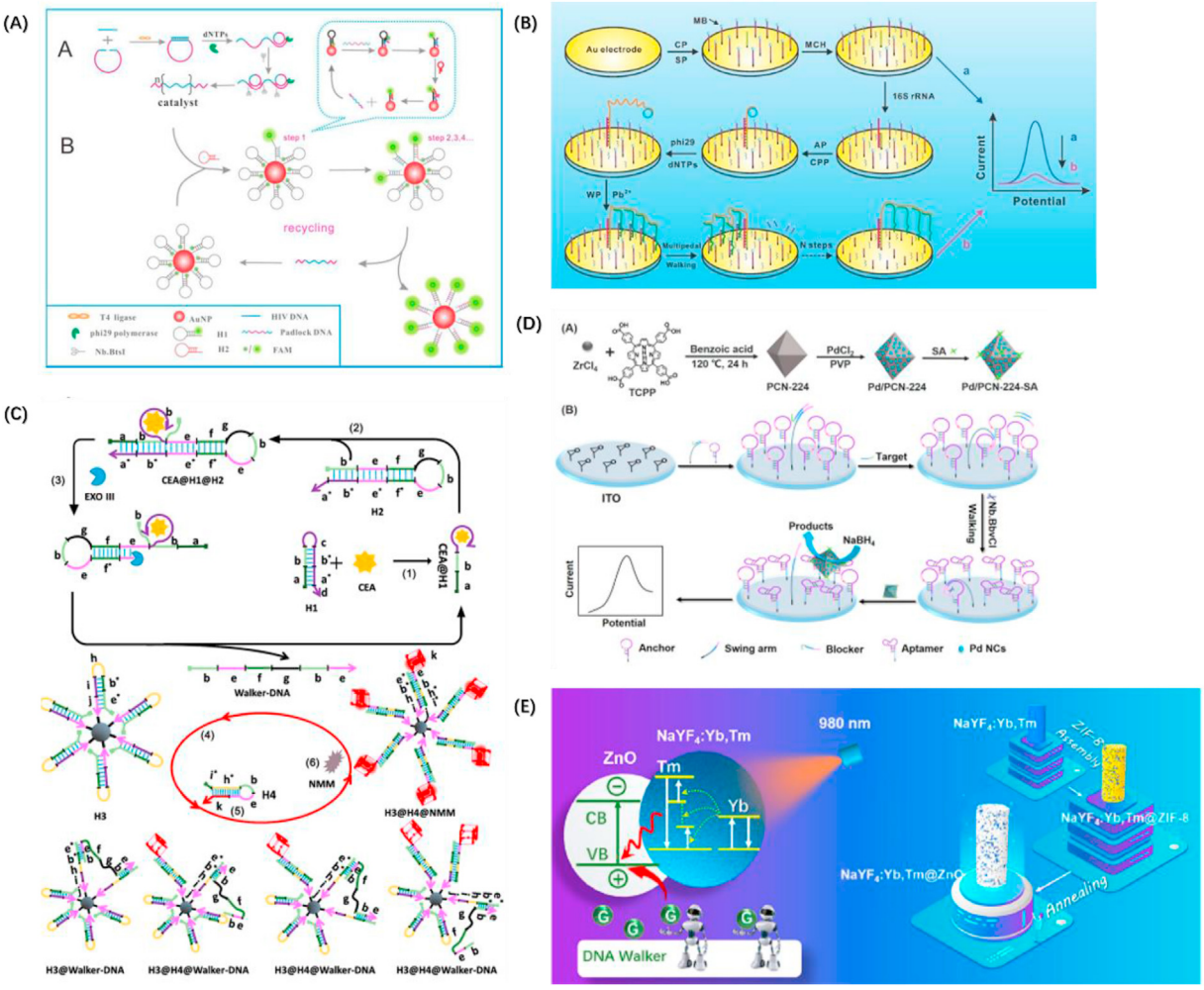


Fig. 4. DNA walker machines coupled with enzyme-assisted amplification strategies and nanoparticles. (A) and (B) Rolling circle amplifications [104,105], (C) Exo III-assisted target recycling amplification [106], (D) metal-organic frameworks [114] and (E) upconversion nanoparticles [107].

cascade amplification protocol for merging the ERA with a DNA walker has been innovatively explored for the construction of sensitive and specific sensing platforms. As a representative example, Wang's group [106] reported a smart DNA machine for the label-free determination of carcinoembryonic antigens by incorporating ERA with a DNA walker (Fig. 4C). Based on specific CEA-aptamer recognition, the machine was designed following an ERA strategy to yield copious single-stranded products as walker DNA. Autonomous walking was initiated by the walker DNA on the surfaces of silica microspheres, and H3 hybridized with H4 to form G-quadruplex structures, resulting in the production of a prominent fluorescence signal aided by N-methylmesoporphyrin IX. Given the two amplification stages of ERA and the DNA walker, this machine displayed a low detection limit of 1.2 pg mL^{-1} during the isothermal amplification process, in which the complicated thermal cycling module was discarded. This design exploits both the catalytic amplification ability of Exo-III and the efficient cargo loading capacity of the DNA walker to allow hundreds of signal probes to respond to a single target, thereby achieving high sensitivity and high specificity.

4.3. DNA walker amplification strategies coupled with nanoparticles

In addition to nucleic acid-related isothermal signal amplification strategies, nanoparticles have unique advantages, including simple preparation methods, easily controllable sizes and facile surface modifications, that meet the requirements for designing efficient signal amplification strategies. Nanomaterials can not only be functionalized to accelerate electron transfer on biosensing interfaces but can also be utilized as catalysts by mimicking enzymes and signal transmitters to amplify sensing signals and label recognition molecules. Common nanoparticles include metal-organic frameworks [107–109], upconversion nanoparticles [33,49,110], silver nanoparticle-based magnification approaches [111–113] and so on. Based on the outstanding advantages of nanoparticles and DNA walkers, innovative biosensors have been developed through the incorporation of DNA walkers with nanoparticles, enabling low background noise, high sensitivity and high accuracy.

Metal-organic frameworks (MOFs) with high surface areas and chemical stabilities have been widely employed in various biosensors. The catalytic performance and the enlargement of the reaction range have been improved due to the permanent porosity and high tenability of MOFs to confine guest species. In particular, the integration of the respective MOF and metal nanoparticle advantages enables the implantation of signal transduction and amplification in biosensing platforms. Lei's group [114] developed a tandem signal amplification tactic based on the use of a DNA-walker-induced conformation switch to fix Pd/MOF (Pd/PCN-224) tags for ultrasensitive identification of DNA (Fig. 4D). The Pd/PCN-224 composite was synthesized by reducing Pd nanocrystals on PCN-224, and this composite not only demonstrated the hydrogen adsorption/desorption property of PdNPs but also possessed the short electron-transport distance of PCN-224, demonstrating brilliant electrocatalytic activity towards $NaBH_4$ oxidation. In the presence of target DNA, the released swing arms were activated by cleavage enzymes to drive DNA walker movement and induce structural conversion from a hairpin to a stable streptavidin (SA) aptamer. Then, the Pd/PCN-224-SA composites were immobilized on the surface via SA-aptamer recognition to produce a sufficient electrochemical signal. This biosensor based on the tandem signal amplification of MOF and DNA walkers displayed a working scope that encompassed 6 orders of magnitude, a detection limit on the femtomolar scale and a single-mismatch differentiation capacity.

Upconversion nanoparticles (UCNPs), a class of rare earth-doped nanoparticles with a high signal-to-noise ratio and outstanding luminescence, have been employed in biosensing and medical imaging applications. Our team [49] established a manganese dioxide nanosheet-upconversion nanoparticle (MnO_2–UCNP) system as a FRET platform, displaying little background interference and low autofluorescence. The sensitive amplification strategy for the telomerase activity assay was designed by coupling a 3D DNA walker with a MnO_2–UCNP-based FRET system. Once the trigger strands were released by the DNA walking machines, they interacted with the complementary strands modified on UCNPs to break the FRET system, and the fluorescence of UCNPs was recovered, implementing the quantitative measurement of telomerase activity. Moreover, the MOFs grown on UCNPs could enhance photoelectric properties upon NIR light excitation. Lv et al. [107] fabricated a zeolitic imidazolate framework (ZIF)-8-assisted UCNPs@ZnO composite photosensitive material for photoelectrochemical (PEC) biosensing, which exhibited favorable conductivity and stability as well as a slow electron-hole recombination rate (Fig. 4E). The synthesized $NaYF_4$:Yb,Tm@ZnO composite converted near-infrared (NIR) excitation into UV emission to yield a photocurrent signal. Upon adding the target CEA, the 3D DNA walker, which possessed a strong enrichment ability, was driven by a burnt-bridge mechanism to release guanine bases, which enhanced the PEC responses and strengthened the sensitivity of the sensing platform. Therefore, a highly effective signal amplification mode can be accomplished depending on the integration of UCNPs@MOF materials with 3D DNA walkers.

In addition, sliver nanoparticles (AgNPs) featuring sharp silver stripping peaks have attracted much attention for use in electrochemical sensing assays. Chai et al. [65] exploited a bipedal DNA walker-based electrochemical gene sensor by making use of the AgNP signal sources. In the absence of target DNA, the amino groups modified on top of tetrahedral DNA could interact with AgNPs to generate an intense linear sweep voltammetry peak. With the production of probe B, as triggered by the target, DNA walking was activated to cleave the DNA segments. The amino groups were kept away from the surface of the electrode, which disabled the localization of AgNPs; thus, the silver stripping peak current decreased significantly. By studying the electrochemical signals, the target DNA was quantitatively analyzed based on a DNA walker machine with a low detection limit of 0.22 fM.

5. Conclusions and perspectives

The development of DNA walker machines has undergone phenomenal progress for the past decade in both quantity and quality. Diverse biosensors with precise programmability and addressability based on DNA walkers have exhibited comprehensive application capabilities in clinical diagnosis, targeted drug delivery and ultrahigh-density data storage. The innovative incorporation of DNA walkers with different amplification strategies has been attributed to the excellent properties of high motility, sensitivity and accuracy for the quantitative detection of biomolecules in vitro or in living cells. However, restricted by some artificial design deficiencies in DNA walkers, the operation efficiency is far lower than that of natural molecular machines, and the applications of this technology in living areas still encompass only a small fraction of the possibilities. Therefore, DNA walkers face some challenges that remain to be overcome.

First, the walking efficiency of DNA walkers must be improved in nanosystems. Enhancing the concentration of substrate strands is conducive to advancing walking efficiency, whereas walking strand derailment may occur due to the inappropriate distance and uniformity of substrate DNA. In addition, nonrigid single strands are

inclined to attach to the surface of nanoparticles constructed for walking tracks, impeding walking movement. Researchers have discovered rotating or rolling machines and favorable nanostructures [115,116] that have been used to overcome the derailment problem and accelerate the walking speed when the running mode changed from step-by-step to high-speed rolling. Accordingly, we have seen that a single target often activates the forward motion of one walking strand. There is no doubt that if a single target can be recycled to initiate multiple walking strands, the efficiency will massively improve.

Second, hyphenated techniques, combined DNA walkers with a variety of signal amplification strategies, have made outstanding achievements in the sensitivity and specificity of biosensors, but some issues remain to be solved. The key issues are as follows: how to decrease the number of operation steps, how to shorten the response time of the sensing system, how to decrease the false positive signal caused by non-specific adsorption, and so on. The design of nanomachines can be simplified to have more integrated molecular components for generating faster reaction kinetics, ensuring the high operating efficiency of DNA walkers. In addition, by changing or screening aptamer sequences, multi-target simultaneous detection methods can be constructed to enhance the specificity of detection systems.

Third, the analysis of for actual samples by biosensing systems based on DNA walkers is more complicated than that performed using other DNA machines. For example, high concentrations of serum proteins may generate a protein corona that masks the dynamic interactions of DNA walking. In addition, characterization approaches, such as high-resolution atomic force microscopy and transmission electron microscopy, are expensive and limit the extensive application of complex systems. Real-time monitoring is desirable, and novel easy-to-observe characterization may be useful for realizing accurate visualization methods. Furthermore, molecular simulation will be a vital tool for the study of the experimental parameters that influence DNA walker efficiency, sensitivity and specificity.

Fourth, researchers have focused on employing DNA walkers for the detection of a series of specific target molecules. It is urgent to expand this application scope to other targets, such as pathogens and notable intracellular substances. In particular, aptamers, as excellent recognition probes, can be integrated with DNA walkers to detect highly sensitive nucleic acids, mycotoxins and other small molecules. For intracellular analysis and in vivo detection, more endeavors based on DNA walkers should be made in the future. The establishment of highly integrated DNA molecular machines can enable the assembly of as many necessary components in the same stable nanosystem as possible, followed by integral transport to the targeted location in living cells, boosting the controllability of each component distribution at the targeted site and advancing the performance efficiencies of molecular machines. In addition to the aforementioned applications coupled with signal amplification strategies, DNA walker machines are also expected to be combined with point-of-care tests, e.g., using commercial blood glucometers, laptops or smartphones.

In summary, the future directions of DNA walker development can be summarized as follows: (i) to further excavate the characteristics of various nanomaterials by developing develop diverse sensing platforms based on multi-dimensional tracks for clinical diagnosis, environmental monitoring and food safety analysis; (ii) to create a more efficient and simpler walking mode, e.g., to simplify the design of nanomachine, which can improve the operating efficiency of DNA walkers; and (iii) to build a miniaturized, intelligent and integrated DNA walker by combining portable detection devices that can quickly read out the sensing signals and analyze the detection results. In brief, to appreciate the universality and practicability of DNA walker machines in biological analysis, researchers still have a long explorative journey ahead to realize these substantial goals.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

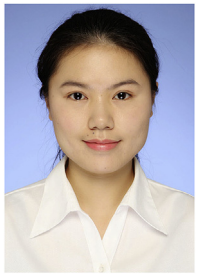
This work was supported by the National Natural Science Foundation of China (201874022 & 21675029), the Natural Science Foundation of Fujian Province (2020J05182), the Nature Science Foundation of Fujian Education Department (JT180322), the Open Project Program of Key Laboratory for Analytical Science of Food Safety and Biology, Ministry of Education (FS2012) and the-Foundation in Fujian University of Technology (GY-Z18042).

References

[1] Y. Hu, C.M. Niemeyer, From DNA nanotechnology to material systems engineering, Adv. Mater. 31 (2019) 1806294.
[2] M. Madsen, K.V. Gothelf, Chemistries for DNA nanotechnology, Chem. Rev. 119 (2019) 6384–6458.
[3] S. Nummelin, J. Kommeri, M.A. Kostiainen, V. Linko, DNA nanotechnology: evolution of structural DNA nanotechnology (Adv. Mater. 24/2018), Adv. Mater. 30 (2018) 1870175.
[4] N.C. Seeman, H.F. Sleiman, DNA nanotechnology, Nat. Rev. Mater. 3 (2017) 17068.
[5] W. Wang, S. Yu, S. Huang, S. Bi, H. Han, J.-R. Zhang, Y. Lu, J.-J. Zhu, Bioapplications of DNA nanotechnology at the solid-liquid interface, Chem. Soc. Rev. 48 (2019) 4892–4920.
[6] A. Ebrahimi, H. Ravan, S. Khajouei, DNA nanotechnology and bioassay development, Trends Anal. Chem. 114 (2019) 126–142.
[7] M. Xiao, W. Lai, F. Wang, L. Li, C. Fan, H. Pei, Programming drug delivery kinetics for active burst release with DNA toehold switches, J. Am. Chem. Soc. 141 (2019) 20354–20364.
[8] T. Patino, A. Porchetta, A. Jannasch, A. Lladó, T. Stumpp, E. Schäffer, F. Ricci, S. Sánchez, Self-sensing enzyme-powered micromotors equipped with pH-responsive DNA nanoswitches, Nano Lett. 19 (2019) 3440–3447.
[9] S.G. Harroun, C. Prévost-Tremblay, D. Lauzon, A. Desrosiers, X. Wang, L. Pedro, A. Vallée-Bélisle, Programmable DNA switches and their applications, Nanoscale 10 (2018) 4607–4641.
[10] J. Tang, C. Yao, Z. Gu, S. Jung, D. Luo, D. Yang, Super-soft and super-elastic DNA robot with magnetically driven navigational locomotion for cell delivery in confined space, Angew. Chem. Int. Ed. 59 (2020) 2490–2495.
[11] S. Nummelin, B. Shen, P. Piskunen, Q. Liu, M.A. Kostiainen, V. Linko, Robotic DNA nanostructures, ACS Synth. Biol. 9 (2020) 1923–1940.
[12] R. Peng, X. Zheng, Y. Lyu, L. Xu, X. Zhang, G. Ke, Q. Liu, C. You, S. Huan, W. Tan, Engineering a 3D DNA-logic gate nanomachine for bispecific recognition and computing on target cell surfaces, J. Am. Chem. Soc. 140 (2018) 9793–9796.
[13] J. Dong, M. Wang, Y. Zhou, C. Zhou, Q. Wang, DNA-based adaptive plasmonic logic gates, Angew. Chem. Int. Ed. 59 (2020) 15038–15042.
[14] J. Li, W. Wang, H. Zhang, Z. Lu, W. Wu, M. Shu, H. Han, Programmable DNA tweezer-actuated SERS probe for the sensitive detection of AFB1, Anal. Chem. 92 (2020) 4900–4907.
[15] L. Yue, S. Wang, A. Cecconello, J.-M. Lehn, I. Willner, Orthogonal operation of constitutional dynamic networks consisting of DNA-tweezer machines, ACS Nano 11 (2017) 12027–12036.
[16] A. Bazrafshan, T.A. Meyer, H. Su, J.M. Brockman, A.T. Blanchard, S. Piranej, Y. Duan, Y. Ke, K. Salaita, Tunable DNA origami motors translocate ballistically over μm distances at nm/s speeds, Angew. Chem. Int. Ed. 59 (2020) 9514–9521.
[17] J. Wang, D.-X. Wang, A.-N. Tang, D.-M. Kong, Highly integrated, biostable, and self-powered DNA motor enabling autonomous operation in living bodies, Anal. Chem. 91 (2019) 5244–5251.
[18] X. Yang, Y. Tang, S.D. Mason, J. Chen, F. Li, Enzyme-powered three-dimensional DNA nanomachine for DNA walking, payload release, and biosensing, ACS Nano 10 (2016) 2324–2330.
[19] S.D. Mason, G.A. Wang, P. Yang, Y. Li, F. Li, Probing and controlling dynamic interactions at biomolecule-nanoparticle interfaces using stochastic DNA walkers, ACS Nano 13 (2019) 8106–8113.
[20] J.-S. Shin, N.A. Pierce, A synthetic DNA walker for molecular transport, J. Am. Chem. Soc. 126 (2004) 10834–10835.
[21] T.-G. Cha, J. Pan, H. Chen, H.N. Robinson, X. Li, C. Mao, J.H. Choi, Design principles of DNA enzyme-based walkers: translocation kinetics and

photoregulation, J. Am. Chem. Soc. 137 (2015) 9429–9437.
[22] F. Chen, J. Xue, M. Bai, J. Qin, Y. Zhao, Programming in situ accelerated DNA walkers in diffusion-limited microenvironments, Chem. Sci. 10 (2019) 3103–3109.
[23] M. Oishi, K. Saito, Simple single-legged DNA walkers at diffusion-limited nanointerfaces of gold nanoparticles driven by a DNA circuit mechanism, ACS Nano 14 (2020) 3477–3489.
[24] J. Valero, M. Famulok, Regeneration of burnt bridges on a DNA catenane walker, Angew. Chem. Int. Ed. 59 (2020) 16366–16370.
[25] M. Xiao, K. Zou, L. Li, L. Wang, Y. Tian, C. Fan, H. Pei, Stochastic DNA walkers in droplets for super-multiplexed bacterial phenotype detection, Angew. Chem. Int. Ed. 58 (2019) 15448–15454.
[26] P. Yang, Y. Li, S.D. Mason, F. Chen, J. Chen, R. Zhou, J. Liu, X. Hou, F. Li, Concentric DNA amplifier that streamlines in-solution biorecognition and on-particle biocatalysis, Anal. Chem. 92 (2020) 3220–3227.
[27] P. Miao, Y. Tang, Gold nanoparticles-based multipedal DNA walker for ratiometric detection of circulating tumor cell, Anal. Chem. 91 (2019) 15187–15192.
[28] S.D. Mason, Y. Tang, Y. Li, X. Xie, F. Li, Emerging bioanalytical applications of DNA walkers, Trends Anal. Chem. 107 (2018) 212–221.
[29] J. Chen, Z. Luo, C. Sun, Z. Huang, C. Zhou, S. Yin, Y. Duan, Y. Li, Research progress of DNA walker and its recent applications in biosensor, Trends Anal. Chem. 120 (2019) 115626.
[30] J. Pan, F. Li, T.-G. Cha, H. Chen, J.H. Choi, Recent progress on DNA based walkers, Curr. Opin. Biotechnol. 34 (2015) 56–64.
[31] Y. Xing, B. Liu, J. Chao, L. Wang, DNA-based nanoscale walking devices and their applications, RSC Adv. 7 (2017) 47425–47434.
[32] M. Xu, Y. He, Z. Gao, G. Chen, D. Tang, Isothermal cycling and cascade signal amplification strategy for ultrasensitive colorimetric detection of nucleic acids, Microchimica Acta 182 (2015) 449–454.
[33] Z.L. Qiu, J. Shu, D.P. Tang, $NaYF_4$:Yb,Er upconversion nanotransducer with in situ fabrication of Ag_2S for near-infrared light responsive photoelectrochemical biosensor, Anal. Chem. 90 (2018) 12214–12220.
[34] P. Irmisch, T.E. Ouldridge, R. Seidel, Modeling DNA-strand displacement reactions in the presence of base-pair mismatches, J. Am. Chem. Soc. 142 (2020) 11451–11463.
[35] F.C. Simmel, B. Yurke, H.R. Singh, Principles and applications of nucleic acid strand displacement reactions, Chem. Rev. 119 (2019) 6326–6369.
[36] M.-X. Li, C.-H. Xu, N. Zhang, G.-S. Qian, W. Zhao, J.-J. Xu, H.-Y. Chen, Exploration of the kinetics of toehold-mediated strand displacement via plasmon rulers, ACS Nano 12 (2018) 3341–3350.
[37] T.E. Tomov, R. Tsukanov, Y. Glick, Y. Berger, M. Liber, D. Avrahami, D. Gerber, E. Nir, DNA bipedal motor achieves a large number of steps due to operation using microfluidics-based interface, ACS Nano 11 (2017) 4002–4008.
[38] C. Jung, P.B. Allen, A.D. Ellington, A stochastic DNA walker that traverses a microparticle surface, Nat. Nanotechnol. 11 (2016) 157–163.
[39] Z. Zhou, Y.S. Sohn, R. Nechushtai, I. Willner, DNA tetrahedra modules as versatile optical sensing platforms for multiplexed analysis of miRNAs, Endonucleases, and Aptamer–Ligand Complexes, ACS Nano 14 (2020) 9021–9031.
[40] C. Wang, D. Zhang, Y. Tang, W. Wei, Y. Liu, S. Liu, Label-free imaging of flap endonuclease 1 in living cells by assembling original and multifunctional nanoprobe, ACS Applied Bio Materials 3 (2020) 4573–4580.
[41] Z. Wang, P. Li, L. Cui, Q. Xu, C. Zhang, Construction of a universal and label-free chemiluminescent sensor for accurate quantification of both bacteria and human methyltransferases, Anal. Chem. 92 (2020) 13573–13580.
[42] P. Yin, H. Yan, X.G. Daniell, A.J. Turberfield, J.H. Reif, A unidirectional DNA walker that moves autonomously along a track, Angew. Chem. Int. Ed. 43 (2004) 4906–4911.
[43] J. Bath, S.J. Green, A.J. Turberfield, A Free-running DNA motor powered by a nicking enzyme, Angew. Chem. Int. Ed. 44 (2005) 4358–4361.
[44] M.D. Xu, Z.Q. Gao, Q.H. Wei, G.N. Chen, D.P. Tang, Label-free hairpin DNA-scaffolded silver nanoclusters for fluorescent detection of Hg^{2+} using exonuclease III-assisted target recycling amplification, Biosens. Bioelectron. 79 (2016) 411–415.
[45] K.Y. Zhang, S.Z. Lv, D.P. Tang, Novel 3D printed device for dual-signaling ratiometric photoelectrochemical readout of biomarker using lambda-exonuclease-assisted recycling amplification, Anal. Chem. 91 (2019) 10049–10055.
[46] S. Lv, K.Y. Zhang, Z.Z. Lin, D.P. Tang, Novel photoelectrochemical immunosensor for disease-related protein assisted by hemin/G-quadruplex-based DNAzyme on gold nanoparticles to enhance cathodic photocurrent on p-$CuBi_2O_4$ semiconductor, Biosens. Bioelectron. 96 (2017) 317–323.
[47] X. Qu, D. Zhu, G. Yao, S. Su, J. Chao, H. Liu, X. Zuo, L. Wang, J. Shi, L. Wang, W. Huang, H. Pei, C. Fan, An exonuclease III-powered, on-particle stochastic DNA walker, Angew. Chem. Int. Ed. 56 (2017) 1855–1858.
[48] K.Y. Zhang, S.Z. Lv, Z.Z. Lin, D.P. Tang, CdS:Mn quantum dot-functionalized g-C_3N_4 nanohybrids as signal-generation tags for photoelectrochemical immunoassay of prostate specific antigen coupling DNAzyme concatamer with enzymatic biocatalytic precipitation, Biosens. Bioelectron. 95 (2017) 34–40.
[49] M. Xu, J. Zhuang, X. Jiang, X. Liu, D. Tang, A three-dimensional DNA walker amplified FRET sensor for detection of telomerase activity based on the MnO2 nanosheet-upconversion nanoparticle sensing platform, Chem. Commun. 55 (2019) 9857–9860.
[50] T. Nakama, Y. Takezawa, D. Sasaki, M. Shionoya, Allosteric regulation of DNAzyme activities through intrastrand transformation induced by Cu(II)-mediated artificial base pairing, J. Am. Chem. Soc. 142 (2020) 10153–10162.
[51] S. Lilienthal, G.-F. Luo, S. Wang, L. Yue, A. Fischer, A. Ehrlich, Y. Nahmias, I. Willner, Constitutional dynamic networks-guided synthesis of programmed "genes", transcription of mRNAs, and translation of proteins, J. Am. Chem. Soc. 142 (2020) 21460–21468.
[52] H. Peng, X.F. Li, H. Zhang, X.C. Le, A microRNA-initiated DNAzyme motor operating in living cells, Nat. Commun. 8 (2017) 14378.
[53] Y.-L. Liu, E.P. Perillo, P. Ang, M. Kim, D.T. Nguyen, K. Blocher, Y.-A. Chen, C. Liu, A.M. Hassan, H.T. Vu, Y.-I. Chen, A.K. Dunn, H.-C. Yeh, Three-dimensional two-color dual-particle tracking microscope for monitoring DNA conformational changes and nanoparticle landings on live cells, ACS Nano 14 (2020) 7927–7939.
[54] J.J. King, K.L. Irving, C.W. Evans, R.V. Chikhale, R. Becker, C.J. Morris, C.D. Peña Martinez, P. Schofield, D. Christ, L.H. Hurley, Z.A.E. Waller, K.S. Iyer, N.M. Smith, DNA G-quadruplex and i-motif structure formation is interdependent in human cells, J. Am. Chem. Soc. 142 (2020) 20600–20604.
[55] M. You, Y. Chen, X. Zhang, H. Liu, R. Wang, K. Wang, K.R. Williams, W. Tan, An autonomous and controllable light-driven DNA walking device, Angew. Chem. Int. Ed. 51 (2012) 2457–2460.
[56] Y. Yang, M.A. Goetzfried, K. Hidaka, M. You, W. Tan, H. Sugiyama, M. Endo, Direct visualization of walking motions of photocontrolled nanomachine on the DNA nanostructure, Nano Lett. 15 (2015) 6672–6676.
[57] Z.G. Wang, J. Elbaz, I. Willner, DNA machines: bipedal walker and stepper, Nano Lett. 11 (2011) 304–309.
[58] M. Skugor, J. Valero, K. Murayama, M. Centola, H. Asanuma, M. Famulok, Orthogonally photocontrolled non-autonomous DNA walker, Angew. Chem. Int. Ed. 58 (2019) 6948–6951.
[59] M. Xiao, X. Wang, L. Li, H. Pei, Stochastic RNA walkers for intracellular microRNA imaging, Anal. Chem. 91 (2019) 11253–11258.
[60] D. Wang, C. Vietz, T. Schroder, G. Acuna, B. Lalkens, P. Tinnefeld, A DNA walker as a fluorescence signal amplifier, Nano Lett. 17 (2017) 5368–5374.
[61] J.F. Berengut, C.K. Wong, J.C. Berengut, J.P.K. Doye, T.E. Ouldridge, L.K. Lee, Self-limiting polymerization of DNA origami subunits with strain accumulation, ACS Nano (2020) 17428–17441.
[62] A. Czogalla, D.J. Kauert, R. Seidel, P. Schwille, E.P. Petrov, DNA origami nanoneedles on freestanding lipid membranes as a tool to observe isotropic-nematic transition in two dimensions, Nano Lett. 15 (2015) 649–655.
[63] P. Carnevali, G. Tóth, G. Toubassi, S.N. Meshkat, Fast protein structure prediction using Monte Carlo simulations with modal moves, J. Am. Chem. Soc. 125 (2003) 14244–14245.
[64] J. Chao, J. Wang, F. Wang, X. Ouyang, E. Kopperger, H. Liu, Q. Li, J. Shi, L. Wang, J. Hu, L. Wang, W. Huang, F.C. Simmel, C. Fan, Solving mazes with single-molecule DNA navigators, Nat. Mater. 18 (2019) 273–279.
[65] H. Chai, P. Miao, Bipedal DNA walker based electrochemical genosensing strategy, Anal. Chem. 91 (2019) 4953–4957.
[66] J. Ge, Y. Zhao, X. Gao, H. Li, G. Jie, Versatile electrochemiluminescence and photoelectrochemical detection of glutathione using Mn(2+) substitute target by DNA-walker-induced allosteric switch and signal amplification, Anal. Chem. 91 (2019) 14117–14124.
[67] L. Zhu, Q. Liu, B. Yang, H. Ju, J. Lei, Pixel counting of fluorescence spots triggered by DNA walkers for ultrasensitive quantification of nucleic acid, Anal. Chem. 90 (2018) 6357–6361.
[68] C. Zhou, X. Duan, N. Liu, A plasmonic nanorod that walks on DNA origami, Nat. Commun. 6 (2015) 8102.
[69] H. Zhang, M. Lai, A. Zuehlke, H. Peng, X.-F. Li, X.C. Le, Binding-induced DNA nanomachines triggered by proteins and nucleic acids, Angew. Chem. Int. Ed. 54 (2015) 14326–14330.
[70] S. Lv, K. Zhang, Y. Zeng, D. Tang, Double photosystems-based 'Z-Scheme' photoelectrochemical sensing mode for ultrasensitive detection of disease biomarker accompanying three-dimensional DNA walker, Anal. Chem. 90 (2018) 7086–7093.
[71] M. You, Y. Lyu, D. Han, L. Qiu, Q. Liu, T. Chen, C. Sam Wu, L. Peng, L. Zhang, G. Bao, W. Tan, DNA probes for monitoring dynamic and transient molecular encounters on live cell membranes, Nat. Nanotechnol. 12 (2017) 453–459.
[72] Q. Zhou, D.P. Tang, Catalytic hairpin assembly-mediated surface charge density on the electrode for sensitive potentiometric detection of microRNA-21 in IgA-nephropathy, Biochem. Eng. J. 140 (2018) 9–16.
[73] L. Zhu, M. Zhang, J. Ye, M. Yan, Q. Zhu, J. Huang, X. Yang, Ratiometric electrochemiluminescent/electrochemical strategy for sensitive detection of microRNA based on duplex-specific nuclease and multilayer circuit of catalytic hairpin assembly, Anal. Chem. 92 (2020) 8614–8622.
[74] K.Y. Zhang, S.Z. Lv, Z.Z. Lin, M.J. Li, D.P. Tang, Bio-bar-code-based photoelectrochemical immunoassay for sensitive detection of prostate-specific antigen using rolling circle amplification and enzymatic biocatalytic precipitation, Biosens. Bioelectron. 101 (2018) 159–166.
[75] K.Y. Zhang, S.Z. Lv, M.H. Lu, D.P. Tang, Photoelectrochemical biosensing of disease marker on p-type Cu-doped $Zn_{0.3}Cd_{0.7}S$ based on RCA and exonuclease III amplification, Biosens. Bioelectron. 117 (2018) 590–596.
[76] Z.L. Qiu, J. Shu, Y. He, Z.Z. Lin, K.Y. Zhang, S.Z. Lv, D.P. Tang, CdTe/CdSe quantum dot-based fluorescent aptasensor with hemin/G-quadruplex DNzyme for sensitive detection of lysozyme using rolling circle amplification and strand hybridization, Biosens. Bioelectron. 87 (2017) 18–24.
[77] J. Zhuang, D. Tang, W. Lai, M. Xu, D. Tang, Target-induced nano-enzyme

reactor mediated hole-trapping for high-throughput immunoassay based on a split-type photoelectrochemical detection strategy, Anal. Chem. 87 (2015) 9473–9480.
[78] R.J. Zeng, L.J. Zhang, L.S. Su, Z.B. Luo, Q. Zhou, D.P. Tang, Photoelectrochemical bioanalysis of antibiotics on rGO-Bi_2WO_6-Au based on branched hybridization chain reaction, Biosens. Bioelectron. 133 (2019) 100–106.
[79] M.D. Xu, Z.Q. Gao, Q.H. Wei, G.N. Chen, D.P. Tang, Hemin/G-quadruplex-based DNAzyme concatamers for in situ amplified impedimetric sensing of copper(II) ion coupling with DNAzyme-catalyzed precipitation strategy, Biosens. Bioelectron. 74 (2015) 1–7.
[80] Q. Zhou, Y.X. Lin, K.Y. Zhang, M.J. Li, D.P. Tang, Reduced graphene oxide/$BiFeO_3$ nanohybrids-based signal-on photoelectrochemical sensing system for prostate-specific antigen detection coupling with magnetic microfluidic device, Biosens. Bioelectron. 101 (2018) 146–152.
[81] M. Hu, C. Yuan, T. Tian, X. Wang, J. Sun, E. Xiong, X. Zhou, Single-step, salt-aging-free, and thiol-freefreezing construction of AuNP-based bioprobes for advancing CRISPR-based diagnostics, J. Am. Chem. Soc. 142 (2020) 7506–7513.
[82] J. Shu, Z.L. Qiu, D.P. Tang, Self-referenced smartphone imaging for visual screening of H_2S using Cu_xO-polypyrrole conductive aerogel doped with graphene oxide framework, Anal. Chem. 90 (2018) 9691–9694.
[83] R. Ren, G. Cai, Z. Yu, Y. Zeng, D. Tang, Metal-polydopamine framework: an innovative signal-generation tag for colorimetric immunoassay, Anal. Chem. 90 (2018) 11099–11105.
[84] Z. Yu, G. Cai, X. Liu, D. Tang, Platinum nanozyme-triggered pressure-based immunoassay using a three-dimensional polypyrrole foam-based flexible pressure sensor, ACS Appl. Mater. Interfaces 12 (2020) 40133–40140.
[85] G. Cai, Z. Yu, P. Tong, D. Tang, Ti_3C_2 MXene quantum dot-encapsulated liposomes for photothermal immunoassays using a portable near-infrared imaging camera on a smartphone, Nanoscale 11 (2019) 15659–15667.
[86] Y. Lin, Q. Zhou, Y. Lin, D. Tang, R. Niessner, D. Knopp, Enzymatic hydrolysate-induced displacement reaction with multifunctional silica beads doped with horseradish peroxidase-thionine conjugate for ultrasensitive electrochemical immunoassay, Anal. Chem. 87 (2015) 8531–8540.
[87] Z. Gao, M. Xu, L. Hou, G. Chen, D. Tang, Magnetic bead-based reverse colorimetric immunoassay strategy for sensing biomolecules, Anal. Chem. 85 (2013) 6945–6952.
[88] W.Q. Lai, Q.H. Wei, M.D. Xu, J.Y. Zhuang, D.P. Tang, Enzyme-controlled dissolution of MnO_2 nanoflakes with enzyme cascade amplification for colorimetric immunoassay, Biosens. Bioelectron. 89 (2017) 645–651.
[89] L.J. Zhang, Z.B. Luo, L.S. Su, D.P. Tang, A surface plasmon resonance enhanced photoelectrochemical immunoassay based on perovskite metal oxide@gold nanoparticle heterostructures, Analyst 144 (2019) 5717–5723.
[90] L. Huang, Z. Yu, J. Chen, D. Tang, Pressure-based bioassay perceived by a flexible pressure sensor with synergistic enhancement of the photothermal effect, ACS Appl. Bio Mater. 3 (2020) 9156–9163.
[91] Z.H. Yu, L.T. Huang, J.L. Chen, Y. Tang, B.Y. Xia, D.P. Tang, Full-spectrum responsive photoelectrochemical immunoassay based on beta-In2S3@carbon dot nanoflowers, Electrochim. Acta 332 (2020) 135473.
[92] J.L. Chen, P. Tong, L.T. Huang, Z.H. Yu, D.P. Tang, Ti_3C_2 MXene nanosheet-based capacitance immunoassay with tyramine-enzyme repeats to detect prostate-specific antigen on interdigitated micro-comb electrode, Electrochim. Acta 319 (2019) 375–381.
[93] E. Xiong, D. Zhen, L. Jiang, X. Zhou, Binding-induced 3D-bipedal DNA walker for cascade signal amplification detection of thrombin combined with catalytic hairpin assembly strategy, Anal. Chem. 91 (2019) 15317–15324.
[94] D. Yao, S. Bhadra, E. Xiong, H. Liang, A.D. Ellington, C. Jung, Dynamic programming of a DNA walker controlled by protons, ACS Nano 14 (2020) 4007–4013.
[95] C. Li, H. Li, J. Ge, G. Jie, Versatile fluorescence detection of microRNA based on novel DNA hydrogel-amplified signal probes coupled with DNA walker amplification, Chem. Commun. 55 (2019) 3919–3922.
[96] R. Wang, L. Wang, X. Xu, W. Jiang, An enzyme-free and label-free fluorescence biosensor for microRNA detection based on cascade amplification of DNAzyme-powered three-dimensional DNA walker and hybridization chain reaction, Sensor. Actuator. B Chem. 268 (2018) 287–292.
[97] D.Y. Zhang, A.J. Turberfield, B. Yurke, E. Winfree, Engineering entropy-driven reactions and networks catalyzed by DNA, Science 318 (2007) 1121–1125.
[98] C. Zhang, Z. Wang, Y. Liu, J. Yang, X. Zhang, Y. Li, L. Pan, Y. Ke, H. Yan, Nicking-assisted reactant recycle to implement entropy-driven DNA circuit, J. Am. Chem. Soc. 141 (2019) 17189–17197.
[99] F. Ma, S.-h. Wei, C.-y. Zhang, Construction of a robust entropy-driven DNA nanomachine for single-molecule detection of rare cancer cells, Anal. Chem. 91 (2019) 7505–7509.
[100] M. Bai, F. Chen, X. Cao, Y. Zhao, J. Xue, X. Yu, C. Fan, Y. Zhao, Intracellular entropy-driven multi-bit DNA computing for tumor progression discrimination, Angew. Chem. Int. Ed. 59 (2020) 13267–13272.
[101] C.P. Liang, P.Q. Ma, H. Liu, X. Guo, B.C. Yin, B.C. Ye, Rational engineering of a dynamic, entropy-driven DNA nanomachine for intracellular microRNA imaging, Angew. Chem. Int. Ed. 56 (2017) 9077–9081.
[102] K. Wang, M. Feng, M.Q. He, F.H. Zhai, Y. Dai, R.H. He, Y.L. Yu, DNA-fueled target recycling-induced two-leg DNA walker for amplified electrochemical detection of nucleic acid, Talanta 188 (2018) 685–690.
[103] Y. Zhou, S. Yu, J. Shang, Y. Chen, Q. Wang, X. Liu, F. Wang, Construction of an exonuclease III-propelled integrated DNAzyme amplifier for highly efficient microRNA detection and intracellular imaging with ultralow background, Anal. Chem. 92 (2020) 15069–15078.
[104] J. Zheng, X. Ji, M. Du, S. Tian, Z. He, Rational construction of a DNA nanomachine for HIV nucleic acid ultrasensitive sensing, Nanoscale 10 (2018) 17206–17211.
[105] H. Zhou, S. Duan, J. Huang, F. He, An ultrasensitive electrochemical biosensor for Pseudomonas aeruginosa assay based on a rolling circle amplification-assisted multipedal DNA walker, Chem. Commun. 56 (2020) 6273–6276.
[106] M.Q. He, K. Wang, W.J. Wang, Y.L. Yu, J.H. Wang, Smart DNA machine for carcinoembryonic antigen detection by exonuclease III-assisted target recycling and DNA walker cascade amplification, Anal. Chem. 89 (2017) 9292–9298.
[107] S. Lv, K. Zhang, L. Zhu, D. Tang, ZIF-8-assisted $NaYF_4$:Yb,Tm@ZnO converter with exonuclease III-powered DNA walker for near-infrared light responsive biosensor, Anal. Chem. 92 (2020) 1470–1476.
[108] S.Z. Lv, K.Y. Zhang, L. Zhu, D.P. Tang, R. Niessner, D. Knopp, H_2-Based electrochemical biosensor with Pd nanowires@ZIF-67 molecular sieve bilayered sensing interface for immunoassay, Anal. Chem. 91 (2019) 12055–12062.
[109] R.J. Zeng, Z.B. Luo, L.J. Zhang, D.P. Tang, Platinum nanozyme-catalyzed gas generation for pressure-based bioassay using polyaniline nanowires-functionalized graphene oxide framework, Anal. Chem. 90 (2018) 12299–12306.
[110] Z.B. Luo, L.J. Zhang, R.J. Zeng, L.S. Su, D.P. Tang, Near-infrared light-excited core-core-shell UCNP@Au@CdS upconversion nanospheres for ultrasensitive photoelectrochemical enzyme immunoassay, Anal. Chem. 90 (2018) 9568–9575.
[111] P. Teengam, W. Siangproh, A. Tuantranont, T. Vilaivan, O. Chailapakul, C.S. Henry, Multiplex paper-based colorimetric DNA sensor using pyrrolidinyl peptide nucleic acid-induced AgNPs aggregation for detecting MERS-CoV, MTB, and HPV oligonucleotides, Anal. Chem. 89 (2017) 5428–5435.
[112] H. Chai, M. Wang, C. Zhang, Y. Tang, P. Miao, Highly sensitive genosensing coupling rolling circle amplification with multiple DNAzyme cores for DNA walking, Bioconjugate Chem. 31 (2020) 764–769.
[113] W. Peng, Y. Qin, W. Li, M. Chen, D. Zhou, H. Li, J. Cui, J. Chang, S. Xie, X. Gong, B. Tang, Nonenzyme cascaded amplification biosensor based on effective aggregation luminescence caused by disintegration of silver nanoparticles, ACS Sens. 5 (2020) 1912–1920.
[114] T. Yan, L. Zhu, H. Ju, J. Lei, DNA-walker-induced allosteric switch for tandem signal amplification with palladium nanoparticles/metal-organic framework tags in electrochemical biosensing, Anal. Chem. 90 (2018) 14493–14499.
[115] N. Wu, K. Wang, Y.-T. Wang, M.-L. Chen, X.-W. Chen, T. Yang, J.-H. Wang, Three-dimensional DNA nanomachine biosensor by integrating DNA walker and rolling machine cascade amplification for ultrasensitive detection of cancer-related gene, Anal. Chem. 92 (2020) 11111–11118.
[116] J. Vyskočil, C.C. Mayorga-Martinez, E. Jablonská, F. Novotný, T. Ruml, M. Pumera, Cancer cells microsurgery via asymmetric bent surface Au/Ag/Ni microrobotic scalpels through a transversal rotating magnetic field, ACS Nano 14 (2020) 8247–8256.



Mingdi Xu received her Ph.D. degree from the college of chemistry, Fuzhou University in 2017. She is currently an associate professor in the college of ecological environment and urban construction, Fujian University of Technology, China. Her research interests focus on nanomaterials-based sensing, fluorescent aptasensors, the development of DNA walker machines and their applications coupled with signal amplification strategies.

Dianping Tang (1972) is a Full Professor for Analytical Chemistry at the Fuzhou University, China. He received the Alexander von Humboldt Fellowship in 2008, and worked Technische Universitat Munchen, Germany, from 2008 to 2009. Importantly, he was selected amongst the 100 Most Influential People in the Analytical Scientist in 2013. Now he is a member within the editorial boards of "Analytical Chemistry" (2016–2018), "Analytica Chimica Acta", "Scientific Reports" and "Microchimica Acta". His research interests mainly include Clinical/Environmental immunoassays, Synthesis and application of advanced functional nanomaterials.