As a result, these translation events are important for information processing with nucleic acids and molecular computing.

SUMMARY

[0006] In one aspect, the present invention refers to a nucleic acid-based molecular computing system, comprising: (i) an input nucleic acid strand comprising a first fragment (A) and a second fragment (B); (ii) a first target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand, wherein the first strand comprises a first fragment (B') and a second fragment (A'), the second strand comprises a first fragment (B) and a second fragment (C) and the first target duplex comprises a duplex region formed by base-pairing between B and B' and two single-stranded regions, A' and C, and wherein A and B of the input strand can bind with A' and B' of the first strand of the first target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a first output duplex; (iii) a second target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand, wherein the first strand comprises a first fragment (C') and a second fragment (B'), the second strand comprises a first fragment (C) and a second fragment (D) and the second target duplex comprises a duplex region formed by base-pairing between C and C' and two single-stranded regions B' and D, wherein B and C of the second strand of the first target duplex can bind with B' and C' of the first strand of the second target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a second output duplex, and wherein the second fragment (B) of the input strand can bind with the single-stranded region B' of the second target duplex under hybridizing conditions; and (iii) a third target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand, wherein the first strand comprises a first fragment (D') and a second fragment (C'), the second strand comprises a first fragment (D) and a second fragment (E) and the third target duplex comprises a duplex region formed by base-pairing between D and D' and two single-stranded regions C' and E, wherein C and D of the second strand of the second target duplex can bind with C' and D' of the first strand of the third target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a third output duplex, and wherein the second fragment (C) of the second strand of the first target duplex can bind with the single-stranded region C' of the third target duplex under hybridizing conditions, wherein the first fragment (B) of the second strand of the first target duplex comprises a first chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (B') of the first strand of the second target duplex to have a decreased hybridization free energy and/or the second fragment (B) of the input strand comprises a second chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (B') of the first strand of the second target duplex to have an increased hybridization free energy, such that the first fragment (B) of the second strand of the first target duplex, as compared to the second fragment (B) of the input strand, binds to the second fragment (B') of the first strand of the second target duplex to form a more stable duplex

region; and wherein the first fragment (C) of the second strand of the second target duplex comprises a third chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (C') of the first strand of the third target duplex to have a decreased hybridization free energy and/or the second fragment (C) of the second strand of the first target duplex comprises a fourth chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (C') of the first strand of the third target duplex to have an increased hybridization free energy, such that the first fragment (C) of the second strand of the second target duplex, as compared to the second fragment (C) of the second strand of the first target duplex, binds to the second fragment (C') of the first strand of the third target duplex to form a more stable duplex region. In accordance with one example, a method is disclosed for improving a nucleic acid-based molecular computing system. The method includes: (A) identifying a computing system comprised of (i) a nucleic acid structure that includes an incompletely base-paired duplex domain, (ii) at least one polynucleotide displacement molecule that can bind with the nucleic acid structure under hybridizing conditions, such that the nucleic acid structure undergoes a transition in energy state due to a branch migration reaction involving the duplex domain, and (iii) a clashing polynucleotide molecule that competes with the polynucleotide displacement molecule for binding the nucleic acid structure under the hybridizing conditions but that cannot produce a branch migration reaction involving the duplex domain; then (B) reconfiguring at least one of the displacement molecule and the nucleic acid structure, respectively, to incorporate a chemical modification relative to a first reference molecule that comprises natural nucleosides and has the same sequence content as the displacement molecule or the nucleic acid structure, as the case may be. The aforementioned the modification causes binding of the displacement molecule and the nucleic acid structure to have a hybridization free energy, differing from that of a first reference binding between the displacement molecule or the nucleic acid structure and the first reference molecule, such that the branch migration reaction is facilitated relative to the first reference binding. After or in place of step (B) is a step (C) of reconfiguring at least one of the clashing molecule and the nucleic acid structure, respectively, to incorporate a chemical modification relative to a second reference molecule that comprises natural nucleosides and has the same sequence content as the clashing molecule or the nucleic acid structure, as the case may be. The modification causes binding of the clashing molecule and the nucleic acid structure to have a hybridization free energy, differing from that of a second reference binding between the clashing molecule or the nucleic acid structure and the second reference molecule, such that binding of the clashing molecule is impeded relative to the second reference binding.

[0007] The disclosure also describes, in another of its examples, a system that includes (A) a nucleic acid structure that comprises an incompletely base-paired duplex domain; (B) at least one polynucleotide displacement molecule to effect binding with the nucleic acid structure under hybridizing conditions, such that the nucleic acid structure undergoes a transition in energy state due to a

branch migration reaction involving the duplex domain; and (C) at least one polynucleotide clashing molecule capable of binding with the nucleic acid structure under hybridizing conditions, such that the nucleic acid structure and the clashing molecule are bound and prevent the binding of the polynucleotide displacement molecule. At least one of the displacement molecule and the nucleic acid structure, respectively, has a chemical modification relative to a reference molecule that comprises natural nucleosides and has the same sequence content as the displacement molecule or the nucleic acid structure, as the case may be. The modification causes the binding to have a hybridization free energy, differing from that of a reference binding between the displacement molecule or the nucleic acid structure and a reference molecule, such that the branch migration reaction is facilitated relative to the reference binding. In addition or in the alternative, at least one of the clashing molecule and the nucleic acid structure, respectively, has a chemical modification relative to a reference molecule that comprises natural nucleosides and has the same sequence content as the displacement molecule or the nucleic acid structure, as the case may be. The modification causes the binding to have a hybridization free energy, differing from that of a reference binding between the displacement molecule or the nucleic acid structure and a reference molecule, such that binding of the clashing molecule is impeded relative to the reference binding.

[0008] In yet another example, a system is disclosed for propagating information. The system includes a first molecule and a second molecule configured to bind with the first molecule. At least one of the first molecule and the second molecule, respectively, has a chemical modification relative to a reference molecule that has the same sequence content as the first molecule or the second molecule, as the case may be. The modification causes the binding to have a free energy different from that of a reference binding between the reference molecule and the first or second molecule, such that at least one of the following is realized in the system: a probability of a productive binding is raised, or a probability of an unproductive binding is reduced.

WHAT IS CLAIMED IS:

1. A nucleic acid-based molecular computing system, comprising:

(i) an input nucleic acid strand comprising a first fragment (A) and a second fragment (B);

(ii) a first target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand,

wherein the first strand comprises a first fragment (B') and a second fragment (A'), the second strand comprises a first fragment (B) and a second fragment (C) and the first target duplex comprises a duplex region formed by base-pairing between B and B' and two single-stranded regions, A' and C, and

wherein A and B of the input strand can bind with A' and B' of the first strand of the first target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a first output duplex;

(iii) a second target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand,

wherein the first strand comprises a first fragment (C') and a second fragment (B'), the second strand comprises a first fragment (C) and a second fragment (D) and the second target duplex comprises a duplex region formed by base-pairing between C and C' and two single-stranded regions B' and D,

wherein B and C of the second strand of the first target duplex can bind with B' and C' of the first strand of the second target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a second output duplex, and

wherein the second fragment (B) of the input strand can bind with the single-stranded region B' of the second target duplex under hybridizing conditions; and

(iii) a third target, incompletely base-paired nucleic acid duplex comprising a first strand and a second strand,

wherein the first strand comprises a first fragment (D') and a second fragment (C'), the second strand comprises a first fragment (D) and a second

fragment (E) and the third target duplex comprises a duplex region formed by base-pairing between D and D' and two single-stranded regions C' and E,

wherein C and D of the second strand of the second target duplex can bind with C' and D' of the first strand of the third target duplex, respectively, under hybridizing conditions to invoke a strand displacement reaction to produce a third output duplex, and

wherein the second fragment (C) of the second strand of the first target duplex can bind with the single-stranded region C' of the third target duplex under hybridizing conditions,

wherein

the first fragment (B) of the second strand of the first target duplex comprises a first chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (B') of the first strand of the second target duplex to have a decreased hybridization free energy and/or

the second fragment (B) of the input strand comprises a second chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (B') of the first strand of the second target duplex to have an increased hybridization free energy,

such that the first fragment (B) of the second strand of the first target duplex, as compared to the second fragment (B) of the input strand, binds to the second fragment (B') of the first strand of the second target duplex to form a more stable duplex region; and

wherein

the first fragment (C) of the second strand of the second target duplex comprises a third chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (C') of the first strand of the third target duplex to have a decreased hybridization free energy and/or

the second fragment (C) of the second strand of the first target duplex comprises a fourth chemical modification, relative to a natural nucleic acid, that causes binding with the second fragment (C') of the first strand of the third target duplex to have an increased hybridization free energy,

such that the first fragment (C) of the second strand of the second target duplex, as compared to the second fragment (C) of the second strand of the first target duplex, binds to the second fragment (C') of the first strand of the third target duplex to form a more stable duplex region.

2. The system of claim 1, wherein the input strand, the first target duplex, and the second target duplex form part of an enzyme-free, nucleic acid logic gate selected from the group consisting of an AND gate, a NOT gate, an OR gate, a NAND gate, a NOR gate, an XOR gate, and an XNOR gate.

3. The system of claim 1, wherein the first, the second, the third, or the fourth chemical modification is selected from the group consisting of (i) replacing the sugar-phosphodiester backbone of nucleotides with a pseudo-peptide backbone, (ii) modifying the sugar moiety of nucleotides, and (iii) substituting an analogue for the nitrogenous base of at least one of nucleotides.

4. The system of claim 3, wherein the first, the second, the third, or the fourth chemical modification comprises replacing the sugar-phosphodiester backbone of said nucleotides with a pseudo-peptide backbone into which a guanidinium functional group is incorporated.

5. The system of claim 4, wherein the first, the second, the third, or the fourth chemical modification comprises introducing a heteroatom at the 2'-position of said sugar moiety.

6. The system of claim 4, wherein the first, the second, the third, or the fourth chemical modification comprises substituting a tricyclic cytosine analogue for the nitrogenous base of at least one of said nucleotides.

7. The system of claim 1, wherein the strand displacement reaction comprises a toe-hold-mediated strand displacement.

8. The system of claim 1, wherein the first chemical modification is the same as the third chemical modification.

9. The system of claim 1, wherein the second chemical modification is the same as the fourth chemical modification.