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

SUMMARY OF THE INVENTION

[0005a] In one aspect, there is provided a method for preparing an improved nucleic acid-based molecular computing system, comprising:

(1) identifying a nucleic acid-based computing system that comprises

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

(ii) a 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 target duplex comprises a duplex region formed by base-pairing between B and B' and two single-stranded regions, A' and C, and

wherein the input strand can bind with the first strand of the target duplex under hybridizing conditions to invoke a strand displacement reaction to produce an output duplex formed between the input strand (A-B) and the first strand of the target duplex (B'-A'),

and

(iii) a clashing, 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 clashing duplex comprises a duplex region formed by base-pairing between C and C' and two single-stranded regions B' and D,

wherein the second strand of the target duplex can bind with the first strand of the clashing duplex under hybridizing conditions to invoke a strand displacement reaction to produce an output duplex formed between the second strand of the target duplex (B-C) and the first strand of the clashing duplex (C'-B'), and

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

and then

(2) synthesizing, in an aqueous solution, a variant of said nucleic acid-based molecular computing system that differs from the latter by

(i) an incorporation into the first fragment (B) of the second strand of the target duplex a first chemical modification that causes binding with the second fragment (B') of the first strand of the clashing duplex to have a decreased hybridization free energy, and/or

(ii) an incorporation into the second fragment (B) of the input strand a second chemical modification that causes binding with the second fragment (B') of the first strand of the clashing duplex to have an increased hybridization free energy,

such that the first fragment (B) of the second strand of the 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 clashing duplex to form a more stable duplex region,

whereby the variant is improved over the nucleic acid-based molecular computing system in terms of a reduced incidence of hybridization between the input strand and the clashing duplex.

[0006] Also disclosed is ~~In accordance with one aspect of the present invention,~~ a method ~~is provided~~ 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] Also disclosed is~~The invention also provides, in another of its aspects,~~ 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] Also disclosed is~~In yet another aspect,~~ a system ~~is provided~~ 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 method for improving a nucleic acid-based molecular computing system, comprising

(A) identifying a computing system comprised of (i) a nucleic acid structure that comprises an incompletely base-paired duplex domain, (ii) at least one polynucleotide displacement molecule that can bind with said nucleic acid structure under hybridizing conditions, such that said nucleic acid structure undergoes a transition in energy state due to a branch migration reaction involving said duplex domain, and (iii) a clashing polynucleotide molecule that competes with said polynucleotide displacement molecule for binding said nucleic acid structure under said conditions but that cannot produce a branch migration reaction involving said duplex domain; then

(B) reconfiguring at least one of said displacement molecule and said 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 said displacement molecule or said nucleic acid structure, as the case may be,

wherein said modification causes binding of said displacement molecule and said nucleic acid structure to have a hybridization free energy, differing from that of a first reference binding between said displacement molecule or said nucleic acid structure and said first reference molecule, such that said branch migration reaction is facilitated relative to said first reference binding; and/or

(C) reconfiguring at least one of said clashing molecule and said 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 said clashing molecule or said nucleic acid structure, as the case may be,

wherein said modification causes binding of said clashing molecule and said nucleic acid structure to have a hybridization free energy, differing from that of a second reference binding between said clashing molecule or said nucleic acid structure and said second reference molecule, such that binding of said clashing molecule is impeded relative to said second reference binding.

2. The method of claim 1, wherein said branch migration reaction is facilitated by:

increasing a probability of productive reactions in which binding of said nucleic acid structure by said displacement molecule has, by virtue of said chemical modification, a lower hybridization free energy than does a first reference binding reaction; or

3. The method of claim 1, wherein said branch migration reaction is facilitated by:

reducing a probability of unproductive reactions in which binding of said nucleic acid structure by said clashing molecule has, by virtue of said chemical modification, a higher hybridization free energy than does a second reference binding reaction.

4. The method of claim 1, wherein said nucleic acid structure is 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.

5. The method of claim 1, wherein said chemical modification is selected from the group consisting of (i) replacing the sugar-phosphodiester backbone of said nucleosides with a pseudo-peptide backbone, (ii) modifying the sugar moiety of said nucleosides, and (iii) substituting an analogue for the nitrogenous base of at least one of said nucleosides.

6. The method of claim 5, wherein said chemical modification comprises replacing the sugar-phosphodiester backbone of said nucleosides with a pseudo-peptide backbone into which a guanidinium functional group is incorporated.

7. The method of claim 5, wherein said chemical modification comprises substituting a tricyclic cytosine analogue for the nitrogenous base of at least one of said nucleosides.

8. The method of claim 5, wherein said chemical modification comprises introducing a heteroatom at the 2'-position of said sugar moiety.

9. The method of claim 1, wherein said branch migration reaction comprises a toe-hold-mediated strand displacement.

10. A nucleic acid-based system for propagating information, the system comprising:

(A) a nucleic acid structure that comprises an incompletely base-paired duplex domain;

(B) at least one polynucleotide displacement molecule to effect binding with said nucleic acid structure under hybridizing conditions, such that said nucleic acid structure undergoes a transition in energy state due to a branch migration reaction involving said duplex domain; and

(C) at least one polynucleotide clashing molecule capable of binding with said nucleic acid structure under hybridizing conditions, such that said nucleic acid structure and said clashing molecule are bound and prevent the binding of the polynucleotide displacement molecule,

wherein at least one of said displacement molecule and said nucleic acid structure, respectively, has a chemical modification relative to a reference molecule that comprises natural nucleosides and has the same sequence content as said displacement molecule or said nucleic acid structure, as the case may be,

wherein said modification causes said binding to have a hybridization free energy, differing from that of a reference binding between said displacement molecule or said nucleic acid structure and a reference molecule, such that said branch migration reaction is facilitated relative to said reference binding,

and/or

wherein at least one of said clashing molecule and said nucleic acid structure, respectively, has a chemical modification relative to a reference molecule that comprises natural nucleosides and has the same sequence content as said displacement molecule or said nucleic acid structure, as the case may be,

wherein said modification causes said binding to have a hybridization free energy, differing from that of a reference binding between said displacement molecule or said nucleic acid structure and a reference molecule, such that binding of said clashing molecule is impeded relative to said reference binding.

11. The system of claim 10, wherein said nucleic acid structure is 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.

12. The system of claim 11, wherein said system comprises one or more circuits comprised of a plurality of enzyme-free, nucleic acid logic gates.

13. The system of claim 10, wherein said chemical modification is selected from the group consisting of (i) replacing the sugar-phosphodiester backbone of said nucleosides with a pseudo-peptide backbone, (ii) modifying the sugar moiety of said nucleosides, and (iii) substituting an analogue for the nitrogenous base of at least one of said nucleosides.

14. The system of claim 13, wherein said chemical modification comprises replacing the sugar-phosphodiester backbone of said nucleosides with a pseudo-peptide backbone into which a guanidinium functional group is incorporated.

15. The system of claim 14, wherein said chemical modification comprises substituting a tricyclic cytosine analogue for the nitrogenous base of at least one of said nucleosides.

16. The system of claim 14, wherein said chemical modification comprises introducing a heteroatom at the 2'-position of said sugar moiety.

17. The system of claim 10, wherein said branch migration reaction comprises a toe-hold-mediated strand displacement.

18. A system for propagating information, the system comprising a first molecule, anda second molecule configured to bind with the first molecule, wherein

(A) at least one of the first molecule or 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, and

(B) the modification causes said 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: (i) the probability of a productive binding is raised; and (ii) the probability of an unproductive binding is reduced.

19. The system of claim 18, wherein the productive binding comprises a binding that propagates information, and wherein the unproductive binding comprises a binding that does not propagate information.

20. The system of claim 18, wherein the free energy difference as a result of the modification decreases for the productive binding, and increases for the unproductive binding.

21. The system of claim 18, wherein the first and second molecules include an incompletely base-paired duplex domain configured as a translator, and a single-stranded stretch of nucleic acids configured as an input molecule.

WHAT IS CLAIMED IS:

1. A method for preparing an improved nucleic acid-based molecular computing system, comprising:

(1) identifying a nucleic acid-based computing system that comprises

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

(ii) a 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 target duplex comprises a duplex region formed by base-pairing between B and B' and two single-stranded regions, A' and C, and

wherein the input strand can bind with the first strand of the target duplex under hybridizing conditions to invoke a strand displacement reaction to produce an output duplex formed between the input strand (A-B) and the first strand of the target duplex (B'-A'),

and

(iii) a clashing, 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 clashing duplex comprises a duplex region formed by base-pairing between C and C' and two single-stranded regions B' and D,

wherein the second strand of the target duplex can bind with the first strand of the clashing duplex under hybridizing conditions to invoke a strand displacement reaction to produce an output duplex formed between the second strand of the target duplex (B-C) and the first strand of the clashing duplex (C'-B'), and

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

and then

(2) synthesizing, in an aqueous solution, a variant of said nucleic acid-based molecular computing system that differs from the latter by

(i) an incorporation into the first fragment (B) of the second strand of the target duplex a first chemical modification that causes binding with the second fragment (B') of the first strand of the clashing duplex to have a decreased hybridization free energy, and/or

(ii) an incorporation into the second fragment (B) of the input strand a second chemical modification that causes binding with the second fragment (B') of the first strand of the clashing duplex to have an increased hybridization free energy,

such that the first fragment (B) of the second strand of the 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 clashing duplex to form a more stable duplex region,

whereby the variant is improved over the nucleic acid-based molecular computing system in terms of a reduced incidence of hybridization between the input strand and the clashing duplex.

2. The method of claim 1, wherein the variant comprises the first chemical modification.

3. The method of claim 1, wherein the variant comprises the second chemical modification.

4. The method of claim 1, wherein the input strand, the target duplex, and the clashing 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.

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

6. The method of claim 5, wherein the first or second chemical modification comprises replacing the sugar-phosphodiester backbone of said nucleosides with a pseudo-peptide backbone into which a guanidinium functional group is incorporated.

7. The method of claim 5, wherein the first or second chemical modification comprises substituting a tricyclic cytosine analogue for the nitrogenous base of at least one of said nucleosides.

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

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