Claims

1. A method of detecting a conformationally changed nucleic acid polymerase, the method comprising:

contacting a nucleic acid polymerase attached to an electrically-conducting channel with a template nucleic acid sequence and a nucleotide that is an unmodified nucleotide or a modified nucleotide, wherein the modified nucleotide comprises: (i) a substitution on its phosphate moiety; (ii) a substitution on its nucleobase; (iii) a substitution on its sugar; or (iv) a combination of two or more of (i), (ii), and (iii); thereby forming the conformationally changed nucleic acid polymerase bound to the nucleotide and the template nucleic acid sequence; and

detecting the conformationally changed nucleic acid polymerase by measuring an electrical signal change in the electrically-conducting channel between the nucleic acid polymerase and the conformationally changed nucleic acid polymerase.

2. The method of claim 1, wherein the nucleotide is a chemically modified nucleotide analog that comprises the substitution on its phosphate moiety; and the substitution is a sulfur atom.

3. The method of claim 2, wherein the phosphate moiety is a triphosphate moiety, and wherein the sulfur atom is at an α-position of the triphosphate moiety.

4. The method of claim 3, wherein the nucleotide is selected from the group consisting of α-thio-dATP, α-thio-dGTP, α-thio-dCTP, and α-thio-dTTP.

5. The method of claim 1, wherein the nucleotide is a chemically modified nucleotide analog that comprises the substitution on its nucleobase; and the substitution is selected from the group consisting of a halogen atom, a nitrogen atom, and a sulfur atom.

6. The method of claim 5, wherein the substitution is the halogen atom, and wherein the modified nucleotide is 6-Cl-dGTP.

7. The method of claim 5, wherein the substitution is the sulfur atom or comprises the sulfur atom and the nitrogen atom, and wherein the modified nucleotide is selected from the

group consisting of 2-thio-dATP, 2-thio-dGTP, 2-thio-dCTP, 2-thio-CTP, 2-thio-dTTP, 2-thio-TTP, 4-thio dTTP, 6-aza-2-thio-dTTP, and 6-aza-2-thio-TTP.

8. The method of claim 5, wherein the substitution is the nitrogen atom, and wherein the modified nucleotide is 6-aza dUTP.

9. The method of claim 1, wherein the nucleotide is a chemically modified nucleotide analog that comprises at least one of (i), (ii), and (iii); the substitution on the phosphate moiety is a first sulfur atom; and the substitution on the nucleobase is selected from the group consisting of a halogen atom and a second sulfur atom.

10. The method of claim 9, wherein the nucleotide is selected from the group consisting of α-thio-2-thio-dTTP, α-thio-2-thio-dCTP, and α-thio-6-Cl-2-APTP.

11. The method of claim 1, wherein the electrically-conducting channel comprises a metal, a metal oxide, or a semiconductor.

12. The method of claim 1, wherein the electrically-conducting channel is a nanometer-scale conductor.

13. The method of claim 12, wherein the nanometer-scale conductor is selected from the group consisting of a nanowire and a nanotube.

14. The method of claim 1, wherein the electrically-conducting channel is a semiconductor nanowire.

15. The method of claim 1, further comprising identifying the nucleotide based on the electrical signal change.

16. The method of claim 15, wherein the electrical signal change is increased or decreased relative to a second electrical signal change produced when a native nucleotide is contacted with the nucleic acid polymerase.

17. The method of claim 1, wherein the electrical signal change is a change in conductance.

18. The method of claim 1, wherein the nucleic acid polymerase is covalently attached to the electrically-conducting channel.

19. The method of claim 1, wherein the nucleotide is a chemically modified nucleotide analog that comprises the substitution on its phosphate moiety; and the phosphate moiety comprises multiple phosphate groups, and at least one of the multiple phosphate groups comprises the substitution.

20. The method of claim 19, wherein the phosphate moiety is selected from the group consisting of a tri-phosphate, a tetra-phosphate, and a penta-phosphate.