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 mixture of non-labeled modified nucleotides,

wherein each of the non-labeled modified nucleotides comprises a phosphate moiety and a nucleobase comprising a purine or a pyrimidine,

wherein at least one of the non-labeled modified nucleotides comprises a sulfur substitution on its phosphate moiety; or

wherein at least one of the non-labeled modified nucleotides comprises a substitution at position 6 of its purine or at position 2 or 6 of its pyrimidine;

thereby forming the conformationally changed nucleic acid polymerase bound to one of the nucleotides of the mixture 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 caused by a conformational transition between the nucleic acid polymerase and the conformationally changed nucleic acid polymerase.

2. The method of claim 1, wherein the phosphate moiety is a triphosphate moiety, and wherein the sulfur atom is at an α-position of the triphosphate moiety.

3. The method of claim 2, wherein at least one of the non-labeled modified nucleotides is selected from the group consisting of α-thio-dATP, α-thio-dGTP, α-thio-dCTP, and α-thio-dTTP.

4. The method of claim 1, wherein at least one of the non-labeled modified nucleotides comprises the substitution on its purine or pyrimidine; and the substitution is selected from the group consisting of a halogen atom, a nitrogen atom, and a sulfur atom.

5. The method of claim 4, wherein at least one of the non-labeled modified nucleotides has the halogen atom substitution at position 6 of the purine, and wherein the non-labeled modified nucleotide is 6-Cl-dGTP.

6. The method of claim 4, wherein at least one of the non-labeled modified nucleotides has the sulfur substitution at position 2 of the pyrimidine or wherein at least one of the non-labeled modified nucleotides has the nitrogen substitution at position 6 of the pyrimidine, and wherein the non-labeled 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, 6-aza-2-thio-dTTP, and 6-aza-2-thio-TTP.

7. The method of claim 4, wherein the at least one of the non-labeled modified nucleotides has the nitrogen substitution at position 6 of the pyrimidine, and wherein the non-labeled modified nucleotide is 6-aza dUTP.

8. The method of claim 1, wherein at least one of the non-labeled modified nucleotides has the sulfur substitution at a non-bridging, α-phosphoryl oxygen atom; and the substitution at position 2 or 6 of the pyrimidine is selected from the group consisting of a halogen atom and a second sulfur atom.

9. The method of claim 8, wherein at least one of the non-labeled modified nucleotides is selected from the group consisting of α-thio-2-thio-dTTP, α-thio-2-thio-dCTP, and α-thio-6-Cl-2-APTP.

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

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

12. The method of claim 11, wherein the nanometer-scale conductor is selected from the group consisting of a nanowire and a nanotube.

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

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

15. 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.

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

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

18. The method of claim 1, wherein at least one of the non-labeled modified nucleotides has the sulfur substitution at a non-bridging, α-phosphoryl oxygen atom of its phosphate moiety; and the phosphate moiety comprises multiple phosphate groups.

19. The method of claim 18, wherein the phosphate moiety is selected from the group consisting of a tri-phosphate, a tetra-phosphate, and a penta-phosphate.

20. The method of claim 1, wherein at least one of the non-labeled modified nucleotides has the sulfur substitution at a non-bridging, α-phosphoryl oxygen atom of its phosphate moiety; and

wherein at least one of the non-labeled modified nucleotides has a halogen, nitrogen, or sulfur substitution at position 6 of its purine or at position 2 or 6 of its pyrimidine.