

What is Claimed is:

1. A device for direct measurement of protein activity, the device comprising:

a first and a second electrode, the first and second electrode being co-planar and separated by a gap; and

a protein attached to one or both electrodes;

wherein the first electrode and the second electrodes are configured for contact with a sample to be analyzed.

2. The device of claim 1, wherein the gap has a width of about 1.0 nm to about 20.0 nm.

3. A device for direct measurement of protein activity, the device comprising:

(a) a dielectric substrate;

(b) a first electrode disposed on the dielectric substrate;

(c) an insulating dielectric layer disposed on the first electrode;

(d) a second electrode disposed on the insulating dielectric layer;

(e) a passivation layer disposed on the second electrode;

(f) a protein attached to one or both the electrodes;

wherein the first electrode, the insulating dielectric layer, the second electrode and passivation layer have an opening formed therethrough.

4. The device of claim 1 or 3, wherein the protein is selected from the group consisting of a polymerase, a nuclease, a proteasome, a glycopeptidase, a glycosidase, a kinase and an endonuclease.

5. The device of claim 4, wherein the protein is a polymerase.

6. The device of claim 5, wherein the polymerase is attached to one electrode.
7. The device of claim 5, wherein the polymerase is attached to the electrode via a linker.
8. The device of claim 5, wherein the protein is a biotinylated polymerase.
9. The device of claim 8, wherein the biotinylated polymerase is attached to the electrode via a thio-streptavidin linker.
10. The device of claim 1, wherein the first and/or second electrode comprise a metal selected from the group consisting of gold, platinum, palladium, and ruthenium.
11. The device of claim 10, wherein the first and/or second electrode comprise palladium.
12. A device for direct measurement of protein activity, the device comprising:
 - (a) a dielectric substrate;
 - (b) a first electrode disposed on the dielectric substrate;
 - (c) a second electrode disposed on the dielectric substrate, wherein the first and second electrode being separated by a gap between 1 and 20 nm;
 - (d) a passivation layer disposed on top of the electrodes; and
 - (e) a protein attached to one or both the electrodes;wherein the passivation layer has an opening formed therethrough positioned to allow a sample to pass to the gap between the first and second electrode.
13. A system for direct electrical measurement of protein activity comprising
 - (a) a device of claim 1;
 - (b) a means for introducing a chemical entity that is capable of interacting with the protein;

(c) a means for applying a bias between the first and second electrode; and

(d) a means for monitoring fluctuations that occur as the chemical entity interacts with the protein.

14. The system of claim 13, wherein the protein is a polymerase.

15. The system of claim 13, wherein the protein is an exonuclease, proteasome, or glycan.

16. The system of claim 13, wherein the protein is a kinase.

17. A method of detecting the activity of a single protein molecule, the method comprising

(a) introducing a chemical entity that is capable of interacting with the protein molecule to the system of claim 13;

(b) applying a bias between the two electrodes chosen so that a steady DC current is observed; and

(c) observing fluctuations in current between the two electrodes that arise when the chemical entity interacts with the protein.

18. The method of claim 17, wherein the protein is selected from the group consisting of a polymerase, a nuclease, a proteasome, a glycopeptidase, a glycosidase, a kinase and an endonuclease.

19. The method of claim 17, wherein the chemical entity is selected from the group consisting of a nucleotide triphosphate, a nucleic acid, a peptide, a glycan and a kinase.

20. A method of sequencing DNA, said method comprising

(a) introducing a primed DNA template to the system of claim 13;

(b) introducing a solution comprising the four dNTPs;

(c) applying a bias between the two electrodes chosen so that a steady DC current is observed;

(d) detecting fluctuations in current between the two electrodes that arise when each new nucleotide is incorporated to the primer; and

(e) determining the identity of each of nucleotides being incorporated.

21. The method of claim 20, wherein the solution comprises the four dNTPs at about the same concentration relative to each other.

22. The method of claim 20, wherein the concentrations of the dNTPs are about equal to or above the saturation concentration of the template-bound polymerase.

23. The method of claim 20, wherein step (d) comprises detecting the presence of one or more current spike(s).

24. The method of claim 20, wherein step (e) comprises using the characteristics of each spike.

25. A method of sequencing a biopolymer, said method comprising

(a) introducing a biopolymer to the system of claim 15;

(b) applying a bias between the two electrodes chosen so that a steady DC current is observed;

(c) detecting fluctuations in current between the two electrodes that arise when a monomer is removed from the end of the biopolymer; and

(d) determining the identity of each monomer removed from the biopolymer.

26. The method of claim 25, wherein the biopolymer is DNA, a peptide, or a glycan.

27. A method of detecting the activity of kinase, the method comprising

(a) introducing a candidate kinase inhibitor molecule to the system of claim 16;

(b) applying a bias between the two electrodes chosen so that a steady DC current is observed;

- (c) detecting fluctuations in current between the two electrodes that arise when the kinase interacts with the candidate kinase inhibitor molecule; and
- (d) determining whether the kinase has activity in the presence of the candidate kinase inhibitor molecule.

28. An array for sequencing DNA comprising:

an arrangement of a plurality of devices, wherein each device comprises:

- (a) a dielectric substrate;
- (b) a first electrode disposed on the dielectric substrate;
- (c) an insulating dielectric layer disposed on the first electrode;
- (d) a second electrode disposed on the insulating dielectric layer;
- (e) a passivation layer disposed on the second electrode; and
- (f) a polymerase molecule attached to the first and second electrode,

wherein the first electrode, the insulating dielectric layer, the second electrode and passivation layer have an opening formed therethrough.

29. An array for sequencing DNA comprising:

an arrangement of a plurality of devices, wherein each device comprises:

- (a) a dielectric substrate;
- (b) a first electrode disposed on the dielectric substrate;
- (c) a second electrode disposed on the dielectric substrate;
- (d) a passivation layer disposed on top of the electrodes; and
- (e) a polymerase molecule attached to one or both the electrodes;

wherein the passivation layer has an opening formed therethrough.

30. The array of claim 28 or 29, wherein the arrangement is a grid.

31. A system for direct measurement of polymerase activity comprising:
- (a) an array of claim 28 or 29;
 - (b) optionally a means for introducing and removing a solution to the array;
 - (c) a means for applying a bias between the first and second electrode; and
 - (d) a means for monitoring the current generated between the first and second electrodes.
32. A method for sequencing DNA, the method comprising:
- (a) introducing a solution comprising a DNA template to a system of claim 31;
 - (b) measuring a first current generated when a bias is applied to a system as described herein;
 - (c) introducing a solution comprising a dNTP to the system under conditions that allow for incorporation of the dNTP complementary to the DNA template;
 - (d) measuring a second current generated in step (c);
 - (e) removing the solution comprising unincorporated dNTP;
 - (f) repeating steps (c) through (e) with each of the remaining three types of dNTPs not used in step (c); and
 - (g) repeating steps (c) through (f);
- wherein the DNA is sequenced from the generated current signals.
33. A method for sequencing DNA, the method comprising:
- (a) introducing a solution comprising a DNA template to a system of claim 31;

(b) measuring a first current generated when a bias is applied to a system as described herein;

(c) introducing a solution comprising at least two types of dNTPs to the system under conditions that allow for incorporation of the dNTP complementary to the DNA template, wherein the types of dNTPs are present in the solution at different concentrations;

(d) measuring a second current generated in step (c);

(e) removing the solution comprising the unincorporated dNTPs;

(f) repeating steps (c) through (e) with the remaining types of dNTPs not used in step (c); and

(g) repeating steps (c) through (f);

wherein the DNA is sequenced from the generated current signals.

34. The method of claim 33, wherein the solution in step (c) comprises four types of dNTPs.

35. The method of claim 33, wherein the solution in step (c) comprises at least two types of dNTPs.