

CLAIMS

1. A device for sensing local chemical or electrical perturbations in a fluid, the device comprising:
one or more sensors configured to detect a change in one or more of impedance, charge, pH, and temperature of a fluid proximal to a chemical or biological reaction on a reaction carrier, to thereby generate a signal indicative of said biological or chemical reaction;
a supporting substrate comprising a fluidic channel configured to pass a fluid comprising reaction substrates or biological materials over the reaction carrier,
at least two electrodes,
wherein the electrodes measuring a steady state change in the environment proximate to a reaction event, and optionally measuring at least one transient event,
wherein the shape and/or proximity of at least one sensor relative to the reaction carrier substantially increases said change in impedance, charge, pH, and/or temperature relative to said fluid.
2. The device of claim 1, wherein the steady state change is due to the modulation of the Debye layer around the environment or the fluid proximal to the chemical or biological reaction.
3. The device of claim 1, wherein electrodes of at least one sensor are within the Debye length of the reaction carrier.
4. The device of claim 1 to 3, wherein the device is a substantially planar nanosensor array.
5. The device of claim 1 to 4, wherein the steady state or transient change is due to a change in ion concentration around the environment or the fluid proximal to the chemical or biological reaction or in proximity to the said electrodes.
6. The device of claim 5, wherein the change in ion concentration associated with the biological or chemical reaction can be from the mobile or fixed ions.
7. The device of any one of claims 1 to 6, wherein the reaction is a DNA sequencing reaction, and the sensor measures impedance associated with incorporation of one or more nucleotides into a DNA strand or a clonal population of DNA strands.
8. The device of any one of claims 1 to 6, wherein the reaction is an amplification of a polynucleotide.
9. The device of any one of claims 1 to 8, wherein the chemical reaction involves target biological material bound directly or indirectly to the reaction carrier.
10. The device of claim 9, wherein the reaction carrier is a bead.
11. The device of claim 10, wherein the bead is reversibly held proximate to the sensor.
12. The device of claim 11, wherein the bead is held in a depression.
13. The device of claim 11 or 12, wherein the sensor electrodes form an arc substantially conforming to the edge of the depression and/or bead.

14. The device of claim 11, wherein an electrode of at least one sensor positions the bead in a fixed location, and a second electrode of the sensor is in contact with the surface of the sensor underneath the bead.
15. The device of claim 11, wherein two electrodes of at least one sensor are fabricated on the substrate underneath the bead, and form a slope substantially conforming to the shape of the bead.
16. The device of any one of claims 9 to 15, wherein the bead is magnetic.
17. The device of claim 16, wherein the bead is held by at least one of an electrical or magnetic field.
18. The device of any one of claims 9 to 15, wherein the bead is held by a physical linker.
19. The device of any one of claims 1 to 18, wherein one or more electrodes of the sensor are shielded by a dielectric substrate.
20. The device of claim 19, wherein a portion of the electrodes is covered by a dielectric layer.
21. The device of claim 19, wherein a tip of one or more electrodes is coated with a thin dielectric layer, or the tip of one or more electrodes remains uncovered by a dielectric layer.
22. The device of any one of claims 1 to 21, wherein the sensor operates in at least one of AC mode, DC mode, or both.
23. The device of claim 22, wherein the supporting substrate comprises a ground layer.
24. The device of claim 22, wherein the ground layer is located above the electrodes and surrounded by a dielectric layer.
25. The device of claim 23, wherein the ground layer covers a portion of the transmitter electrodes but not the receiving electrodes.
26. The device of any one of claims 1 to 25, further comprising at least one local capacitor associated with at least one electrode.
27. The device of any one of claims 1 to 26, wherein the sensor is a nanobridge.
28. The device of claim 27, wherein the nanobridge forms a ring structure around the bead.
29. The device of claim 28, wherein the nanobridge ring size substantially increases the signal to noise ratio.
30. The device of any one of claims 27 to 29, wherein the nanobridge comprises electrical conductors that are connected to heavily doped regions of said nanobridge.
31. The device of any one of claims 1 to 26, wherein the nanosensor is a nanoneedle.
32. The device of claim 31, wherein the nanoneedle forms a ring structure around the bead.
33. The device of any one of claims 1 to 32, further comprising a reference electrode.
34. The device of claim 33, further comprising a back gate.

35. The device of claim 34, wherein the back gate is segmented.
36. The device of any one of claims 1 to 35, further comprising an integrator incorporated with the sensor.
37. The device of claim 36, wherein the integrator includes a capacitor associated with the sensor.
38. The device of any one of claims 1 to 37, further comprising a plurality of readout ports, optionally at one or more corners or sides of the supporting substrate.
39. The device of any one of claims 1 to 38, comprising at least one sensor selected from a Fin FET, a nanoneedle, a nanobridge, an ISFET, a CHEMFET, a pH sensor, and a microcantilever.
40. The device of any one of claims 1 to 39, further comprising an enrichment module to separate reaction carriers comprising charged target molecules from reaction carriers not comprising charged target molecules.
41. The device of claim 40, wherein the enrichment module comprises a microfluidic channel, a first fluidic input configured for passing the reaction carriers, a second fluidic input configured for passing a buffering solution, a first output port collecting reaction carriers with said charged target molecules, a second output port collecting reaction carriers without said charged target molecules; and an electric field generating component for directing the reaction carriers comprising the charged target molecules toward the first output port.
42. The device of claim 41, wherein there are a plurality of output ports for the separation of reaction carriers with said charged target molecules.
43. The device of claim any one of claims 41 to 42, wherein the electric field is generated perpendicular to the flow path.
44. The device of any one of claims 40 to 43, wherein the charged target molecules are polynucleotides.
45. The device of any one of claims 1 to 44, further comprising a plurality of electrodes associated with each sensor, and configured to form a confinement cell by generation of an electric field.
46. The device of any one of claims 1 to 45, further comprising a relaxation oscillator circuit associated with said at least one sensor.
47. A device for sensing local chemical or electrical perturbations in a fluid, the device comprising:
one or more sensors configured to detect a change in one or more of impedance, charge, pH, and temperature of a fluid proximal to a chemical or biological reaction, to thereby generate a signal indicative of said biological or chemical reaction;
a supporting substrate comprising a fluidic channel configured to pass a fluid comprising reaction substrates or biological materials over the reaction carrier,
at least two electrodes,
wherein the detection is through direct measurement of the impedance modulation between the said electrodes, due to the modulation of the Debye layer or the change of mobile ion concentration around the biological molecules due to the said reaction in the solution between the said electrodes,

wherein the shape and/or proximity of at least one sensor relative to the reaction carrier substantially increases said change in impedance, charge, pH and/or temperature relative to said fluid.

48. A method for detecting a biological or chemical reaction, comprising: passing a bulk fluid containing one or more reaction substrates or biological molecules in the device of any one of claims 1 to 47, and measuring one or more of a change in pH, charge, impedance, and temperature.

49. The method of claim 48, wherein the reaction is a DNA sequencing reaction.

50. The method of claim 49, further comprising, adjusting voltage of the sensors based on length of the DNA on the reaction carriers.

51. The method of claim 50, wherein the sensor signals comprise steady state impedance measurements.

52. The method of claim 51, wherein buffer suitable for DNA synthesis is supplied to the reaction for nucleotide incorporation, followed by low ionic strength buffer for steady state impedance measurements indicative of nucleotide incorporation.

53. The method of any one of claims 48 to 52, further comprising using a differential measurement to remove noise from an output signal that results from said measurements.

54. The method of claim 53, wherein the differential measurement utilizes one or a plurality of null reaction carriers as references.

55. The method of claim 53, wherein the differential measurement utilizes an area in said device that does not have a biological or chemical reaction as a reference.

56. The method of claim 53, wherein the differential measurement utilizes a sensor without a reaction carrier as a reference.

57. The method of any one of claims 53 to 56 wherein the reaction carrier is a magnetic bead.

58. The method of claim 53, wherein the differential measurement utilizes an adjacent sensor as a reference.

59. The method of any one of claim 53 to 58, wherein the differential measurement utilizes a sensor area in said device as a reference.

60. The method of any one of claims 53 to 59, further comprising using a cross-talk deconvolution function matrix to remove noise from said output signal.

61. The method of any one of claims 53 to 60, wherein the differential measurement is utilized based on the time required for a reagent slug to traverse a flow cell.

62. The method of any one of claims 48 to 61, further comprising reducing the data output of the device by synchronizing the readout of the sensor electronics with the movement of the reagent slug through the flow cell.

63. A device comprising:
a microfluidic channel,

- a first fluidic input configured for passing carrier beads,
a second fluidic input configured for passing a buffering solution,
a first output port collecting carrier beads with a higher charge density,
a second output port collecting carrier beads having a lower charge density; and
an electric field generating component for directing the carrier beads having the higher charge density toward the first output port.
64. The device of claim 63, wherein the higher charge density is due to associated polynucleotides.
65. The device of claim 64 wherein the polynucleotides are clonal populations of polynucleotides.
66. The device of any one of claims 63 or 65, wherein the electric field is generated perpendicular to the flow path.
67. The device of any one of claims 63 to 66, wherein the microfluidic channel is configured to reduce electroosmotic flow.
68. The device of any one of claims 63 to 67, wherein the buffered solution is configured to reduce electroosmotic flow.
69. The device of any one of claims 63 to 68, wherein the device is functionally coupled to a nanosensor array.
70. The device of claim 69, wherein the carrier beads are magnetic beads.
71. The device of claim 70, wherein the nanosensor array comprises an array of magnetic regions each configured to hold one of said beads in proximity to at least one sensor.
72. The device of claim 71, wherein each sensor has a plurality of associated electrodes configured to produce an electric field confinement cell.
73. A method for separating carrier beads having a higher charge density from carrier beads that have a lower charge density, comprising: passing the carrier beads and the buffered solution along the microfluidic channel of any one of claims 63 to 72, and applying the electric field to direct carrier beads with a higher charge density toward the first output port.
74. A device for confinement or concentration of charged materials in a fluid, comprising:
a plurality of magnetic structures on a substrate, the magnetic structures configured for retention of magnetic carriers;
a plurality of electrodes configured for confinement of the charged materials proximate to the magnetic structure by an electric field;
a source supplying an electric signal that is connected to said at least one electrode for the generation of an electric field, wherein the electric signal has a waveform that does not substantially interfere with a chemical or biological reaction proximal to the magnetic carrier.

75. The device of claim 74, wherein the waveform is a modified sinusoidal waveform with voltage removed near the top of the sinusoid.
76. The device of claim 74 or 75, wherein the signal is interrupted from one to a plurality of times during a cycle.
77. The device of any one of claims 74 to 76, wherein the electric signal is at least one of a DC signal, an AC signal, or a mixed signal with both AC and DC components.
78. The device of claim 77, comprising one or more inner electrodes and one or more outer electrodes.
79. The device of claim 78, wherein the one or more inner electrodes have alternating positive and negative charges.
80. The device of claim 78, wherein the one or more outer electrodes have a negative charge.
81. The device of any one of claims 74 to 80, wherein some portion of the electrodes are covered with a dielectric material.
82. The device of claim 81, wherein the tips of the electrodes proximate to the magnetic carriers are covered with a thin dielectric layer.
83. The device of any one of claims 74 to 82, wherein the device comprises a microfluidic channel.
84. The device of claim 83, wherein the channel height is at least 3-5 times the height of the magnetic carrier.
85. The device of claim 83, wherein the magnetic structure is ferromagnetic or paramagnetic.
86. The device of claim 85, wherein the magnetic structure is magnetized with an adhesion layer.
87. The device of claim 85, wherein the magnetic structure has a sandwich layer composition.
88. The device of claim 85, wherein the sandwich layer is comprised of alternating layers of non-magnetic and magnetic materials.
89. The device of claim 85, wherein the non-magnetic and magnetic materials are chromium and platinum respectively.
90. The device of claim 85, wherein the magnetic structure further comprise at least one base layer.
91. The device of claim 85, wherein the magnetic structures further comprise at least one oxide layer.
92. The device of any one of claims 85 to 91, wherein a plurality of magnetic structures have sharp edges.
93. The device of any one of claims 74 to 92, wherein a plurality of magnetic structures in a confinement cell create a gap.
94. The device of claim 93, wherein a magnetic carrier rests within the gap.

95. The device of any one of claims 74 to 92, wherein there are one or more magnets associated with the microfluidic channel and located across from the electrodes and the magnets associated with the electrodes.
96. The device of claim 95, wherein the magnet associated with the microfluidic channel is a magnetic layer.
97. The device of any one of claims 74 to 96, further comprising a trench for the delivery or removal of charged materials and/or reaction substrates.
98. The device of claim 97, wherein the trench is associated with the carrier, maximizing the surface area of the carrier available to the charged materials.
99. The device of any one of claims 74 to 98, wherein magnets are in contact with and located above the electrodes.
100. The device of any one of claims 74 to 98, wherein magnets are in contact with and located beneath the electrodes.
101. The device of any one of claims 74 to 100, wherein the charged material is DNA.
102. The device of any one of claims 74 to 101, wherein the electric field is dielectrophoretic or electrophoretic.
103. The device of any one of claims 74 to 102, further comprising a magnetic carrier retained by a plurality of the one or more magnetic structures.
104. The device of claim 103, wherein the magnetic carrier is a magnetic bead.
105. The device of claim 104, wherein the charged material confined is at least one of DNA or dNTP.
106. The device of claim 105, where in a target biological molecule is bound to the carrier by a linker.
107. A system comprising the device of any one of claims 74 to 106, and the device of one or more of claims 1 to 47, and/or the device of one or more of claims 63 to 72.
108. A method for measuring the profile of incorporation of DNA bases by a DNA polymerase, comprising:
- providing a primer region of a template DNA in a microfluidic chamber;
 - adding to the microfluidic chamber a DNA polymerase and at least one nucleotide for incorporation;
 - measuring a steady state change in the environment proximate to an incorporation event, and optionally measuring at least one transient event.
109. The method of claim 108, comprising, measuring a change in environment selected from an increase in the byproducts of the incorporation reaction, impedance of the fluid environment, pH, or temperature.

110. The method of claim 108, wherein nucleotide incorporation occurs in a buffer solution containing ionic components required for nucleotide incorporation, and the steady state change is measured in a low ionic strength buffer.
111. The method of claim 110, comprising:
- performing a sequencing reaction to the full length possible, melting off the extended primer strand, introducing new primers, and proceeding with the synthesis reaction.
112. A method for performing a plurality of sequencing reactions in close proximity, comprising: contacting components of said sequencing reaction with DNA templates spaced on a carrier so as to reduce steric hindrance.
113. The method of claim 112, wherein the DNA templates are spaced by contacting the templates with a binding moiety that forms a complex with double stranded or single stranded DNA and said moiety is larger than a polymerase, and contacting the spaced DNA templates with said polymerase under nucleotide incorporation conditions.
114. The method of claim 113, wherein the moieties are processive polymerases.
115. The method of any one of claims 108 to 114, wherein dNTPs are added one at a time, and incorporation measured.
116. The method of any one of claims 108 to 115, wherein parallel sequencing reactions proceed on an array.
117. The method of claim 116, wherein each reaction involves a sensor and a confinement cell, the confinement cell formed by an electric field.
118. The method of claim 116 or 117, wherein the sequencing reaction takes place on a bead array.
119. The method of claim 118, wherein the beads are magnetic, and are held in proximity to the sensors by magnetic structures.
120. The method of claim 119, wherein sensor electrodes are within the Debye length of the bead.
121. A system for polynucleotide sequencing, the system comprising a plurality of sensors adapted to sense nucleotide incorporation to a plurality of polynucleotides, and a plurality of integrators, each of the plurality of integrators coupled to one of the plurality of sensors and adapted to reduce noise in each of the plurality of sensors.
122. The system of claim 121, wherein the system is adapted to measure accumulation of charge instead of current.
123. A method for reducing steric hindrance in DNA sequencing by sensing nucleotide incorporation on DNA with a first polymerase, the method comprising using a compound selected from a group of a second polymerase which is larger than the first polymerase, and a protein or moiety that bounds to DNA, such that the compound helps space out DNA and thereby reduce steric hindrance.
124. The method of claim 123, wherein the second polymerase is a processive polymerase.

125. A method for reducing the effect of carbonic acid on pH measurement for sensing incorporation of a nucleotide to a polynucleotide, the method comprising using two buffers to provide both sufficient buffering and low ionic strength at the same time.
126. The method of claim 125, wherein the combined Tris and HEPES is used to contribute to buffering.
127. A method for reducing charge from a polynucleotide carrier, the method comprising changing the amount of SO₄ on the surface of the polynucleotide carrier.
128. A method for reducing charge from a polynucleotide carrier, the method comprising adding an amount of negative charge on the surface of the polynucleotide carrier.
129. The method of claim 128, wherein the amount of negative charge is sufficient to reduce polynucleotide or nucleotide binding to the surface of the polynucleotide carrier, but not sufficient to affect the dynamic range of a sensor coupled to the polynucleotide carrier.
130. A method for polynucleotide sequencing by sensing nucleotide incorporation to a polynucleotide, the method comprising providing four nucleotide or nucleotide analogs onto a polynucleotide, wherein three of the four nucleotides or nucleotide analogs are unincorporable nucleotide analogs.
131. The method of claim 130 wherein the unincorporable nucleotide or nucleotide analogues are selected from a group of: PNA nucleotide, LNA nucleotide, adenine monophosphate, adenine diphosphate, adenosine, deoxyadenosine, guanine monophosphate, guanine diphosphate, guanosine, deoxyguanosine, thymine monophosphate, thymine diphosphate 5-Methyluridine, thymidine, cytosine diphosphate, uridine, and deoxyuridine.
132. The method of claim 130, wherein concentration levels of nucleotides and nucleotide analogs is matched to relative polymerase activity.
133. The method of claim 130, wherein concentration level of unincorporable nucleotides or nucleotide analogs is higher than concentration level of equivalent polymerase binding efficiency for an incorporable nucleotide.
134. A method for sensing nucleotide incorporation on a polynucleotide with a sensor, the method comprising coupling to the sensor a relaxation oscillator circuit to generate a clock signal with a frequency proportional to the sensor conductance.
135. A method for using reagents in polynucleotide sequencing, the method comprising using at least two different reagents, wherein a first reagent is used at least for one of increasing polymerase accuracy and reducing dephasing, and wherein a second reagent is used to increase accuracy of a sensing device.
136. A system for polynucleotide sequencing, the system comprising a substrate and a nano-needle device adapted to sense nucleotide incorporation to a polynucleotide, the nano-needle having first and second electrodes, the first electrode being attached directly to the substrate, the second electrode being attached upon a sensor which sensor is utilized to position a polynucleotide carrier in a substantially fixed location.
137. A system for polynucleotide sequencing, the system comprising a substrate and a nano-needle device adapted to sense nucleotide incorporation to a polynucleotide, the nano-needle having first and

second electrodes, the first electrode being attached directly to the substrate or an adhesion layer, the second electrode being situated above a dielectric layer, which dielectric layer covers the first electrode.

138. A system for polynucleotide sequencing, the system comprising a nano-needle device adapted to sense nucleotide incorporation to a polynucleotide, the nano-needle being coupled to at least one capacitor to reduce at least one of an influence of a DC bias level from a driver circuit and a leakage from a chip sensor.

139. A system for polynucleotide sequencing, the system comprising a nano-bridge sensor adapted to sense nucleotide incorporation to a polynucleotide, the nano-bridge sensor having an active area, the active area partially encircling and being in immediate proximity of a polynucleotide carrier.

140. The system of claim 139, wherein the polynucleotide carrier is a bead.

141. The system of claim 140, wherein the bead is a magnetic.

142. The system of claim 139, wherein an inner portion of the active area is within the Debye length of the polynucleotide carrier.

143. The system of claim 139, wherein the active area is smaller than a diameter of the polynucleotide carrier

144. A system for polynucleotide sequencing, the system comprising a nano-bridge sensor adapted to sense nucleotide incorporation to a polynucleotide, the nano-bridge sensor having an active area, the active area being heavily doped to provide better electrical connection.

145. A system for polynucleotide sequencing comprising a plurality of nanosensors adapted to detect one or more of charge, pH, and impedance change caused by nucleotide incorporation to a polynucleotide, the plurality of nanosensors having an additional reference electrode to provide high dynamic range and high sensitivity.

146. The system of claim 145, wherein a variable voltage may be impressed between the reference electrode and an active area of plurality of nanosensors.

147. The system of claim 145 wherein the plurality of sensors is one of a ChemFET and a non-bridge.

148. A method for polynucleotide sequencing, the method comprising measuring nucleotide incorporation to a polynucleotide by measuring byproducts of the nucleotide incorporation.

149. The method of claim 148, wherein the byproducts include at least one of PPI and hydronium ion.

150. The method of claim 148, wherein a measurement of byproducts is performed significantly during the nucleotide incorporation.

CLAIMS

1. A method for sequencing a nucleic acid sample, comprising:
 - a. providing a plurality of particles adjacent to a sensor array, wherein an individual particle of said plurality of particles is positioned adjacent to an individual sensor of said sensor array and is coupled to a nucleic acid molecule generated from said nucleic acid sample;
 - b. hybridizing a primer to said nucleic acid molecule;
 - c. performing a primer extension reaction by contacting said nucleic acid molecule and said primer with nucleotides in the presence of a polymerase; and
 - d. sequencing said nucleic acid sample by detecting steady state signals indicative of individual incorporation events associated with said nucleotides.
2. The method of Claim 1, wherein said steady state signals are detected subsequent to each of said individual incorporation events.
3. The method of Claim 1, wherein said steady signals are detected at a time period selected such that each of said individual incorporation events has reached completion.
4. The method of Claim 1, further comprising performing said individual incorporation events in the presence of a reaction buffer that is suitable for the completion of said individual incorporation events, and performing said detecting in the presence of a measurement buffer that is suitable for detecting said steady state signals.
5. The method of Claim 4, wherein said reaction buffer and said measurement buffer are different buffers.
6. The method of Claim 4, wherein the conductivity of said measurement buffer is lower than the conductivity of said reaction buffer.
7. The method of Claim 1, wherein said nucleic acid molecule is contacted with each of said individual nucleotides one at a time.
8. The method of Claim 1, wherein said signals are indicative of impedance changes, charge changes, ion concentration changes or conductivity changes accompanying said primer extension reaction.
9. The method of Claim 1, wherein said individual sensor measures an impedance, charge, or conductivity change within the Debye length of said individual particle or said nucleic acid molecule.

10. The method of Claim 1, wherein said individual sensor comprises at least two electrodes that are electrically coupled to the Debye length of said individual particle or said nucleic acid molecule.
11. The method of Claim 1, wherein said sequencing further comprises determining a sequence of incorporation of said nucleotides into a strand that is complementary to said nucleic acid molecule by said polymerase.
12. The method of Claim 1, wherein said particles are magnetically immobilized to said sensor array.
13. The method of Claim 1, further comprising processing said steady state signals with signals from differential measurement.
14. The method of Claim 13, wherein said differential measurement utilizes (i) at least one particle that does not comprise a nucleic acid as a reference, (ii) a sensor that is not positioned adjacent to a particle as a reference, (iii) another individual sensor of said sensor array that is not subject to a nucleotide incorporation event as a reference, (v) another nucleic acid molecule of known sequence that is coupled to said nucleic acid molecule as a reference, or (vi) a cross-talk deconvolution function matrix.
15. The method of Claim 1, wherein said detecting does not include detecting a transient pH signal accompanying said individual incorporation events.
16. A nucleic acid sequencing system, comprising:
 - an array of sensors, wherein an individual sensor of said array is disposed adjacent to a particle comprising a nucleic acid molecule coupled thereto;
 - a fluid flow channel in communication with said array of sensors, wherein said fluid flow channel delivers reagents for performing a primer extension reaction with said nucleic acid molecule; and
 - a computer coupled to said array of sensors, wherein said computer detects steady-state signals that are indicative of individual nucleotide incorporation into a strand that is complementary to said nucleic acid molecule during said primer extension reaction.
17. The system of Claim 16, wherein said steady state signals are detected when said individual sensor is coupled to a Debye length of said particle or said nucleic acid molecule.
18. The system of Claim 16, wherein said individual sensor comprises at least two electrodes.
19. The system of Claim 18, wherein each electrode is electrically coupled to said Debye length associated with said particle.

20. The system of Claim 18, wherein said at least two electrodes comprises a first electrode and a second electrode that are separated by a dielectric layer.
21. The system of Claim 18, further comprising another electrode that is for performing concentration or confinement of a chemical species, a biological species, or a combination thereof at said individual sensor.
22. The system of Claim 16, wherein said individual sensor is configured to measure an impedance, charge, ion concentration or conductivity change associated with said particle or said nucleic acid molecule.
23. The system of Claim 16, further comprising a reaction buffer that is suitable for the completion of said individual incorporation events, and a measurement buffer that is suitable for detecting said steady state signals.
24. The system of Claim 23, wherein said reaction buffer and said measurement buffer are different buffers.
25. The system of Claim 23, wherein the conductivity of said measurement buffer is lower than the conductivity of said reaction buffer.
26. The system of Claim 16, wherein said particle is magnetic.
27. The system of Claim 16, wherein said individual sensor is configured to apply a magnetic field to magnetically immobilize said particle.
28. The system of Claim 16, wherein said array of sensors comprises a substantially flat surface.
29. The system of Claim 16, wherein said individual sensor is configured to generate a electric field, a magnetic field, or a combination thereof to provide a confinement cell that isolates said individual sensor from other sensors of said array of sensors.
30. The system of Claim 16, wherein said nucleic acid molecule is coupled to said particle such that said nucleic molecule is not sterically hindered by another nucleic acid molecule coupled to said particle.
31. The system of Claim 16, wherein said individual sensor comprises a well.
32. The system of Claim 31, wherein said particle is held in said well.