CLAIMS

1. A system for sequencing one or more polynucleotides, the system comprising:

a) a stage configured to hold a solid substrate having one or more polynucleotides attached thereto;

b) a fluid direction system for controllably moving one or more reagents having fluorescent labels into contact with the polynucleotides;

c) a temperature control system for regulating a temperature of at least one of the solid substrate and the reagents;

d) an illumination system for exciting the fluorescent labels via total internal reflection (TIR), the illumination system comprising at least one excitation laser coupled to a multimode optical fiber having an index of refraction, said at least one excitation laser comprising one of (a) an excitation laser that is coupled to the multimode optical fiber and (b) multiple excitation lasers coupled through a fiberoptic device and to the multimode optical fiber, wherein the index of refraction of the multimode optical fiber is dynamically changed to obtain a substantially uniform illumination footprint;

e) a detector component configured to be proximal to the solid substrate for detecting fluorescence produced from excitation of the fluorescent labels by the illumination system; and

f) a computer system operably coupled to the detector component wherein the computer system comprises an instruction set for acquiring fluorescence images from the detector component.

2. The system of claim 1, wherein the mounting stage is movable and is configured to move the solid substrate distal to the detector component in order for the temperature control system to regulate the temperature of the solid substrate.

3. The system of claim 1, wherein the solid substrate comprises a flowcell having one or more fluidic channels in which the polynucleotides are attached.

4. The system of claim 1, wherein the solid substrate comprises glass, silicon, or plastic.

5. The system according to claim 1, wherein said solid substrate is an array of beads.

6. The system of claim 1, wherein the reagents comprise components to extend a second sequence complementary to the one or more polynucleotides.

7. The system according to claim 6, wherein said reagents are fluorescently labeled nucleoside triphosphates.

8. The system according to claim 6, wherein said reagents are fluorescently labeled oligonucleotides.

9. The system of claim 1, wherein the illumination system comprises multiple excitation lasers coupled through the multimode optical fiber.

10. The system according to claim 1, wherein said multimode optical fiber is physically deformed to obtain the substantially uniform illumination footprint.

11. The system according to claim 10, wherein said physical deformation includes squeezing the multimode optical fiber.

12. The system according to claim 1, wherein said dynamically changing the index of refraction includes vibrating the multimode optical fiber.

13. The system of claim 1, wherein the detector component comprises a CCD camera.

14. The system of claim 1, wherein said detector component comprises two CCD cameras.

15. The system of claim 1, wherein said detector component comprises four CCD cameras.

16. The system of claim 1, wherein the detector component further comprises one or more optic filters appropriate to a fluorescence emission of the fluorescently labeled reagent and to one or more wavelength of light from the at least one excitation laser.

17. The system of claim 1, wherein the detector component comprises an autofocus mechanism.

18. The system of claim 1 comprising two fluidics stations for operating on two flowcells simultaneously.

19. The system of claim 1, wherein the illumination system comprises two excitation lasers coupled through a fiberoptic device, wherein said two excitation lasers illuminate at least part of a same area.

20. The system of claim 16, wherein the reagents include four different nucleotides having respective fluorescent labels, the detector component further comprises four optic filters appropriate to a fluorescence emission of the four fluorescently labeled nucleotides and to the wavelength of light from the lasers.

21. The system of claim 19, wherein said two excitation lasers emit at a wavelength of 532 nm and 660 nm, respectively.

22. The system of claim 3, wherein the flowcell comprises a channel layer and a cover layer that is overlaid upon the channel layer, the channel layer including the fluidic channel, the cover layer having an inlet or outlet to the fluidic channel.

23. The system of claim 22, wherein the flowcell comprises photosensitive glass.

24. The system of claim 3, wherein the fluidic channel has one or more inlets at a first end of the channel and one or more outlets at a second end of the channel, the inlets and outlets being located with respect to each other to facilitate maintaining a uniform flow of a liquid through the fluidic channel.

25. The system of claim 1, wherein said multimode optical fiber includes a core having one of a rectangular or square shape to provide a rectangular or square beam shape.

26. The system of claim 1, wherein the illumination system is configured to provide an autofocus spot that is detected by the detector, the computer system using the autofocus spot to focus the detector.

27. The system of claim 1, wherein the polynucleotides comprise nucleic acid clusters and the reagents comprise bases having the fluorescent labels, each nucleic acid cluster including a plurality of single-stranded DNA fragments having a common sequence; and

wherein the fluid direction system, the temperature control system, the illumination system, the detector component, and the computer system cooperate with one another to perform a DNA sequencing cycle including the steps of:

(i) incorporating at least one base onto the DNA fragments of the nucleic acid clusters;

(ii) illuminating the nucleic acid clusters to excite the fluorescent labels of the bases;

(iii) capturing an image of emitted fluorescence from the nucleic acid clusters; and

(iii) identifying the base incorporated onto the DNA fragments of the nucleic acid clusters based upon the emitted fluorescence from the nucleic acid clusters;

(iv) removing the fluorescent labels from the bases.

28. The system of claim 27, wherein the base is one of four types of bases, the bases of each type having a unique fluorophore.

29. The system of claim 27, wherein the computer system is configured to repeat steps (i)-(iv) to determine the sequences of the DNA fragments.

30. The system of claim 1, wherein the reagents include four different bases in which each base has a different fluorescent label, the illumination system including first and second lasers, each of the first and second lasers exciting two of the four fluorescent labels so that the four fluorescent labels are excited by the first and second lasers.

31. The system of claim 30 further comprising four different optical filters for selecting fluorescence emission wherein two of the four filters have a narrower bandwidth than the other two of the four filters.

32. The system of claim 3 wherein the fluid direction system comprises a pump placed after the flowcell to pull reagents into the flowcell.

33. The system of claim 27 wherein the detector is a CCD camera and a density of nucleic acid clusters recorded on the CCD camera is about 5,000 to 50,000 clusters per million pixels.

34. The system of claim 1 wherein the index of refraction is changed at a frequency faster than an image acquisition time.

35. The system of claim 1 wherein dynamically changing the index of refraction causes scrambling of modes of the multimode fiber to average light output from the multimode fiber.

36. The system of claim 1 wherein the multimode optical fiber includes a core, the core being shaped so that the illumination footprint matches a shape of the detector component.

37. The system of claim 1 further comprising the solid substrate having the one or more polynucleotides attached thereto.

38. A system for imaging biological substances, the system comprising:

a) a stage configured to hold a solid substrate that is configured to have one or more biological substances attached thereto;

b) an illumination system comprising at least one excitation laser coupled to a multimode optical fiber having an index of refraction, said at least one excitation laser comprising one of (a) an excitation laser that is coupled to the multimode optical fiber and (b) multiple excitation lasers coupled through a fiberoptic device and to the multimode optical fiber, wherein the index of refraction is dynamically changed to obtain a substantially uniform illumination footprint on the solid substrate;

c) a detector component for detecting light emissions produced from excitation of the biological substances; and

d) a computer system operably coupled to the detector component wherein the computer system comprises an instruction set for acquiring images from the detector component.

39. The system of claim 38 further comprising:

e) a fluid direction system for controllably moving one or more reagents into contact with the biological substances; and

f) a temperature control system for regulating the temperature of at least one of the solid substrate and the reagents.

40. The system of claim, 38 wherein the biological substances are polynucleotides, and the illumination system, the fluid direction system, the temperature control system, the detector component, and the computer system cooperate with one another to perform multiple sequencing cycles.

41. The system of claim 38, wherein said multimode optical fiber includes a core having one of a rectangular or square shape to provide a rectangular or square beam shape.

42. The system of claim 38, wherein the multimode optical fiber includes a core, the core being shaped so that the illumination footprint matches a shape of the detector component.

CLAIMS

1. A system for sequencing one or more polynucleotides, the system comprising:

a) a stage configured to hold a solid substrate comprising one or more polynucleotides attached thereto;

b) a fluid direction system for controllably moving one or more reagents having fluorescent labels into contact with the polynucleotides;

c) a temperature control system for regulating a temperature of at least one of the solid substrate and the reagents;

d) an illumination system for exciting the fluorescent labels via total internal reflection (TIR), the illumination system comprising a multimode optical fiber that provides an illumination beam having multiple optical modes, wherein the optical modes of the illumination beam are scrambled by changing an index of refraction of the optical fiber to obtain a substantially uniform illumination footprint, wherein the index of refraction is dynamically changed;

e) a detector component configured to be proximal to the solid substrate for detecting fluorescence produced from excitation of the fluorescent labels by the illumination system;

f) a computer system operably coupled to the detector component wherein the computer system comprises an instruction set for acquiring fluorescence images from the detector component.

2. The system of claim 1, wherein the solid substrate can be moved distal to the detector component in order for the temperature control system to regulate the temperature of the solid substrate.

3. The system of claim 1, wherein the solid substrate comprises a flowcell having one or more fluidic channels in which the polynucleotides are attached.

4. The system of claim 1, wherein the solid substrate comprises glass, silicon, or plastic.

5. The system according to claim 1, wherein said solid substrate is an array of beads.

6. The system of claim 1, wherein the reagents comprise components to extend a second sequence complementary to the one or more polynucleotides.

7. The system according to claim 6, wherein said reagents are fluorescently labeled nucleoside triphosphates.

8. The system according to claim 6, wherein said reagents are fluorescently labeled oligonucleotides.

9. The system of claim 1, wherein the illumination system comprises at least one excitation laser coupled through the optical fiber.

10. The system according to claim 9, wherein said optical fiber is physically deformed to obtain the uniform illumination footprint.

11. The system according to claim 10, wherein said physical deformation is squeezing.

12. The system according to claim 10, wherein said physical deformation is vibrating.

13. The system of claim 1, wherein the detector component comprises a CCD camera.

14. The system of claim 1, wherein said detector component comprises two CCD cameras.

15. The system of claim 1, wherein said detector component comprises four CCD cameras.

16. The system of claim 1, wherein the detector component further comprises one or more optic filters appropriate to the fluorescence emission of the fluorescently labeled reagent and to one or more wavelength of light from the laser.

17. The system of claim 1, when the detector component comprises an autofocus mechanism.

18. The system of claim 1 comprising two fluidics stations for operating on two flowcells simultaneously.

19. The system of claim 1, wherein the illumination system comprises two excitation lasers that illuminate at least part of the same area.

20. The system of claim 16, wherein the reagents include four different reagents having respective fluorescent labels, the detector component further comprises four optic filters appropriate to the fluorescence emission of the four fluorescently labeled reagents and to the wavelength of light from the lasers.

21. The system of claim 19, wherein said lasers emit at a wavelength of 532 nm and 660 nm.

22. The system of claim 3, wherein the flowcell comprises a channel layer and a cover layer that is overlaid upon the channel layer, the channel layer including the fluidic channel, the cover layer having a through-hole that provides access to the fluidic channel.

23. The system of claim 22, wherein the channel layer comprises photosensitive glass.

24. The system of claim 3, wherein the fluidic channel has one or more inlet ports at a first end of the channel and one or more outlet ports at a second end of the channel, the inlet and outlet ports being located with respect to each other to facilitate maintaining a uniform flow of a liquid through the fluidic channel.

25. The system of claim 9, wherein said fiber includes a core having a substantially rectangular cross-sectional shape.

26. The system of claim 1, wherein the illumination system is configured to provide an autofocus spot that is detected by the detector component, the computer system using the autofocus spot to focus the detector component.

27. The system of claim 1, wherein the polynucleotides comprise DNA clusters and the reagents comprise bases having the fluorescent labels, each DNA cluster including a plurality of single-stranded DNA fragments having a common sequence; and

wherein the fluid direction system, the temperature control system, the illumination system, the detector component, and the computer system cooperate with one another to perform a DNA sequencing cycle including the steps of:

(i) incorporating at least one base onto the DNA fragments of the DNA clusters;

(ii) illuminating the DNA clusters to excite the fluorescent labels of the bases;

(iii) capturing an image of emitted fluorescence from the DNA clusters; and

(iii) identifying the base incorporated onto the DNA fragments of the DNA clusters based upon the emitted fluorescence from the DNA clusters;

(iv) removing the fluorescent labels from the bases.

28. The system of claim 27, wherein the base is one of four types of bases, the bases of each type having a unique fluorescent label.

29. The system of claim 27, wherein the computer system is configured to repeat steps (i)-(iv) to determine the sequences of the DNA fragments.

30. The system of claim 1, wherein the reagents include four different bases in which each base has a different fluorescent label, the illumination system including first and second lasers, each of the first and second lasers exciting two of the four fluorescent labels so that the four fluorescent labels are excited by the first and second lasers.

31. The system of claim 30 further comprising four different optical filters for selecting the fluorescence emission wherein two of the four filters have a narrower bandwidth than the other two of the four filters.

32. The system of claim 3 wherein the fluid direction system comprises a pump placed after the flowcell to pull reagents through the flowcell.

33. The system of claim 27 wherein the detector component is a CCD camera and a density of DNA clusters recorded on the CCD camera is 5,000 to 50,000 clusters per million pixels.