

WHAT IS CLAIMED IS:

1. A method for controlling a biological manufacturing system, the method comprising:
directing a light beam to pass through a wall of a vessel containing a first fluid
5 generated by the biological manufacturing system;
measuring an angle of refraction of the light beam in the first fluid, the angle of
refraction corresponding to an angle between a propagation direction of the light beam in the
first fluid and a normal to an interface between the vessel wall and the first fluid;
determining information about the first fluid based on the measured angle of
10 refraction; and
adjusting a parameter of the biological manufacturing system based on the
information about the first fluid.
2. The method of claim 1, wherein the information about the first fluid comprises a
15 concentration of a substance in the first fluid.
3. The method of claim 1, wherein the information about the first fluid comprises a pH
value of the first fluid.
- 20 4. The method of claim 1, wherein the first fluid comprises a fluid discharged from a
purification unit of the system.
5. The method of claim 4, wherein the purification unit comprises at least one
chromatography column.
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6. The method of claim 1, wherein the first fluid comprises a feed fluid introduced into a
reactor of the system.
7. The method of claim 1, wherein the first fluid comprises a fluid discharged from a
30 diafiltration unit of the system.
8. The method of claim 1, wherein the parameter of the biological manufacturing system
comprises a fluid flow path that selectively directs a successive portion of the first fluid to
one of multiple purification units of the system.

9. The method of claim 1, wherein the parameter of the biological manufacturing system comprises a feed rate of a substance into a reactor of the system.
- 5 10. The method of claim 1, wherein the parameter of the biological manufacturing system comprises a feed rate of a substance into a diafiltration unit of the system.
11. The method of claim 1, wherein the parameter of the biological manufacturing system comprises a feed rate of a substance into a purification unit of the system.
- 10 12. The method of claim 1, wherein the parameter of the biological manufacturing system comprises a feed rate of successive portions of the first fluid into a purification unit of the system.
- 15 13. The method of claim 2, further comprising determining the concentration of the substance from a calibration equation derived from measured calibration data, wherein the calibration equation expresses the concentration as a function of the angle of refraction.
14. The method of claim 13, wherein the calibration equation expresses the concentration
20 as a linear function of the angle of refraction.
15. The method of claim 13, wherein the calibration equation expresses the concentration as a nonlinear function of the angle of refraction.
- 25 16. The method of claim 13, further comprising transmitting the concentration information to a controller of the system, wherein the controller is configured to receive the concentration information and to adjust the parameter of the system.
17. The method of claim 2, wherein the substance comprises a protein.
- 30 18. The method of claim 2, wherein the substance comprises a recombinant protein-based drug product.

19. The method of claim 2, wherein the substance comprises a nucleic acid-based product.
20. The method of claim 1, wherein the first fluid is a process fluid generated by the
5 system as part of a biological manufacturing process.
21. The method of claim 1, wherein the first fluid comprises an eluate discharged from a chromatography column.
- 10 22. The method of claim 1, wherein the first fluid comprises an eluate solution from a first purification unit of the system and the information comprises a concentration of a substance in the first fluid, and wherein the parameter adjustment comprises directing eluate solution from the first purification unit into an inlet of a second purification unit when the concentration of the substance in the first fluid exceeds a threshold value.
- 15 23. The method of claim 22, wherein the first and second purification units each comprise at least one chromatography column.
24. The method of claim 1, wherein the first fluid comprises an eluate solution from a
20 first purification unit of the system, the information comprises a concentration of a substance in the first fluid, and an inlet of the first purification unit is connected to a conduit that delivers a feed solution to the first purification unit, the method further comprising, when a concentration of the substance in the first fluid exceeds a threshold value:
disconnecting the inlet of the first purification unit from the conduit; and
25 connecting an inlet of a second purification unit of the system to the conduit to deliver the feed solution to the second purification unit.
25. The method of claim 1, further comprising:
directing a second light beam to pass through a wall of a second vessel containing a
30 second fluid generated by the biological manufacturing system;
measuring an angle of refraction of the second light beam in the second fluid, the angle of refraction corresponding to an angle between a propagation direction of the second light beam in the second fluid and a normal to an interface between the wall of the second vessel and the second fluid;

determining information about the second fluid based on the measured angle of refraction of the second light beam; and

adjusting a second parameter of the biological manufacturing system based on the information about the second fluid.

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26. The method of claim 25, wherein the information about the second fluid comprises a concentration of a buffer solution component in the second fluid.

27. The method of claim 25, wherein the information about the second fluid comprises a
10 concentration of an ionic compound or a dissolved salt thereof in the second fluid.

28. The method of claim 25, wherein adjusting the second parameter comprises adjusting a feed rate of the second fluid into a purification unit of the system.

15 29. The method of claim 16, further comprising repeating the directing, measuring, determining, and transmitting steps to provide the concentration information as a feedback signal to the controller to adjust the parameter of the system during a biological manufacturing process.

20 30. A biological manufacturing system, comprising:
a vessel configured to hold or transport a first fluid generated by the system and comprising a wall defining at least a portion of the vessel;
a light source configured to direct a light beam to pass through the wall;
a detector configured to measure an angle of refraction of the light beam in the first
25 fluid, the angle of refraction corresponding to an angle between a propagation direction of the light beam in the first fluid and a normal to an interface between the wall and the first fluid;
and

a first controller connected to the detector and configured to:
receive information about the angle of refraction from the detector, and to
30 determine information about the first fluid based on the measured angle of refraction; and
adjust a parameter of the system based on the information about the first fluid.

31. The system of claim 30, wherein the information about the first fluid comprises a concentration of a substance in the first fluid.

32. The system of claim 30, wherein the information about the first fluid comprises a pH value of the first fluid.

5 33. The system of claim 30, further comprising a purification unit, wherein the first fluid comprises a fluid discharged from the purification unit.

34. The system of claim 33, wherein the purification unit comprises at least one chromatography column.

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35. The system of claim 30, further comprising a reactor, wherein the first fluid comprises a feed fluid introduced into the reactor.

15 36. The system of claim 30, further comprising a diafiltration unit, wherein the first fluid comprises a fluid discharged from the diafiltration unit.

37. The system of claim 30, further comprising multiple purification units, wherein the parameter of the system comprises a fluid flow path that selectively directs a successive portion of the first fluid to one of the multiple purification units.

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38. The system of claim 30, further comprising a reactor, wherein the parameter of the system comprises a feed rate of a substance into the reactor.

25 39. The system of claim 30, further comprising a diafiltration unit, wherein the parameter of the system comprises a feed rate of a substance into the diafiltration unit.

40. The system of claim 30, further comprising a purification unit, wherein the parameter of the system comprises a feed rate of a substance into the purification unit.

30 41. The system of claim 30, further comprising a purification unit, wherein the parameter of the system comprises a feed rate of successive portions of the first fluid into the purification unit.

42. The system of claim 31, wherein the first controller is configured to determine the concentration of the substance from a calibration equation derived from measured calibration data, and wherein the calibration equation expresses the concentration as a function of the angle of refraction.

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43. The system of claim 42, wherein the calibration equation expresses the concentration as a linear function of the angle of refraction.

44. The system of claim 42, wherein the calibration equation expresses the concentration
10 as a nonlinear function of the angle of refraction.

45. The system of claim 31, wherein the substance comprises a protein.

46. The system of claim 31, wherein the substance comprises a recombinant protein-
15 based drug product.

47. The system of claim 31, wherein the substance comprises a nucleic acid-based product.

20 48. The system of claim 30, wherein the first fluid is a process fluid generated by the system as part of a biological manufacturing process.

49. The system of claim 30, further comprising a purification unit, wherein the first fluid comprises an eluate discharged from the purification unit.

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50. The system of claim 30, further comprising:
a first purification unit and a second purification unit,
wherein the first fluid comprises an eluate solution from the first purification unit;
wherein the information comprises a concentration of a substance in the first fluid;
30 and
wherein the parameter adjustment comprises directing eluate solution from the first purification unit into an inlet of the second purification unit when the concentration of the substance in the first fluid exceeds a threshold value.

51. The system of claim 50, wherein the first and second purification units each comprise at least one chromatography column.

52. The system of claim 30, further comprising:

5 a first purification unit and a second purification unit, the first purification unit comprising an inlet connected to a conduit that delivers a feed solution to the first purification unit,

wherein the first fluid comprises an eluate solution from the first purification unit;

wherein the information comprises a concentration of a substance in the first fluid;

10 and

wherein the parameter adjustment comprises disconnecting the inlet of the first purification unit from the conduit and connecting an inlet of the second purification unit to the conduit to deliver the feed solution to the second purification unit when the concentration of the substance in the first fluid exceeds a threshold value.

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53. The system of claim 30, further comprising:

a second vessel configured to hold or transport a second fluid generated by the system and comprising a second wall defining at least a portion of the second vessel;

20 a second light source configured to direct a second light beam to pass through the second wall; and

a second detector configured to measure an angle of refraction of the second light beam in the second fluid, the angle of refraction corresponding to an angle between a propagation direction of the second light beam in the second fluid and a normal to an interface between the second wall and the second fluid,

25 wherein the first controller is connected to the second detector and configured to: receive information about the angle of refraction from the second detector, and to determine information about the second fluid based on the measured angle of refraction; and

30 adjust a second parameter of the system based on the information about the second fluid.

54. The system of claim 53, wherein the information about the second fluid comprises a concentration of a buffer solution component in the second fluid.

55. The system of claim 53, wherein the information about the second fluid comprises a concentration of an ionic compound or a dissolved salt thereof in the second fluid.
56. The system of claim 53, further comprising a purification unit, wherein adjusting the
5 second parameter comprises adjusting a feed rate of the second fluid into the purification unit.
57. The system of claim 30, wherein during a biological manufacturing process:
the light source is configured to repeatedly direct the light beam to pass through the
10 wall;
the detector is configured to repeatedly measure the angle of refraction of the light beam in the first fluid; and
the first controller is configured to repeatedly:
receive information about the angle of refraction from the detector;
15 determine information about the first fluid based on the measured angle of refraction; and
adjust the parameter of the system based on the information about the first fluid.
- 20 58. The system of claim 30, further comprising:
multiple purification units each comprising at least one chromatography column;
a column switching mechanism; and
a second controller connected to the column switching mechanism and in communication with the first controller,
25 wherein the first controller is configured to adjust the parameter of the system by transmitting a signal to the second controller causing the second controller to adjust the column switching mechanism to selectively direct a fluid into one of the multiple purification units.
- 30 59. The system of claim 58, wherein the selectively directed fluid comprises an additional portion of the first fluid.
60. The system of claim 30, further comprising:
a reservoir comprising a second fluid; and

a second controller in communication with the first controller,
wherein the first controller is configured to adjust the parameter of the system by
transmitting a control signal to the second processor based on the information about the first
fluid; and

5 wherein the second controller is configured to introduce a portion of the second fluid
from the reservoir into a successive portion of the first fluid in response to the control signal.

61. The system of claim 60, wherein the second fluid comprises a buffer solution.

10 62. The system of claim 60, wherein the second fluid comprises a solution of an ionic
compound or a dissolved salt thereof.

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