CLAIMS

1. A method of controlling additive delivery during a bioreaction in a bioreactor, the method comprising:

running a bioreaction in a bioreactor including adding additive into the bioreactor during spaced-apart feed events, where contents of the bioreactor equilibrate during a stabilisation period after a feed event;

making in situ measurements of a bulk physical property of the bioreactor contents during the bioreaction to obtain process trend data;

calculating a derivative of process trend data obtained over a measurement period beginning after a stabilisation period, the derivative being a metabolic rate index (MRI); and

using the MRI to determine a time for starting a next feed event.

2. A method according to claim 1, in which the process trend data obtained via the in situ measurements is actual process trend data, the method further comprises applying a mathematical method to actual process trend data obtained over a measurement period beginning after a stabilisation period to produce calculated process trend data representing a damped version of the actual process trend data, and the calculating a derivative comprises calculating a derivative of the calculated process trend data.

3. A method according to claim 2, in which the mathematical method comprises an averaging of the actual process trend data, or a fitting of a mathematical curve to the actual process trend data.

4. A method according to claim 3, in which the mathematical method comprises fitting a second order polynomial curve to the actual process trend data.

5. A method according to any preceding claim, in which the bulk physical property is refractive index.

6. A method according to claim 5, in which making in situ measurements of refractive index comprises using a sensor configured to detect changes in a propagating evanescent wave.

7. A method according to claim 6, in which the sensor detects changes in a modal index.

8. A method according to claim 7, in which the sensor is based on a Bragg grating.

9. A method according to any one of claims 1 to 4, in which the bulk physical property is density, conductivity, inductance, impedance, viscosity, turbidity, or spectral absorption at a single wavelength.

10. A method according to any one of claims 1 to 9, comprising using the MRI directly to determine a time for starting the next feed event.

11. A method according to any one of claims 1 to 9, in which using the MRI to determine a time for starting the next feed event comprises calculating a ratio by dividing the instantaneous MRI value by an absolute maximum value of the MRI since the previous feed event, comparing the ratio to a threshold value, and starting the next feed event when the ratio passes the threshold value.

12. A method according to claim 11, in which the threshold value is in the range of 0.3 to 0.9.

13. A method according to any preceding claim, in which the measurement period commences with a minimum temporal window, and the applying of the mathematical method and calculating of the derivative begins on process trend data collected during the minimum temporal window after the minimum temporal window expires.

14. A method according to claim 13, in which the minimum temporal window has a duration such that sufficient process trend data is collected for the corresponding MRI to have a minimum error or noise value compared to that for other durations.

15. A method according to claim 13 or claim 14, in which the duration of the minimum temporal window is adjusted based on previous process trend data.

16. A method according to any preceding claim, in which the stabilisation period has a duration determined by observation of process trend data obtained during a calibration run of the bioreactor.

17. A method according to any preceding claim, further comprising applying noise filtering to the obtained process trend data.

18. A method according to any preceding claim, further comprising varying the amount of additive delivered in a feed event in response to the MRI.

19. A method according to any one of claims 1 to 18, in which no additive is added into the bioreactor between feed events.

20. A method according to any one of claims 1 to 18, in which additive is added into the bioreactor at a first rate during each feed event, and additive is added continuously into the bioreactor between feed events at a second rate lower than the first rate.

21. A method according to claim 20, in which one or both of the first rate and the second rate are varied over time.

22. A method according to any preceding claim, in which different additives are added into the bioreactor during different feed events, the MRI during a current measurement time being used to determine the additive for the next feed event.

23. A method according to any preceding claim, in which the or each additive is a direct or indirect feedstock.

24. A method according to any preceding claim, further comprising using the MRI to determine values for one or more operating conditions of the bioreactor.

25. A controller for controlling additive delivery during a bioreaction in a bioreactor, the control configured to:

receive in situ measurements of a bulk physical property of contents of a bioreactor during a bioreaction, the bioreaction including additive being delivered into the bioreactor during spaced-apart feed events, where contents of the bioreactor equilibrate during a stabilisation period after a feed event, the received measurements being process trend data;

calculate a derivative of process trend data obtained over a measurement period beginning after a stabilisation period, the derivative being a metabolic rate index (MRI);

use the MRI to determine a time for starting a next feed event; and

generate a control signal configured to cause an additive supply mechanism to deliver additive into the bioreactor at the determined time for the next feed event.

26. A controller according to claim 25, in which the received process trend data is actual process trend data, and the controller is further configured to apply a mathematical method to actual process trend data obtained over a measurement period beginning after a stabilisation period to produce calculated process trend data representing a damped version of the actual process trend data, and to calculate the derivative by calculating a derivative of the calculated process trend data.

27. A controller according to claim 26, in which the mathematical method comprises an averaging of the actual process trend data, or a fitting of a mathematical curve to the actual process trend data.

28. A controller according to claim 27, in which the mathematical method comprises fitting a second order polynomial curve to the actual process trend data.

29. A controller according to any one of claims 25 to 28, in which the controller uses the MRI directly to determine a time for starting the next feed event.

30. A controller according to any one of claims 25 to 28, in which the controller uses the MRI to determine a time for starting the next feed event by calculating a ratio by dividing the instantaneous MRI value by an absolute maximum value of the MRI since the previous feed event, comparing the ratio to a threshold value, and starting the next feed event when the ratio passes the threshold value.

31. A controller according to claim 30, in which the threshold value is in the range of 0.3 to 0.9.

32. A controller according to any one of claims 25 to 31, in which the measurement period commences with a minimum temporal window, and the applying of the mathematical method and calculating of the derivative begins on process trend data

collected during the minimum temporal window after the minimum temporal window expires.

33. A controller according to claim 32, in which the controller is configured to set the minimum temporal window to have a duration such that sufficient process trend data is collected for the corresponding MRI to have a minimum error or noise value compared to that for other durations.

34. A controller according to claim 32 or 33, in which the controller is further configured to adjust the duration of the minimum temporal window based on previous process trend data.

35. A controller according to any one of claims 25 to 34, in which the controller is configured such that a user can set a duration for the stabilisation period following observation of process trend data during a calibration run of the bioreactor.

36. A controller according to any one of claims 25 to 35, in which the controller is configured to apply noise filtering to the received process trend data.

37. A controller according to any one of claims 25 to 36, in which the controller is further configured to configure the control signal to cause the additive supply mechanism to deliver an amount of additive determined by the controller in response to the MRI.

38. A controller according to any one of claims 25 to 37, in which the controller is further configured to generate no control signals for the additive supply mechanism between feed events.

39. A controller according to any one of claims 25 to 37, in which the controller is further configured to generate control signals for the additive supply mechanism to deliver additive at a first rate during each feed event, and at a second rate lower than the first rate between feed events.

40. A controller according to claim 39, in which the control signals are configured to vary one or both of the first rate and the second rate over time.

41. A controller according to any one of claims 25 to 40, in which the controller is further configured to configure the control signals to cause the additive supply mechanism to deliver different additives during different feed events, the controller using the MRI during a current measurement to determine the additive for the next feed event.

42. A controller according to any one of claims 25 to 41, in which the controller is further configured to use the MRI to determine values for one or more operating conditions of the bioreactor, and generate further control signals to control the operating conditions at the determined values.

43. A system for controlling additive delivery during a bioreaction in a bioreactor, the system comprising:

a bioreactor

an additive supply mechanism configured to deliver additive into the bioreactor during feed events, in response to a control signal;

a sensor associated with the bioreactor and configured to make in situ measurements of a bulk physical property of the bioreactor contents during a bioreaction, thereby obtaining process trend data; and

a controller configured to:

receive process trend data from the sensor;

calculate a derivative of process trend data obtained over a measurement period beginning after a stabilisation period during which contents of the bioreactor equilibrate after a feed event, the derivative being a metabolic rate index MRI;

use the MRI to determine a time for starting a next feed event; and

send a control signal to the additive supply mechanism to deliver additive at the determined time for the next feed event.

44. A system according to claim 43, in which the process trend data obtained via the in situ measurements is actual process trend data, and the controller is further configured to apply a mathematical method to actual process trend data obtained over a measurement period beginning after a stabilisation period to produce calculated process trend data representing a damped version of the actual process trend data, and to calculate the derivative by calculating a derivative of the calculated process trend data.

45. A system according to claim 44, in which the mathematical method comprises an averaging of the actual process trend data, or a fitting of a mathematical curve to the actual process trend data.

46. A system according to claim 45, in which the mathematical method comprises fitting a second order polynomial curve to the actual process trend data.

47. A system according to any one of claims 43 to 46, in which the bulk physical property is refractive index.

48. A system according to claim 47, in which the sensor is configured to detect changes in a propagating evanescent wave.

49. A system according to claim 48, in which the sensor detects changes in a modal index.

50. A system according to claim 49, in which the sensor is based on a Bragg grating.

51. A system according to any one of claims 43 to 46, in which the bulk physical property is density, conductivity, inductance, impedance, viscosity, turbidity, or spectral absorption at a single wavelength.

52. A system according to any one of claims 43 to 51, in which the controller uses the MRI directly to determine a time for starting the next feed event.

53. A system according to any one of claims 43 to 51, in which the controller uses the MRI to determine a time for starting the next feed event by calculating a ratio by dividing the instantaneous MRI value by an absolute maximum value of the MRI since the previous feed event, comparing the ratio to a threshold value, and starting the next feed event when the ratio passes the threshold value.

54. A system according to claim 53, in which the threshold value is in the range of 0.8 to 0.9.

55. A system according to any one of claims 43 to 54, in which the measurement period commences with a minimum temporal window, and the applying of the

mathematical method and calculating of the derivative begins on process trend data collected during the minimum temporal window after the minimum temporal window expires.

56. A system according to claim 55, in which the controller is configured to set the minimum temporal window to have a duration such that sufficient process trend data is collected for the corresponding MRI to have a minimum error or noise value compared to that for other durations.

57. A system according to claim 55 or claim 56, in which the controller is further configured to adjust the duration of the minimum temporal window based on previous process trend data.

58. A system according to any one of claims 43 to 57, in which the controller is configured such that a user can set a duration for the stabilisation period following observation of process trend data obtained during a calibration run of the bioreactor.

59. A system according to any one of claims 43 to 58, in which the controller is configured to apply noise filtering to the received process trend data.

60. A system according to any one of claims 43 to 59, in which the controller is further configured to configure the control signal to cause the additive supply mechanism to deliver an amount of additive in the next feed event determined by the controller in response to the MRI.

61. A system according to any one of claims 43 to 60, in which the controller is further configured to send no control signals to the additive supply mechanism between feed events.

62. A system according to any one of claims 43 to 60, in which the controller is further configured to send control signals to the additive supply mechanism to deliver additive at a first rate during each feed event, and at a second rate lower than the first rate between feed events.

63. A system according to claim 62, in which the control signals are configured to vary one or both of the first rate and the second rate over time.

64. A system according to any one of claims 43 to 63, in which the additive supply mechanism is configured to deliver two or more different additives, and the controller is further configured to configure the control signals to cause the additive supply mechanism to deliver different additives during different feed events, the controller using the MRI during a current measurement time to determine the additive for the next feed event.

65. A system according to any one of claims 43 to 64, in which the controller is further configured to use the MRI to determine values for one or more operating conditions of the bioreactor, and send further control signals to cause elements of the system to implement the determined values of the one or more operating conditions.

CLAIMS

1. A method of controlling additive delivery during a bioreaction in a bioreactor, the method comprising:

running a bioreaction in a bioreactor including adding additive into the bioreactor during spaced-apart feed events, where contents of the bioreactor equilibrate during a stabilisation period after a feed event;

making in situ measurements of a bulk physical property of the bioreactor contents during the bioreaction to obtain process trend data;

calculating a derivative of process trend data obtained over a measurement period beginning after a stabilisation period, the derivative being a metabolic rate index (MRI); and

using the MRI to determine a time for starting a next feed event.

2. A method according to claim 1, in which the process trend data obtained via the in situ measurements is actual process trend data, the method further comprises applying a mathematical method to actual process trend data obtained over a measurement period beginning after a stabilisation period to produce calculated process trend data representing a damped version of the actual process trend data, and the calculating a derivative comprises calculating a derivative of the calculated process trend data.

3. A method according to claim 2, in which the mathematical method comprises an averaging of the actual process trend data, or a fitting of a mathematical curve to the actual process trend data, or a fitting of a second order polynomial curve to the actual process trend data.

4. A method according to any preceding claim, in which the bulk physical property is refractive index.

5. A method according to claim 4, in which making in situ measurements of refractive index comprises using a sensor configured to detect changes in a propagating evanescent wave.

6. A method according to claim 5, in which the sensor detects changes in a modal index.

7. A method according to claim 6, in which the sensor is based on a Bragg grating.

8. A method according to any one of claims 1 to 3, in which the bulk physical property is density, conductivity, inductance, impedance, viscosity, turbidity, or spectral absorption at a single wavelength.

9. A method according to any one of claims 1 to 8, comprising using the MRI directly to determine a time for starting the next feed event.

10. A method according to any one of claims 1 to 8, in which using the MRI to determine a time for starting the next feed event comprises calculating a ratio by dividing the instantaneous MRI value by an absolute maximum value of the MRI since the previous feed event, comparing the ratio to a threshold value, and starting the next feed event when the ratio passes the threshold value.

11. A method according to claim 10, in which the threshold value is in the range of 0.3 to 0.9.

12. A method according to any preceding claim, in which the measurement period commences with a minimum temporal window, and the applying of the mathematical method and calculating of the derivative begins on process trend data collected during the minimum temporal window after the minimum temporal window expires.

13. A method according to claim 12, in which the minimum temporal window has a duration such that sufficient process trend data is collected for the corresponding MRI to have a minimum error or noise value compared to that for other durations.

14. A method according to claim 12 or claim 13, in which the duration of the minimum temporal window is adjusted based on previous process trend data.

15. A method according to any preceding claim, in which the stabilisation period has a duration determined by observation of process trend data obtained during a calibration run of the bioreactor.

16. A method according to any preceding claim, further comprising applying noise filtering to the obtained process trend data.

17. A method according to any preceding claim, further comprising varying the amount of additive delivered in a feed event in response to the MRI.

18. A method according to any one of claims 1 to 17, in which additive is added into the bioreactor at a first rate during each feed event, and additive is added continuously into the bioreactor between feed events at a second rate lower than the first rate.

19. A method according to claim 18 in which one or both of the first rate and the second rate are varied over time.

19. A method according to any preceding claim, in which different additives are added into the bioreactor during different feed events, the MRI during a current measurement time being used to determine the additive for the next feed event.

20. A method according to any preceding claim, in which the or each additive is a direct or indirect feedstock.

21. A method according to any preceding claim, further comprising using the MRI to determine values for one or more operating conditions of the bioreactor.

22. A controller for controlling additive delivery during a bioreaction in a bioreactor, the control configured to:

receive in situ measurements of a bulk physical property of contents of a bioreactor during a bioreaction, the bioreaction including additive being delivered into the bioreactor during spaced-apart feed events, where contents of the bioreactor equilibrate during a stabilisation period after a feed event, the received measurements being process trend data;

calculate a derivative of process trend data obtained over a measurement period beginning after a stabilisation period, the derivative being a metabolic rate index (MRI);

use the MRI to determine a time for starting a next feed event; and

generate a control signal configured to cause an additive supply mechanism to deliver additive into the bioreactor at the determined time for the next feed event.

23. A system for controlling additive delivery during a bioreaction in a bioreactor, the system comprising:

a bioreactor

an additive supply mechanism configured to deliver additive into the bioreactor during feed events, in response to a control signal;

a sensor associated with the bioreactor and configured to make in situ measurements of a bulk physical property of the bioreactor contents during a bioreaction, thereby obtaining process trend data; and

a controller configured to:

receive process trend data from the sensor;

calculate a derivative of process trend data obtained over a measurement period beginning after a stabilisation period during which contents of the bioreactor equilibrate after a feed event, the derivative being a metabolic rate index MRI;

use the MRI to determine a time for starting a next feed event; and

send a control signal to the additive supply mechanism to deliver additive at the determined time for the next feed event.