SUMMARY OF THE INVENTION

Accordingly, a first aspect of the present invention is directed to 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 the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate; and using the MRI to determine a time for starting a next feed event.

In some embodiments, the process trend data obtained via the in situ measurements is actual process trend data, and 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. The mathematical method may comprise an averaging of the actual process trend data, or a fitting of a mathematical curve such as a second order polynomial curve to the actual process trend data. Other mathematical methods and curves may also be used.

The bulk physical property may be refractive index. In this case, making in situ measurements of refractive index may comprise using a sensor configured to detect changes in a propagating evanescent wave, such as a sensor the detects changes in a modal index, and/or a sensor which is based on a Bragg grating.

Alternatively, the bulk physical property may be density, conductivity, inductance, impedance, viscosity, turbidity, or spectral absorption at a single wavelength.

The method may comprise using the MRI directly to determine a time for starting the next feed event. The MRI may alternatively be used indirectly. For example, the method may comprise 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. In some embodiments, the threshold value may be in the range of 0.3 to 0.9.

The measurement period may commence with a minimum temporal window, with the applying of the mathematical method and calculating of the derivative beginning on process trend data collected during the minimum temporal window after the minimum temporal window expires. This can improve accuracy of the mathematical method and

beginning after a stabilisation period, the derivative being a metabolic rate index (MRI), and the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate; 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.

A third aspect of the invention is directed to 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, and the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate; 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.

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 the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate; 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.

20. 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.

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

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

23. 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), and the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate;

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.

24. 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, and the stabilisation period being a transient stabilisation period during which chemical mixing and transient biological and metabolic processes equilibrate;

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.