In another aspect, the present disclosure refers to a system for the production of a biological substance by culturing cells that produce said biological substance, comprising:

- a plurality of bioreactors (10, 15) each arranged to incubate a cell culture of cells suspended in a culture medium in said bioreactor,
- said system further comprising a culture medium feed (16) arranged to compensate effluent loss by feeding culture medium or a component thereof into the at least one bioreactor,
- a cell detector to detect that incubation of a cell culture in one of said bioreactors has reached the exponential phase, the early stationary phase or stationary phase,
- a harvesting filter module (20) arranged to harvest the biological substance from the culture medium containing the biological substance, and
- a separator (30) communicatively coupled between the harvesting filter module and the plurality of bioreactors, said separator arranged to separate the cells from the culture medium containing the biological substance, and
- a pump and switching unit (40) arranged between the separator (30) and said plurality of bioreactors (10, 15), arranged to input, upon detection of said exponential phase, early stationary phase or stationary phase in one of said plurality of bioreactors (10, 15), cells and culture medium from said one (10) of said plurality of bioreactors into the separator, and feeding essentially all cells, from the separator (30) via said pump and switching unit (40), back into another one (15) of said plurality of bioreactors for continued culture together with fresh culture medium;

wherein the separator (30) comprises a centrifuge (35), arranged to maintain cells as a concentrated fluidized bed through the continuous balanced action of centrifugal and fluid flow forces, said centrifuge comprising an inlet of fresh medium arranged to provide said fluid flow

force thereby separating the cells from the culture medium with the biological substance.

Detailed Description

The present invention is in particular concerned with large scale fed-batch culture or fermentation. There are two basic approaches to the fed-batch fermentation; the constant volume fed-batch culture and the variable volume fed-batch culture.

In fixed volume fed-batch, the limiting substrate is fed without diluting the culture. The culture volume can also be maintained practically constant by feeding the growth limiting substrate in undiluted form, for example, as a very concentrated liquid or gas (ex. oxygen). A certain type of extended fed-batch - the cyclic fed-batch culture for fixed volume systems - refers to a periodic withdrawal of a portion of the culture and use of the residual culture as the starting point for a further fed-batch process. Basically, once the fermentation reaches a certain stage, (for example, when aerobic conditions cannot be maintained anymore) part of the culture is removed and the remaining biomass is diluted to the original volume with sterile water or medium containing the feed substrate. The dilution decreases the biomass concentration and typically results in an increase in the specific growth rate. Subsequently, as feeding continues, the growth rate will decline gradually as biomass increases and approaches the maximum sustainable in the vessel once more, at which point part of the culture may again be replaced by fresh culture medium.

Claims

1. A method for the production of a biological substance by culturing cells that produce said biological substance in a bioreactor, said method comprising: providing a bioreactor with a cell culture comprising said cells suspended in a culture medium; and
said method further comprising performing at least one culture and harvest cycle comprising incubating said cell culture in a bioreactor until the cell culture has reached the exponential phase, the early stationary phase or the stationary phase, and harvesting the culture medium with the biological substance by separating the cells from the culture medium containing the biological substance and feeding essentially all cells back into a different bioreactor for continued culture together with fresh culture medium, wherein the culture medium with the biological substance is harvested by flowing the cell culture into a centrifuge that maintains the cells as a concentrated fluidized bed through the continuous balanced action of centrifugal and fluid flow forces, whereby the fluid flow force is applied by the inflow of fresh medium thereby separating the cells from the culture medium with the biological substance.
2. A method according to claim 1, comprising at least 2 culture and harvest cycles.
3. A method according to claim 1 or claim 2, wherein during incubation of the cell culture at least part of the cell culture is continuously flowed into a separation system that comprises a size selective semipermeable membrane, wherein the membrane separates the cells and the biological substance from substances having a lower molecular weight than the biological substance, thereby creating a cell- and biological substance-free effluent that is outputted, and
a cell- and biological substance-containing fluid stream that is fed back into the bioreactor, and wherein effluent loss is at least compensated by feeding culture medium or a component thereof into the bioreactor.
4. A method according to any one of claims 1-3, wherein the cells are mammalian cells.
5. A method according to claim 4, wherein said cells are CHO cells.

6. A method according to any one of claims 1-5, wherein said biological substance is an antibody or antigen binding fragment thereof.

7. A method according to any one of claims 1-6, wherein said cells are cultured in a fed-batch culture system.

8. A system for the production of a biological substance by culturing cells that produce said biological substance, comprising:

- a plurality of bioreactors (10, 15) each arranged to incubate a cell culture of cells suspended in a culture medium in said bioreactor,
- said system further comprising a culture medium feed (16) arranged to compensate effluent loss by feeding culture medium or a component thereof into the at least one bioreactor.
- a cell detector to detect that incubation of a cell culture in one of said bioreactors has reached the exponential phase, the early stationary phase or stationary phase,
- a harvesting filter module (20) arranged to harvest the biological substance from the culture medium containing the biological substance, and
- a separator (30) communicatively coupled between the harvesting filter module and the plurality of bioreactors, said separator arranged to separate the cells from the culture medium containing the biological substance, and
- a pump and switching unit (40) arranged between the separator (30) and said plurality of bioreactors (10, 15), arranged to input, upon detection of said exponential phase, early stationary phase or stationary phase in one of said plurality of bioreactors (10, 15), cells and culture medium from said one (10) of said plurality of bioreactors into the separator, and feeding essentially all cells, from the separator (30) via said pump and switching unit (40), back into another one (15) of said plurality of bioreactors for continued culture together with fresh culture medium;

wherein

the separator (30) comprises a centrifuge (35), arranged to maintain cells as a concentrated fluidized bed through the continuous balanced action of centrifugal and fluid flow forces, said centrifuge comprising an inlet of fresh medium arranged to provide said fluid flow force thereby separating the cells from the culture medium with the biological substance.

9. A system according to claim 8, wherein at least one bioreactor (10) is in fluid communication with a membrane separator (50) that comprises a size selective semipermeable membrane (55) and a membrane separator outlet (56), said membrane separator being in fluid communication with said at least one bioreactor (10), and arranged to continuously flow at least part of the cell culture from said at least one bioreactor into said membrane separator; said membrane (55) arranged to separate the cells and the biological substance from substances having a lower molecular weight than the biological substance, thereby creating a cell- and biological substance-free effluent that is outputted via said membrane separator outlet (56), and a cell- and biological substance-containing fluid stream that is fed back into the bioreactor.

10. A system according to claim 8, wherein the harvesting filter module (20) comprises a waste outlet (21) and a depth filter (22) that is arranged to separate the biological substance from substances having a higher molecular weight than the biological substance, thereby creating a biological substance-free effluent that is outputted via the waste outlet, and wherein the biological substance is outputted to downstream processing.