CLAIMS

1. A process for producing an inoculum for a subsequent cell culture production process comprising:
introducing a cell culture into a perfusion bioreactor;
feeding a nutrient media at a flow rate to the perfusion bioreactor and withdrawing fluid media from the perfusion bioreactor;
determining biomass concentrations over time within the perfusion bioreactor using a biomass sensor, the biomass sensor being in communication with a controller; and
adjusting the nutrient media flow rate into the perfusion bioreactor based on biomass concentrations sensed by the biomass sensor, the controller being configured to adjust the media flow rate based on information received from the biomass sensor,
wherein the nutrient media flow rate is adjusted based on the following relationship:

$$P = K^{*}\varphi$$

wherein K is the biovolume specific perfusion rate (mL feed/mL biovolume/day);

φ is the biovolume fraction and is the volume of the perfusion bioreactor that is inside the cell membranes of the cells, expressed as a percentage or fraction (mL biovolume/mL bioreactor); and

P is the perfusion rate expressed in mL feed/mL bioreactor/day.

2. A process according to claim 1, wherein the biomass sensor is a capacitance sensor.

3. A process according to claim 1 or claim 2, wherein the controller is configured to increase the flow rate of the nutrient media as the biomass concentration increases.

4. A process according to any one of the preceding claims, further comprising the step of determining the amount of fluid media within the perfusion bioreactor and based on the amount, selectively increasing or decreasing a rate at which the fluid media is withdrawn from the perfusion bioreactor.

5. A process according to claim 4, wherein the amount of fluid media within the perfusion bioreactor is determined by weighing the perfusion bioreactor using a weighing device.

6. A process according to claim 5, wherein the weighing device is in communication with the controller, and based on weight information from the weighing device, the controller is configured to control a pumping device in fluid communication with the perfusion bioreactor for selectively increasing or decreasing the rate at with fluid media is withdrawn.

7. A process according to claim 4, wherein the amount of fluid media within the perfusion bioreactor is determined by measuring volume.

8. A process according to any one of the preceding claims, wherein the cell density in the cell culture in the perfusion bioreactor increases over time such as by at least 60% per day.

9. A process according to any one of the preceding claims, wherein the biomass sensor determines the biomass concentration within the perfusion reactor at least every 6 hours.

10. A process according to any one of the preceding claims, wherein the perfusion bioreactor has a volume of from about 10L to about 4000L.

11. A process according to any one of the preceding claims, wherein after an incubation period, the process further includes transferring the cell culture from the perfusion bioreactor to a second bioreactor, the second bioreactor having a volume that is larger than a volume of the perfusion bioreactor, the volume ratio between the perfusion bioreactor and the second bioreactor being from 1:3 to 1:40, such as from about 1:4 to about 1:10.

12. A process according to claim 11, wherein the cell culture continues to grow in the second bioreactor in a fed batch-type manner.

13. A process according to claim 11 or 12, wherein the cell culture remains in the perfusion bioreactor from about 3 days to about 12 days and remains in the second bioreactor for less than about 12 days, such as less than about 10 days.

14. A process according to any one of the preceding claims, wherein the cell culture reaches a cell density within the perfusion bioreactor of greater than about 10 x 10^6 cells/ mL, such as greater than about 30 x 10^6 cells/mL, such as greater than about 50 x 10^6 cells/mL, such as greater than about 70 x 10^6 cells/mL.

15. A process according to any one of the preceding claims, wherein the cell culture reaches a cell density within the perfusion bioreactor of 100 x 10^6 cells/mL or greater.

16. A process according to any one of the preceding claims, wherein the cell culture comprises mammalian cells.

17. A system for producing an inoculum for a subsequent cell culture production process comprising;

a perfusion bioreactor;

a nutrient media feed in fluid communication with the perfusion bioreactor, the nutrient media feed for feeding a nutrient media to the perfusion bioreactor for growing a cell culture;

an effluent for withdrawing fluid media from the perfusion bioreactor;

a pumping device in fluid communication with the effluent of the perfusion bioreactor for withdrawing controlled amounts of fluid media from the perfusion bioreactor;

a weighing device for monitoring a weight of the perfusion bioreactor;

a biomass sensor, such as a capacitance sensor, in fluid communication with the perfusion bioreactor for determining biomass concentrations within the perfusion bioreactor; and

a controller in communication with the biomass sensor and the weighing device, the controller being configured to control the nutrient media feed for increasing or decreasing a flow rate of nutrient media being fed to the perfusion bioreactor based on information received from the biomass sensor, the controller also being configured to control the pumping device for increasing or decreasing a flow rate of fluid media being withdrawn from the perfusion bioreactor based on information received from the weighing device,

wherein the controller controls the flow weight of the nutrient media in to the perfusion bioreactor based upon the following relationship:

$$P = K^{*}\varphi$$

wherein K is the biovolume specific perfusion rate (mL feed/mL biovolume/day);

φ is the biovolume fraction and is the volume of the perfusion bioreactor that is inside the cell membranes of the cells, expressed as a percentage or fraction (mL biovolume/mL bioreactor); and

P is the perfusion rate expressed in mL feed/mL bioreactor/day.

18. A cell culture production process comprising:

producing an inoculum by the method of any one of claims 1 to 15 comprising host cells that express a bioproduct;

introducing the inoculum into a production bioreactor ;

culturing the host cells to produce the bioproduct;

harvesting the bioproduct from the cell culture; and

optionally subjecting the bioproduct to one or more purification steps.