CLAIMS

What is claimed is:

1. A method of controlling a bioreactor system, comprising:

providing a cell culture in a bioreactor, wherein conditions in the bioreactor enable the cell culture to produce a protein of interest (POI);

measuring one or more process parameters (PPs) of the culture within the bioreactor by a RAMAN probe, wherein the process parameters are selected from the group consisting of nutrient concentration, viable cell concentration, and protein attributes;

measuring a weight of the bioreactor with cell culture contents;

removing cell-free spent media from the cell culture using a first output conduit at a first specified rate;

removing cells from the cell culture using a second output conduit at a second specified rate;

introducing one or both of fresh media or nutrients into the cell culture using an input conduit at a third specified rate; and

wherein the input and output conduits are adjusted based on the RAMAN probe measurements and weight measurement of the bioreactor to maintain (i) one or more of the process parameters within predetermined ranges, (ii) the weight of the bioreactor with the cell culture within a predetermined range, and (iii) the third specified rate of the input conduit and the first and second specified rates of each of the output conduits within their respective predetermined ranges.

2. The method of claim 1, wherein measuring the one or more process parameters of the culture within the bioreactor by RAMAN occurs at least once per hour.

3. The method of any one of the preceding claims, wherein the method is configured to maintain the cell culture at an average viable cell concentration of at least 30 million cells per mL for 30 days at steady state.

4. The method of any one of the preceding claims, wherein the bioreactor has a volume of at least 10L, and the method is configured to maintain the weight of the bioreactor and cell culture within a 20g range.

5. The method of any one of the preceding claims, wherein the bioreactor has a volume of at least 10L, and the method is configured to maintain the weight of the bioreactor with the cell culture within 0.1 percent of an initial weight of the bioreactor with the cell culture.

6. The method of any one of the preceding claims, wherein, when a process parameter deviates from a set point value within a respective desired range, one or more of removing cell-free media, removing cells, or introducing one or both of fresh media or nutrients, is adjusted to reduce the deviation.

7. The method of any one of the preceding claims, wherein at least two bioreactor volumes of spent media are removed through the first output conduit per day.

8. The method of any one of the preceding claims, wherein up to three bioreactor volumes of spent media are removed through the first output conduit per day.

9. The method of any one of the preceding claims, wherein the process parameters include temperature of the cell culture and pH of the cell culture, and the temperature is maintained between 35 and 36 degrees C, and the pH is maintained between 6.85 and 7.15.

10. The method of any one of the preceding claims, wherein the process parameters include cell specific productivity, and the method is configured to maintain

cells within the cell culture at a cell specific productivity of at least 15-25 pg/cell/day for at least 25-37 days.

11. The method of any one of the preceding claims, wherein the process parameters include glucose concentration, and the method is configured to maintain a glucose concentration between about 5 mM to about 85 mM, or about 1 g/L to about 15.5 g/L.

12. The method of any one of the preceding claims, wherein the process parameters include lactate concentration, and the method is configured to maintain a lactate concentration less than about 60 mM, or less than about 6 g/L.

13. The method of any one of the preceding claims, wherein the process parameters include ammonia concentration, and the method is configured to maintain an ammonia concentration less than about 15 mM.

14. The method of any one of the preceding claims, wherein each of removing cell-free spent media, removing cells, and introducing one or both of fresh media or nutrients, is controlled by a respective pump.

15. The method of any one of the preceding claims, wherein the bioreactor includes a filter configured to retain cells and allow fluid to pass through.

16. A method of controlling a bioreactor system, comprising:

providing a cell culture in a bioreactor;

measuring one or more process parameters of the cell culture within the bioreactor by a RAMAN probe;

removing cell-free spent media from the cell culture using a first output conduit at a first specified rate;

removing cells from the cell culture using a second output conduit at a second specified rate;

introducing one or both of fresh media or nutrients into the cell culture using an input conduit at a third specified rate; and

changing one or more of the first specified rate, the second specified rate, or the third specified rate based on the RAMAN probe measurements.

17. A bioreactor culture system, comprising:

a tank having an input conduit and at least one output conduit;

at least one pump;

a filter coupled to the tank;

a RAMAN probe coupled to the tank; and

a controller coupled to the at least one pump and the RAMAN probe, the controller being configured to control the at least one pump based on an input from the RAMAN probe.

18. A bioreactor culture system, comprising:

a tank having an input conduit and at least one output conduit;

at least one pump;

a filter coupled to the tank;

a scale in contact with the tank;

a RAMAN probe coupled to the tank; and

a controller coupled to the at least one pump, the scale, and the RAMAN probe, the controller being configured to control the at least one pump based on an input from the RAMAN probe and an input from the scale.

19. A bioreactor culture system, comprising:

a tank having an input conduit for connection to a first pump configured to control fluid delivery to the tank, a first output conduit for connection to a second pump configured to control removal of fluid from the tank, and a second output conduit for connection to a third pump configured to control removal of cells from the tank;

a filter coupled to the tank, wherein the filter is configured to retain cells in the tank and to allow fluid to pass through the filter;

a scale configured to measure a weight of the tank with a cell culture within the tank;

a RAMAN probe disposed within the tank; and

a controller coupled to the first pump, the second pump, the third pump, the scale, and the RAMAN probe, wherein the controller is configured to:

receive weight data from the scale;

compare the weight of the tank with a set point for the weight;

receive spectral data from the RAMAN probe;

determine, based on the received spectral data, a parameter of the cell culture;

compare the determined parameter to a set point of the parameter; and

based on the comparisons, adjust one or more of a throughput of the first pump, the second pump, and the third pump.

20. A bioreactor culture system, comprising:

a tank having an input conduit and at least one output conduit;

at least one pump;

a filter coupled to the tank;

a RAMAN probe coupled to the tank; and

a controller coupled to the at least one pump and the RAMAN probe, the controller being configured to control the at least one pump based on an input from the RAMAN probe.

21. A bioreactor culture system, comprising:

a tank having an input conduit for connection to a first pump configured to control fluid delivery to the tank, a first output conduit for connection to a second pump configured to control removal of fluid from the tank, and a second output conduit for connection to a third pump configured to control removal of cells from the tank;

a filter coupled to the tank, wherein the filter is configured to retain cells in the tank and to allow fluid to pass through the filter;

a scale configured to measure a weight of the tank with a cell culture within the tank;

a RAMAN probe disposed within the tank; and

a controller coupled to the first pump, the second pump, the third pump, the scale.