

Time (hrs) Feedback Control	Glucose Concentration Feedback Control (g/L)	Time (hrs) Bolus Fed	Glucose Concentration Bolus Fed (g/L)
320.5222222	2.16041		
320.9663889	2.30146		
321.4102778	2.35759		
321.8544444	2.06147		
322.2986111	2.2465		
322.5216667	1.90065		
322.9658333	2.42279		
323.41	2.29138		
323.8541667	2.21841		
324.2980556	2.42145		
324.5211111	2.35336		
324.9652778	2.25286		
325.4094444	2.25769		
325.8536111	2.31652		
326.2975	2.24343		
326.5205556	2.28121		
326.9644444	2.32713		
327.4086111	2.38217		
327.8527778	2.14074		
328.2966667	2.30334		
328.5197222	2.2444		
328.9638889	2.10546		
329.4080556	2.16617		
329.8522222	2.30982		
330.2961111	2.12672		
330.5191667	2.19646		
330.9633333	1.81375		
331.4075	2.20783		

Example 2: Comparison of Feedback Control and Bolus Fed Strategy

Materials and Methods

Cells were cultured under feedback control or bolus fed strategy as described above.

Results

Figure 11 shows the difference in PTMs in cells cultured using the feedback control or bolus fed strategy. Each pair of columns represents a batch day. For each pair of columns, the left column is the feedback control data, and the right column is the bolus fed data. The feedback control strategy (left column for each pair of columns) was confirmed to reduce the level of %PTM in the subsequent experiment as compared to the bolus feed strategy (right column for each pair of columns). Controlling the nutrient set point at a constant level, the %PTM was steadily maintained over the course of the production. The %PTM was also reduced from the bolus feed strategy thus demonstrating the ability to control antibody quality through Raman Spectroscopy feedback control.

The disclosed feedback control culture systems and methods provide real-time multi-component analysis without sample removal. Real time data enables automatic feedback control for continuous nutrient addition. Reduced, steady bioreactor concentrations of reactive nutrients results in lower level of antibody PTM by over 50% from standard bolus nutrient feed thus improving product quality and consistency.

While in the foregoing specification this invention has been described in relation to certain embodiments thereof, and many details have been put forth for the purpose of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein can be varied considerably without departing from the basic principles of the invention.

All references cited herein are incorporated by reference in their entirety. The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

THE CLAIMS

What is claimed is:

1. A method for controlling cell culture medium conditions comprising:
quantifying one or more analytes in the cell culture medium using in situ Raman spectroscopy; and
adjusting the one or more analyte concentrations in the cell culture medium to match predetermined analyte concentrations that maintain post-translational modifications of proteins in the cell culture medium to 1.0 to 30 percent.
2. The method of claim 1, wherein the post-translational modification comprises glycation.
3. The method of claim 1, wherein proteins in the cell culture comprise an antibody or antigen-binding fragment thereof.
4. The method of claim 1, wherein proteins in the cell culture comprise a fusion protein.
5. The method of claim 1, wherein the cell culture medium comprises mammalian cells.
6. The method of claim 5, wherein the mammalian cells comprise Chinese Hamster Ovary cells.
7. The method of claim 1, wherein the analyte is glucose.
8. The method of claim 7, wherein the predetermined glucose concentration is 0.5 to 8.0 g/L.
9. The method of claim 7, wherein the glucose concentration is 1.0 g/L to 3.0 g/L.
10. The method of claim 7, wherein the glucose concentration is 2.0 g/L.
11. The method of claim 7, wherein the glucose concentration is 1.0 g/L.
12. The method of claim 1, wherein the predetermined analyte concentrations maintain post-translation modifications of proteins in the cell culture medium to 1.0 to 20 percent.
13. The method of claim 1, wherein the predetermined analyte concentrations maintain post-translation modifications of proteins in the cell culture medium to 5.0 to 10 percent.
14. The method of claim 1, wherein the quantifying of analytes is performed continuously.
15. The method of claim 1, wherein the quantifying of analytes is performed intermittently.
16. The method of claim 1, wherein the quantifying of analytes is performed in intervals.
17. The method of claim 1, wherein the quantifying of analytes is performed in 5 minute intervals.