

CLAIMS

1. A method for controlling cell culture medium conditions comprising:
quantifying ~~the concentrations of~~ one or more analytes in the cell culture medium using *in situ* Raman spectroscopy to determine concentrations of the one or more analytes; and
adjusting with a duty cycle feedback controlled continuous nutrient feed the concentrations of the one or more analytes ~~s-concentrations~~ in the cell culture medium to maintain steady-state concentrations of the one or more analytes in the cell culture medium at a predefined set point between about 1 g/L to about 10 g/L by providing ~~provide~~ steady-state addition of ~~small doses~~ a dose of nutrients continuously over time near or at the rate the nutrients are taken up or consumed by cells in the culture medium,
wherein adjusting the concentrations of the one or more analytes ~~at least one of the predetermined analyte concentrations that~~ maintains post-translational modifications of ~~proteins~~ a protein bioproduct in the cell culture medium to 1.0 to 30 percent,
wherein the post-translational modifications comprise more than one nutrient-sensitive post-translational modification selected from the group consisting of glycation, glycosylation, acetylation, phosphorylation, amidation, derivatization by a protecting/blocking group, proteolytic cleavage, and modification by a non-naturally occurring amino acid.
2. The method of claim 1, wherein the post-translational modification comprises glycation.
3. The method of claim 1, wherein the protein bioproduct ~~proteins in the cell culture~~ comprises an antibody or antigen-binding fragment thereof.
4. The method of claim 1, wherein the protein bioproduct ~~proteins in the cell culture~~ comprises 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 one or more analytes is glucose.
8. The method of claim 7, wherein the predefined set point comprises a ~~predetermined~~ glucose concentration is of 0.5 to 8.0 g/L.
9. The method of claim 8, wherein the ~~predetermined~~ glucose concentration is 1.0 g/L to 3.0 g/L.

10. The method of claim 8, wherein the ~~predetermined~~ glucose concentration is 2.0 g/L.
11. The method of claim 8, wherein the ~~predetermined~~ 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 one or more analytes is performed continuously.
15. The method of claim 1, wherein the quantifying of one or more analytes is performed intermittently.
16. The method of claim 1, wherein the quantifying of one or more analytes is performed in intervals.
17. The method of claim 1, wherein the quantifying of one or more analytes is performed in 5 minute intervals.
18. ~~1~~The method of claim 1, wherein the quantifying of one or more analytes is performed in 10 minute intervals.
19. The method of claim 1, wherein the quantifying of one or more analytes is performed in 15 minute intervals.
20. The method of claim 1, wherein the quantifying of one or more analytes is performed hourly.
21. The method of claim 1, wherein the quantifying of one or more analytes is performed at least daily.
22. The method of claim 1, wherein the adjusting of one or more analyte concentrations is performed automatically.
23. The method of claim 1, wherein at least two different analytes are quantified.
24. The method of claim 1, wherein at least three different analytes are quantified.
25. The method of claim 1, wherein at least four different analytes are quantified.
26. A method for reducing post-translation modifications of a secreted protein bioproduct comprising:
culturing cells secreting the protein bioproduct in a cell culture medium comprising ~~0.5 to 8.0 g/L~~ about 1 g/L to about 8.0 g/L glucose;

incrementally determining the concentration of glucose in the cell culture medium during culturing of the cells using *in situ* Raman spectroscopy by using a duty cycle feedback controlled continuous nutrient feed to provide steady-state addition of ~~small doses~~ a dose of nutrients continuously over time near or at the rate the nutrients are taken up or consumed by cells in the culture medium; and

adjusting the glucose concentration to maintain the concentration of glucose to ~~0.5 to 8.0 g/L~~ about 1 g/L to about 8.0 g/L by automatically delivering multiple doses of glucose per hour to maintain post-translational modifications of the secreted protein bioproduct to 1.0 to 30.0 percent,

wherein the post-translational modifications comprise more than one nutrient-sensitive post-translational modification selected from the group consisting of glycation, glycosylation, acetylation, phosphorylation, amidation, derivatization by a protecting/blocking group, proteolytic cleavage, and modification by a non-naturally occurring amino acid.

27. The method of claim 26, wherein the concentration of glucose is 1.0 to 3.0 g/L.