CLAIMS

1. A method of controlling the number of disulfide bonds between polypeptides of a multimeric protein produced by a bioprocess, the method comprising:

(a) contacting the polypeptides with a conditioned solution at a specific time point during the bioprocess, wherein the conditioned solution has a pH between 3.4 to 6; and wherein the conditioned solution comprises a redox reagent, wherein the redox reagent is 2-mercaptoethylamine (2-MEA);

(b) incubating the conditioned solution comprising the polypeptides for a predetermined time at a predetermined temperature, wherein the predetermined temperature of the incubation is between 2°C and 23°C; and

wherein the incubation of the polypeptides with the conditioned solution increases the number of disulfide bonds formed between the polypeptides of the protein, and wherein the multimeric protein is an antibody or antibody fragment.

2. The method of claim 1, wherein the ratio of redox reagent molarity to protein molarity is at least about 4:1, 8:1, 16:1, or 32:1.

3. The method of claim 1 or 2, wherein the conditioned solution comprising the polypeptides is mixed during incubation.

4. The method of any one of claims 1 to 3, further comprising removing the polypeptides from the bioprocess at the specific time point during the bioprocess.

5. The method of claim 4, further comprising returning the polypeptides to the bioprocess after incubation.

6. The method of any one of claims 1 to 5, wherein the bioprocess comprises a batch, semi-continuous, or continuous bioprocess.

7. The method of any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point after a bioreactor operation or fed batch cell culture operation in the bioprocess.

8. The method of any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are in a solution comprising a plurality of cells.

9. The method of claim 8, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are located in a bioreactor, holding tank, or a non-bioreactor unit operation vessel comprising a plurality of cells.

10. The method of any one of claims 1 to 6, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are in a cell-free solution.

11. The method of claim 10, wherein the specific time point during the bioprocess comprises a time point wherein the polypeptides are located in a holding tank.

12. The method of claim 10 or 11, wherein the specific time point during the bioprocess comprises a time point during the step of viral inactivation, adjustment, chromatography, filtration, dilution, concentration, or any bioprocess step that is cell-free.

13. The method of any one of claims 10 to 12, wherein the specific time point during the bioprocess comprises a time point during the clarification stage, clarified harvest stage, capture stage, intermediate chromatography stage, or polishing chromatography stage of the bioprocess.

14. The method of any one of claims 10 to 13, wherein the cell-free solution comprises clarified harvest.

15. The method of any one of claims 10 to 14, wherein the cell-free solution comprises Protein A eluate.

16. The method of any one of claims 1 to 15, wherein the polypeptides of the multimeric protein comprise heavy chain polypeptides, light chain polypeptides or heavy chain and light chain polypeptides.

17. The method of any one of claims 1 to 16, wherein the polypeptides are monomers or multimers of the protein.

18. A method of controlling the proportion of half antibody molecules in a solution comprising a population of antibody molecules, the method comprising:

(a) contacting the solution comprising the population of antibody molecules with a conditioned solution, wherein the conditioned solution has a pH between 3.4 to 6; and

wherein the conditioned solution comprises a redox reagent, wherein the redox reagent is 2-mercaptoethylamine (2-MEA);

(b) incubating the conditioned solution comprising the antibody molecules for a predetermined time at a predetermined temperature, wherein the predetermined temperature of the incubation is between 2°C and 23°C;

wherein the incubation of the antibody molecules with the conditioned solution decreases the proportion of half antibody molecules in the conditioned antibody solution.

19. The method of any one of claims 1 to 18, wherein the antibody is an IgG4 antibody.

20. The method of claim 18, wherein the antibody is an antibody fragment.

21. The method of any one of claims 1 to 18 or 20, wherein the antibody fragment is an IgG4 antibody fragment.

22. The method of any one of claims 18 to 21, wherein the proportion of half antibody molecules in the conditioned antibody solution is less than 30 percent.

23. The method of any one of claims 18 to 22, wherein the proportion of half antibody molecules in the conditioned antibody solution is less than 15 percent.

24. The method of claim 18 or 19, wherein the antibody solution comprises natalizumab, gemtuzumab, or fresolimumab.