CLAIMS

1. A method of culturing cells in a bioreactor comprising providing a mass transfer of a gas to/from the bioreactor without generating bubbles inside the bioreactor.

2. The method of claims 1, wherein the bioreactor is a perfusion bioreactor.

3. The method of claim 1, wherein the bioreactor is a batch-fed bioreactor.

4. The method of claim 1, wherein the mass transfer of a gas to/from the bioreactor is provided by a gas transfer module.

5. The method of claim 4, wherein the gas transfer module comprises a non-porous membrane.

6. The method of claim 5, wherein the non-porous membrane is a polymer, metal, or ceramic.

7. The method of claim 6, wherein the polymer comprises silicone gum homopolymer, polydimethylsiloxane (PDMS), or silicone-polycarbonate copolymer. The method of claims 5, wherein the non-porous membrane comprises a plurality of hollow fibers.

8. The method of claim 8, wherein the gas transfer module comprises a first flow path through the hollow fibers for passage of one or more gases and a second flow path around the hollow fibers for a flow of cell culture media and/or cells.

9. The method of claim 8, wherein the gas transfer module is located outside of the bioreactor.

10. The method of claim 8, wherein the plurality of hollow fibers provide a flow path for culture media and cells to travel through spaces separating the hollow fibers.

11. The method of claim 12, wherein the spaces are homogenous or heterogenous.

12. The method of claim 10, wherein the spaces are of sufficient size to allow passage of a cell without causing shear forces on the cell.

13. The method of claim 10, wherein the spaces comprise a distance of about 15 μm to about 2000 μm.

14. The method of claim 13, wherein the spaces comprise a distance 15-30 μm, 20-40 μm, 30-60 μm, 40-80 μm, 60-120 μm, 80-160 μm, 100-200 μm, 150-300 μm, 200-400 μm, 200-500 μm, 200-600 μm, 200-700 μm, 200-800 μm, 200-900 μm, 200-1000 μm, or 500-2000 μm, or a combination thereof.

15. The method claim 9, wherein the flow of cell culture media and/or cells comprises tangential, axial flow or a combination thereof.

16. The method of claim 9, wherein the flow of the cell culture media and/or cells is at a rate that is sufficient to maintain culture homogeneity without causing shear forces on the cells.

17. The method of claim 1, wherein the gas is air, carbon dioxide, oxygen, and/or nitrogen, or a mixture thereof.

18. The method of claim 1, wherein the bioreactor comprises a cell density of about 20 x 10^6 cells/ml, about 30 x 10^6 cells/ml, about 40 x 10^6 cells/ml, about 50 x 10^6 cells/ml, about 60 x 10^6 cells/ml, about 70 x 10^6 cells/ml, about 80 x 10^6 cells/ml, about 90 x 10^6 cells/ml, about 100 x 10^6 cells/ml, about 110 x 10^6 cells/ml, about 120 x 10^6 cells/ml, about 130 x 10^6 cells/ml, about 140 x 10^6 cells/ml, about 150 x 10^6 cells/ml, about 160 x 10^6 cells/ml, about 170 x 10^6 cells/ml, or about 180 x 10^6 cells/ml.

19. The method claim 1, wherein the method avoids production of foam.

20. The method of claim 1, wherein the bioreactor comprises no headspace or substantially no headspace. The method of claim 1, wherein the method requires no anti-foaming agent during cell culture.

21. The method of claim 4, wherein the bioreactor comprises two or more gas transfer modules.

22. The method of claim 21, wherein the two or more gas transfer modules provide mass transfer of different gases comprising air, oxygen, carbon dioxide, or nitrogen gas.

23. A bioreactor system for high-density cell culture comprising a bioreactor vessel for growing cells in cell culture media and a liquid flow path in fluid communication with the bioreactor vessel, wherein the liquid flow path forms a circuit exterior to the bioreactor vessel for translocating cell culture media through a first and a second membrane gas transfer module.

24. The bioreactor system of claim 23, wherein the first membrane gas transfer module is for adding oxygen to the cell culture media.

25. The bioreactor system of claim 23, wherein the second membrane gas transfer module is for stripping carbon dioxide from the cell culture media.

26. The bioreactor system of claim 24, wherein the first membrane gas transfer module comprises a oxygen flow path and a cell culture medium flow path, wherein the gas flow path and cell culture flow path are separated by a gas-permeable membrane.

27. The bioreactor system of claim 25, wherein the first membrane gas transfer module comprises an air/carbon dioxide flow path and a cell culture medium flow path, wherein the air/carbon dioxide flow path and cell culture flow path are separated by a gas-permeable membrane.

28. The bioreactor system of claim 23, wherein the liquid flow path that forms a circuit further comprises one or more additional elements.

29. The bioreactor system of claim 28, wherein the one or more additional elements is a cell harvesting filter.

30. The bioreactor system of claim 28, wherein the one or more additional elements is a

perfusion pump.

31. The bioreactor system of claim 23, further comprises a source of oxygen.

32. The bioreactor system of claim 23, further comprises a source of an air/carbon dioxide mixture.

33. The bioreactor system of claim 24, further comprising an oxygen sensor that regulates the level of oxygen introduced into the cell culture media through the first membrane gas transfer module.

34. The bioreactor system of claim 25, further comprising a pH sensor that regulates the level of carbon dioxide introduced into the cell culture media through the second membrane gas transfer module.

35. The bioreactor system of claim 23, wherein the cells of the high-density cell culture are at a density of about 20 x 10^6 cells/ml, about 30 x 10^6 cells/ml, about 40 x 10^6 cells/ml, about 50 x 10^6 cells/ml, about 60 x 10^6 cells/ml, about 70 x 10^6 cells/ml, about 80 x 10^6 cells/ml, about 90 x 10^6 cells/ml, about 100 x 10^6 cells/ml, about 110 x 10^6 cells/ml, about 120 x 10^6 cells/ml, about 130 x 10^6 cells/ml, about 140 x 10^6 cells/ml, about 150 x 10^6 cells/ml, about 160 x 10^6 cells/ml, about 170 x 10^6 cells/ml, or about 180 x 10^6 cells/ml.

36. The bioreactor system of claim 23, wherein the first and second membrane gas transfer modules add and/or remove gasses to/from the cell culture medium without forming bubbles.