CLAIMS

1. A bioreactor system comprising:

(a) four or more fluidically coupled vessels configured to collectively carry out a bioreaction;

(b) fluidic paths coupling the four or more vessels to one another, wherein the fluidic paths are configured to provide flow of culture medium between the four or more vessels during the bioreaction, the four or more vessels and the fluidic paths being arranged to provide the bioreactor system in a configuration where one of the four or more vessels is a master vessel and the others of the four or more vessels are satellite vessels, each of the satellite vessels being fluidically coupled in parallel to the master vessel by each of the satellite vessels having a separate one of the fluidic paths extending directly from the satellite vessel to the master vessel;

(c) one or more fluid transfer devices along at least some of the fluidic paths; and

(d) a control system programmed to (i) read or receive values of one or more parameters characterizing the culture medium in one or more of the vessels during the bioreaction, (ii) use said values to determine an adjusted flow rate in at least one of the fluidic paths to maintain substantially uniform values of the one or more parameters in the culture medium from vessel-to-vessel among the four or more vessels, and (iii) control at least one of the one or more fluid transfer devices to adjust the flow rate determined in (ii), wherein:

the one or more fluid transfer devices includes a two-way fluid transfer device along each of the separate one of the fluidic paths extending directly from the satellite vessels to the master vessel, the control system being programmed to operate each two-way fluid transfer device such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels, and/or

each of the satellite vessels having two or more separate fluidic paths extending directly from the satellite vessel to the master vessel, the control system

being programmed to operate the one or more fluid transfer devices such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels by the two or more of the separate fluidic paths extending directly from the satellite vessel to the master vessel.

2. The bioreactor system of claim 1, wherein the one or more parameters comprise a parameter selected from the group consisting of pH, temperature, a cell metabolite concentration, and dissolved oxygen concentration of the culture medium.

3. The bioreactor system of claim 1, wherein each vessel has a working volume of not greater than ~~about~~ 100 liters.

4. The bioreactor system of claim 1, wherein the ratio of total working volume of the four or more vessels to the working volume of largest of the four or more vessels is at least ~~about~~ 3.

5. The bioreactor system of claim 1, wherein the four or more vessels comprise polymeric vessel walls.

6. The bioreactor system of claim 1, comprising five or more fluidically coupled vessels, including the four or more vessels.

7. The bioreactor system of claim 1, wherein the master vessel comprises a mixing system within the master vessel and configured to agitate the culture medium, the satellite vessels being free of any mixing system.

8. The bioreactor system of claim 7, wherein the control system is programmed to read or receive the values of the one or more parameters characterizing the culture medium in only the master vessel, the master vessel comprising one or more sensors for collecting values of pH, temperature, a cell metabolite concentration, and dissolved oxygen in the culture medium.

9. The bioreactor system of claim 7, wherein the master vessel comprises at least one sparger and at least one impeller, the master vessel having a larger working volume than any of the satellite vessels such that the master vessel provides both ballast and a reservoir for the culture medium.

10. The bioreactor system of claim 1, wherein the ~~two~~four or more vessels and the ~~one or more~~ fluidic paths provide the bioreactor system in a star configuration.

11. The bioreactor system of claim 1, wherein the four or more vessels are provided on one or more scales and/or load cells to monitor their masses during the bioreaction.

12. The bioreactor system of claim 11, wherein the control system is further programmed to:

read or receive at least one output of the one or more scales and/or load cells, as at least one of the values of one or more parameters; and

based on the outputs of the scales and/or load cells, control the one or more of fluid transfer devices to transfer the culture medium between the four or more vessels such that a volume of the culture medium in the four or more vessels is controlled.

13. The bioreactor system of claim 1, wherein the fluidic paths attach proximate to bottoms of the four or more vessels.

14. The bioreactor system of claim 1, wherein the control system is further programmed to adjust the flow rate between the four or more vessels to ensure that the mean pH of the culture medium in the four or more vessels does not vary from one vessel to another by more than ~~about~~ 0.1.

15. The bioreactor system of claim 14, wherein the four or more vessels and the control system are configured such that the pH of the culture medium within any of the vessels has variance of at most ~~about~~ 0.1 pH units.

16. The bioreactor system of claim 1, wherein the control system is further programmed to adjust conditions in the four or more vessels to ensure that shear forces experienced by cells in the four or more vessels are substantially equal from one vessel to another during the bioreaction.

17. The bioreactor system of claim 1, wherein the control system is further programmed to adjust conditions in the four or more vessels to ensure that culture medium gas transfer rates in the four or more vessels are substantially equal from one vessel to another during the bioreaction.

18. The bioreactor of claim 1, wherein the control system comprises a single control loop that is configured to control the master vessel, wherein the master vessel comprises a mixing system configured to agitate the culture medium.

19. The bioreactor system of claim 1, wherein at least one of the four or more fluidically coupled vessels comprises a fluidic inlet and a fluidic outlet and wherein the bioreactor system is configured to introduce the culture medium to the at least one vessel through the fluidic inlet, exchange the culture medium in the vessel while retaining the biological cells in that vessel, and flow the culture medium out the fluidic outlet, to thereby operate the at least one vessel in a perfusion mode.

20. The bioreactor system of claim 19, wherein the fluidic outlet comprises a filter configured to prevent the biological cells in the at least one vessel from leaving the at least one vessel and the fluidic outlet.

21. The bioreactor system of claim 19, wherein the master vessel is configured to provide culture media to the at least one vessel through the fluidic inlet to provide perfusion.

22. The bioreactor system of claim 21, wherein the control system and master vessel are together configured to substantially maintain defined values of dissolved oxygen concentration, temperature, and pH in the culture medium in the master vessel and in the at least one vessel.

23. The bioreactor system of claim 21, wherein each of the satellite vessels comprises a fluidic inlet and a fluidic outlet, the fluidic outlet comprising a filter configured to prevent the biological cells in the satellite vessels from leaving the satellite vessels,

wherein some of the fluidic paths fluidically couple the master vessel to the fluidic inlet of each of the satellite vessels for providing the culture media to the satellite vessels from the master vessel and some of the fluidic paths fluidically couple the master vessel to the fluidic outlet of each of the satellite vessels for providing the culture media to the master vessel from the satellite vessels,

wherein the master vessel comprises a mixing system, while the satellite vessels not include any mixing system.

24. The bioreactor system of claim 19, wherein the at least one vessel further comprises one or more micro-carriers, hollow fibers, and/or adhesion plates.

25. The bioreactor of claim 1, wherein the control system is further programmed to control the one or more fluid transfer devices to transfer the culture medium between the four or more vessels, via the fluidic paths, such that the time required to exchange the culture medium in the four or more vessels is at most ~~about~~ one-tenth the time required for cells in the vessels to double under conditions in the four or more vessels.

26. A method of carrying out a bioreaction in a bioreactor system comprising: (i) four or more fluidically coupled vessels configured to collectively carry out a bioreaction; (ii) fluidic paths coupling the four or more vessels to one another, wherein the fluidic paths are configured to provide flow of culture medium between the four or more vessels during the bioreaction, the four or more vessels and the fluidic paths being arranged to provide the bioreactor system in a configuration where one of the four or more vessels is a master vessel and the others of the four or more vessels are satellite vessels, each of the satellite vessels being fluidically coupled in parallel to the master vessel by each of the satellite vessels having a separate one of the fluidic paths extending directly from the satellite vessel to the master vessel; and (iii) one or more fluid transfer devices along at least some of the fluidic paths, the method comprising:

(a) reading or receiving values of one or more parameters characterizing the culture medium in one or more of the vessels during the bioreaction;

(b) using said values to determine an adjusted flow rate in at least one of the fluidic paths to maintain substantially uniform values of the one or more parameters in the culture medium from vessel-to-vessel among the four or more vessels, and

(c) controlling at least one of the fluid transfer devices to adjust the flow rate determined in (b);

wherein:

the one or more fluid transfer devices includes a two-way fluid transfer device along each of the separate one of the fluidic paths extending directly from the satellite vessels to the master vessel, the control system being programmed to operate each two-way fluid transfer device such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels, and/or

each of the satellite vessels having two or more separate fluidic paths extending directly from the satellite vessel to the master vessel, the control system being programmed to operate the one or more fluid transfer devices such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels by the two or more of the separate fluidic paths extending directly from the satellite vessel to the master vessel.

27. A method of scaling a bioprocess working volume from that of a small-scale bioreactor to that of a large-scale bioreactor, the method comprising:

(a) determining process conditions for performing the bioprocess in a test vessel having a working volume of no greater than ~~about~~ 700 liters, wherein the process conditions comprise test values of one or more parameters characterizing culture medium in the vessel during the bioprocess;

(b) designing a bioreactor system comprising a control system and four or more fluidically connected production vessels, each having a working volume of not greater than ~~about~~ 1.5 times the working volume of the test vessel, and the sum of the working volumes of the four or more production vessels being at least ~~about~~ 2 times larger than the working volume of the test vessel, and fluidic paths coupling the four or more vessels to one another, wherein the fluidic paths are configured to provide flow of culture medium between the four or more vessels during the bioreaction, the four or more vessels and the fluidic paths being arranged to provide the bioreactor system in a configuration where one of the four or more vessels is a master vessel and the others of the four or more vessels are satellite vessels, each of the satellite vessels being fluidically coupled in parallel to the master vessel by each of the satellite vessels having a separate one of the fluidic paths extending directly from the satellite vessel to the master vessel,

wherein:

designing the bioreactor system comprises designing the control system to (i) read or receive production values of the one or more parameters characterizing the culture medium in one or more of the four or more production vessels during the bioprocess, (ii) use said read or received production values to determine an adjusted flow rate of the culture medium between the four or more production vessels to maintain substantially uniform production values of the one or more parameters in the culture medium from vessel-to-vessel among the four or more production vessels during the bioprocess, and (iii) control one o~~fr~~ ~~the~~more fluid transfer devices disposed between the four or more production vessels to adjust the flow rate as determined in (ii), and

wherein:

the one or more fluid transfer devices includes a two-way fluid transfer device along each of the separate one of the fluidic paths extending directly from the satellite vessels to

the master vessel, the control system being programmed to operate each two-way fluid transfer device such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels, and/or

each of the satellite vessels having two or more separate fluidic paths extending directly from the satellite vessel to the master vessel, the control system being programmed to operate the one or more fluid transfer devices such that during use bidirectional flow of the culture medium occurs between the master vessel and each of the satellite vessels by the two or more of the separate fluidic paths extending directly from the satellite vessel to the master vessel; and

(c) constructing and/or arranging the four or more production vessels and the control system as specified in (b) to produce the large-scale bioreactor; wherein

the one or more parameters comprise a parameter selected from the group consisting of pH, temperature, a cell metabolite concentration, and dissolved oxygen concentration of the culture medium.

28. A bioreactor system comprising:

(a) three or more fluidically coupled vessels configured to collectively carry out a bioreaction;

(b) fluidic paths coupling the three or more vessels to one another, wherein the fluidic paths are configured to provide flow of culture medium between the three or more vessels during the bioreaction, each one of the three or more vessels having a separate one of the fluidic paths extending directly from said one of the three or more vessels to another of the three or more vessels;

(c) one or more fluid transfer devices along at least some of the fluidic paths; and

(d) a control system programmed to (i) read or receive values of one or more parameters characterizing the culture medium in one or more of the vessels during the bioreaction, (ii) use said values to determine an adjusted flow rate in at least one of the fluidic paths to maintain substantially uniform values of the one or more parameters in the culture medium from vessel-to-vessel among the three or more vessels, (iii) control at least one of the one or more fluid transfer devices to adjust the flow rate determined in (ii);

wherein:

the one or more fluid transfer devices includes a two-way fluid transfer device along each of the fluidic paths, the control system being programmed to operate each two-way fluid transfer device such that during use bidirectional flow of the culture medium occurs between two of the three or more vessels, said bidirectional flow of the culture medium including simultaneous flow of the culture medium: i) out of a first of the two vessels and directly through one of the separate fluidic paths into a second of the two vessels, and ii) out of the second of the two vessels and directly through one of the separate fluidic paths into the first of the two vessels.

29. The bioreactor system of claim 28, wherein at least one of said vessels is a perfusion vessel having a fluidic inlet, a fluidic outlet, and a filter or other cell retaining structure configured to prevent biological cells from leaving the perfusion vessel during the bioreaction; and

wherein one of the three or more vessels is a master vessel configured to provide culture media to the perfusion vessel through the fluidic inlet to provide perfusion.

30. The bioreactor system of claim 29, wherein the control system and master vessel are together configured to maintain values of dissolved oxygen concentration, temperature, and pH in the culture medium in the master vessel and in the perfusion vessel.

31. The bioreactor system of claim 29, wherein the master vessel comprises a mixing system, while the perfusion vessel does not include any mixing system.

32. The bioreactor system of claim 30, wherein the bioreactor system is configured to at least partially fill the perfusion vessel with culture medium from one or more other vessels during the bioreaction.

33. The bioreactor system of claim 30, wherein the perfusion vessel is configured to be removed from the bioreactor system, along with the perfusion vessel's culture medium and cells grown in the culture medium, before the bioreaction completes.

34. The bioreactor system of claim 30, wherein the cell retaining structure comprises one or more micro-carriers, hollow fibers, and/or adhesion plates.