SMALL VOLUME BIOREACTORS WITH SUBSTANTIALLY CONSTANT WORKING VOLUMES AND ASSOCIATED SYSTEMS AND METHODS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 61/869,116, filed August 23, 2013, and entitled "Small Volume Bioreactors with Substantially Constant Working Volumes and Associated Systems and Methods," which is incorporated herein by reference in its entirety for all purposes. This application also claims priority to European Patent Application Number EP 14306161, filed July 17, 2014, and entitled "Small Volume Bioreactors With Substantially Constant Working Volumes and Associated Systems and Methods," which is incorporated herein by reference in its entirety for all purposes.

TECHNICAL FIELD

Control of volume in small volume bioreactors and associated systems is generally described.

SUMMARY

Small volume bioreactors with substantially constant working volumes, and associated systems and methods, are generally described. In one aspect, the present invention refers to a method of operating a bioreactor, comprising: performing, within a bioreactor, a biochemical reaction in which at least one eukaryotic cell is grown within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during the biochemical reaction; and removing a second amount of liquid from the liquid medium in the bioreactor during the biochemical reaction; wherein, during at least about 80% of the time over which the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than about 20% from an average of the volume of liquid within the bioreactor. In another aspect, the present invention refers to a method of operating a bioreactor, comprising: performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed; removing a second amount of liquid having a

volume that is within 10% of a volume of the first amount of liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first period of time; and repeating the adding and removing steps at least one time; wherein the adding step and the removing step are performed such that, between the adding step and the removing step, substantially no liquid is removed from the bioreactor via a non-evaporative pathway, and substantially no liquid is added to the bioreactor. In yet another aspect, the present invention refers to a method of operating a bioreactor, comprising: performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed; removing a second amount of liquid having a volume that is within 10% of a volume of the first amount of liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first period of time; and repeating the adding and removing steps at least one time; wherein the adding step and the removing step are performed such that, between the adding step and the removing step, no liquid is removed from the bioreactor via a non-evaporative pathway, and no liquid is added to the bioreactor, and wherein, during at least 80% of the time over which the biochemical reaction is performed, the osmolarity of the liquid medium within the bioreactor is maintained within a range of from 200 osmoles per kilogram of the liquid medium to 600 osmoles per kilogram of the liquid medium. In certain examples, feeding and/or sampling strategies can be employed such that the working volume within the bioreactor remains substantially constant. The bioreactors may be operated in a fed-batch mode of operation, in some examples. The subject matter of the present disclosure involves, in some cases, interrelated products, alternative solutions to a particular problem, and/or a plurality of different uses of one or more systems and/or articles.

Certain examples relate to a method of operating a bioreactor. The method comprises, in some examples, performing, within the bioreactor, a biochemical reaction in which at least one eukaryotic cell is grown within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during the biochemical reaction; and removing a second amount of liquid from the liquid medium in the bioreactor during the biochemical reaction. In some such examples, during at least about 80% of the time over which

the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than about 20% from an average of the volume of liquid within the bioreactor.

In certain examples, the method comprises performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during the biochemical reaction; and removing a second amount of liquid from the liquid medium in the bioreactor during the biochemical reaction. In some such examples, during at least about 80% of the time over which the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than about 20% from an average of the volume of liquid within the bioreactor, and the osmolarity of the liquid medium within the bioreactor is maintained within a range of from about 200 osmoles per kilogram of the liquid medium to about 600 osmoles per kilogram of the liquid medium.

According to some examples, the method comprises performing, within the bioreactor, a biochemical reaction in which at least one eukaryotic cell is grown within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed; and removing a second amount of liquid having a volume that is within 10% of a volume of the first amount of liquid from the liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first period of time; and repeating the adding a removing steps at least one time. In some such examples, the adding step and the removing step are performed such that, between the adding step and the removing step, substantially no liquid is removed from the bioreactor via a non-evaporative pathway, and substantially no liquid is added to the bioreactor.

The method comprises, in certain examples, performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than about 50 milliliters; adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed; removing a second amount of liquid having a volume that is within 10% of a volume of the first amount of liquid from the liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first

period of time; and repeating the adding a removing steps at least one time. In some such examples, the adding step and the removing step are performed such that, between the adding step and the removing step, substantially no liquid is removed from the bioreactor via a non-evaporative pathway, and substantially no liquid is added to the bioreactor. In some such examples, during at least about 80% of the time over which the biochemical reaction is performed, the osmolarity of the liquid medium within the bioreactor is maintained within a range of from about 200 osmoles per kilogram of the liquid medium to about 600 osmoles per kilogram of the liquid medium.

Other advantages and novel features of the present invention will become apparent from the following detailed description of various non-limiting embodiments of the invention when considered in conjunction with the accompanying figures. In cases where the present specification and a document incorporated by reference include conflicting and/or inconsistent disclosure, the present specification shall control.

BRIEF DESCRIPTION OF THE DRAWINGS

Non-limiting embodiments of the present invention will be described by way of example with reference to the accompanying figures, which are schematic and are not intended to be drawn to scale. In the figures, each identical or nearly identical component illustrated is typically represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. In the figures:

FIG. 1 is an exemplary cross-sectional side view schematic illustration of a bioreactor, according to one set of embodiments;

FIG. 2 is, according to certain embodiments, a cross-sectional side view schematic illustration of an exemplary reactor system;

FIGS. 3A-3C are cross-sectional side view schematic illustrations of a reactor chamber and a mode of operating the same, according to some embodiments;

FIG. 4 is a bottom-view cross sectional schematic illustration of a reactor system including a plurality of reactor chambers arranged in series, according to one set of embodiments;

FIG. 5 is an exemplary top-view schematic illustration of a micro-bioreactor, according to one set of embodiments;

CLAIMS

1. A method of operating a bioreactor, comprising:

performing, within a bioreactor, a biochemical reaction in which at least one eukaryotic cell is grown within a liquid medium having a volume of less than about 50 milliliters;

adding a first amount of liquid to the liquid medium in the bioreactor during the biochemical reaction; and

removing a second amount of liquid from the liquid medium in the bioreactor during the biochemical reaction;

wherein, during at least about 80% of the time over which the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than about 20% from an average of the volume of liquid within the bioreactor.

2. The method of claim 1, wherein during at least 90% of the time over which the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than 20% from an average of the volume of liquid within the bioreactor.

3. The method of claim 1 or 2, wherein during at least 80% of the time over which the biochemical reaction is performed including during the adding and removing steps, the total volume of liquid within the bioreactor does not fluctuate by more than 10% from an average of the volume of liquid within the bioreactor.

4. The method of any one of claims 1-3, wherein the adding step is performed over a first period of time, the removing step is performed over a second period of time, and the first and second periods of time do not overlap with each other.

5. A method of operating a bioreactor, comprising:

performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than about 50 milliliters;

adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed;

removing a second amount of liquid having a volume that is within 10% of a volume of the first amount of liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first period of time; and

repeating the adding and removing steps at least one time;

wherein the adding step and the removing step are performed such that, between the adding step and the removing step, substantially no liquid is removed from the bioreactor via a non-evaporative pathway, and substantially no liquid is added to the bioreactor.

6. A method of operating a bioreactor, comprising:

performing, within the bioreactor, a biochemical reaction within a liquid medium having a volume of less than 50 milliliters;

adding a first amount of liquid to the liquid medium in the bioreactor during a first period of time over which the biochemical reaction is performed;

removing a second amount of liquid having a volume that is within 10% of a volume of the first amount of liquid medium in the bioreactor during a second period of time over which the biochemical reaction is performed that does not overlap with the first period of time; and

repeating the adding and removing steps at least one time;

wherein the adding step and the removing step are performed such that, between the adding step and the removing step, no liquid is removed from the bioreactor via a non-evaporative pathway, and no liquid is added to the bioreactor, and

wherein, during at least 80% of the time over which the biochemical reaction is performed, the osmolarity of the liquid medium within the bioreactor is maintained within a range of from 200 osmoles per kilogram of the liquid medium to 600 osmoles per kilogram of the liquid medium.

7. The method of claim 5 or 6, wherein the adding step and the removing step are performed such that, between the adding step and the removing step, no liquid is removed from the bioreactor.

8. The method of any one of claims 5-7, wherein the second amount of liquid has a volume that is within 5% of the volume of the first amount of liquid.

9. The method of claim 8, wherein the second amount of liquid has a volume that is within 1% of the volume of the first amount of liquid.

10. The method of any one of claims 1-9, wherein the biochemical reaction is performed within a liquid medium having a volume of less than 10 milliliters.

11. The method of claim 10, wherein the biochemical reaction is performed within a liquid medium having a volume of less than 5 milliliters.

12. The method of any one of claims 1-11, wherein adding the first amount of liquid to the liquid medium comprises transporting the first amount of liquid into the bioreactor via a liquid inlet.

13. The method of claim 12, wherein the liquid inlet comprises a channel.

14. The method of claim 13, wherein the liquid inlet channel comprises a microfluidic channel.

15. The method of any one of claims 1-14, wherein removing the second amount of liquid from the liquid medium in the bioreactor comprises transporting the second amount of liquid out of the bioreactor via a liquid outlet.

16. The method of claim 15, wherein the liquid outlet comprises a channel.

17. The method of claim 16, wherein the liquid outlet channel comprises a microfluidic channel.

18. The method of any one of claims 1-17, wherein the liquid medium comprises a cell growth medium.

19. The method of any one of claims 5-18, wherein at least one biological cell is grown during the biochemical reaction.

20. The method of claim 19, wherein the biological cell is a eukaryotic cell.

21. The method of any one of claims 1-4 and 20, wherein the eukaryotic cell is a mammalian cell.

22. The method of claim 21, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

23. The method of any one of claims 1-22, wherein the first amount of liquid added to the liquid medium comprises at least one biochemical reactant.

24. The method of any one of claims 1-23, wherein the second amount of liquid removed from the liquid medium comprises a product of a biochemical reaction.