

HUMIDITY CONTROL IN CHEMICAL REACTORS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No.
5 61/719,085, filed October 26, 2012, and entitled "Humidity Control in Chemical
Reactors"; U.S. Provisional Patent Application Serial No. 61/869,118 filed August 23,
2013, and entitled "Humidity Control in Chemical Reactors"; and European Application
No. 13306464.2 filed October 23, 2013 and entitled "Humidity Control in Chemical
Reactors," each of which is incorporated herein by reference in its entirety for all
10 purposes.

TECHNICAL FIELD

Systems and methods for the control of humidity in chemical reactors are
generally described.
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BACKGROUND

There is currently a great deal of interest in developing small volume bioreactors
for growing cells, for example, for biopharmaceutical production. Controlling liquid
levels in such reactors can be challenging. For example, evaporation of small amounts
20 of liquid medium within the reactor can lead to relatively large changes in volume, which
can adversely impact bioreactor operation. Improved systems and methods for
controlling humidity in such chemical reactors are therefore desirable.

SUMMARY

25 Control of humidity in chemical reactors, as well as associated systems and
methods, are generally described. Certain examples relate to the control of humidity
within gas transport conduits. 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.

30 In one aspect, the disclosure refers to a method of culturing a biological cell, the
method comprising: (a) providing a reactor system comprising: a reactor chamber
comprising a liquid and the biological cell; a reactor chamber gas inlet conduit
configured to transport gas into the reactor chamber through a reactor chamber gas inlet;

a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas inlet conduit at a rate of equal to or less than about 1 milliliter per second; a humidifier configured to humidify the gas transported through the reactor chamber gas inlet conduit, the humidifier positioned between the flow control mechanism and the reactor chamber gas inlet; a reactor chamber gas outlet conduit configured to transport gas out of the reactor through a reactor chamber gas outlet; and a gas bypass conduit external to the reactor chamber, connecting the gas inlet conduit to the gas outlet conduit; and (b) culturing the biological cell using the reactor system.

In another aspect, the present disclosure refers to a method of culturing a biological cell, the method comprising: (a) providing a reactor system comprising: a reactor chamber comprising a liquid and the biological cell; a reactor chamber gas inlet conduit configured to transport gas into the reactor chamber through a reactor chamber gas inlet; a reactor chamber gas outlet conduit configured to transport gas out of the reactor chamber through a reactor chamber gas outlet; a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas outlet conduit at a rate of equal to or less than about 1 milliliter per second; a liquid trap configured to remove liquid vapor from the gas within the reactor chamber gas outlet conduit, the liquid trap positioned between the flow control mechanism and the reactor chamber gas outlet; and a gas bypass external to the reactor chamber, connecting the gas inlet conduit to the gas outlet conduit; and (b) culturing the biological cell using the reactor system.

In certain examples, a reactor system is provided. In some examples, the reactor system comprises a reactor chamber; a reactor chamber gas inlet conduit configured to transport gas into the reactor chamber through a reactor chamber gas inlet; a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas inlet conduit at a rate of equal to or less than about 1 milliliter per second; and a humidifier configured to humidify the gas transported through the reactor chamber gas inlet conduit, the humidifier positioned between the flow control mechanism and the reactor chamber gas inlet.

In some examples, the reactor system comprises a reactor chamber; a reactor chamber gas outlet conduit configured to transport gas out of the reactor chamber through a reactor chamber gas outlet; a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas outlet conduit at a rate of equal to or less than about 1 milliliter per second; and a liquid trap configured to remove liquid vapor

from the gas within the reactor chamber gas outlet conduit, the liquid trap positioned between the flow control mechanism and the reactor chamber gas outlet.

The reactor system comprises, in certain examples, a reactor chamber, comprising a liquid sub-chamber configured to contain a liquid growth medium including at least one biological cell; a gas sub-chamber configured to contain a gaseous headspace above the liquid growth medium; and a gas-permeable flexible membrane separating the liquid sub-chamber from the gas sub-chamber. In certain examples, the reactor system comprises a gas inlet conduit configured to transport gas into the gas sub-chamber; a gas outlet conduit configured to transport gas out of the gas sub-chamber; and a gas bypass conduit external to the reactor chamber, connecting the gas inlet conduit to the gas outlet conduit.

Certain examples relate to methods of operating a reactor. In certain examples, the method comprises providing a reactor chamber, comprising a liquid sub-chamber configured to contain a liquid growth medium including at least one biological cell; a gas sub-chamber configured to contain a gaseous headspace above the liquid growth medium; and a flexible membrane separating the liquid sub-chamber from the gas sub-chamber. In some examples, the method comprises transporting a gas from a gas source through a gas inlet conduit to the gas sub-chamber to deform the gas-permeable flexible membrane such that liquid is at least partially removed from the liquid sub-chamber; reducing the supply of the gas to the gas sub-chamber such that the flexible membrane returns toward its original position; transporting gas from the gas source through a gas bypass connected to the gas inlet conduit and external to the reactor chamber to remove liquid from the gas inlet conduit; and supplying gas from the gas source to the gas sub-chamber at least a second time to deform the gas-permeable flexible membrane such that liquid is at least partially evacuated from the liquid sub-chamber.

Other advantages and novel features of the present disclosure will become apparent from the following detailed description of various non-limiting examples of the disclosure 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
5 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 a cross-sectional schematic illustration of a reactor system, according to certain embodiments;

10 FIGS. 2A-2C are cross-sectional schematic illustrations of a reactor chamber and a mode of operating the same, according to one set of embodiments;

FIG. 3 is a bottom-view cross sectional schematic illustration of a reactor system including a plurality of reactor chambers arranged in series;

FIG. 4A-B are A) a cross-sectional schematic illustration of a reactor system with
15 a long path and B) a cross-sectional schematic illustration of a reactor system with a short path, according to certain embodiments;

FIG. 5 is a cross-sectional schematic illustration of a reactor system, according to certain embodiments;

FIG. 6 is a cross-sectional schematic illustration of a gas manifold for a reactor
20 system, according to one set of embodiments;

FIG. 7 is a cross-sectional schematic illustration of a gas manifold for a reactor system, according to some embodiments; and

FIG. 8 is a photograph of a reactor system, according to certain embodiments.

CLAIMS

1. A method of culturing a biological cell, the method comprising:

(a) providing a reactor system comprising:

5 a reactor chamber comprising a liquid and the biological cell;
a reactor chamber gas inlet conduit configured to transport gas into the reactor chamber through a reactor chamber gas inlet;

a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas inlet conduit at a rate of equal to or less than about 1 milliliter per
10 second;

a humidifier configured to humidify the gas transported through the reactor chamber gas inlet conduit, the humidifier positioned between the flow control mechanism and the reactor chamber gas inlet;

a reactor chamber gas outlet conduit configured to transport gas out of the reactor
15 through a reactor chamber gas outlet; and

a gas bypass conduit external to the reactor chamber, connecting the gas inlet conduit to the gas outlet conduit; and

(b) culturing the biological cell using the reactor system.

20 2. A method of culturing a biological cell, the method comprising:

(a) providing a reactor system comprising:

a reactor chamber comprising a liquid and the biological cell;

a reactor chamber gas inlet conduit configured to transport gas into the reactor chamber through a reactor chamber gas inlet;

25 a reactor chamber gas outlet conduit configured to transport gas out of the reactor chamber through a reactor chamber gas outlet;

a flow control mechanism configured to regulate the flow of gas through the reactor chamber gas outlet conduit at a rate of equal to or less than about 1 milliliter per second;

30 a liquid trap configured to remove liquid vapor from the gas within the reactor chamber gas outlet conduit, the liquid trap positioned between the flow control mechanism and the reactor chamber gas outlet; and

a gas bypass external to the reactor chamber, connecting the gas inlet conduit to the gas outlet conduit; and

(b) culturing the biological cell using the reactor system.

5 3. The method of claim 2, wherein the reactor system further comprises a humidifier configured to humidify the gas transported through the reactor chamber gas inlet conduit.

10 4. The method of claim 3, wherein the reactor system further comprises an inlet flow control mechanism configured to regulate the flow of gas through the reactor chamber gas inlet conduit at a rate of equal to or less than about 1 milliliter per second.

15 5. The method of claim 4, wherein the humidifier is positioned between the inlet flow control mechanism and the reactor chamber gas inlet.

6. The method of any one of claims 1-5, wherein the biological cell is a eukaryotic cell.

20 7. The method of claim 6, wherein the biological cell is a mammalian cell.

8. The method of claim 7, wherein the mammalian cell is selected from the group consisting of primate cells, bovine cells, horse cells, porcine cells, goat cells, dog cells, cat cells, rodent cells, and human cells.

25 9. The method of claim 7, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

30 10. The method of any one of claims 6-8, wherein the biological cell is a cardiac cell, a fibroblast, a keratinocyte, a hepatocyte, a chondrocyte, a neural cell, an osteocyte, a muscle cell, a blood cell, an endothelial cell, an immune cell, or a stem cell.

11. The method of any one of claims 1-10, wherein the reactor chamber has a volume of less than or equal to 50 milliliters.

12. The method of any one of claims 1-11, wherein the gas comprises carbon dioxide and/or oxygen.

13. The method of any one of claims 1 and 3-12, wherein the humidifier
5 comprises a vessel including a first liquid having a temperature at least about 1 °C higher than the temperature of the liquid phase.

14. The method of any one of claims 2-13, wherein the liquid trap comprises a
vessel including a second liquid having a temperature at least 1 °C lower than the
10 temperature of the liquid phase.

15. The method of any one of claims 1-14, wherein the flow control mechanism
comprises a gas supply conduit comprising a constriction.

16. The method of claim 15, wherein a cross-sectional dimension of the gas
15 supply conduit within the constriction is at least about 10% smaller than cross-sectional dimensions of the gas supply conduit at locations upstream and downstream of the constriction.

17. The method of any one of claims 1-16, wherein the flow control mechanism
20 comprises a pressure regulator.

18. The method of any one of claims 1-17, wherein the reactor chamber is
configured to contain a volume of the liquid medium that is equal to or less than 50
25 milliliters and equal to or greater than 10 microliters.