NON-INVASIVE BIOREACTOR MONITORING

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ABSTRACT
A pair or receptacles capable of housing an emitter probe and a detector probe installed inside a bioreactor to monitor the properties of the nutrient media without contacting the nutrient media.

7 Claims, 2 Drawing Sheets
NON-INVASIVE BIOREACTOR MONITORING

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. patent application Ser. No. 13/279,220 entitled “NON-INVASIVE BIOREACTOR MONITORING” filed on Oct. 21, 2011, now U.S. Pat. No. 8,545,759, the contents of which are incorporated herein by reference in its entirety.

BACKGROUND

Bioreactors used for growing cells and organisms need frequent monitoring of the nutrient media to adjust its characteristics to optimize growth. Most commonly it is done by sampling the nutrient media through a port in the bioreactor, which carries the risk of contaminating the bioreactor; also used is the method of routing the nutrient media through a flow cell, which still contains the risk of contamination. More recently, the monitoring has been done by using disposable sensors, which are installed inside a bioreactor and reading their responses from outside the bag; while this method offers a practical choice, it remains less desirable due to its high variability of responses and the high cost of using this method.

There remains an unmet need to create a method for directly monitoring the characteristics of the nutrient media in a bioreactor without removing the nutrient media from the bioreactor to record such parameters as pH, optical density, cell count, dissolved oxygen, dissolved carbon dioxide, glucose concentration and other specific parameters for which a detector is available.

The present invention allows placement of emitter probes of electromagnetic or sound waves inside a bioreactor without contacting the nutrient media and also places a detector of electromagnetic or sound waves inside the bioreactor without contacting the nutrient media. Disposable receptacles receptacle the emitter probe and detector probes are fully transparent to the chosen radiation or wave type employed. The distance between the emitter probe and the detector probe are adjusted by positioning these at different heights when using a V-shaped receptacle or by installing them apart at a pre-determined distance inside a bioreactor. The nutrient media between the transmitter and detector serves as the tested sample.

The angle of probes determines whether the measured radiation is transmitted or diffracted; when facing, the measurement is of transmitted radiation and when placed at an angle such that the path of the line of sight of the probes crosses, measured radiation is diffracted radiation.

The method of present invention involves installing a receptacle inside a disposable bioreactor such that the receptacles for emitter probes and detectors are accessible from outside; the receptacle can also be used in non-disposable bioreactors.

The present invention offers a cost-effective solution to monitoring bioreactors since the expensive emitter probes and detectors are re-used and only the receptacle that houses them is disposed after a single use.

DESCRIPTION OF THE DRAWINGS

FIG. 1 shows many view of a V-shaped receptacle. FIG. 1(a) is the side view of a V-shaped receptacle showing placement of probes; FIG. 1(b) is a side view of a V-shaped receptacle showing probes and the path of radiation to measure diffraction; FIG. 1(c) is a side view of a V-shaped receptacle showing probes and a straight path of radiation to measure transmitted radiation; FIG. 1(d) is a side view of a bioreactor showing a V-shaped receptacle disposed inside the bioreactor showing direct access of the cavity inside the receptacle from the outside of bioreactor.

FIG. 2 shows many views of two receptacles installed at a fixed distance from each other; FIG. 2(a) is a side view of two receptacles and probes placed inside the receptacles; FIG. 2(b) is an angled view of two receptacles and probes placed inside both receptacles and the paths of radiation.

DETAILS OF THE INVENTION

Optimal operations of a process in a bioreactor require monitoring such parameters as pH, dissolved oxygen, dissolved carbon dioxide, optical density, cell count, glucose concentration and a variety of other parameters specific to the process. The reason for monitoring these parameters is to allow adjustment of the conditions or chemical composition of the nutrient media to optimize the growth profile of cells and organisms in the bioreactor.

Great advances have been made in spectrophotometric technique wherein several parameters of the property of nutrient media can be monitored using visible, ultraviolet and infra red wave lengths of light; the use of ultrasound and microwave along with lasers has further improved the ability of the spectrometers to detect the properties of nutrient media; additionally, improvements in electronic designs, more versatile and miniaturized emitter probes and detectors in the future will make it more convenient and practical to monitor the characteristics of the nutrient media in a bioreactor more effectively and efficiently if it is possible to use these probes non-invasively inside the bioreactor.

The most effective method of monitoring the properties of the nutrient media is to subject its sample to photo or acoustic radiation and from the differences in the emitted radiation and the detected radiation allow assessment of the specific property of nutrient media. There is an unmet need to allow the spectrophotometers and acoustic meters to operate without removing the nutrient media from the bioreactor and without contacting the nutrient media.

This is accomplished in the present invention by installing a V-shaped receptacle made of a material that is transparent to the radiation used; the two arms of the V-shaped receptacle are accessible from the outside to insert emitter probe and detectors. The position of probes determines the distance between them; pushing the probes deep into the receptacle reduces the distance between them. Since the nutrient media monitored resides between the two arms of the receptacle, monitoring the nutrient media of higher concentration will require reducing the length of the passage of light by pushing the probes upwards toward the junction of the two arms of the V-shaped receptacle.

In a more general use of the invention, the probes are inserted in independent receptacles that are attached to the bottom of a bioreactor.

The emitter and emitter probes can be rotated to an angle such that the emitted radiation is detected from the dispersion or diffraction of the radiation by the detector. This will be analogous to measuring turbidity rather than transmission, which is measured when the two probes face each other.

A first preferred embodiment is shown in FIG. 1, wherein a V-shaped receptacle 5 has an inner cavity capable of holding probes 1 and 2 and openings 3 and 4 to insert the
probes. The path of radiation emitted at an angle to the
detector probe path shows how diffracted radiation is
detected. When the probes are facing they create a straight
path that allows measurement of transmitted radiation. The
receptacle is installed inside a bioreactor preferably
attached to the bottom surface of the bioreactor such that the
openings and allow fluid communication of the cavity inside the receptacle from the outside of the bioreactor,
which may additionally contain an inlet and an outlet and nutrient media totally submerging the receptacle.

FIG. 2 is another preferred embodiment wherein instead
one V-shaped receptacle as shown in FIG. 1, there are two
independent receptacles, one receptacle to hold the emitter
probe and one receptacle to hold the receptor; the path of
transmission across the two receptacles and when the
path of radiation is placed at an angle, it used to
determine diffraction. When installed in container, the
devices are attached to the bottom of container that may
have an inlet port and an exhaust port.

The present invention thus offers a practical solution to
monitoring the nutrient media non-invasively while using
traditional methods of recording the properties of the nutri-
tent media.

The present invention will prove to be continuously
beneficial as new probes are developed enhancing the utility
of the present invention to monitor the nutrient media inside
a bioreactor without affecting its sterility or without breach-
ing the integrity of the bioreactor and without removing a
tax from the bioreactor.

The emitter probes and detectors used in the present
invention are non-disposable and thus the cost of operation is
reduced substantially while affording the highest sensi-
tivity and reliability of the monitoring operations.

The ability to monitor a variable depth of nutrient media
is of great advantage to monitor the nutrient media over a
wide range of the concentration of the entities monitored;
this is analogous to diluting samples to study their proper-
ties. The distance between the probes represents the depth of
liquid monitored and this is changed by moving the probes
up or down toward the apex of the V-shaped receptacle.

The present invention also provides a solution to moni-
toring the nutrient media by installing a disposable recept-
acle inside a bioreactor—a receptacle that is accessible
from the outside of the bioreactor to insert emitter probes
and detectors inside the bioreactor without touching the
nutrient media. The material of construction of the recept-
acle is same as it is used in spectrophotometers, wherein the
walls of the receptacle are transparent to specific electro-
magnetics or sound waves; these receptive elements are
inexpensive to construct and eliminate the need for using a
disposable emitter probe or detector.

The present invention also offers a novel solution combi-
ning the use of disposible patches or probes installed
inside a bioreactor wherein these probes emit fluorescence
upon reacting with the content of the nutrient media. The
fluorescence is then detected by the detector housed in the
receptacle to allow for a high degree of accuracy in measure-
ments. Using the present invention, these probes can be
monitored more closely and more accurately by bringing the
detector element closer to these patches inside the bioreac-
tor. In this instance, the patches can be attached to the
receptacle portions that are exposed to the nutrient media
and the detector may include a source of light as well to
excite the fluorescent probe.

The present invention can be used to measure various
parameters non-invasively inside a bioreactor; these param-
eters include but not limited to temperature, pH, optical
density, dissolved oxygen, dissolved carbon dioxide, glu-
cose concentration and other chemical entities.

While optical density is a good indicator of the growth of
bacterial culture, mammalian cell culture requires counting
the cells in a specific volume. Since a small volume of liquid
media is present between the receptacles holding the emitter
probe and the emitter probe, installing a optical element
such as a microscope lens or a camera pointed towards the
liquid between the two receptacles to count the cells
remotely. It is noteworthy that the material used for the
construction of receptacle is transparent to light without
producing any distortion and thus allowing the microscopy
work more reliable. Alternately, a camera can record the
images of cells and the photograph then read to calculate the
density of cells.

The use of acoustic waves, both sound and ultrasound, in
analytical methods is a fast developing science; materials
transparent to sound and ultrasound waves are widely avail-
able and receptacles can be made out of these materials to
allow probing using sound and ultrasound waves as well in
the present invention.

What is claimed is:
1. A device for non-invasive, non-contact monitoring of a
nutrient media in a bioreactor comprised of a container with
a top surface, a bottom surface, and an inner volume capable
of holding the nutrient media, the device comprising:
at least one pair of receptacles suitable for housing probes,
the receptacles configured for hermetically sealing the
probes from the nutrient media; and each comprising
one open end in fluid communication with the outside
of the bioreactor via the bottom surface and one sealed
end;
an emitter probe capable of producing an electromagnetic
or acoustic signal disposed in a first receptacle of the at
least one pair of receptacles;
a detector probe capable of detecting an electromagnetic
or acoustic signal disposed in a second receptacle of the
at least one pair of receptacles;
wherein the distance between the first receptacle and the
second receptacle can be varied by adjusting the first
receptacle and the second receptacle up and down, or
sideways, wherein the distance between the receptacles
represents the depth of the nutrient media monitored;
and
an electronic means for converting a signal received from
the detector probe into physical and chemical proper-
ties of the nutrient media.

2. The device of claim 1, wherein the electromagnetic
signal comprises long wave, radio wave, microwave, ther-
mal infrared, infrared, visible, fluorescent, ultraviolet, x-rays
and gamma ray signal.

3. The device of claim 1, wherein the acoustic signal
comprises sound wave and ultrasound wave signal.

4. The device of claim 1, wherein the device is used to
monitor temperature, pH, optical density, cell count, dis-
solved oxygen, dissolved carbon dioxide, and glucose con-
centration in the nutrient media either continuously or
intermittently.

5. The device of claim 1, wherein the receptacles are made
of plastic, glass or fused quartz.

6. The device of claim 1, wherein the receptacles are
round, square or rectangular tubes.

7. The device of claim 1, wherein the sealed ends of
receptacles are joined.

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