C l a i m s

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1. A method for determining if a first pH measuring device (108; 146) operatively coupled to a first tank (104; 106) is affected by a pH-measuring problem, the problem being that the first pH measuring device is calibrated differently than a second pH measuring device (142) operatively coupled to a second tank (102), the method comprising:
   - receiving (202), by a comparison unit (130), a first CO2 concentration and a first pH value, the first CO2 concentration being a CO2 concentration of a first gas volume above a medium (M1) in the first tank, the first CO2 concentration and the first pH value being measured at a first time, the first time being a time when the medium in the first tank is in pH-CO2 equilibrium state with the first gas volume at a predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the first pH value being a measured value provided by the first pH measuring device (108; 146);
   - receiving (202), by the comparison unit (130), a second CO2 concentration and a second pH value, the second CO2 concentration being a CO2 concentration of a second gas volume above the same type of medium (M1) contained in the second tank, the second CO2 concentration and the second pH value being measured at a second time, the second time being a time when the medium in the second tank is in pH-CO2 equilibrium state with the second gas volume at the predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the second pH value being a measured value provided by the second pH measuring device (142);
   - comparing (206), by the comparison unit, the first and second pH values and comparing the first and second CO2 concentrations for determining if the first pH measuring device is affected by the pH-measuring problem.

2. The method of claim 1, the determination that the first pH measuring device has a pH measuring problem being made in case:
   - the first and second CO2 concentrations are identical and the first and

second pH values differ from each other by more than a threshold value; or

- the first and second pH values are identical and the first and second CO2 concentrations differ from each other by more than a further threshold value; or
- a first data value differs from a second data value by more than a further threshold, the first data value being derived from the first pH value and the first CO2 concentration, the second data value being derived from the second pH value and the second CO2 concentration.

3. The method of any one of the previous claims,
   - the first tank being a bioreactor or a harvest tank and/or
   - the second tank being a bioreactor, in particular a reference bioreactor, or a harvest tank, in particular a reference harvest tank.

4. A method for determining if a first pH measuring device (108; 146; 160) operatively coupled to a first tank (104; 106) is affected by a pH-measuring problem, the problem being that the first pH measuring device is calibrated wrongly, the method comprising:
   - receiving (202), by a comparison unit(130), a first CO2 concentration and a first pH value, the first CO2 concentration being a CO2 concentration of a first gas volume above a medium (M1) in the first tank, the first CO2 concentration and the first pH value being measured at a first time, the first time being a time when the medium in the first tank is in pH-CO2 equilibrium state with the first gas volume at a predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the first pH value being a measured value provided by the first pH measuring device (108; 146);
   - computing (204), by the comparison unit, a second pH value as a function of the first CO2 concentration, the second pH value being the pH value predicted for said type of medium (M1) when said medium is in pH-CO2 equilibrium state with a second gas volume above said medium (M1) at the predefined temperature and pressure, the second gas volume in said equilibrium having a second CO2 concentration that is identical to the first CO2 concentration,

said equilibrium state being unaffected by the metabolism of any cell culture;

- comparing (206), by the comparison unit, the first and second pH values for determining if the first pH measuring device is affected by the pH-measuring problem,

wherein the computing (204) of the second pH value comprises:

- reading, by the comparison unit (130), a medium-specific relation (136) from a data storage medium (114), the medium-specific relation being specific for the medium (M1) and indicating a relation between the pH value of the medium (M1) and a respective fraction of CO2 gas in a gas volume when said medium is in pH-CO2 equilibrium state with said gas volume and lacks a cell culture;
- inputting the first CO2 concentration into the medium specific relation for calculating an absolute pH value expected for the medium in pH-CO2 equilibrium at the predefined temperature and pressure and under the absence of a cell culture, the absolute pH value being used as the computed second pH value.

5. The method of claim 4, the medium-specific relation being an equation $PPH_{M1}(CO2) = REL\text{-}M1(CO2)$ obtained by mathematically fitting multiple empirically determined pairs of a pH-value of the medium (M1) and a respectively measured fraction of CO2 gas in a gas volume, wherein:
   - $PPH_{M1}(CO2)$ is the predicted pH value in a medium (M1) when said medium lacks a cell culture and is at pH-CO2 equilibrium with a gas volume above said medium, said gas volume comprising the CO2 concentration used as input parameter;
   - the CO2 is an input parameter value and represents the CO2 concentration in a gas volume above the medium (M1) in pH-CO2 equilibrium state under the absence of the cell culture;
   - wherein REL-M1 is a set of one or more parameters (a1, a2, b1, b2, b3) connected by operators, the parameters having been obtained by:
     - adjusting samples of the medium (M1) lacking the cell culture to multiple different pH values, thereby letting the samples reach pH-CO2 equilibrium with the gas volume above the medium in the respective

sample,

- determining the fraction of CO2 gas in a in respective gas volume being in ph-CO2 equilibrium with the medium in the samples,
- plotting the determined CO2 gas fractions against the respective equilibrium pH values of the samples,
- fitting a curve (502) in the plotted values and deriving the parameters (a1, a2 or b1, b2, b3) of the medium-specific relation from the fitted curve.

6. The method of any one of claims 4-5, the determination that the first pH measuring device has a pH measuring problem being made in case:
   - the first and second pH values differ from each other by more than a threshold value; or
   - a first data value differs from a second data value by more than a further threshold, the first data value being derived from the first pH value, the second data value being derived from the second pH value.

7. The method of any one of the previous claims 4-6, the first tank being a bioreactor or a harvest tank or a calibration box.

8. A method for calibrating or re-calibrating a first pH measuring device (108; 146) comprising:
   a) performing the method according to any one of claims 1-3 for determining that the first pH measuring device is affected by a pH-measuring problem; and calibrating the first pH measuring device such that it outputs the same pH value like the second pH measuring device in case the first and second CO2 concentrations are identical; or
   b) performing the method according to any one of claims 4-7 for determining that the first pH measuring device is affected by a pH-measuring problem; and calibrating the first pH measuring device such that it outputs the same pH value like the pH value computed as a function of the first CO2 concentration.

9. A method of operating a tank comprising a first pH measuring device (108;

146), the first pH measuring device being an online measuring device, the method comprising:

- growing a cell culture in the tank, the tank comprising a growth medium, thereby repeatedly measuring the pH in the growth medium by the first pH measuring device;
- replacing the growth medium and the cell culture contained therein in the tank with a medium (M1) for which a relation between pH and CO2 in equilibrium is known;
- after having replaced the growth medium, performing the method according to any one of claims 4-8 for determining if the first pH measuring device is affected by a pH-measuring problem;
- if a pH measuring problem was detected, calibrating the first pH measuring device such that it outputs the same pH value like the pH value computed as a function of the first CO2 concentration for the medium (M1);
- after having calibrated the first pH measuring device, replacing the medium in the tank with the growth medium.

10. A method of determining pH offset effects caused by taking a medium sample from a first tank, the method comprising providing a tank-external, offline pH measuring device (160) and providing the first tank (104, 106), the first tank comprising a first pH measuring device (108, 146) , the first pH measuring device being an online pH measuring device located within the first tank and being at least partially surrounded by the medium (M1) in the first tank, the method further comprising:

- performing the method according to claim 8 b) for calibrating the first pH measuring device;
- transferring the tank-external, offline pH measuring device (160) into a calibration box comprising the same type of medium (M1) as the first tank; and performing the method according to claim 8 b) using the calibration box as the tank comprising the pH measuring device to be calibrated (160), thereby using the calibration box as a container whose CO2 offgas sensor is used for measuring the first CO2 concentration and using the same function for computing the second pH value as used for calibrating the first pH

measuring device;

- after having calibrated the first pH measuring device (108, 146) and the tank-external pH measuring device (160):
  - measuring, by the first pH measuring device, a first current pH value of the medium in the first tank, the first current pH value being an online-measurement value;
  - taking a sample of the medium of the first tank and filling the sample into a portable container (162);
  - positioning the tank-external pH measuring device such that it is at least partially surrounded with the medium in the sample container;
  - measuring, by the tank-external pH measuring device, a second current pH value of the medium in the sample container, the second current pH value being an offline-measurement value;
  - in case the first and the second current pH values differ by more than a threshold, determining that the sampling process caused an pH offset effect, and optionally determining the strength of the offset effect as the difference of the first and second current pH value.

11. The method of any one of the previous claims, further comprising:
    - receiving (202) a third CO2 concentration and a third pH value, the third CO2 concentration being a CO2 concentration of a third gas volume above the medium in the first tank, the third CO2 concentration and the third pH value being measured at a third time, the third time being a time when the medium in the first tank is in pH-CO2 equilibrium state at a predefined temperature and pressure with the third gas volume and after said equilibrium state is modified by the metabolism of the cell culture in the first tank, the third pH value being a measured value provided by the first pH measuring device (142);
    - receiving (204) a fourth CO2 concentration and a fourth pH value, the fourth CO2 concentration being a CO2 concentration of a fourth gas volume above the medium in the second tank, the fourth CO2 concentration and the fourth pH value being measured at a fourth time, the fourth time being a time when the medium in the second tank is in pH-

CO2 equilibrium state at the predefined temperature and pressure with the second gas volume and after said equilibrium state is modified by the metabolism of the cell culture in the second tank, the fourth pH value being a measured value provided by the second pH measuring device (108, 146), the lapsed time between the third time and the inoculation of the first tank being identical to the lapsed time between the fourth time and the inoculation of the second tank;

- receiving a measured first oxygen uptake rate of the cell culture in the first tank at the third time;
- receiving a measured second oxygen uptake rate of the cell culture in the second tank at the fourth time;
- in case the first and second oxygen uptake rates are identical, comparing (206) the third and fourth pH values and CO2 concentrations for determining if the first and second pH measuring devices are calibrated differently.

12. The method of any one of the previous claims, the first pH measuring device being at least partially surrounded by the medium within the first tank, wherein:
    - the first tank lacks means for manually or automatically taking a sample of the medium in the second tank; or
    - the first tank comprises means for manually or automatically taking a sample of the medium in the first tank, the method further comprising: during a time interval after filling the medium in the first tank and before adding a cell culture to the medium in the first tank, keeping all openings of the sampling means closed.

13. The method of any one of the previous claims, the second pH measuring device being at least partially surrounded by the medium within the second tank wherein:
    - the second tank lacks means for manually or automatically taking a sample of the medium in the second tank; or
    - the second tank comprises means for manually or automatically taking a sample of the medium in the second tank, the method further comprising:

during a time interval after filling the medium in the second tank and before adding a cell culture to the medium in the second tank, keeping all openings of the sampling means closed.

14. The method of any one of the previous claims 1-3, 10-13, the method being used for determining if the second pH measuring device is calibrated differently than the first pH measuring device, the determination if the first and second pH measuring device are calibrated differently being performed while the second pH measuring device is at least partially surrounded with the medium in the second tank and without taking a sample of the medium of the second tank for performing said determination.

15. The method of any one of the previous claims 1-3, 10-14, the determination if the first pH measuring device is affected by a pH measuring problem being performed by using the first and second CO2 concentrations and the first and second pH values as the only data input for said determination.

16. The method of any one of the previous claims, the method further comprising:
    - performing an online-measurement with the first pH measuring device for measuring the first pH-value, the first pH measuring device being at least partially surrounded with the medium in the first tank; and/or
    - performing an online-measurement by a first CO2 sensor (124, 126) in the off gas of the first tank for providing the first CO2 concentration.

17. The method of any one of the previous claims 1-3, 10-16, further comprising:
    - performing an online-measurement with the second pH measuring device for measuring the second pH-value, the second pH measuring device being at least partially surrounded with the medium in the second tank; and/or
    - performing an online-measurement by a second CO2 sensor (122) in the off gas of the second tank for providing the second CO2 concentration.

18. The method of any one of the previous claims, the method comprising, in case

of determining that the first pH measuring device is affected by a pH measuring problem , performing one or more of the following steps by the comparison unit:

- outputting a warning message;
- automatically performing or triggering the performing of a recalibration of the first pH measuring device;
- automatically performing or triggering the performing of a replacement of the first pH measuring device by a new first pH measuring device.

19. The method of any one of the previous claims 1-3, 10-18, the first tank (104, 106) differing from the second tank (102) in respect to one or more of the following features:
    a) the gas volume in the tank,
    b) the medium volume in the tank,
    c) the Reynolds number of the tank,
    d) the Newton number of the tank,
    e) the dimensions of the tank,
    f) geometrical features of the tank and/or tank baffles,
    g) the stirrer configuration,
    h) the stirring rate,
    i) the volumetric mass transfer coefficient for oxygen (kLa) of the tank,
    j) total gas influx rate and/or O2 influx rate and/or N2 influx rate and/or CO2 influx rate,
    k) power input,
    l) pressure in the tank,
    m) gas bubble hold time in the medium,
    n) gas bubble size and distribution in the medium,
    o) surface speed,
    p) a parameter calculated as a derivative from one or more of the parameters a)-o);
    q) the geographic location of the two tanks.

20. A comparison unit (130) configured for:
    - receiving (202), a first CO2 concentration and a first pH value, the first CO2

concentration being a CO2 concentration of a first gas volume above a medium (M1) in a first tank, the first CO2 concentration and the first pH value being measured at a first time, the first time being a time when the medium in the first tank is in pH-CO2 equilibrium state with the first gas volume at a predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the first pH value being a measured value provided by the first pH measuring device (108; 146);

- receiving (202) a second CO2 concentration and a second pH value, the second CO2 concentration being a CO2 concentration of a second gas volume above the same type of medium (M1) contained in the second tank, the second CO2 concentration and the second pH value being measured at a second time, the second time being a time when the medium in the second tank is in pH-CO2 equilibrium state with the second gas volume at the predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the second pH value being a measured value provided by the second pH measuring device (142);
- comparing (206) the first and second pH values and comparing the first and second CO2 concentrations for determining if the first pH measuring device is affected by the pH-measuring problem.

21. A comparison unit (130) configured for:

- receiving (202) a first CO2 concentration and a first pH value, the first CO2 concentration being a CO2 concentration of a first gas volume above a medium (M1) in a first tank, the first CO2 concentration and the first pH value being measured at a first time, the first time being a time when the medium in the first tank is in pH-CO2 equilibrium state with the first gas volume at a predefined temperature and pressure, said equilibrium state being unaffected by the metabolism of any cell culture, the first pH value being a measured value provided by the first pH measuring device (108; 146);
- computing (204) a second pH value as a function of the first CO2 concentration, the second pH value being the pH value predicted for said type of medium (M1) when said medium is in pH-CO2 equilibrium state with a second gas volume above said medium (M1) at the predefined temperature

and pressure, the second gas volume in said equilibrium having a second CO2 concentration that is identical to the first CO2 concentration, said equilibrium state being unaffected by the metabolism of any cell culture;

- comparing (206) the first and second pH values for determining if the first pH measuring device is affected by the pH-measuring problem.

22. A system (100) configured for monitoring and/or controlling a state of a first tank, the system comprising:
    - the comparison unit (130) of claim 20 or 21;
    - a control unit (132) operatively coupled to the comparison unit (130); and
    - the first tank (104, 106) and the first pH measuring device;
    - the control unit being configured to monitor and/or control a state of a cell culture in the first tank, thereby using pH values repeatedly measured by the first pH measuring device as input.