CLAIMS

1. A method for monitoring cell density during cell expansion resulting from a cell culture process in a bioreactor comprising the steps of:

a) cultivating cells in a bioreactor culture chamber according to a cell culture process having cell culture parameters;

b) during said process, introducing cell culture fluid inputs and generating waste materials;

c) determining the intensity of volatile organic compounds (VOCs) and their chemical species ———in the waste materials; and

d) estimating the density or population of cells in the bioreactor based on said determination.

2. The method of claim 1, wherein said waste materials include bioreactor headspace gases, and/or filtered liquid or solid waste, and said VOCs include gas phase and/or dissolved or suspended VOCs respectively.

3. The method of claim 1 or 2, wherein the waste materials are isolated or removed from the bioreactor chamber prior to said determining.

4. The method of claim 3 ~~or 4~~, wherein said isolation is achieved by an isolation filter allowing only the passage of gases out of the chamber and inhibiting the passage of contaminants into the chamber.

5. The method of in any one of the preceding claims wherein, during or after said process, the VOCs are collected from said waste materials prior to said determining.

6. The method of claim 5 wherein, said collecting includes exposing the waste materials to a collective element and said determining step includes subjecting the collective element to a chemical detector, for example mass spectrometry (MS) or proton transfer reaction MS, to provide said intensity and profile of VOCs.

7. The method of claims 5 or 6, wherein said collecting and said determining are conducted continually, periodically or intermittently.

8. The method of any one of the preceding claims, wherein said estimating includes assessing the change, and/or rate of change of the VOC concentration/profile.

9. The method of any one of the preceding claims, wherein said cells are CHO or T cells and the estimation of cell density includes the measurement of the concentration of one or more of alkanes, alkenes~~, alkynes~~, carbonyls, esters, alcohols, arenes, acids~~, amides~~, amines, ~~carbohydrates,~~ steroids~~, proteins, nucleic acids~~ and oximes.

10. The method of claim 9, wherein said measurement includes the measurement of the increase in concentration of VOCs, for example, docosane and/or other alkanes.

11. The method of claim 9~~ or 10~~, wherein a) where said cells are CHO cells or T cells, then the measurement includes the measurement of the decrease in concentration of VOCs~~ or b) where said cells are T cells, then the measurement includes the measurement of the decrease in concentration of VOCs~~, for example, benzaldehyde and/or other aldehydes.

12. The method of claim 8, 9 or 10, wherein the ratio of VOCs, for example the ratio of measured alkanes, esters, alcohols and oximes, is used to determine cell density/concentration.

13. The method as claimed in any one of the preceding claims, wherein said estimation is used to control at least one process parameter related to the cell culture process.

14. The method as claimed in claim 13, wherein said estimation is used to alter or enhance said cell culture parameters and/or said cell culture fluid inputs.

15. The method as claimed in any one of the preceding claims, further comprising providing an indication of cell viability, health, and/or nutrient utilization based upon the estimated density or population of cells over time.

16. A cell culture system arranged for monitoring cell density during cell expansion resulting from a cell culture process; the system comprising:
a) a bioreactor including a culture chamber (100) suitable for cultivating cells;
b) a controller (150) for conducting a cell culture process according to cell culture parameters;

c) at least one cell culture fluid input (110/120) and at least one waste materials output (130/140);
d) one or more VOCs sensors or collectors (132/134/136) present in or at the waste output (130/140); and
e) means for determining the intensity of VOCs sensed or collected and their chemical species.

17. The system of claim 16, wherein the controller is configured to estimate the density or population of cells in the bioreactor based on a determined intensity of VOCs.

18. The system of claim 16, wherein said at least one waste materials volume includes: a bioreactor headspace (102) for head space waste gases, and/or a waste gas outlet, and/or an area in the chamber where waste fluids collect, and/or a fluid waste collection line or vessel, and/or a fluid circulation line, and/or an area in the chamber where waste solids collect, and/or a solid waste collection line or vessel, and/or a solid waste circulation line.

19. The system of claim 16, 17, or 18, wherein said one or more VOC collectors include a collection element such as sorptive element at least partially within the waste materials volume.

20. The system of any one of the claims 16-19, wherein the system further includes an isolation filter allowing only the passage of gases out of the chamber and inhibiting the passage of contaminants into the chamber, and wherein said waste material volume is downstream of said filter thereby isolating the volume from the chamber.

21. The system of any one of the claims 16-20, wherein means for determining the intensity of VOCs collected and their chemical species is a chemical detector, for example mass spectrometer (MS) or proton transfer reaction MS.

22. The system claimed in any one of claims 16-21, wherein said controller is adapted to control at least one process parameter related to the cell culture process based the determination of the intensity of VOCs collected and their chemical species.

23. The system claimed in claim 22, wherein said controller is adapted to alter the cell culture parameters in response to the determination of the intensity of VOCs collected and their chemical species.

24. The system claimed in any one of claims 16-21, wherein the controller is configured to provide an indication of cell viability, health, and/or nutrient utilization based upon the estimated density or population of cells over time.