

Claims

1. A method of predicting a parameter of a medium to be observed in a bioprocess based on Raman spectroscopy, the method comprising the steps of:
- acquiring a first series of preparatory Raman spectra of an aqueous medium
 - 5 using a first measuring assembly;
 - normalizing the first series of preparatory Raman spectra based on a characteristic band of water from at least one Raman spectrum acquired with the first measuring assembly;
 - building a multivariate model for the parameter based on the normalized
 - 10 preparatory Raman spectra;
 - acquiring predictive Raman spectra of the medium to be observed during the bioprocess acquired with another measuring assembly;
 - normalizing the predictive Raman spectra based on a characteristic band of water from at least one Raman spectrum acquired with the other measuring
 - 15 assembly; and
 - applying the built model to the predictive Raman spectra for predicting the parameter.
2. The method according to claim 1, characterized in that the characteristic water band at about 1640 cm^{-1} is used for normalizing.
- 20 3. The method according to any of the preceding claims, characterized in that a peak value (intensity) of the characteristic water band is used for normalizing.
4. The method according to any of the preceding claims, characterized in that a peak area (integral) of the characteristic water band is used for normalizing.
5. The method according to any of the preceding claims, further comprising
- 25 the steps of
- acquiring at least a second series of preparatory Raman spectra of an aqueous medium using a second measuring assembly; and
 - normalizing the second series of preparatory Raman spectra based on the characteristic band of water from at least one Raman spectrum acquired with the
 - 30 second measuring assembly;

wherein the step of building a multivariate model for the parameter is based on the normalized first and second series of preparatory Raman spectra.

6. The method according to any of the preceding claims, characterized in that each of the preparatory and/or predictive Raman spectra is normalized using the characteristic water band from the very same Raman spectrum, respectively.

7. The method according to any of claims 1 to 5, characterized in that each spectrum of a series of preparatory and/or predictive Raman spectra acquired with one measuring assembly is normalized using a statistical average, especially a median or a mean value, of the characteristic water band derived from the same or another series of Raman spectra acquired with the same measuring assembly.

8. The method according to any of the preceding claims, characterized in that the predictive Raman spectra of the medium to be observed during the bioprocess are acquired using a measuring assembly different from the measuring assemblies used for acquiring the preparatory Raman spectra.

9. The method according to any of the preceding claims, characterized in that the preparatory Raman spectra are acquired in one or more small-scale bioreactors, which are preferably arranged in a multi-parallel set-up.

10. The method according to any of the preceding claims, characterized in that the predictive Raman spectra are acquired in a large-scale bioreactor, preferably in a single-use bioreactor having an inherent spectroscopy port.

11. The method according to any of the preceding claims, characterized in that for building a quantitative model a sample of the aqueous medium is taken, a sample reference measurement of the parameter is performed, and at least one of the preparatory Raman spectra is linked to the sample reference measurement, preferably a preparatory Raman spectrum acquired at the same time as the sample was taken.

12. The method according to any of the preceding claims, characterized in that for building a qualitative model a statistical value from the preparatory Raman spectra is derived, in particular score values from a principal component analysis (PCA) or an (orthogonal) partial least squares ((O)PLS) regression.

13. A device assembly for predicting a parameter of a medium to be observed in a bioprocess, the device assembly being adapted to carry out a method according to any of claims 1 to 12.

14. The device assembly according to claim 13, characterized by a plurality of small-scale bioreactors containing aqueous media from which the preparatory Raman spectra are acquired, the small-scale bioreactors being preferably arranged in a multi-parallel set-up.

15. The device assembly according to claim 14, characterized in that each small-scale bioreactor is associated with an individual measuring assembly for acquiring the preparatory Raman spectra.

16. The device assembly according to claim 15, characterized in that each small-scale bioreactor is connectable to a single measuring assembly for acquiring the preparatory Raman spectra.

17. The device assembly according to any of claims 13 to 16, characterized by a large-scale single-use bioreactor (22) having an inherent spectroscopy port (24) for acquiring the predictive Raman spectra.

18. The device assembly according to any of claims 13 to 17, characterized by a Multivariate Data Analysis software module (36) for building the multivariate model and applying the multivariate model in real-time.

19. The device assembly according to any of claims 13 to 18, characterized by a control software module (34) for controlling a spectrometer (28) of the measuring assembly used for acquiring the predictive Raman spectra during the bioprocess.

20. A method of controlling a bioprocess, comprising the steps of:

- predicting a parameter of a medium to be observed in the bioprocess by a method according to any of claims 1 to 12; and
- modifying at least one process parameter of the bioprocess based on the prediction in real-time; and/or
- initiating a control action based on the prediction in real-time.

21. The method according to claim 20, characterized in that the initiated control action includes one of the following: controlling a feed supply; adding an antifoam; sampling.

22. A device assembly for controlling a bioprocess, the device assembly being
5 adapted to carry out a method according to claim 20 or 21.

23. The device assembly according to claim 22, comprising

- a device assembly for predicting a parameter according to any of claims 13 to 19; and

- a control unit (32) connected to the control software module (34) and the
10 Multivariate Data Analysis software module (36);

the control unit (32) being adapted to modify at least one process parameter of the bioprocess based on the prediction in real time and/or to initiate a control action based on the prediction in real time.