standard. It is to be noted that the result is not normalized to the water band (in this case the function as internal standard would no longer be given). Rather, the extinctions of the Raman intensities are corrected only according to the obtained cell concentration, i.e. this correction only aims at the differences in the cell number (which is evident from the fact that the data was only recorded using a single device or probe). A transfer of models between different assemblies is not addressed in the publication.

Summary

According to an aspect, the present disclosure refers to a method of predicting a parameter of a medium to be observed in a bioprocess based on Raman spectroscopy. The method according to the invention comprises the steps of: acquiring a first series of preparatory Raman spectra of an aqueous medium 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 preparatory Raman spectra; acquiring predictive Raman spectra of the medium to be observed during the bioprocess 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 assembly; and applying the built model to the predictive Raman spectra for predicting the parameter.

According to another aspect, the present disclosure refers to 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 the above aspect.

According to another aspect, the present disclosure refers to 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 the above aspects; 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.

According to another aspect, the present disclosure refers to a device assembly for controlling a bioprocess, the device assembly being adapted to carry out a method according to the above aspects.

It is an object of the invention to enable a more precise prediction of a parameter of a medium to be observed in a bioprocess based on Raman spectroscopy. In particular, the invention aims at eliminating undesired variations caused by differences in the optical hardware used for acquiring the Raman spectra.

The above problem is solved by a method according to ~~claim 1~~the above aspects. Advantageous and expedient embodiments of the invention are apparent from the corresponding dependent claims.

In an example, ~~The~~ the present disclosure~~invention~~ provides a method of predicting a parameter of a medium to be observed in a bioprocess based on Raman spectroscopy. The method according to the invention comprises the steps of: acquiring a first series of preparatory Raman spectra of an aqueous medium 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 preparatory Raman spectra; acquiring predictive Raman spectra of the medium to be observed during the bioprocess 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 assembly; and applying the built model to the predictive Raman spectra for predicting the parameter.

It is to be noted that hereinafter the term “acquired” in connection with a Raman spectrum may refer to a Raman spectrum that has already undergone a dark current correction and/or a baseline correction as commonly known, but not a normalization in accordance with the present invention.

of Raman spectra acquired with the same measuring assembly. For example, one average data set can be applied to all Raman spectra acquired from one batch in the bioprocess. The advantage of this approach is that the normalization data for all Raman spectra of a series can be determined at a time when the signal-to-noise ratio is optimal, especially at the start of the cultivation, possibly even before inoculation in the pure medium. The same normalization data is then applied to all Raman spectra of the series for normalization.

In most cases the bioprocess is run with an equipment different from the experimental set-up with which the multivariate model was built. This means that the predictive Raman spectra of the medium to be observed during the bioprocess are acquired with a measuring assembly which is different from the measuring assemblies used for acquiring the preparatory Raman spectra.

Typically, several small-scale bioreactors, preferably arranged in a multi-parallel set-up, with one or more measuring assemblies are used for modelling, while a large-scale bioreactor with a different measuring assembly, typically a single-use bioreactor having an inherent spectroscopy port, is used for the bioprocess in which the model is to be applied. The spectroscopy port provides an optical interface and may be welded to the bag foil, for example.

In order to build a robust quantitative model for the parameter, it is expedient to take a sample of the aqueous medium, perform a sample reference measurement of the parameter, and link at least one of the preparatory Raman spectra to the sample reference measurement, preferably a preparatory Raman spectrum acquired at the same time as the sample was taken. The sample reference measurement can be performed immediately after sampling. The sample can also be cooled or frozen between sampling and later reference measurement to avoid or minimize further metabolization.

For building a qualitative model a statistical value from the preparatory Raman spectra can be derived, in particular score values from a principal component analysis (PCA) or an (orthogonal) partial least squares ((O)PLS) regression.

In an example, the present disclosure~~The invention~~ also provides a device assembly for predicting a parameter of a medium to be observed in a bioprocess. The device assembly is adapted to carry out the method of predicting a parameter according to the present disclosure~~invention~~.

assembly used for acquiring the predictive Raman spectra during the bioprocess. The software modules can be provided as separate “plug-in” solutions which communicate with other software components of the device assembly via appropriate software interfaces. On the other hand, the software modules may be combined and/or integrated in other software components of the device assembly.

In an example, ~~The~~ the present disclosure ~~invention~~ further provides 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 defined above; 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.

For example, the control unit may initiate a control action like controlling a feed supply; adding an antifoam or taking a sample (sampling).

In an example, the present disclosure further provides a device assembly for controlling a bioprocess. The device assembly for controlling a bioprocess is adapted to carry out a method of controlling a bioprocess according to the invention.

The device assembly may comprise a device assembly for predicting a parameter defined above, and a control unit connected to the control software module and the Multivariate Data Analysis software module. The control unit is 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.

Further features and advantages of the invention will become apparent from the following description and from the accompanying drawings to which reference is made. In the drawings:

- Figure 1 shows a detailed flow chart of a method of controlling a bioprocess in accordance with the invention.

- Figure 2 shows a basic setup for acquiring Raman spectra in a bioprocess;

- Figure 3 shows a schematic block diagram of hardware and software components used in the method of controlling a bioprocess according to the invention;