Supplementary Information A
Validation of the statistical model

To proof the established model we, as described in the main text, did two independent procedures. The first was to relate the calculated loadings of the statistical model to the spectrum of pure PHB. Loadings are weighting coefficients for the original spectra. Due to this, positive loadings relate to positive score values. In the case of our statistical model we were looking for negative loadings in component 2 resulting in negative score values of the second principal component. These negative loadings occur exactly at the wavenumbers which can directly be related to the PHB Raman signals, as can be seen in the spectrum. In fig. 3(C) these bands are highlighted with a black arrow. There are also some bands which cannot be directly related to PHB, but to signals, which can be related to the cell status. These bands are highlighted with a grey arrow. All together this first step in establishing SERS as a semi-quantitative detection method was successful and showed a valid statistical model.
The second process was a test-set validation. Independently repeating the cultivation of the cyanobacteria after two months generated samples, which helped to show that the statistical model is capable for predicting future samples. The samples were prepared and measured as it was done for the establishment of the statistical model. The statistical model was used to predict the validation data set. At the same the PHB content of the validation set was determined via HPLC. The prediction of the test-set validation was successful resulting in a clear separation and grouping of the data points of cultures with low and high PHB content in the predicted segment of the PCA.
This leads us to the conclusion that we have established a valid statistical model which can be used to determine the PHB content in a short time on a cellular level in all following experiments.

Supplementary Information B
Comparison of Ag-colloids applicable for SERS

The aim was to estimate the enhancement factor for different preparations of the colloidal Ag-NPs (common mixed prep.1 and 2, and in-situ generated prep.3a) and hereby to highlight the improvement achieved by application of in-situ generated Ag colloids. Untreated 20 *Synechocystis* cells were randomly selected and measured with "in-situ Ag-*Synechocystis*" method from table 1 as a negative control. As outlined in a publication by Shi et al. in 2018, the calculation of the enhancement factor (EF) provided by the SERS material depends on several parameters (see equation S1.).

$$EF = \frac{I_{\tilde{\nu},SERS}}{I_{\tilde{\nu},Raman}} * \frac{N_{SERS}}{N_{Raman}} * \frac{P_{Raman}}{P_{SERS}} * \frac{T_{Raman}}{T_{SERS}}$$

Equation S1: Enhancement factor for SERS applications, based on the signal intensity (I) at a defined wavenumber ($\tilde{\nu}$), the number of molecules in the laser spot area (N), the laser power (P) and the accumulation time (T) for conventional Raman and SERS respectively. Adapted from [Shi et al., 2018]

Since the laser power and the accumulation time were kept constant in all measurements, the impact of these two parameters on the EF can be disregarded. Calculating the exact number of molecules in the area of illumination can be next to impossible for cells as samples. We therefore were forced to knowingly neglect this part of the equation and to use only the intensity ratio (I_{SERS}/I_{Raman}) for an estimation of the enhancement factor. To compensate for this less than ideal solution, and to reinforce the estimation, we compared the average intensity ratios and considered also the relative standard deviation of the EF values obtained. These intensity ratios were calculated at the wavenumber of 478 cm^{-1}, the most prominent peak in the enhanced spectra, for the randomly selected cells.

To overcome the heterogeneities between different cells we build the statistical model, which we succeeded to validate. This prominent signal does not have an impact on the statistical differentiation between PHB high / low in cyanobacterial cells. Therefore, only the PCA relevant spectral range is shown in fig.3(C).

Supplementary Information C
HPLC Analytics

The sample preparation for the HPLC analysis was done as described in the main text according to the procedure of Karr et al., 1983. Further information about the applied HPLC method is given in tables S1 and S2, and in figures S1, S2 as well.

In table S1 the method parameters are listed.

Table S1: Method parameters for the HPLC analysis (RID = refractive index detector)

Parameter	**Setting**
Flow rate	0.9 mL/min
RID detector	55 °C
Injection volume	40 µL
Column temperature	65 °C
Solvent	100 % 0.01 N sulfuric acid
Total run time	25 min

In figure S1 the chromatogram is shown of crotonic acid extracted from the cyanobacterial dried biomass. The retention time of the crotonic acid signal in the sample (~17,5 min) corresponds to the retention time determined for crotonic acid in the calibration standards.

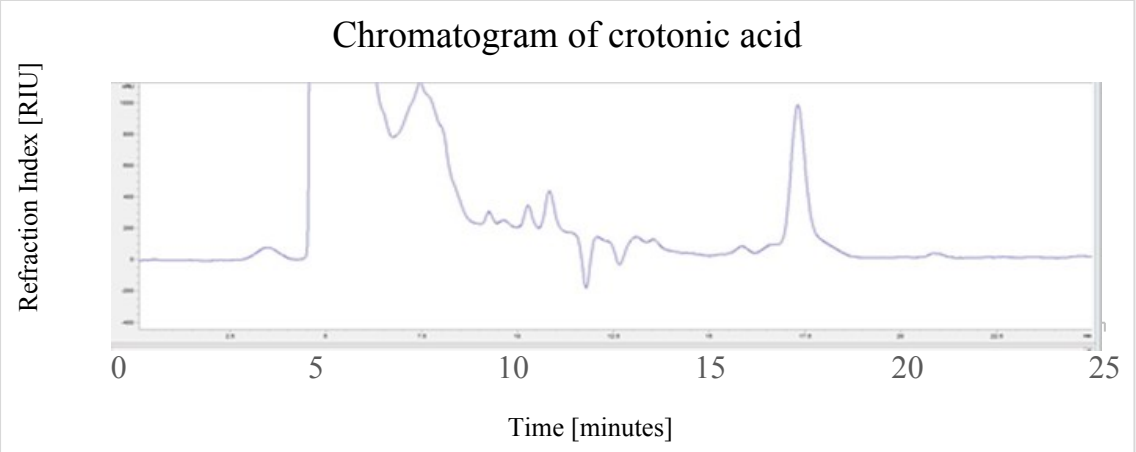

Figure S1: HPLC chromatogram of the extracted derivative of PHB, crotonic acid, with retention time at 17.5 min. The y-axis is re-drawn in excel for better visualization of the ChemStation chromatogram of Agilent 1100.

For the extern calibration 5 levels of different concentrations were measured in triplicate. The crotonic acid peak at 17.5 min was individually baseline corrected and the height at the peak maximum was used for quantification. As an example, the calibration curve applied for the validation test-set data is shown in figure S2. The extracted samples were diluted to fit the range of the calibration curve.

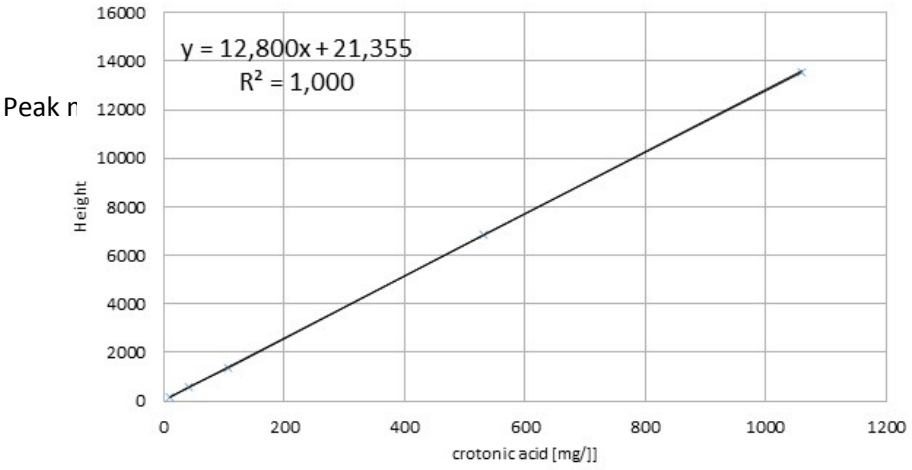

Figure S2: Calibration curve of crotonic acid [mg/L], the levels were measured in triplicate.

In table S2 the results of the HPLC analysis are shown. The same caption of the different media was used here as in the main text. It can be clearly seen that the different media composition result in low and high PHB contents (in % PHB of dry matter obtained from the appropriate cyanobacteria).

Table S2: PHB content in % of dry matter of the two trials (Ag-Synechocystis colloids (prep.3a) & validation data) and media composition (I, II, III)

Treatment	**I**	**II**	**III**
Ag-*Synechocystis* colloids (prep. 3a)	0.805 %	8.558 %	8.596 %
Validation data	near 0 %	7.78 %	-