Project No: 262107
Project Acronym: PATOV
Project Full Name: Process Analytical Technology Unit for Online Verification of the CIP Process in the Pharmaceutical Industry

Appendix I - Additional Visual Material

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° FP7-SME-2010-262107-PATOV

SEVENTH FRAMEWORK
PROGRAMME

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Additional material to illustrate main S & T results

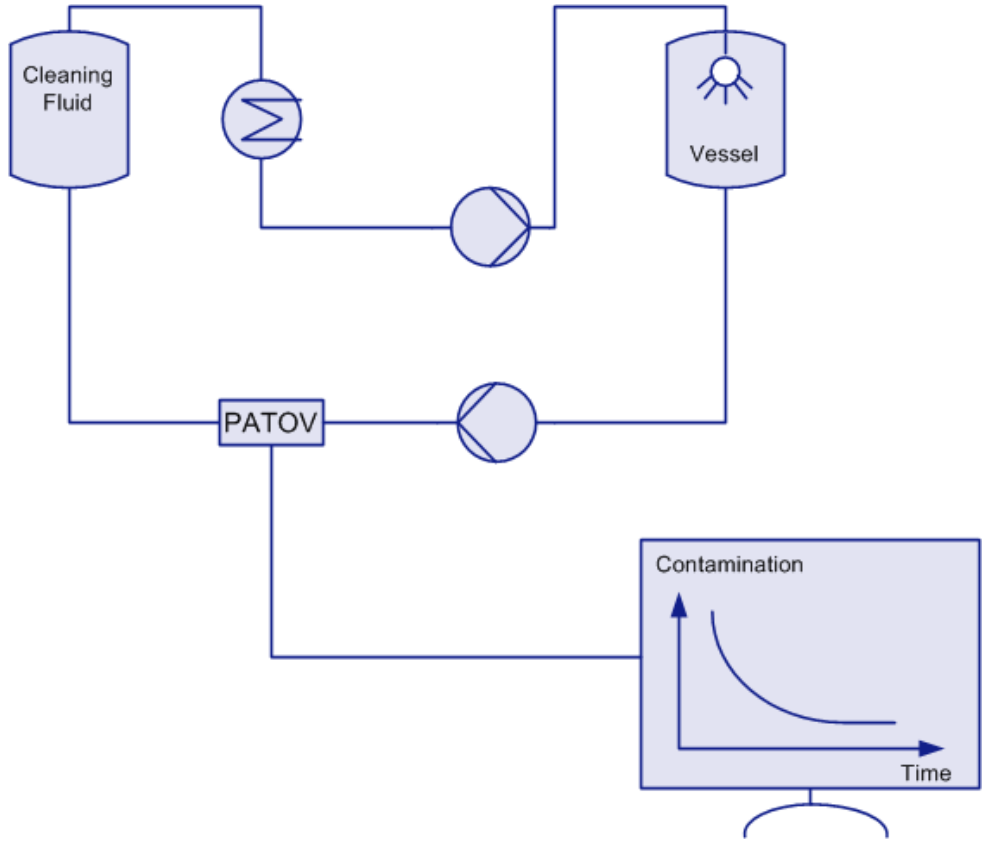

Figure 1: Schematic of the experimental CIP plant installed at TUW including the PATOV analytical device. The plant enables to reproduce CIP procedures by cleaning a vessel of a typical size used in pharmaceutical production processes. The PATOV unit with the implemented IR equipment is placed close to the CIP plant. The contamination in the CIP process water is measured every 1 to 30 seconds to provide information for online verification of the cleaning process.

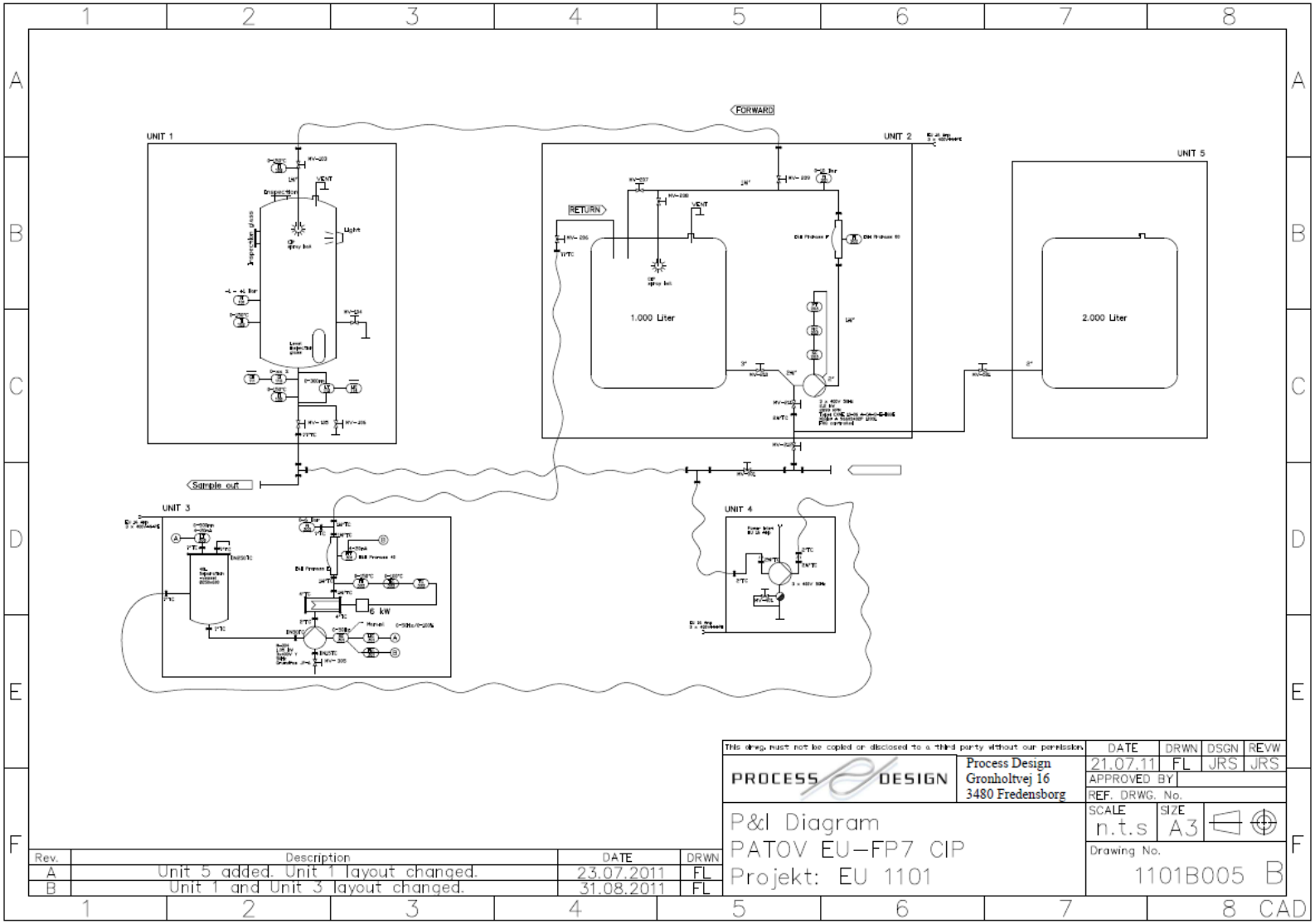

Figure 2: PID for the base case CIP system mainly consisting of the CIP client (Unit 1), the CIP system (Unit 2), the separator unit (Unit 3), the return pump (Unit 4) and the water buffer vessel (Unit 5).

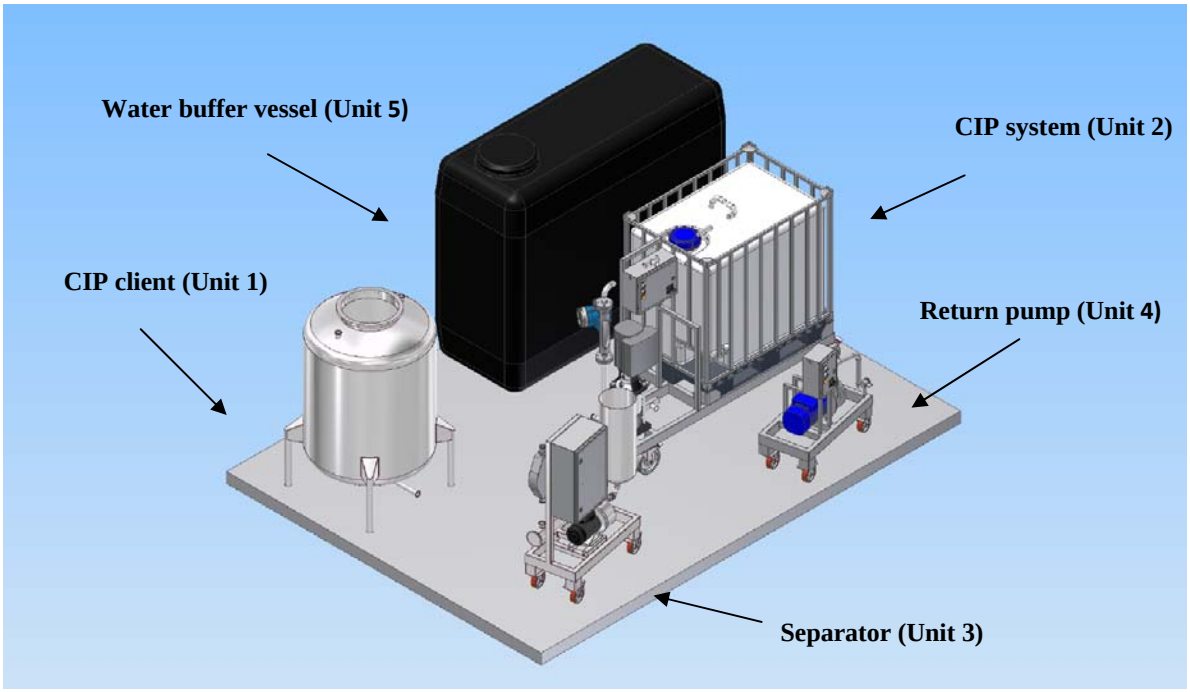

Figure 3: Early 3D CAD drawing of the base case CIP setup with Units 1 to 5.

Step	Notation	Liquid	Temperature	Operation
1	1st rinse	WFI	ambient	once through
2	1st wash	WFI, NaOH, 2%	70°C	recycle 15-60min
3	2nd rinse	WFI	ambient	once through
4	2nd wash	WFI, HNO_3, 2%	ambient	once through
5	Final rinse	WFI	ambient	once through

Table 1: CIP steps defined according to the base case. Mainly the first wash (step 2), the second wash (step 4) four and the final rinse (step 5) are to be considered.

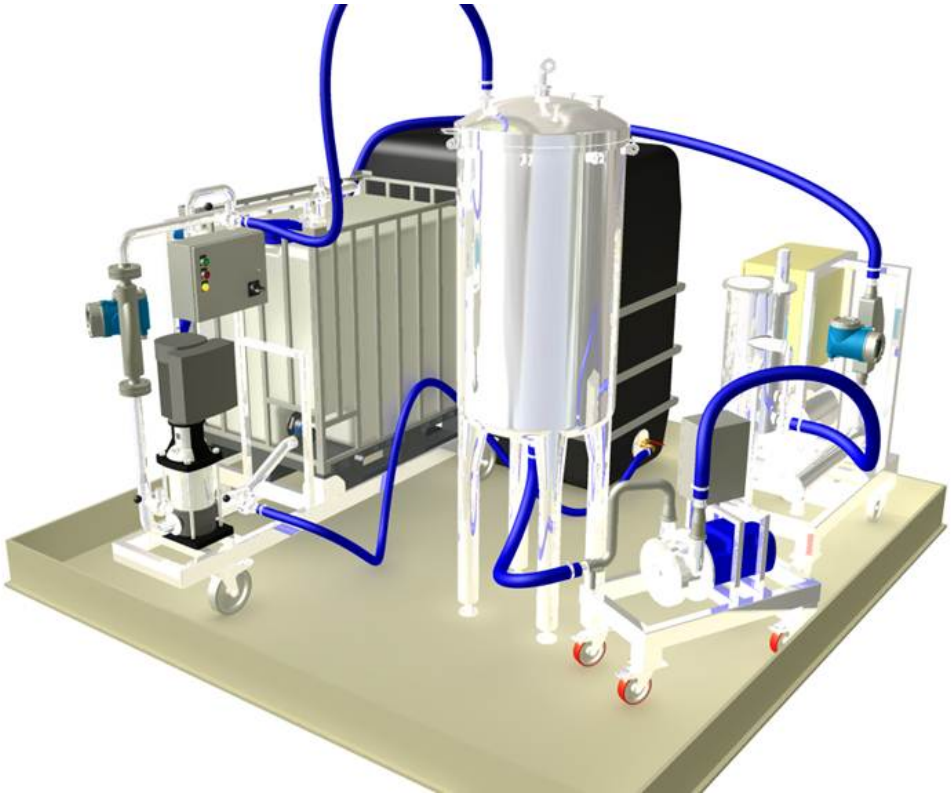

Figure 4: 3D drawing of the base case CIP setup as is was finally installed at TUW.

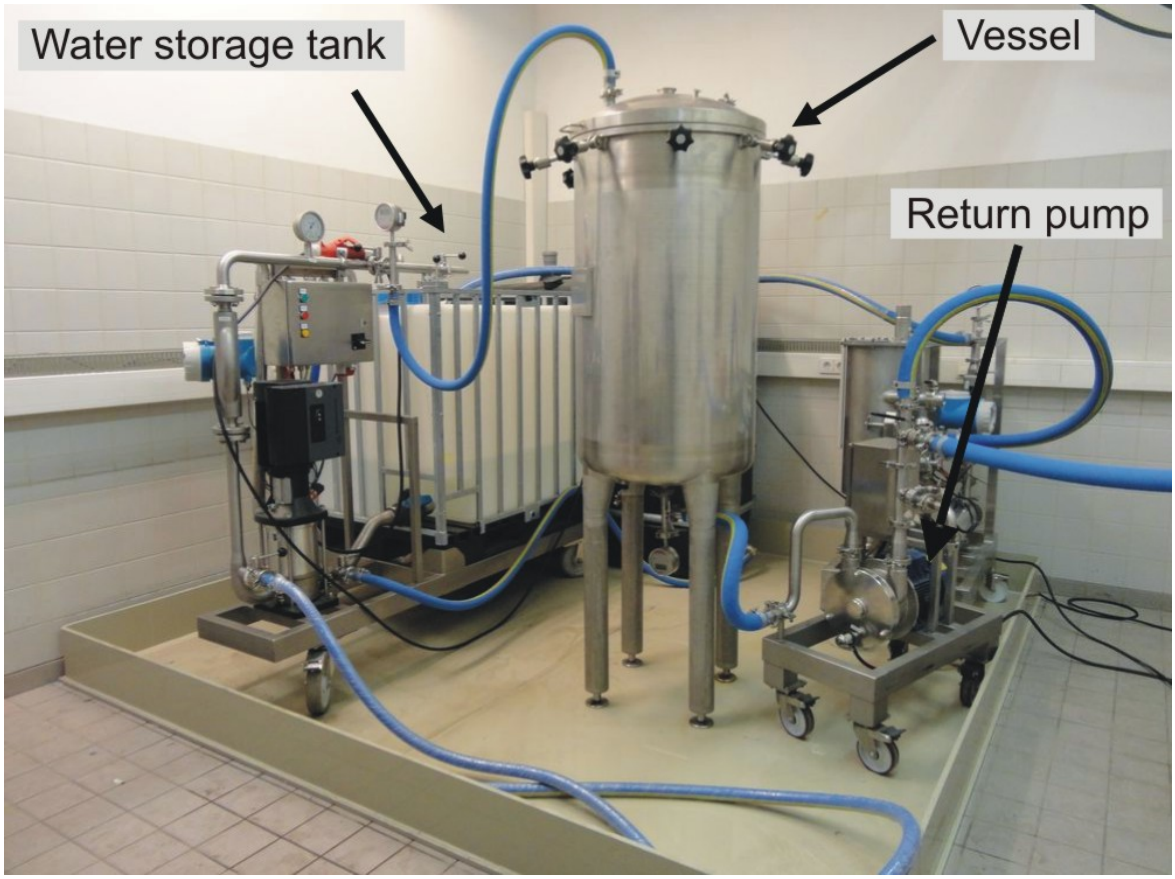

Figure 5: Picture of the experimental CIP plant for laboratory tests at TUW. The vessel in the centre of the picture is the object to be cleaned.

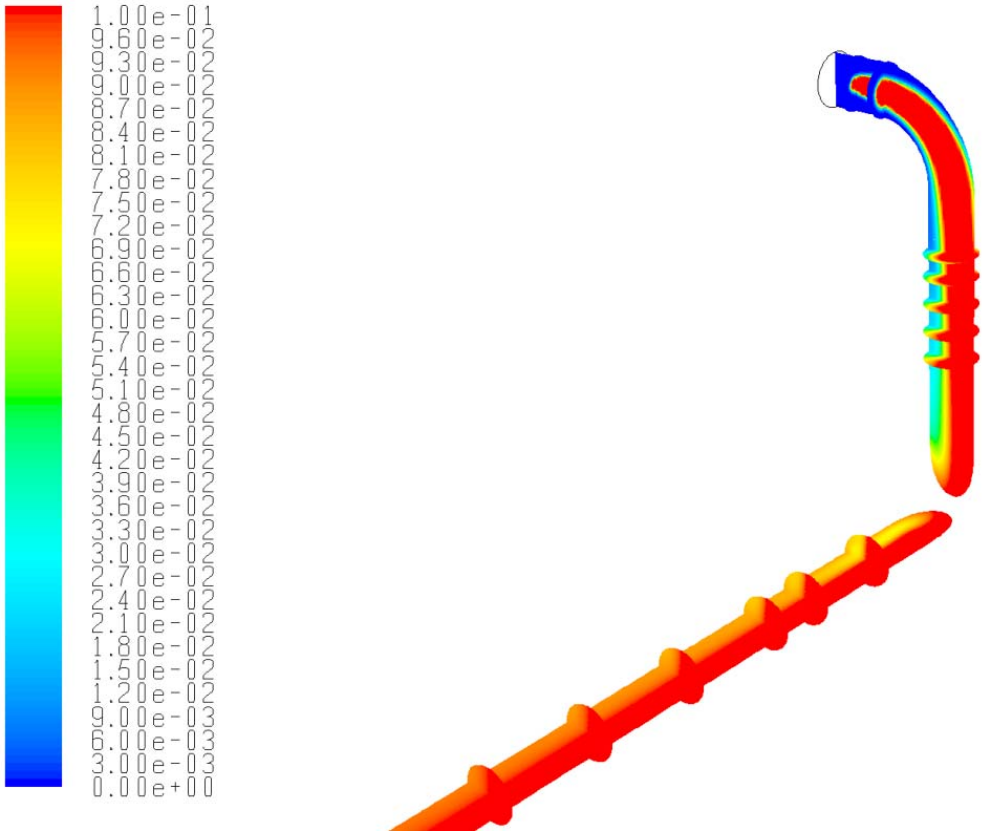

Figure 6: CFD simulation results on the sampling position: Shown is case 4 as an example. Species concentration range from 10% (red) down to 0% (blue). The figure shows the iso-surface with the concentration of the contamination starting at a point source at the beginning of the CIP-piping system. The simulation result displays how the contamination is mixed into the bulk stream. The flow pattern is highly turbulent. The high momentum exchange in the flow allows the contamination to be mixed in the bulk stream in a very short time.

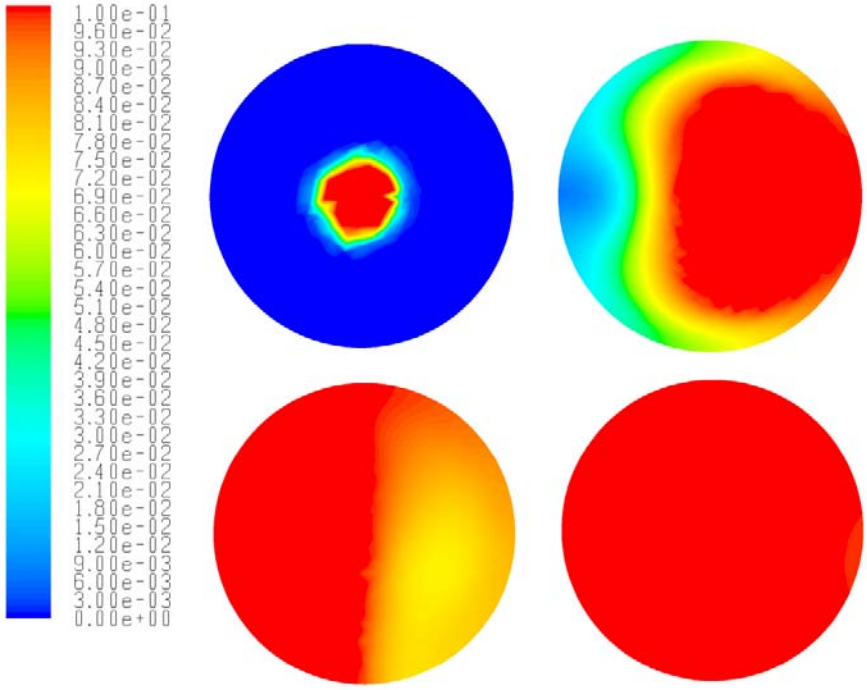

Figure 7: CFD simulation results – sampling position: Shown is case 4 as an example. Species concentration range from 10% (red) down to 0% (blue), cross sections of the piping system, top left direct at the point source of the contamination, top right 5 times the inner diameter of the pipe, bottom left 10 times the inner diameter and bottom right 25 times the diameter. The cross section views of the simulation results clearly demonstrate that the contamination is fully mixed into the bulk stream before the flow reaches the pump with the conditions used for the simulation. Therefore, the turbulence induced by the pump should not have an influence on the results of the other cases. The asymmetric distribution is a result of the arches in the system. The turbulent stream leads to a flow detachment behind the arches so the contamination is mixed faster on the side where the axial velocity is higher.

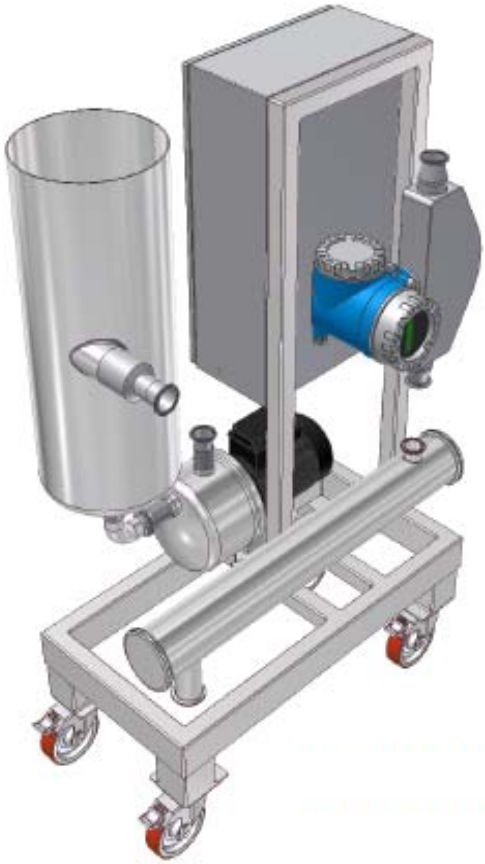

Figure 8: 3D drawing of the gas/liquid separator unit. The separator unit was designed and constructed to eliminate gas bubbles in the CIP off-stream before they enter the PATOV analytical device.

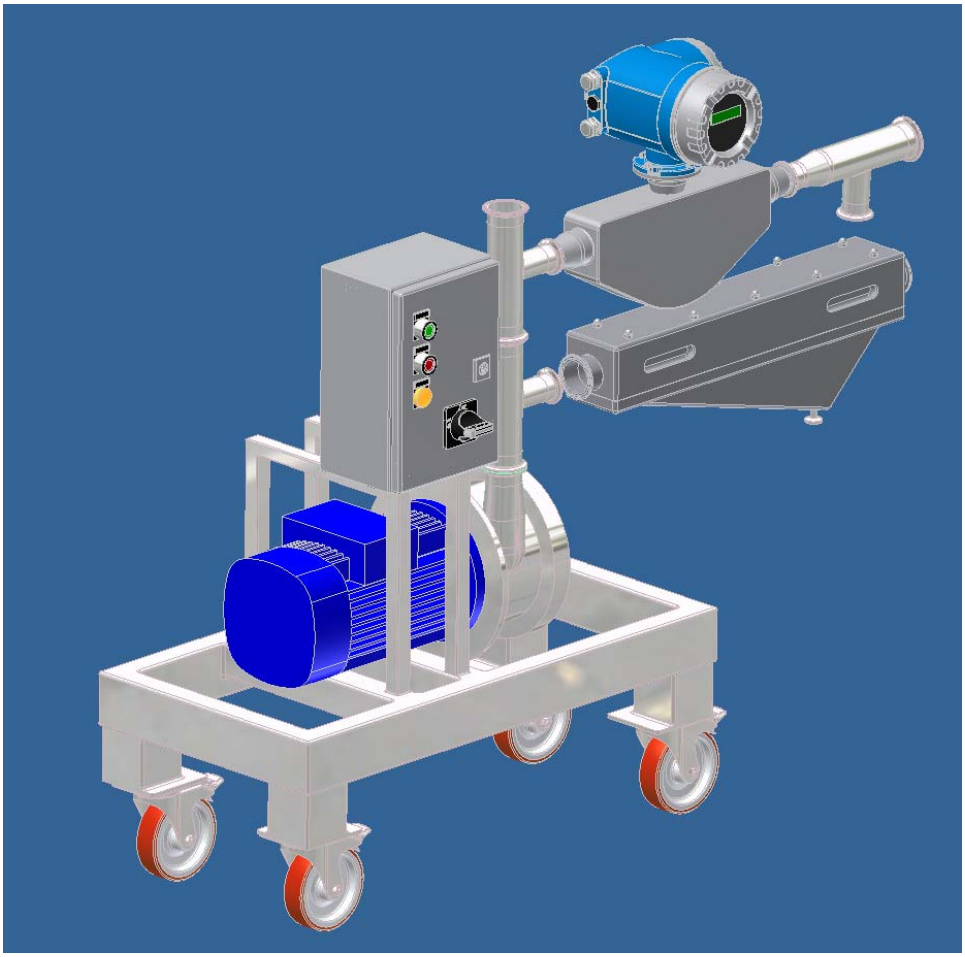

Figure 9: 3D drawing of the combined gas/liquid separator and sampling unit.

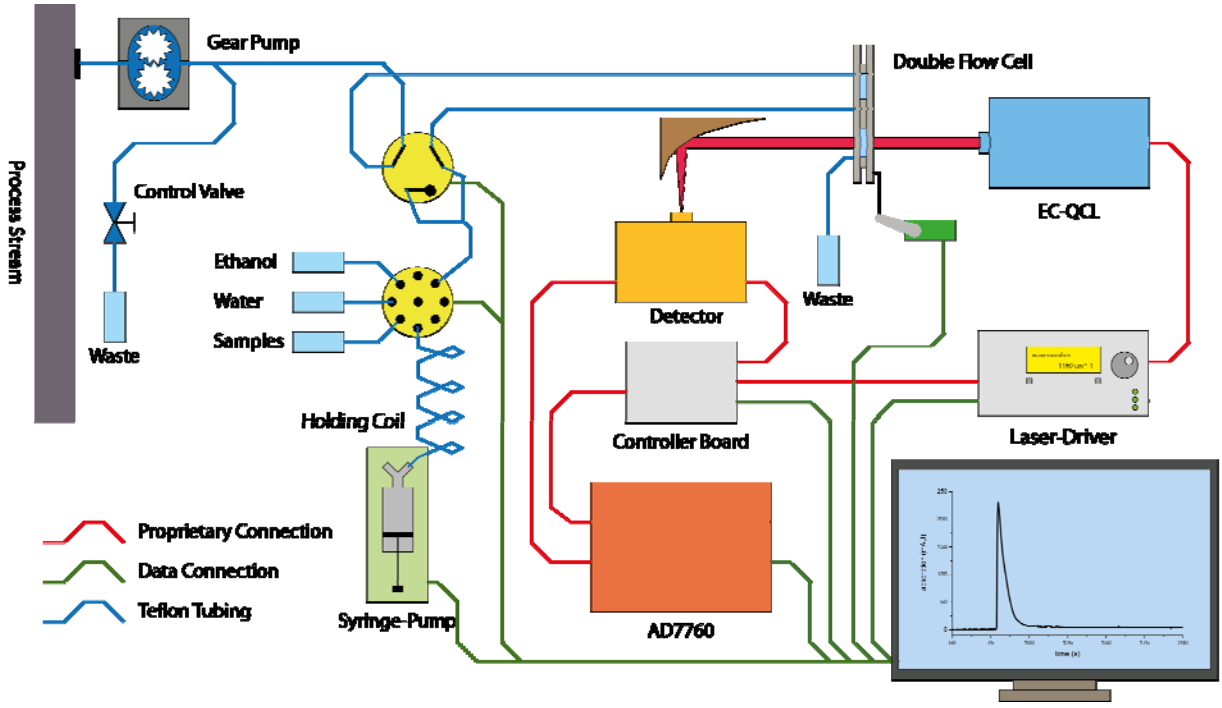

Figure 10: Scheme of the PATOV analytical unit. The schematic shows the devices and parts the PATOV unit consists of and the way they are connected.

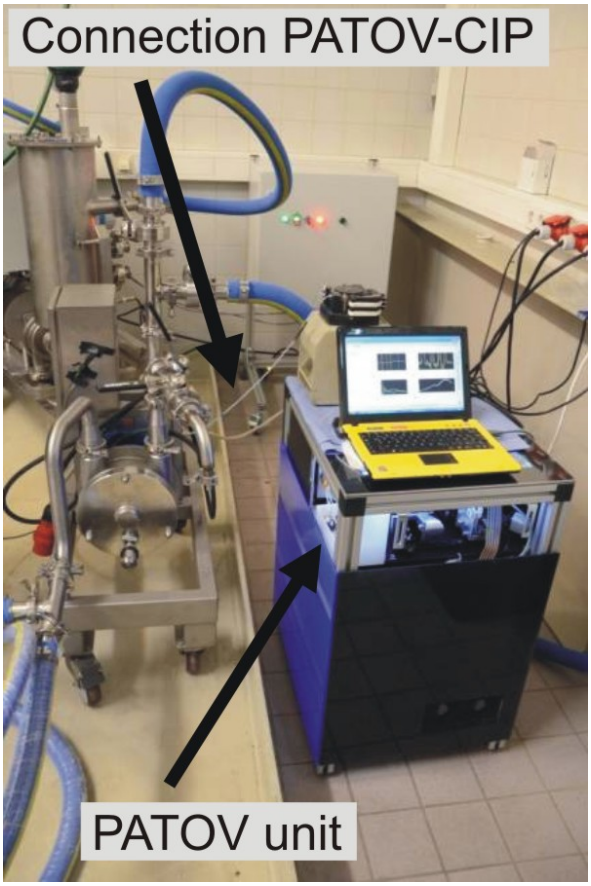

Figure 11: Picture of the PATOV analytical unit. A continuous sample flow is gathered from the CIP off-stream and fed into the PATOV unit which is placed close to the CIP plant.

Figure 12: Electrical enclosure and PLC (RX3i provided by GE-IP®) used for all conducted CIP experiments as well as for the development and analysis of the advanced process control functions

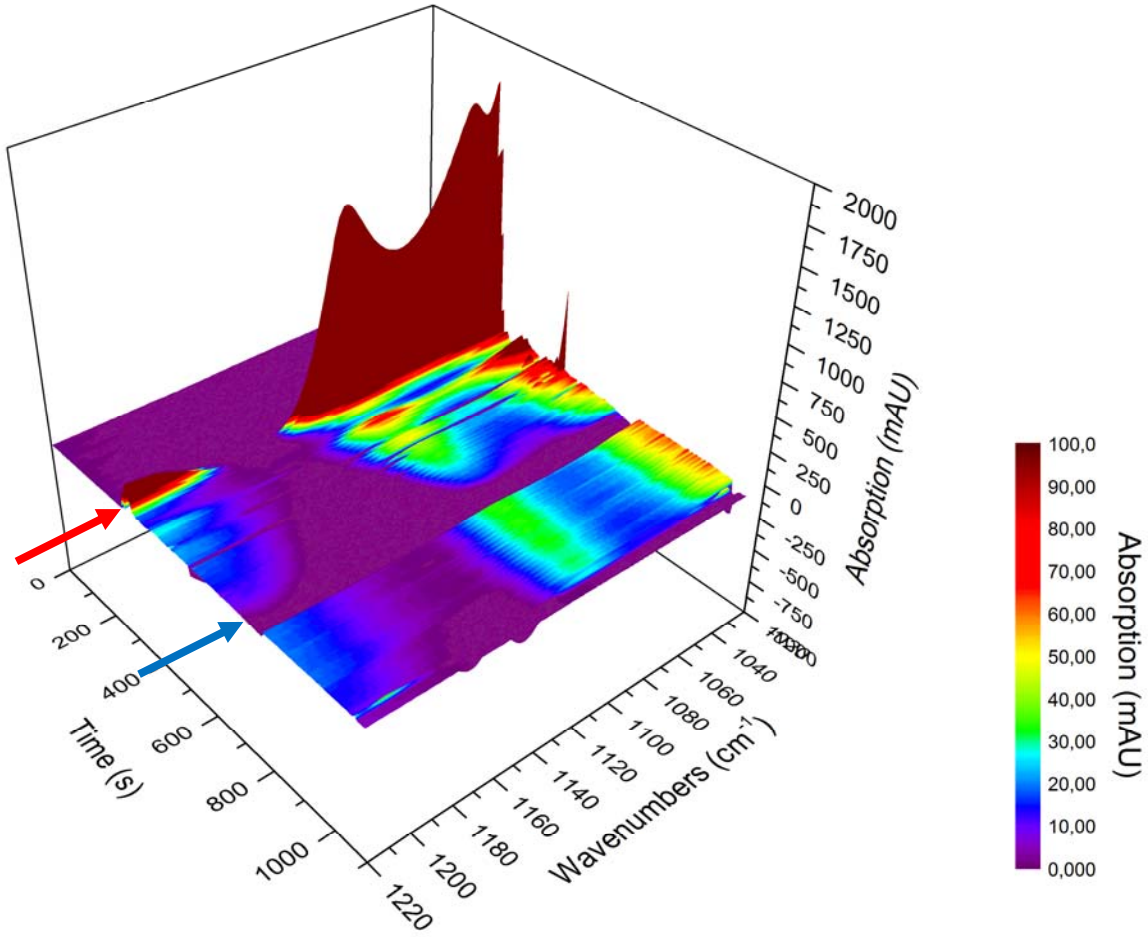

Figure 13: Cleaning cycle with glycerol as contaminant measured in scan mode (operating conditions: flowrate: 2000 kg/h, temperature ~20°C, vessel volume 320 l, spray ball Sani Midget)**.** The diagram shows an example result of on-line measurements performed in scan-mode. The scan-mode offers spectral information of the contamination but has, however, a decreased time resolution compared to single wavelength mode. For the measurement illustrated here the reaction vessel was contaminated with glycerol. The CIP system was used in cycle mode (start of the cleaning process indicated by red arrow). Therefore, the contamination reappears several times before cleaning has finished and the contamination stays constant. The blue arrow indicates a cleaning step of the flow cell. After this step, the measured glycerol contamination remains constant again.

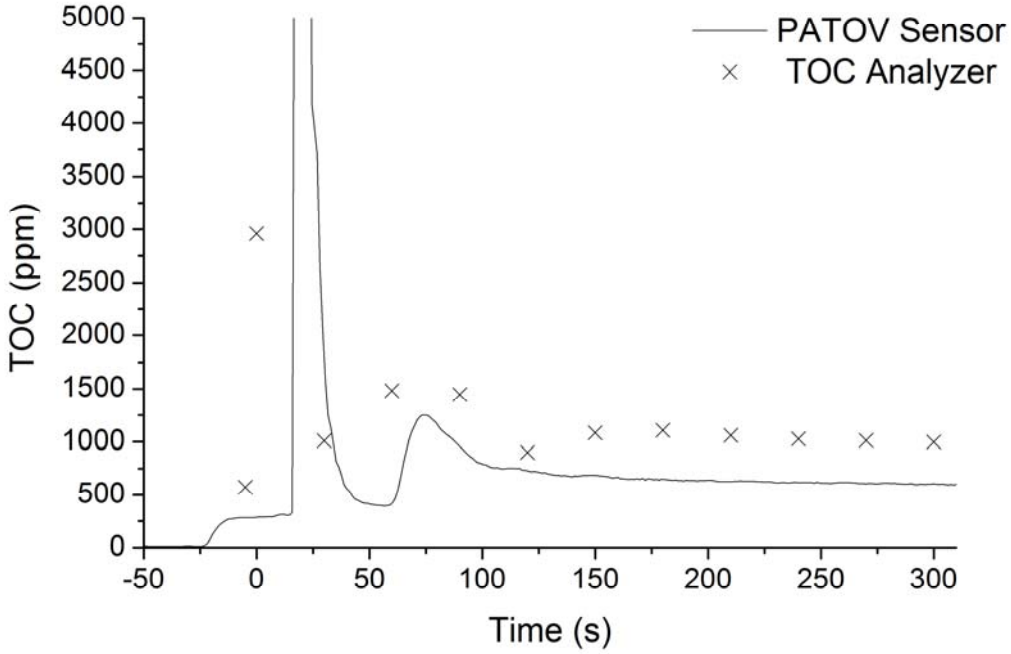

Figure 14: Cleaning cycle with glycerol as contaminant measured in single wavelength mode during laboratory tests (operating conditions: contamination approx. 1000 g glycerol, flowrate 2000 kg/h, temperature ~20°C, vessel volume 320 l, spray ball Sani Midget). Measurements results for TOC-off-line samples are included by symbols. The absorption measured by the PATOV analytical unit was converted to a TOC equivalent using calibration data gained before. The TOC equivalent is shown as a function of time. A first peak appears only a couple of seconds after starting the CIP process as the distance between the contaminated vessel and the sampling unit is very short. After the process water has passed one cycle a second peak is visible, which indicates that the cleaning is still productive. Finally the TOC approaches an asymptotic behavior indicating that further operation will not be worthwhile. The signal gained by the PATOV unit provides valuable on-line process information. Samples for TOC off-line measurements have been taken every 30 s during the cleaning cycle. The measurement results are included by symbols. Evidently, the results show large quantitative deviations, while qualitative agreement is obtained regarding the progression.

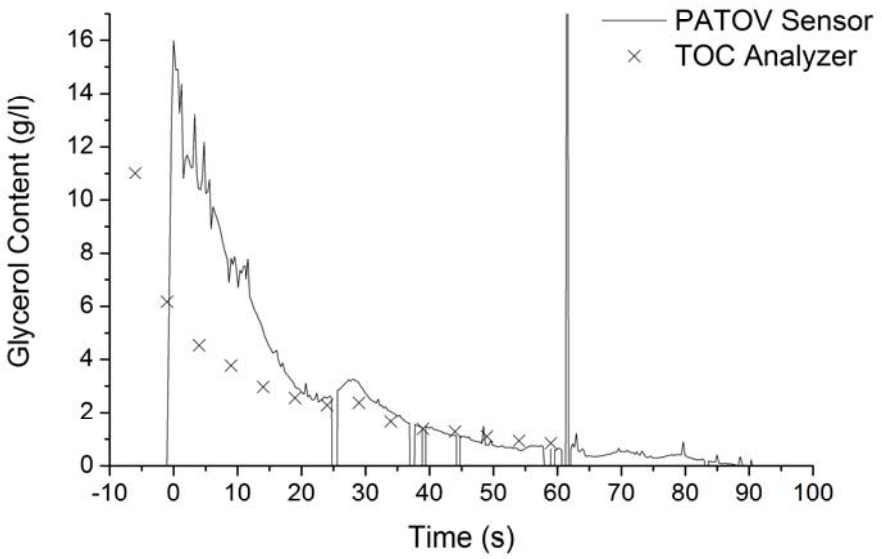

Figure 15: Rinse tests with glycerol as contaminant measured in single wavelength mode during field operational tests (operating conditions: flowrate: 490 kg/h, temperature ~20°C, vessel volume 150 l, spray ball small HAKE). The measurement results for TOC off-line samples are included by symbols. The continuous lines represent the data of the PATOV unit and the symbols are the results off-line sample measurements. Again the off-line measurements show significant deviations, but a qualitative agreement regarding the progression. Certainly various errors have to be considered with the comparison, in particular differing sampling volumes and sampling positions. The PATOV unit works with a continuous pump flow and small dead volume. Each offline sample contained approximately 50 ml of cleaning liquid and it took 2 to 5 s to take each sample.

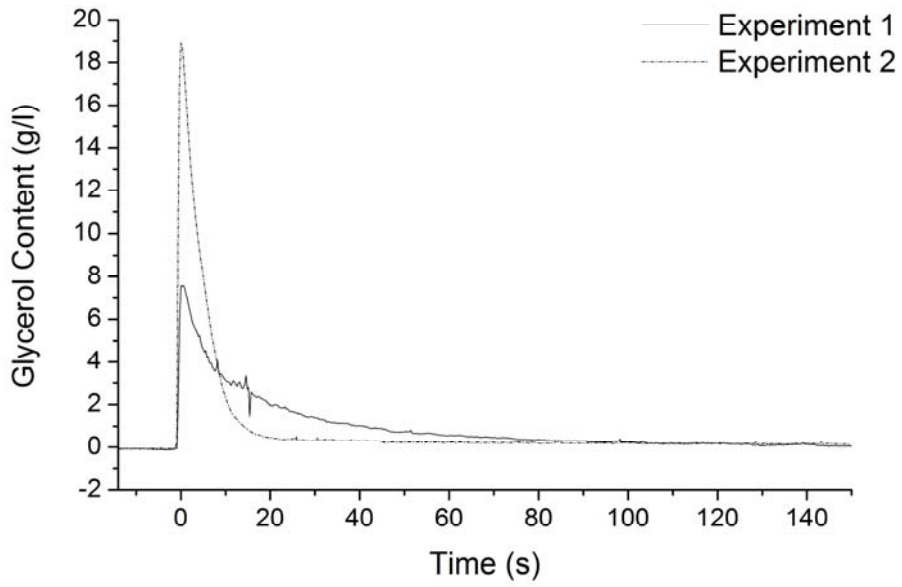

Figure 16: Tests with glycerol as contaminant measured in single wavelength mode (operating conditions: flowrate: 1370 kg/h, temperature ~20°C, vessel volume 150 l, spray ball big HAKE type X1-1). Data of the PATOV unit are shown for two experiments conducted for identical parameters (flow rate, spray ball, temperature, type and amount of contamination, etc.). The curves show a significant difference, which can be expected due to diverging cleaning effects from the different start contaminations at the vessel surface. In fact the line integral matches in the order of about 94 %.

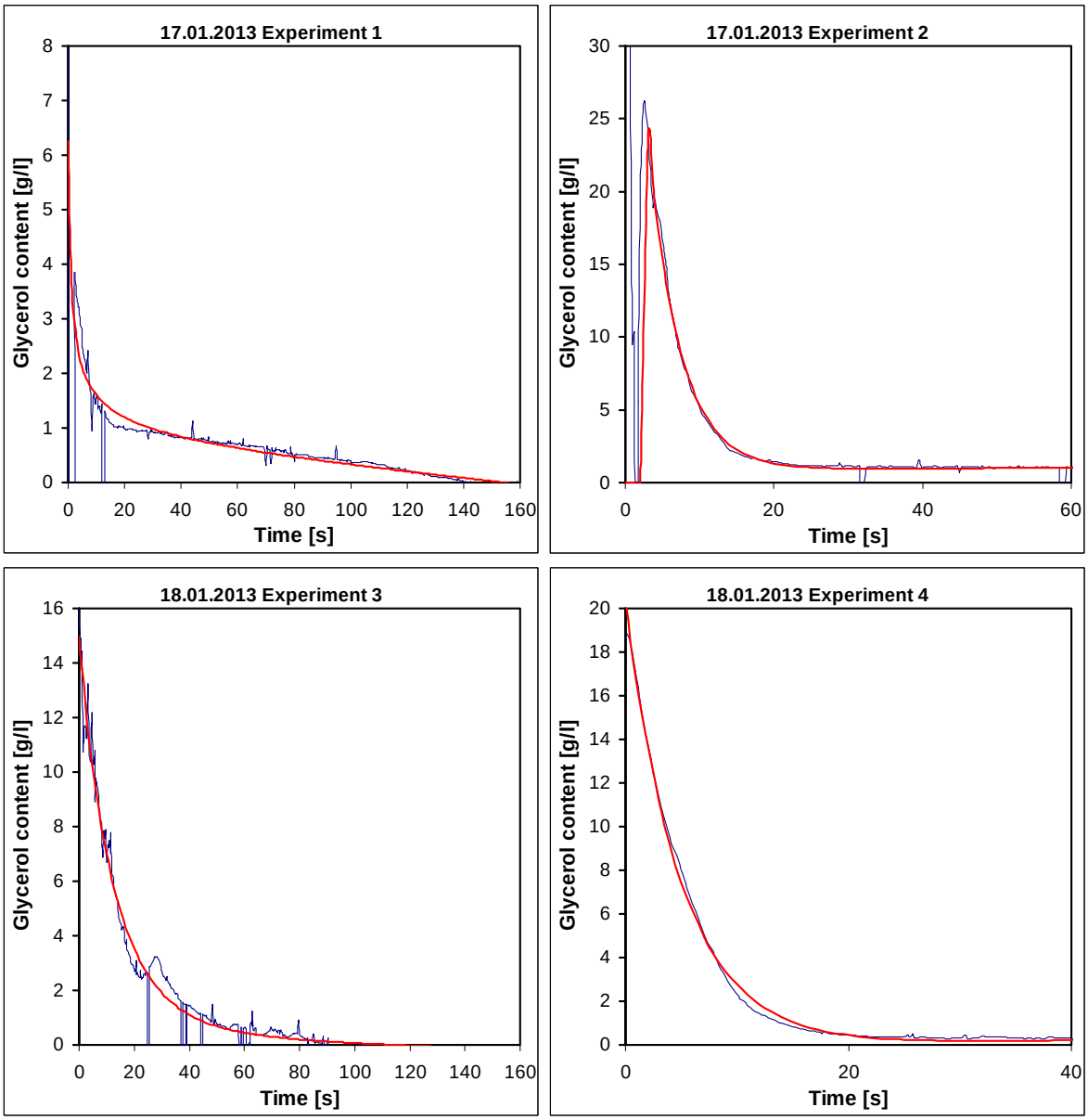

Figure 17: Regression functions for four different CIP experiments conducted on 17. and 18.01.2013 calculated by the Marquardt-Levenberg solver in gnuplot (blue curve: PATOV device, red curve: regression function). In order to get an impression on the flexibility of two different analyzed solver algorithms, both implementations have been applied to a number of different CIP experiments showing different cleaning characteristics. As a result of this analysis the regression curves for four different CIP experiments performed during the mid of January 2013 campaign are shown in this figure. The results given have been achieved by the application of the Marquardt-Levenberg solver of gnuplot. It can be seen that the chosen model function can be adapted to a wide number of curve shapes and that the agreement of experimental data and regression function is excellent.

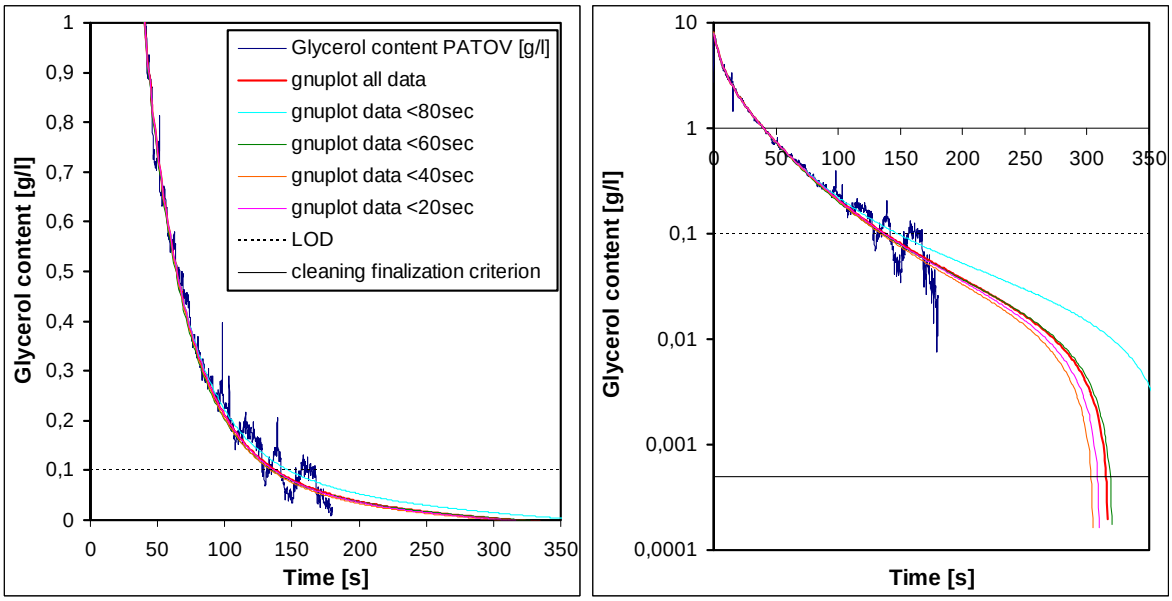

Figure 16: Several regression functions based on data available at different timestamps during a representative CIP experiment performed by Marquardt-Levenberg solver in gnuplot and utilization for the prediction of the CIP finalization timestamp. After having generated a suitable regression function for the contaminant content in the effluent of the ongoing CIP process it is quite straightforward to calculate a forecast for the exact timestamp when the CIP finalization criterion is met or underrun. This is performed by an extrapolation of the current data using the elaborated regression function and determining the time when the contaminant content underruns a given threshold (e.g. 500ppb). From the mathematical point of view, this would require the determination of the inverse function of the model function. In a typical case the inverse function of the model function cannot be calculated directly; therefore an iterative approach is chosen. This iterative approach will be implemented directly on PLC level by a simple Gauss-Newton solver. As the cleaning advances (and the regression function is calculated more and more precisely), the time for CIP finalization is calculated more and more accurately and finally this timestamp will be reached and the cleaning can be stopped. This extrapolation procedure and the determination of the timestamp of reaching the finalization criterion (in this case 500ppb) are depicted in this figure.