INSTITUTE FOR MEDICAL TECHNOLOGY
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Non-invasive In-line Raman Analysis

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INTRODUCTION

- **Non-invasive Raman spectroscopy is an effective tool in process analysis technology (PAT) for monitoring biological and chemical systems in real time**
- **Highly flexible: Use of existing measurement points, e.g. flow indicator armatures of reactors, glass reactors, and many more**
- **No special materials necessary (Hastelloy, tantalum, ceramics) in aggressive process conditions, compared to immersion probes**
- **Installation of immersion probes into product-conducting lines is very cost- and time-intensive**
- **No sample-taking is necessary, which eliminates the danger of contamination in biological processes**

➡ **Simple implementation into the process to be monitored via existing access windows**

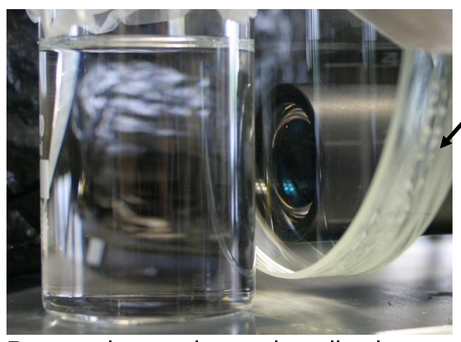
1 Monitoring aerobic batch fermentation through the 12 mm-thick borosilicate glass cladding of a fermenter
2 Determination of conversion dwell-time curves through the quartz glass window of a plate micro-reactor
3 Real-time measurements in a two-phase system via a commercially-available Teflon® (PFA) capillary

MultiSpec® Raman System
(tec5 AG, Germany)

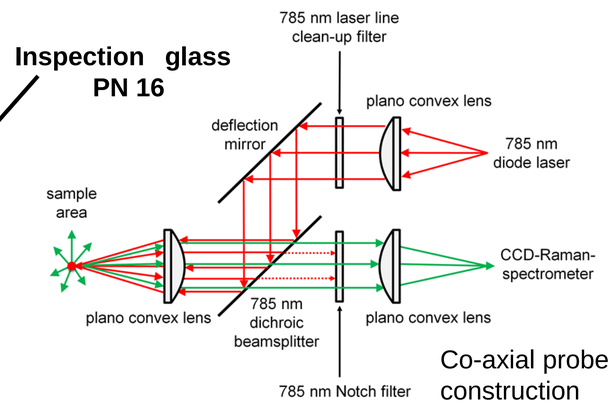
MEASUREMENT METHODS AND RESULTS

Co-axial Raman probe construction with long focal length

- In-line Raman analysis in conjunction with **MultiSpec® Raman System** (tec5 AG, Germany)
- Innovative probe design - uses large-diameter lenses
  - Results in a long focal length with high collection efficiency
  - Raman measurements can be done through inspection glass up to PN 40 [3]
- Combination with Fresnel optics – focal lengths up to a 1 m range are possible [3]

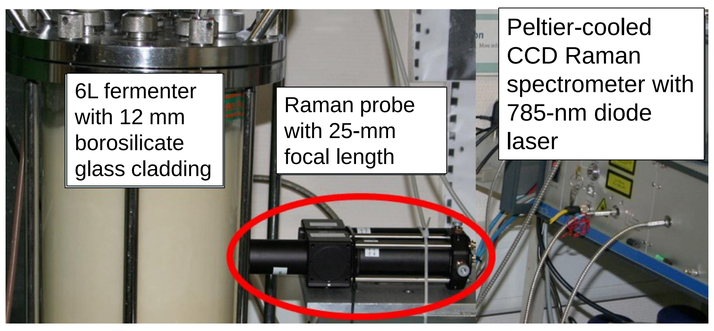


Process integration and application development (BASF SE)

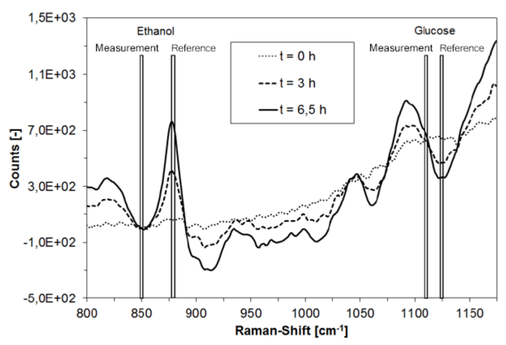


Co-axial probe construction

1 Monitoring an aerobic yeast fermentation (*Saccharomyces cerevisiae*)

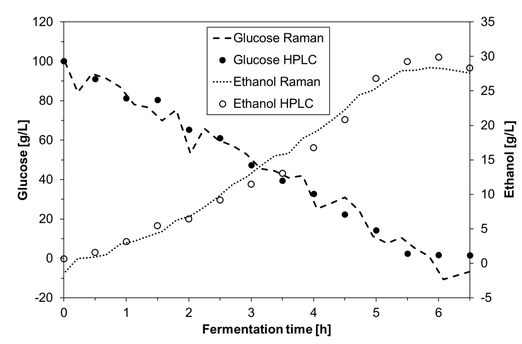


Experimental setup for monitoring fermentation



In-line fermentation monitoring through glass cladding

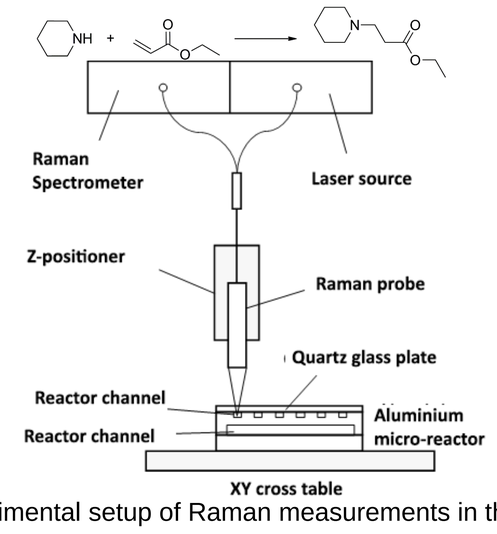
- Monitoring substrate breakdown (glucose) and product formation (ethanol)
- Easy integration into the process
- **No sterilization, pressure testing, cleaning, etc.**



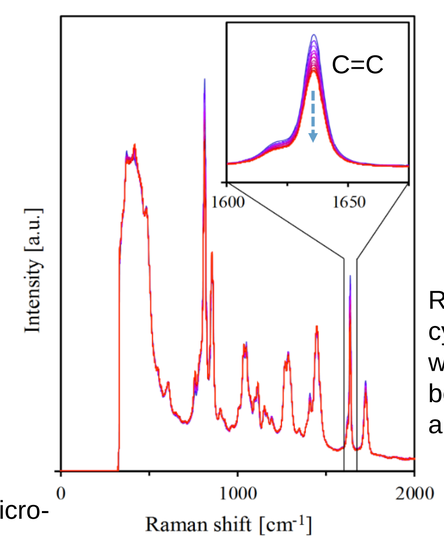
Spectra / Fermentation monitoring

2 Kinetic analyses in a micro-reactor

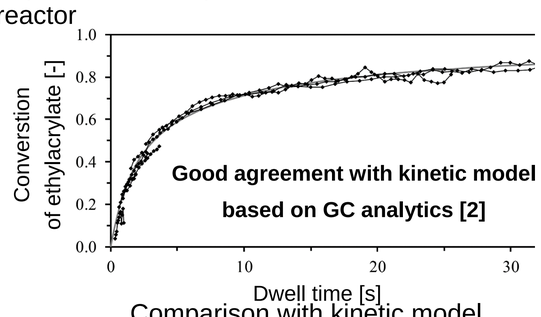
- Synthesis of 3-(piperidino)-propionic acid ethyl ester
- Conversion monitoring of ethyl acrylate (peak height between 1550/1637 cm^{-1} Raman shift)



Experimental setup of Raman measurements in the micro-reactor



Raman spectra during cyclic measurements with dwell times between 0.9 s (blue) and 2.6 s (red).



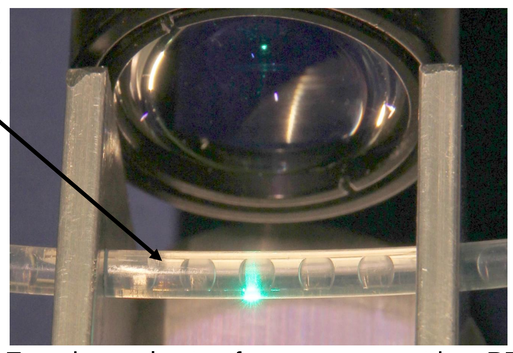
Comparison with kinetic model

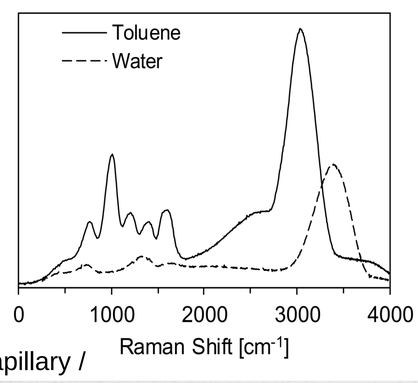
Measurement with dwell-time gradients [1]

- Targeted reductions of volume flow to achieve a linear dwell-time increase
- Total test duration under one hour at 200 data points with dwell times between 0.3 and 49 s

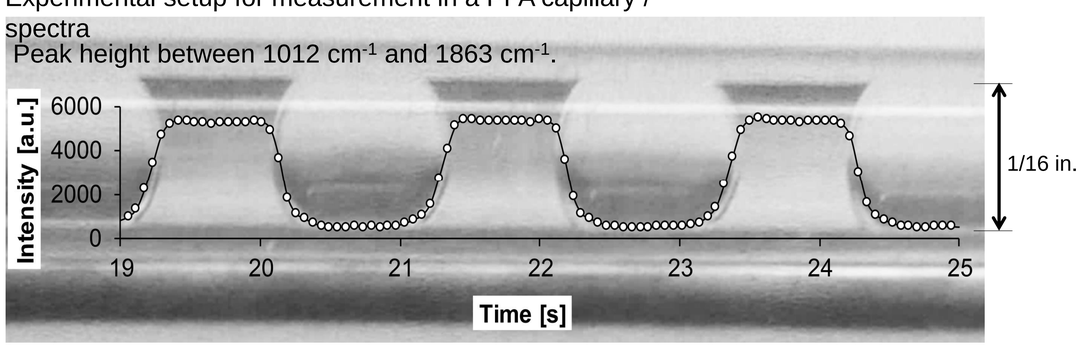
3 Rapid sampling of a two-phase flow (water/toluol)

- Measurement with very high sampling rate (up to 333 Hz) –Raman spectra can be recorded from both phases (water/toluol) in the “focus point”





Experimental setup for measurement in a PFA capillary / spectra



CONCLUSION

Non-invasive Raman measurements via windows available in the process (flow indicator armatures, micro-reactors, fermenters) lead to a versatile measurement system without interference with the process being monitored [3] and high added value through process optimization.

1 Measurements in reactors/bioreactors

- Externally monitoring glucose breakdown and ethanol production during yeast fermentation (*Saccharomyces cerevisiae*)
- Simple-to-implement measurement setup for chemical and pharmaceutical processes
  - **No interference with mechancal systems; mountable on existing windows**
  - **Short amortization time**

2/3 Measurements in micro-structures

- Resource-saving / significant time savings
- Fast assessment of reaction kinetics
  (parameter screening: temperature, catalyst quantity, etc.)
- Very fast continuous measurement of two-phase flows **(maximum sampling rate of 333 spectra per second)**

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Literature

[1] Schwolow, S., Braun, F., Rädle, M., Kockmann, N., Röder, T., 2015. Fast and Efficient Acquisition of Kinetic Data in Microreactors Using In-Line Raman Analysis. Org. Process Res. Dev..
[2] Schwolow, S., Heikenwälder, B., Abahmane, L., Kockmann, N., Röder, T., 2014 . Kinetic and Scale-up Investigations of a Michael Addition in Microreactors. Org. Process Res. Dev.
[3] Braun, F., Schalk, R., Brunner, J., Eckhardt, H. S., Theuer, M., Veith, U., Henning, S., Ferstl, W., Methner, F.-J., Beuermann, T., Gretz, N., Rädle, M., 2016. Nicht-invasive Prozesssonde zur Inline-Ramananalyse durch optische Schaugläser. tm – Technisches Messen. Article in press.