PAT4nano
Real-time Nanoparticle Characterization

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 855867.

NanoFlowSizer

A novel instrument with new capabilities for in-line & offline sizing of nanosuspensions

Rut Besseling
(Scientific Director)
on behalf of the InProcess-LSP team

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Process Analytical Technology (PAT) solutions

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Webinar outline

1. Challenges in nanosuspension (Process) Analysis
2. Spatially Resolved DLS and the benefits
3. Application examples and considerations
4. Conclusions

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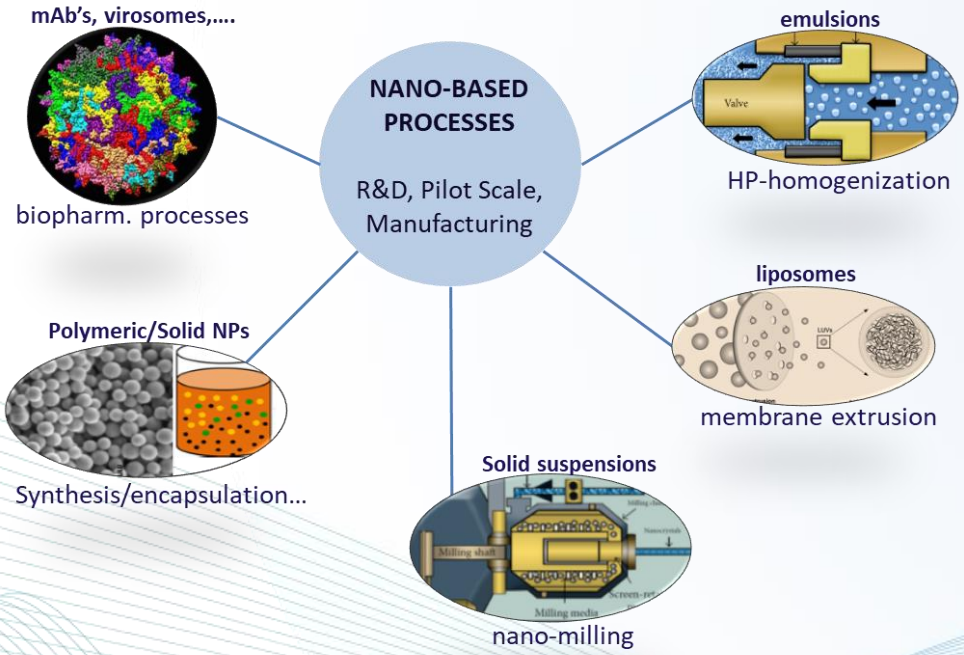
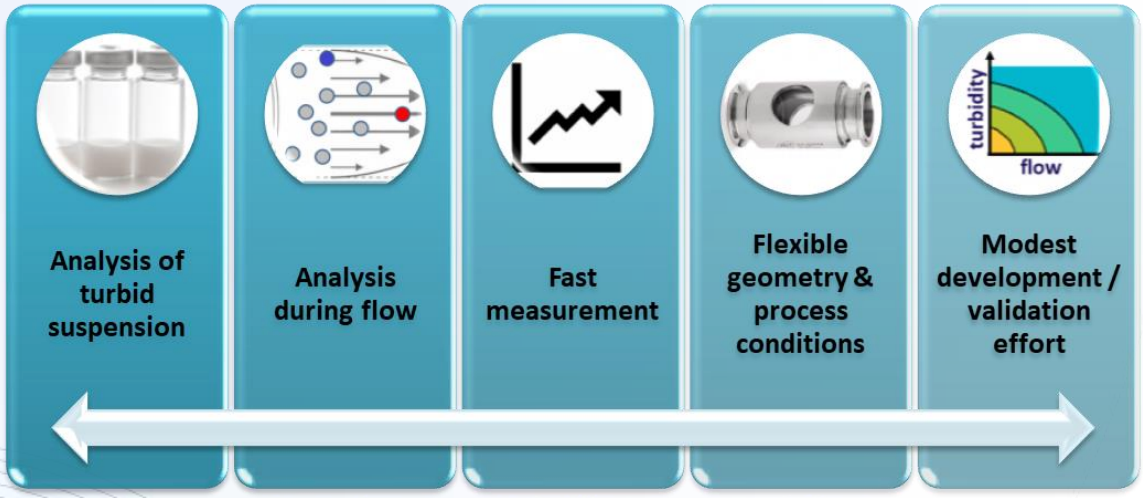
1. Challenges in (Process) Analysis of nanosuspensions



- Strong growth in R&D & Manufacturing of nanosuspensions
- Precise & high quality Manufacturing (Pharma/Chemical/....)
- Required Process/Product knowledge => Process Analytics



Requirements inline nano-sizing

Noninvasive/PAT measurement needs beyond 'standard' instrument capabilities

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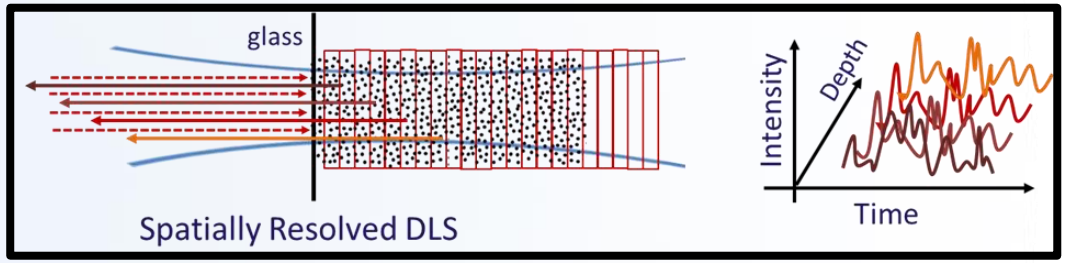
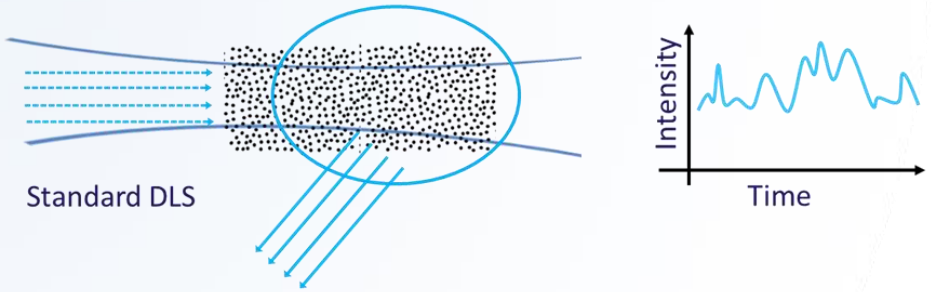
1. New approach: Spatially Resolved DLS

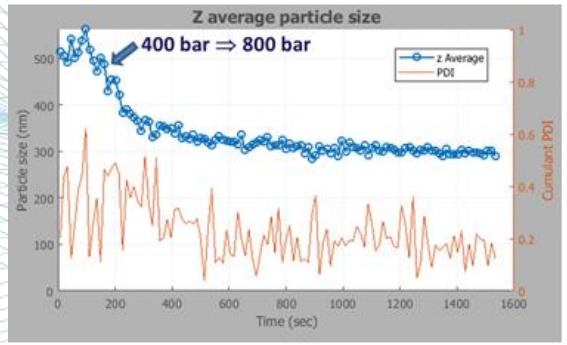
- **'Low coherence' Dynamic Ligth Scattering** with 'instant' depth resolution:
  - **Measurement of highly turbid samples** by pathlength selection
  - **Measurement in process/flow conditions:**
    resolve local flow & extract Brownian diffusion

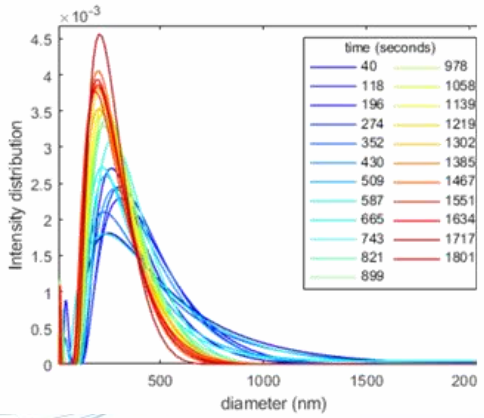
- **Rapid process monitoring**: 10s per measurement
- **Flexible and fully non-invasive implementation possibilities**
- NIR-source (1300nm): optimal for highly turbid samples
- 180° backscattering: limits effect of large particles in polydisperse samples.

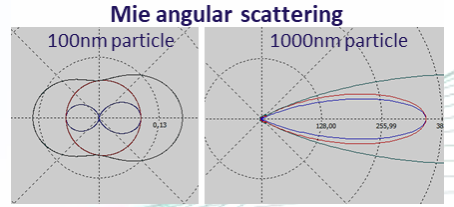




New opportunities for Industrial and Academic R&D







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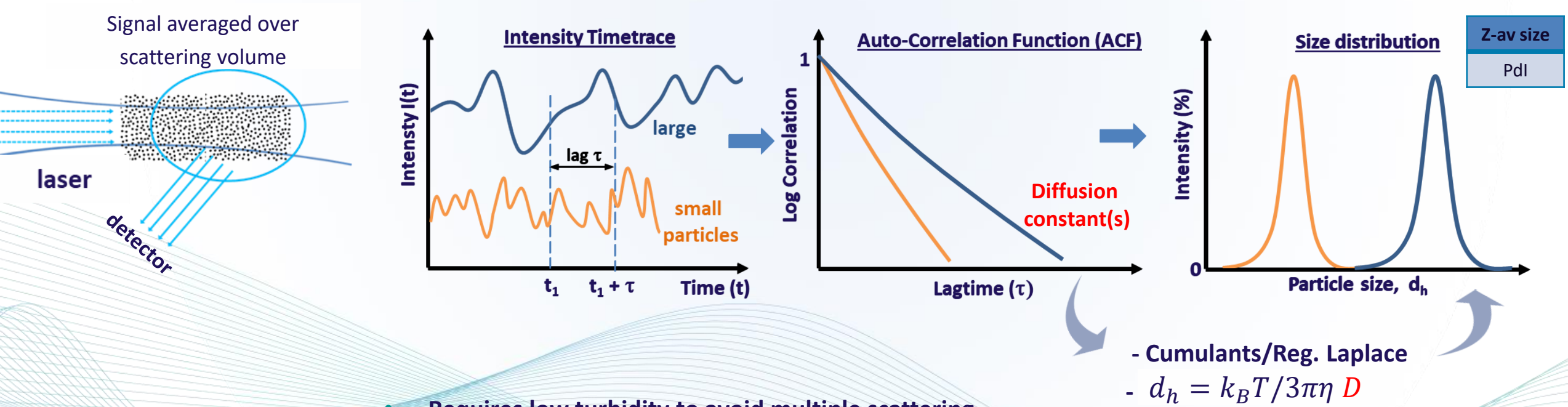
2. Background: standard Dynamic Light Scattering

<u>standard DLS records fluctuations in scattered *laser intensity* due to Brownian diffusion</u>

⇒ fluctuation rates via signalcorrelation ⇒ Diffusion constant(s) ⇒ hydrodynamic size (distribution)



- Cumulants/Reg. Laplace
- $d_h = k_B T / 3\pi\eta\, D$

- **Requires low turbidity to avoid multiple scattering**
- **Requires absence of flow**

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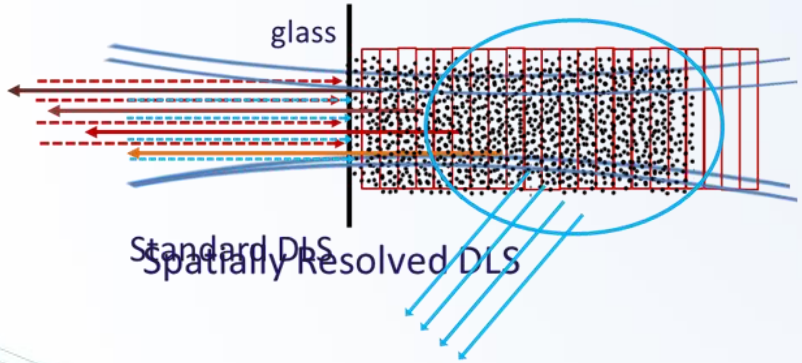
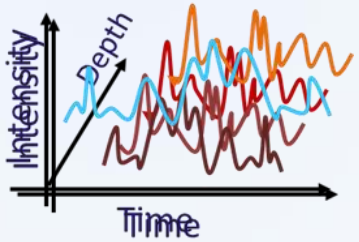
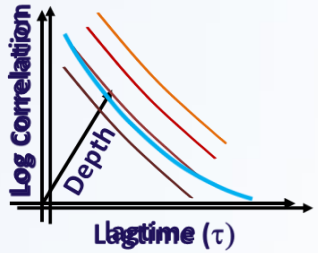
2. Spatially Resolved Dynamic Light Scattering

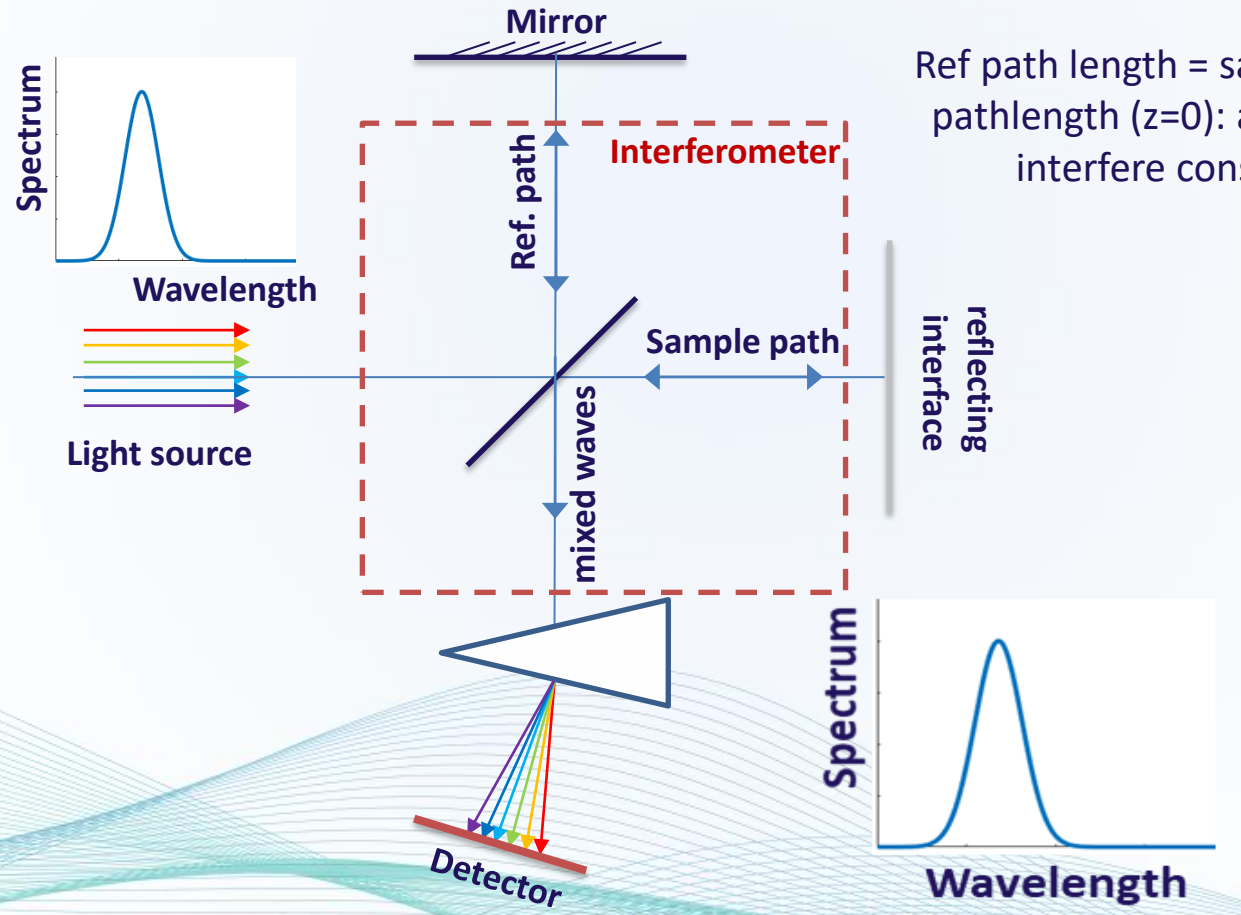
add the spatial dimension to standard DLS:







2. Spatial information via Low Coherence Interferometry



Ref path length = sample reflection pathlength (z=0): all wavelengths interfere constructively

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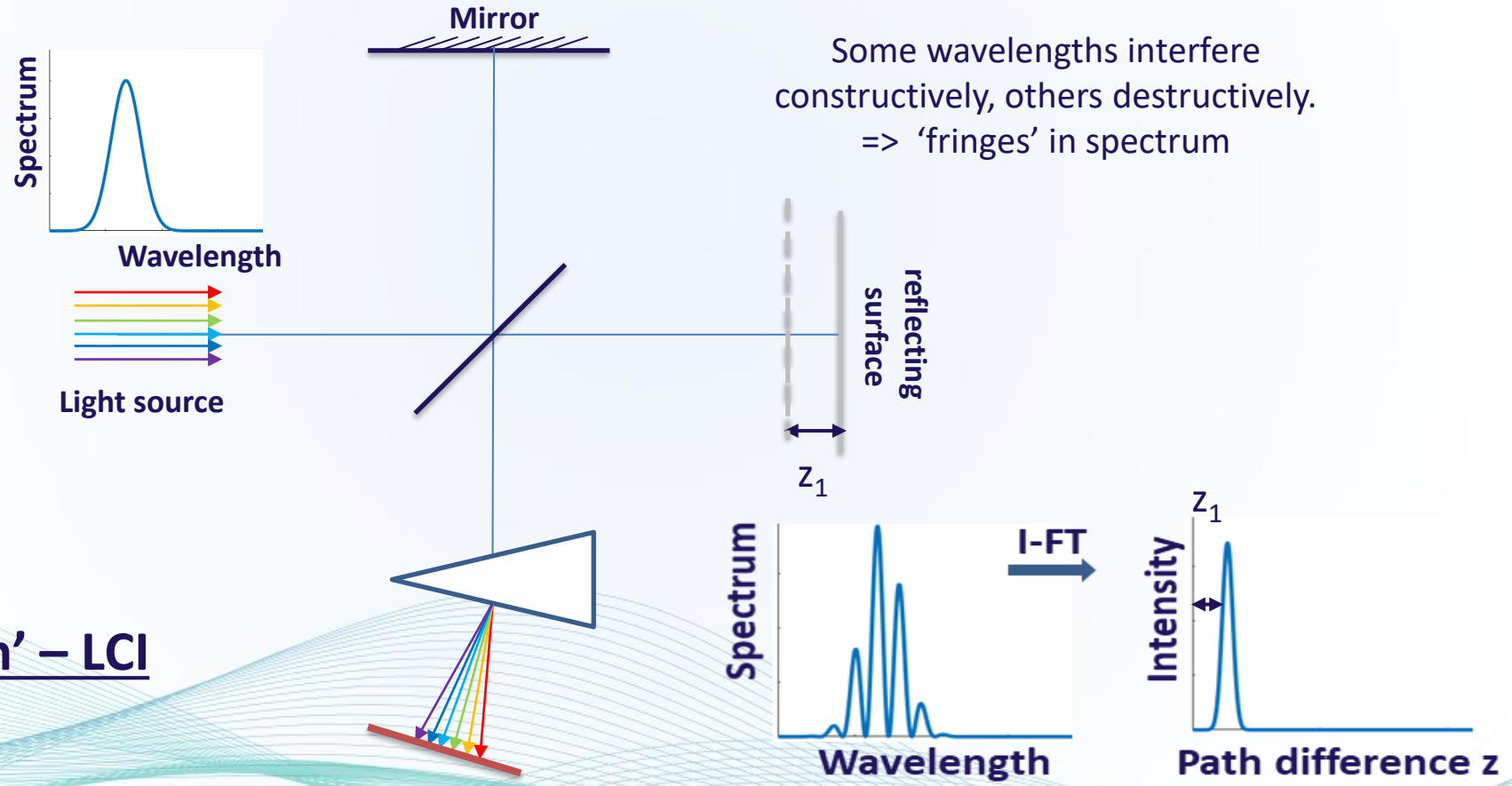
2. Spatial information via Low Coherence Interferometry



'Fourier-Domain' – LCI

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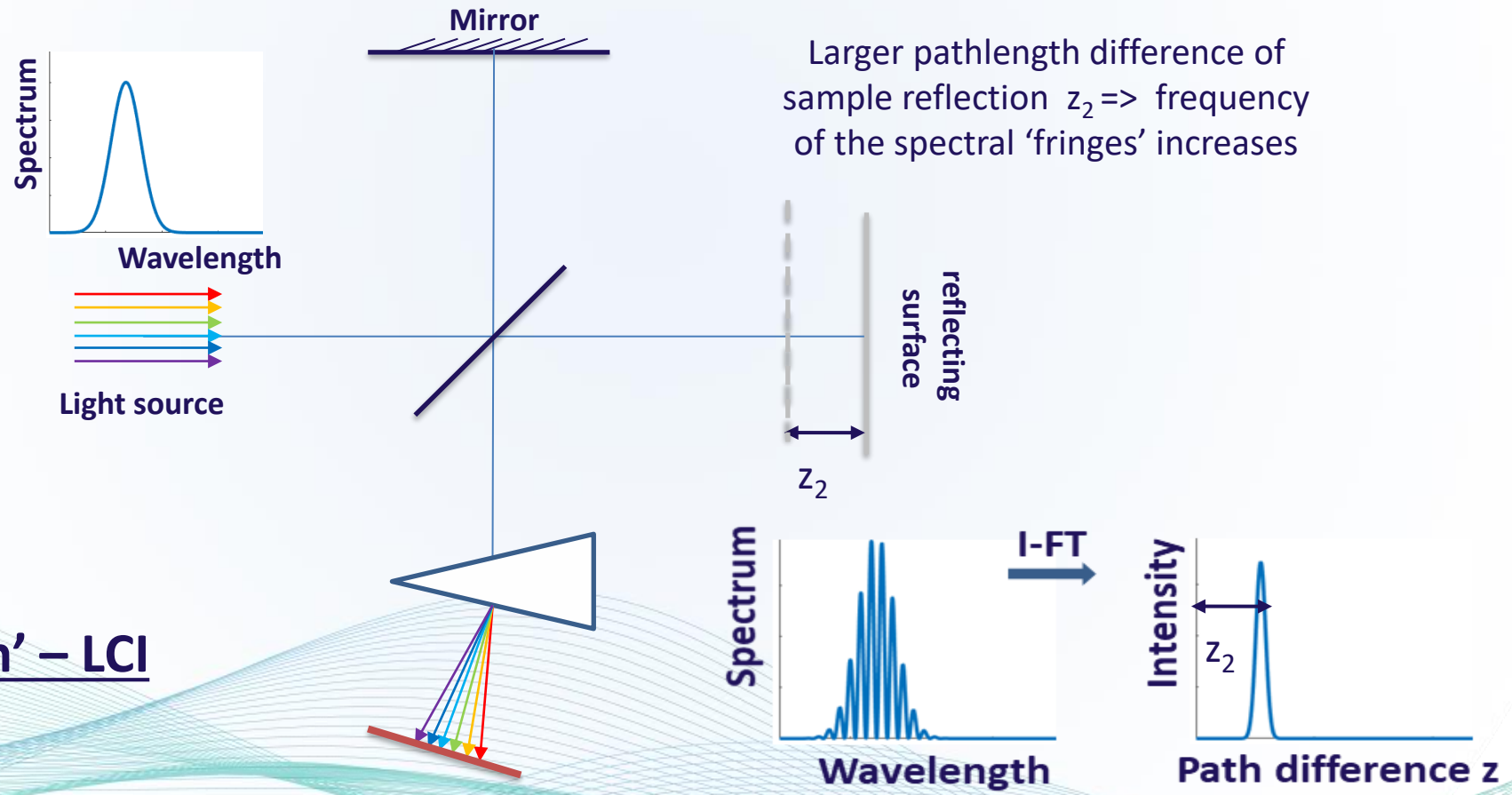

'Fourier-Domain' – LCI

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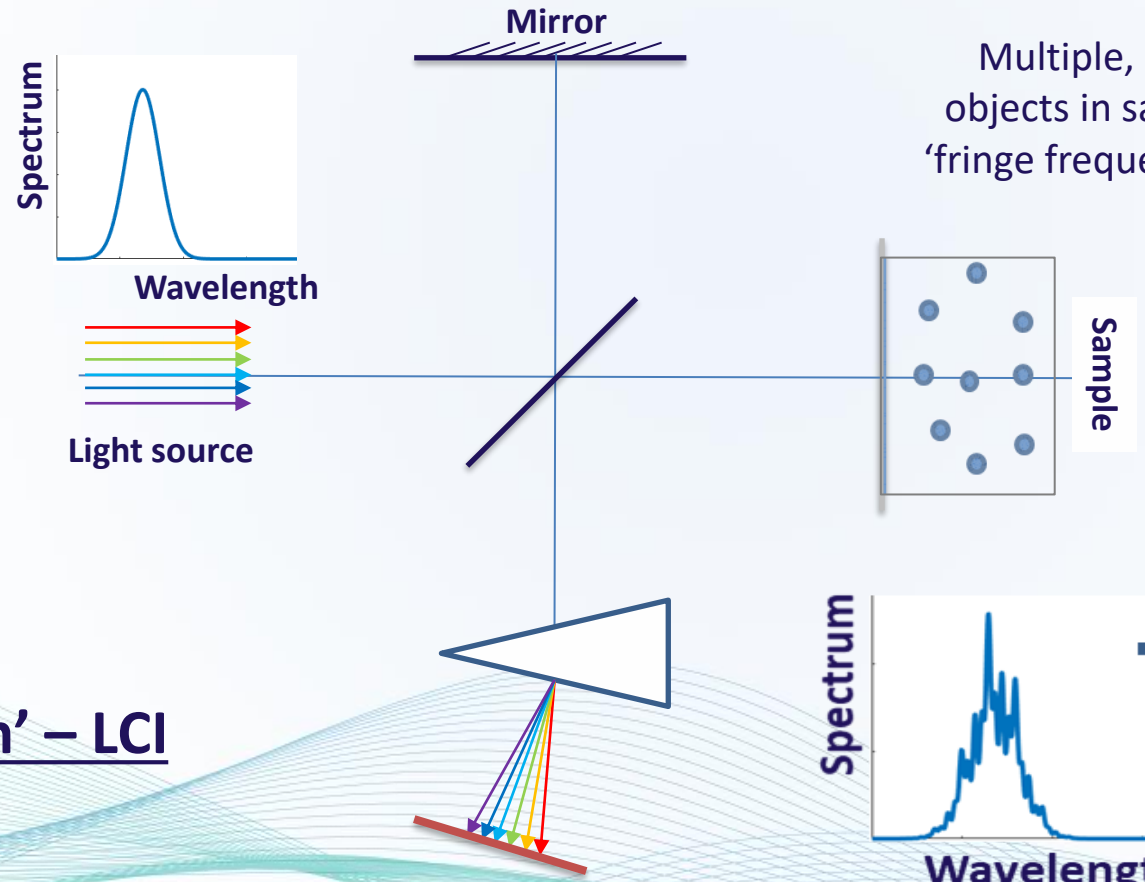
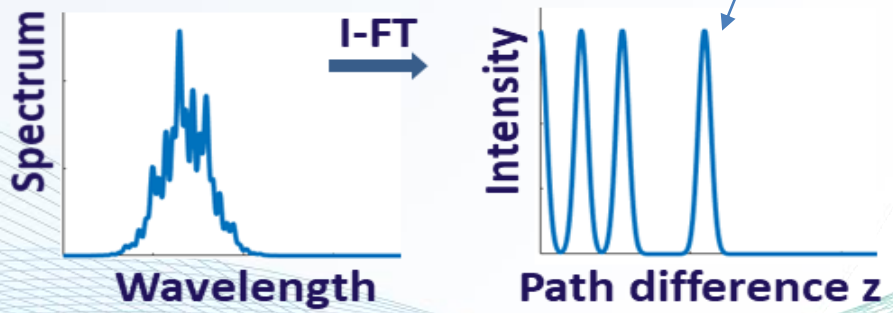


Multiple, partly reflecting objects in sample => multiple 'fringe frequencies' in spectrum

Spatial resolution: coherence length ∝ 1 / spectral width



'Fourier-Domain' – LCI

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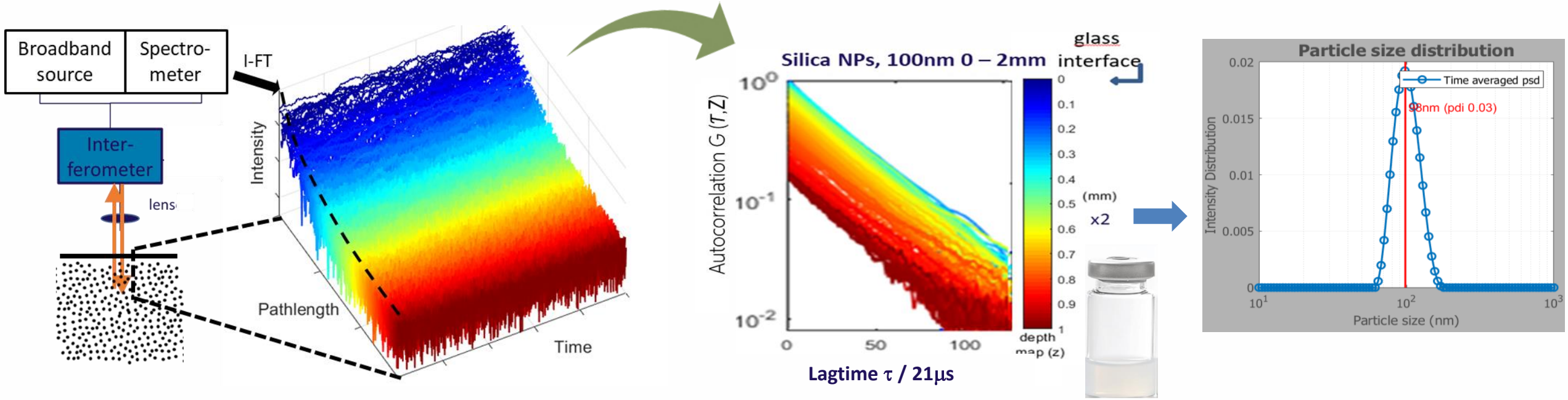
2. SR-DLS in practice



- Acquisition rate 76kHz => I(z) resolved 'instantly' => Fluctuations I(t,z) resolved at each depth.
- > 1000 ACF's per measurement ⇒ Resolve particle motions over ~2.5mm
- High information content ⇒ Z-av and PdI in few seconds

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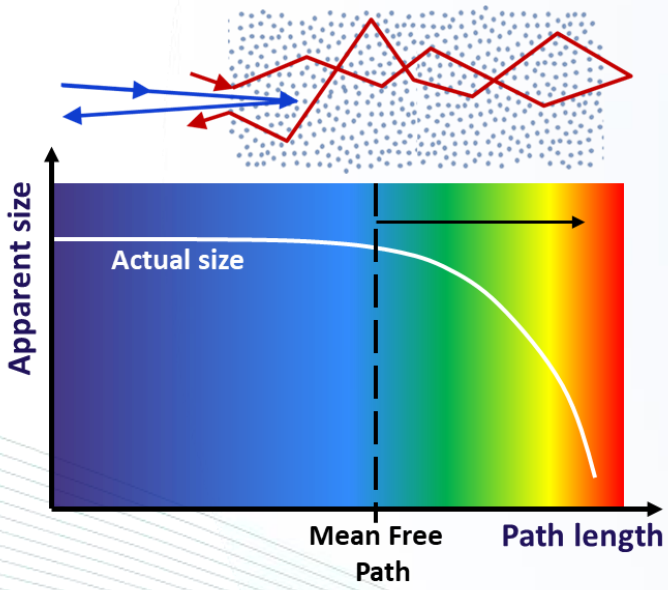
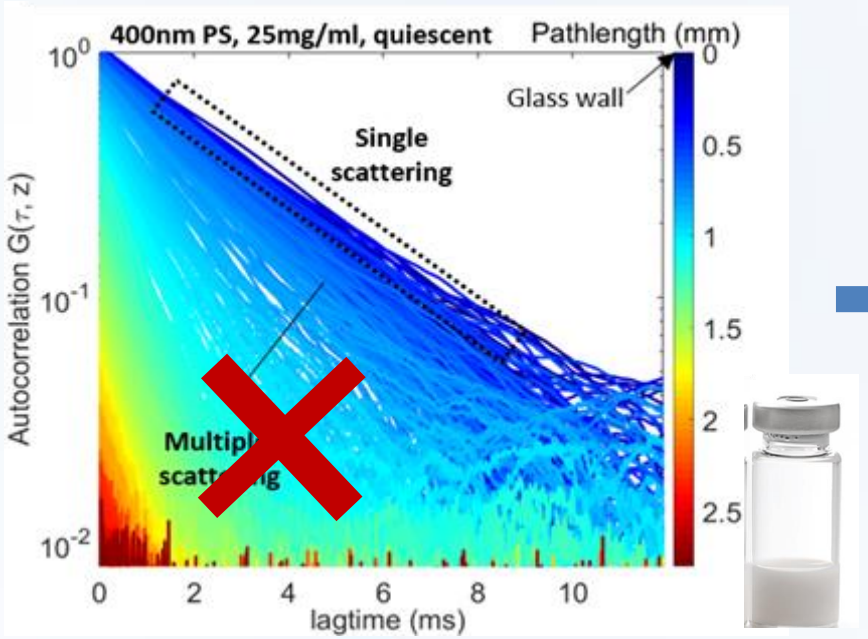
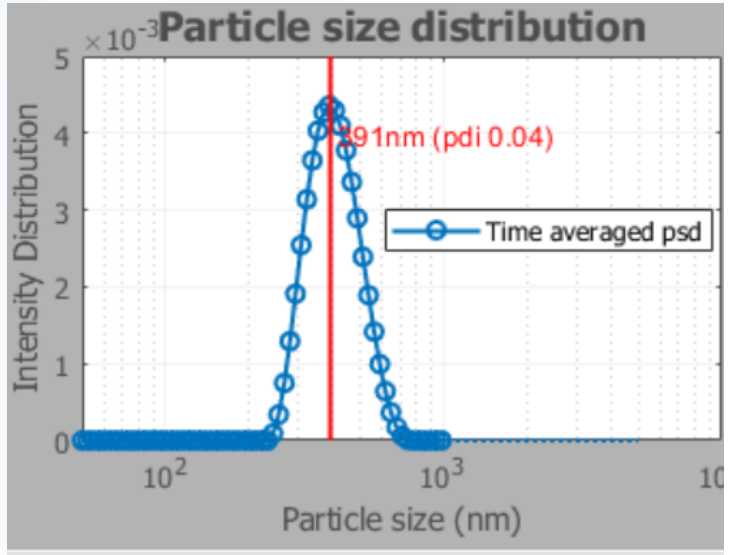
2. SR-DLS benefits: high turbidity







- **Single & Multiple scattering regimes diagnosed automatically**
- **Multiple scattering data filtered (SR-DLS)**
- **<u>Advantage: no dilution needed for turbid samples *</u>**

* photon mean free path down to ~ 100µm @1300nm
e.g. Polystyrene suspensions up to at least 5 vol% (size dependent)

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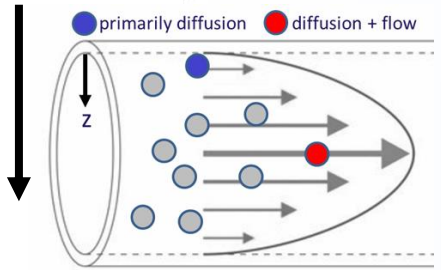
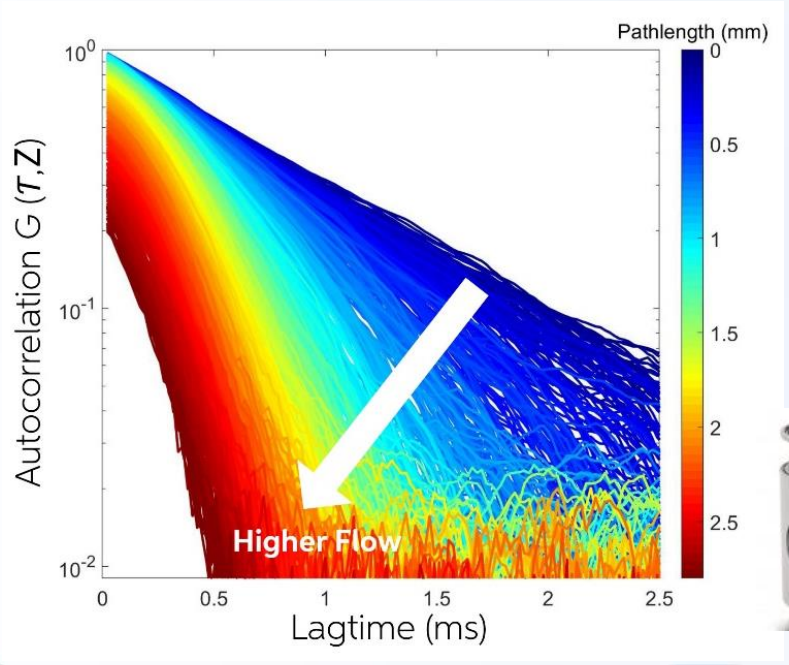
2. SR-DLS benefits: measurement in flow

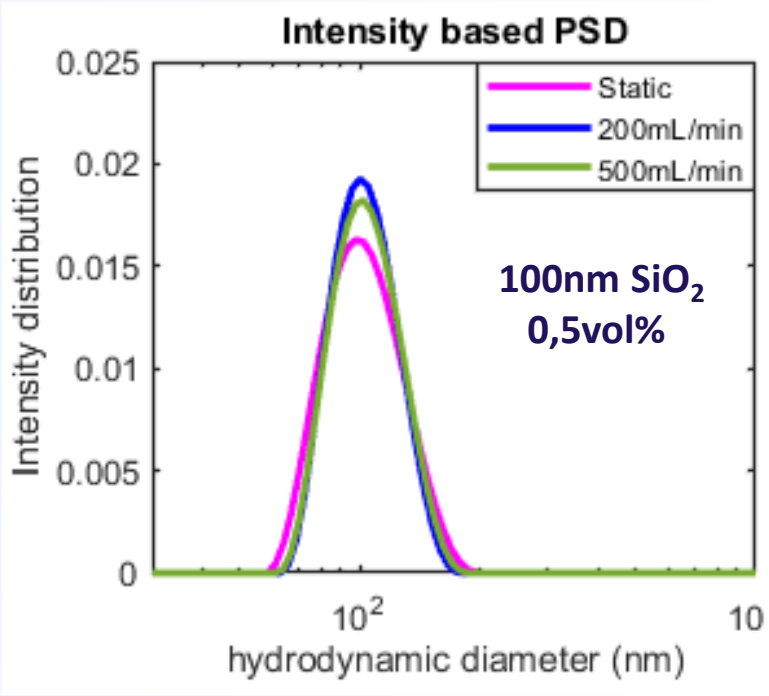
Depth





flow

∅=22mm



Diffusion

$$G(\tau,z) = G_{v=0}(\tau) \times G_{flow}(\tau/\tau_{flow}(z))$$

beam passage time

- **ACF's contain information on diffusion and local flow speed.**
- **Flow measured and corrected for => size analysis from DIFFUSIVE PART OF THE ACF**
- **Flow-independent size measurement. No prior knowledge of flow required.**

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2. NanoFlowSizer system

Probe Unit: Interferometer, Pathlength/focus control

Fiber & connections

Base Unit: light source & detector

Interchangeable modules

XsperGo software:

- handling ~Gb/s data in a continuous manner
- Real time measurement (~10s per point)

Outputs:

- Z-average, PDI (ISO22412)
- PSD: Intensity/volume, $d_{10,50,90}$
- Correlation function
- Flow and Scatter Profile
- Data Quality Diagnostics
- Advanced time & depth resolved diagnostics

MEASUREMENT SPECIFICATIONS	
Central wavelength	1300 nm
Axial scan rate	Up to 76 kHz
Maximum measuring depth / optical path length	3.5 mm
Maximum scattering volume	5 nL
Detection	Backscattering (180°)
Depth resolution	4 µm
Particle size range	10 - 1000 nm (at least)
Maximum process flow	6 L/min for 100nm polystyrene (5 mg/ml) in water

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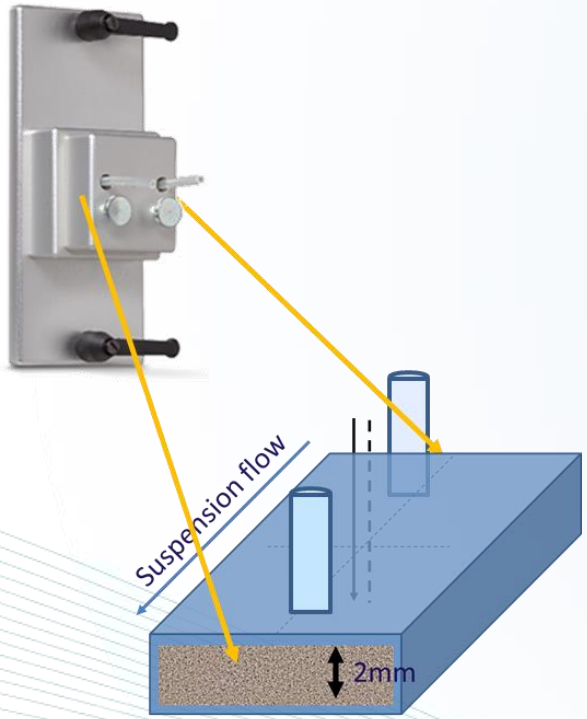
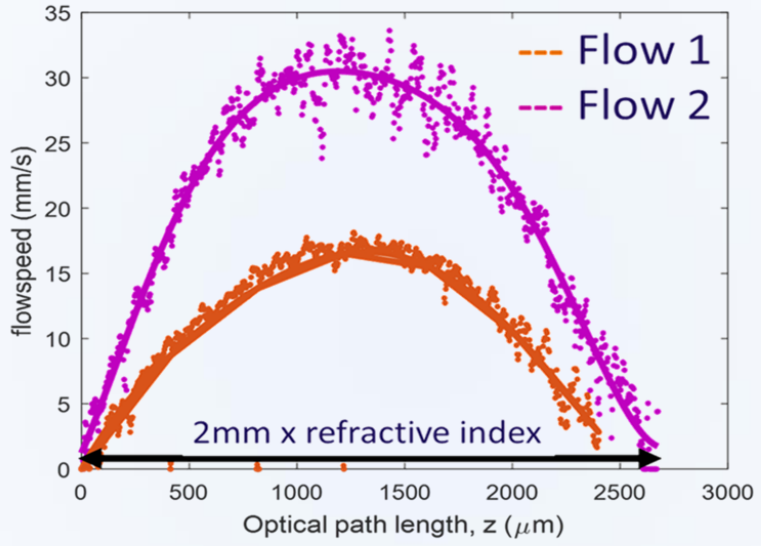
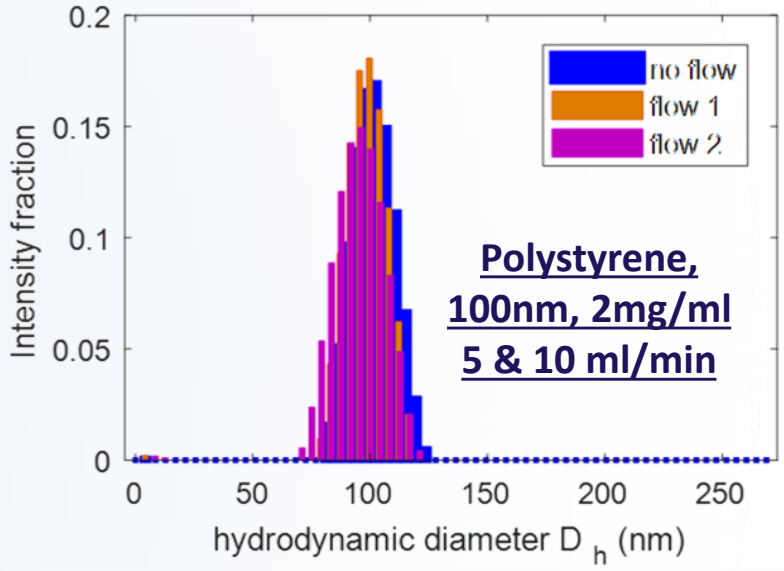
3. Applications: μ-flow cell & TiO_2 synthesis

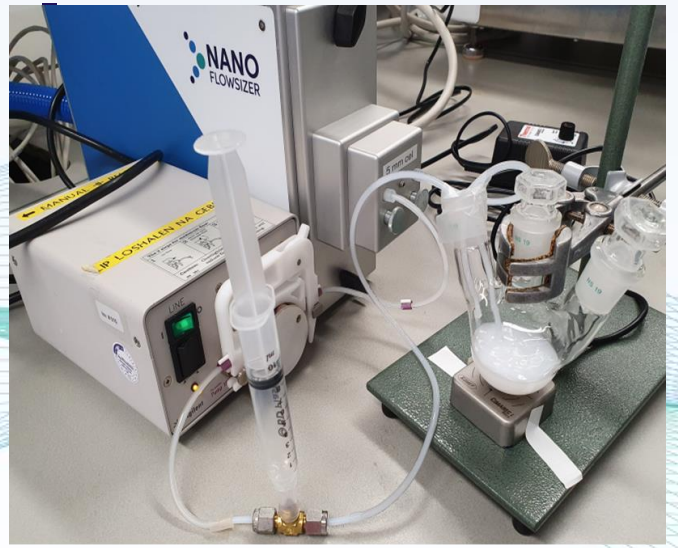


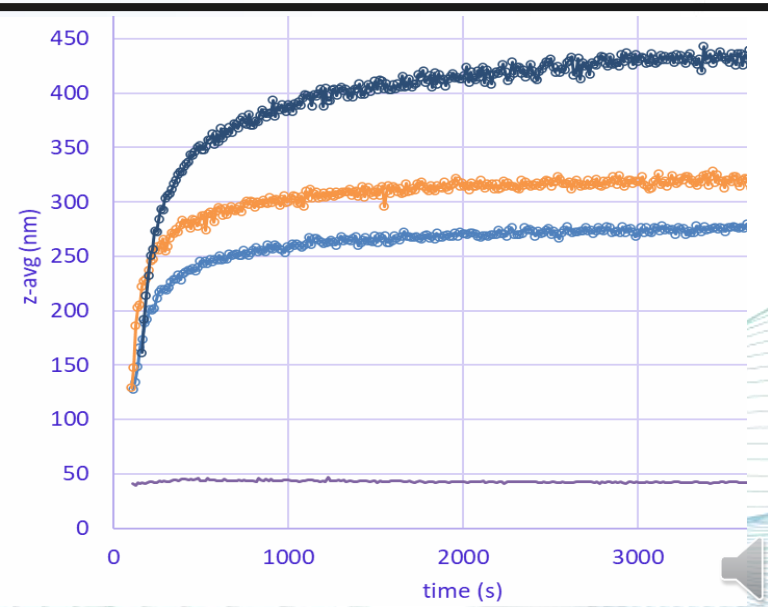




Polystyrene, 100nm, 2mg/ml 5 & 10 ml/min

TiO_2 synthesis microflow sampling loop





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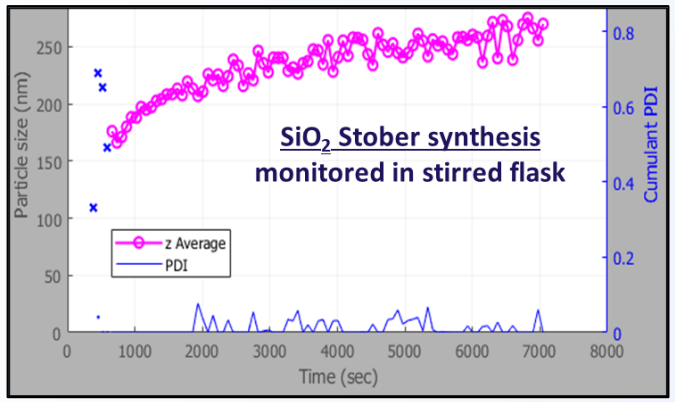
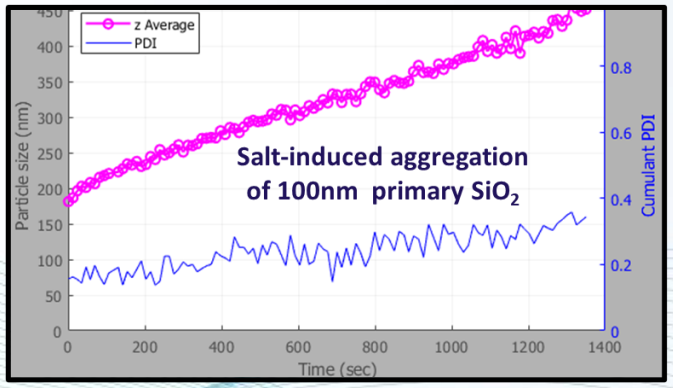
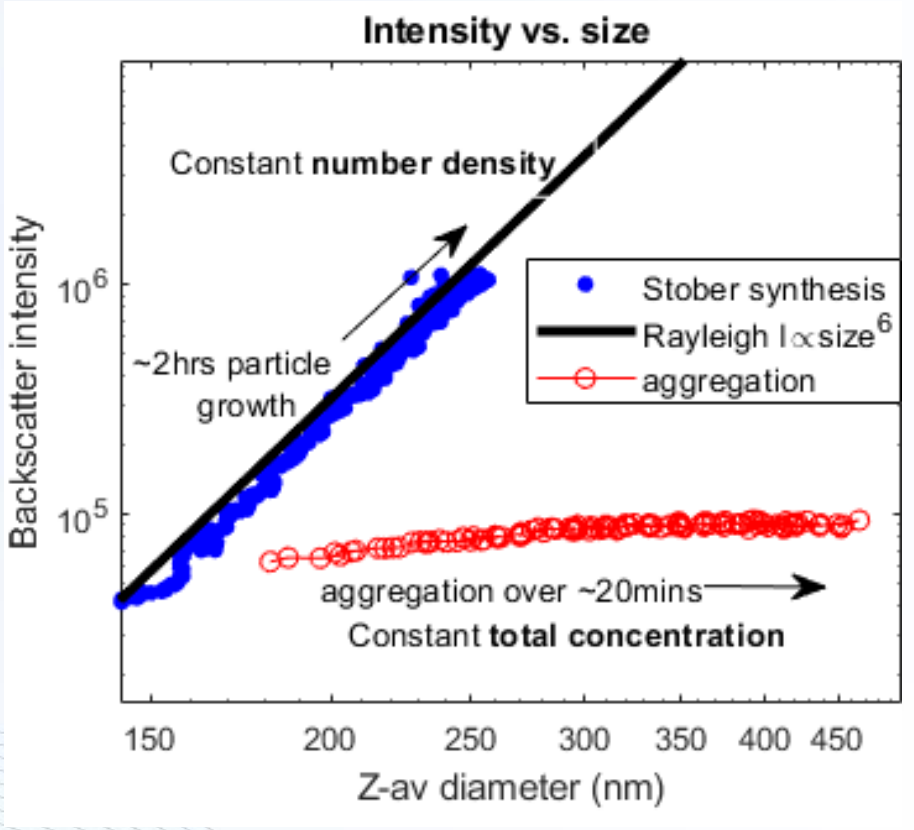
3. Monitoring SiO_2 synthesis & aggregation



+ measured scatter intensity





Note:
λ_{NFS}=1300nm
Rayleigh law valid up to d~250nm

- Study rapid size dynamics (~10sec res.)
- Interpretation of growth mechanisms
- Synthesis /formulation development

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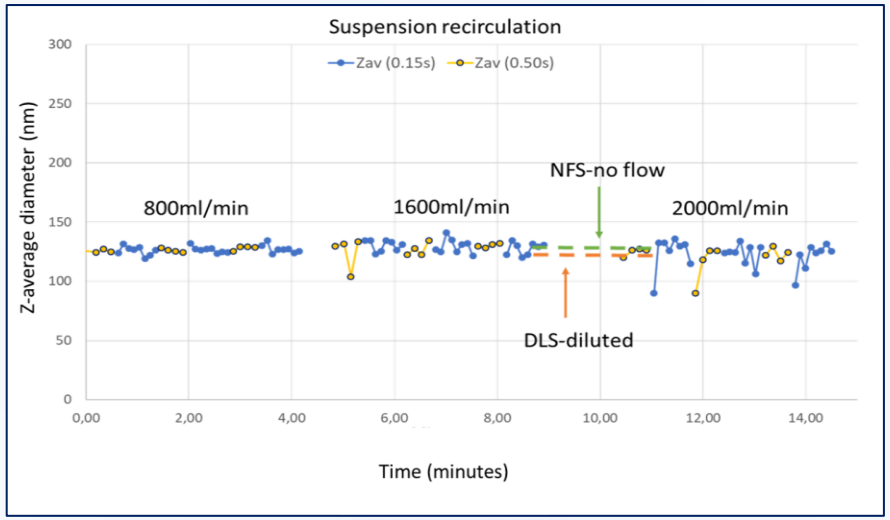
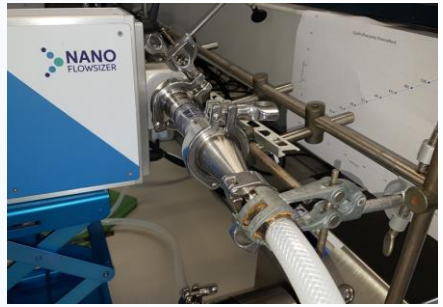
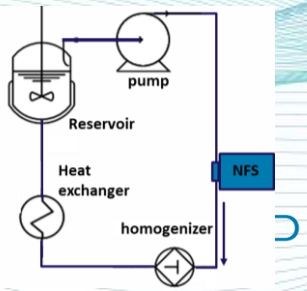
3. Larger scale process monitoring

Process development of drug-conjugated particles





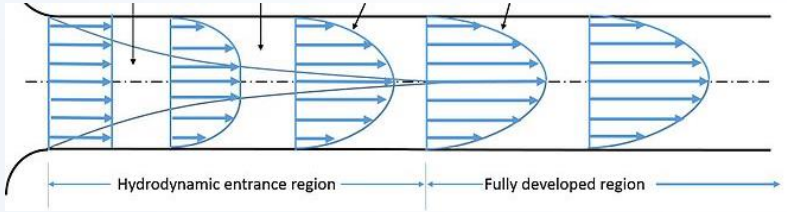


3. Application considerations

Flow requirements:

1. Non-turbulent, fully developed Poiseuille flow

2. Maximum ratio shear rate/diffusion rate (maximum 'Peclet' number)



- both (1) and (2) are checked during measurement
- upscaling via suitable flow cell / process connection

Concentration:

- High concentration => modifies diffusion & Stokes-Einstein relation
- Sizing possible (i) qualitatively or (ii) via calibration/knowledge of interactions
- We develop models (incl. hydrodynamics/structure) for quantitative sizing in this regime.

	Low Turbidity	High Turbidity
Low Concentration	✓	✓
High concentration	Calibration, modeling	Calibration, modeling

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4. Summary

- Spatially Resolved DLS: a significant step forward in nanosuspension characterization for Process Analytics and R&D

- Rapid measurements of highly turbid and/or flowing samples for a broad range of sample /process environments.

=> Process monitoring and/or Process control

We are keen to explore new applications and further broaden the possibilities of the NanoFlowSizer.

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Feel free to contact us to discuss your applications, request an 'NFS questionnaire' or our publication:

info@nanoflowsizer.com
https://www.inprocess-lsp.com/contact/

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New unique PAT method and instrument for real-time inline size characterization of concentrated, flowing nanosuspensions

R. Besseling*, M. Damen, J. Wijgergangs, M. Hermes, G. Wynia, A. Gerich

InProcess-LSP, Kloosterstraat 9, 5349, AB, Oss, the Netherlands

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