BRAVE

ANALYTICS

BRAVE ANALYTICS

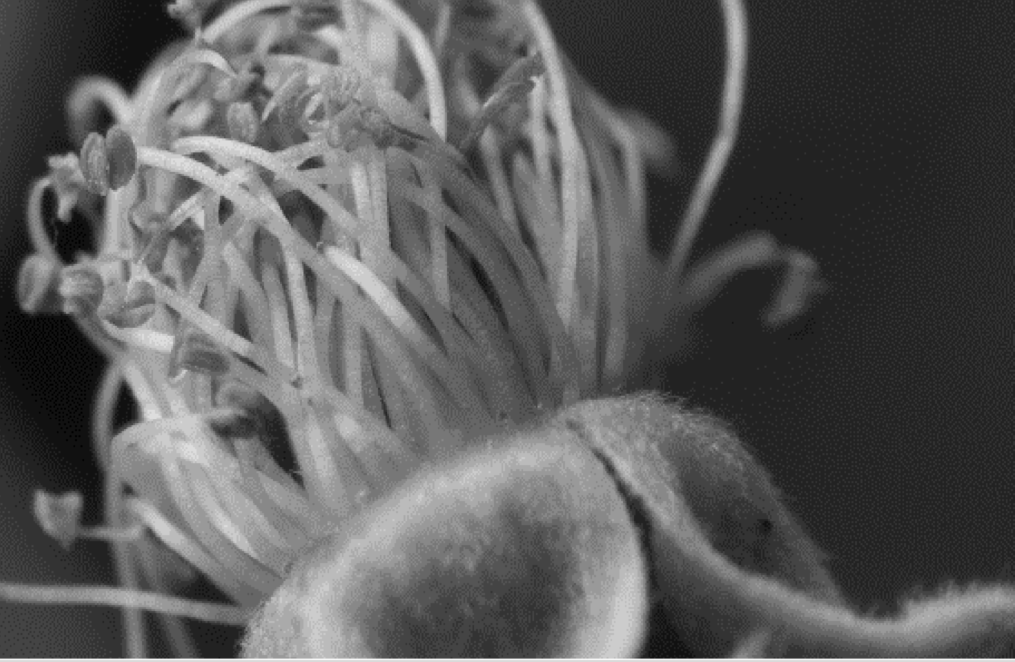
NANOPAT

europact 2021

www.braveanalytics.eu

OF2i training session

2021.11.15



Giving real(time) insights in your production processes and quality control

Ing. Dr. Christian HILL
Dipl. Ing. Gerhard PROSSLINER

nanomedicine Biophysics | Med Uni Graz | Bundesministerium Digitalisierung und Wirtschaftsstandort | austria wirtschafts service aws | FFG Promoting Innovation. | LightMatters OPTOFLUIDIC ANALYSIS | I.E.C.T. HERMANN HAUSER | European Commission | Horizon 2020 European Union funding for Research & Innovation

- Introduction: OF2i® a BRAVE solution
  - use cases
- Live demonstration of BRAVE B1 Sensorstation
- Discussion

Medical University of Graz | Gottfried Schatz Research Center | Division of Biophysics

NEW-MEDCAMPUS GRAZ-AUSTRIA

BRAVE Spin-off

BRAVE
ANALYTICS

Basic Research

Validation

Translation

OF2i

real time
PROCESS ANALYTICAL TECHNOLOGY

BRAVE ANALYTICS

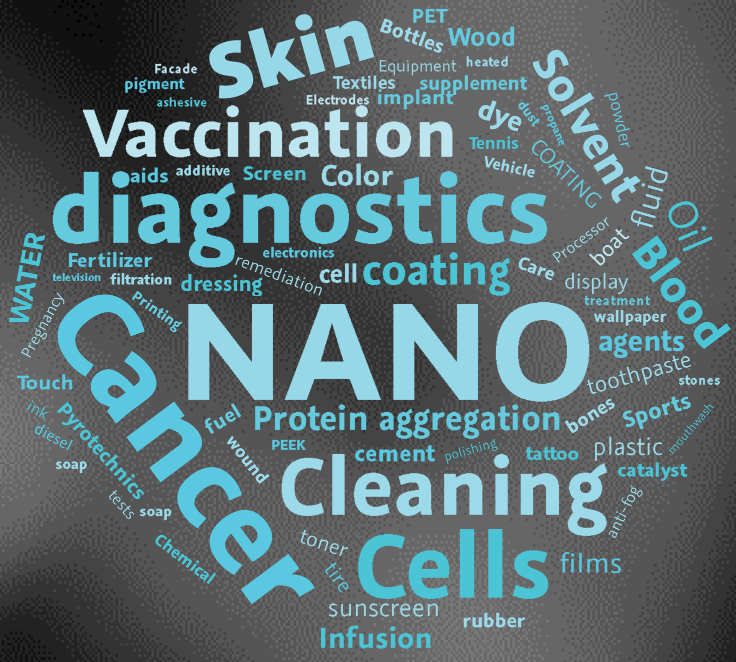
a BRAVE problem to solve

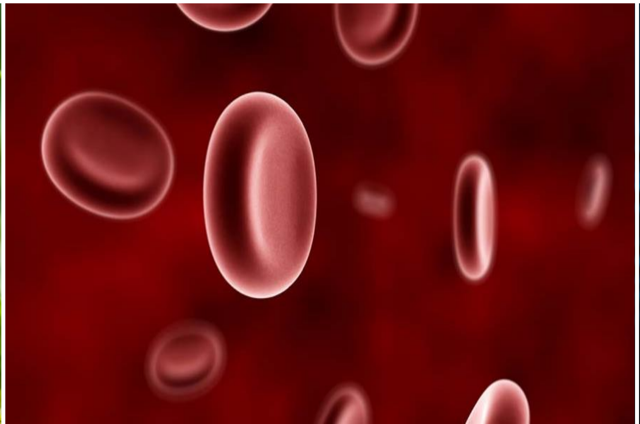
NANOPAT

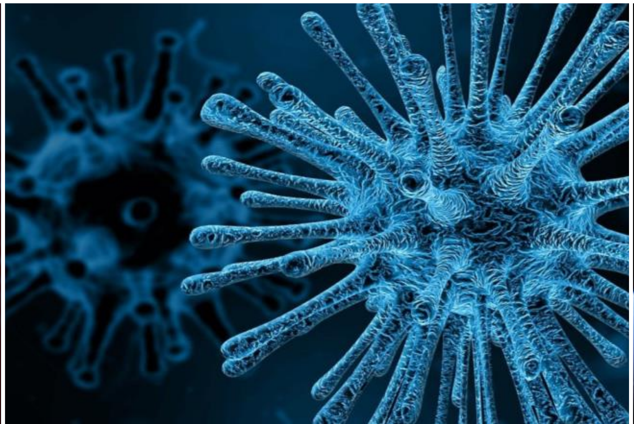
europact 2021

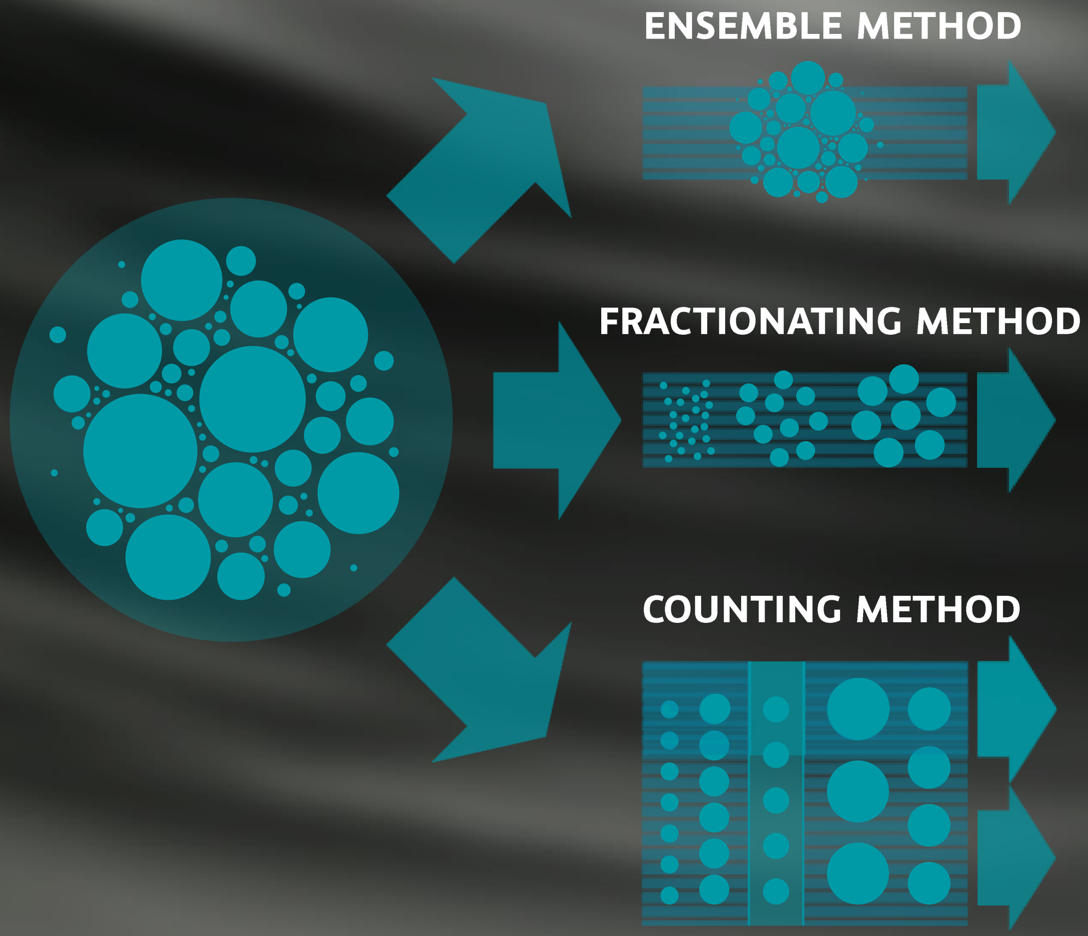
OF2i workshop

…modern nanoparticle research and productions need continuous and real-time characterization for waste reduction and performance control…









DLS, LD, Acoustics, …

Measuring properties of the whole sample, which are resolved in time, space or frequency

FFF, SEC, AUC, …

Measuring of the quantity of each size fraction

Microscopy, NTA, LOD, FACS, …

Measuring properties of each single particle

OF2i® patented optical parallelization

Measuring of the quantity of each size fraction continuously

LOWER RESOLUTION

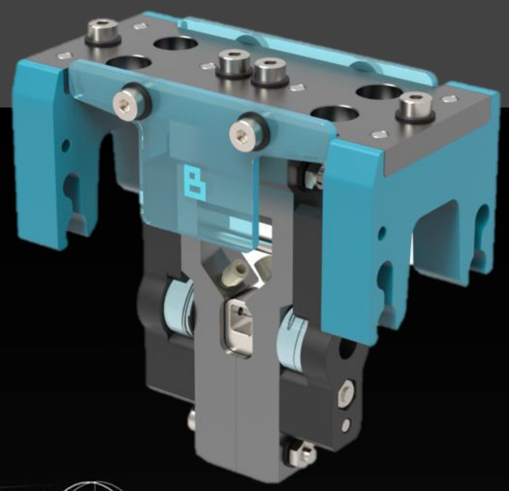
"Less" capable

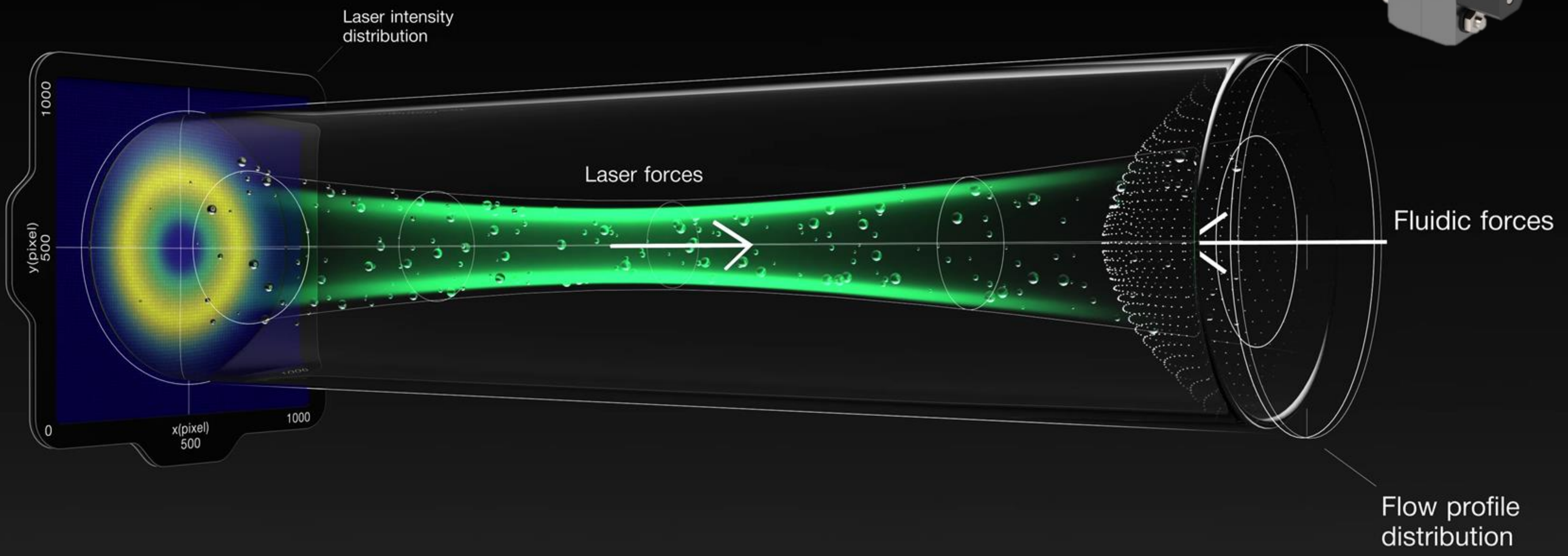
HIGHER RESOLUTION

Increased certainty, "most" capable

A BRAVE TECHNOLOGY as SOLUTION

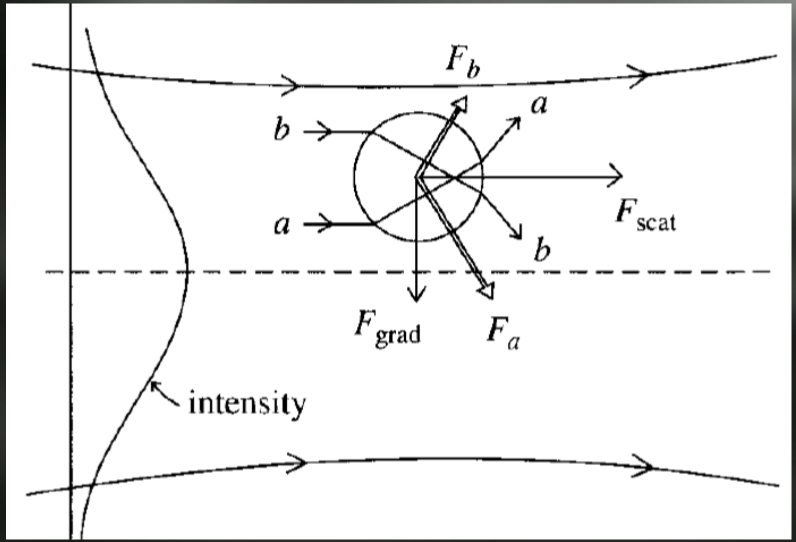
Combining Biophotonics & µ-Fluidics

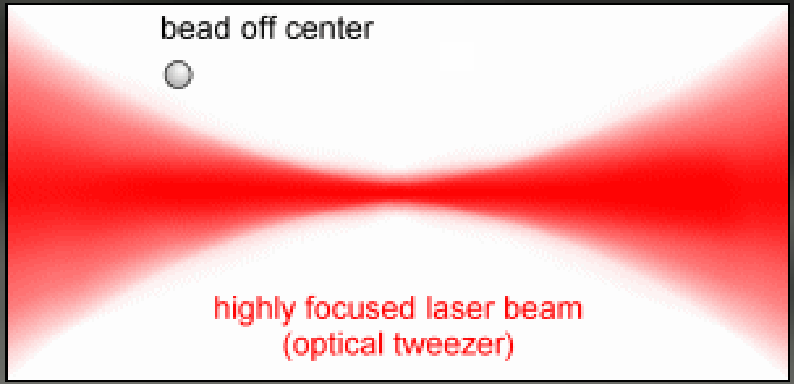


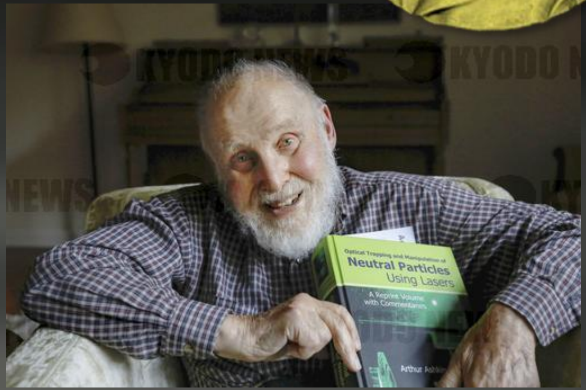


...breaking the barrier of Brownian Motion with actively induced optical and fluidic forces...

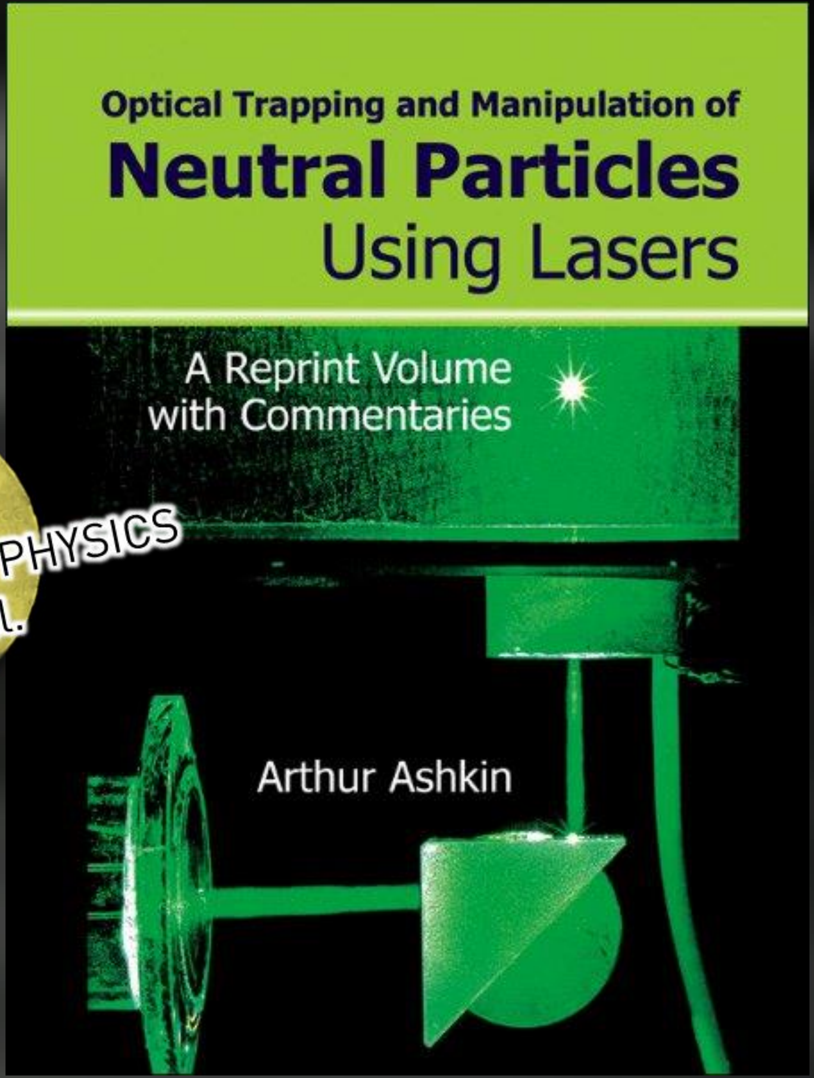
OPTICAL TRAPPING: 2D Trap







Based on
NOBEL PRIZE 2018 PHYSICS
Ashkin et al.



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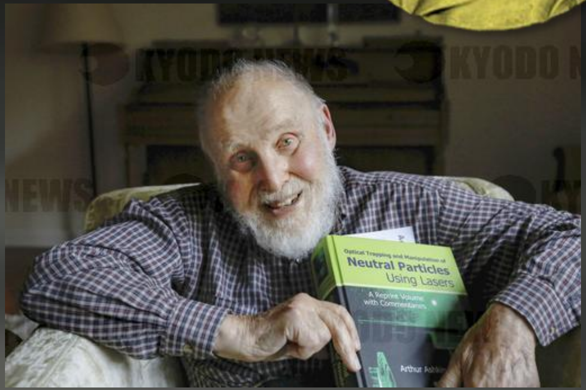

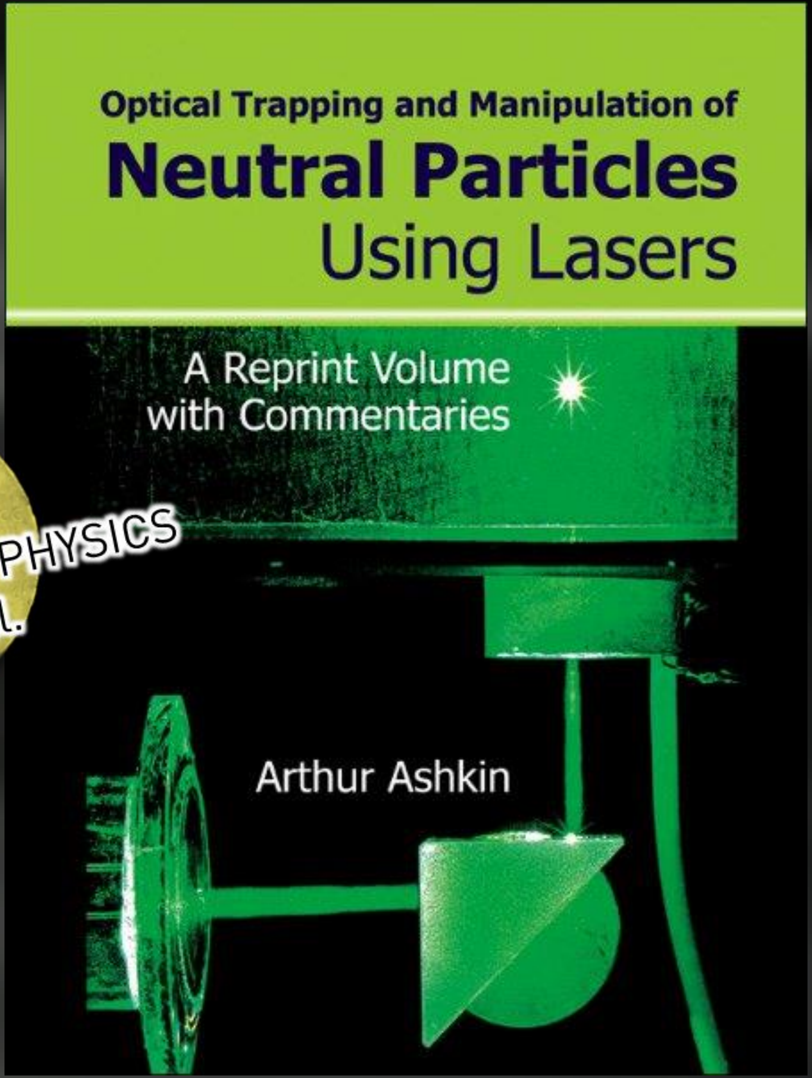

A BRAVE Theory

Optofluidic Force Induction Scheme for the Characterization of Nanoparticle Ensembles

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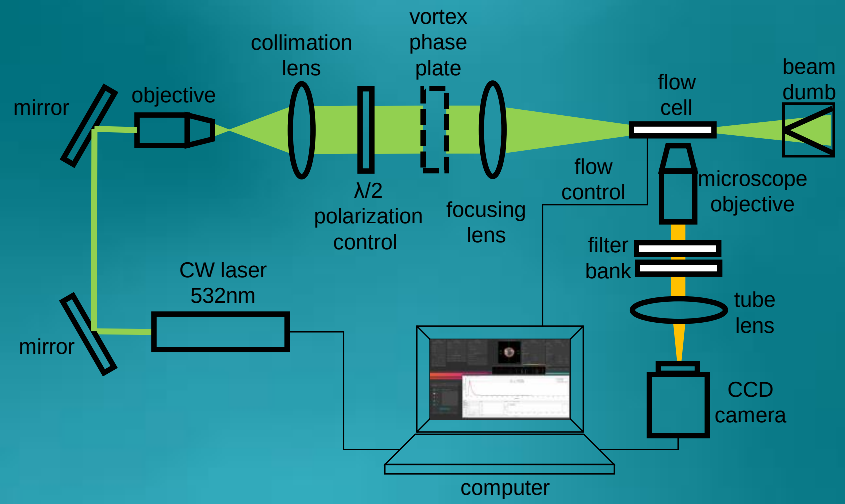
[a] Institute of Physics, University of Graz, Austria; [b] Brave Analytics GmbH, Austria; [c] Institute of Biophysics, Medical University of Graz, Austria



Introduction

Here we employ optofluidic forces on ensembles of nanoparticles using a laser tuned at 532 nm with precise micro-fluidic pumps. Both, optical and fluidic components generate forces acting on dielectric nanoparticles as shown in figure (A) and (B).

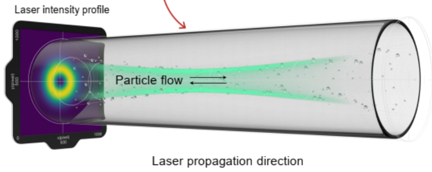


Figure A: Working principle of the OF2i method using optofluidic forces (counter)acting on nanoparticles.

Under certain conditions, particles are constrained to a 2D-optical trap and travel along characteristic trajectories, see figure (B).

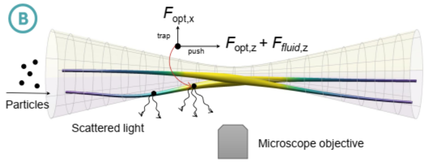


Figure B: Simulated trajectories of two nanoparticles due to optical and fluidic forces. The scattered light is recorded using a CMOS camera.

Single-particle trajectories shown in (C) are processed in real-time by recording single particle light scattering via an ultramicroscope setup and a CMOS camera.

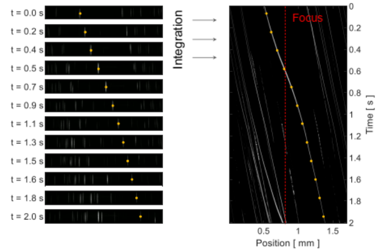


Figure C: Selected frames of raw data (left). Integration over transversal direction results in a waterfall diagram (right).

Methods

In order to simulate particle motion within our capillary, we perform a multipole expansion of the incoming fields $\mathbf{E}_{inc}, \mathbf{H}_{inc}$ and solve for the scattered fields $\mathbf{E}_{sca}, \mathbf{H}_{sca}$ employing Mie's theory for Laguerre-Gaussian beams.

The time-averaged optical forces are computed by

$$\langle \mathbf{F}_{\rm opt}(\mathbf{r})\rangle = \int_{\partial V} \left\langle \overleftrightarrow{\mathbf{T}}(\mathbf{r},t)\right\rangle \cdot \mathbf{n}(\mathbf{r})\, da,$$

where

$$\overleftrightarrow{\mathbf{T}} = \left[\varepsilon_0\varepsilon\mathbf{E}\mathbf{E} - \mu_0\mu\mathbf{H}\mathbf{H} - \frac{1}{2}\left(\varepsilon_0\varepsilon E^2 + \mu_0 H^2\right)\overleftrightarrow{\mathbf{I}}\right]$$

is Maxwell's Stress Tensor. The integration is performed using the total fields $\mathbf{E}, \mathbf{H}$ and a Gauss-Legendre quadrature for spherical particles with ε and μ being material constants.

Simulations

We now combine Newton's equation of motion with Stokes' drag and obtain for the particle's velocity

$$\boldsymbol{v}(\boldsymbol{r}) = \boldsymbol{v}_{\rm fluid} + \frac{\boldsymbol{F}_{\rm opt}(\boldsymbol{r})}{6\pi\eta R},$$

at any position within the capillary. Integrating particle velocity, we obtain the corresponding trajectory using a Runge-Kutta scheme. Figure (D) shows selected trajectories for 200 nm, 400 nm, 600 nm and 900 nm using above's model.

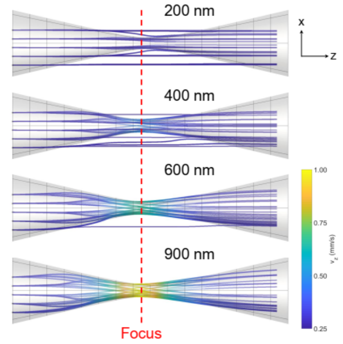
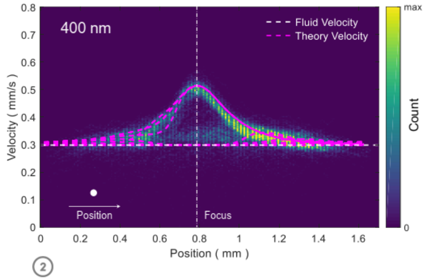


Figure D: Selected trajectories for different nanoparticle sizes. Bigger particles become more easily trapped in transverse direction. Approaching the focal region, the particles velocity increases. The velocity differs in the focal region depending on particle size.

Results

The experimental data for 400 nm Standard-Latex particles is compared to simulated velocities and depicted in figure (E)(1). The resulting size distributions are shown in figure (E)(2) for mono- and polydisperse samples. We compare our results to those of Nanoparticle Tracking Analysis (NTA).



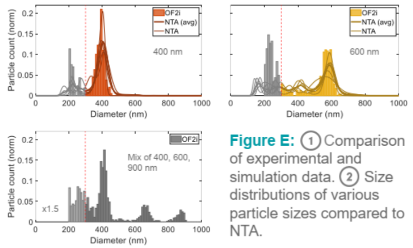


Figure E: (1) Comparison of experimental and simulation data. (2) Size distributions of various particle sizes compared to NTA.

Discussion

The OF2i scheme is presented with its underlying physical principles together with a theoretical description based on Mie's theory and higher order Laguerre-Gaussian modes.

Our results show very good agreement between experimental and theoretical data on the example of various standardized Latex particles. Furthermore, we prove the working principle of OF2i and demonstrate its applicability to various nanoparticles.

Acknowledgments

The authors acknowledge financial support from the European Union funding for Research & Innovation (Grant No. 862583 - Project NanoPAT).

References

[1] Ashkin A. A., PNAS 1997 , 94 , 4853 - 4860
[2] C. Hill. (2020). EU Patent No. 3422364B1. European Patent Office.
[3] A. D. Kiselev and D. O. Plutenko, Phys. Rev. A 2014, 89, 043803.

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BRAVE advantages

ACTIVE
INDUCED MOVEMENT AS A MEASURING PRINCIPLE

FAST & RELIABLE
MEASUREMENT DATA STREAM AS DOCUMENTATION

DETAILED & VISIBLE
SINGLE PARTICLE ACCURACY & LIVE VISUALIZATION

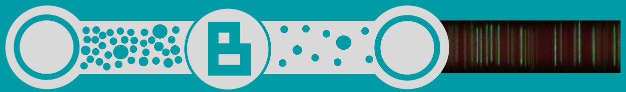
REPRESENTATIVE
STATISTICALLY VALID RESULTS

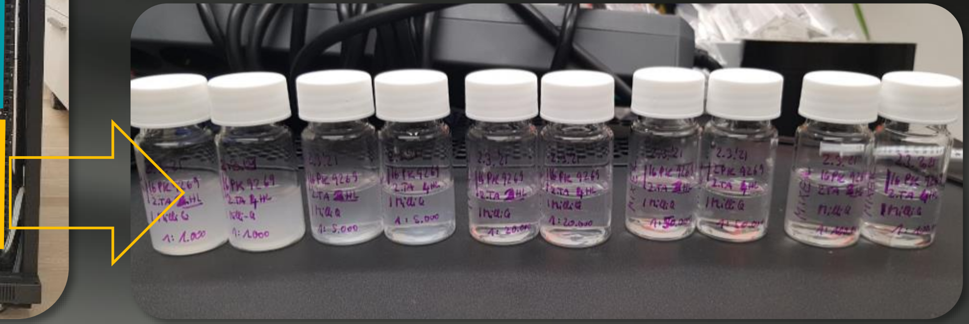
AUTOMATED & INTEGRABLE
PROCESS ANALYTICAL TOOL (PAT SENSOR)

CONTINUOUS
MEASUREMENT DATA IN REALTIME 24/7

Single particle method

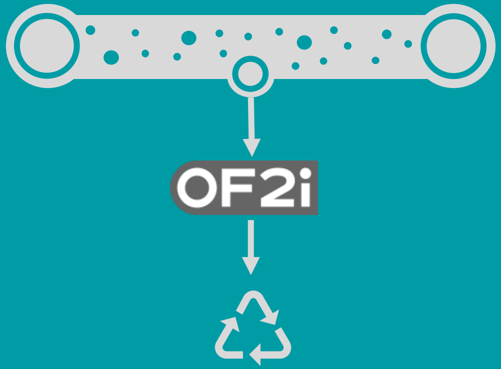
Dilution required for highly concentrated samples

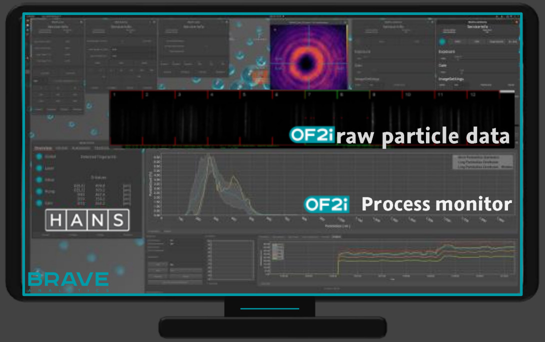




On-Line measurement

Process line interface for sample extraction





Continuous Production

Areas of Application

- Predictive Maintenance
- In Process Quality Control (IPQC) & Realtime Release Testing (RTRT)
- Monitoring of Critical Quality Attributes (CQA)
- Identification of Critical Process Parameters (CPP)
- Basic research

OF2i® Automated Process Analytical Technology (PAT)

PARTICLE SIZING

online PSD measurement

WIDE SIZING RANGE

Measuring “big” particles continously

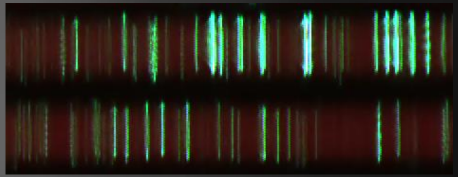
FURTHER INSIGHTS

aggregation and flocculation detection

CONTAMINATION

Towards single particle analytics

REALTIME RELEASE TESTING (RTRT)



OF2i® INSIDE

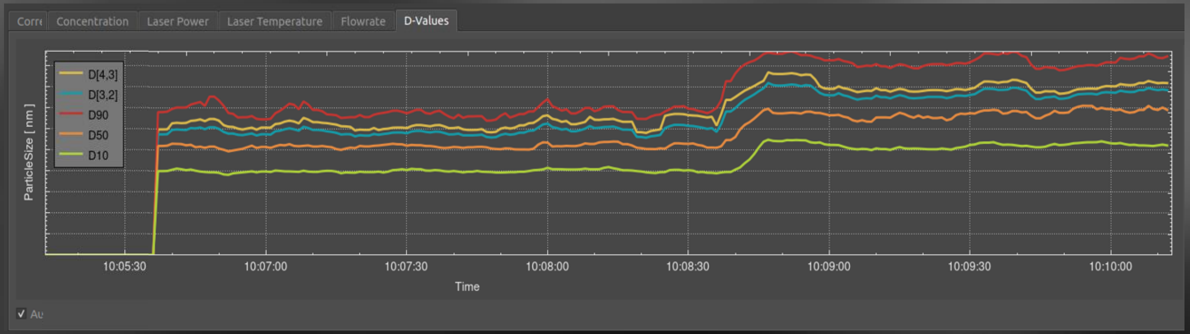
10nm – 50µm*
sample dependent

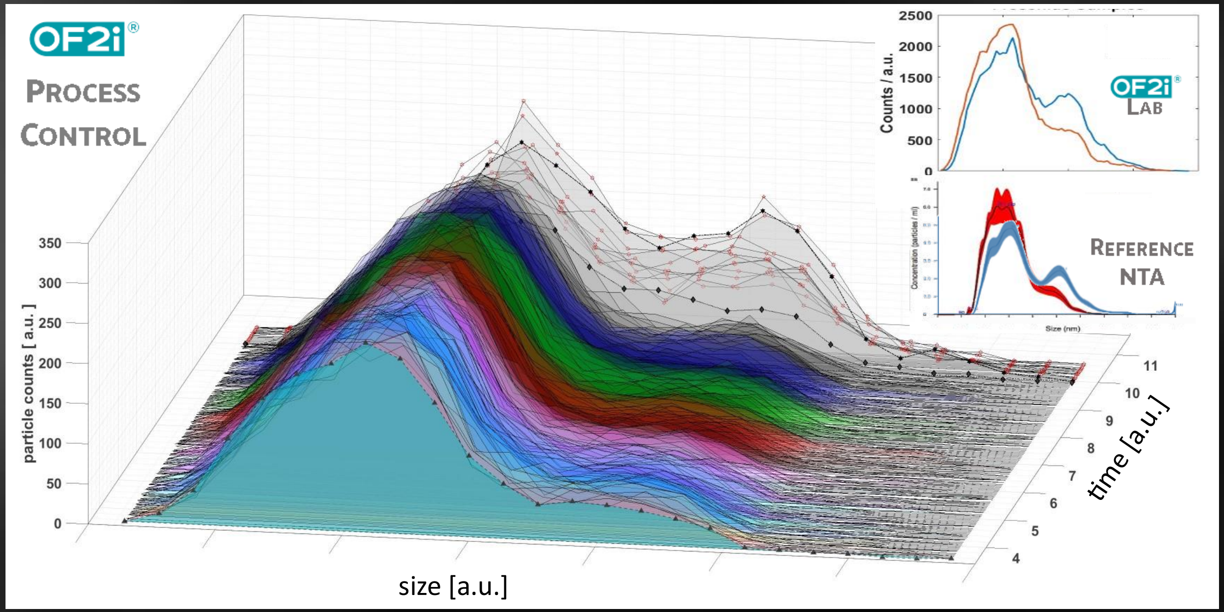
sensitivity over big dynamic range

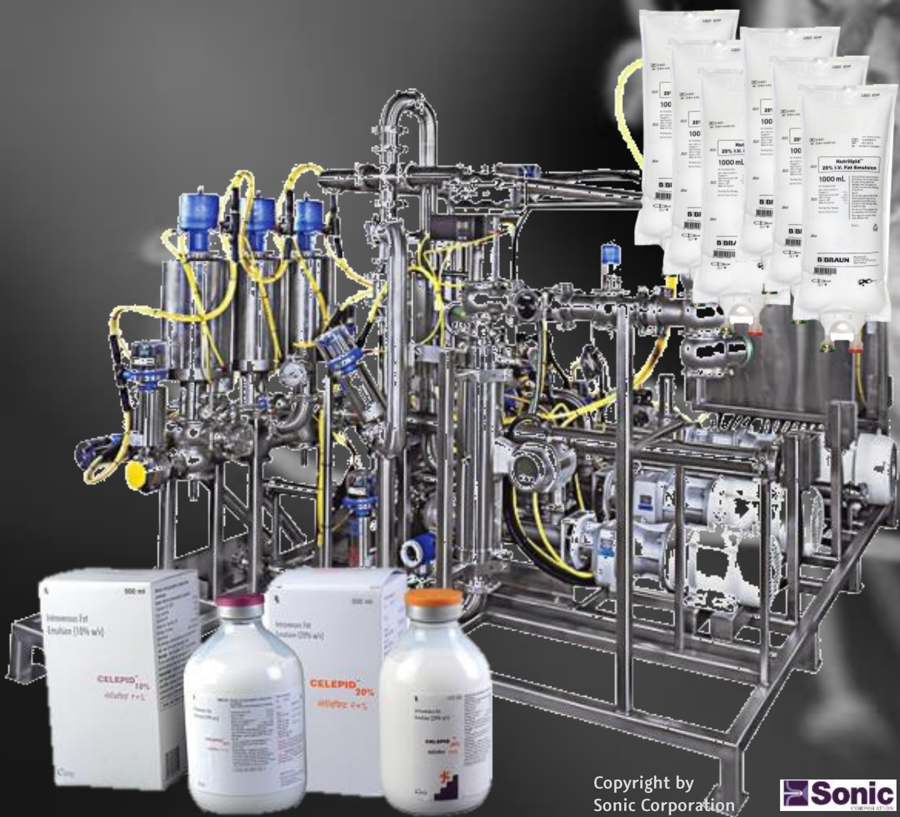
using spectroscopic information on a single particle base

Towards 21 CFR part 11

Continues detection of High-Pressure - Homogenization states

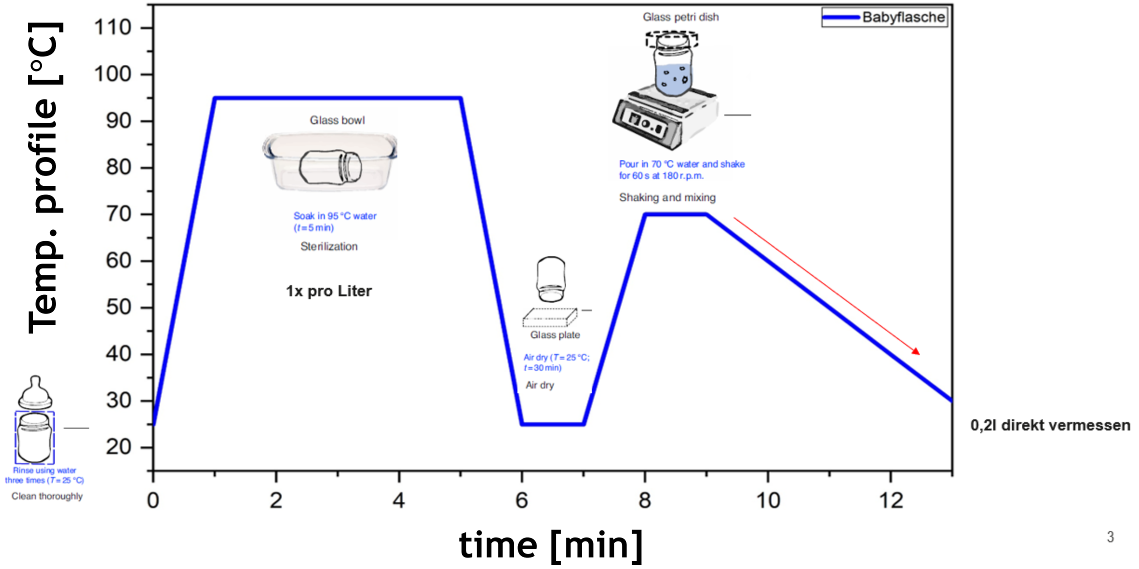






Quality control: Low concentrated samples

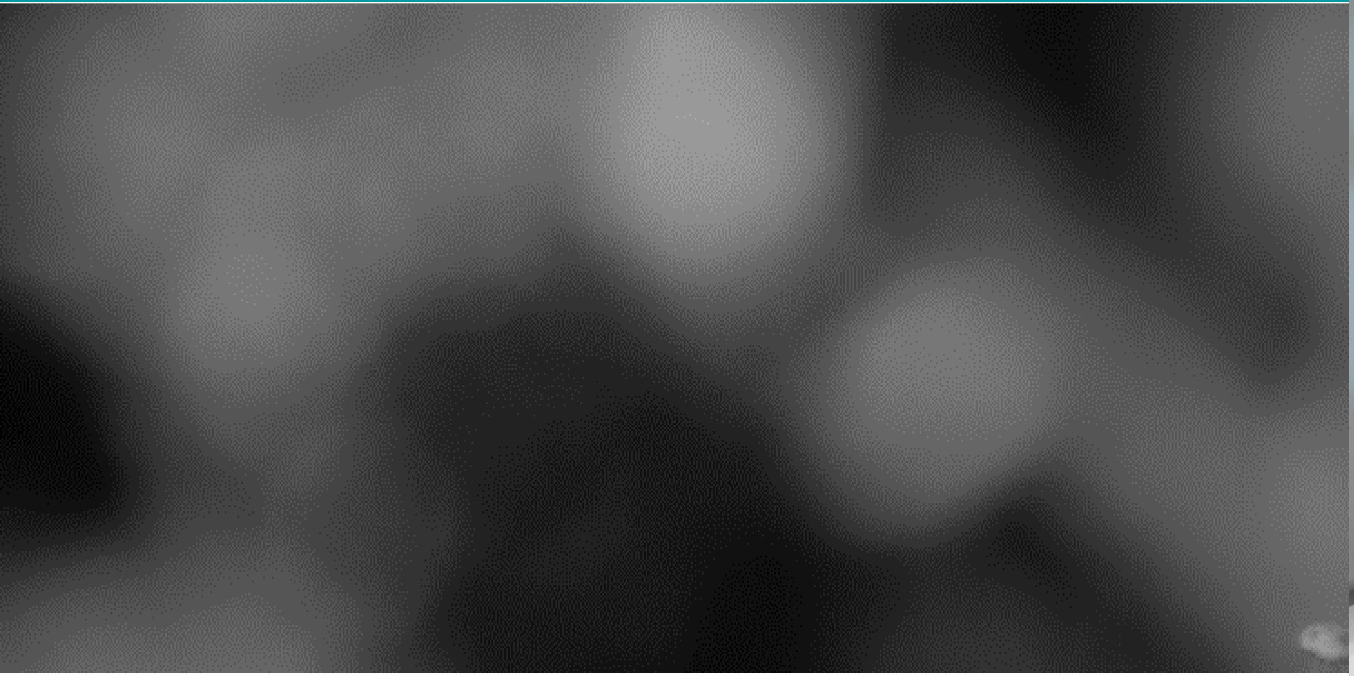
Nano Plastics – Plastic leaching processes (e.g. baby bottles)



OF2i® RAW - signal (concentration measurement)

unpublished data in cooperation with MONTAN UNIVERSITÄT WWW.UNILEOBEN.AC.AT

BRAVE ANALYTICS



SENSORS FOR REAL-TIME ONLINE NANOPARTICLE CHARACTERIZATION

SPECS

Particle sizing range: 10nm – 50µm*

Measuring statistics as number weighted hydrodynamic size distribution

For nanosuspension, nanoemulsions and colloidal formulations:

- continuous phase → liquid
- dispersed phase → solid or liquid

Measuring time specifications:

- continuous, 1x sec sizing data update
- lag time for bypass system: 4 – 20sec*

OPERATION and APPLICATION REQUIREMENTS

Bypass continuous sampling:

- optimal 0.7ml/min (minimum 5µl/min)
- concentration range sizing: minimum 10^4 objects/ml – optimal > 10^{10} objects/ml

CONNECTIONS FOR INSTALLATION

- dilution media supply, waste connection
- electrical 110/240 VAC, 50/60Hz

CONTACT

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* sample dependent

The BRAVE Status (hardware)

BRAVE® ANALYTICS

CONNECTING FLUIDICS & PHOTONICS

PLANNED SALES LAUNCH 2022

WE ARE
BRAVE

BRAVE Expertise
- Biobased particle productions (PAT solutions)
- Process monitoring & Quality control
- Protein/Antibody aggregation
- Lab Application and continuous monitoring

BRAVE Hardware
- Real time nanoparticle PAT Sensors
- On-line particle characterization
- Automated sample dilution systems

BRAVE Service
- Particle characterization & fingerprint
- Consulting & engineering
- Photonics & fluidics

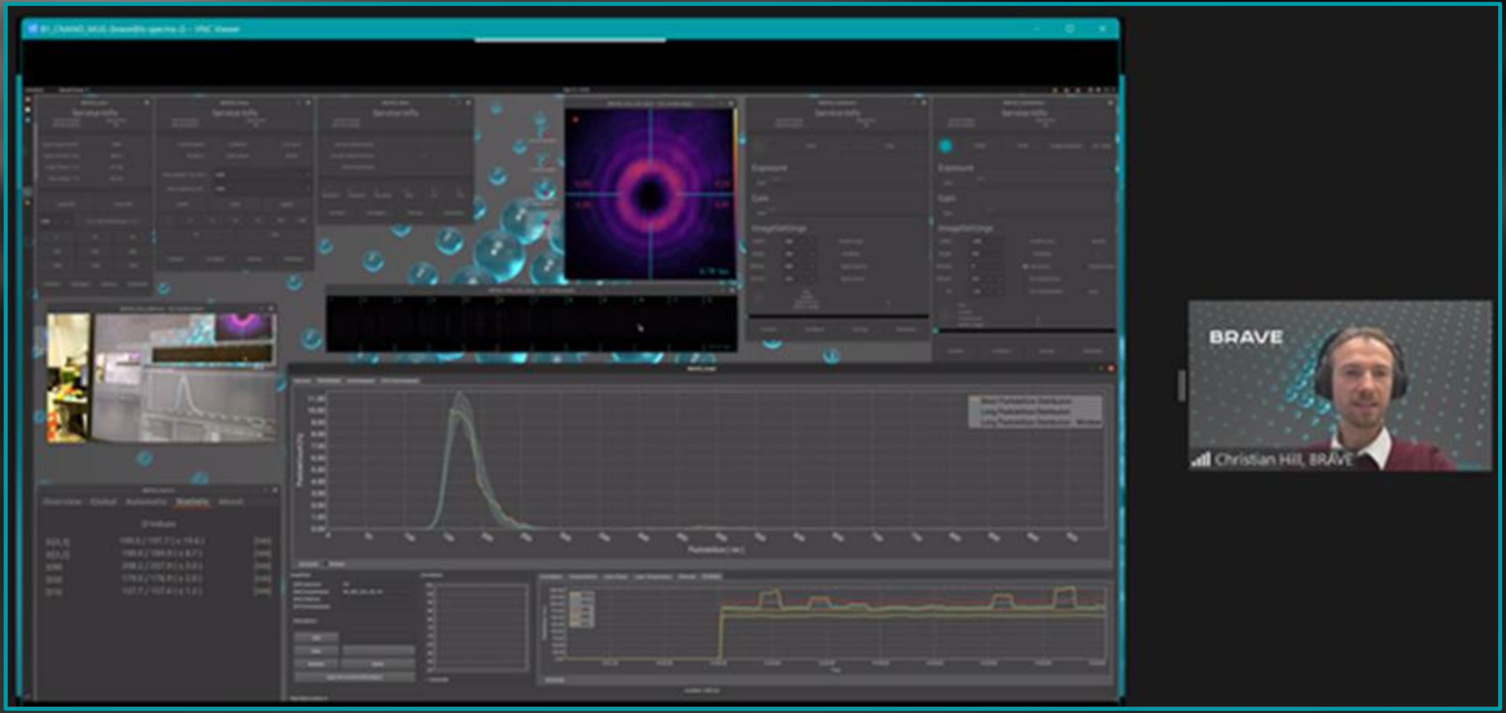
- Introduction: OF2i® a BRAVE solution
  - Live demonstration of BRAVE B1 Sensorstation
    - Discussion

HANS

Setup and Data Evaluation

RUTH

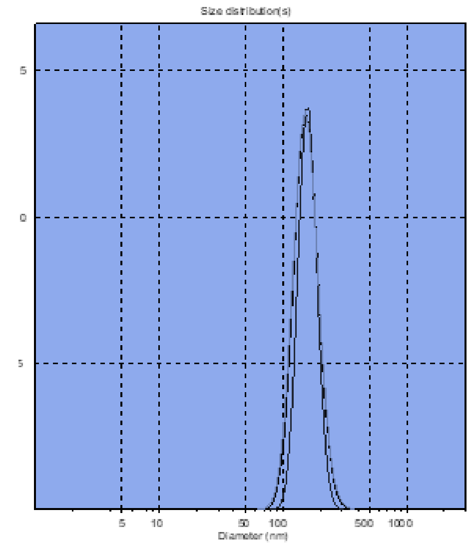
Revisit Specific Points in Time



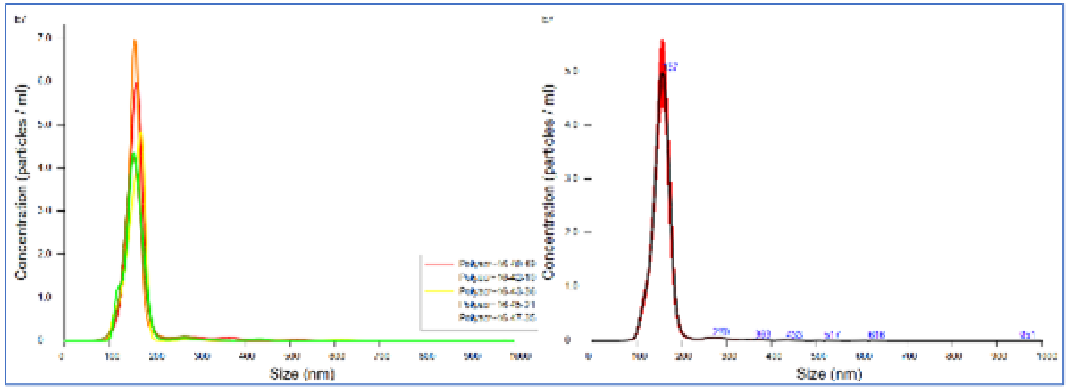
LIVE DEMONSTRATION

Polyacrylate sample (waterborne acrylic dispersion)

static sample characterization
=> live software + principle description



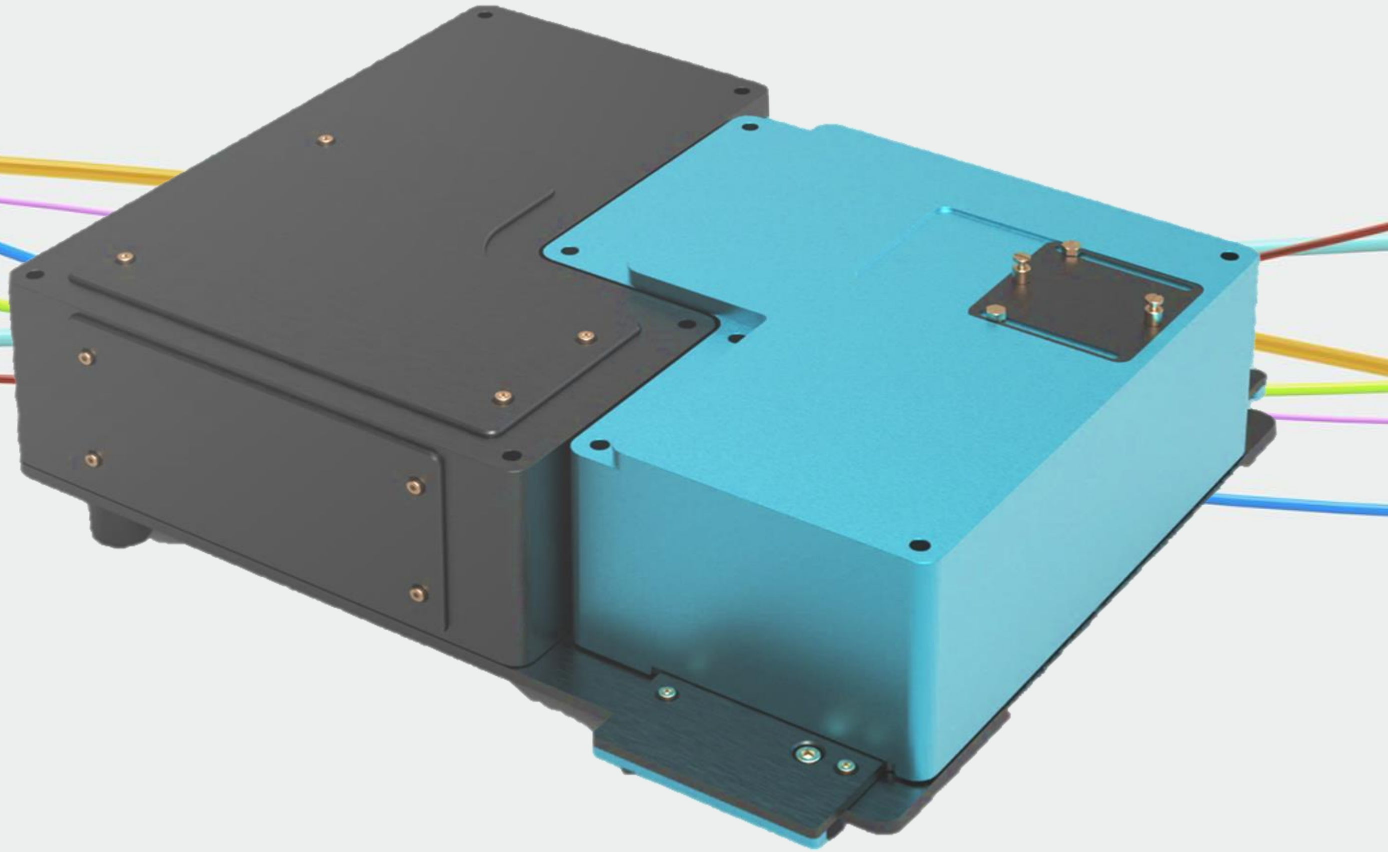
DLS characterization (1:10.000)
size distribution Z_{ave} of 166,4 +/- 0,4 nm
PDI of 0,038 +/- 0,01



NTA characterization (1:500.000)
mean PSD of 158,5nm (SD: 36,7nm)

LIVE

- Introduction: OF2i® a BRAVE solution
- Live demonstration of BRAVE B1 Sensorstation
- Discussion



BRAVE
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