Particle size distributions at process or end-use conditions

From 20 nm to 4 µm in a single acquisition using the VISTA algorithm

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20 nm – 4 µm	0.001 – 10 % m/m	3 – 30 µL	2 minutes	Clear → opaque	No refractive index
validated size range	working concentration (sample specific)	sample volume	per data point	any colour	Only prior knowledge is viscosity

Sample preparation is part of the measurement

A process analytic is only useful if it reports the state of the process, not the state of the sample after it has been prepared for the instrument. Most sizing techniques need the sample brought into a narrow optical working window, which for a concentrated process stream usually means dilution. That is not a neutral operation: self-assembled structures can be lost, osmotic changes can drive growth, and weakly bound early aggregates can be broken. Lumero measures the sample as received, free of disturbance or preprocessing.

1 VISTA: what Lumero measures

Lumero® S1 records a short microscopy video of the sample in a disposable chip, using as little as 3 µL sample. VISTA (Video Intensity Spatio-Temporal Analysis) then analyses image intensity fluctuations (due to Brownian motion of particles) over a range of length- and time-scales, and returns a distribution of diffusivities.

VISTA: Video Intensity Spatio-Temporal Analysis

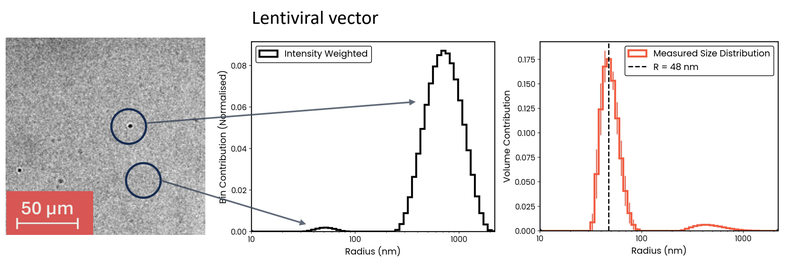


Figure 1. A single frame from a Lumero acquisition. Only the largest particles are individually visible; the sub-resolution population still modulates the image intensity and is still measured by VISTA even though it is invisible to manual inspection.

Because the analysis is statistical rather than single-particle, particles need not be resolved or tracked, and billions of particles can be captured in a measurement. Diffusivity is converted to a hydrodynamic radius through the Stokes–Einstein relation:

$$D = k_b T / 6\pi\eta R$$

Viscosity η is the only sample-specific input. Diffusivity itself is measured without it.

2 Samples measured with Lumero

The technique tolerates a wide range of optical clarity or colour. Samples measured range from transparent buffers through to turbid formulations and strongly light-absorbing products.

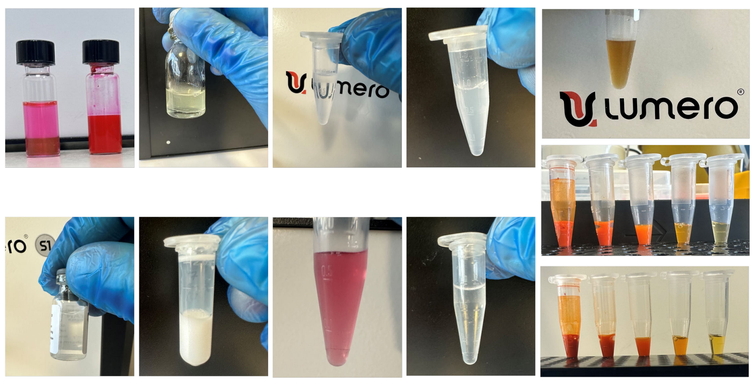
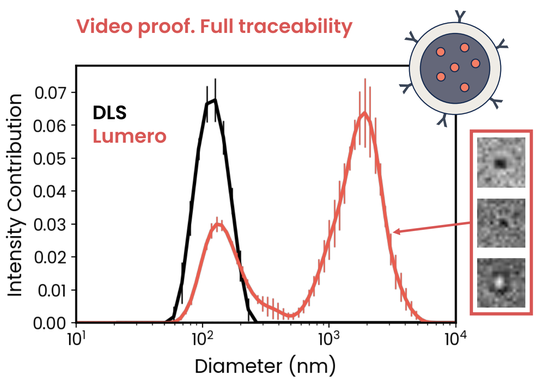


Figure 2. A selection of samples investigated with Lumero, from transparent to turbid and coloured. All measured in the state as imaged.

Validated from 20 nm to 4 µm and 10 – 10^5 µg/mL (0.001 – 10% v/v, system dependent), using 3 – 30 µL per channel, in two minutes per data point. Viscosity is the only sample-specific input; no refractive index is required. Many process streams can therefore be measured as received, including complex mixtures. Dense or highly structured materials, such as creams and pastes, may still need some dilution - the benefit is that dilution becomes a smaller, better controlled choice rather than a fixed requirement of the technique.

3 One acquisition, one distribution

Scattering techniques observe at a fixed scattering vector *q*. Above roughly 40 nm the angular dependence of scattering means the reported signal depends on instrument geometry, and large particles can be strongly under-weighted or omitted **[1]**. Lumero is not subject to this form-factor weighting, and the video gives direct confirmation of what is present. Lumero collects data equivalent to 50 scattering vectors < 8^o scattering angle, so captures populations missed by other tools.



Lumero is less affected by the form factor and thus excels in detecting larger particles in presence of small particles

Lumero can detect as few as ~2 x 10^5 micron-size particles per mL and at a ratio as low as 1 in 10 million.

Figure 3. Lipid nanoparticles measured by DLS (Zetasizer Ultra, black) and Lumero (orange). The micron-scale population recovered by Lumero is confirmed in the video frames (shown right).

[1] Angular dependence after Lin et al., *Meas. Sci. Technol. 33 045202* (2022).

4 Dilution changes what you measure

Dilution is not a neutral operation. It can remove structures that were present, and it can create structures that were not.

Left: lipid nanoparticles treated with triton to induce lysis, measured undiluted at 0.9 mg/mL and after ten-fold dilution in water. Particles robust to dilution would give a ten-fold reduction in signal; the observed reduction is approximately one thousand-fold.

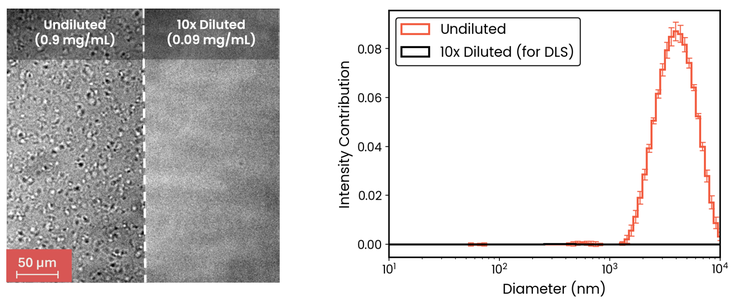


Figure 4. LNPs treated with triton, undiluted (0.9 mg/mL) and 10x diluted (0.09 mg/mL), scale bar 50 µm, with the corresponding intensity-weighted distributions (scaled by signal).

> **A ten-fold dilution that reduces signal by a thousand-fold has not just reduced concentration. It has fundamentally changed the sample.**

Below: a liposome reference material from the National Research Council Canada, measured in its original sucrose-based buffer and after the 3× dilution in PBS specified by the certificate protocol. Viscosity change has been accounted for. Data collected at the UK's national metrology institute.

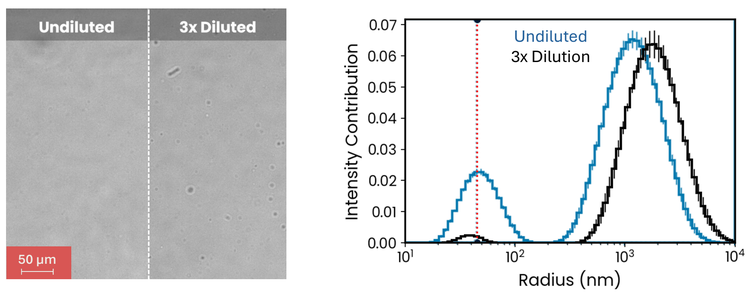
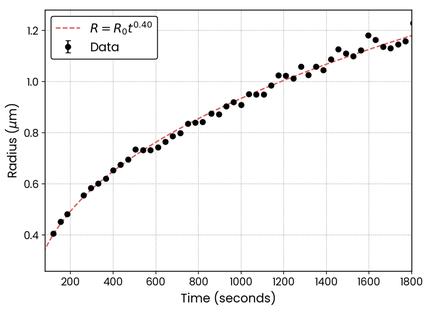


Figure 5. Images and normalised intensity-weighted distributions of NRCC liposome reference sample, with and without dilution in PBS. Here dilution increases the proportion of large particles significantly. The dotted reference value is obtained from the certification, and is specific to one model of DLS at 50x dilution.

5 Following a process as it happens

With no preparation step between sampling and measurement, acquisitions can be repeated to follow a process in time – with a resolution of two minutes per point.



Changes may be driven by:

- Colloidal aggregation
- Crystal growth and nucleation kinetics
- Droplet coalescence and ripening
- Lysis and dissolution

Figure 6. Real-time growth of a DNA complex for gene therapy, measured at-line alongside the bulk process. The radius follows a power law in time, giving an informative growth exponent and predicative power, rather than a single end-point size. Growth rate depends on concentration, so this is only meaningful undiluted.

6 Filtration: did it do what you expect?

Lumero is excellent at detecting coexisting populations, including residual large particles. Intensity weighting (∝ r^6) highlights large-particle populations, so the success of a filtration step is evident; volume weighting (∝ r^3) is dominated by the product itself, showing whether the step altered it.

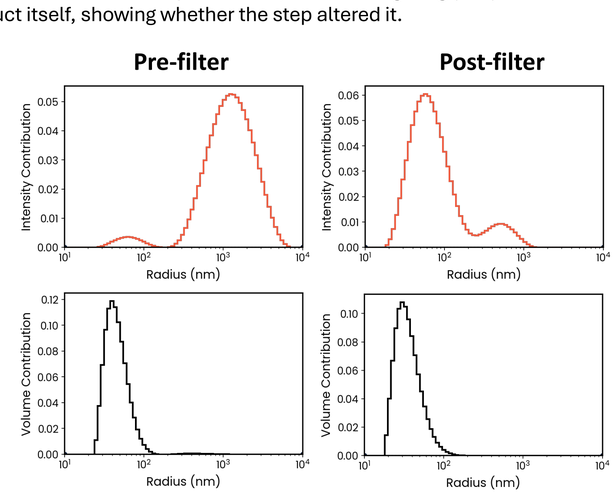


Figure 7. LNP sample before and after filtration, reported with both intensity- and volume-weighting from the same measurement. Aggregates are largely (but not entirely) removed while the product population is essentially unchanged.

7 Stability in hours, not weeks

A sunscreen formulation without stabiliser, diluted ten-fold in water, passes a standard stability test for several weeks but is expected to fail within months. Measured with Lumero, the micro-scale distribution changed measurably within one hour.

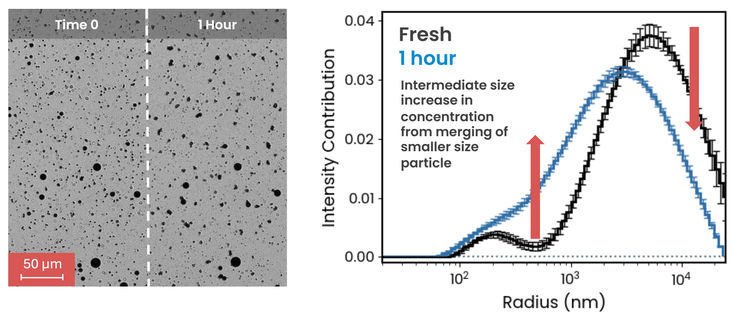


Figure 8. Left: the sample at time 0 after 1 hour, scale bar 50 µm; a wide mixture of particle types is present, including oil droplets and TiO_2. Right: normalised distributions for the same measurements. Small particles grow faster than large ones, increasing their intensity share, giving a quantitative rate of change.

8 Concentrated monoclonal antibodies

A monoclonal antibody formulation at 100 mg/mL was measured unstressed twice, then after physical agitation and after heating to 50 °C for five minutes. Aggregate signal rises with stress, and the large aggregates responsible were qualitatively confirmed by inspection of the videos.

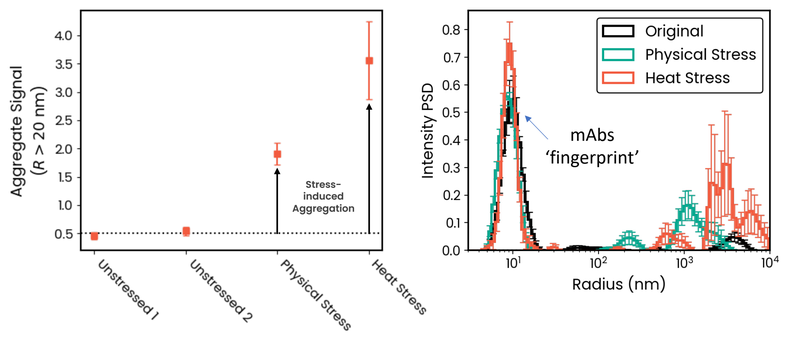
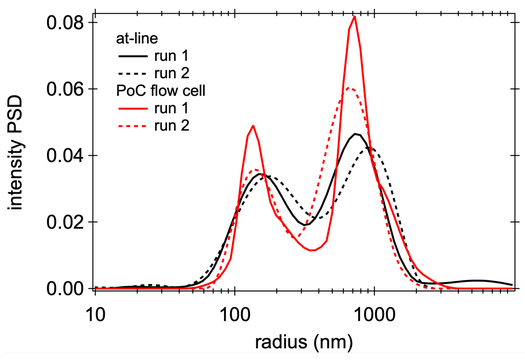


Figure 9. Left: aggregate signal (R > 20 nm) across the four measurements. Right: intensity-weighted distributions before and after each stress, showing the monomer peak and the aggregate population that grows with stress. The aggregates responsible were identified directly in the videos.

Free diffusion in water was assumed and viscosity was not quantified, so reported sizes are systematically overestimated; the peak below 10 nm sits outside the validated range and should be read as a reproducible fingerprint rather than an absolute monomer size.

9 InSPIREmed: towards on-line measurement

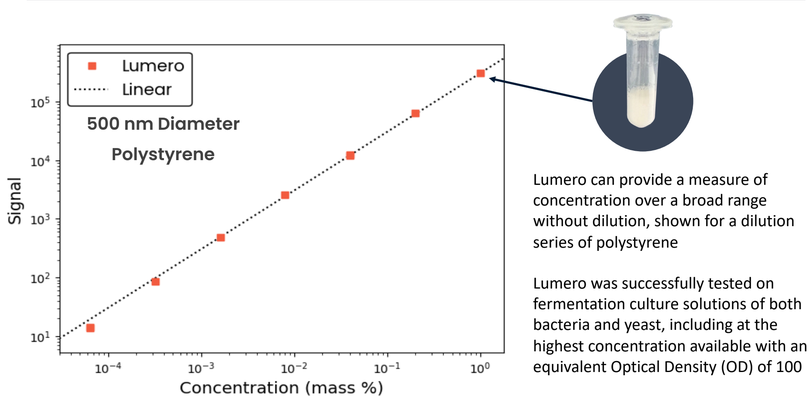
Lumero S1 is an at-line and off-line benchtop instrument. Within the InSPIREmed project, and with CPACT partners, Dyneval is developing an on-line implementation for direct integration into manufacturing pipelines.



Good agreement given it is currently a Proof of Concept with effect from residual flow, vibration and the complexity of the sample

Figure 10. First flow-cell results using a proof of concept on-line Lumero coupled with a syringe pump. Flow-cell measurements were taken by flowing, stopping, waiting about one minute and recording.

10 Concentration (beta)



Lumero can provide a measure of concentration over a broad range without dilution, shown for a dilution series of polystyrene

Lumero was successfully tested on fermentation culture solutions of both bacteria and yeast, including at the highest concentration available with an equivalent Optical Density (OD) of 100

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