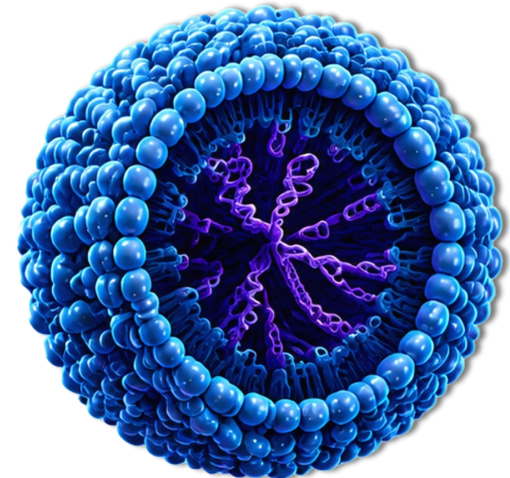


Cedric Devos, Aniket Udepurkar, Peter Sagmeister,
Etienne Boulais, Swathi Ganesh, Martin Z. Bazant,
Bernhardt L. Trout, Richard D. Braatz, Allan S. Myerson

Microflow Systems for the Precipitation-based Manufacturing of Biotherapeutic Products

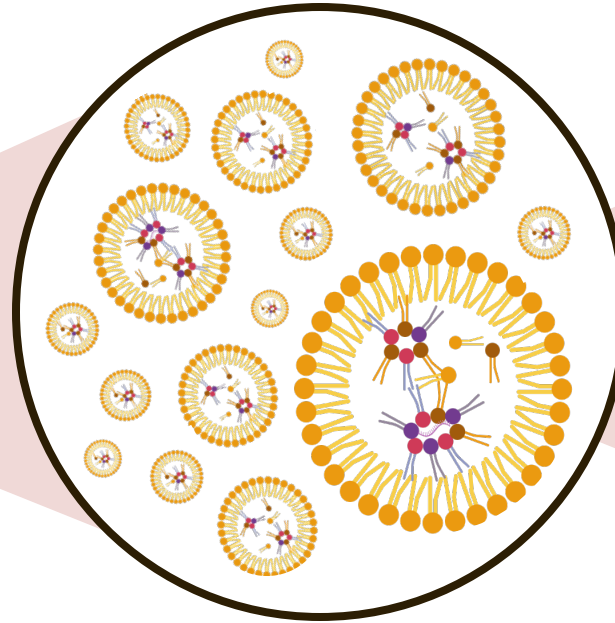
IMRET Meeting, September 2026



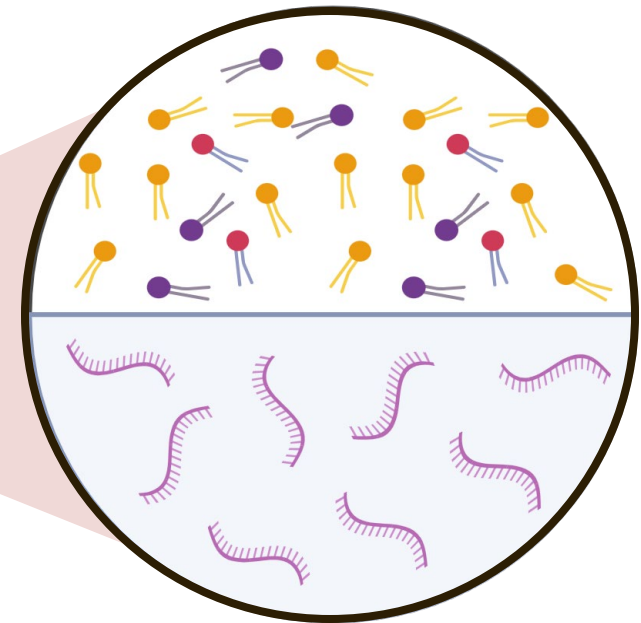
Lipid nanoparticles (LNPs) deliver fragile cargo (e.g., mRNA)



mRNA vaccines



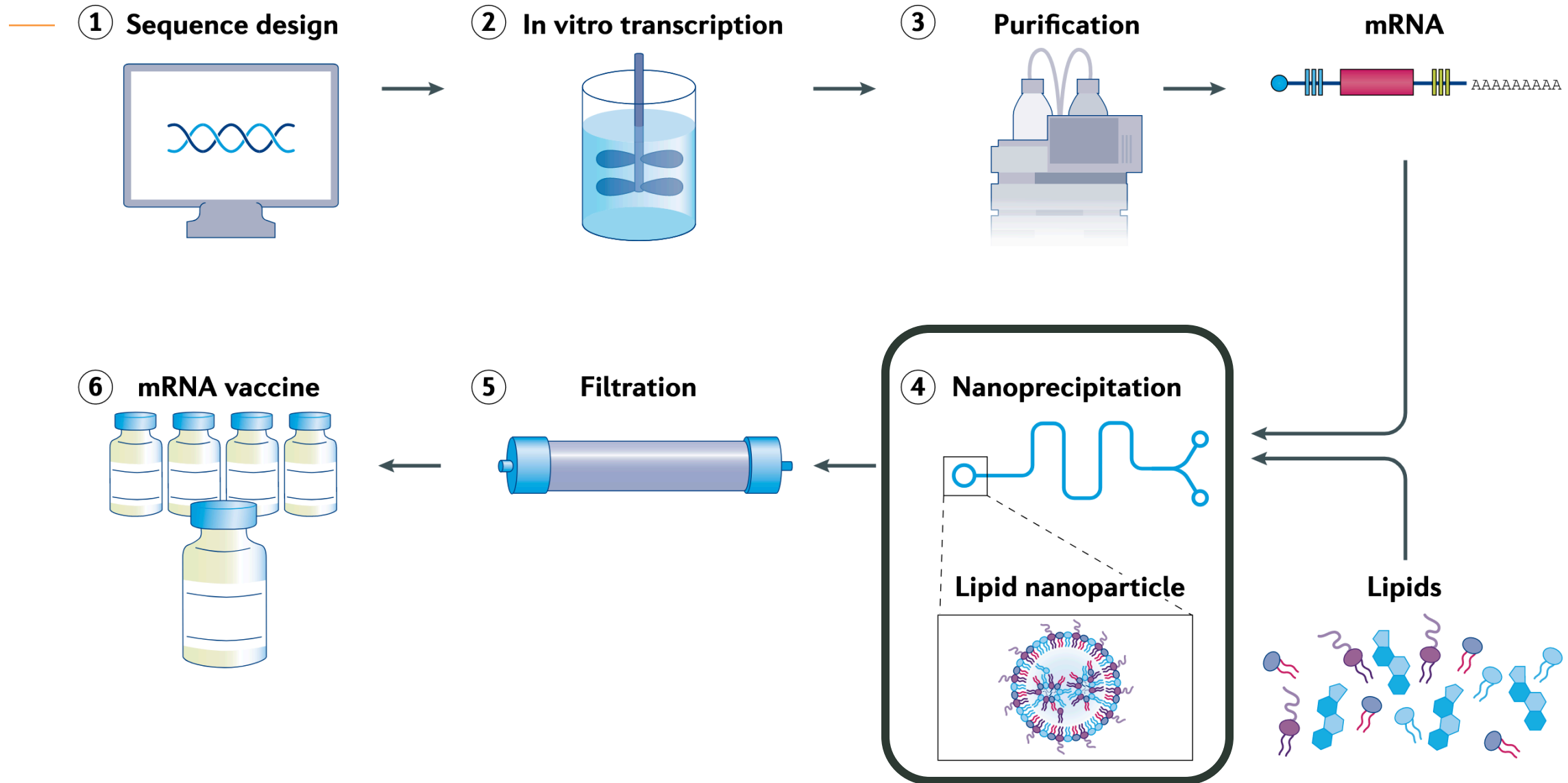
Protective shells



mRNA with lipids

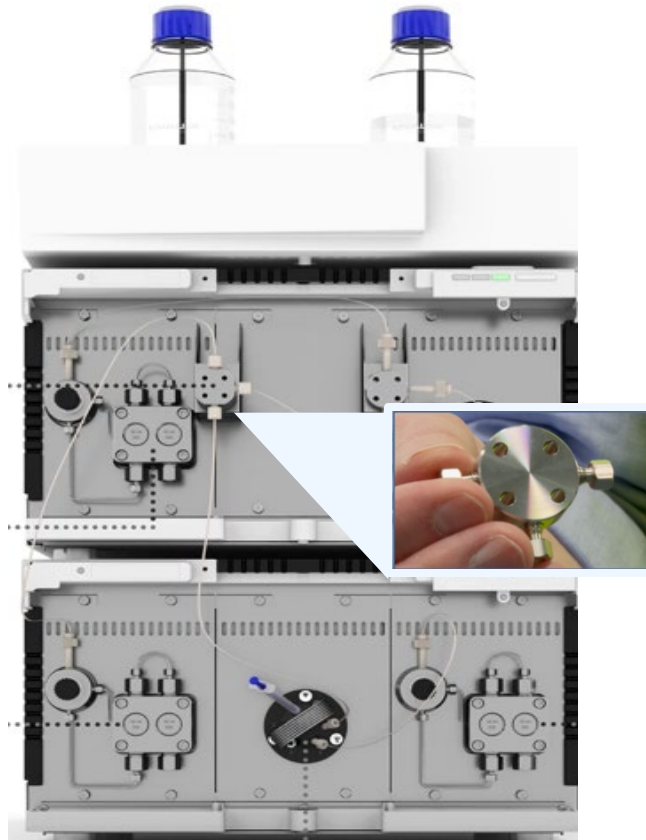
- As of 2024, 13 billion+ COVID-19 doses administered via LNP technology.
- Nanoparticles account for ~1/3 of the advanced drug delivery pipeline.

LNP precipitation is a key step in manufacturing mRNA vaccines

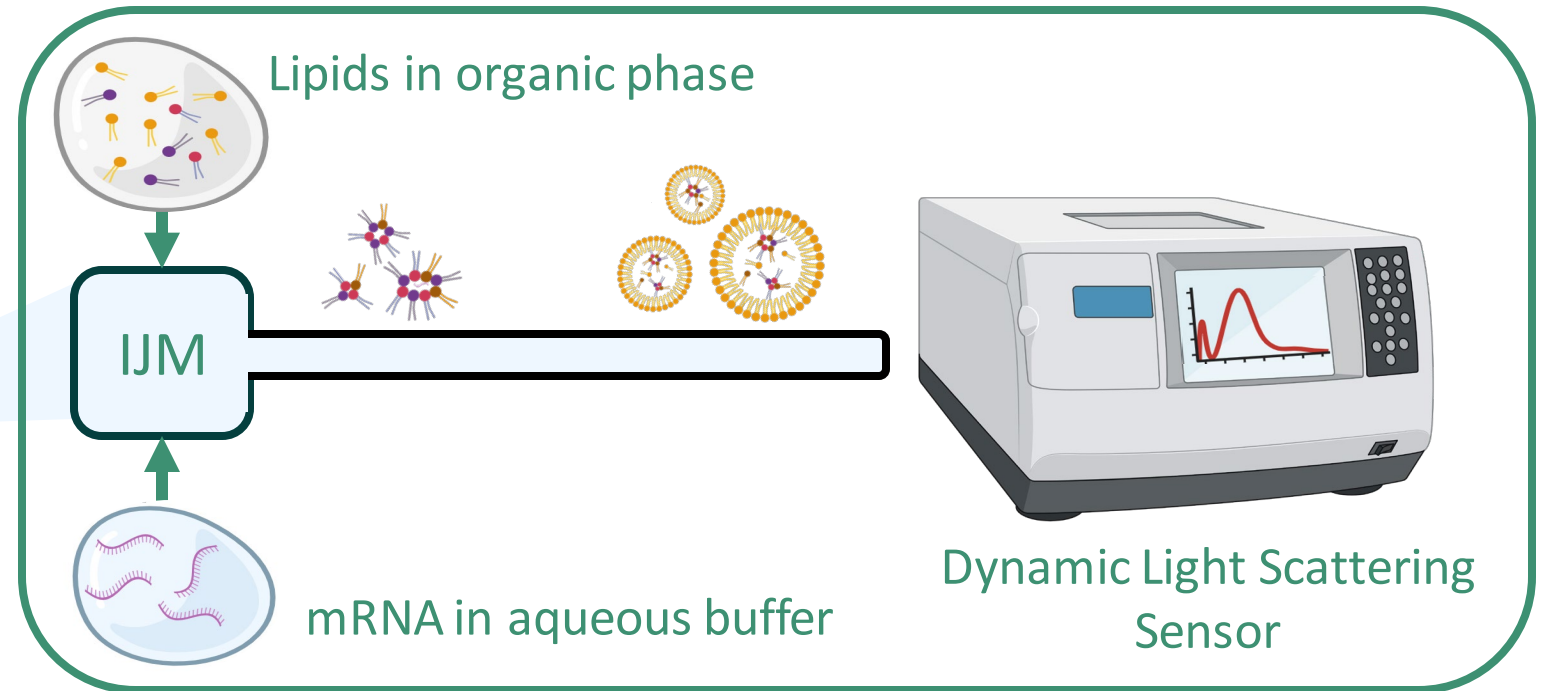


Chaudhary, N., et. al, mRNA vaccines for infectious diseases: principles, delivery and clinical translation. *Nat Rev Drug Discov* **20**, 817–838 (2021).

LNP manufacturing via continuous precipitation in impinging jet mixers



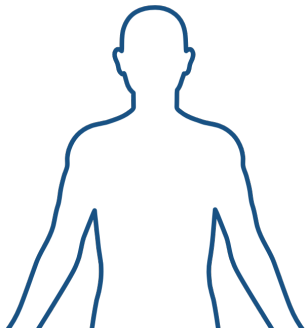
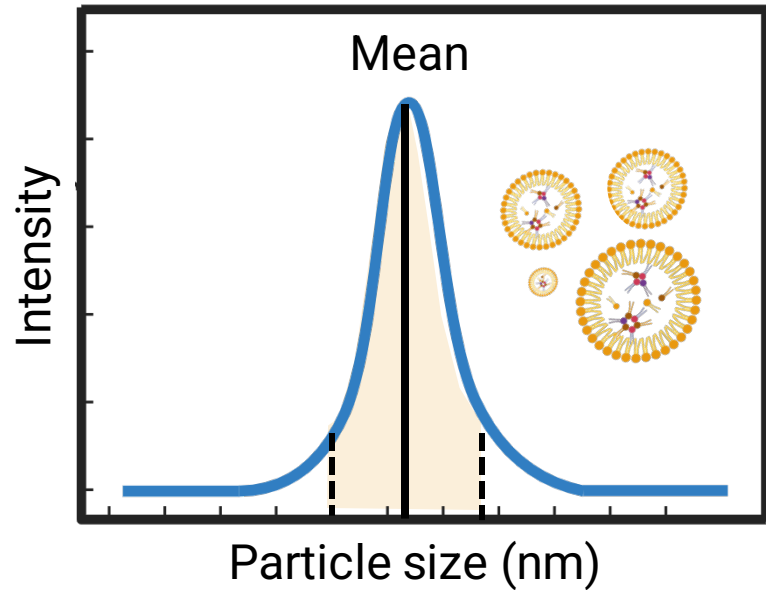
Impinging jet mixer (IJM)



LNP Precipitation

1. CNN: Manufacturing moonshot: How Pfizer makes its millions of Covid-19 vaccine doses, Aamanda Sealy, 2021
2. C. Devos, et al. "Impinging Jet Mixers: A Review of Their Mixing Characteristics, Performance Considerations, and Applications." *AIChE Journal* 71, 2025.
3. C. Devos, et al. "Manufacturing mRNA-Loaded Lipid Nanoparticles with Precise Size and Morphology Control." *ACS Nano* 19, 2025.

Particle size distribution (PSD) is a critical quality attribute for LNPs



- ✓ Biodistribution
- ✓ Drug efficacy

Consequence of poor PSD control



Off-spec drug substance



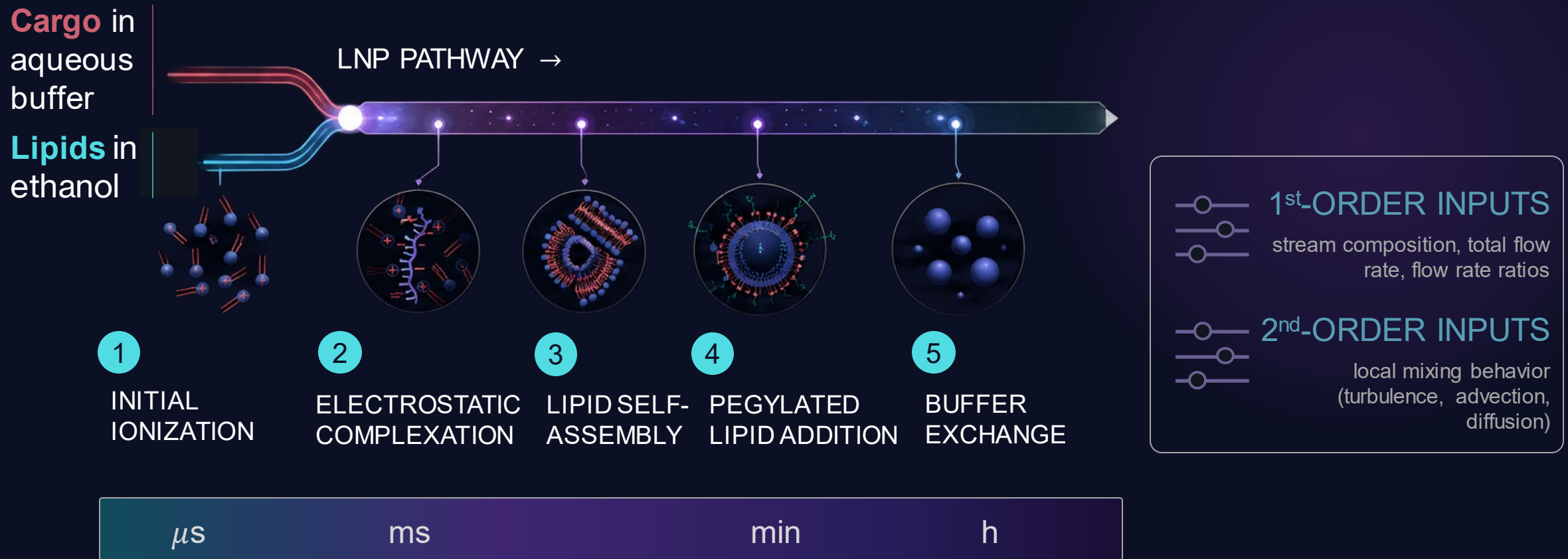
Wasted material costs



Reduced efficacy of the product

LNP self-assembly

Complex **multi-component self-assembly** process occurring on a **millisecond** timeframe



Winning the race between **mixing** and **self-assembly**

LNP SELF-ASSEMBLY

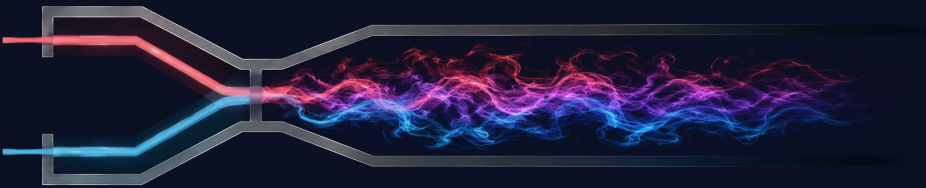


DAMKÖHLER NUMBER

$$Da = \frac{\tau_{\text{mixing}}}{\tau_{\text{LNP assembly}}}$$

$Da \gg 1$

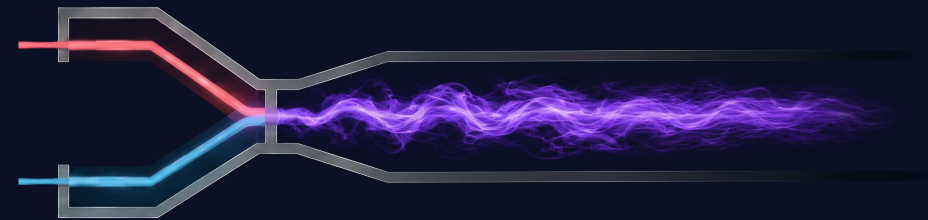
assembly faster than mixing



Assembly occurs in **heterogeneous** environment

$Da \ll 1$

mixing faster than assembly

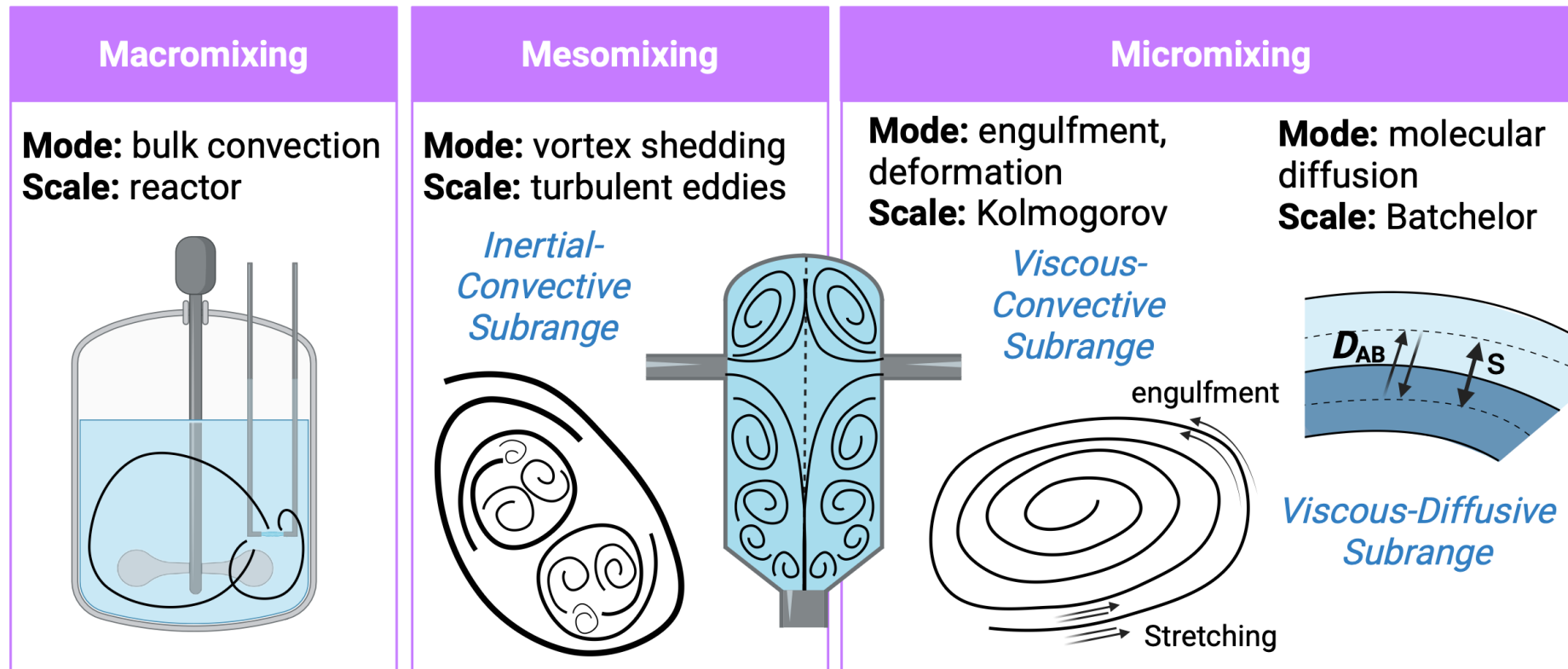


Assembly occurs in **homogeneous** environment

The “macro-micro mixing” framework

Turbulent energy cascades: eddies from larger → smaller scale

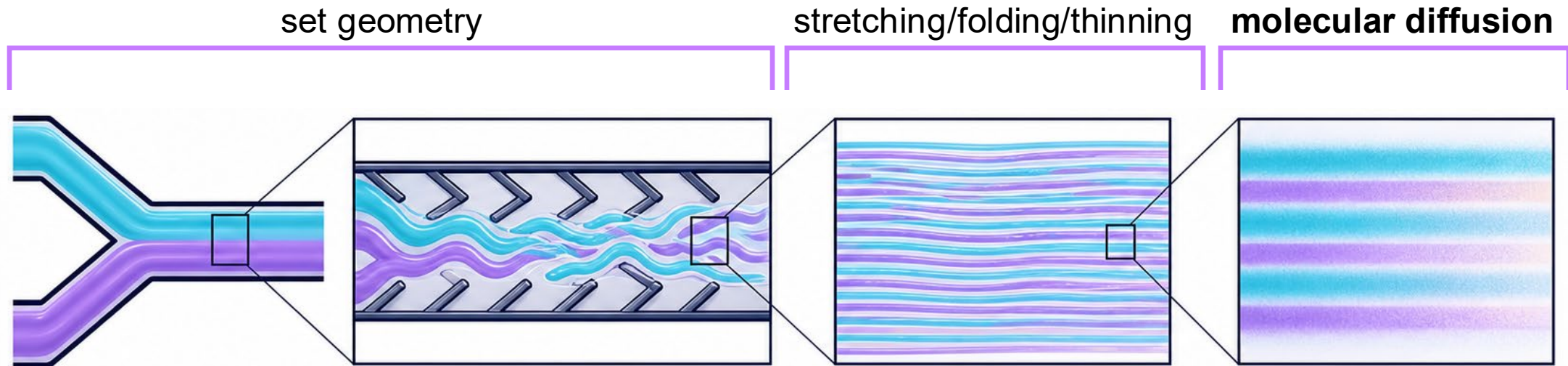
- Viscous-convective subrange: eddy engulfment
- Viscous-diffusive subrange: dissipated into heat



Microfluidic mixers to access the right timescales

Laminar-Advection framework

$$\partial c / \partial t + \mathbf{u} \cdot \nabla c = D \nabla^2 c$$



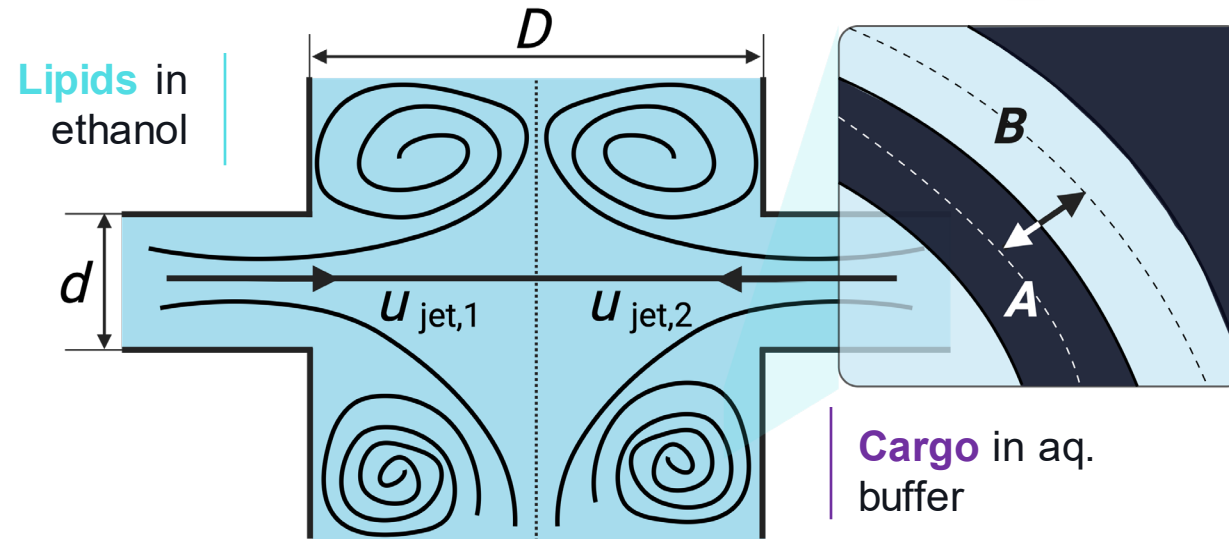
Herringbone Mixer

A.D. Stroock, S.K.W. Dertinger, A. Ajdari, I. Mezić, H.A. Stone, G.M. Whitesides, "Chaotic Mixer for Microchannels," *Science*, 295, 647–651, 2002.

Impinging jet mixers to access the right **timescales**



Pfizer, Kalamazoo, Michigan, Manufacturing facility [1]



MILLISECOND MIXING

Rapid mixing to match the self-assembly timescale.



HIGH VOLUMETRIC THROUGHPUT

Increase throughput by increasing the total flow rate.



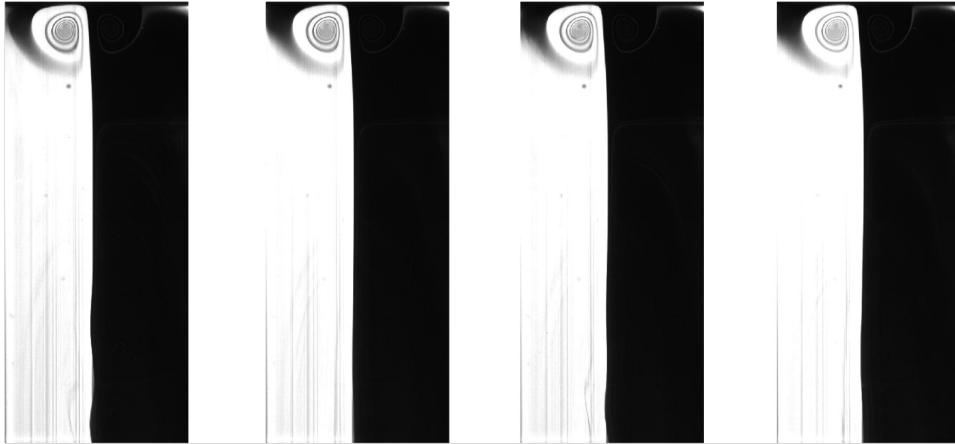
UNIFORM FLOW EXPOSURE

The entire fluid stream is pushed through the same rapid mixing zone.

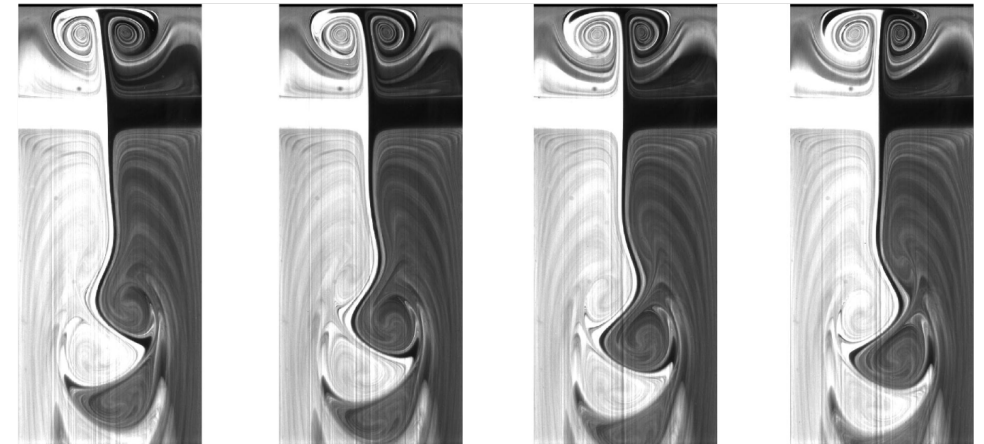
Impinging jet mixers: **intuitive** operation

FLUID TRACER

Re = 103



Re = 104



OPERATIONAL CONSIDERATIONS

$$Re = \frac{\rho u_{\text{jet}} d}{\eta}$$

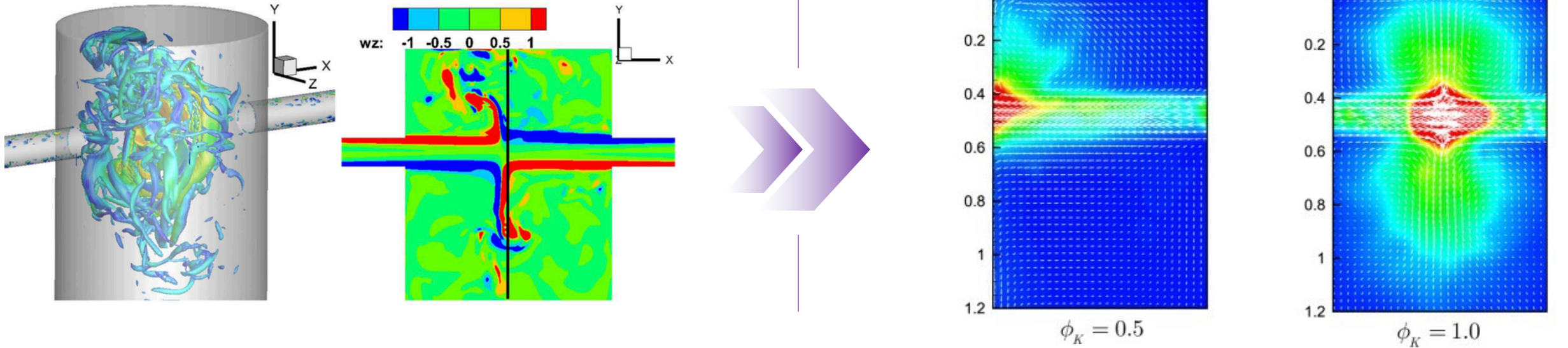
operate above critical
Reynolds number

$$Re_{\text{crit}} = 90 - 150$$



Impinging jet mixers: intuitive operation

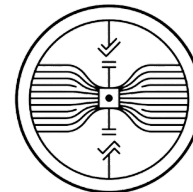
COMPUTATIONAL FLUID DYNAMICS



OPERATIONAL CONSIDERATIONS

$$Re = \frac{\rho u_{jet} d}{\eta}$$

operate above critical
Reynolds number



operate under equal
momentum balance

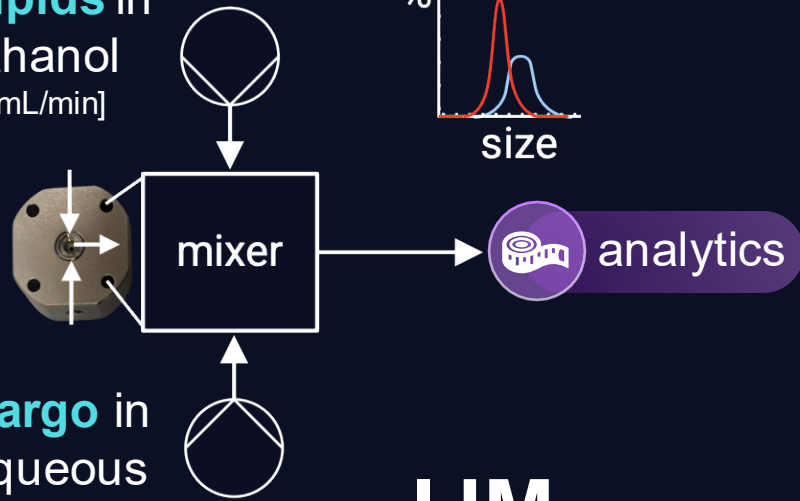
$$\phi = \frac{\rho_1 d_1^2 u_{jet,1}^2}{\rho_2 d_2^2 u_{jet,2}^2}$$

Good mixers to access the right timescales: In practice

SETUP

Lipids in
ethanol
[x mL/min]

Cargo in
aqueous
buffer
[y mL/min]



IJM

impinging jet mixer
Custom made in collaboration with Knauer

FRR = 3:1

TFR = 20 mL/min
Aqueous stream = 15 mL/min
EtOH stream = 5 mL/min

INPUTS

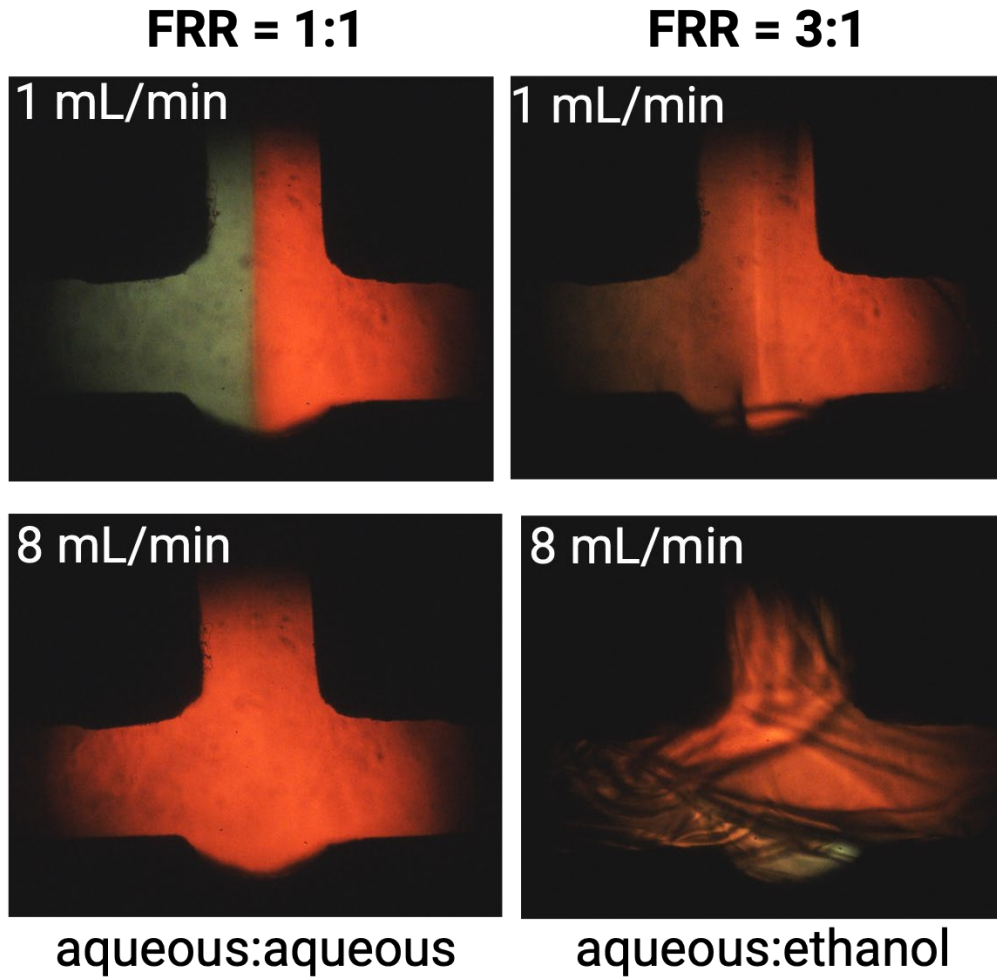
1st-ORDER INPUTS

total flow rate (TFR)
 $\text{TFR} = \text{Aqueous stream} + \text{EtOH stream}$

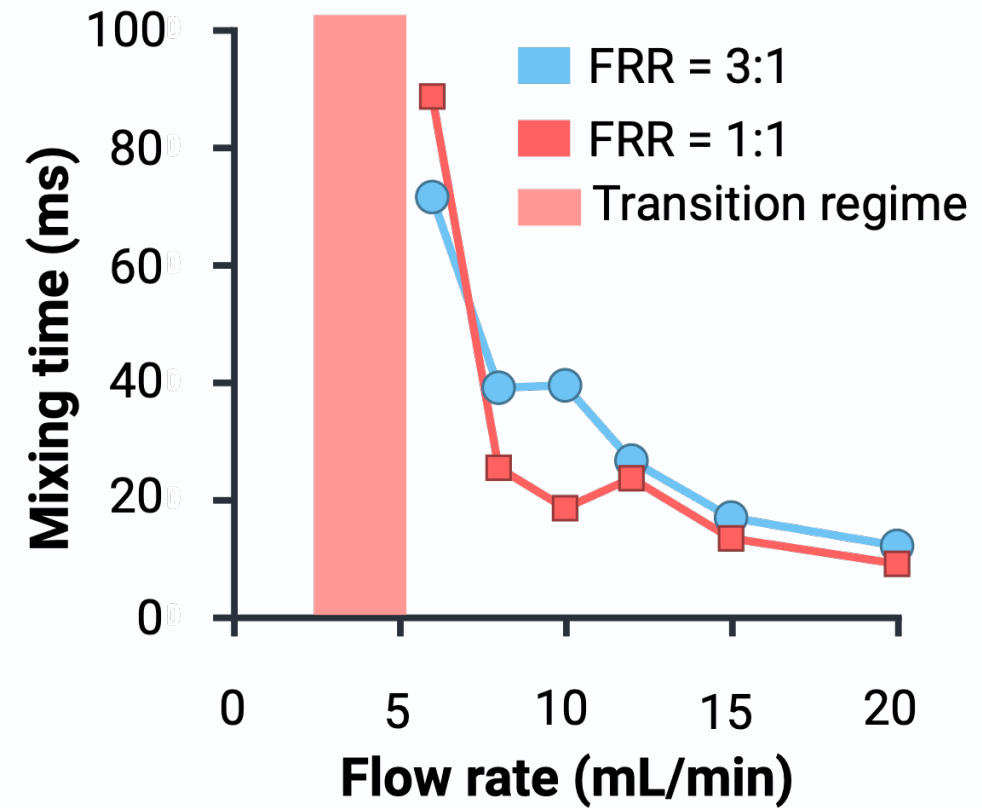
flow rate ratio (FRR)
 $\text{FRR} = \text{Aq. stream} / \text{EtOH stream}$

1st-ORDER INPUTS
stream compositions

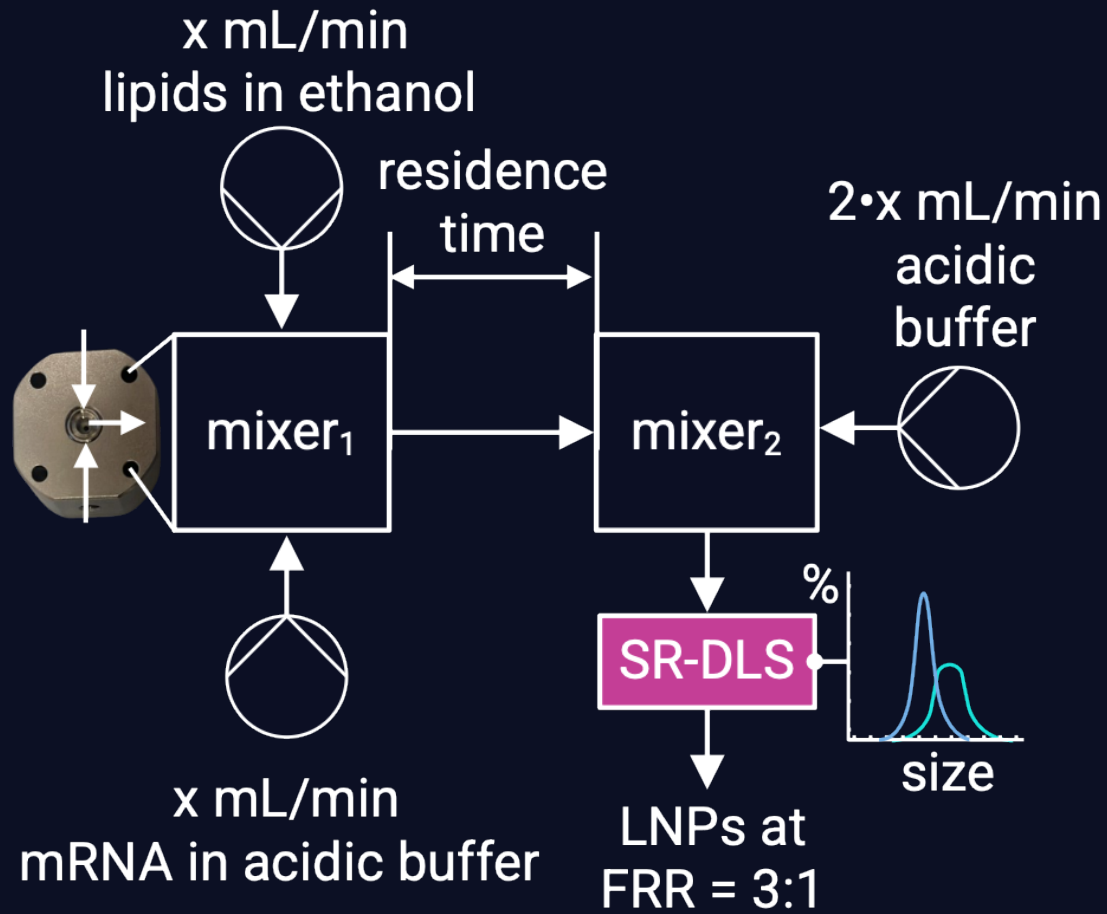
Mixing analysis



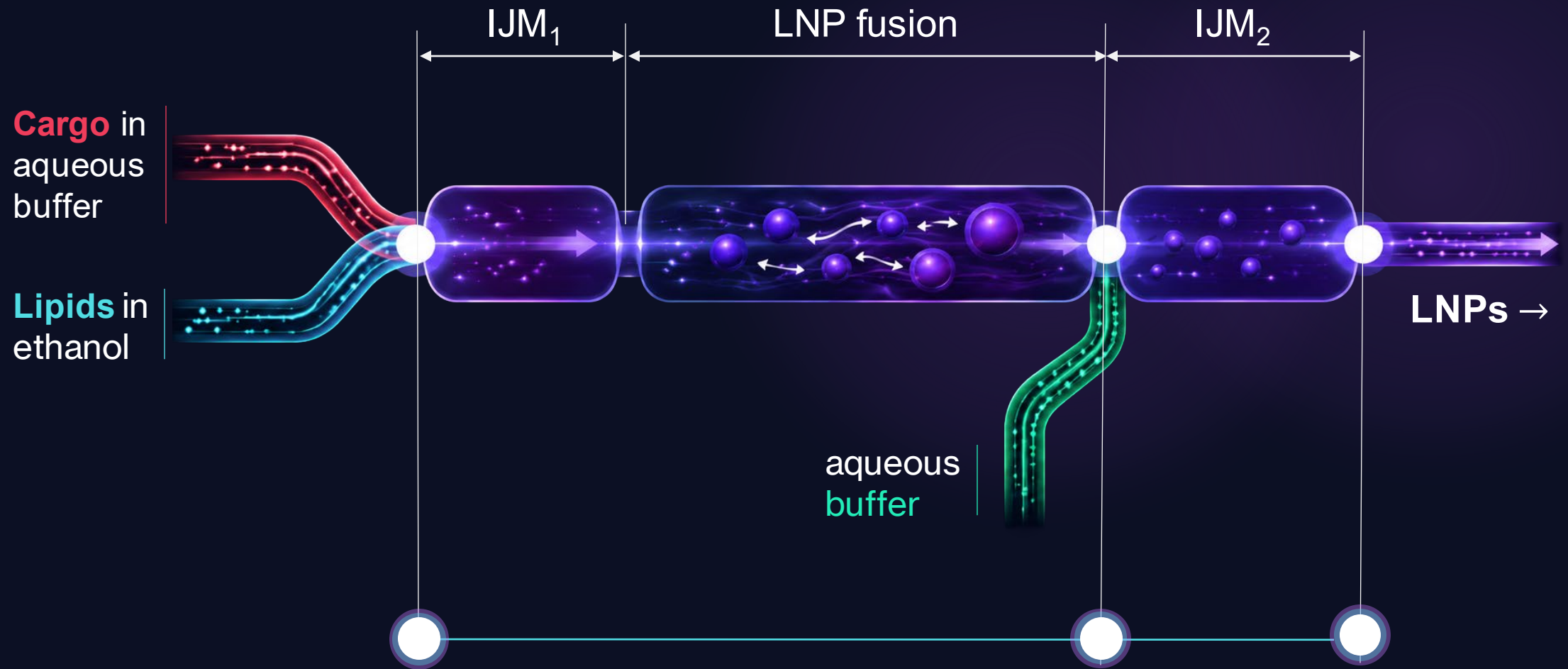
Villermaux-Dushman



Access the right timescales **and intervene in the process**

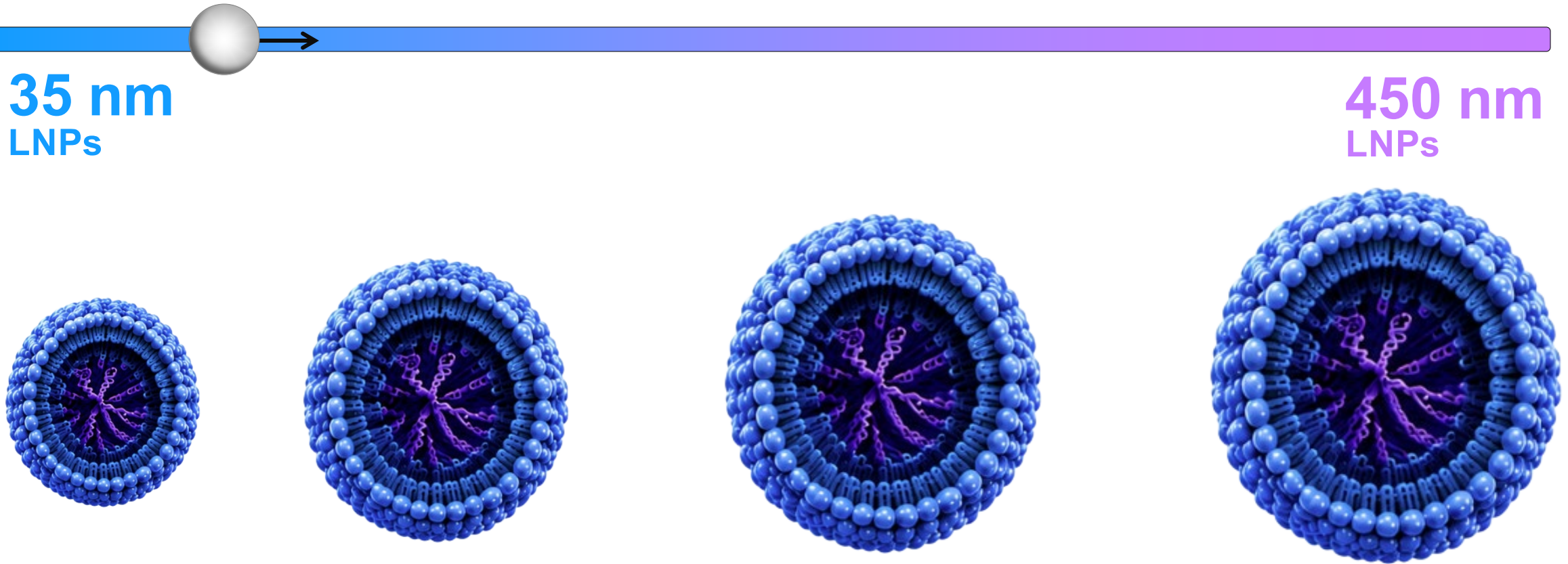


Access the right timescales and intervene in the process

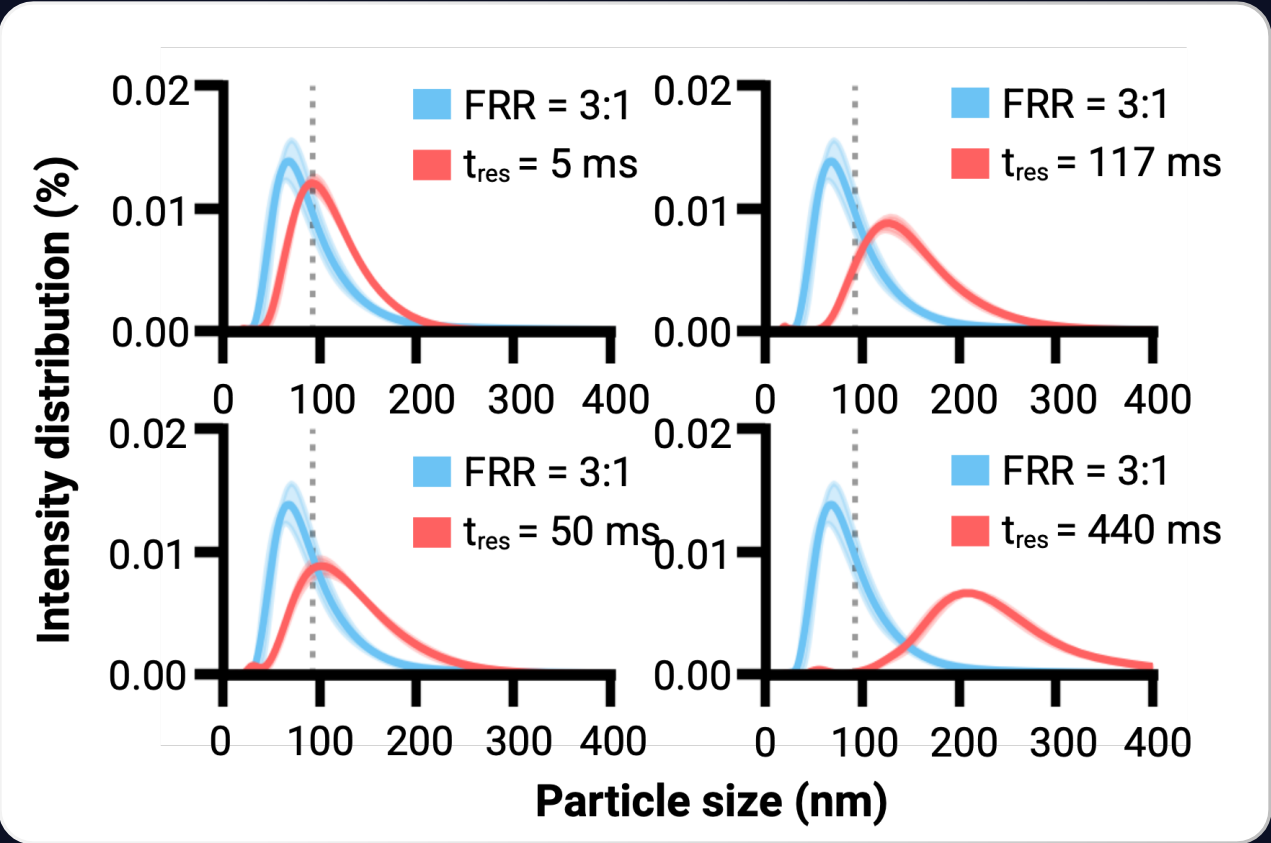


Demonstration of the control: Size tuning

Critical Process Parameter (CPP)



Control the particle size

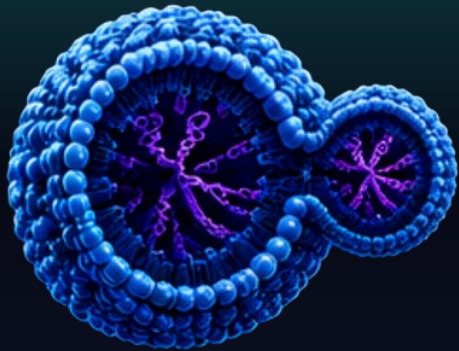
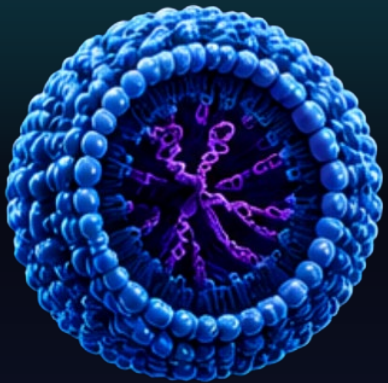
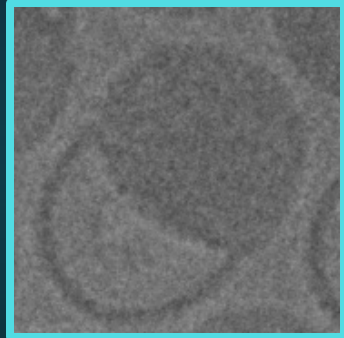
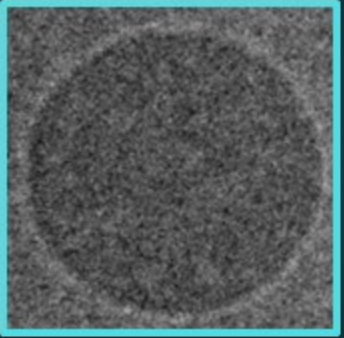


FLuc-mRNA loaded LNPs; ALC-0315:DSPC:Cholesterol:DMG-PEG200 [50:10:38.5:1.5];
N/P ratio: 6); (NaOAc buffer)

		Residence time [ms]			
		5 ms	50 ms	117 ms	440 ms
Buffer concentration [mM]	25 mM	57.1	56.8	64.3	74.5
	50 mM	66.6	72.6	84.6	99.5
	75 mM	82.3	97.3	113.3	158.0
	100 mM	116.2	120.1	149.4	221.2
	300 mM	169.9	175.1	216.5	325.8

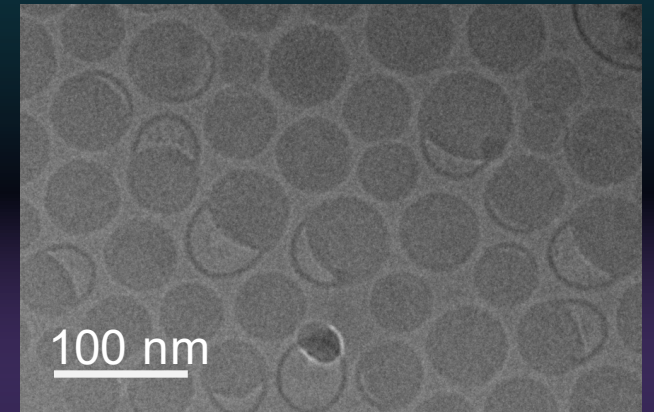
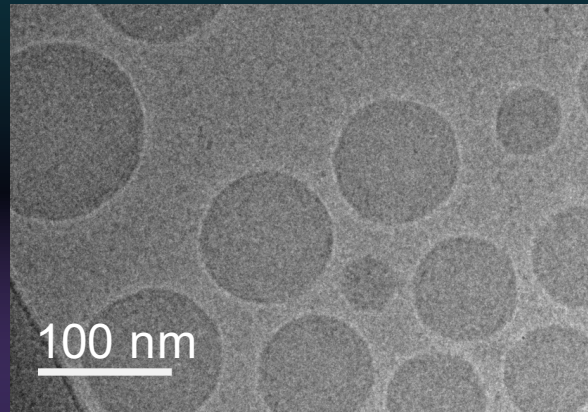
COVID-mRNA loaded LNPs; ALC-0315:DSPC:Cholesterol:DMG-PEG200 [50:10:38.5:1.5];
N/P ratio: 6); (NaOAc buffer)

Size control is necessary, but **not sufficient**.



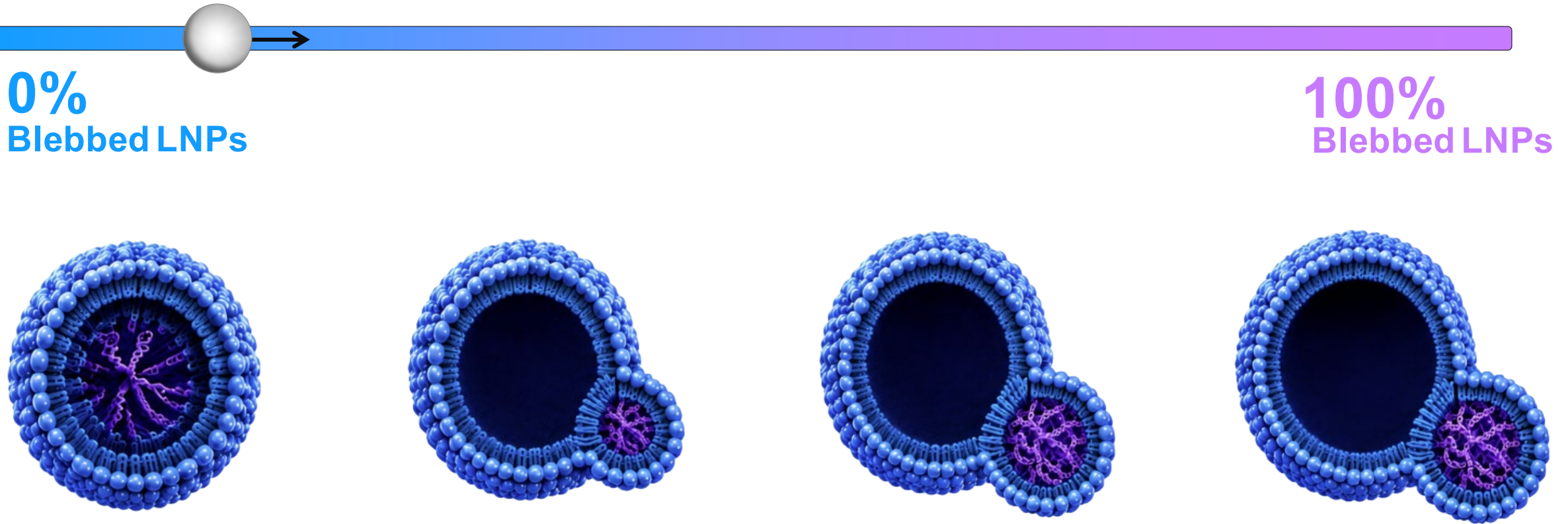
BLEBS

lipid membrane *protrusions* with an aqueous interior that extend outward from the electron-dense core of an LNP

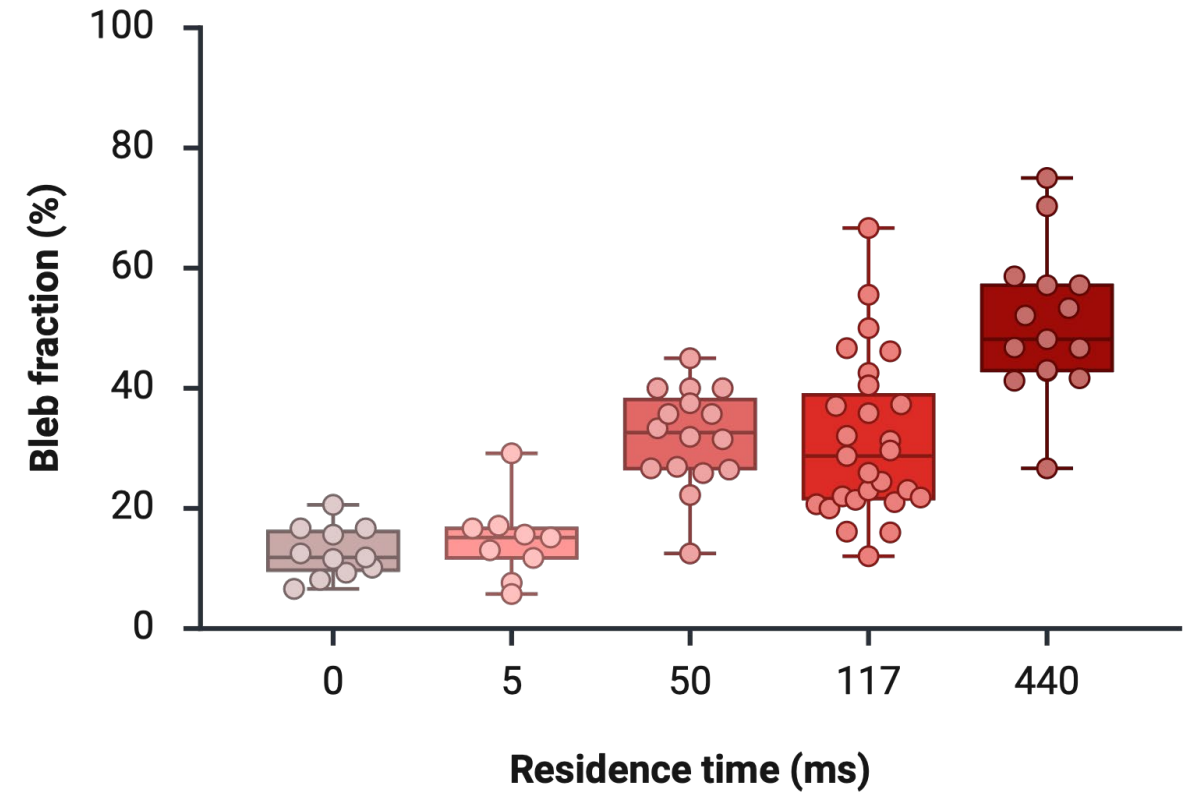
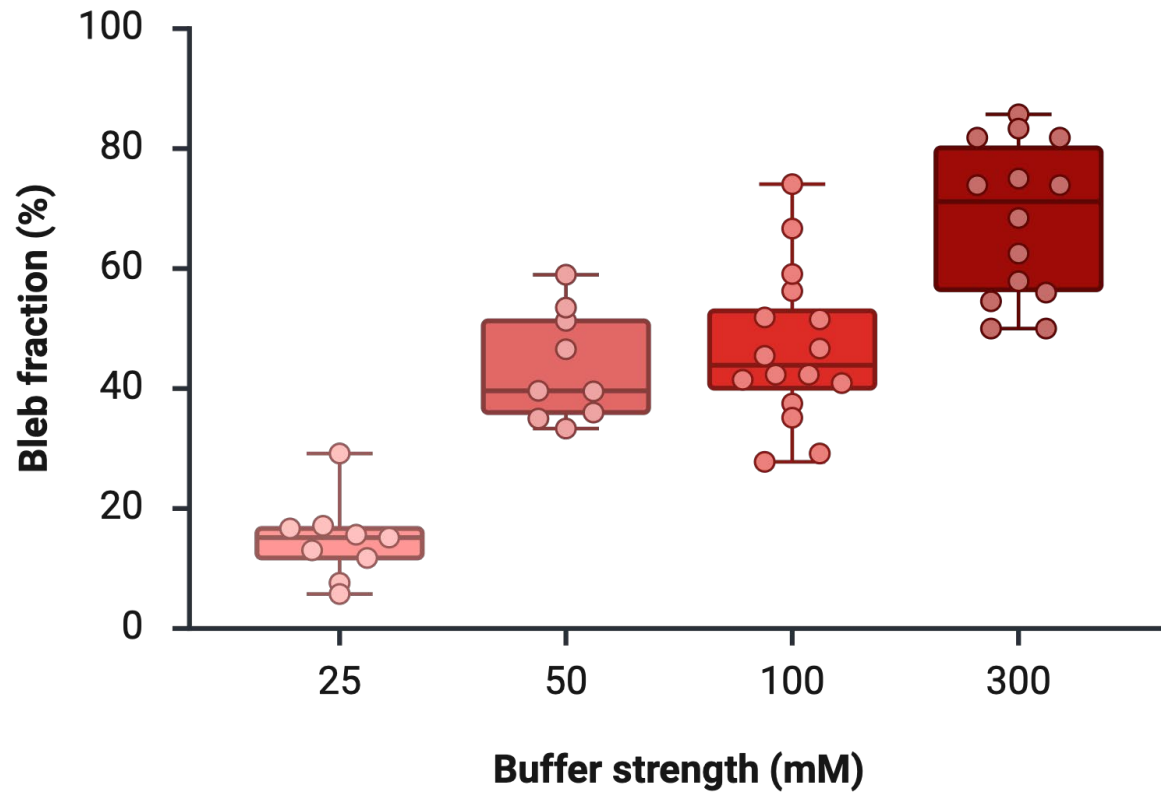


Demonstration of the control: Morphology tuning

Critical Process Parameter (CPP)

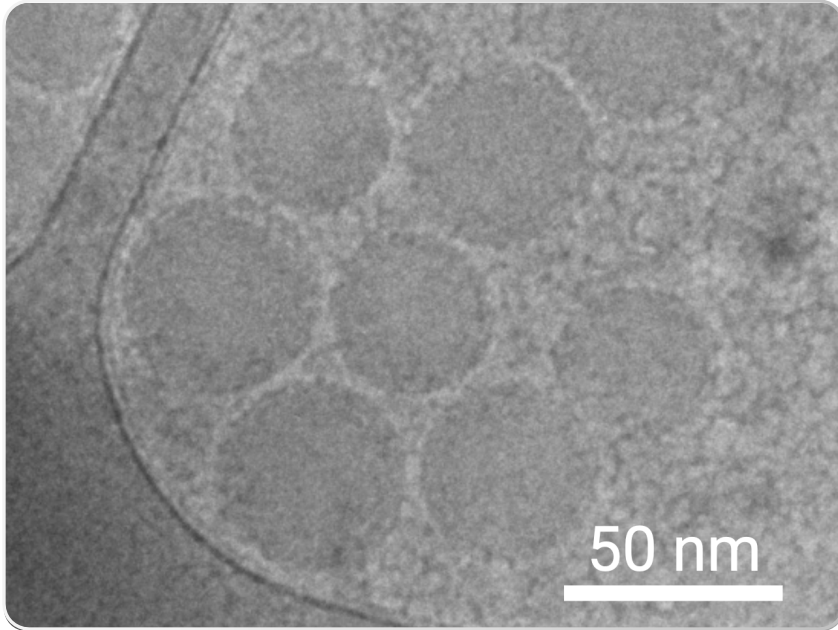


Controlling the fraction of blebbed particles

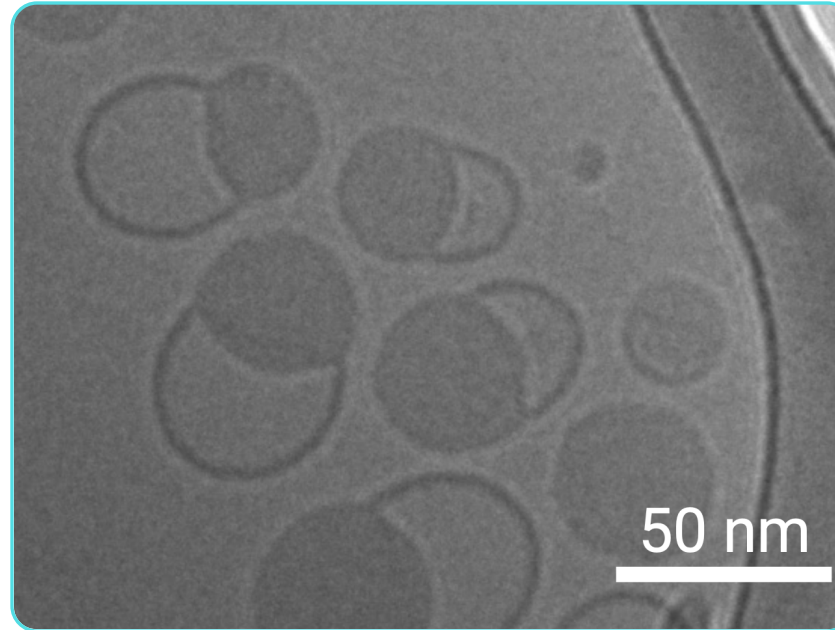


Morphological tuning

CONVENTIONAL

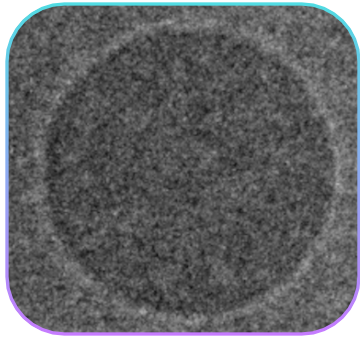


ENGINEERED LNPs

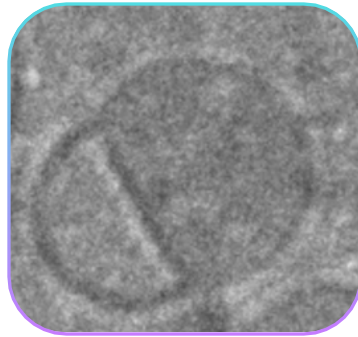


Same chemistry. Different structures. Different impact.

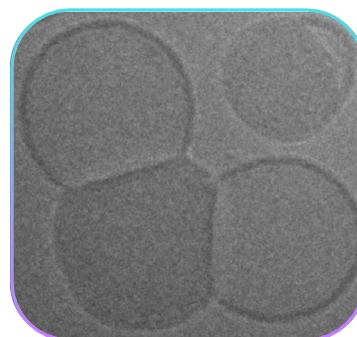
Examples of different LNPs generated.



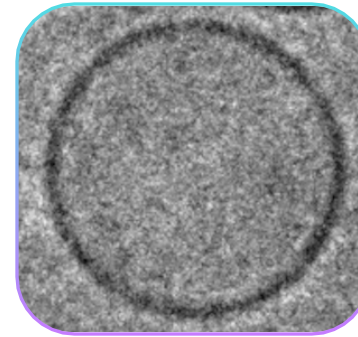
spherical



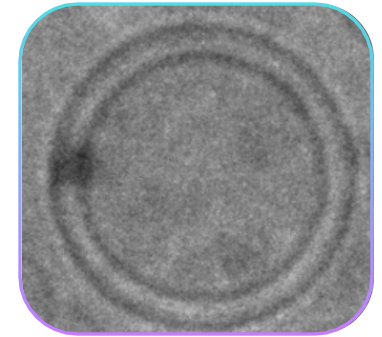
blebbed



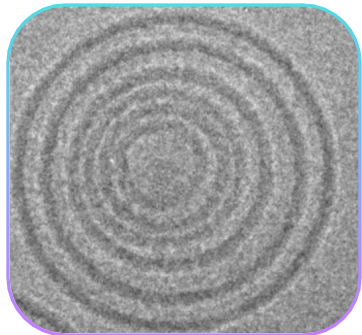
multi-blebbed



vesicular/lipo



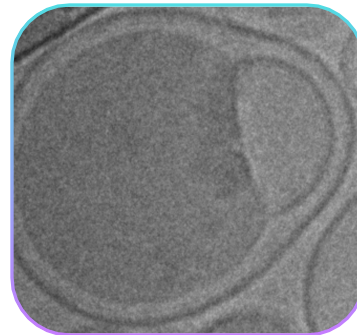
condensed



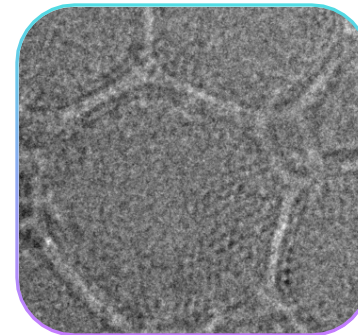
multilamellar



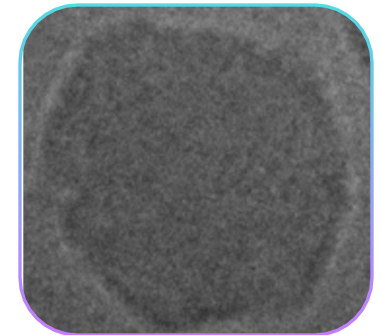
bilayered
bleb



Condensed
bleb



faceted



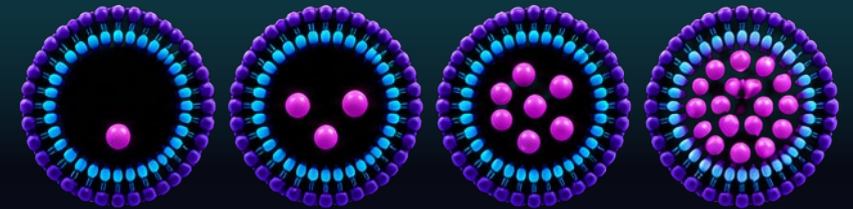
irregular

Payload distribution

CARGO PAYLOAD DISTRIBUTION

Sample	mRNA/LNP no.	% drug-free LNPs
(i)	14.0	25.6
(ii)	10.2	41.7
(iii)	12	32
(iv)	9.9	32.4

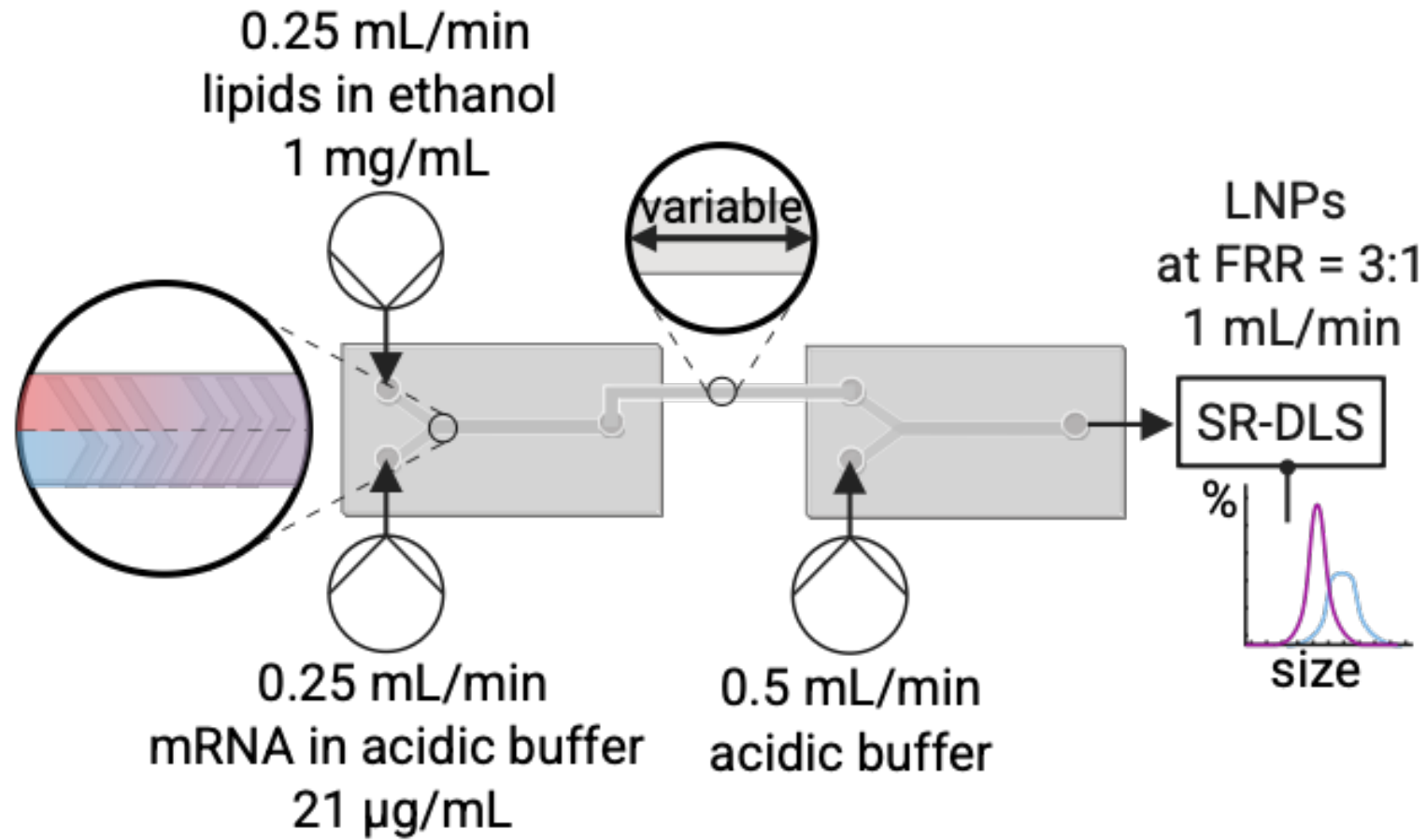
Do blebbed particles have a different payload distribution?



CICs system

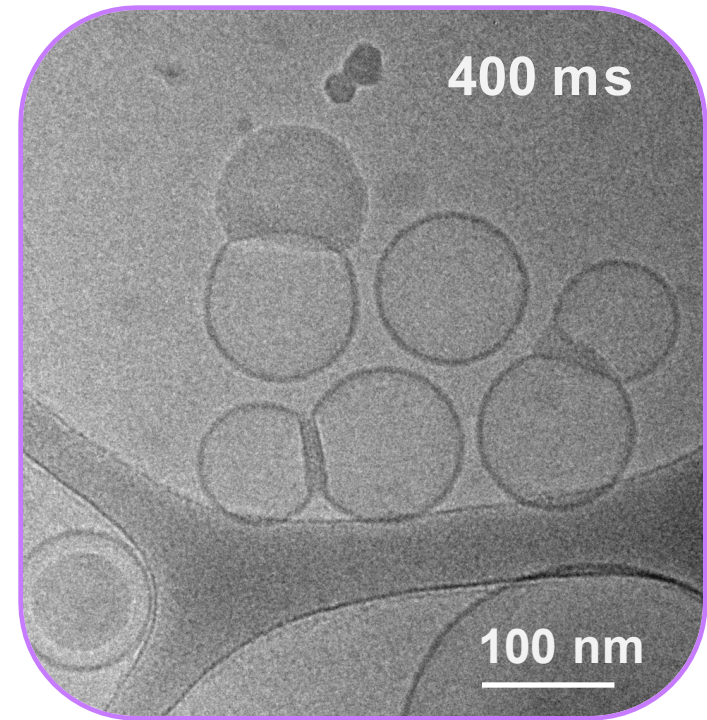
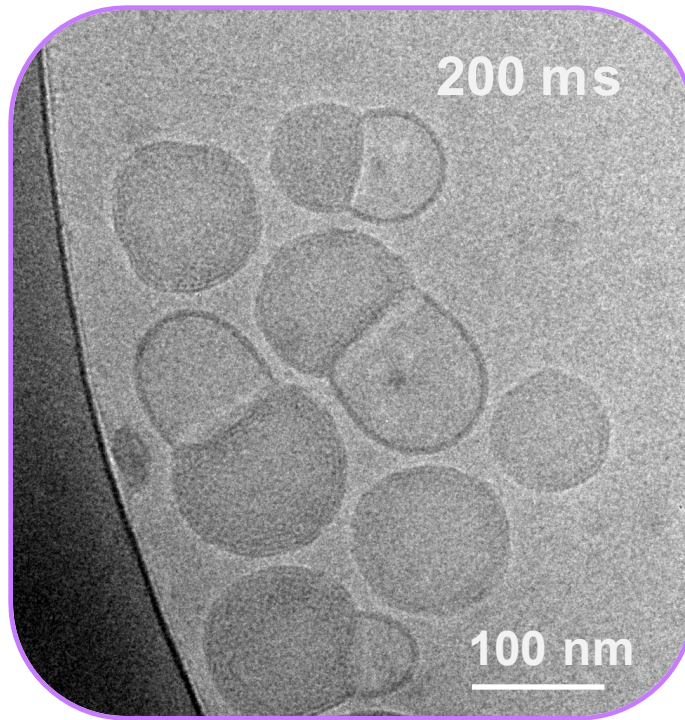
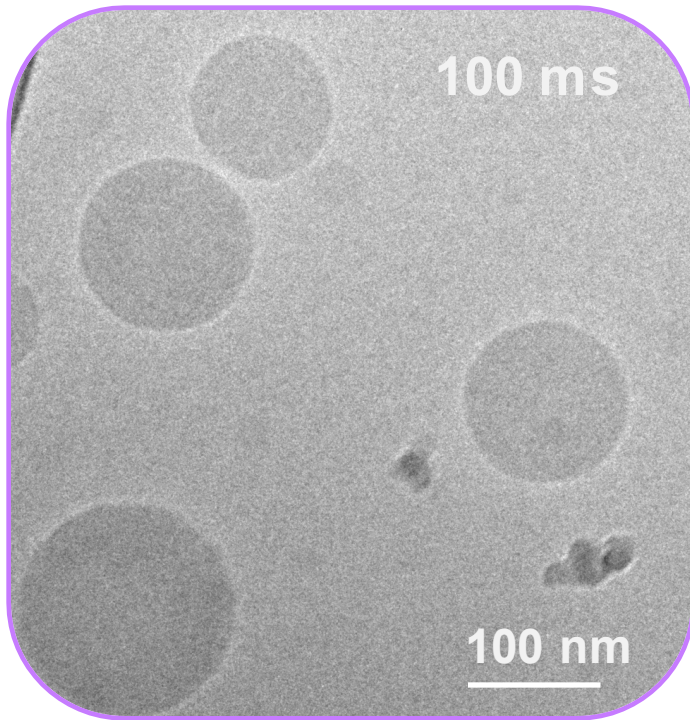
Collaboration with Johns Hopkins Institute (Jeff Wang and Sixuan Li)

Two-stage mixing at low volumetric throughput



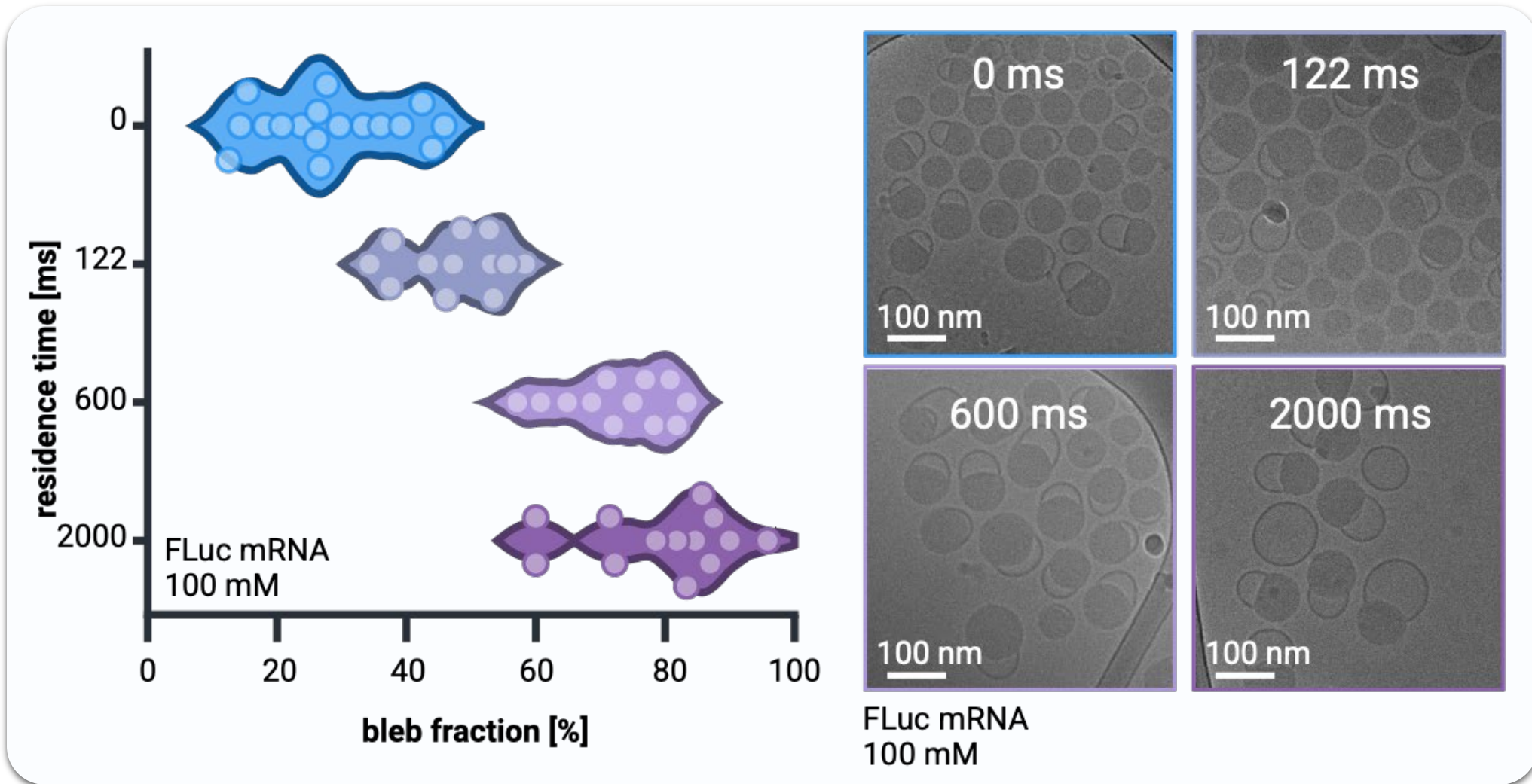
Making **bleb-like** particles in **microfluidics**

EXAMPLE:



ALC-0315:DSPC:cholesterol:DMG-PEG2000 (50:10:38.5:1.5)
HBM-HBM, two-step method w/ varying residence time

Making **bleb-like** particles in **microfluidics**



Fluc-loaded LNPs; ALC-0315:DSPC:Cholesterol:DMG-PEG200 [50:10:38.5:1.5]; (N/P ratio: 6); (NaOAc buffer)

Scaling from microfluidics to jet-based mixers

GOAL: INCREASE VOLUMETRIC THROUGHPUT

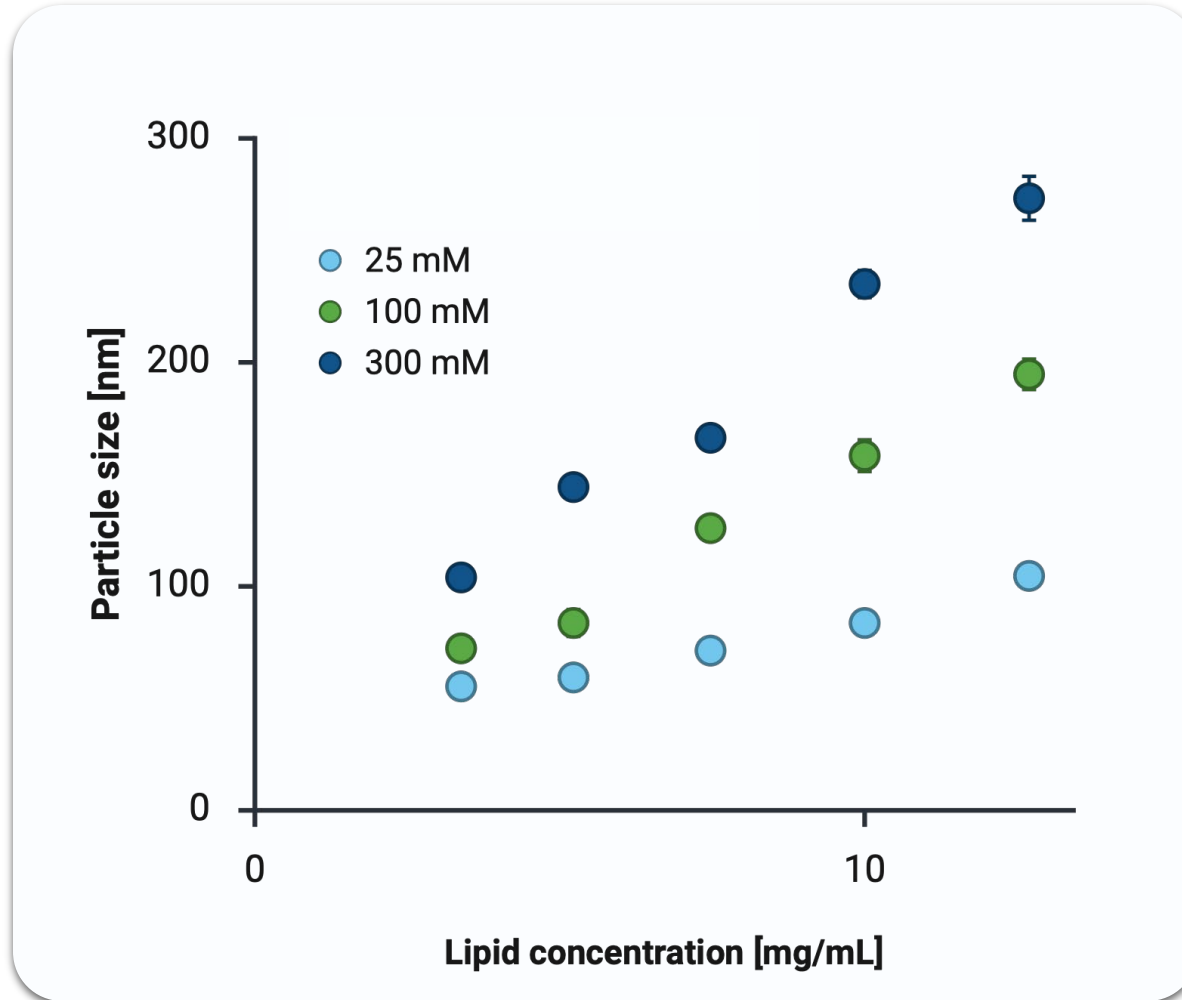
APPROACH: (a) increase concentration, (b) increase flow rates – change mixer to accommodate this

Understand how CPPs evolve through the construction of a **phenomenological scaling map**.

$$\frac{d_p}{d_{\text{ref}}} = F(\text{Da}_{\text{grow}}) + G(B^*) \frac{C_L}{C_{\text{ref}}}$$

d_p = particle at conc. C_L , d_{ref} = particle at conc. reference, $\text{Da}_{\text{grow}} = \frac{\tau_{\text{grow}}}{\tau_{\text{residence time}}}$, B^* = buffer conditions

Demonstration of CQA vs. CPP relationships: Cargo Buffer

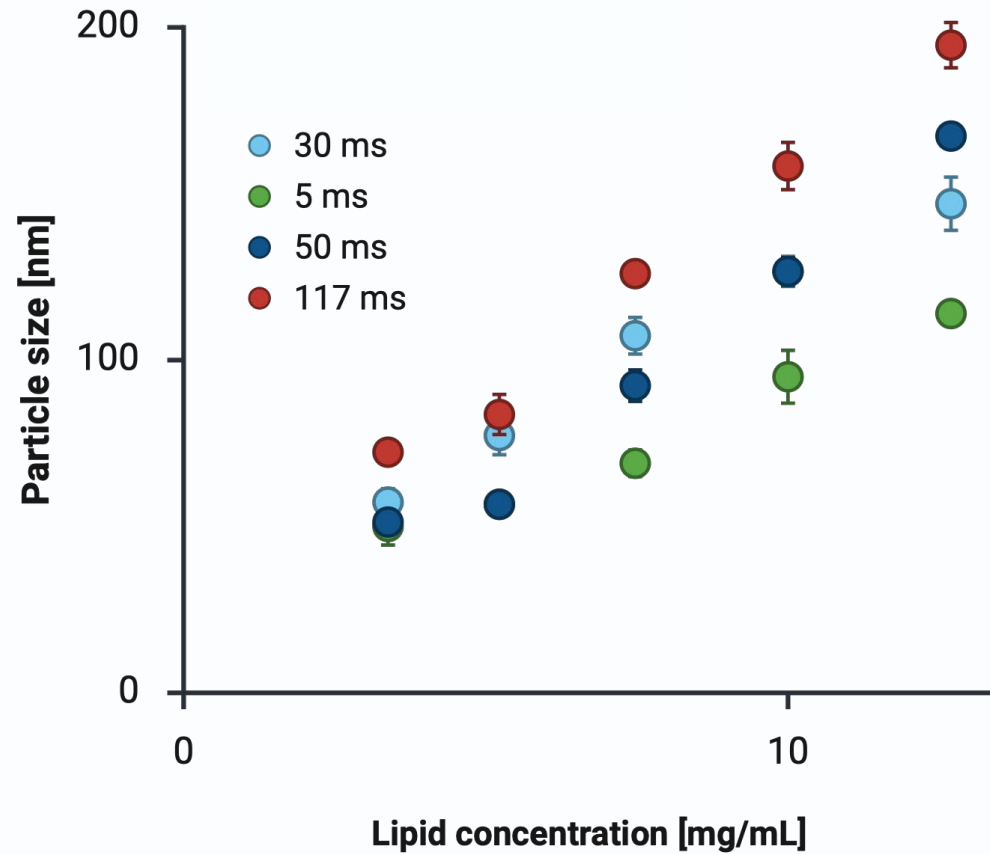


Curves constructed for

- Buffer concentration
- Buffer type
- Buffer pH

ALC0315:DSPC:cholesterol:DMG-PEG2000 (50:10:38.5:1.5)
HBM-HBM, two-step method w/varying residence time

Demonstration of CQA vs. CPP relationships: Residence Time



Curves constructed for

- Different mixers geometries
- Different mixing intensities (flow rate)

ALC0315:DSPC:cholesterol:DMG-PEG2000 (50:10:38.5:1.5)
HBM-HBM, two-step method w/varying residence time

Preserving quality attributes **across scales**

$$\frac{d_p}{d_{\text{ref}}} = F(Da_{\text{grow}}) + G(B^*) \frac{C_L}{C_{\text{ref}}}$$

* the real equation is more complex

Microfluidic Platform

Throughput

10 µg/min

Size

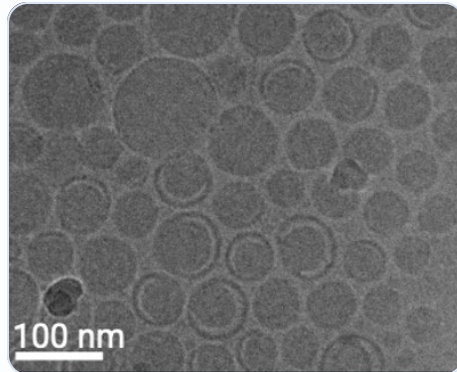
77 nm

PDI

0.13

Blebs

41%



Impinging Jet Platform

Throughput

1000 µg/min

Size

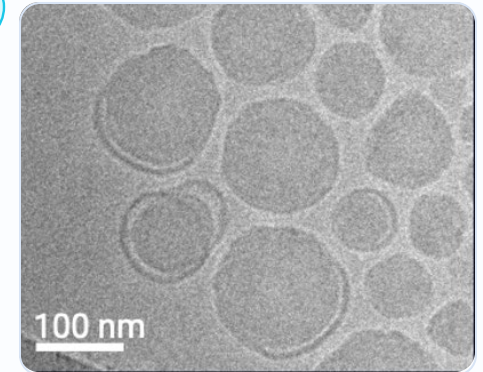
78 nm

PDI

0.14

Blebs

35%



Yeast-loaded LNPs; ALC-0315:DSPC:Cholesterol:DMG-PEG200 [50:10:38.5:1.5]; (N/P ratio: 6); (NaOAc buffer)

Automated LNP Platform for Rapid Process Dev.



Faster
development



Increased
reproducibility



Complex space
exploration



Minimal operator
burden

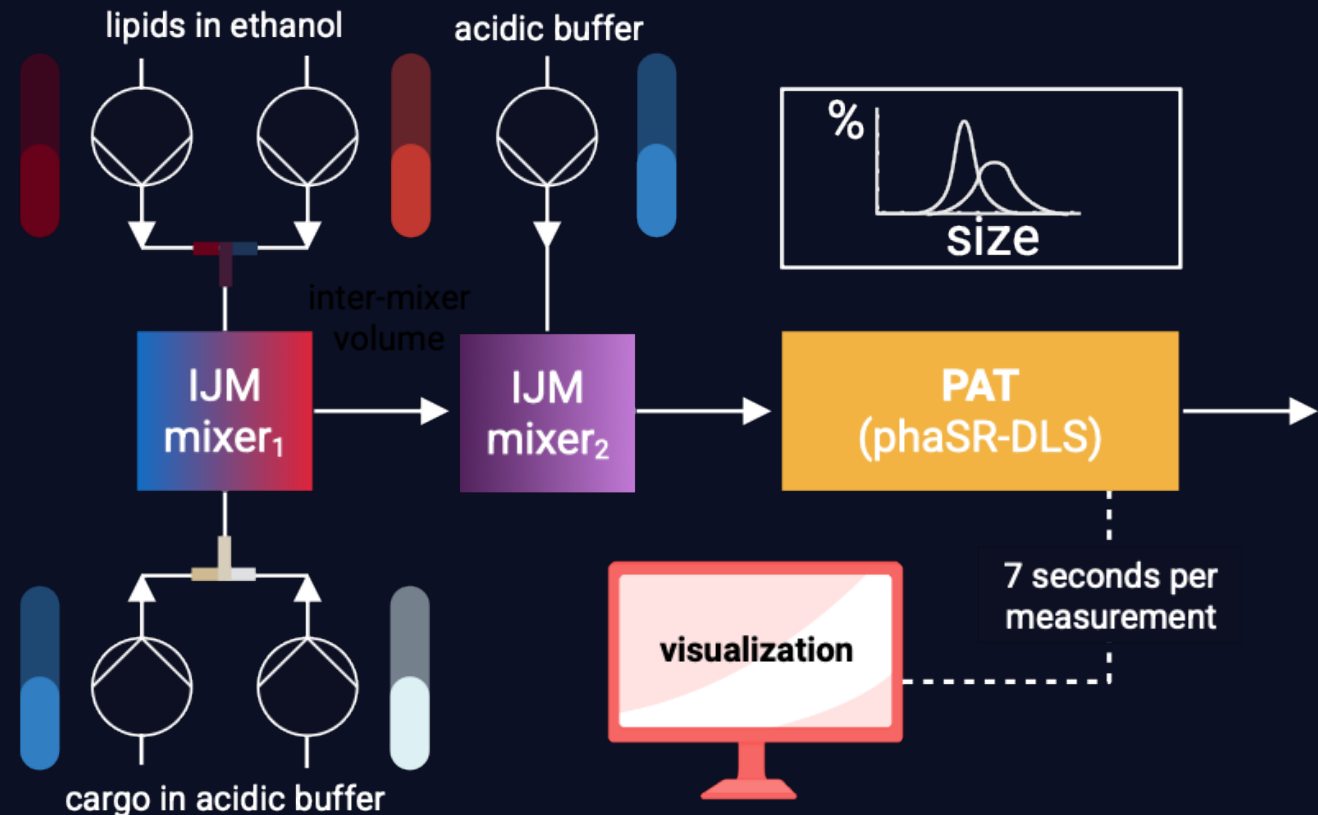
CAPABILITIES

- Automated DoE
- Time-dynamic sweeps
- Self-optimization

Analytics

- PAT: phaSR-DLS
- Encapsulation Efficiency: offline
- CryoTEM: offline

PLATFORM HARDWARE



Automated LNP Platform for Rapid Process Dev.



Faster
development



Increased
reproducibility



Complex space
exploration



Minimal operator
burden

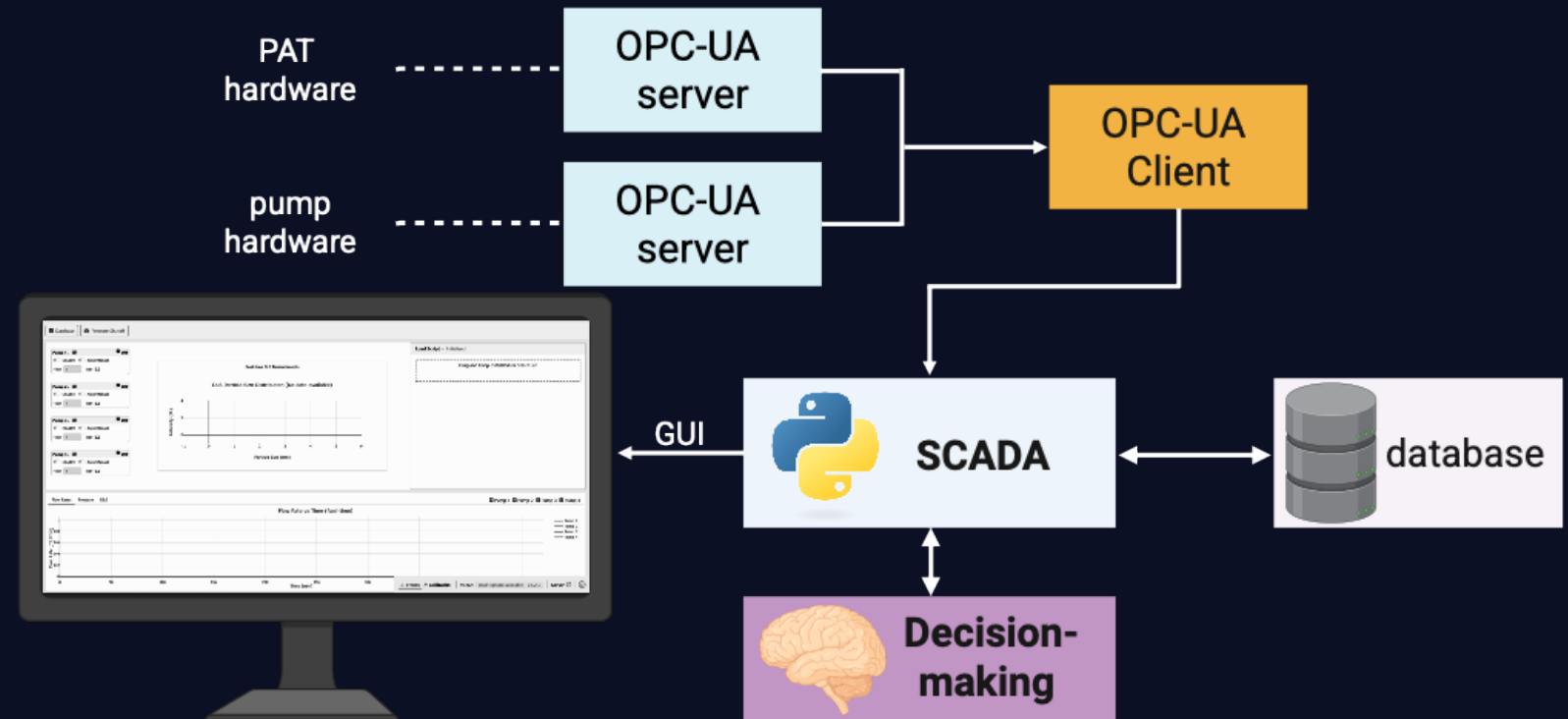
CAPABILITIES

- Automated DoE
- Time-dynamic sweeps
- Self-optimization

Methodology from

Florit et al., *Reaction Chemistry & Engineering*, 10, 656, 2025.

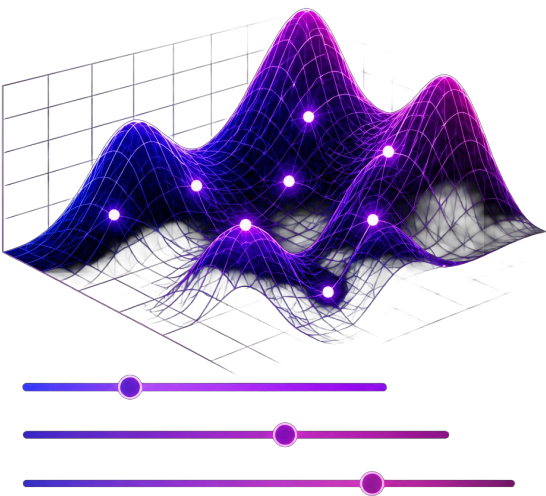
PLATFORM SOFTWARE



CASE STUDY 3: AUTOMATED ADAPTIVE OPTIMIZATION

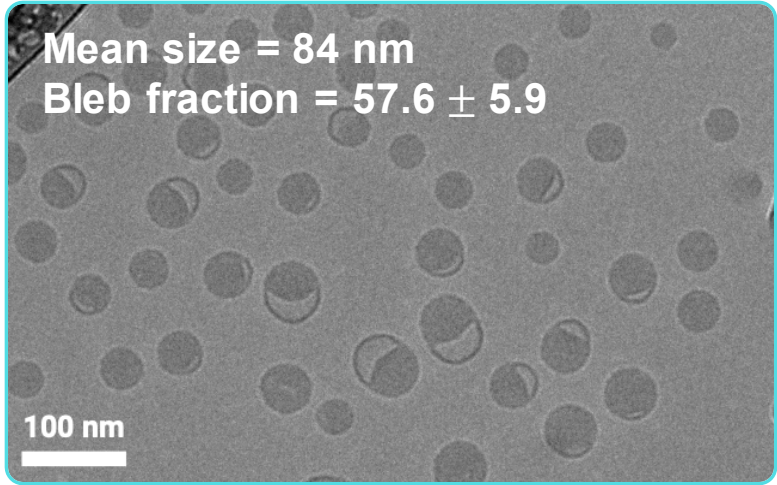
OBJECTIVE

size = 85 nm

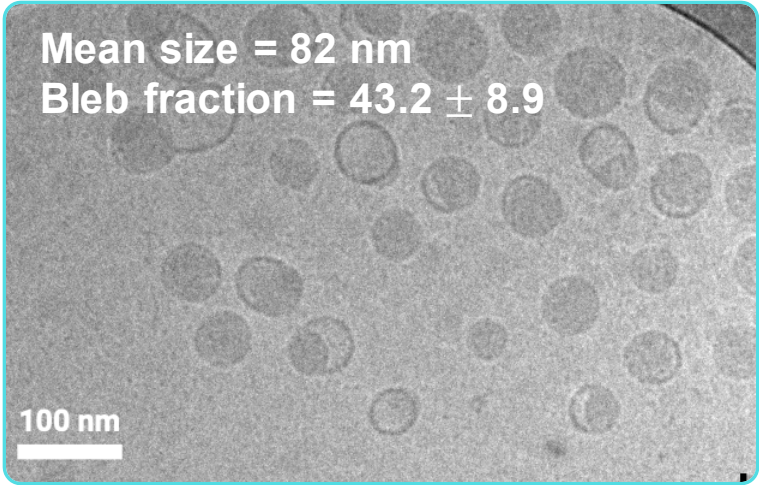


RESULTS

2 conditions | 35 minutes | <1 g of lipids used



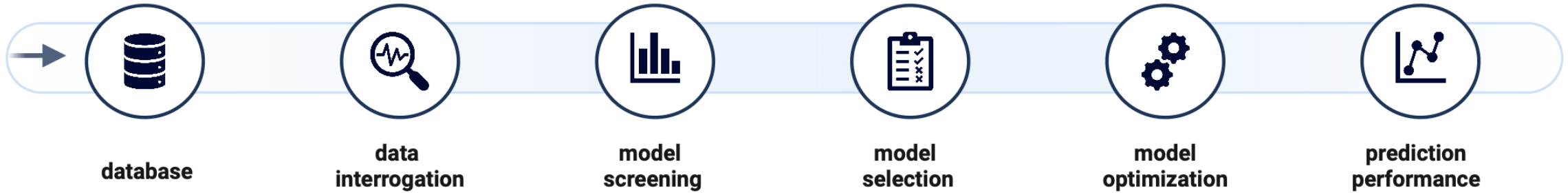
- 20 mL/min TFR
- 4.5 pH
- 75 mM Buffer conc.
- 234 ms Residence time
- Other



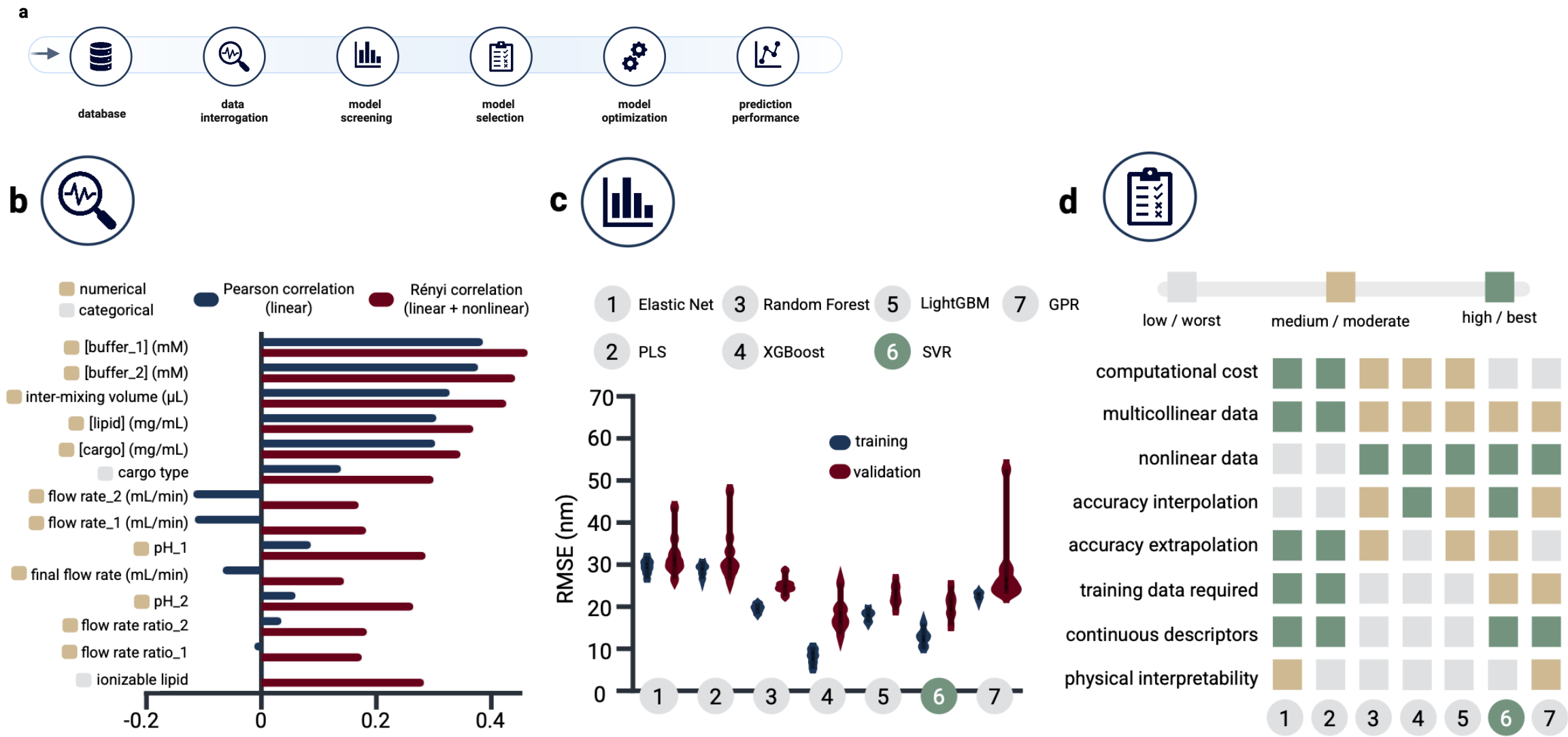
- 40 mL/min TFR
- 4.5 pH
- 99 mM Buffer conc.
- 117 ms Residence time
- Other

Machine Learning-based Modeling

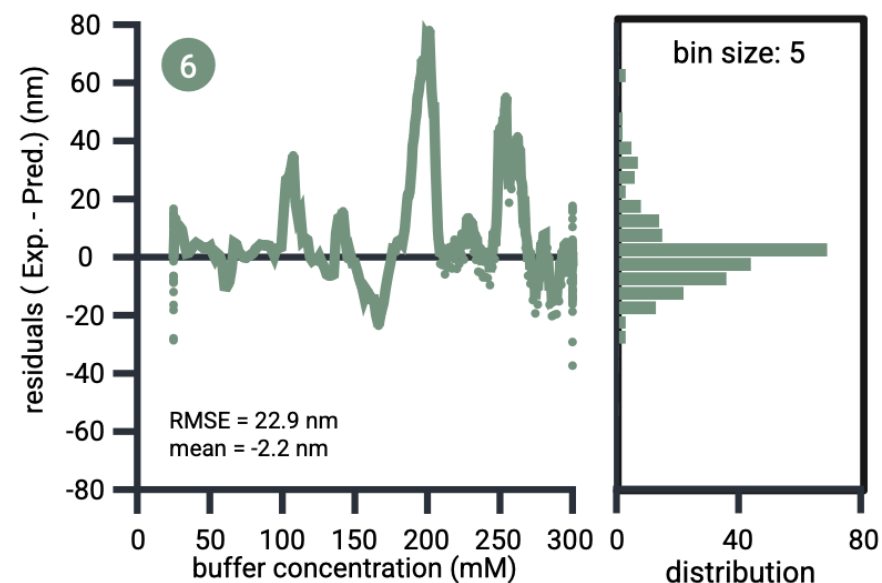
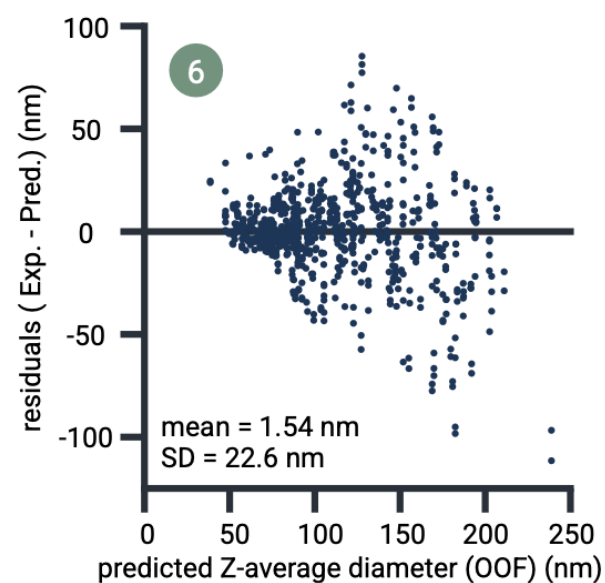
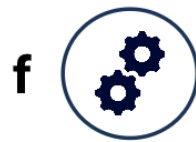
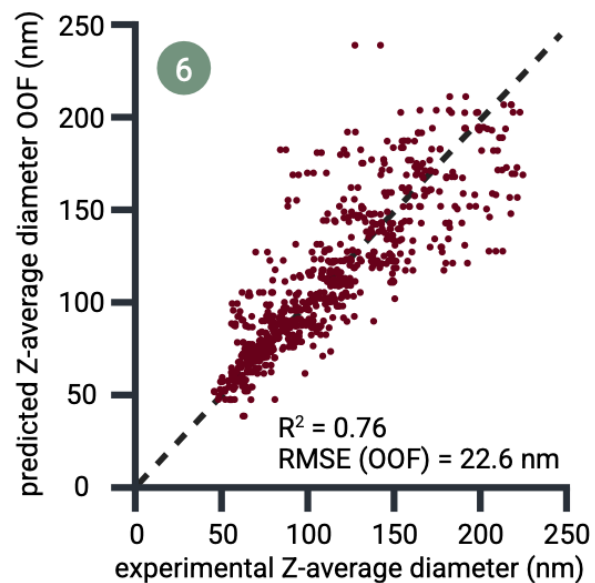
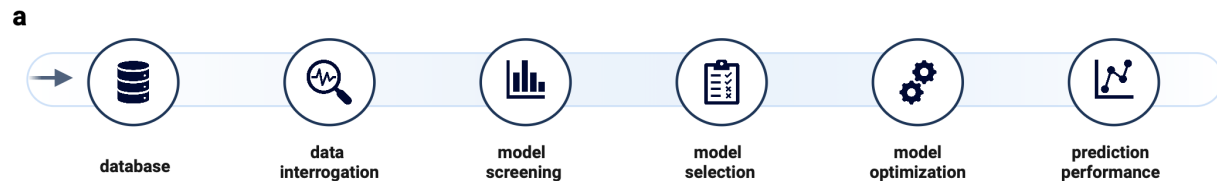
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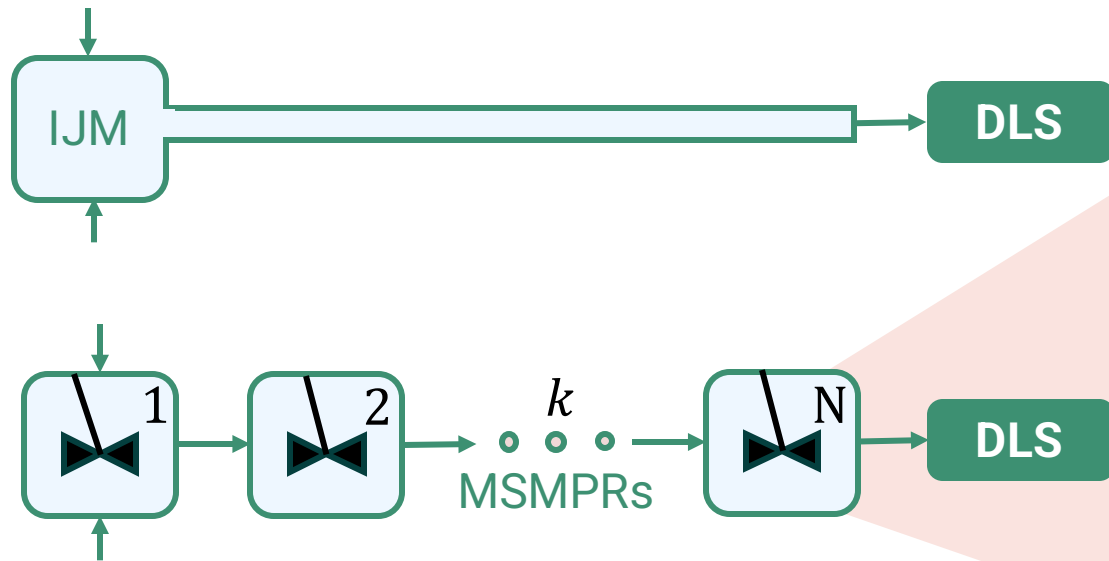
Machine Learning-based Modeling



Machine Learning-based Modeling



Spatially varying population balance models

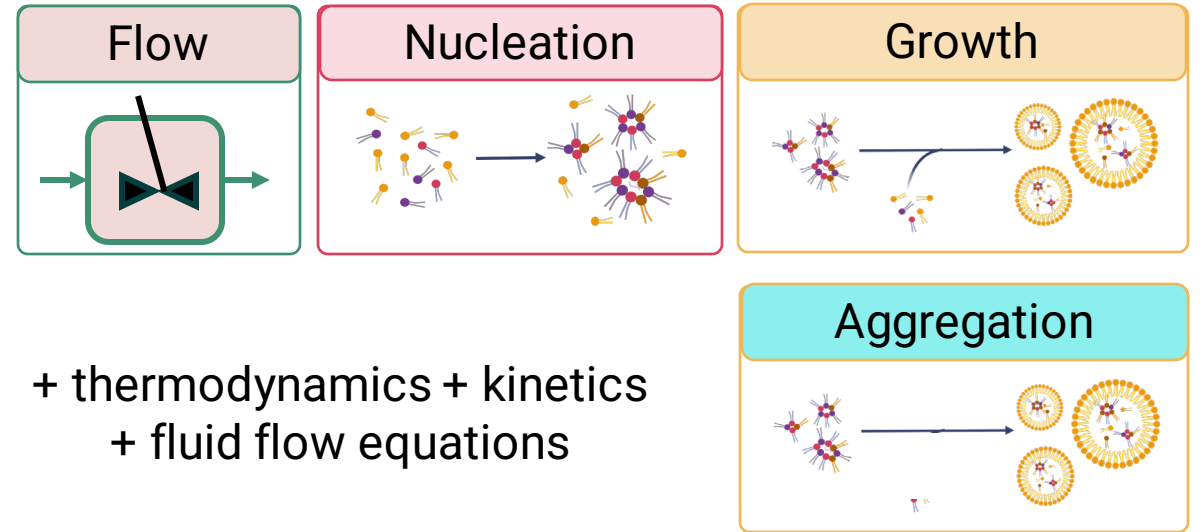


MSMPR = Mixed-Suspension, Mixed-Product-Removal

n_k = number density (#/m⁴) in the k th MSMPR

Each MSMPR is governed by a PBM

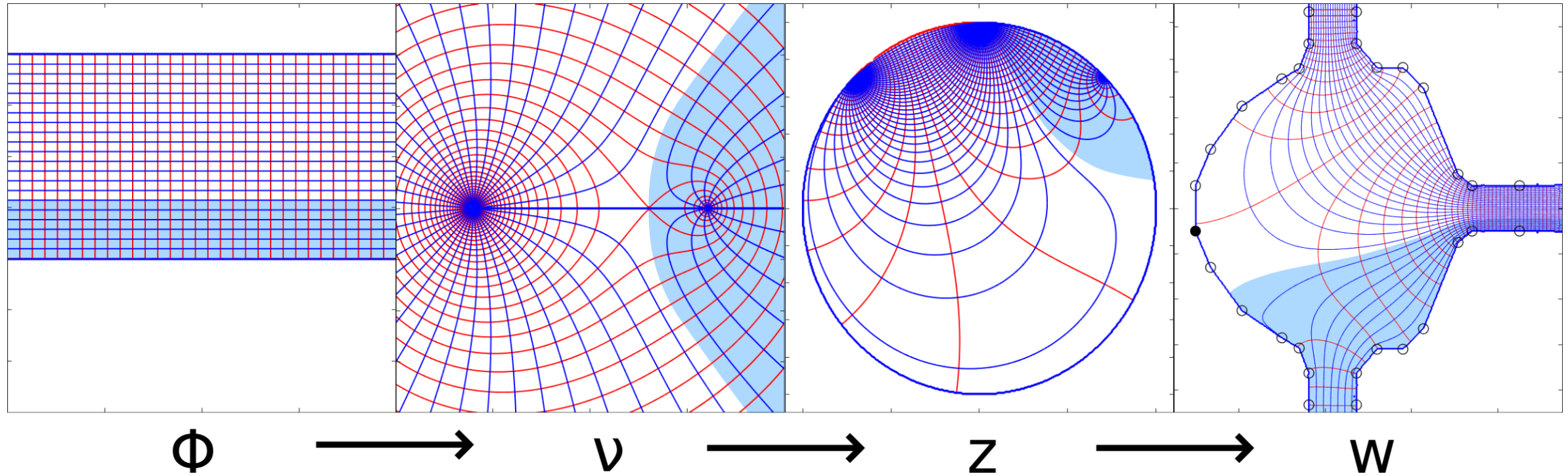
$$\frac{\partial n_k}{\partial t} = \frac{n_{k-1} - n_k}{\tau} + BG(l - l_c) - \frac{\partial(Gn_k)}{\partial l} + \text{agg.}$$



See references for more details

1. PK Inguva et al., Mechanistic modeling of lipid nanoparticle formation for the delivery of nucleic acid therapeutics," Biotechnology Advances, 84, 108643, 2025.
2. S Shin et al., "Mechanistic Modeling of Lipid Nanoparticle (LNP) Precipitation via Population Balance Equations (PBEs)," ChE J, 523, 167786, 2025.
3. S Mukherjee et al., "Understanding Size Distributions during Lipid Nanoparticle Manufacturing through Mechanistic Modeling," ACS Omega 11 (18), 26901, 2026.

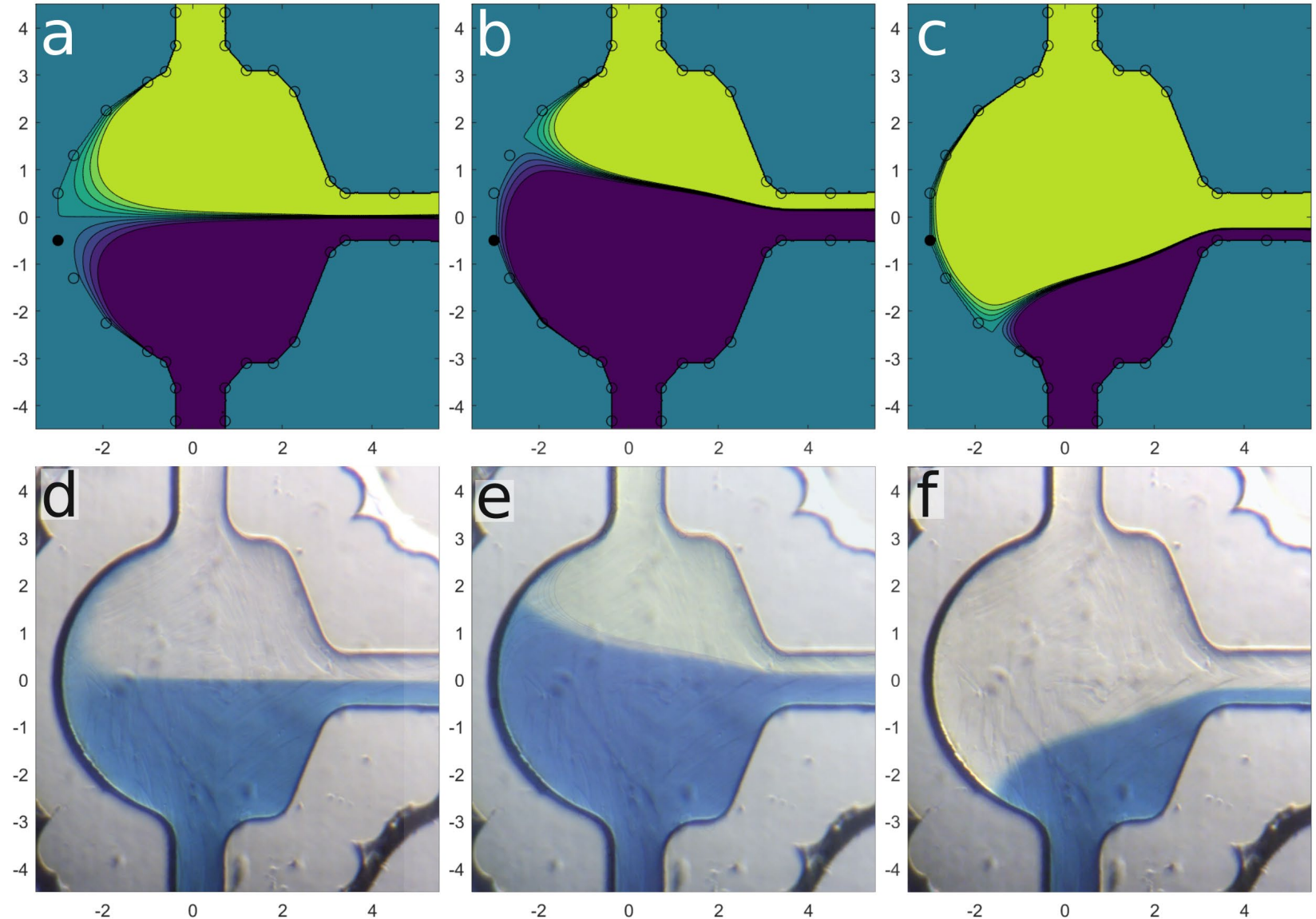
Analytical solutions of the fluid flow equations for micromixers of arbitrary geometries



- We find a sequence of maps that transform the flow and diffusion problem from the complex mixer geometry to a simple domain where the solution is already known analytically

Analytical solutions of the fluid flow equations for micromixers of arbitrary geometries

Comparison of analytical concentration profiles (top), and experimental tracer tests in a microfluidic mixer (bottom)



We are integrating PBMs into the analytical solutions of the fluid flow equations

See upcoming papers for more details

E. Boulais et al., *J Fluid Mechanics*, 1024, A36, 2025.

LNP PUBLICATIONS

- C. Devos, S. Mukherjee, P. Inguva, ..., R.D. Braatz, A.S. Myerson. *AIChE Journal* e18595 (2024).
- A. Udepurkar, C. Devos, P. Sagmeister, ..., R.D. Braatz, A.S. Myerson. *ACS Nano* 19, 21206–21242 (2025).
- S. Shin, C. Devos, A. Udepurkar, ..., A.S. Myerson, R.D. Braatz, *Chem Eng J* 523, 167786 (2025).
- P. Inguva, S. Mukherjee, ..., C. Devos, ..., A.S. Myerson, R.D. Braatz, *Biotechnol. Adv.*, 108643 (2025).
- C. Devos, A. Udepurkar, P. Sagmeister, ..., R. D. Braatz, A.S. Myerson, *ACS Nano* 19, 33991-34002 (2025).
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- S. Mukherjee, S. Shin, C. Devos, ..., A.S. Myerson, R.D. Braatz, *ACS Omega*, 11 (18), 26901 (2026).
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