FluidicLab®

LNP Production with microfluidics

2022.01.20

上海澎赞生物科技有限公司
Prinzen Biomedical Inc.

Outline

Backgroun
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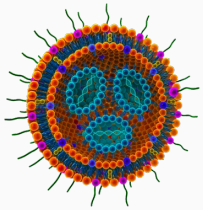
Solutions

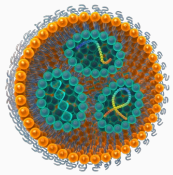
Case Study

Background

Background



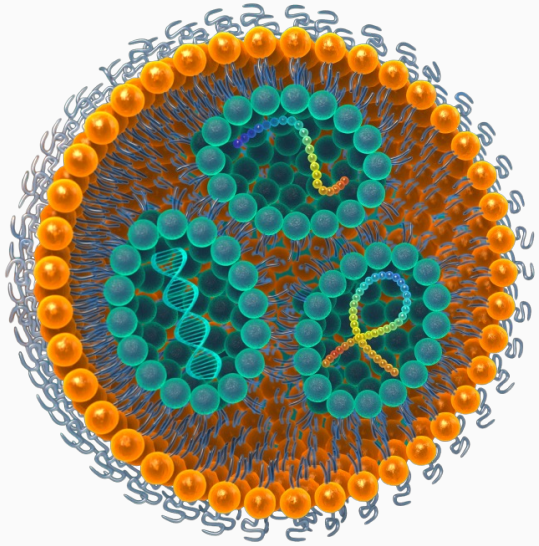
Liposome



Lipid Nanoparticle

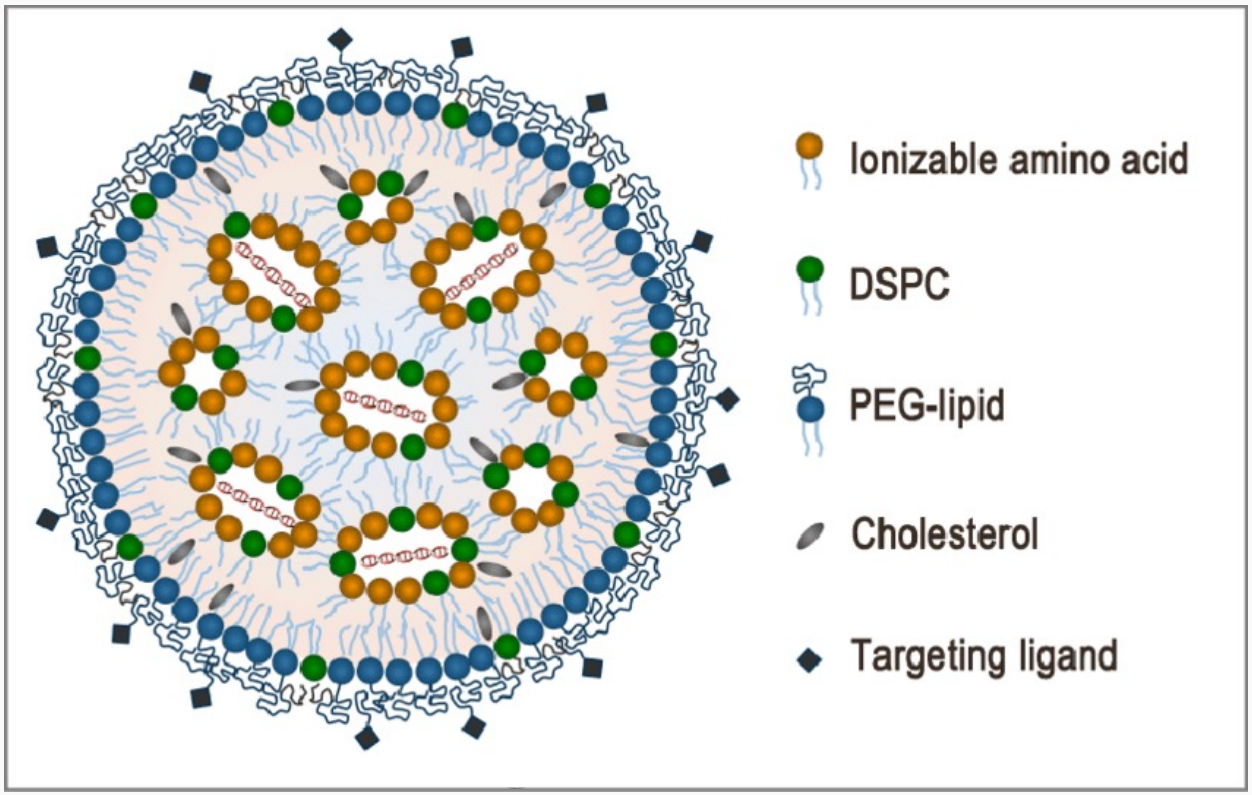
Background

Lipid Nanoparticles for the Delivery of mRNA/siRNA



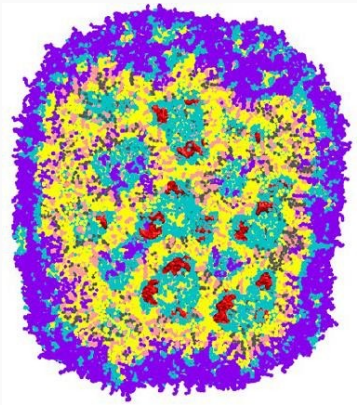
- Package RNA into nanoparticle core
- Protect RNA from degradation
- Facilitate RNA uptake into cells
- Promote RNA release into the cytoplasm

Background

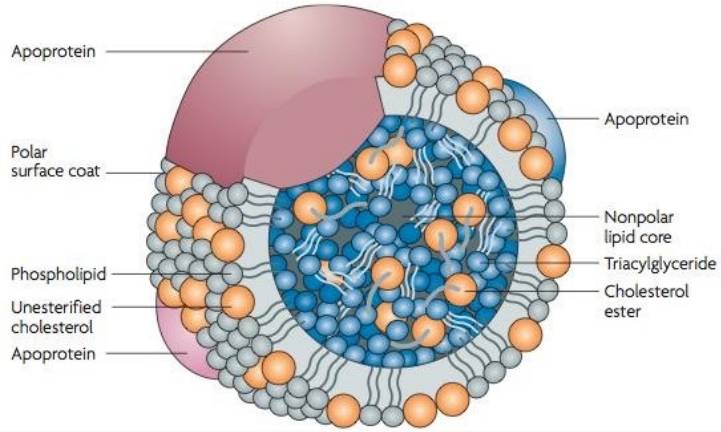


Composition of RNA-Lipid Nanoparticles

Background



Neutral, Solid-Core RNA-Lipid Nanoparticles

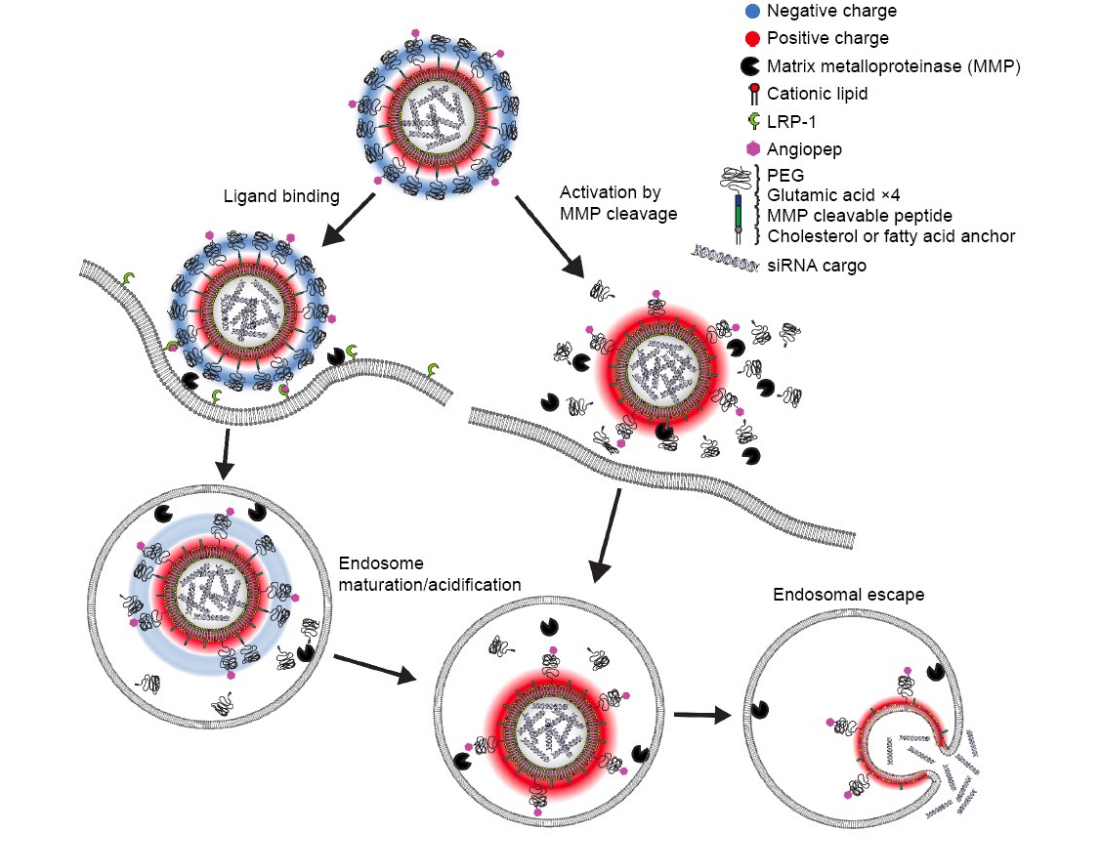


Low Density Lipoprotein (LDL):
Endogenous Lipid Nanoparticles

Neutral RNA - Lipid Nanoparticles Mimic Endogenous Delivery Systems

Wasan K. M . et al. (2008) Impact of Lipoproteins on the Biological Activity & Disposition of Hydrophobic Drugs: Implications for Drug Discovery. *Nat. Rev. Drug Disc. 7: 84- 99*

Background



Ionizable Cationic Lipids Mediate Maximum Endosomal Escape

Background

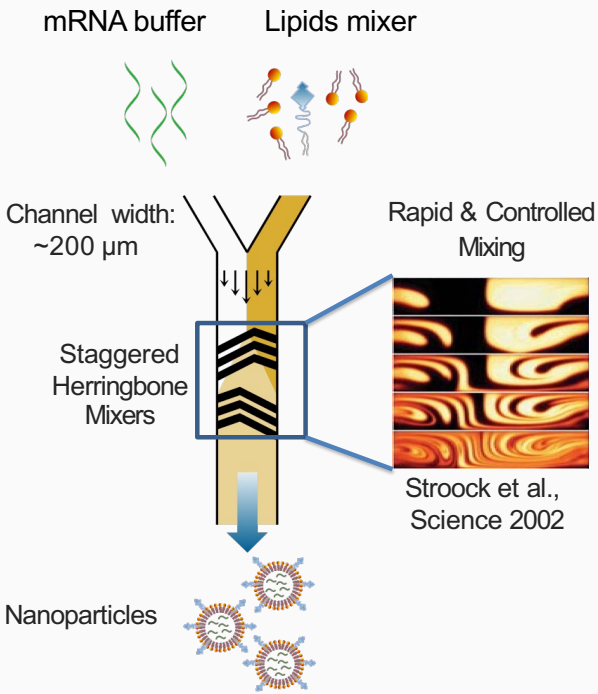
- Ease of use
- Size
- Encapsulation efficiency
- Speed
- Reproducibility
- Seamless Scale-Up

Advantage of Microfluidics in Novel RNA-Nanoparticles

Solutions

Solutions

Microfluidic chaotic mixers

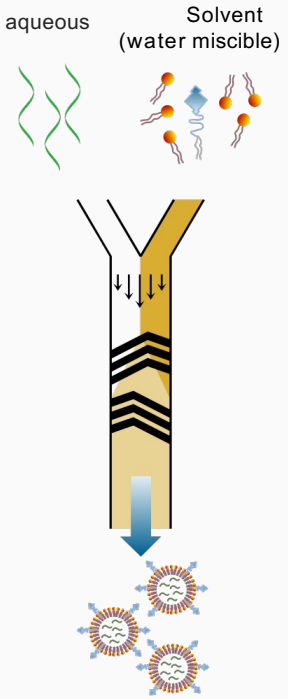


- Chiotic mixing
- Rapid mixing (< 3 ms^{-1})
- Reproducible

SHG microfluidic mixer for LNP production

Solutions

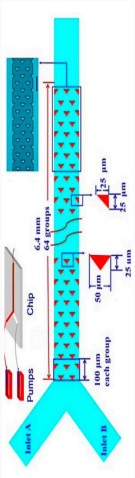
Microfluidic chaotic mixers



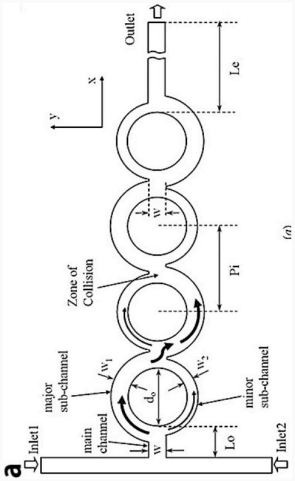
- FRR: aqueous:ethanol flow rates ration (mL/min) . Higer FRR results in small LNP size and more uniform LNP
- TFR: Higher aqueous:ethanol flow rate ratios result in smaller LNP

Process parameters dictate nanoparticle biophysical characteristics

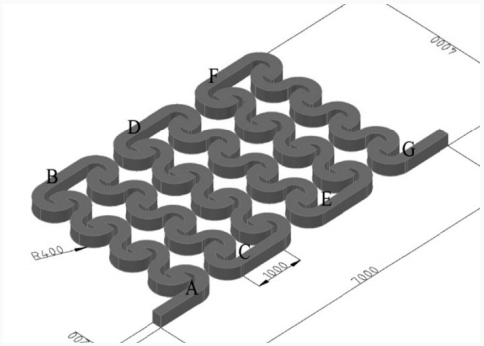
2D Microfluidic chaotic mixers



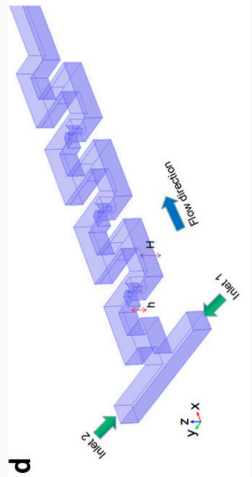
Obstacle Based



Unbalanced Collision

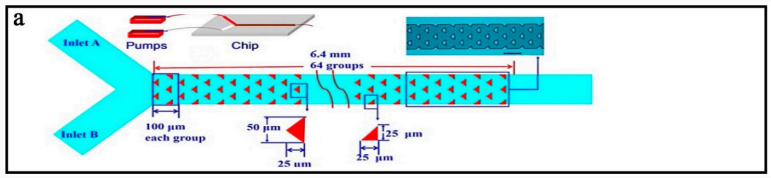


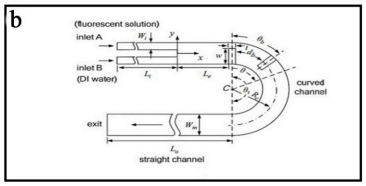
Spiral

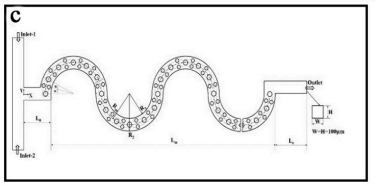


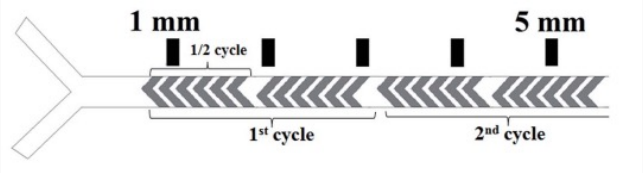
Convergence–Divergence

Obstacle based mixers







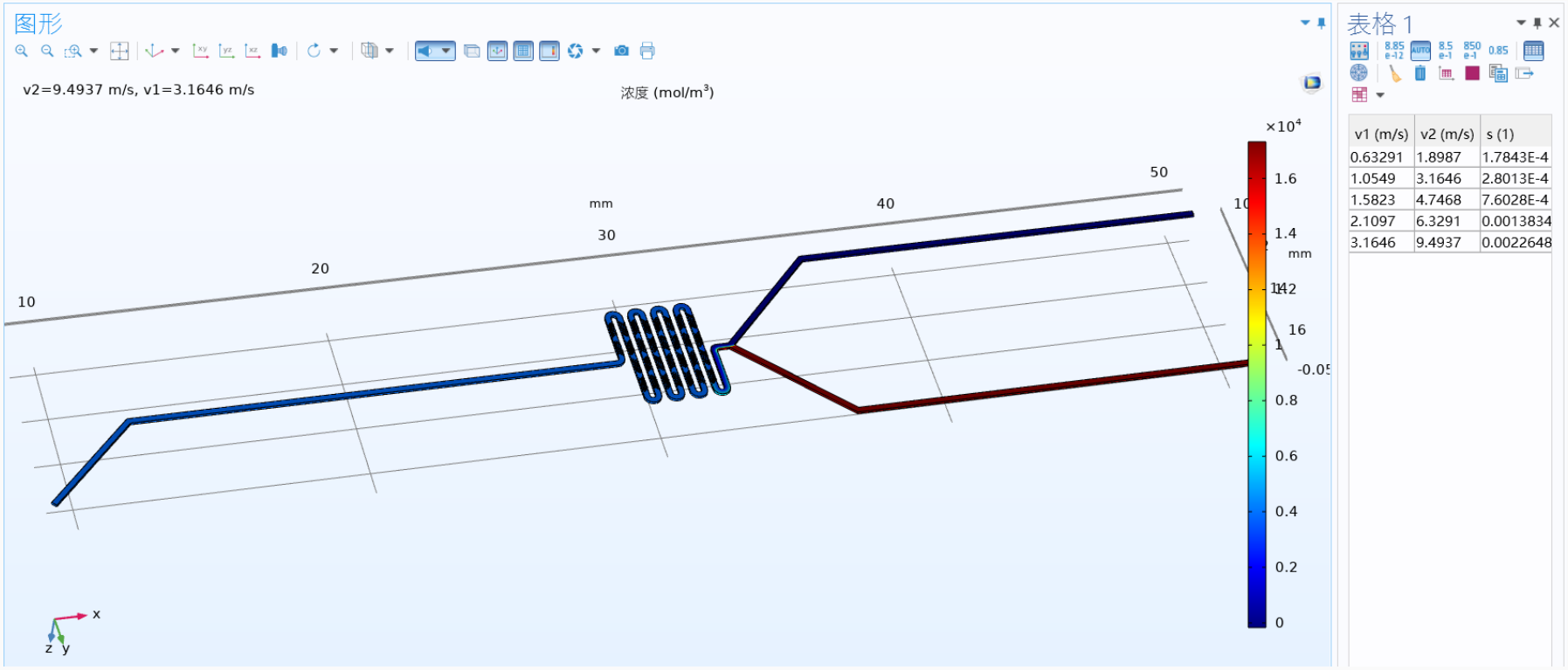


	mixing time	particle size	efficiency
SHG	5-10ms		91.7%

Source：Shakhawat Hossain; Mubashshir A. Ansari; Afzal Husain; Kwang-Yong Kim (2010). Analysis and optimization of a micromixer with a modified Tesla structure. , 158(2), 305–314. doi:10.1016/j.cej.2010.02.002

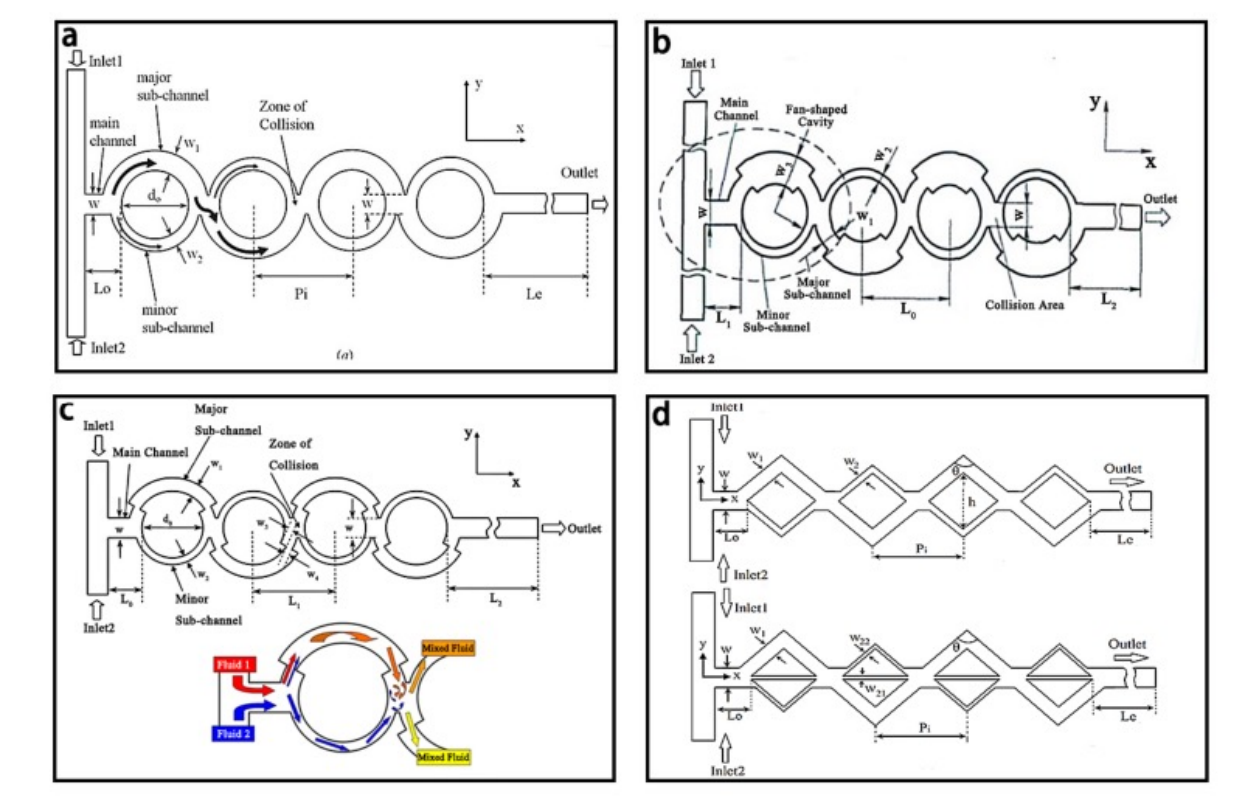
Ianovska, Margaryta A.; Mulder, Patty P. M. F. A.; Verpoorte, Elisabeth (2017). *Development of small-volume, microfluidic chaotic mixers for future application in two-dimensional liquid chromatography. RSC Adv., 7(15), 9090–9099.* doi:10.1039/c6ra28626g

Obstacle based mixers



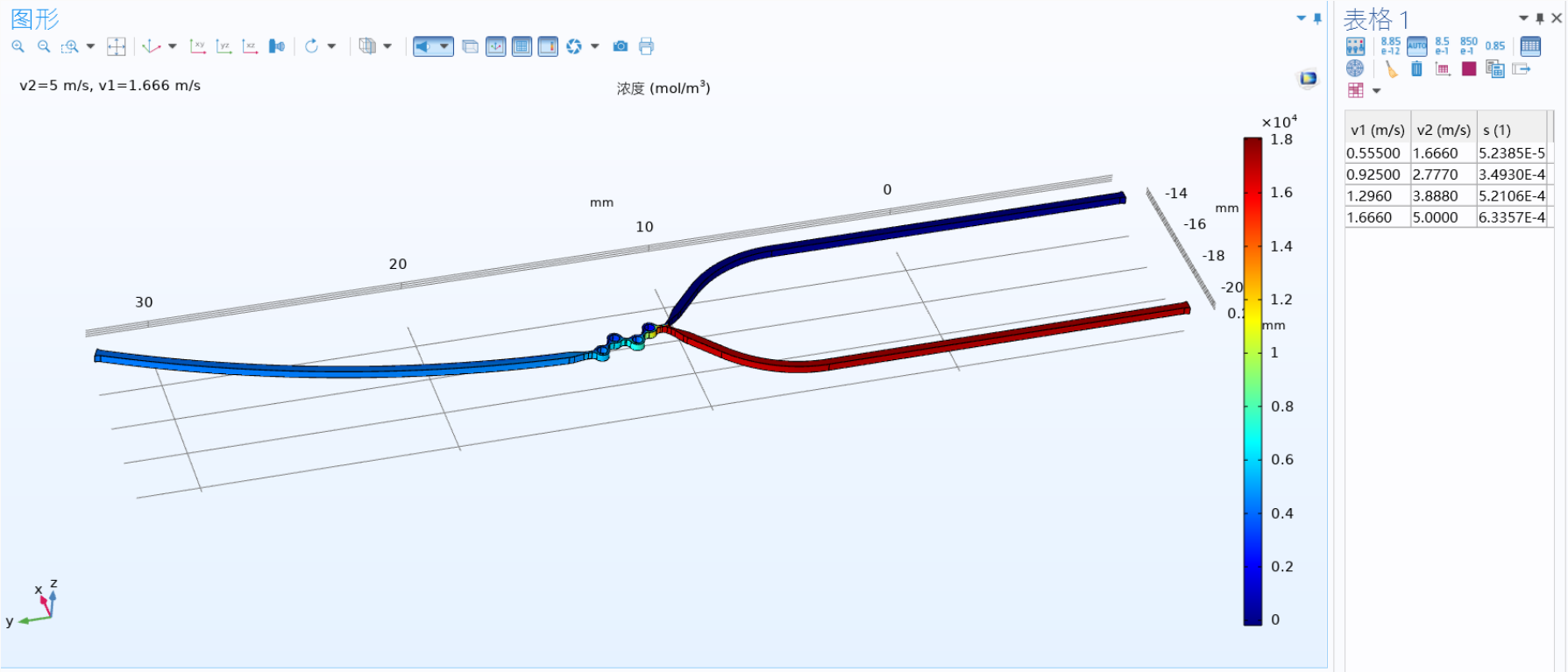
LNP-B0 simulation

Unbalanced Collision based mixers



Source ：Raza, Wasim; Hossain, Shakhawat; Kim, Kwang-Yong (2020). *A Review of Passive Micromixers with a Comparative Analysis. Micromachines, 11(5), 455–.* doi:10.3390/mi11050455

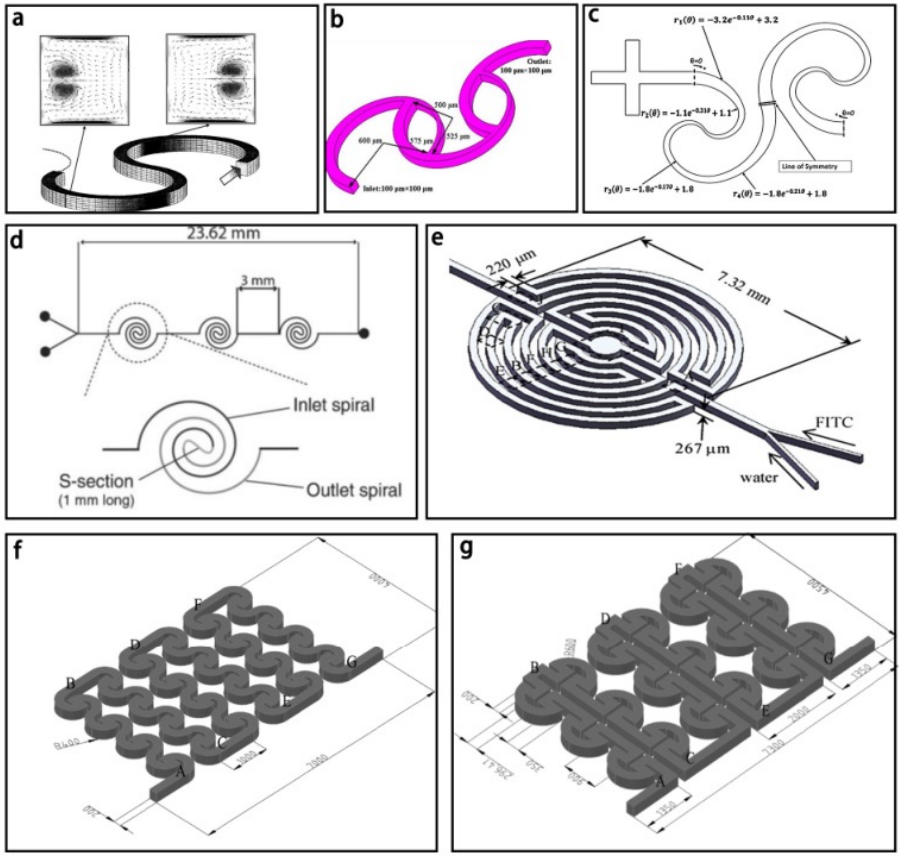
Unbalanced Collision based mixers



表格 1

v1 (m/s)	v2 (m/s)	s (1)
0.55500	1.6660	5.2385E-5
0.92500	2.7770	3.4930E-4
1.2960	3.8880	5.2106E-4
1.6660	5.0000	6.3357E-4

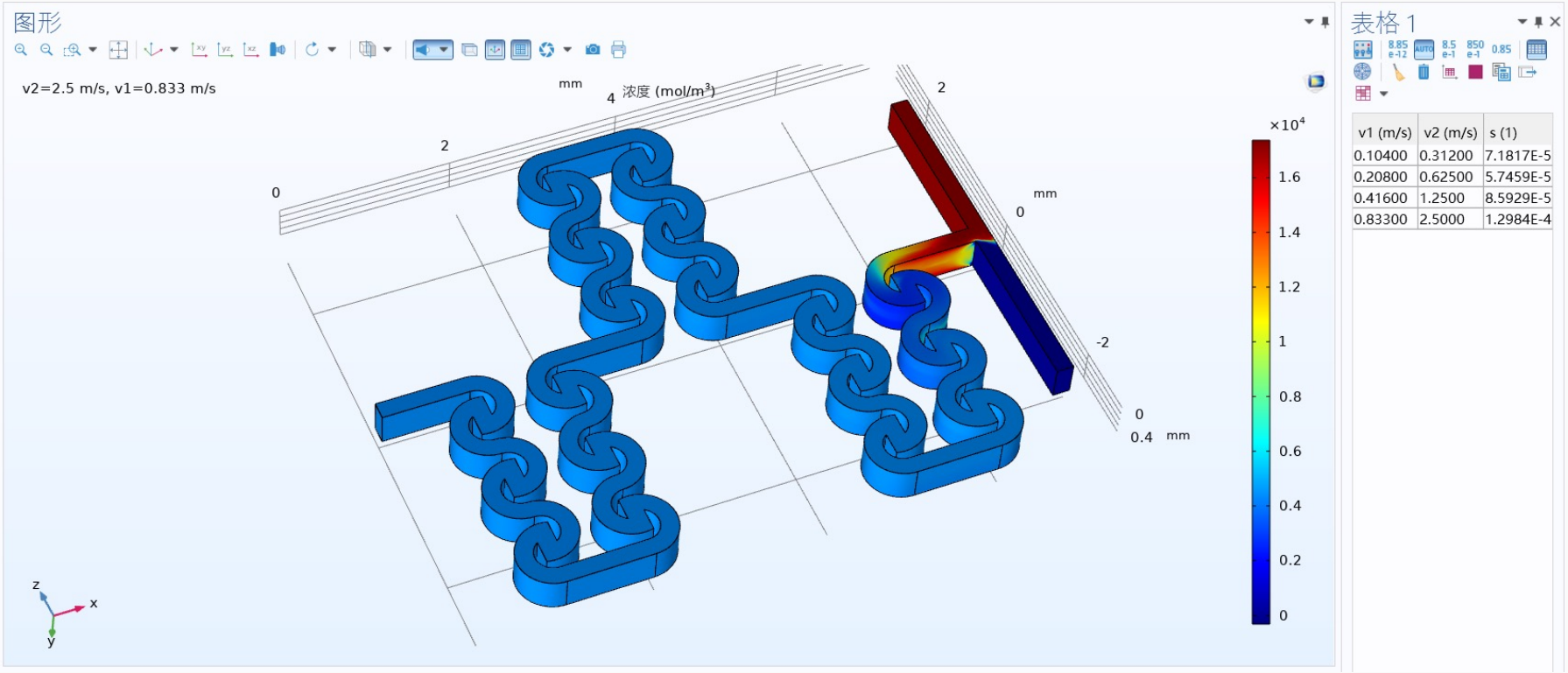
Spiral based mixers



type	Re	mixing time	efficiency
c	67		86%
d			90%
e	2.5~30	9.8ms~32ms	>98%
f.g	0.01 ~ 50		>98%

Source ：Raza, Wasim; Hossain, Shakhawat; Kim, Kwang-Yong (2020). *A Review of Passive Micromixers with a Comparative Analysis. Micromachines, 11(5), 455–.* doi:10.3390/mi11050455

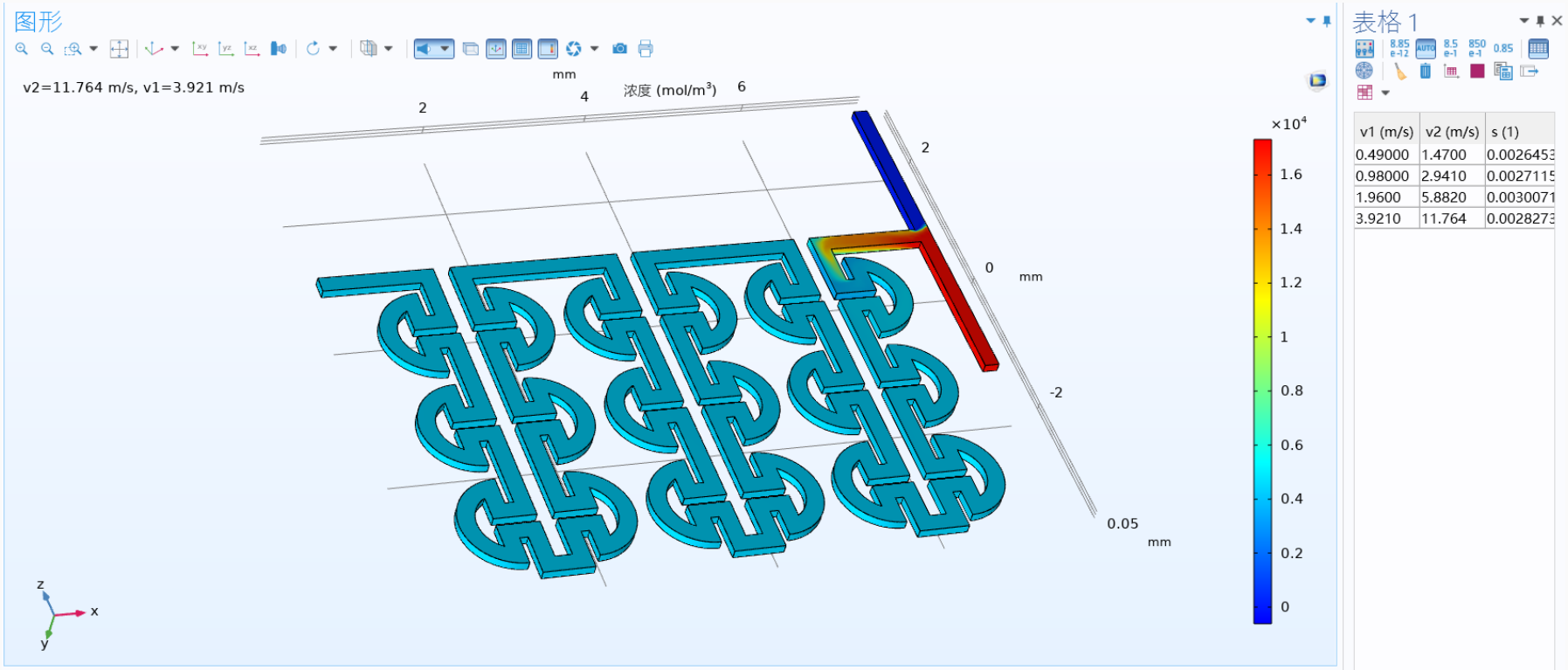
Spiral based mixers



表格 1

v1 (m/s)	v2 (m/s)	s (1)
0.10400	0.31200	7.1817E-5
0.20800	0.62500	5.7459E-5
0.41600	1.2500	8.5929E-5
0.83300	2.5000	1.2984E-4

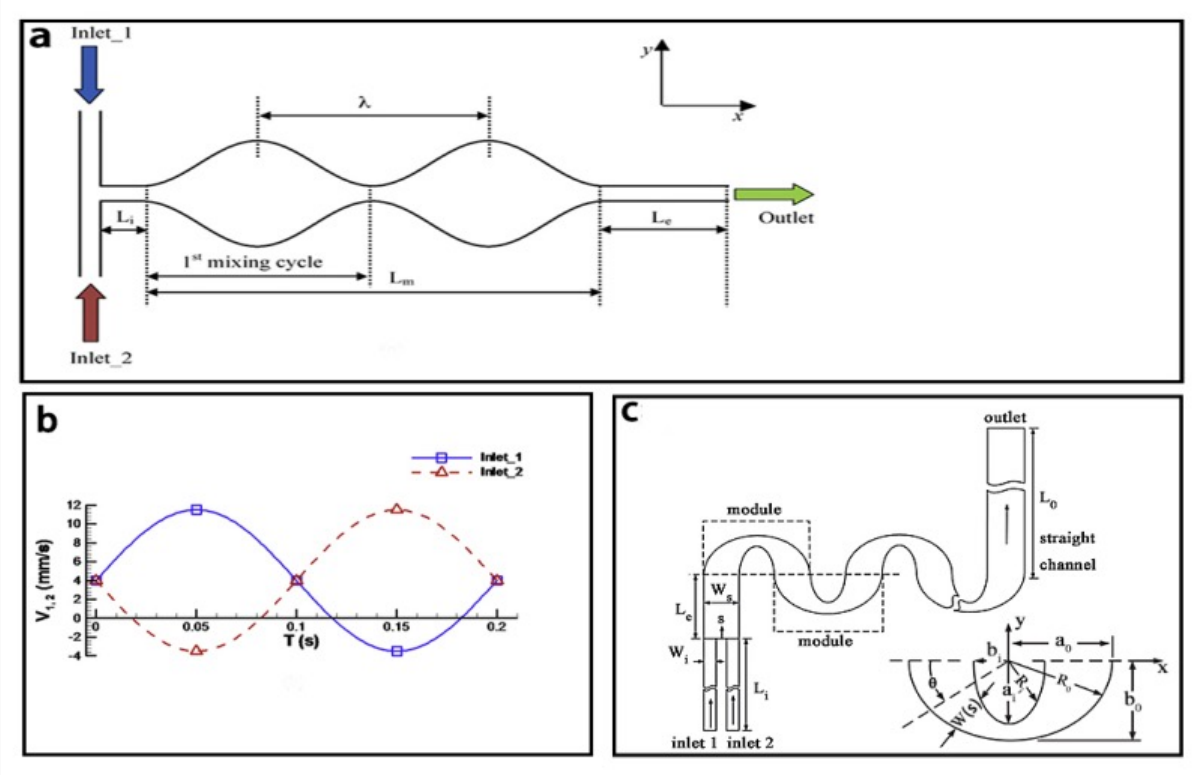
Spiral based mixers

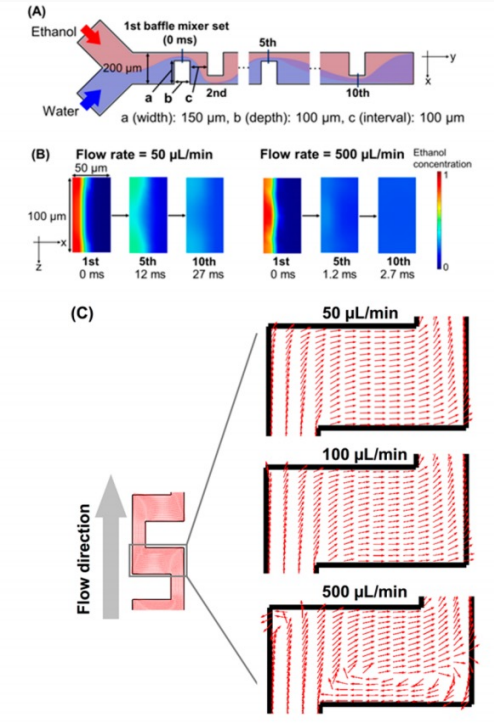


表格 1

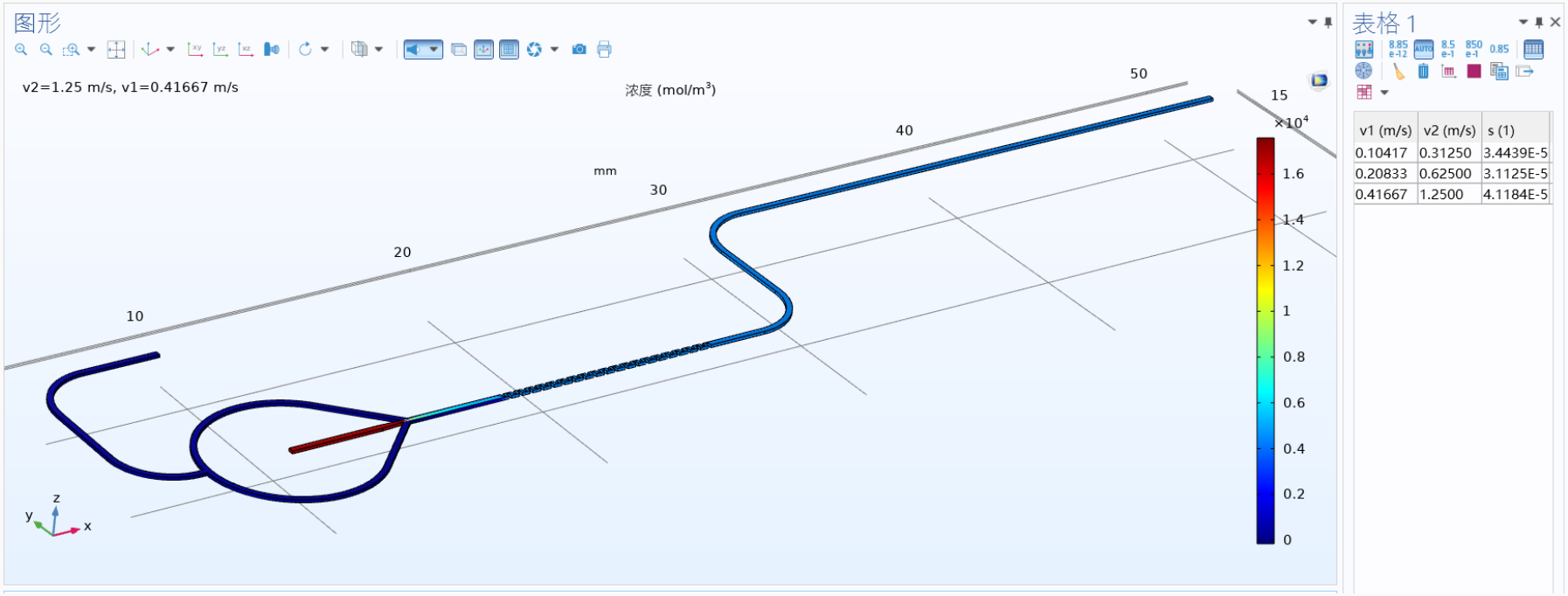
v1 (m/s)	v2 (m/s)	s (1)
0.49000	1.4700	0.0026453
0.98000	2.9410	0.0027115
1.9600	5.8820	0.0030071
3.9210	11.764	0.0028273

Convergence Divergence based mixers

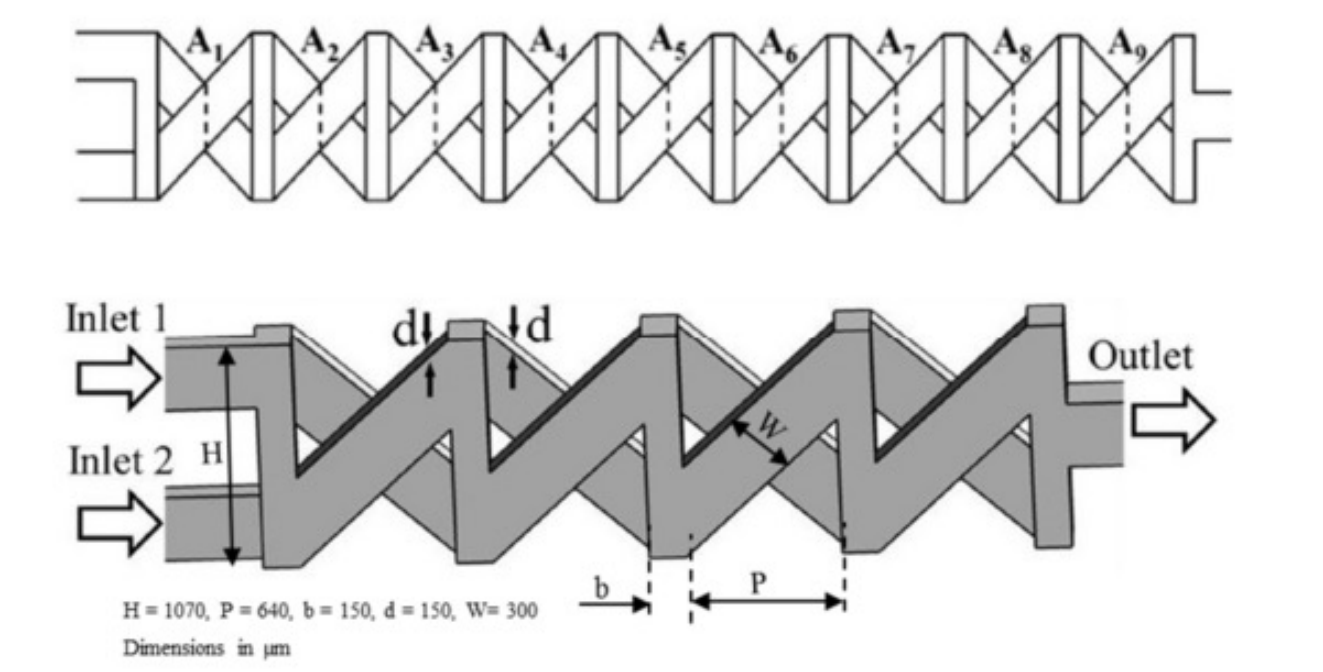




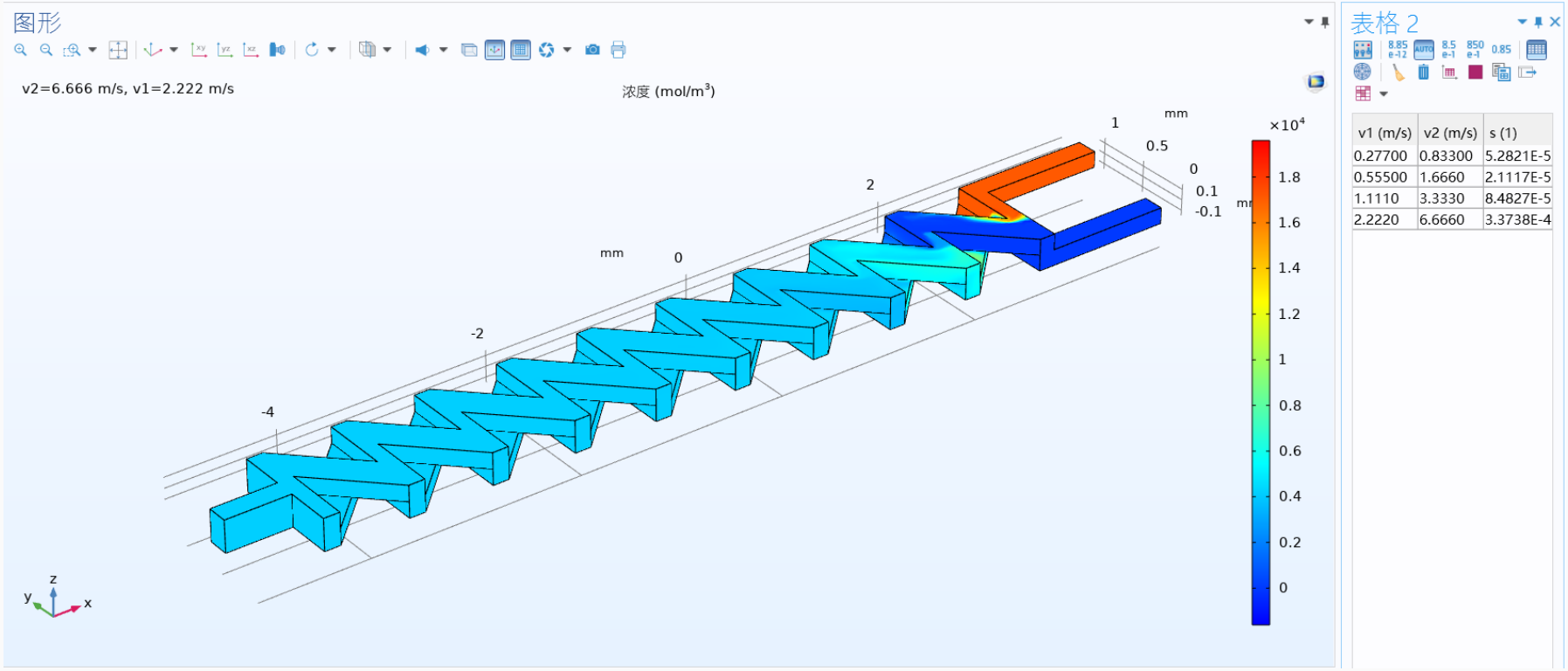
Convergence Divergence based mixers



3D structure based mixers



3D structure based mixers



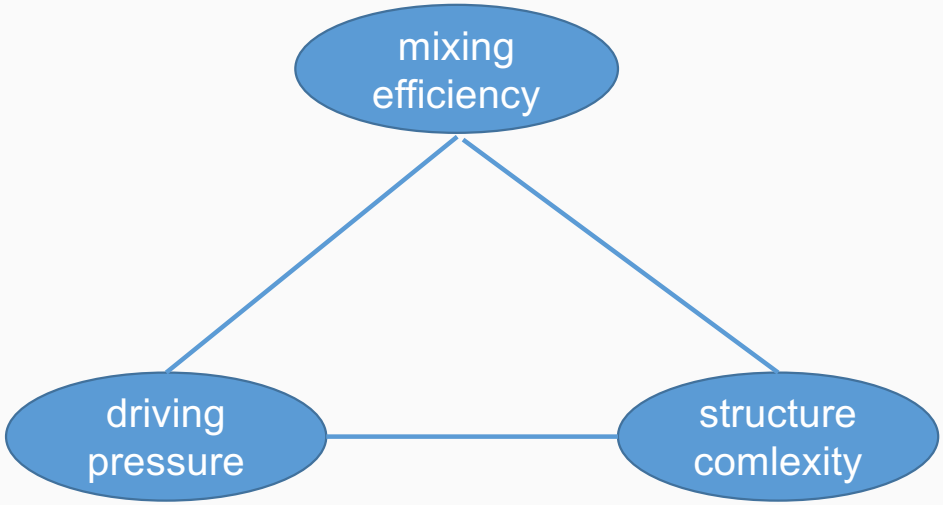
v1 (m/s)	v2 (m/s)	s (1)
0.27700	0.83300	5.2821E-5
0.55500	1.6660	2.1117E-5
1.1110	3.3330	8.4827E-5
2.2220	6.6660	3.3738E-4

Conclusion based on current models

1. Smaller channel size is better for mixing but needs significantly higher pressure.

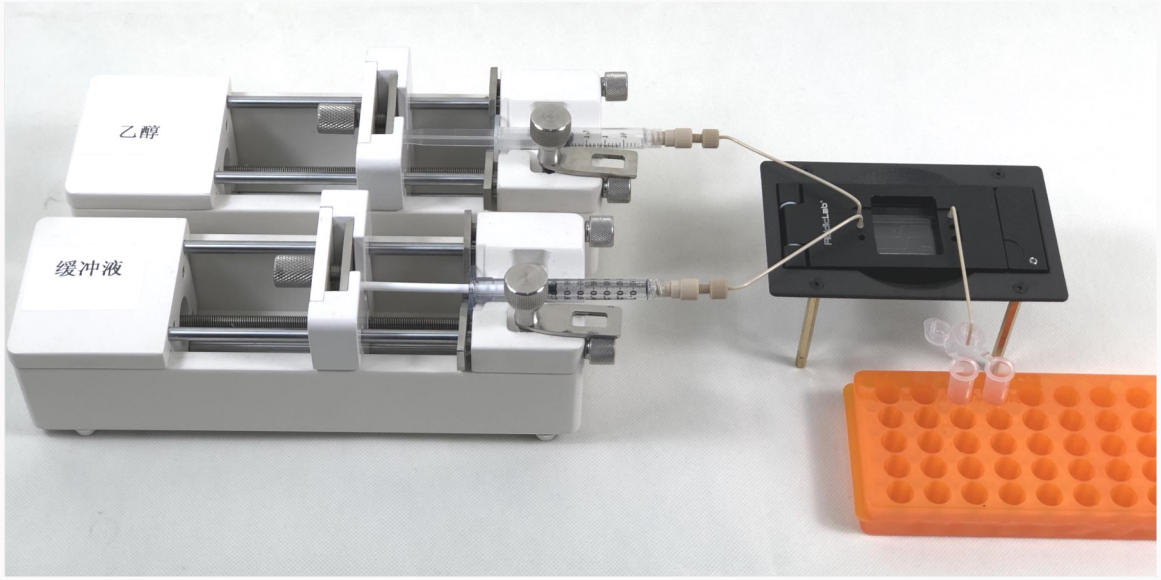
2. There is a maximal speed for mixing efficiency.

3. 3D structure is better than 2D structure.



Solutions

Instrument setup



- LNP-B0
- 1 ml-10 ml total volume

Small volume LNP production with syring pump

Solutions

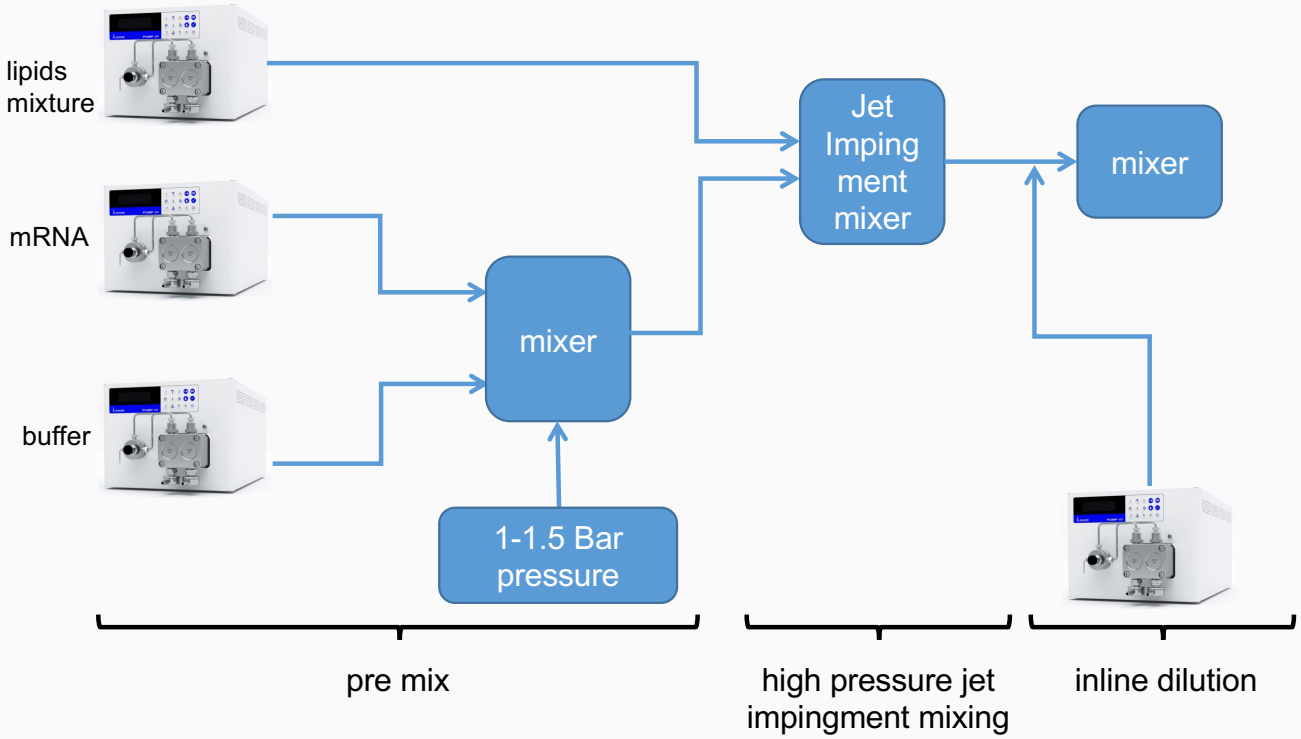
Instrument setup

- LNP-C0
- 50 ml-100 ml total volume

Medium volume LNP production with pressure pump

Solutions

Instrument setup



- size: 70-100 nm
- PDI: 0.03-0.05
- >10 L scale

Large volume LNP production with solvent delivery pump