Synthesizing Complex Microparticles Using Microfluidic Devices

2009 Stratis V. Sotirchos Memorial Lectureship

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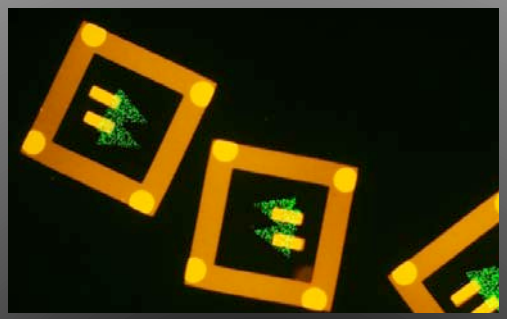
Rothschild-Mayant Fellow
Institut Curie

microparticle
complexity space

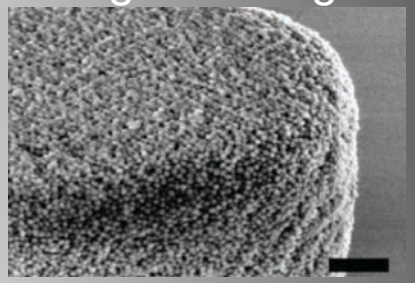
patterned regions



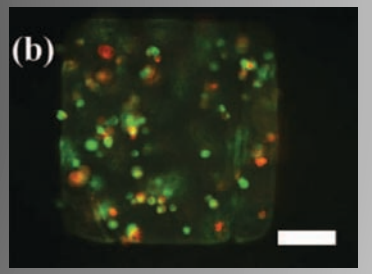
shape

aspect ratio

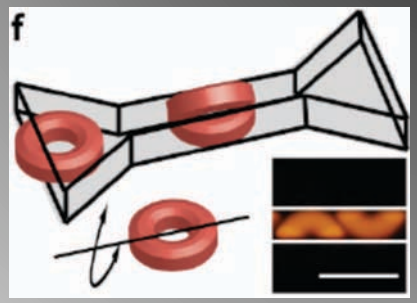
cargo-bearing



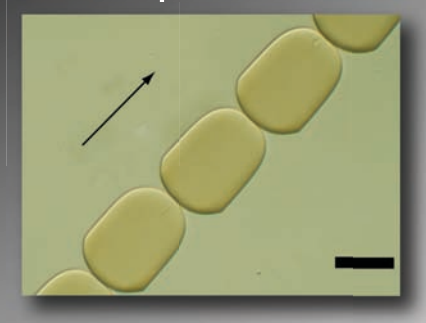
compatibility



mechanical properties

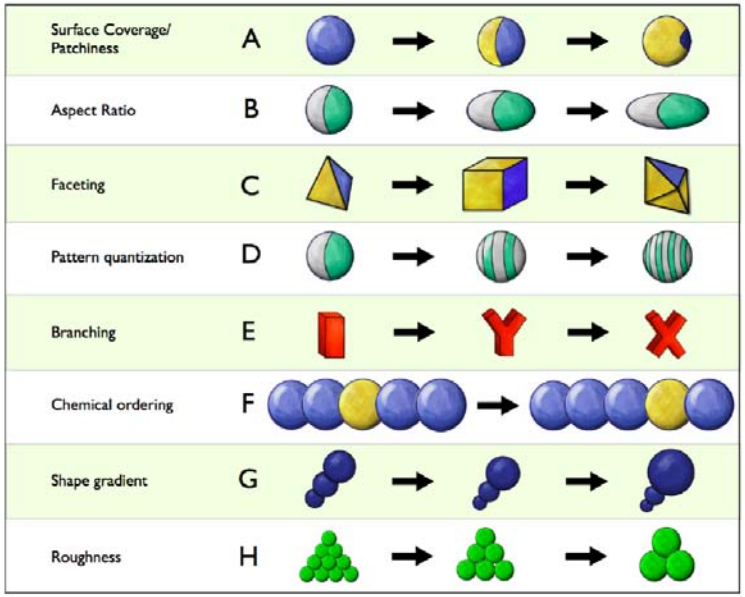


responsive

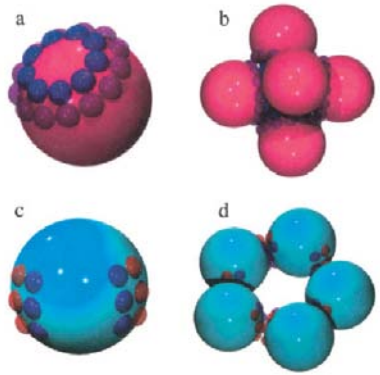


Fundamental Studies of Complex Particles

Self Assembly

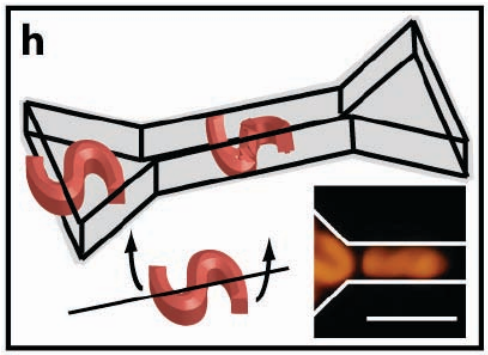


Solomon and Glotzer, Nat. Mater. (2007)



Glotzer et al., AIChE J. (2004)

Flow & Rheology

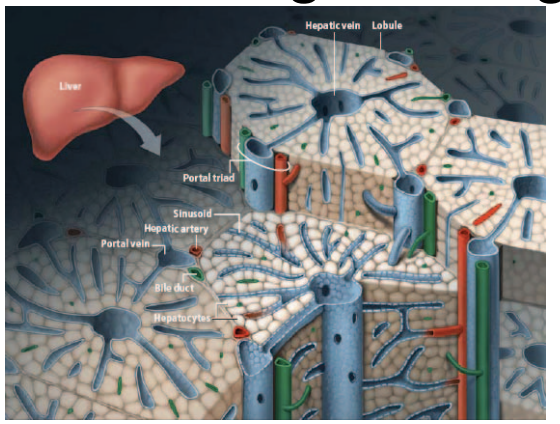


Advanced Applications

Medical Diagnostics

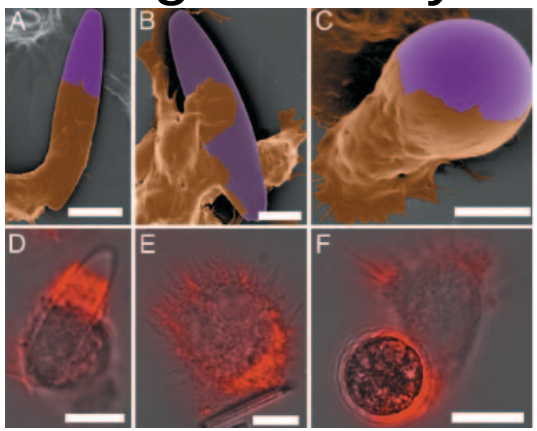
Pregibon, Toner and Doyle, Science (2007)

Tissue Engineering



Khademhosseini, Vacanti, Langer, Scientific American (2009)

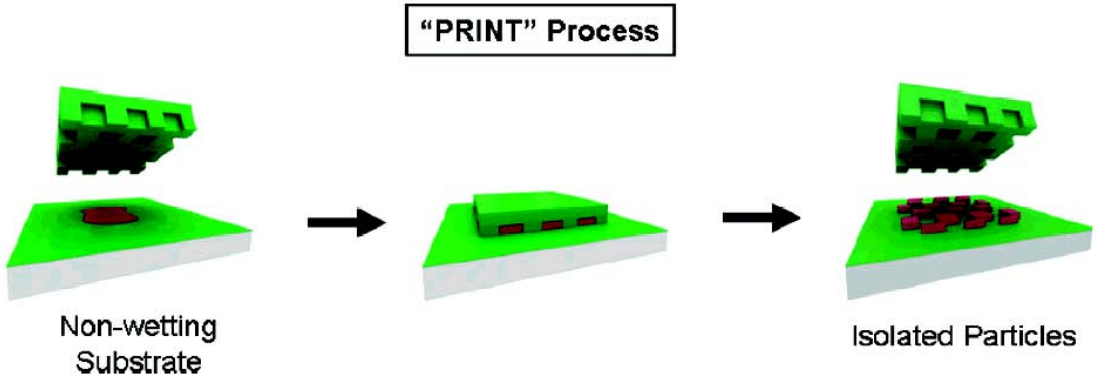
Drug Delivery



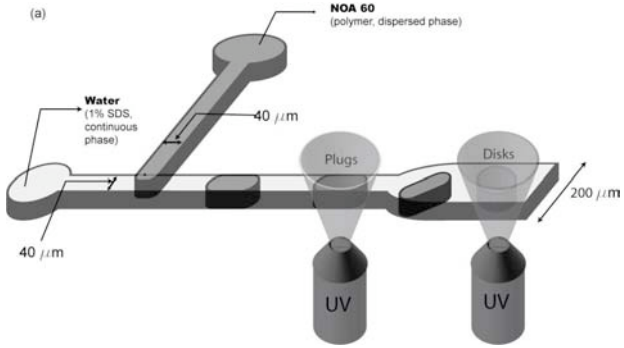
Champion and Mitragotri, PNAS (2006)

e-Paper

Non-spherical particles (custom designed)

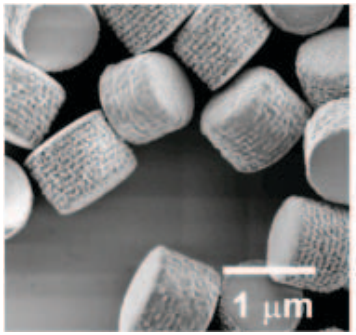


Rolland et al., JACS 2005

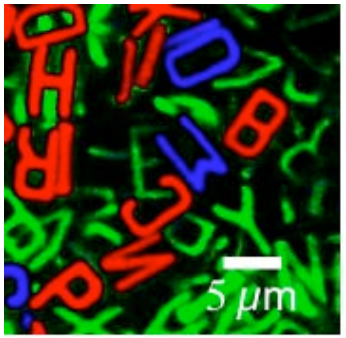


Dendukuri et al., Langmuir 2005

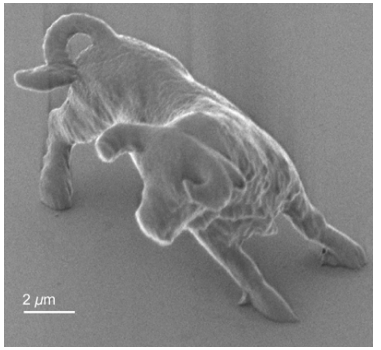
Xu et al. Angew Chem. Int. Ed. 2005



Badaire et al. JACS 2007



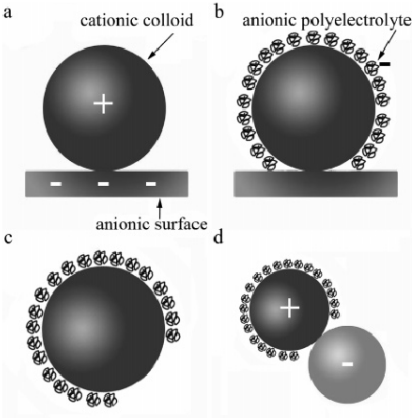
Hernandez & Mason JPC 2007



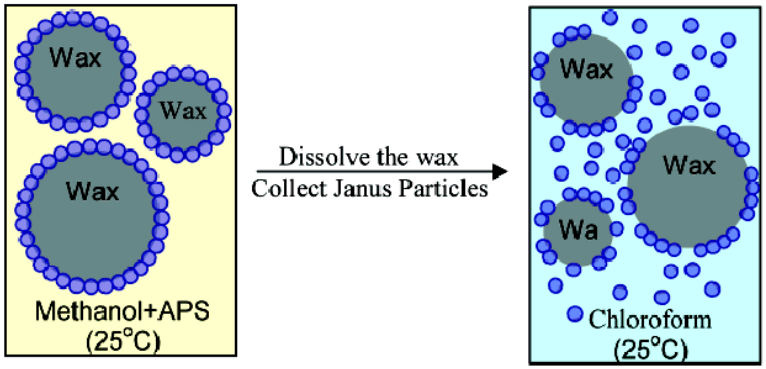
Kawata et al., Nature 2000

Chemically patterned particles

Selective surface modification

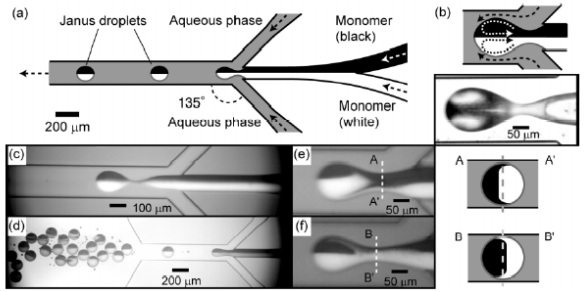


Snyder et al., Langmuir (2005)

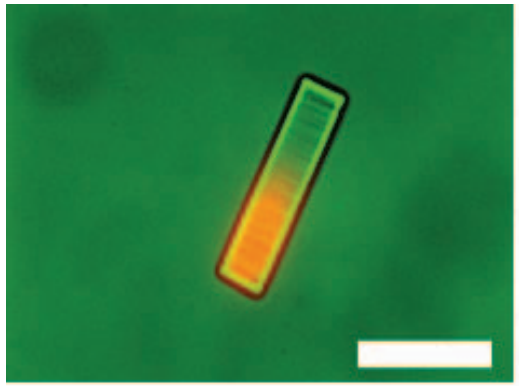


Hong and Granick, Langmuir (2007)

Microfluidics

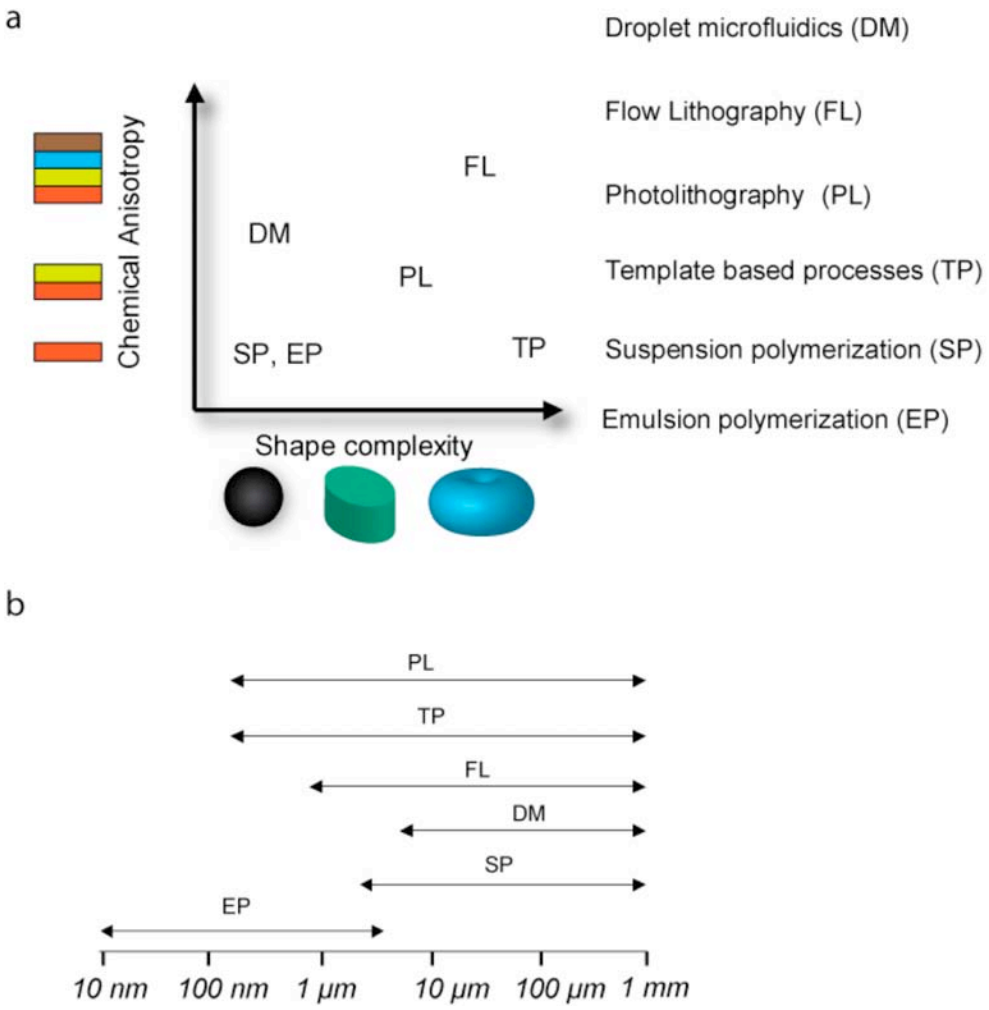


Nisisako et al., Adv. Mater. (2006)



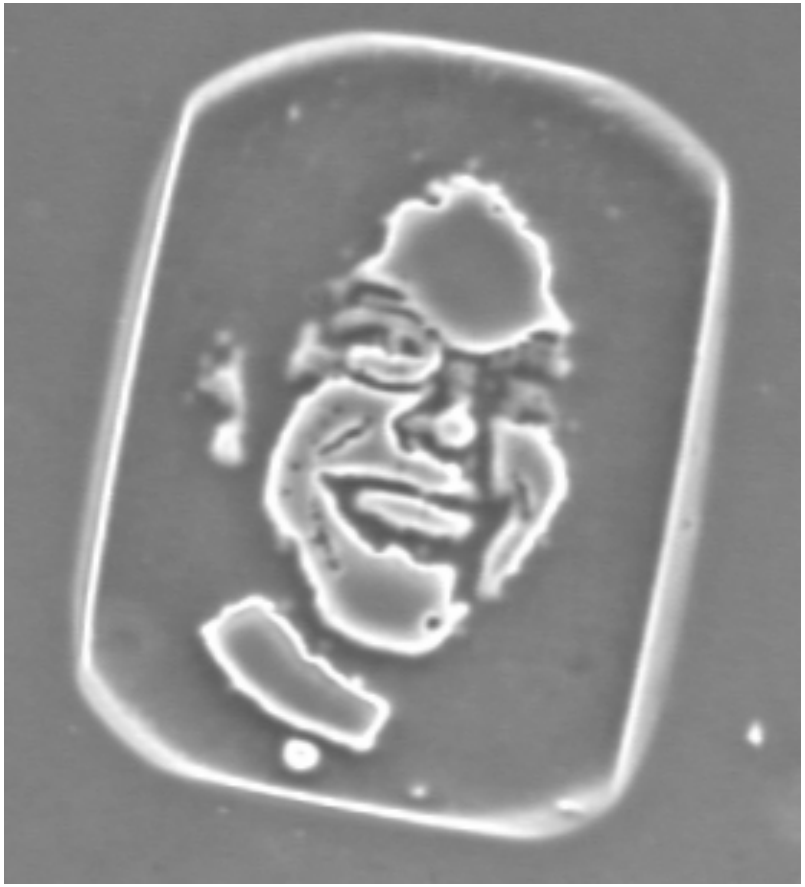
Dendukuri et al., Nat. Mater. (2006)

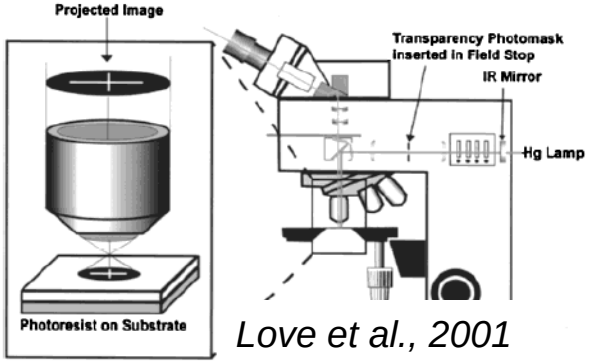
Synthesis Phase Space



Doyle and Dendukuri, Adv. Mat. (2009), *in press*

(re)Discovery…





Love et al., 2001

~ 100 microns

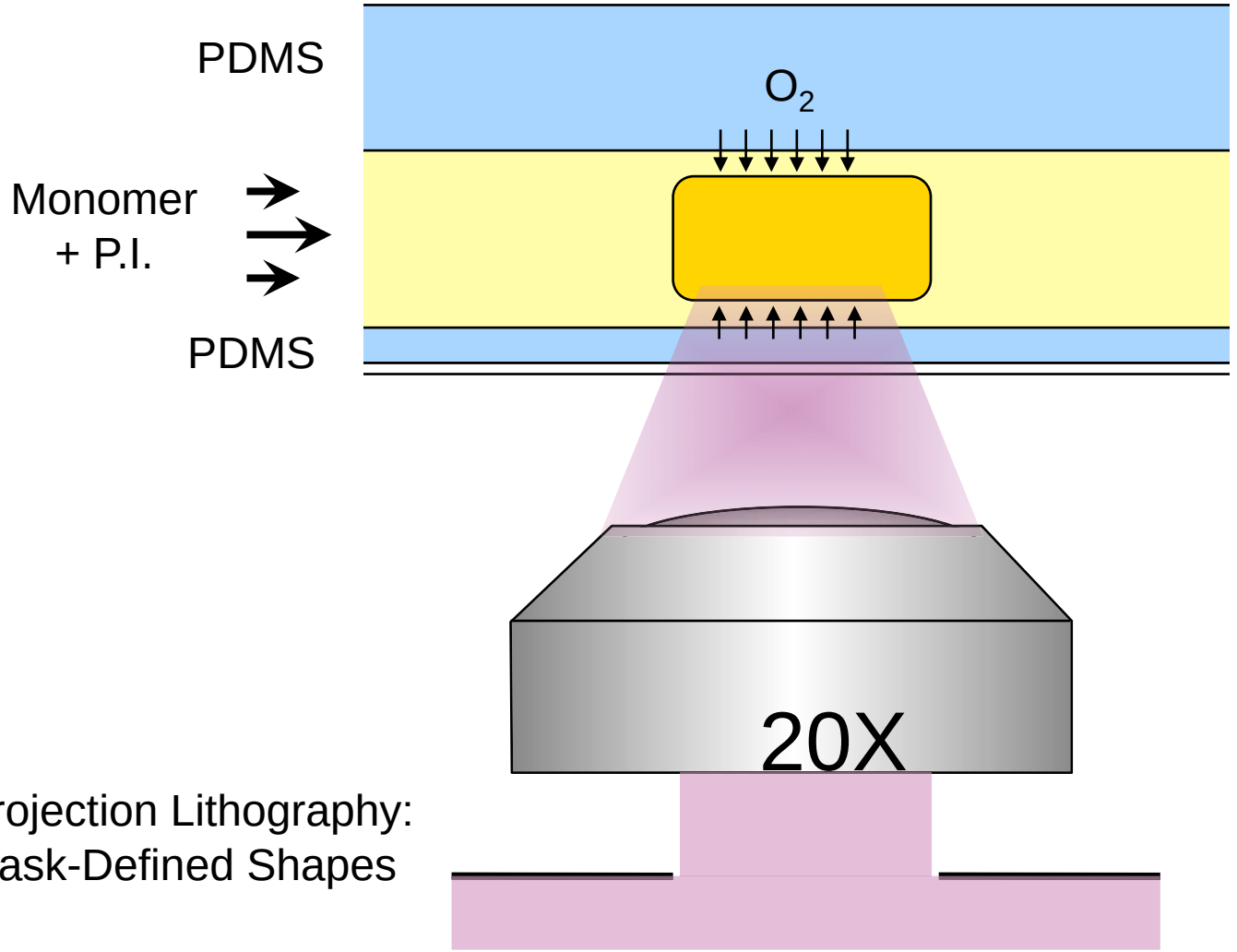
free floating

hydrogel

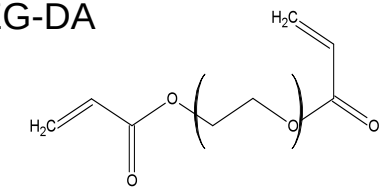
repeatable

Continuous Flow Lithography

Dendukuri et al., Nat. Mater. (2006)



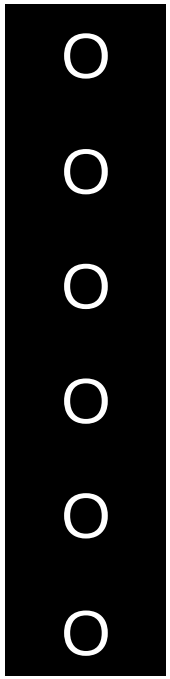
PEG-DA



7.8X – 40X reduction of mask features using 20X and 100X objectives

Projection Lithography:
Mask-Defined Shapes

Real-time Synthesis of Tubes



Transparency mask

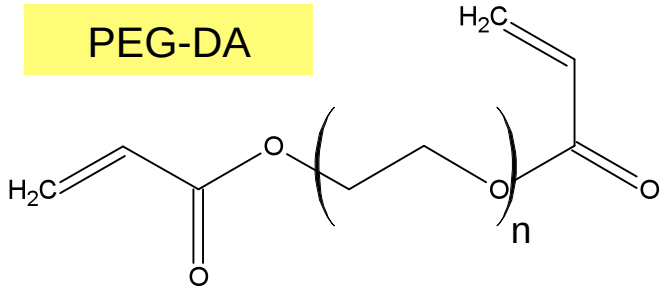
50 μm OD

Objects forming and flowing

Photopolymerization Chemistry

- Several types
- We use free-radical chemistries
  - Acrylate and methacrylate groups
  - UV light initiated (365 nm)

PEG-DA

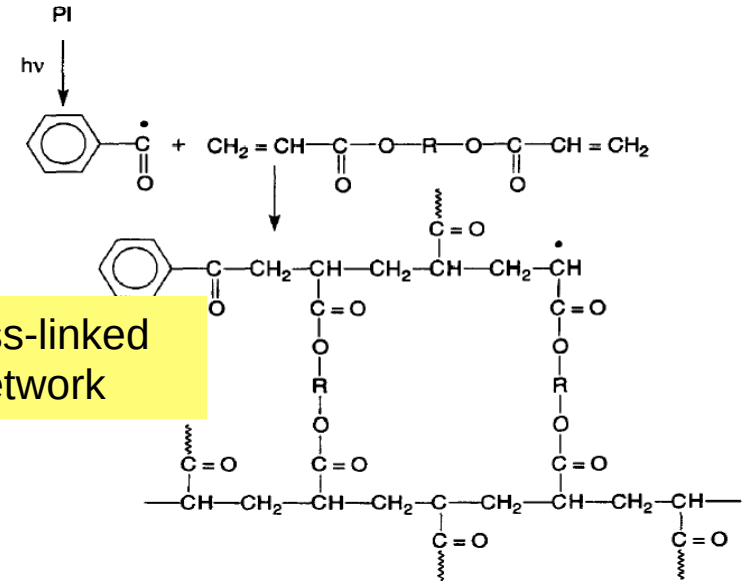


Photoinitiator + Monomer

<u>Mechanism</u>

(Initiator (I), Monomer (M))

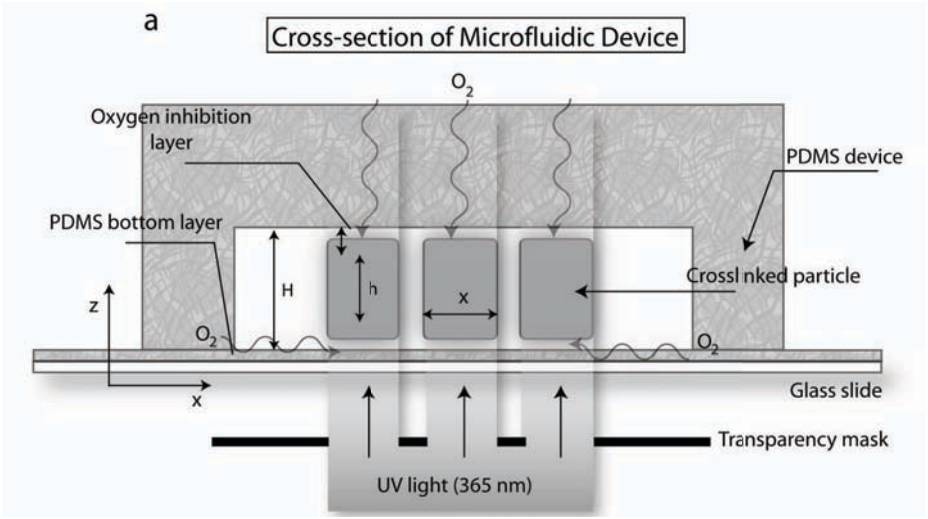
I + hν → I*	initiation
I* + M → M-M…-M-M propagation	chain
I* + O_2 → I*OO	retardation

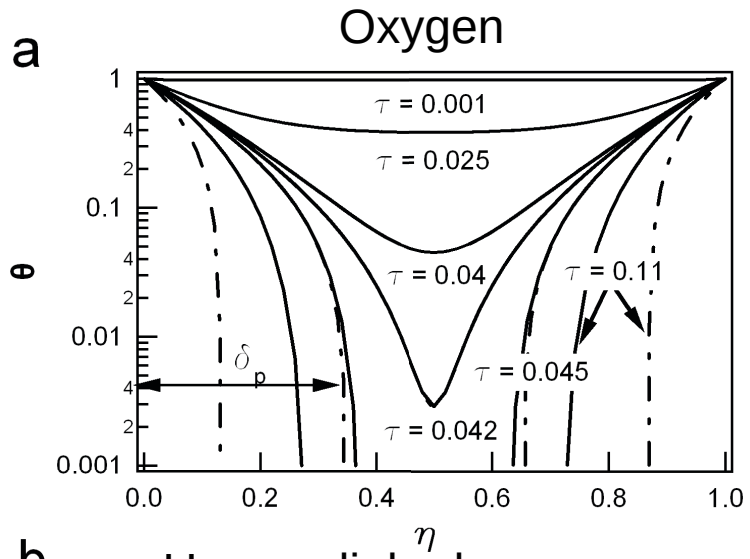


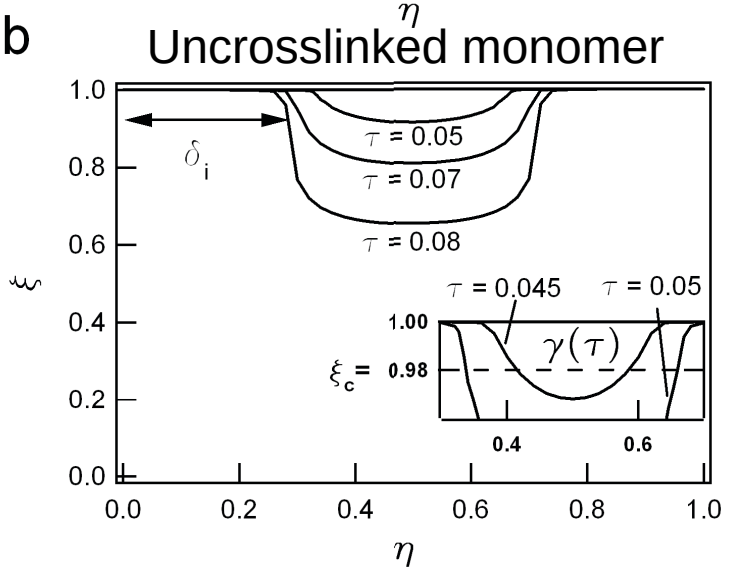
Cross-linked network

- Single acrylate – linear chain
- Multiple acrylate – cross-linking leading to quick solidification
- PEG – biologically friendly

Mechanism







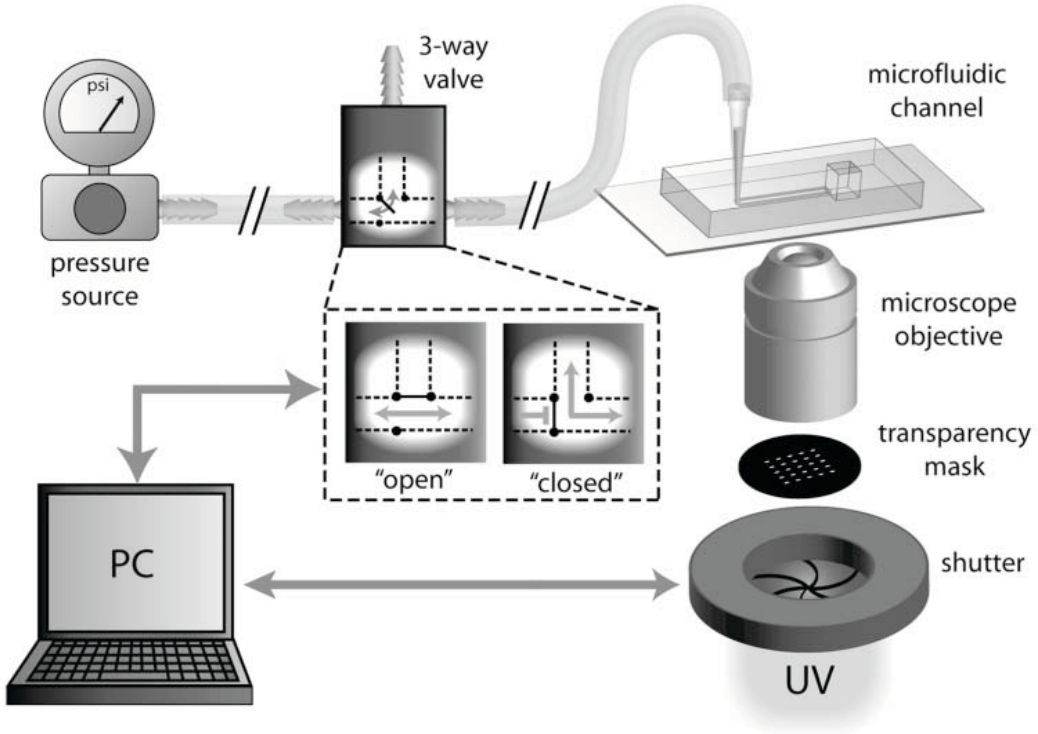
$$\frac{d^2\theta}{d\eta^2} - Da\theta = 0$$

$$Da = \frac{kL^2}{D}$$

$\delta_p \sim (D/k)^{1/2}$

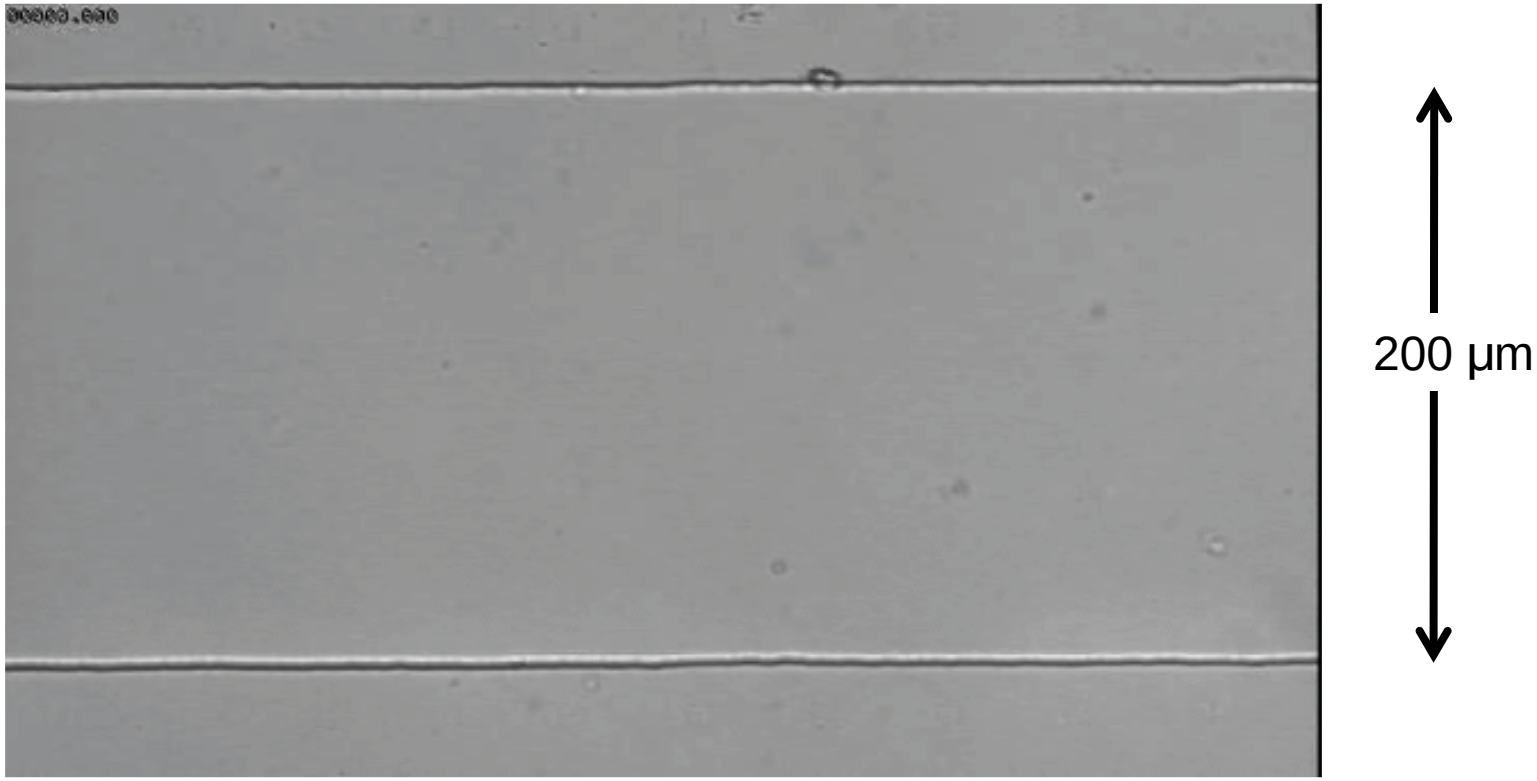
Dendukuri et al.,Macromolecules (2008)

Stop Flow Lithography



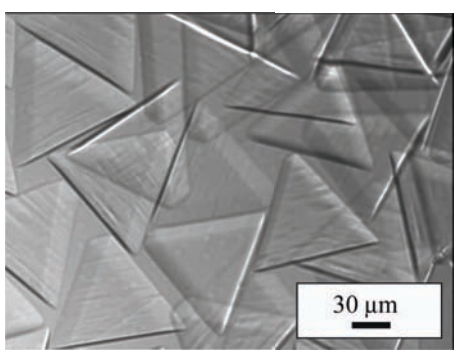
Dendukuri et al., Lab on a Chip. (2007)

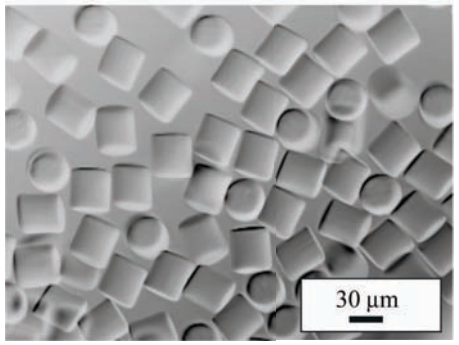
Stop Flow Lithography

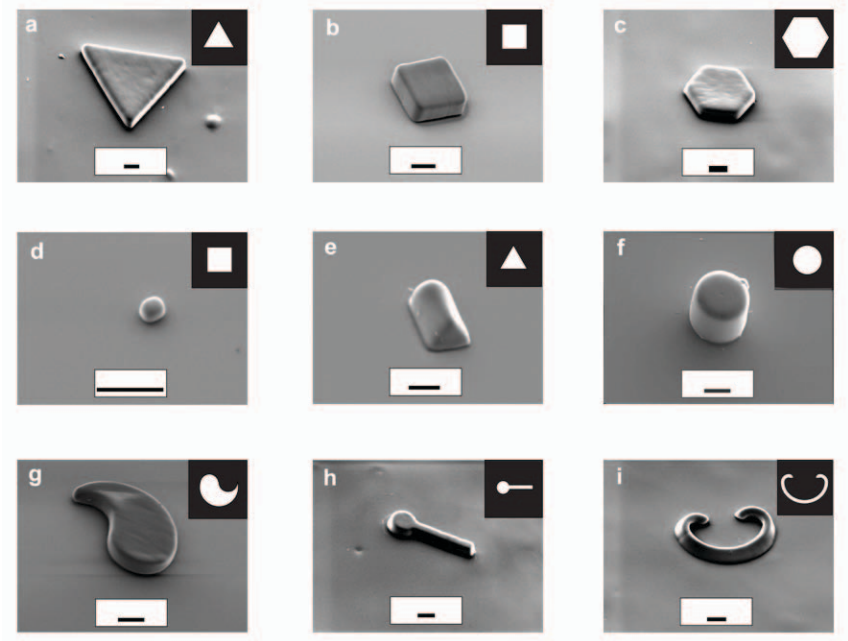


Dendukuri et al., Lab on a Chip. (2007)

Process Attributes





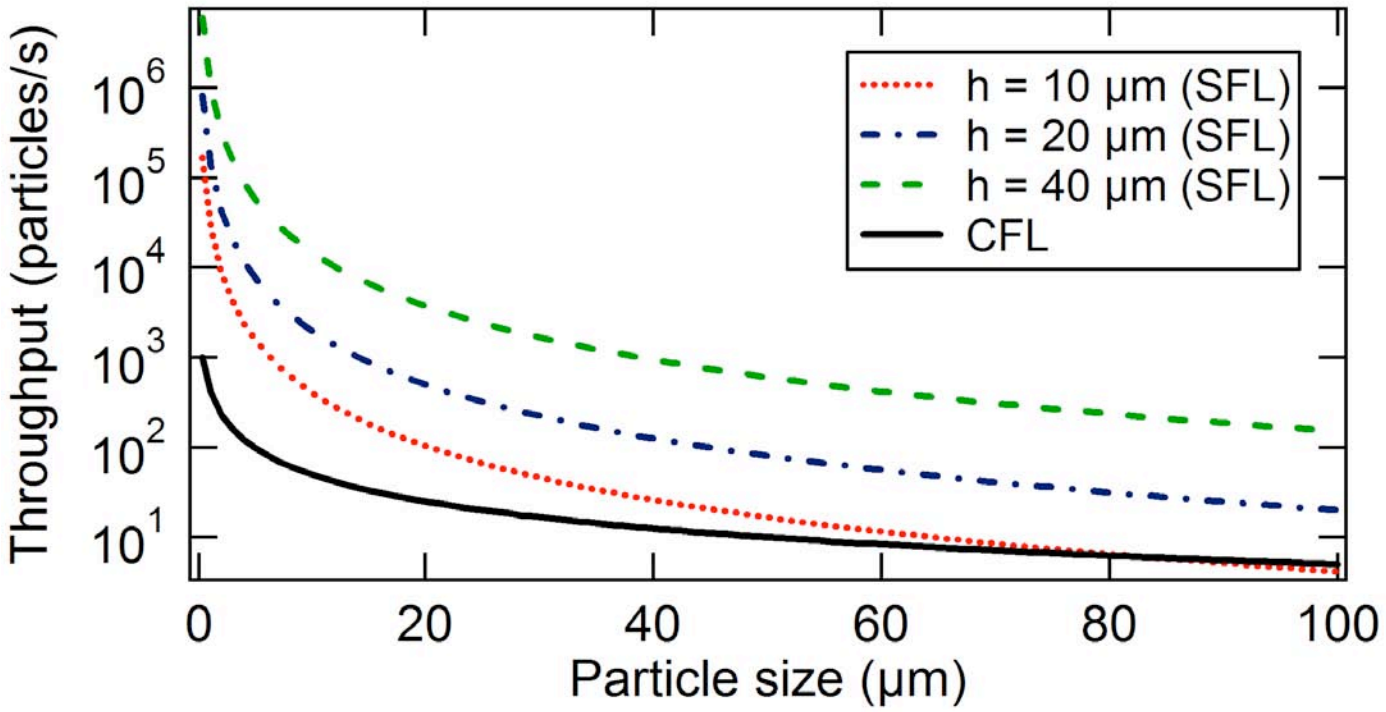


Scalebar: 10 μm

- One-phase (easy to use)
- Transparency masks
- Can use with any free radical polymerization
- Monodisperse (CV<2%)
- Automated Process
- Any extruded 2-D shape
- Incorporated desired chemistry in monomer

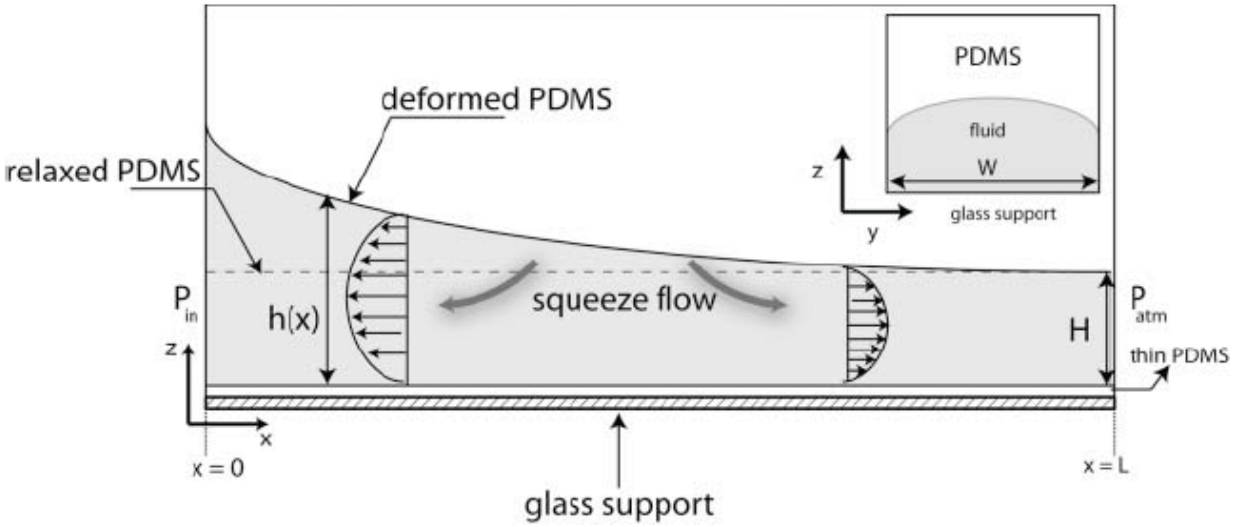
(Fe_2O_3, quantum dots, dyes etc.)

Particle Production Rate



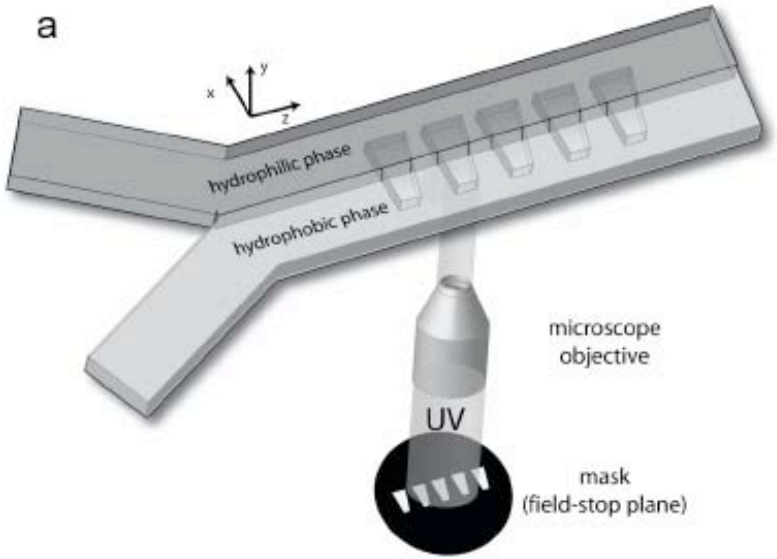
Estimates using only microscope projection lithography ~1mm^2 UV spot size

Elastohydrodynamics



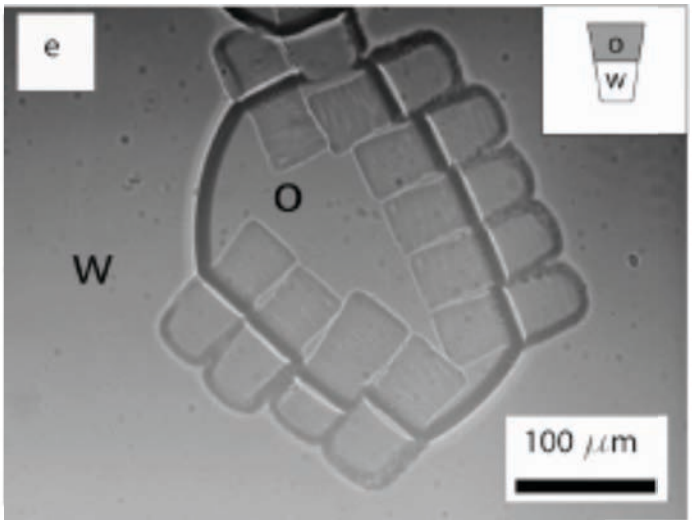
$$\tau_r \sim \frac{\mu L^2 W}{E H^3}$$

SFL Co-Flow Multiple Streams



Dendukuri et al., Langmuir (2006)

"Colloidal Surfactants"

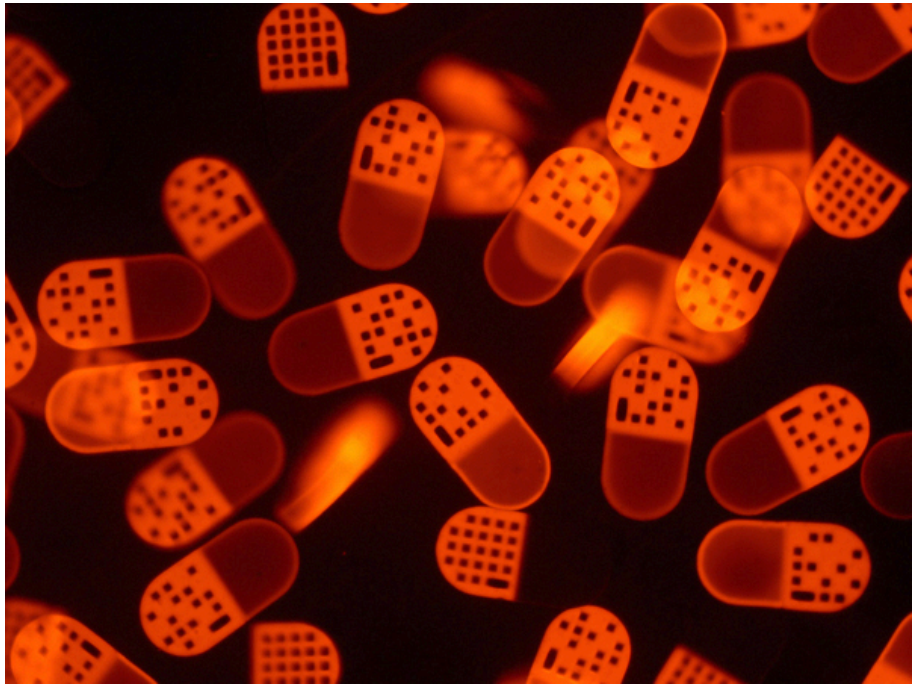


Hydrophilic: PEGDA

Hydrophobic: TMPTA

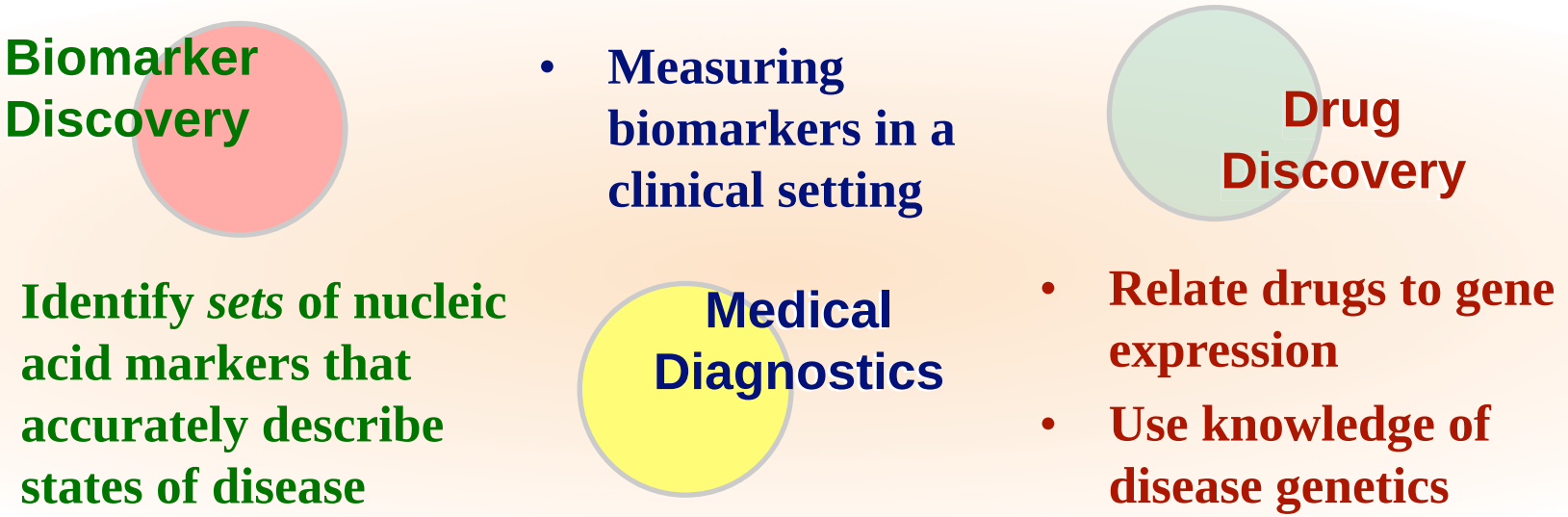
Barcoded microparticles for multiplexed biomolecule analysis

Pregibon, Toner, Doyle, *Science* 2007



Molecular Diagnostics

Using DNA and RNA to detect, monitor, or understand disease.



Drug discovery: 1,000s of targets, 1,000s of samples/day
Neonatal Diagnostics: ~3,000 of targets, 1,000s of samples/day
In vitro Cancer Diagnostics: 100s – 1,000s targets, 1,000s of samples/day

Multiplexing = detecting many targets in one sample

Multiplexing

Definition – Detection of multiple targets using single test

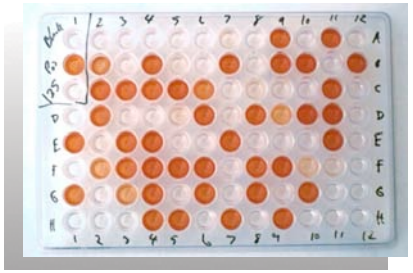
Benefits – Maximize info with minimal sample, time and cost

Difficulties – Accuracy, need to encode for each target

Our interest – Medical Applications:

DNA → RNA → Proteins

- Genetic profiling
  - Disease susceptibility
- Diagnostics
  - Foreign Material, Ab against



Current Approaches: Microarrays

Encoding

- Spatial on planar surface
- Each probe for specific target at different location

Functionalization

- Molecules spotted (DNA, proteins, RNA)
- Photopatterning (DNA only)

Cost

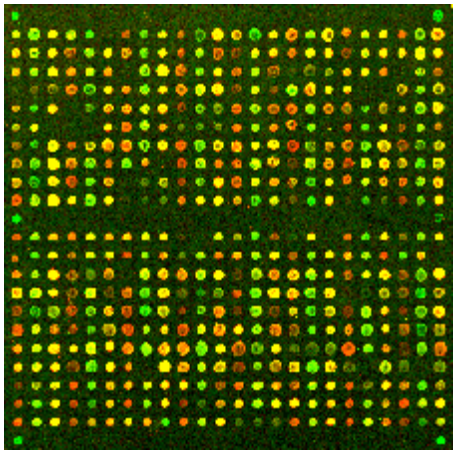
- Capital ~ $300K
- Cost per test ~ $100 - $1,000

Info "Density"

- Order(10,000)

Sample Throughput

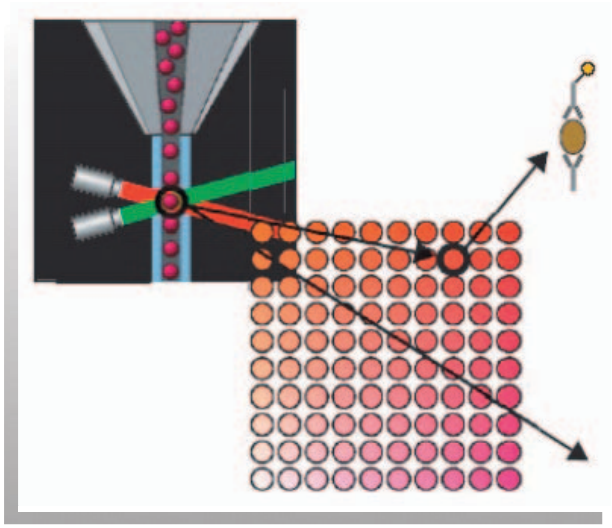
- Low (few)



Current Approaches: Cytometry

Encoding

- Multiple fluorophores at precise blends



xMAP, Luminex ®

Functionalization

- Chemistries to attach biomolecules to bead surfaces
- Detection via fluorescence

Sample Throughput

- High (~100)

Cost

- Capital ~ $30K
- Per test ~ $100?

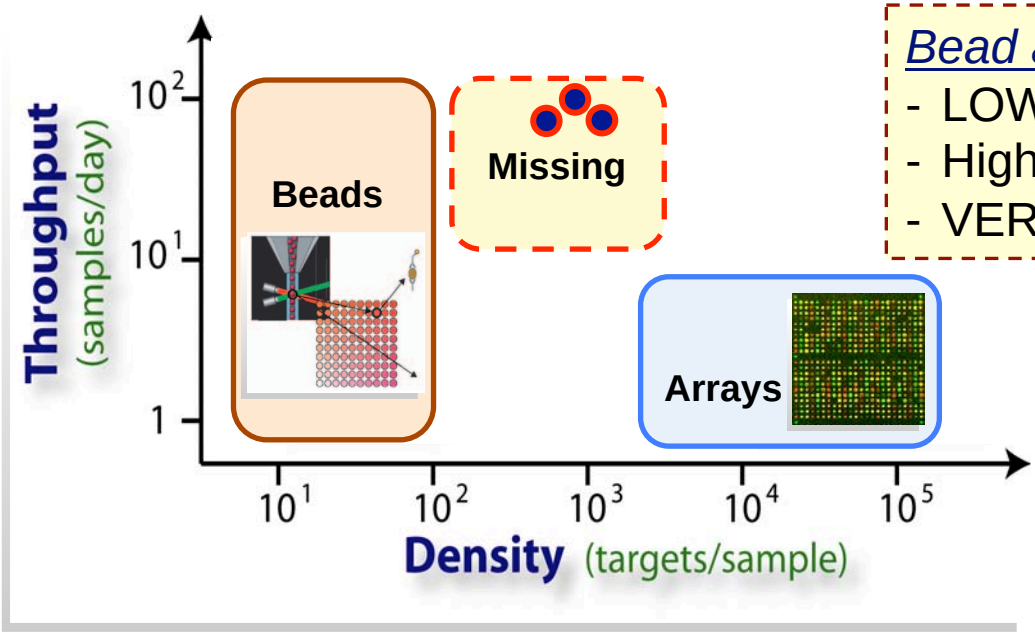
Info "Density"

- <100

Application of SFL to Multiplexing?

SFL Provides:	***Ideal For:***
• Any extruded 2D shape →	**Graphical barcode**
• Multiple adjacent chemistries →	**Spatial separation of code, probes**
• Choice of any free-radical reacting polymers →	**Bio-inert, porous surfaces (PEG)**

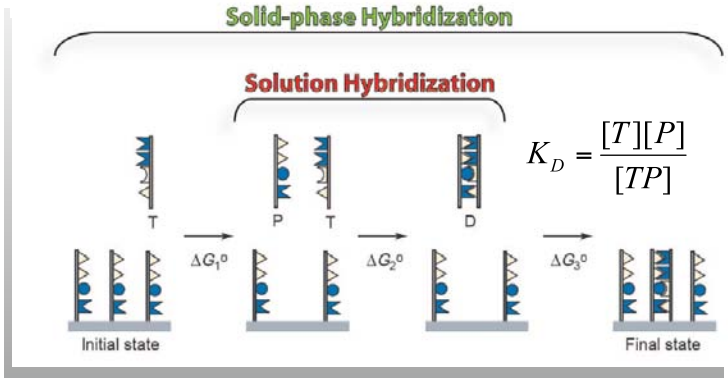
State-of-the-Art Screening Technologies



Bead arrays:
- LOW density
- High throughput
- VERY versatile

Microarrays:
- HIGH density
- Low throughput
- Not versatile
- Very Expensive

WHAT ABOUT:
- In vitro cancer diagnostics?
- Neonatal Screening?
- Drug discovery?



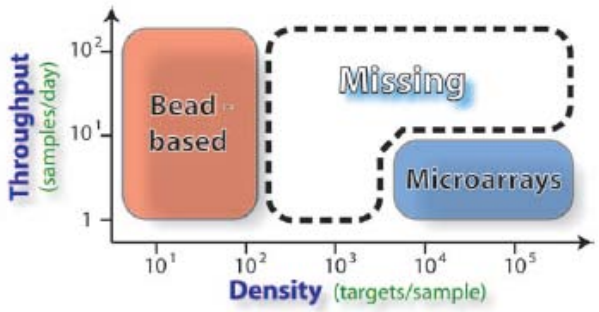
Bottom Line:

- Beads are better than arrays
- Gels are better than solids!
- No technology can efficiently provide medium-density!

Barcoded Hydrogel Microparticles

ADVANTAGES OVER EXISTING PLANAR ARRAYS

- Hydrated scaffold environment provides near-solution binding kinetics
- Probe-set modifications can be made easi
- Efficient mixing and washing
- Redundancy increases data quality



D.C. Pregibon Thesis (2008)

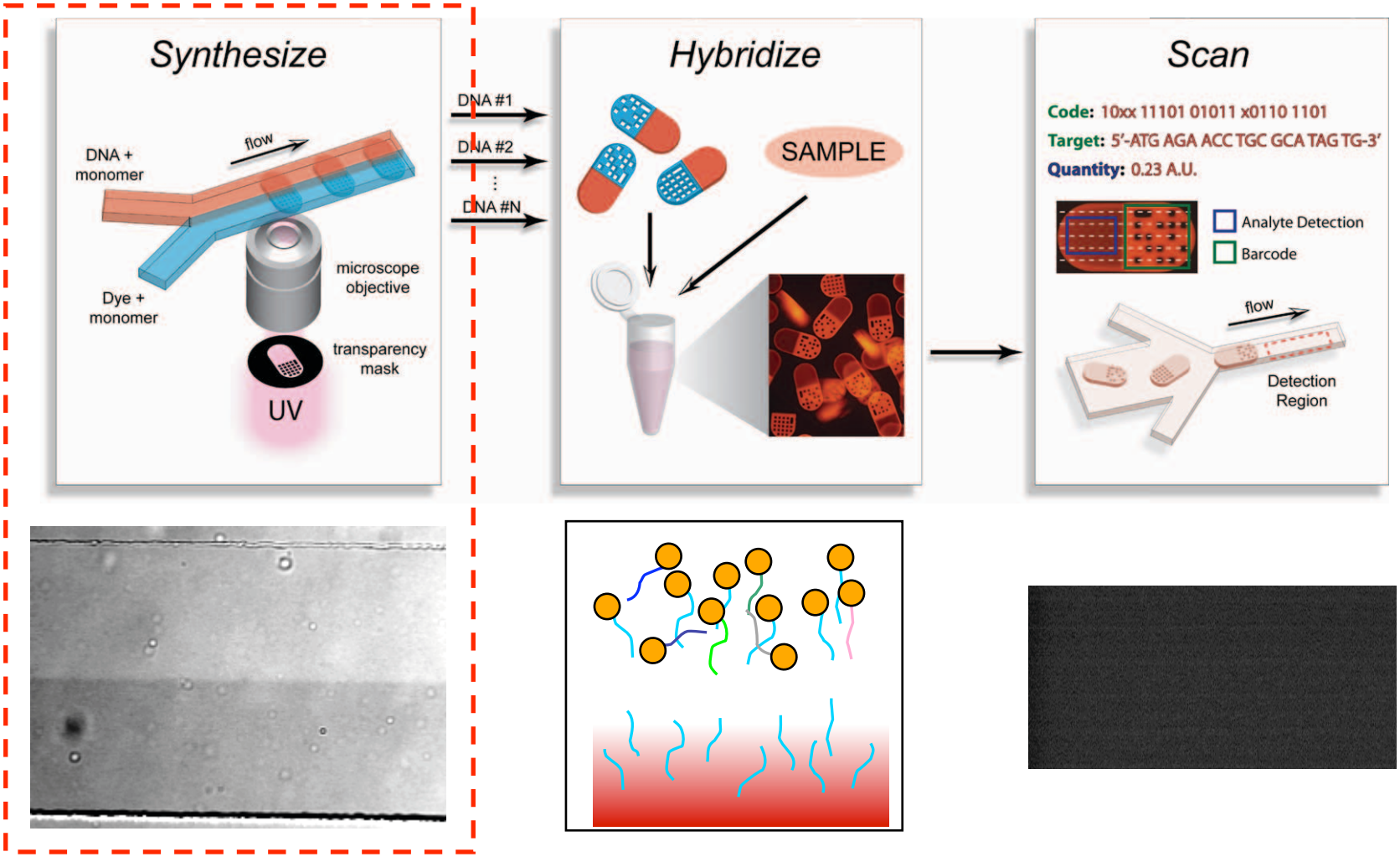
ADVANTAGES OVER EXISTING PARTICLE-BASED ARRAYS

-Extensive code library (>3000)

-Single-color fluorescence for easier detection/decoding

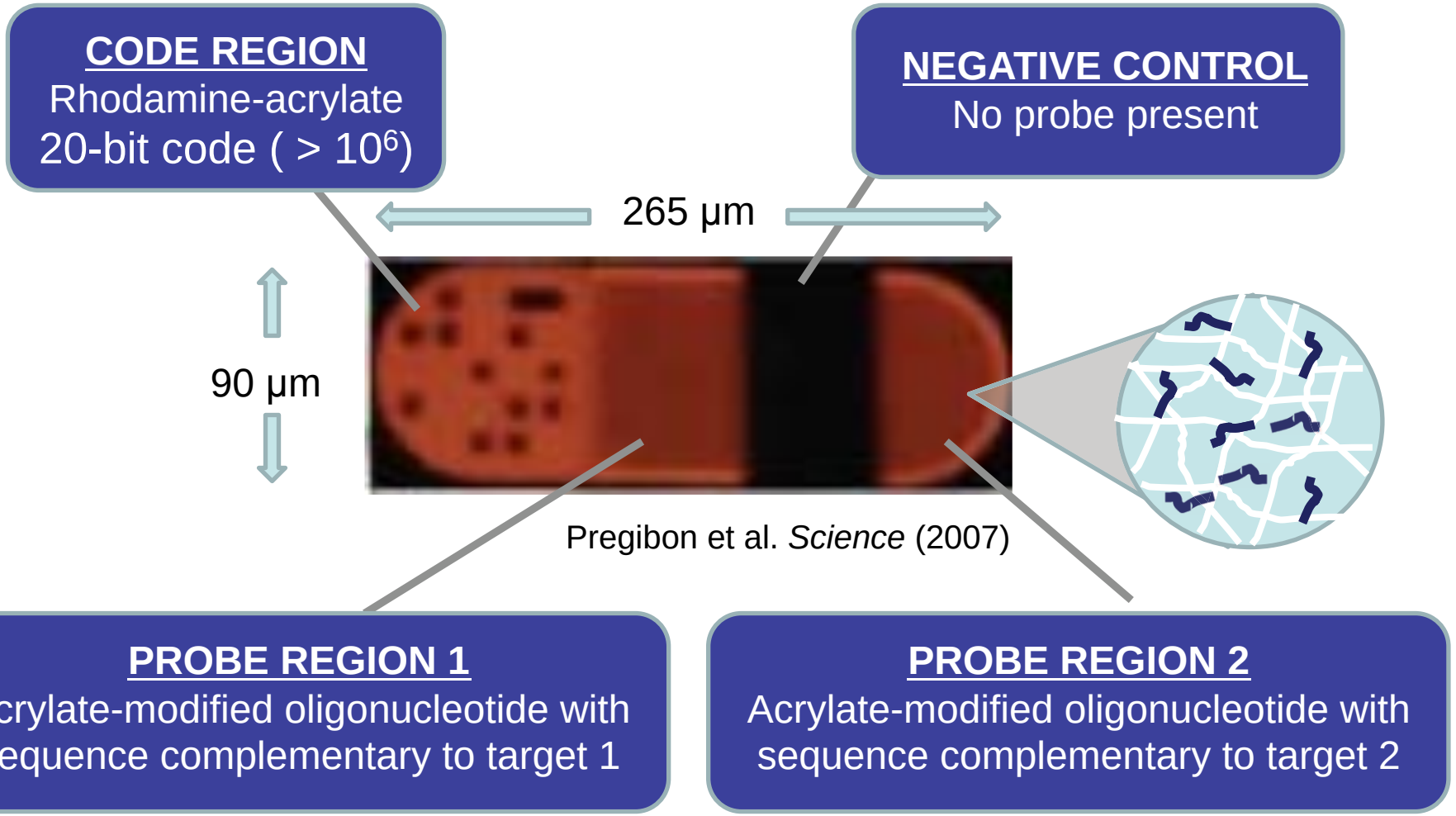
-Highly tunable particle properties (porosity, flexibility, probe density)

Encoded Hydrogel Particles

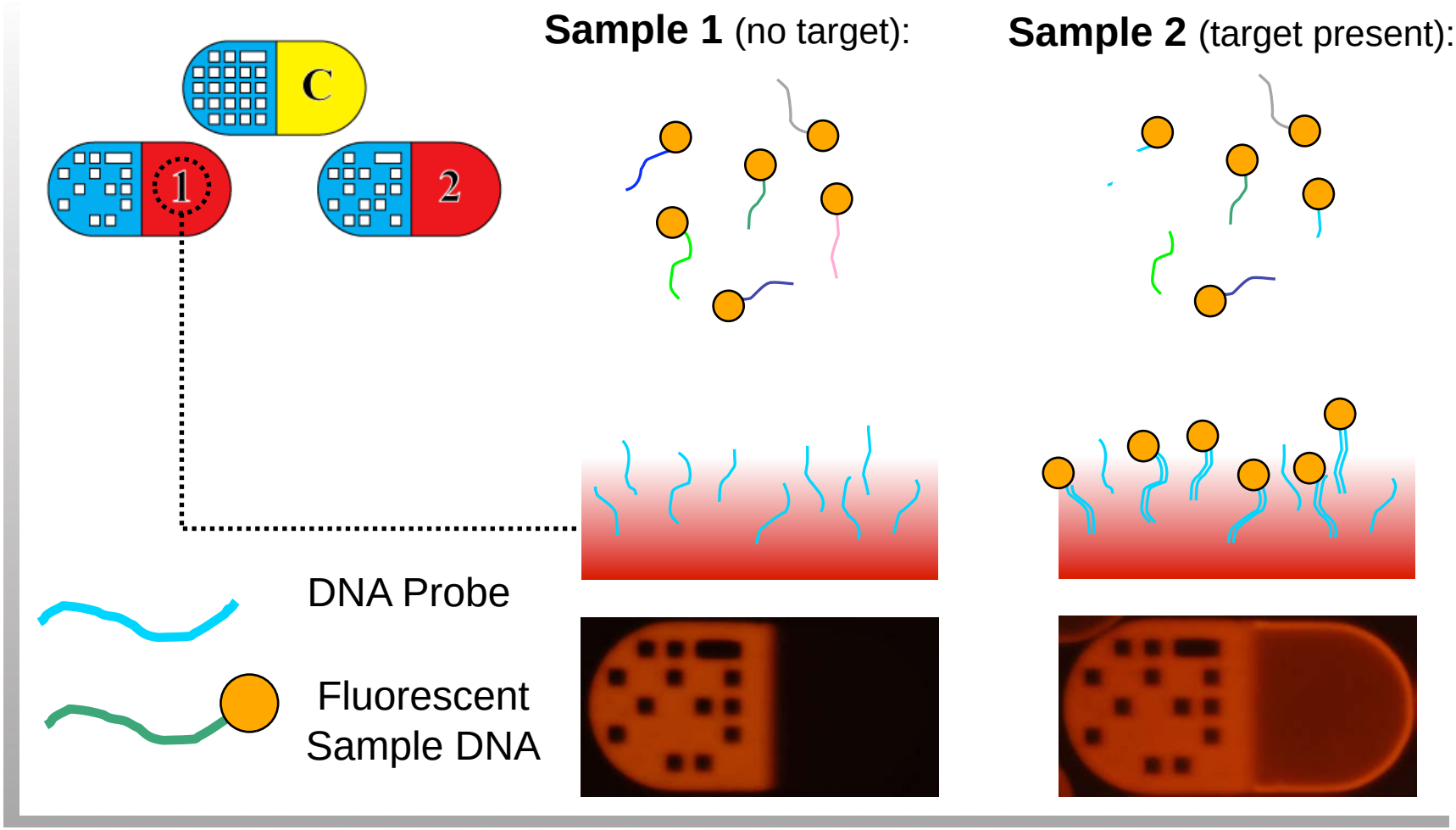


(Pregibon, Toner, Doyle. *Science*, 2007.)

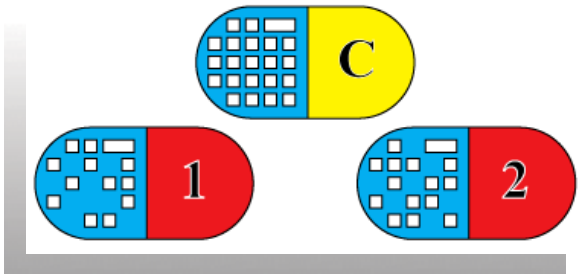
Our Particle Motif

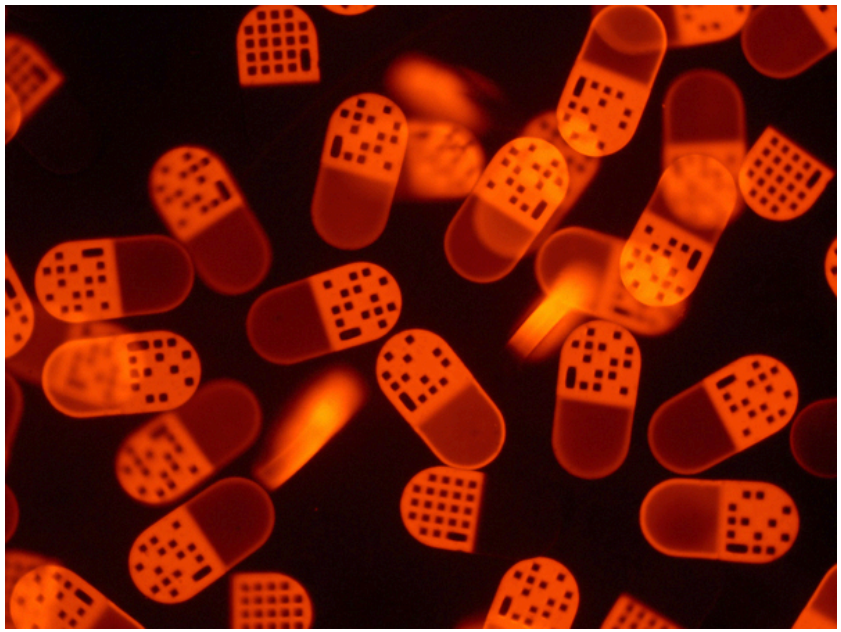


Testing a Sample (DNA example)

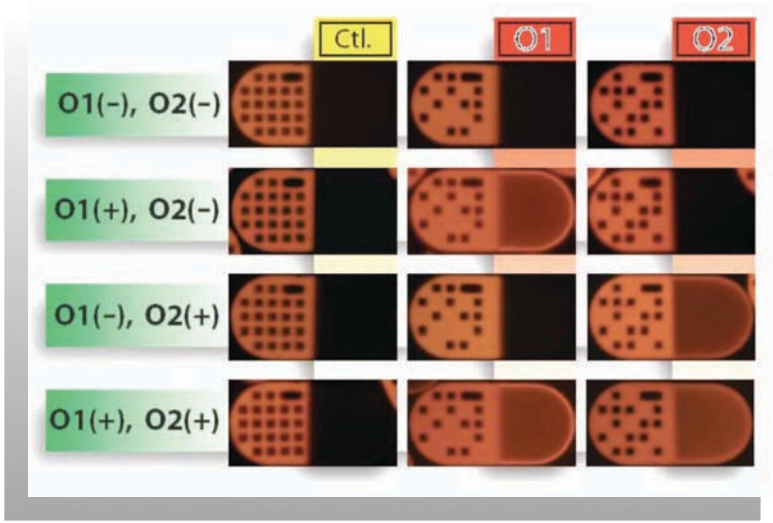


Sensing with Single-Probe Particles

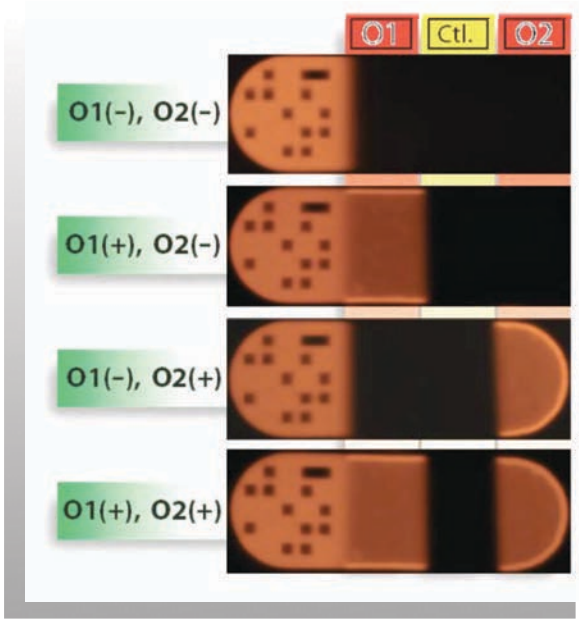




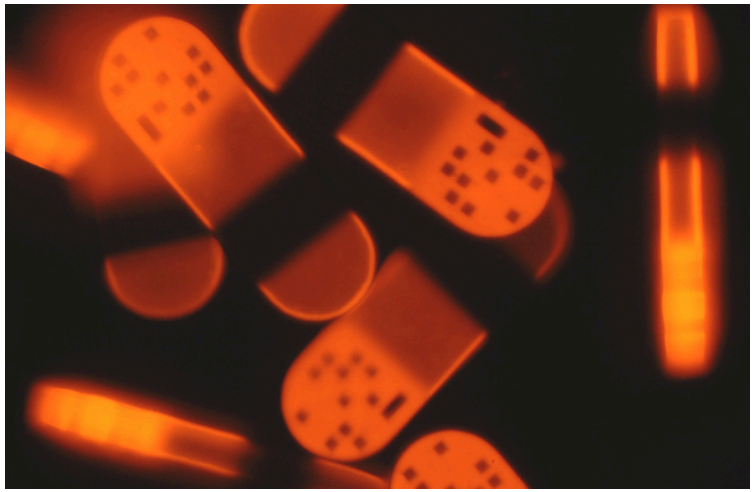
- Library of particles with barcode corresponding to target
- Short 10min incubation
- Particles show great specificity
- Very reproducible



Sensing with Multi-Probe Particles



- Single particle contains several probes – provides an even higher level of multiplexing
- Control built into EVERY particle – quality of information
- No loss of specificity

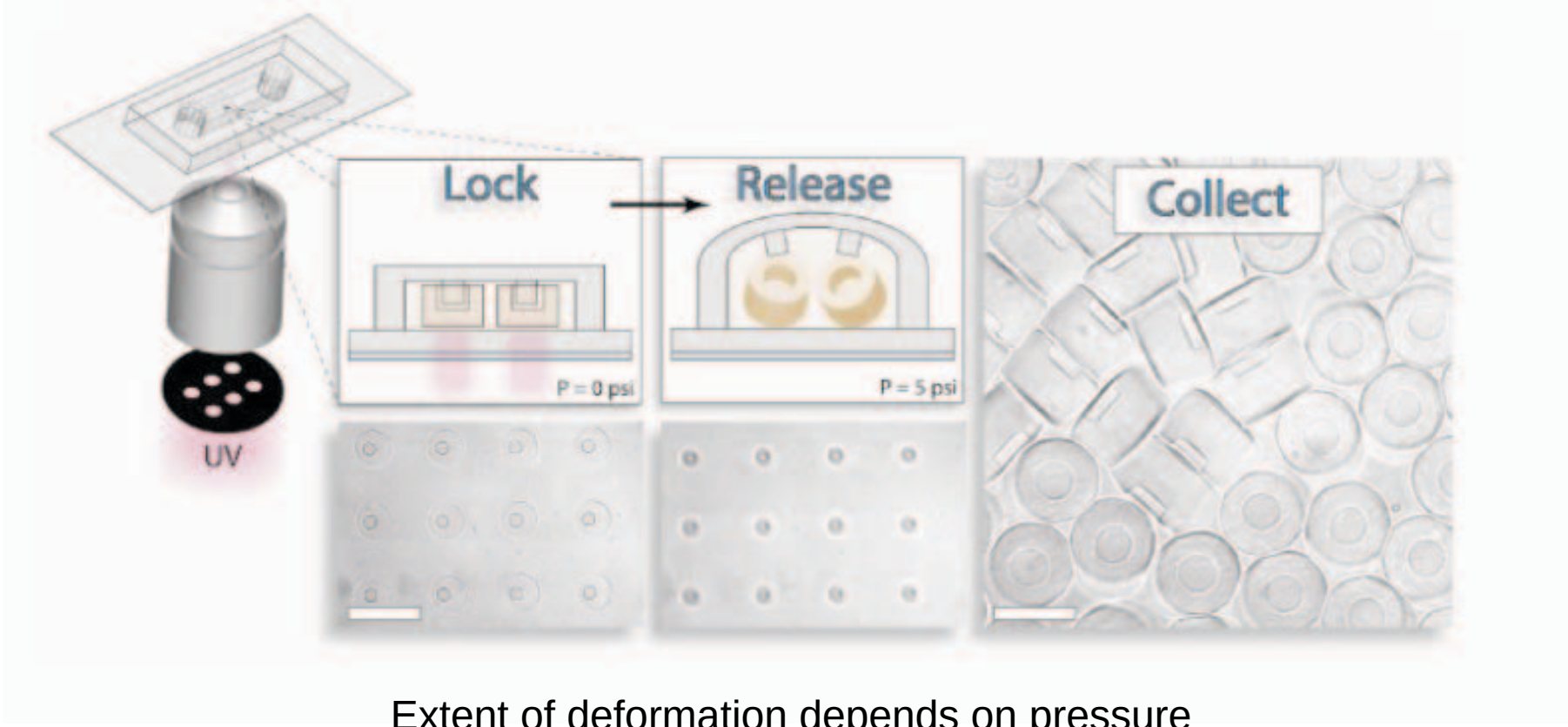


Lock-Release Lithography

K.W. Bong, D. Pregibon & Doyle, P.S.

Lab on Chip, **9**, 863-866, 2009

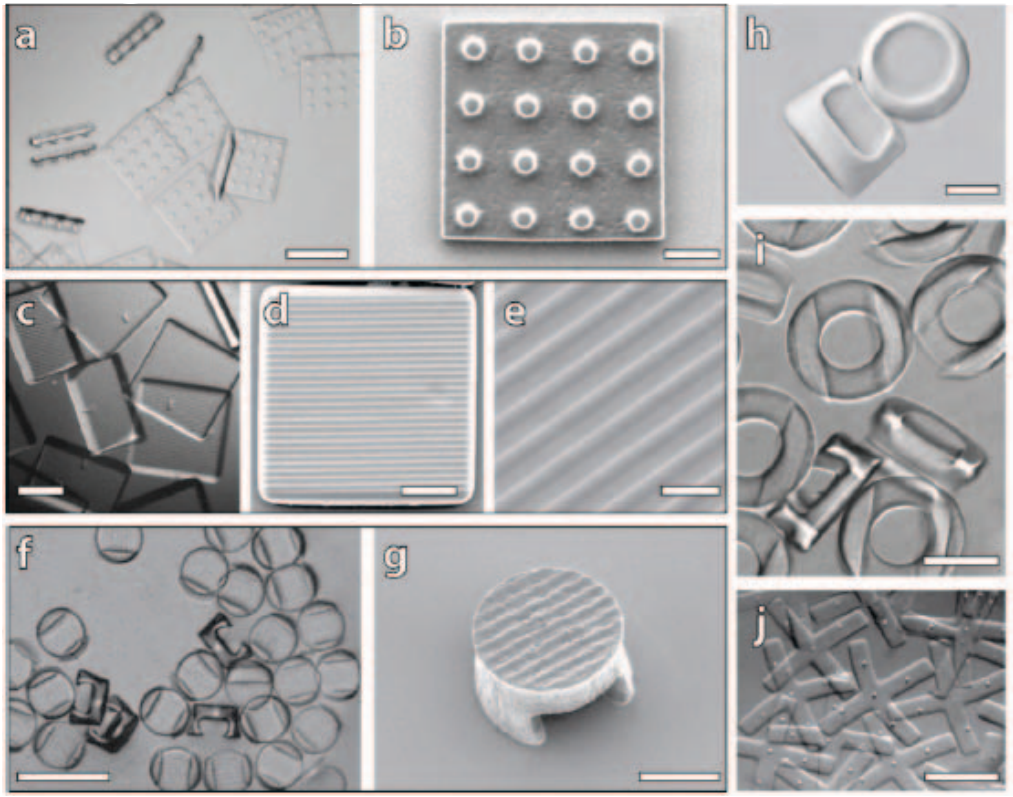
Basic concept: leverage flexible walls



Extent of deformation depends on pressure

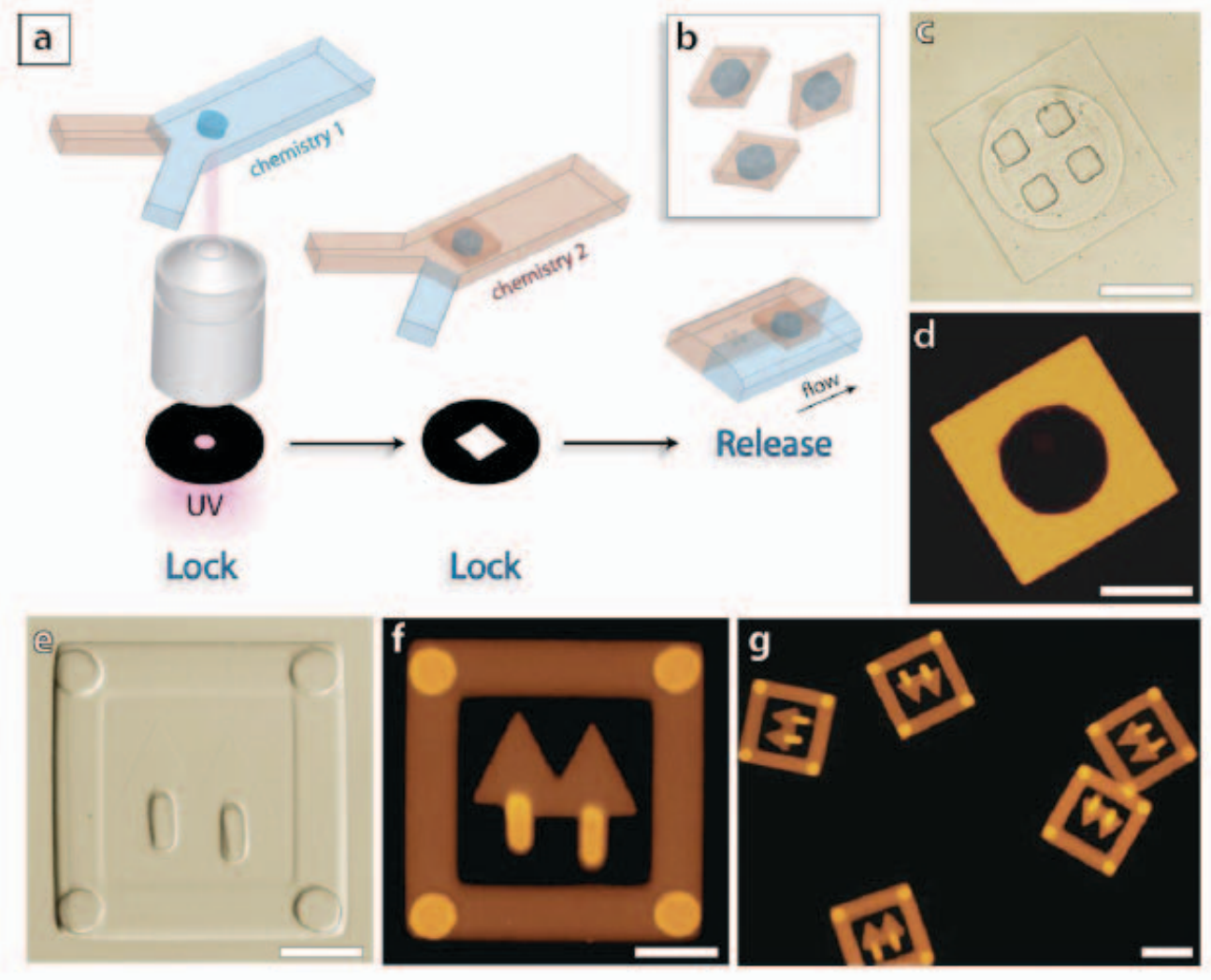
$$\Delta h_{\max} = C_1 \frac{P(z)W}{E}$$

Sampling of quasi-3D particles….

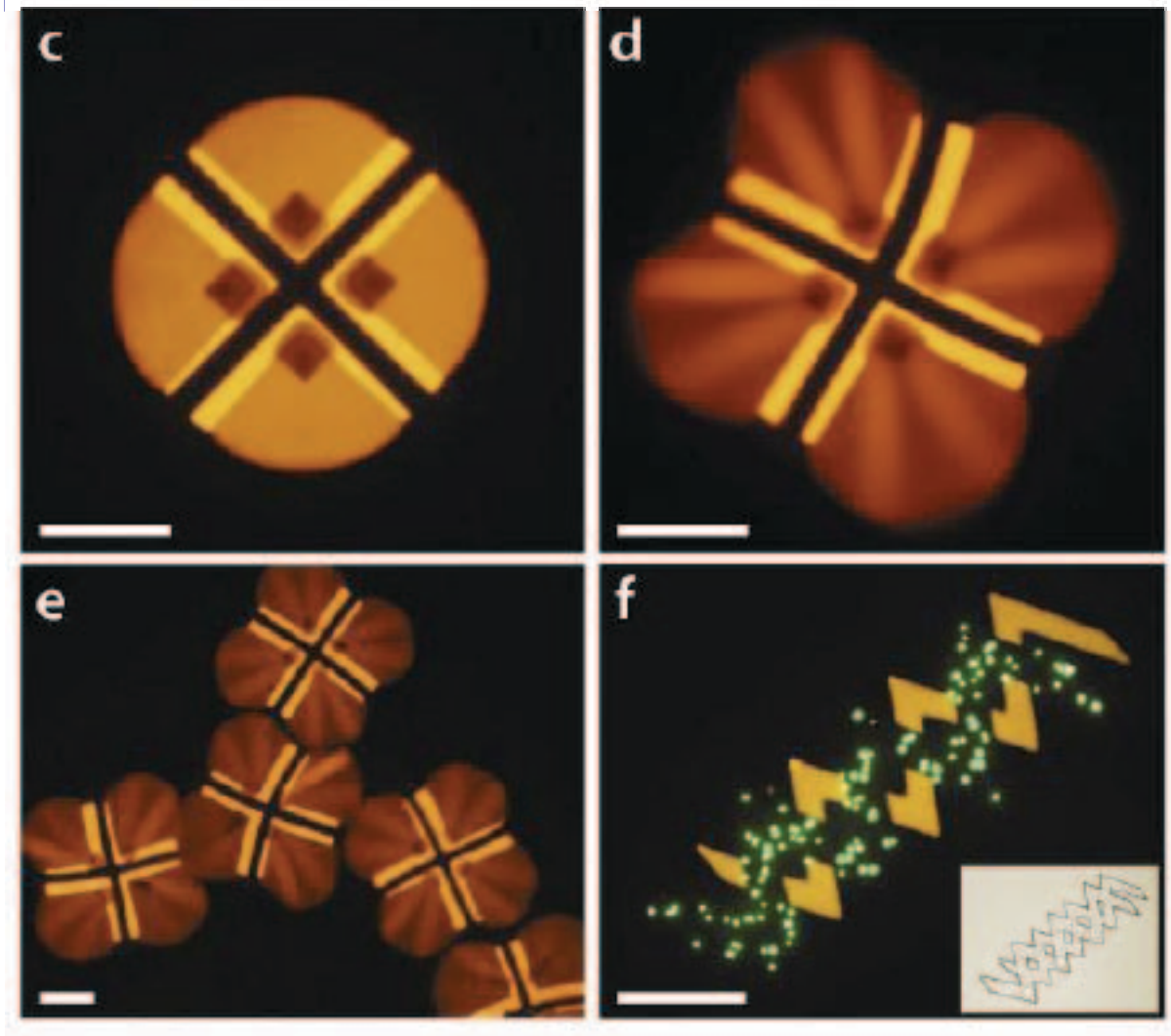


Sort of cool, but not the full story…..

Lock for multiple cycles, then release



Complex patterns can be created…

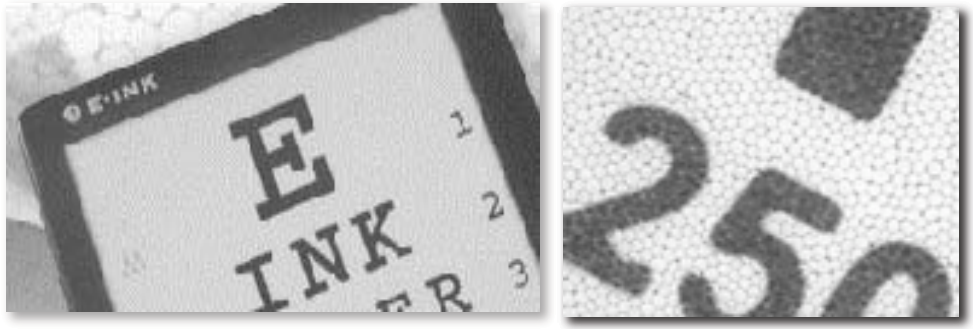


Fabricating Ceramic Microcomponents Using SFL

Shepherd et al., Adv. Mater. (2008)

Engineered Colloidal Granules and Microcomponents

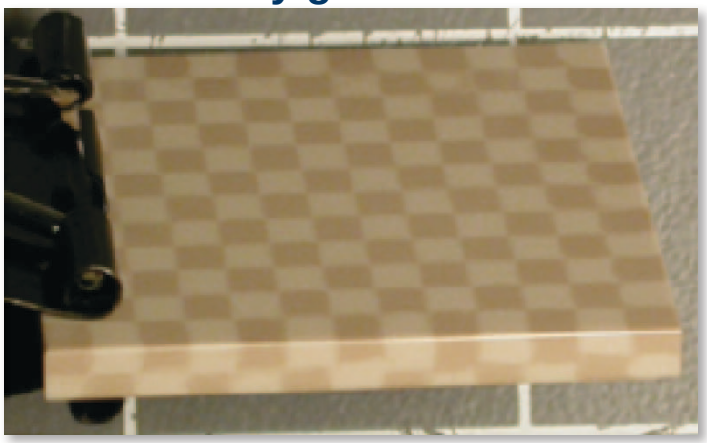
Electronic "paper"



Chen et al., *Nature* (2003)

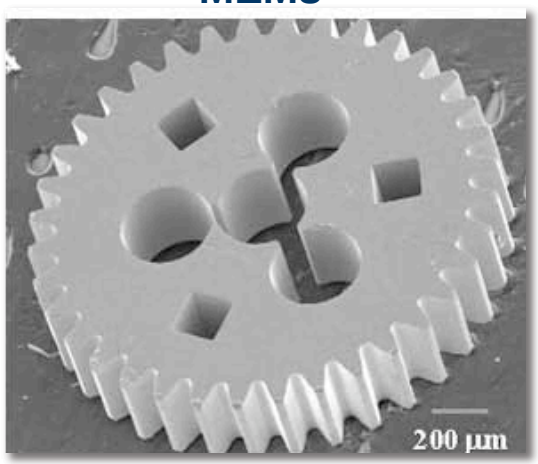
Pharmaceuticals

Functionally graded ceramics



Wing et al., *J. Am. Ceram. Soc.* (2006)

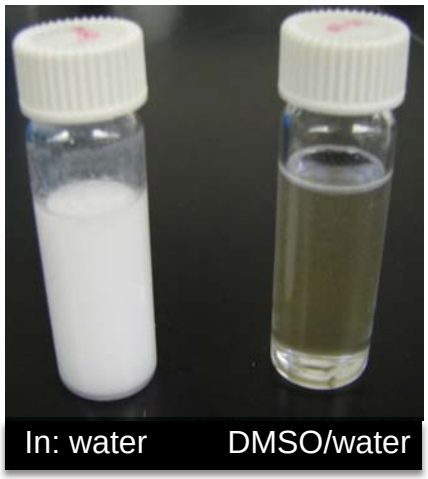
MEMs



R. Rao et al., *Adv. Mater.* (2005)

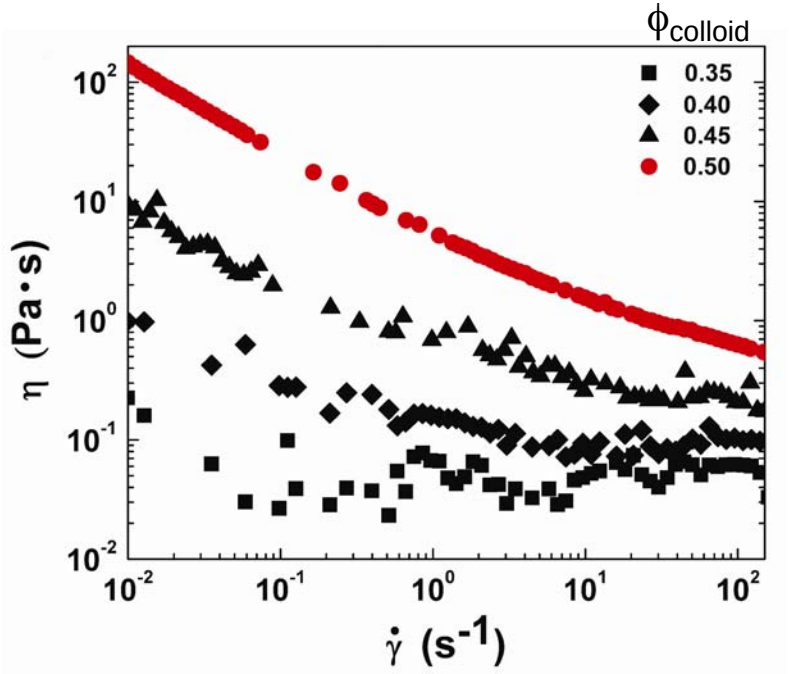
Colloidal System for SFL

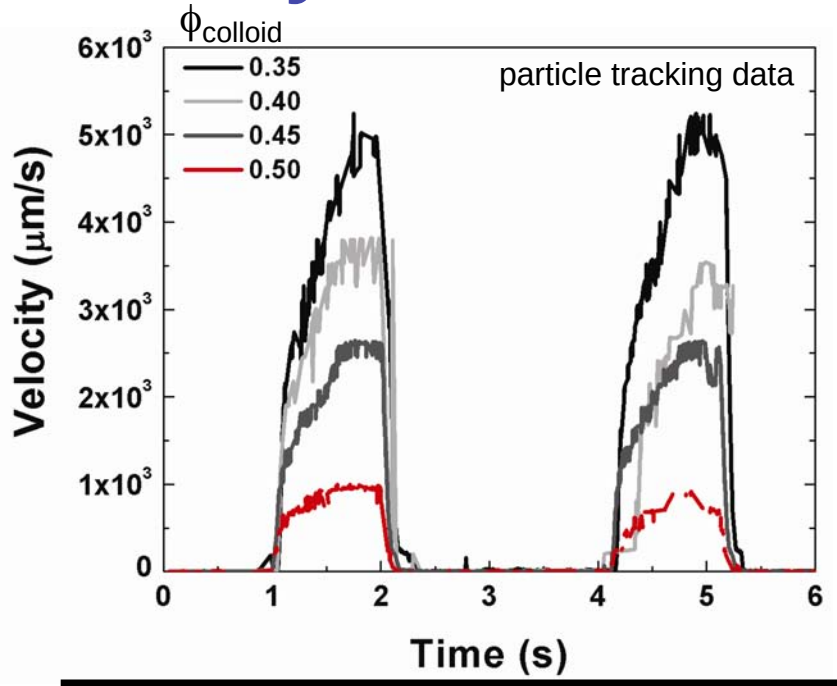
Component	*Chemical*	*Concentration*
Monomer	acrylamide	ϕ_a=0.10
Crosslinker	N,N-methylene bisacrylamide	ϕ_c=0.2ϕ_a
Photoinitiator	Darocur 1173	ϕ_i=0.04
Colloids	RITC core-shell silica, ~500 nm diameter	ϕ_s=0.50



Concentrated colloid-acrylamide suspensions are index-matched in a mixture of DMSO-water to enhance polymerization rate

Rheology is Key





Key process parameters:

t_{stop} ~ 100 - 300 ms (ϕ-dependent)

$t_{polymerize}$ ~ 200 - 400 ms (shape-dependent)

t_{flow} ~ 300 ms

Production rates ~ 60 - 10^3/min (mask-dependent)

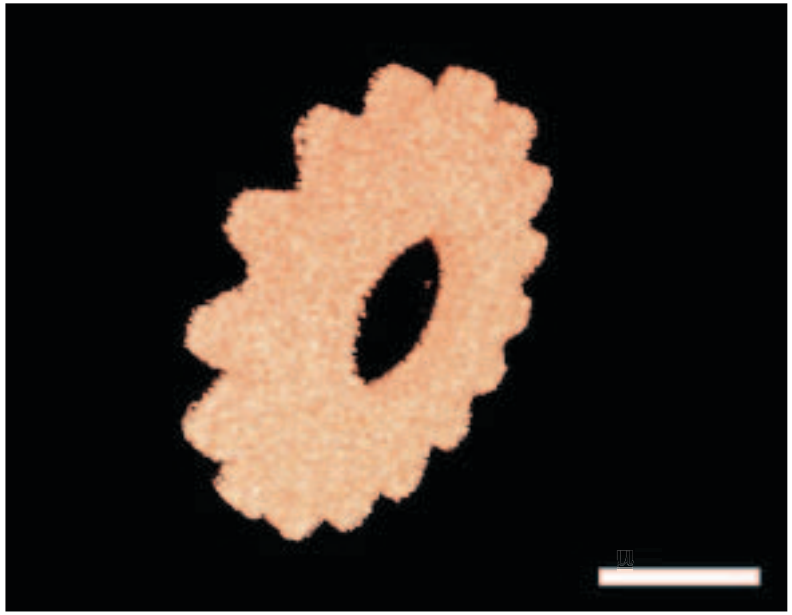
$$V(L) = \frac{H^3 E}{32 W \eta L}\left[\left(1 + \frac{PW}{EH}\right)^4 - 1\right]$$

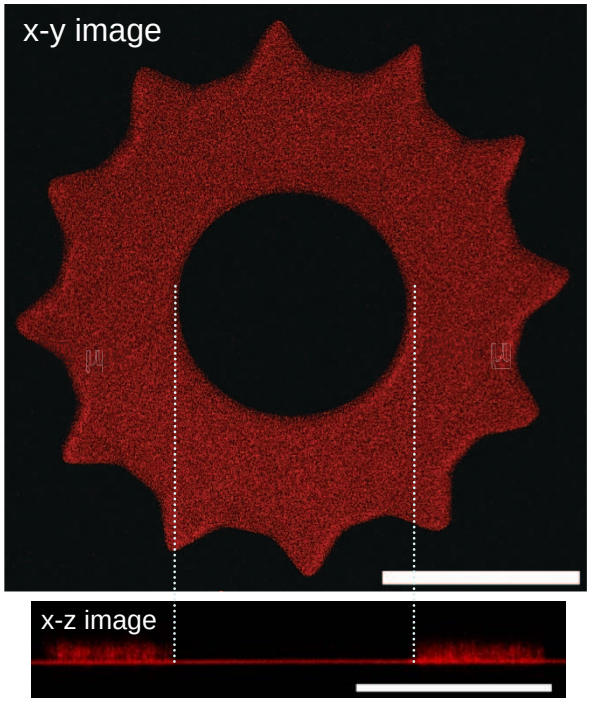
where: H,W,L,P,E, η = channel height, width, length, applied pressure, modulus, viscosity

Dendukuri et al., Lab Chip (2007)

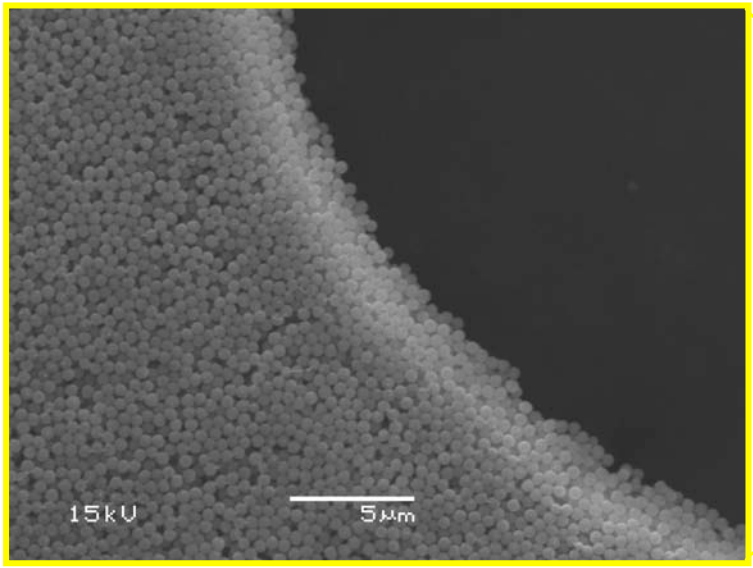
Uniform Packing

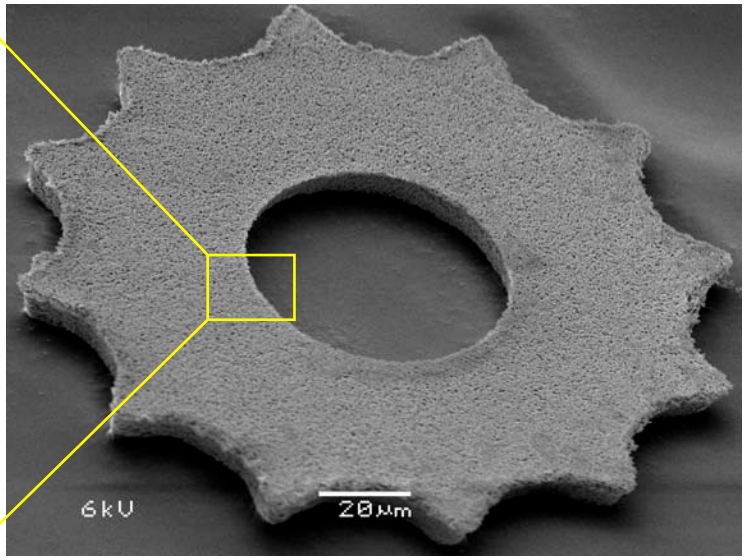
wet





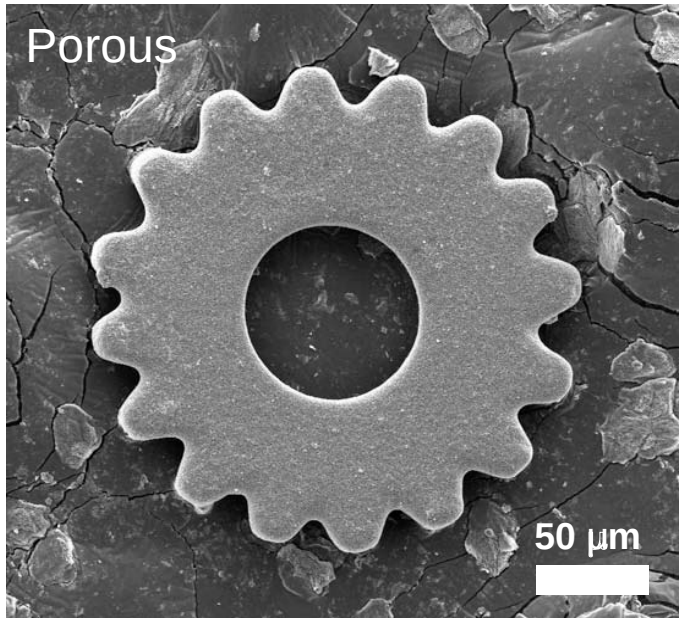
dry



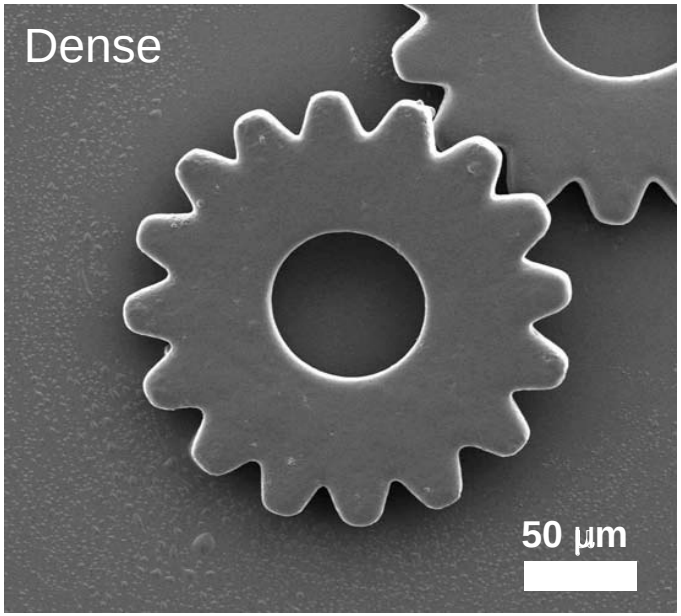


Sintered Silica Gears

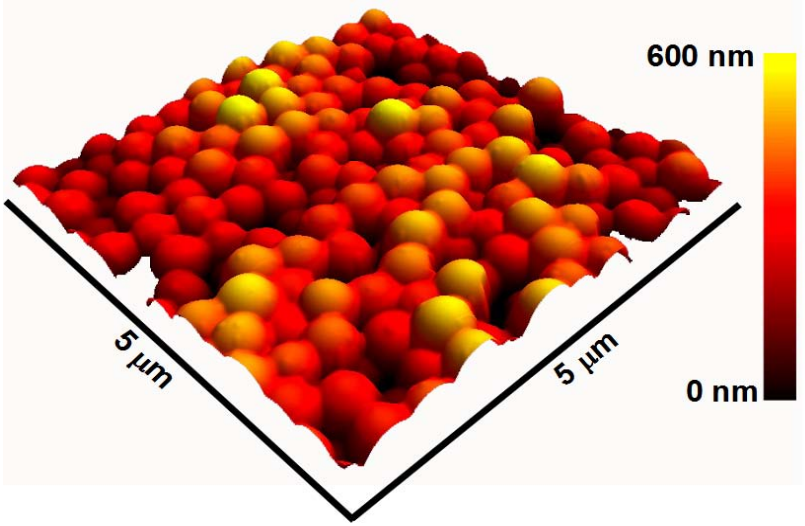
1150 C 1 hour, ϕ ~ 0.77



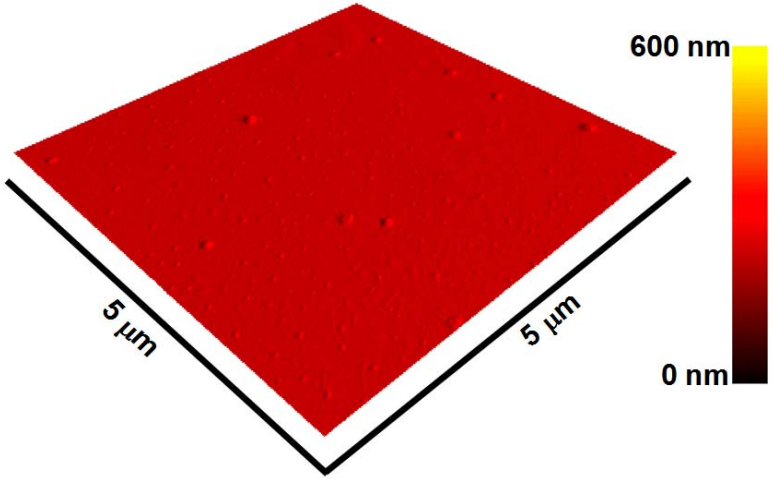
1150 C 10 hours, ϕ ~ 1



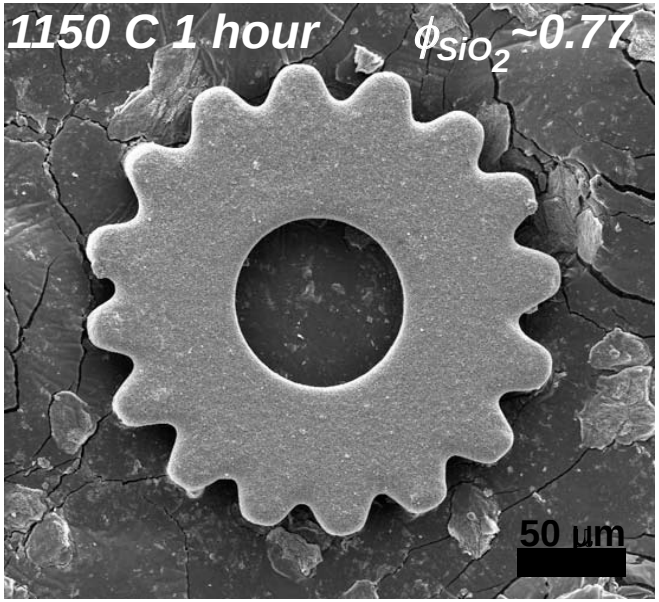
AFM: rms = 130nm

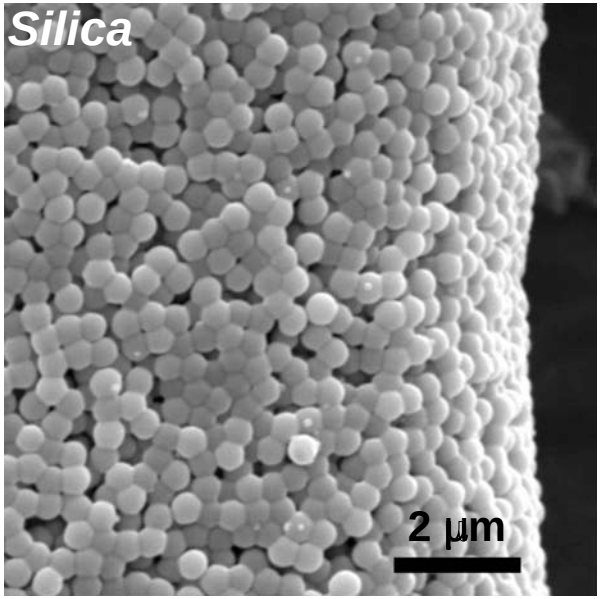


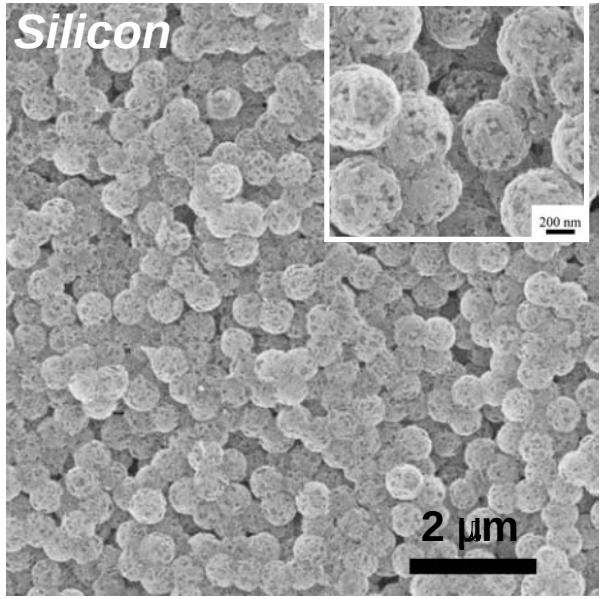
AFM: rms = 6nm

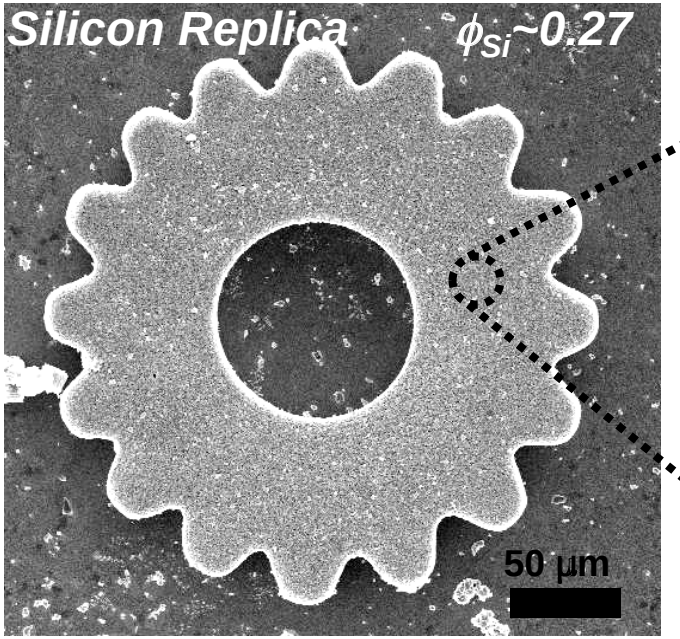


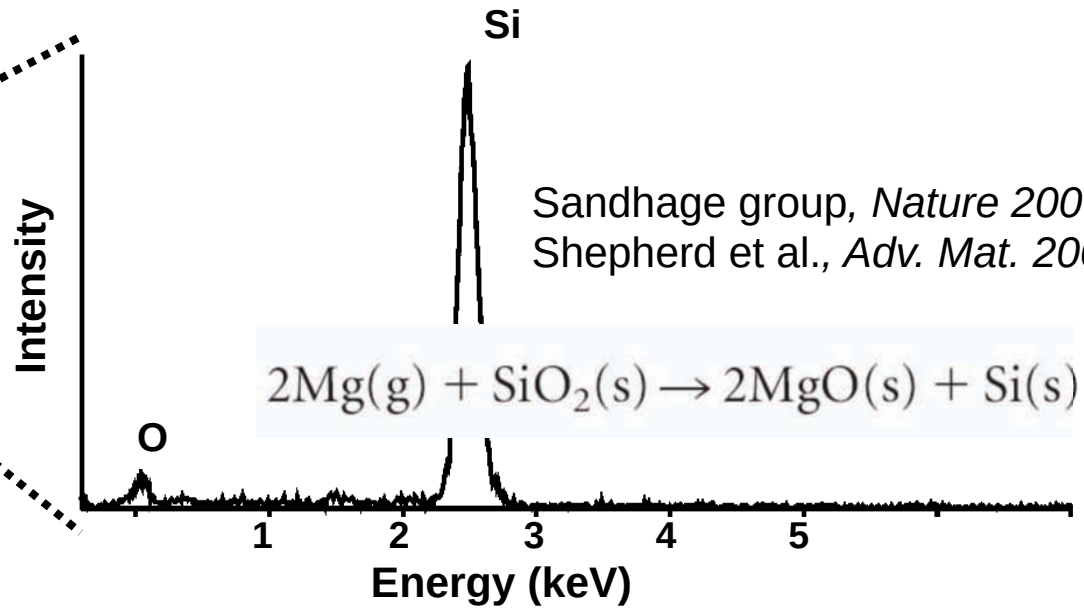
Conversion to Silicon







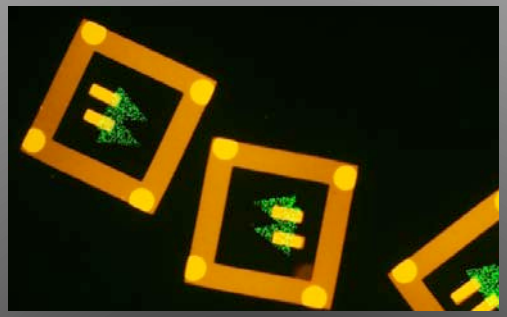




Sandhage group, *Nature 2007*
Shepherd et al., *Adv. Mat. 2008*

$$2Mg(g) + SiO_2(s) \rightarrow 2MgO(s) + Si(s)$$

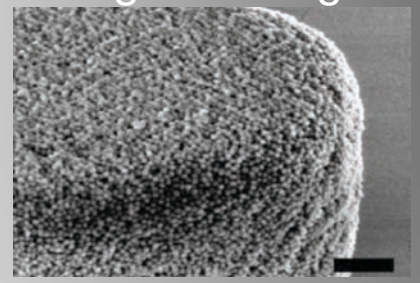
patterned regions



shape

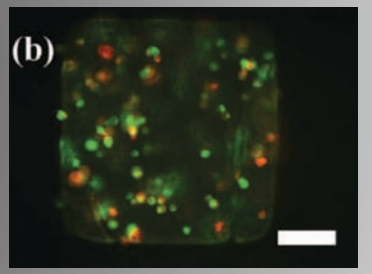
aspect ratio

cargo-bearing

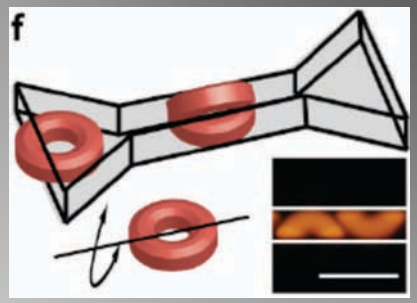


microparticle
complexity space

compatibility



mechanical properties



responsive