Microfluidic Control of Cellular Confinement in Hydrogel Microgels

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Introduction

Cell behaviour is strongly influenced by the surrounding microenvironment, including cellular confinement, geometry and cell density. Droplet microfluidics provides a platform for generating hydrogel microgels with tunable morphologies and controllable cellular loading [1,2,3]. By manipulating flow conditions and crosslinking dynamics, a range of microenvironments can be produced. Understanding how these parameters influence microgel morphology is essential for engineering reproducible culture systems for future organoid applications [4,5].

Aim: To identify microfluidic conditions that generate **reproducible** hydrogel microenvironments with **tunable** cellular confinement.

Methodology

Rayleigh–Plateau instability was exploited to generate hydrogel constructs with tunable morphologies.

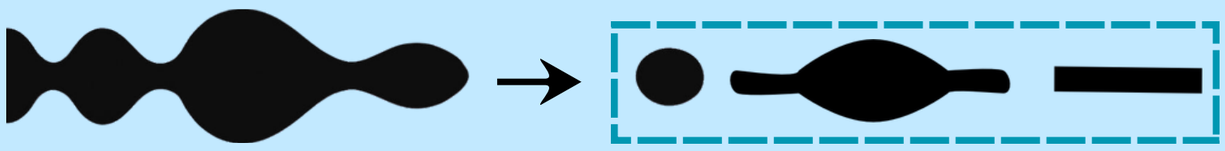

Figure 1. Hydrogel structures generated through manipulation of Rayleigh–Plateau instability.

Figure 2. Representative brightfield images of hydrogel structures generated using a glass capillary microfluidic device. (A) Droplet, (B) interlinked bead, and (C) thread morphology. Scale bar = 500 µm.

By adjusting flow rates and hydrogel precursor concentrations, reproducible microgels with tunable cell loading can be generated.

Microfluidic Device Design

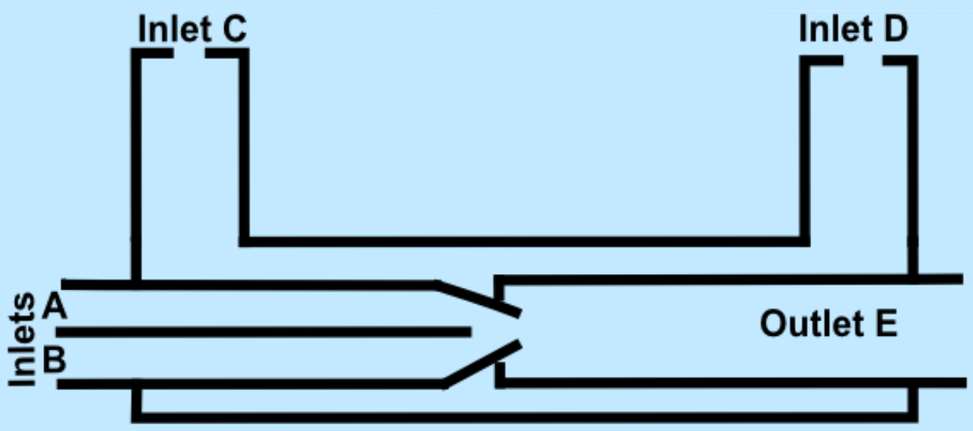

Figure 4. Schematic of the glass capillary microfluidic device. Mineral oil with 2% Span 80 was introduced through inlets C and D, while sodium alginate and calcium chloride were introduced through inlets A and B [1,2].

Conclusion + Future Work

The device enables the reproducible generation of tunable cellular microenvironments with controllable cell loading. Future work will investigate blood–tumour interactions through the co-encapsulation of endothelial cells, pericytes and glioblastoma cells.

Microenvironment Control

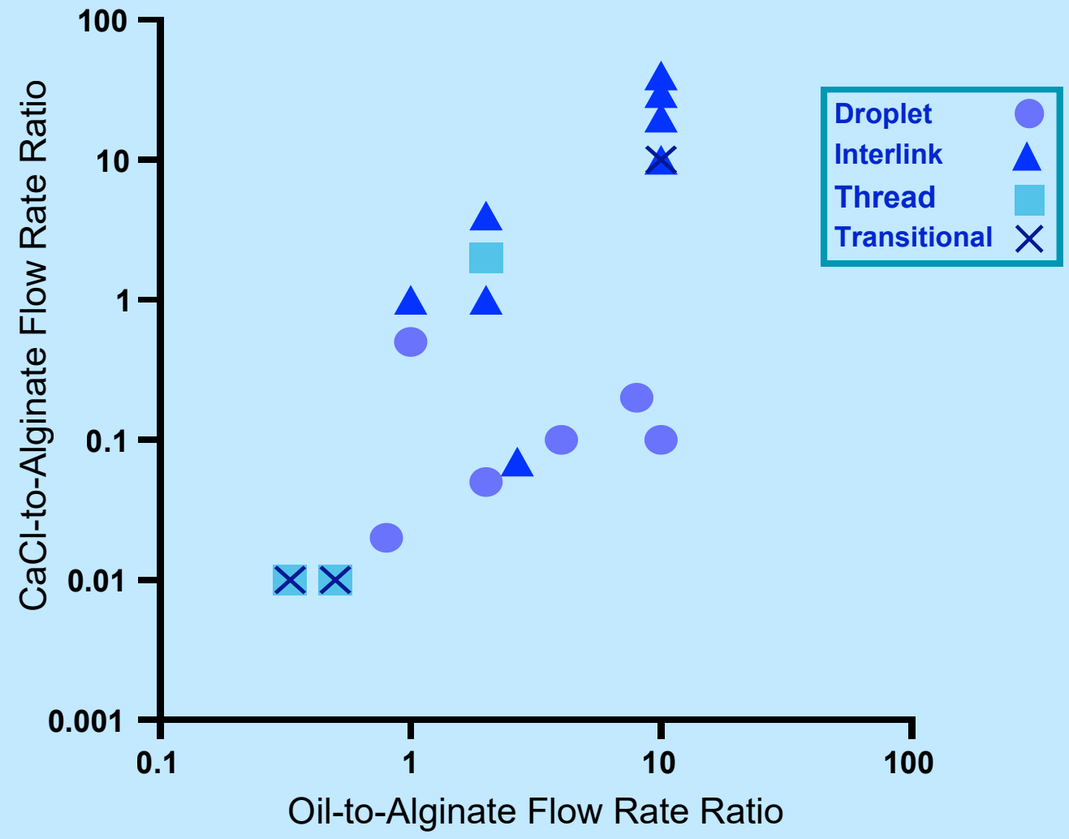

Figure 5. Regime map illustrating the effect of oil-to-alginate and $CaCl_2$-to-alginate flow rate ratios on hydrogel morphology. Data points are classified as droplet, interlink, thread or transitional regimes. Higher $CaCl_2$-to-alginate ratios favoured the formation of interlinked and thread-like structures, whereas lower ratios predominantly produced discrete droplets. **Both axes are shown on logarithmic scales.**

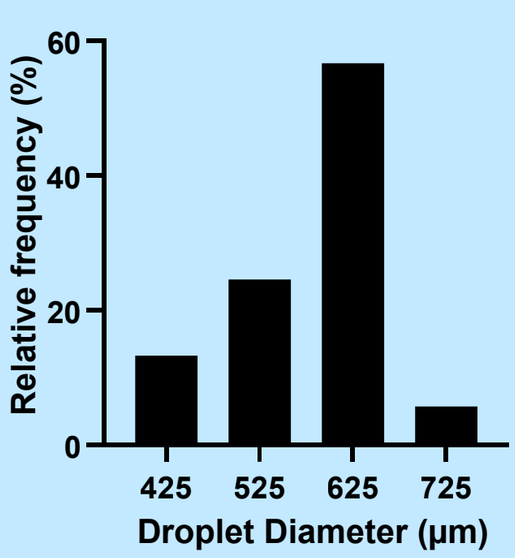

Figure 6. Droplet diameter distribution of hydrogel microgels generated using a glass capillary microfluidic device (n = 53).

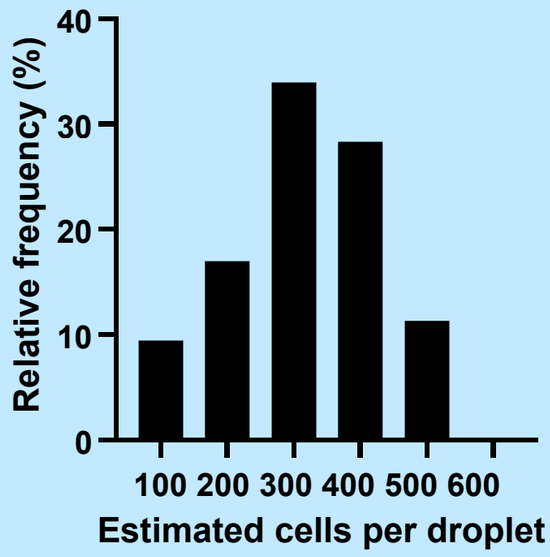

Figure 7. Predicted endothelial cell loading per microgel at an encapsulation density of $3x10^6$ cells/ml.

Biological Application

Encapsulation of endothelial cells within alginate microgels creates defined three-dimensional environments with controlled cellular confinement. This is relevant for blood–brain barrier modelling, where cell organisation is strongly influenced by the surrounding physical environment [4,5].

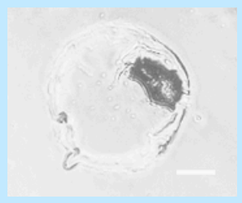

Figure 8. Representative endothelial cell confined within an alginate microgel. Scale bar = 200 µm.

References:
[1] Witte et al., Mater Today Bio, 2019.
[2] Witte et al., Biofabrication, 2020.
[3] Utech et al., Adv Healthcare Mater, 2015.
[4] Urich et al., Sci Rep, 2013.
[5] Cho et al., Nat Commun, 2017.

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