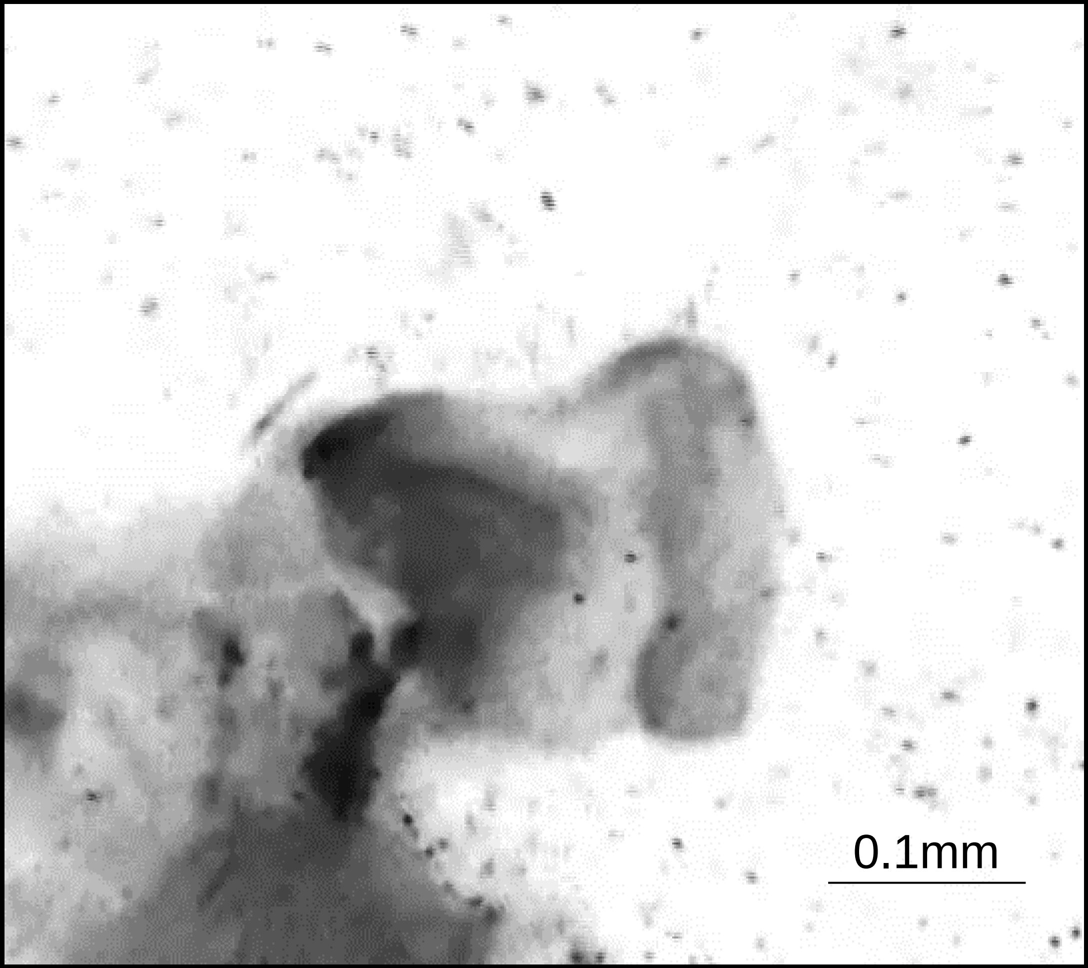
Cilia-driven flow fields for transport and selective capture of bacteria



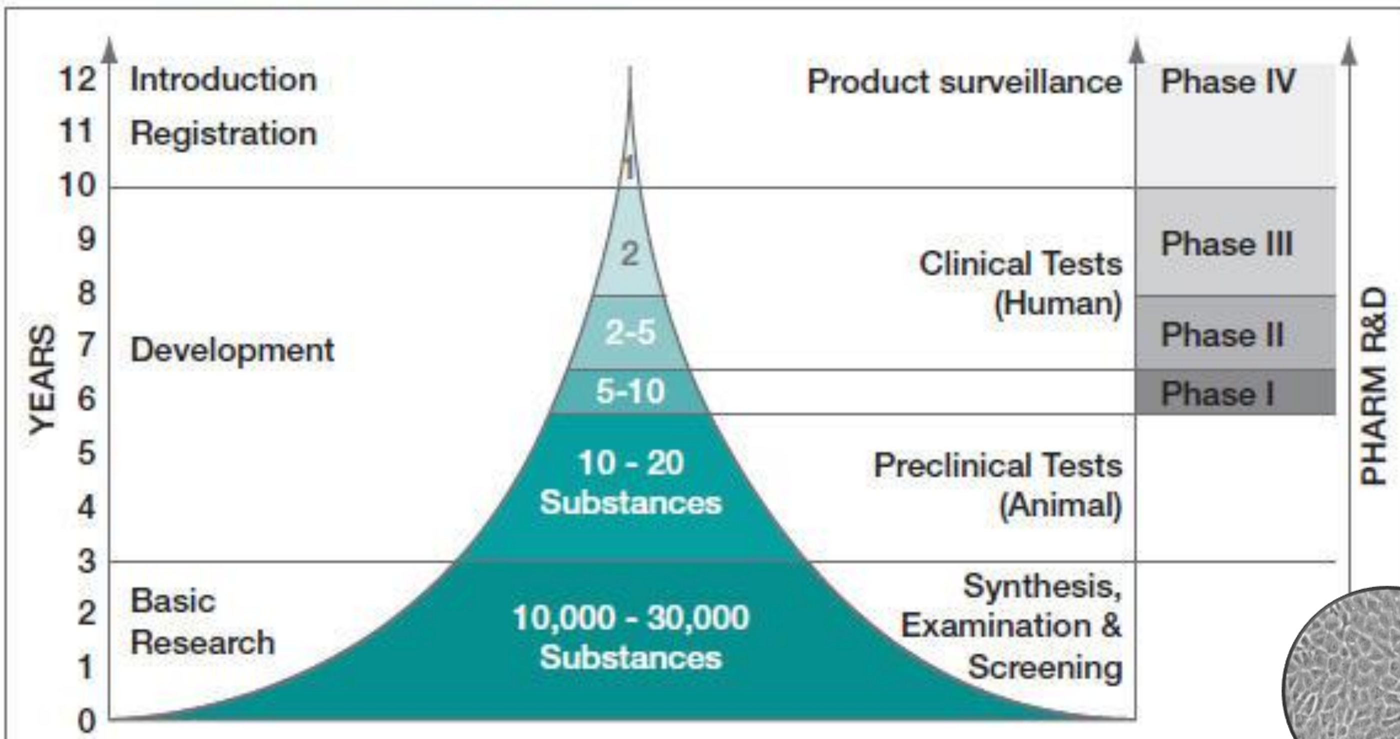
Janna Nawroth, Ph.D.
Wyss Institute for Biologically Inspired Engineering, Harvard University

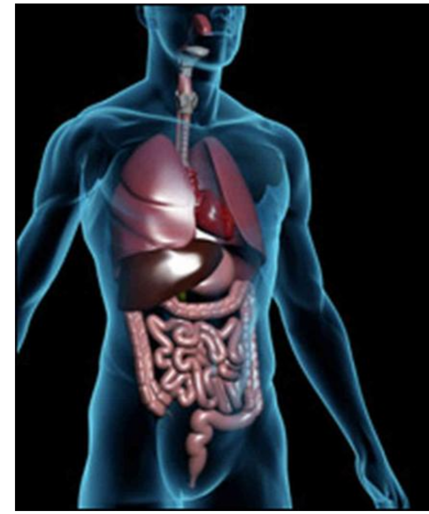
Active Matter | Kavli Institute for Theoretical Physics | May 15th, 2014

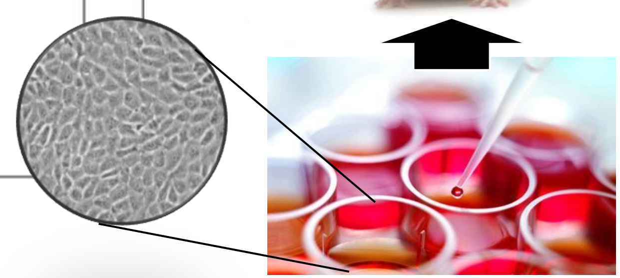
Traditional drug development

Time: 10 years
Cost: $1 Billion/drug

Figure 1: The drug development pyramid



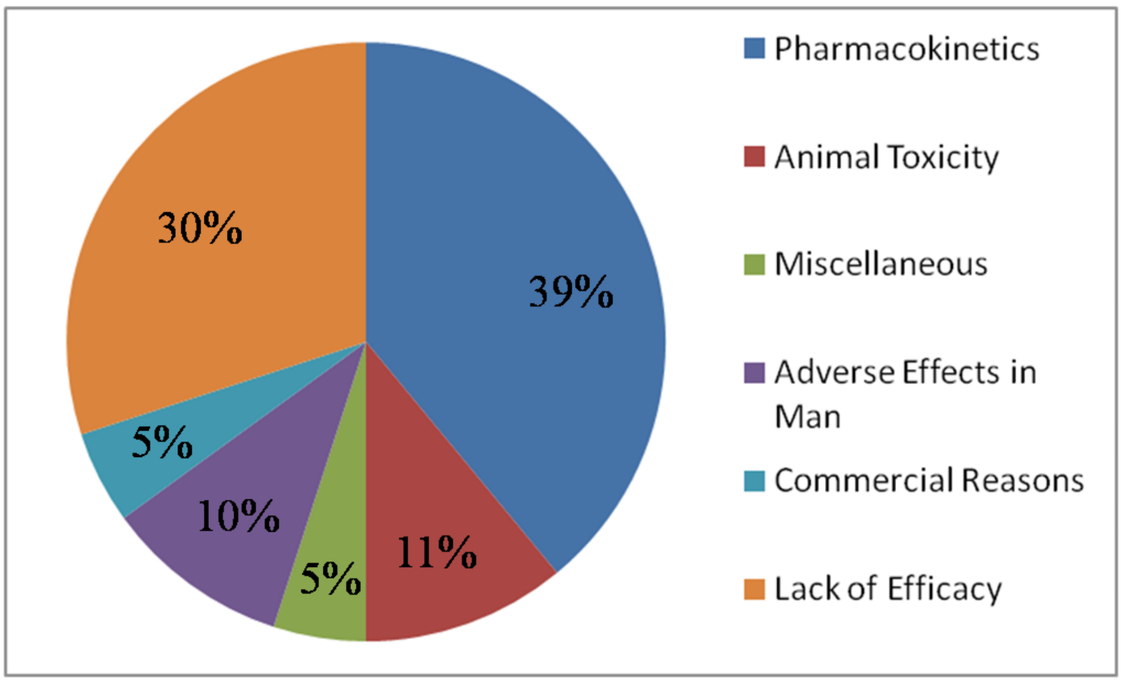


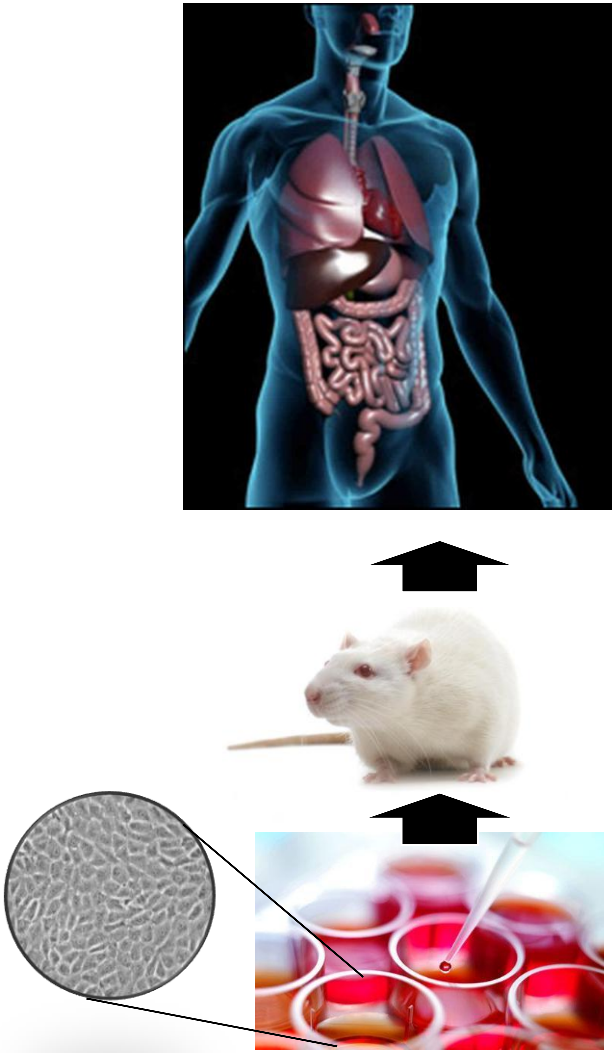


Traditional drug development

Time: 10 years
Cost: $1 Billion/drug

Reasons for drug failure: poor translation between test platforms and humans



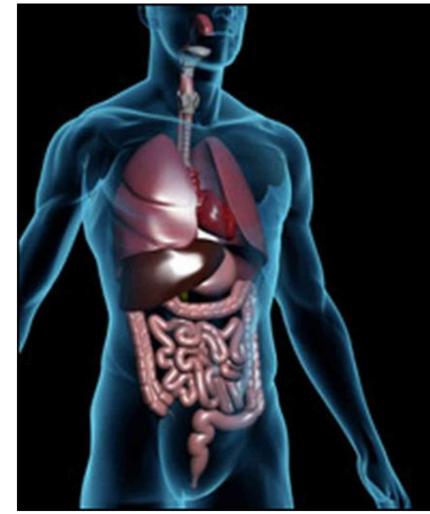


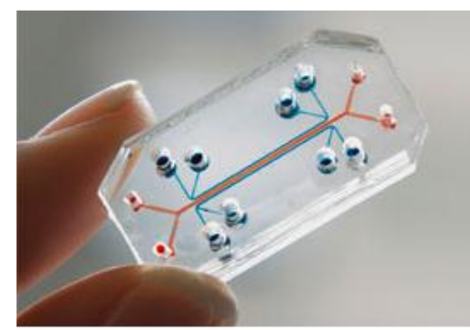
The quest for a better *in-vitro* model of human disease and drug response

Organ-on-a-chip

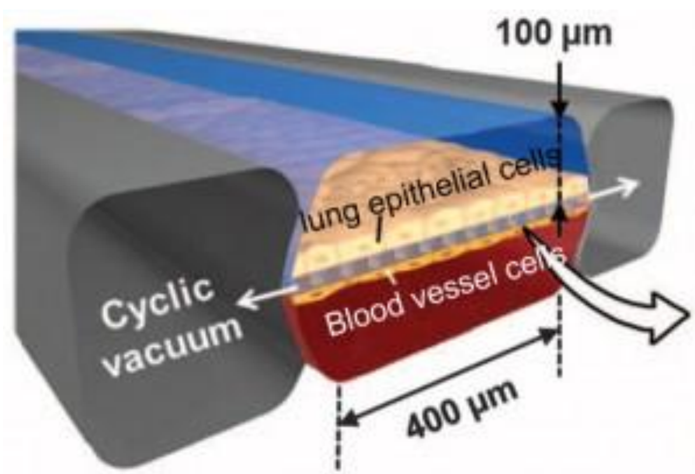
- 3-D microfluidic cell culture chip from human cells
- simulates characteristic mechanics and physiological responses of entire organs

→ “human” platform for drug testing and disease models





Example: lung-blood barrier function



Duh et al. 2010, Science, “Reconstituting Organ-Level Lung Functions on a Chip”

Organ-on-a-chip design

Biology
Identify relevant structure-function relationships

Structure and motion of building blocks (cells, matrix)

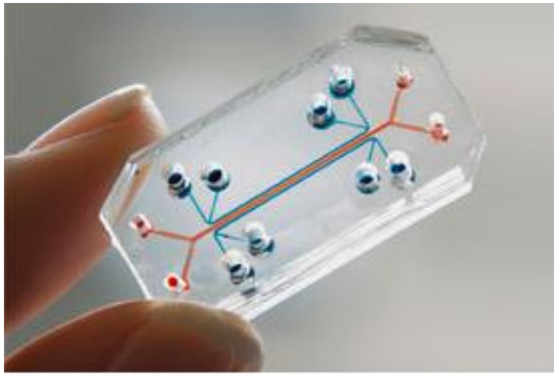
↓

Emergent functions

↓

Quantitative metrics of organ fitness

Engineering
Design, build and test structure-function relationships



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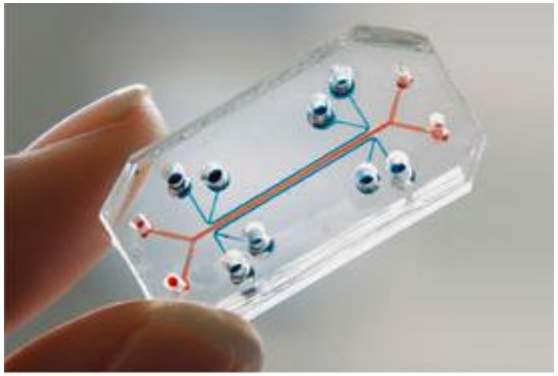


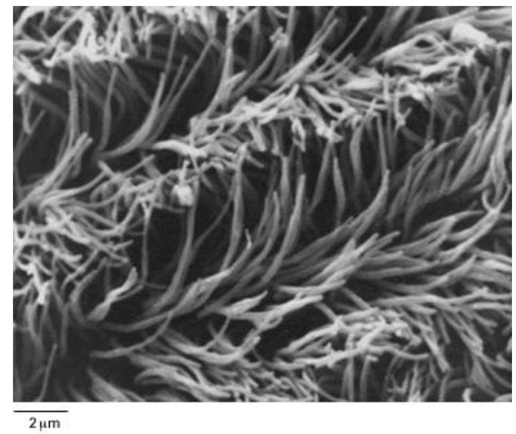
Example lung chip
Metrics of fitness are
- Structural integrity
- Absorption air → blood

2 case studies

Muscle-powered fluid transport
…relevant to cardiovascular system

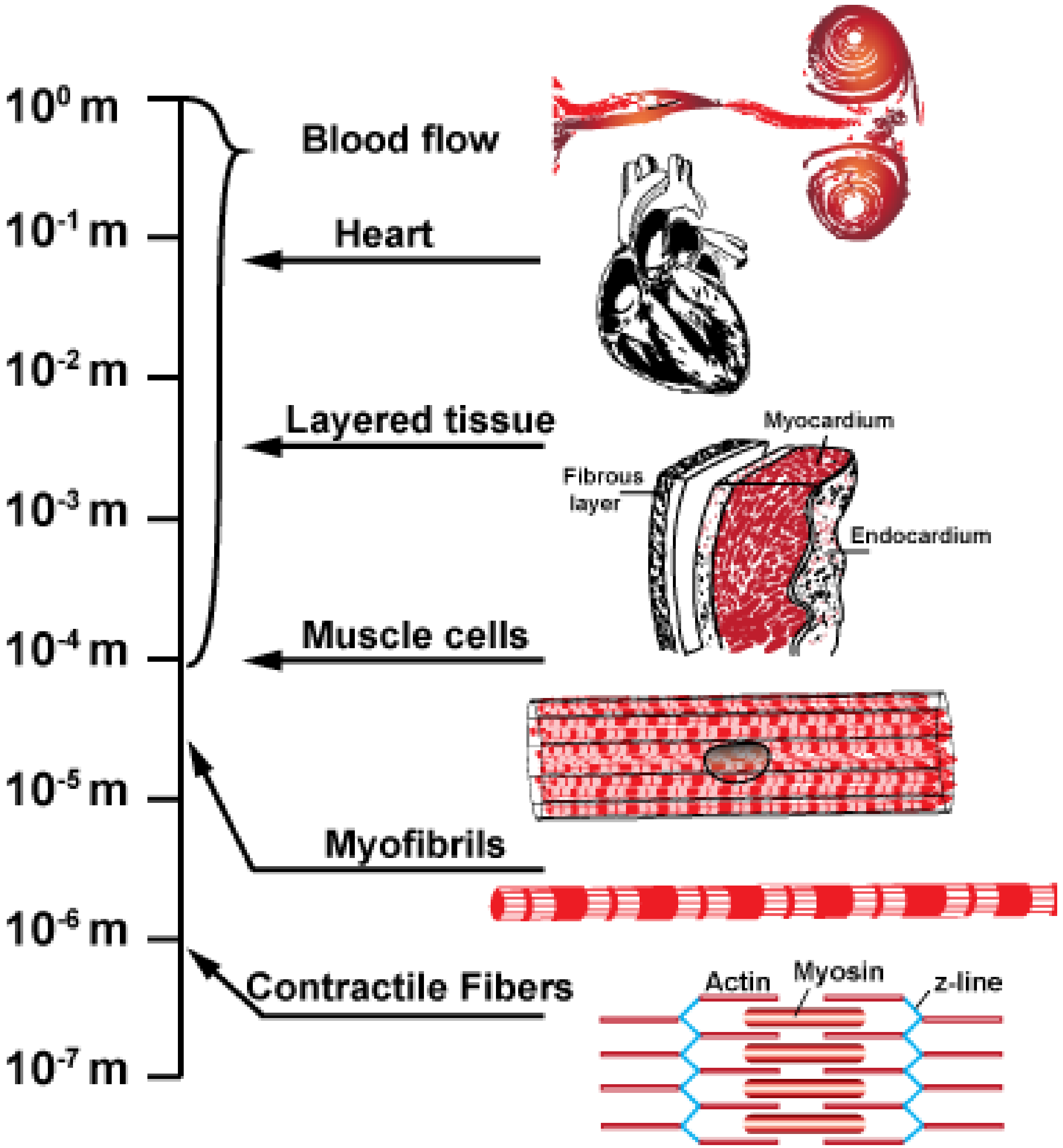
with
John Dabiri (Caltech)
Kit Parker (Harvard)
Donald Ingber (Harvard)

Cilia-powered fluid transport
… relevant to respiratory organs, brain, Fallopian tube



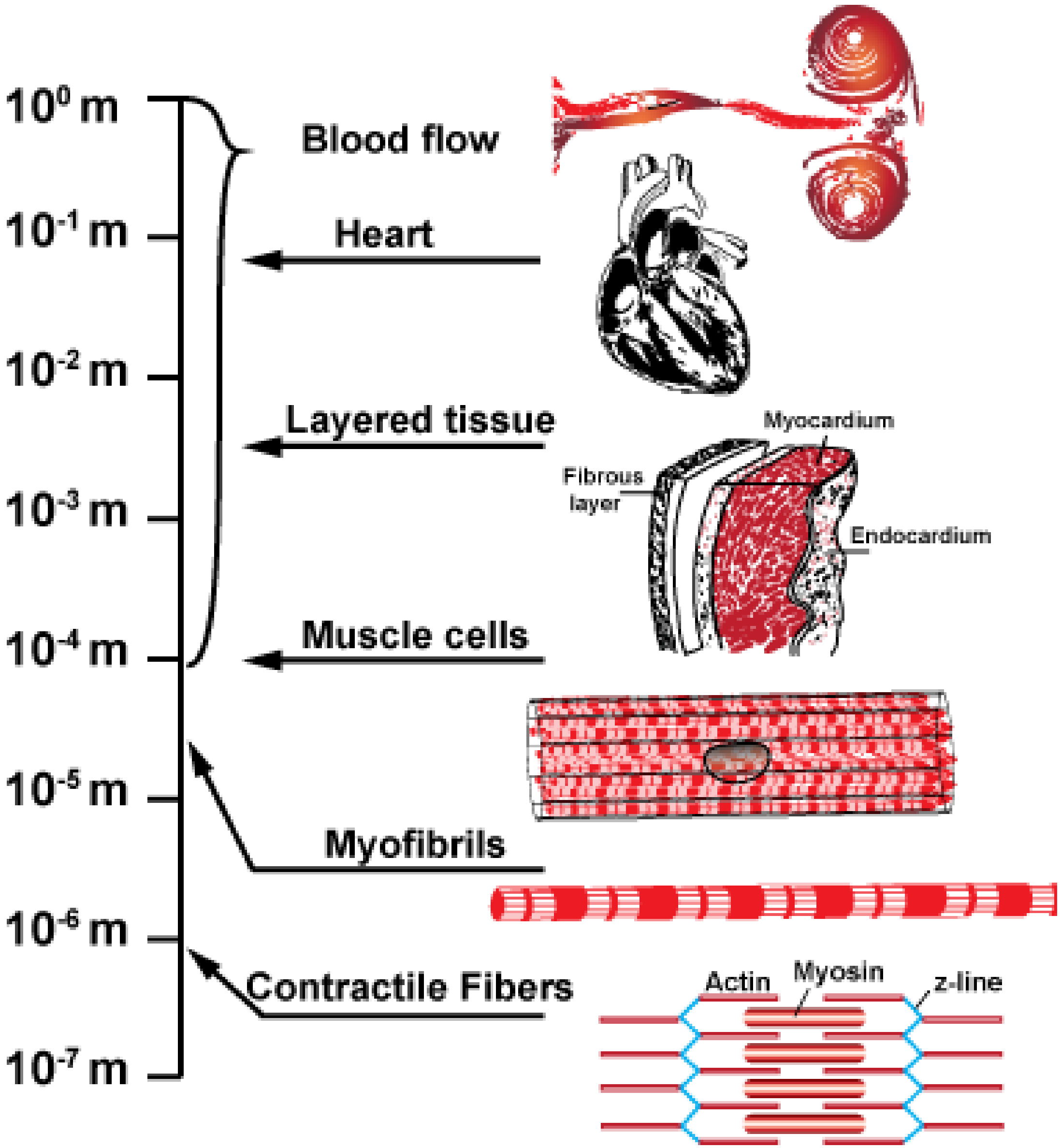
with
Eva Kanso (USC)
Margaret McFall-Ngai (UW Madison)
Edward Ruby (UW Madison)
John Dabiri (Caltech)
Scott Fraser (USC)

Case study: human heart



Heart Function

Case study: human heart



Heart Function

⬆

Body-fluid interaction

⬆

Tissue geometry

+

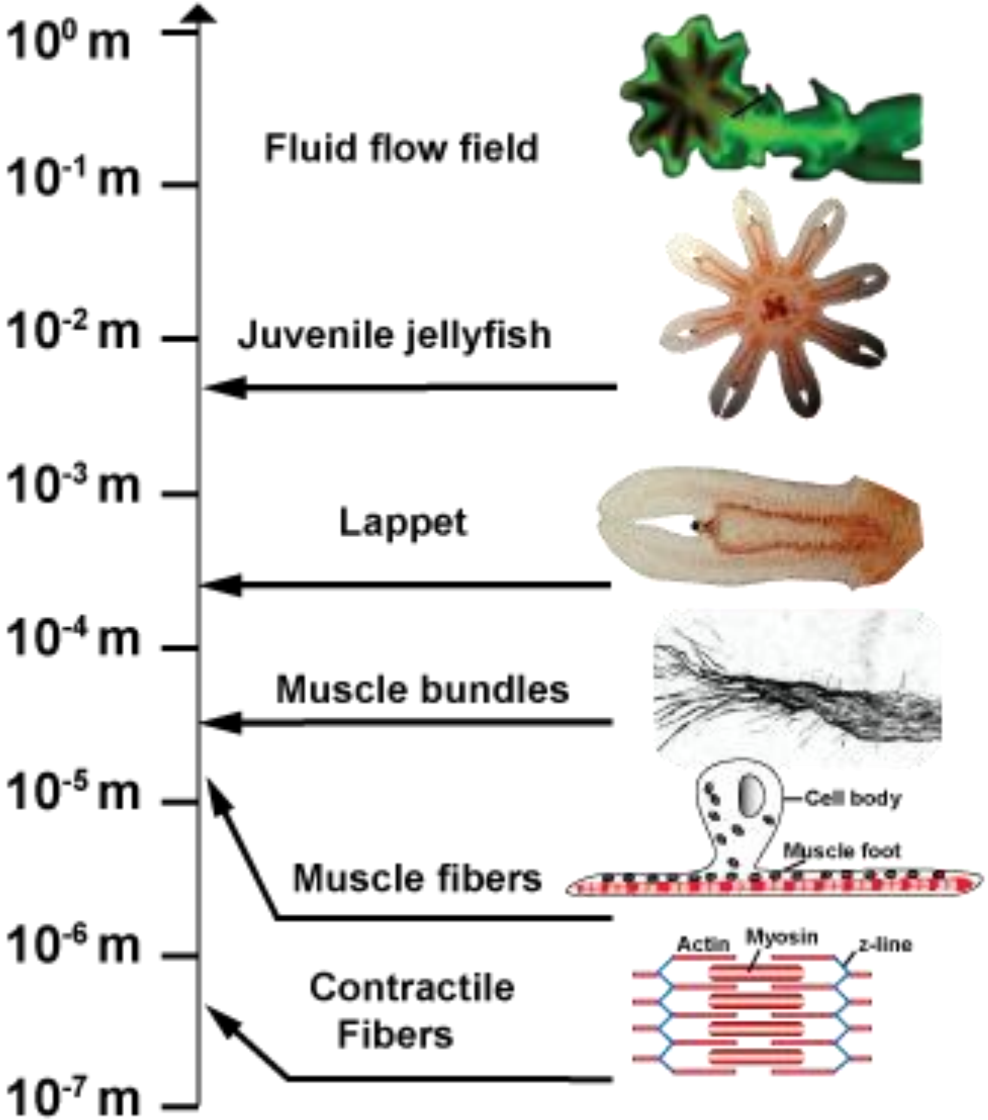
Kinematics

+

Microstructure

A simplified heart: jellyfish

A simplified heart: jellyfish



Jellyfish Function

Body-fluid interaction

Tissue geometry

+

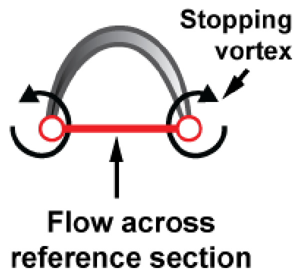
Kinematics

+

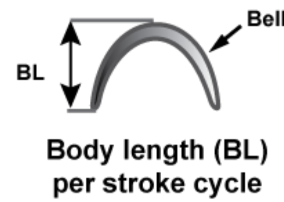
Microstructure

Measuring jellyfish fitness

Feeding metric

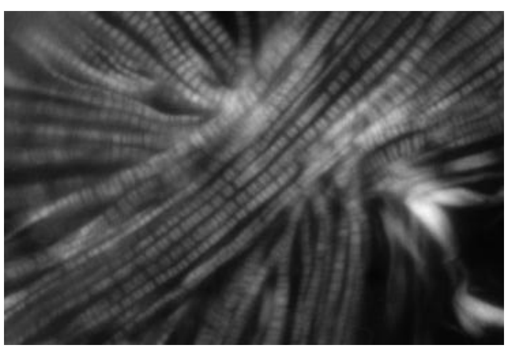


Propulsion metric



Jellyfish function
- Feeding flux
- Propulsion

Fluid transport



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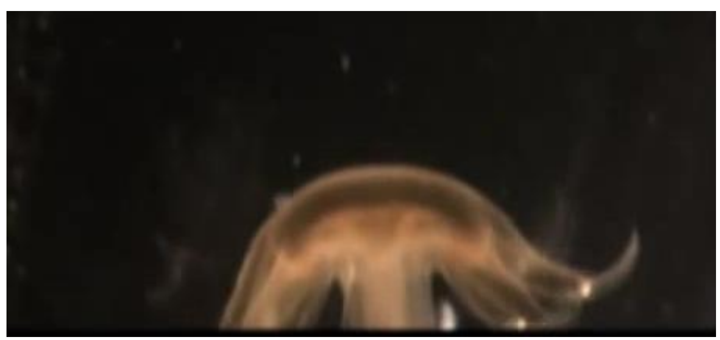
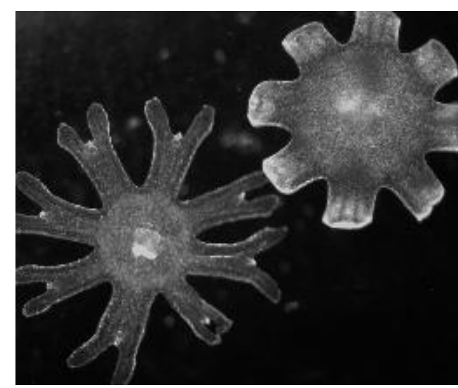


+



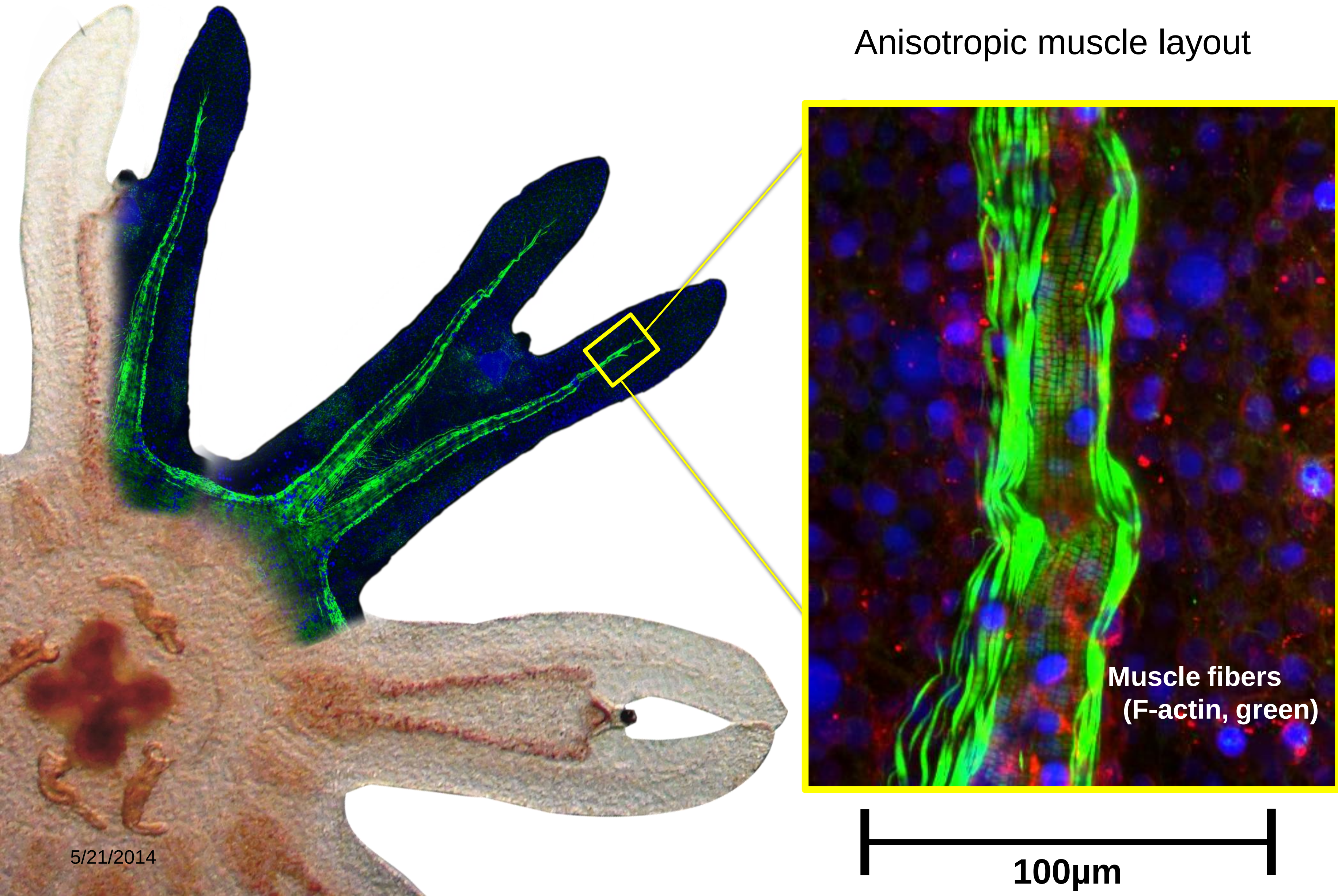
Muscle fiber alignment

Contraction kinematics

Bell geometry

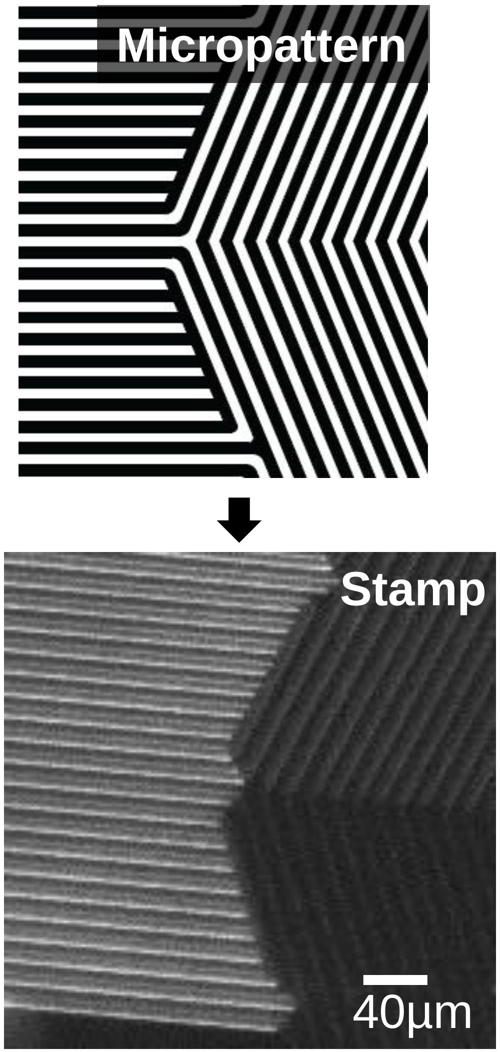
Muscle fiber alignment

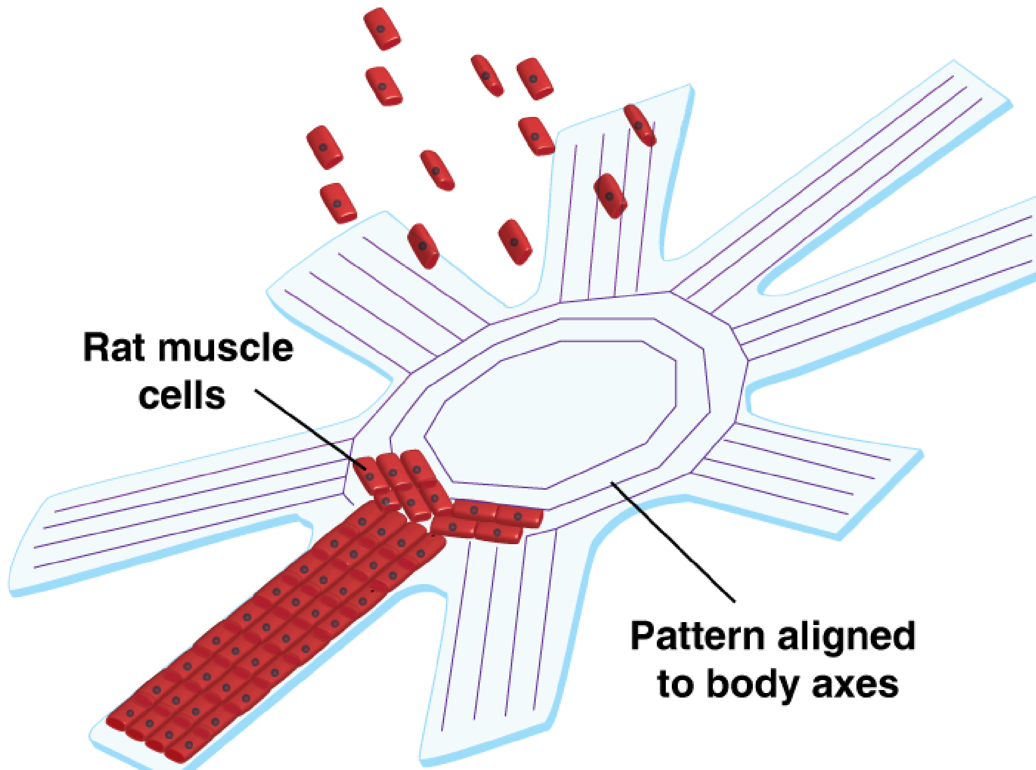
Anisotropic muscle layout



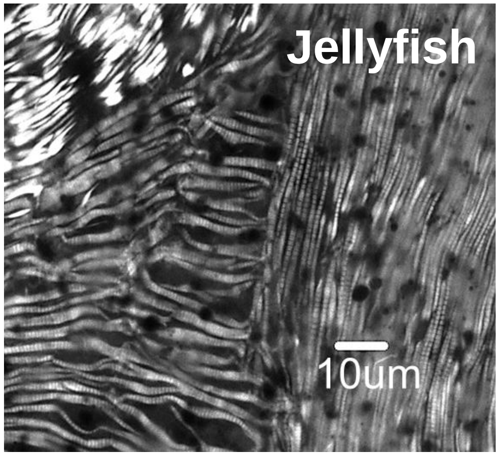
Muscle fiber alignment

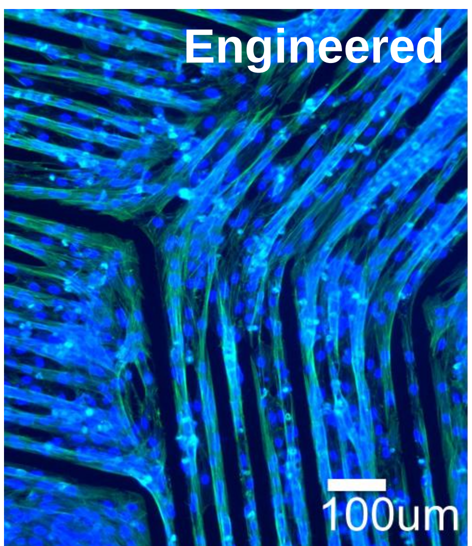
Anisotropic muscle layout

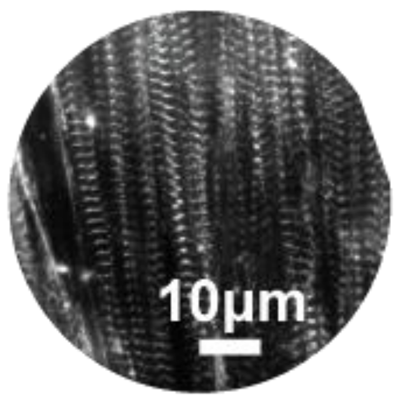


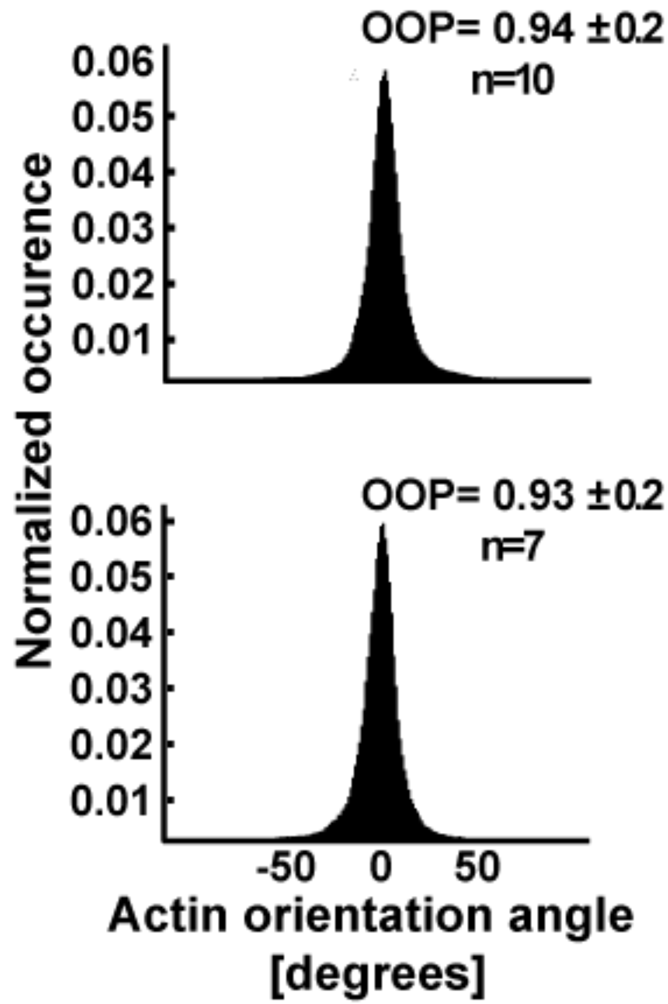


Muscle fiber alignment

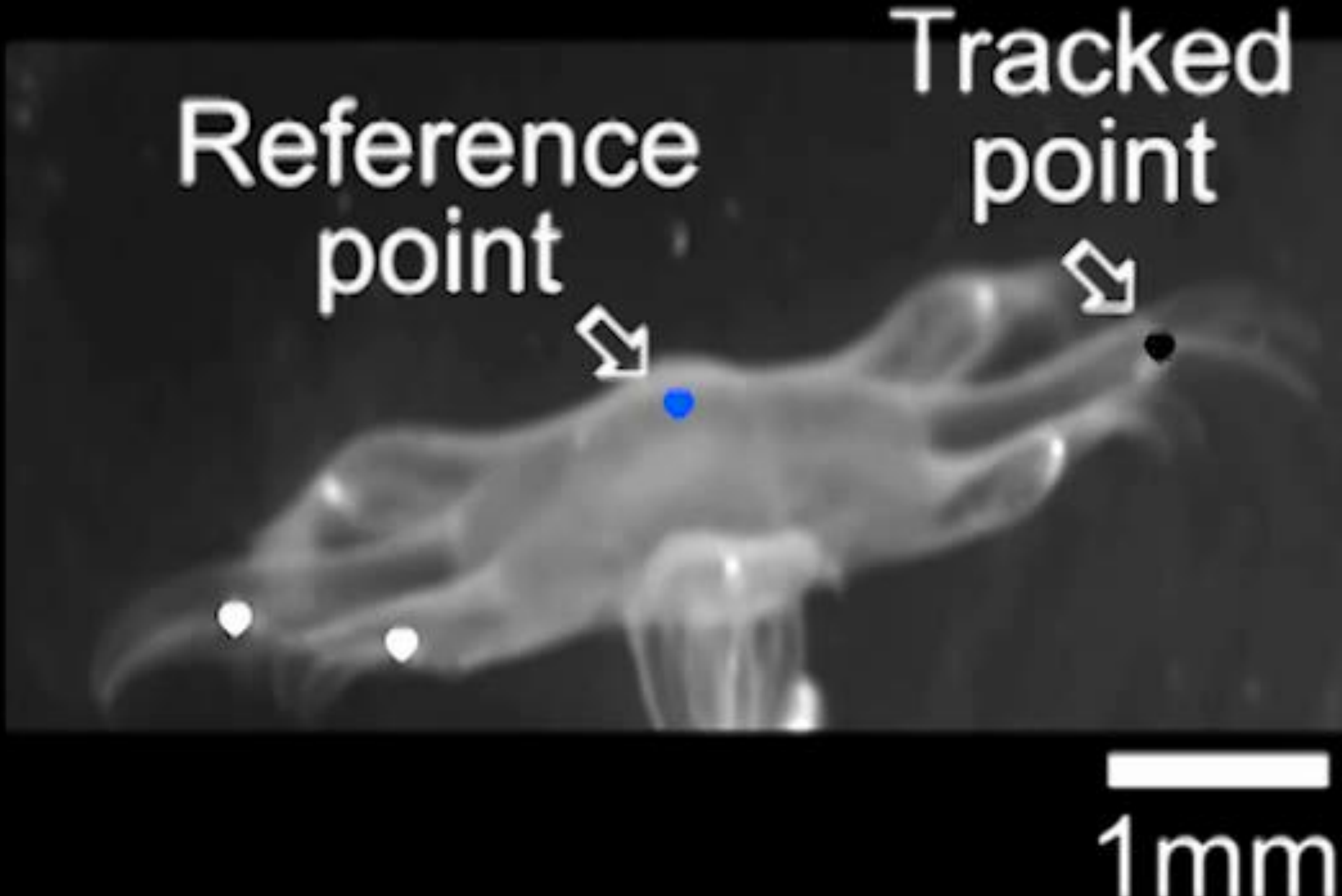






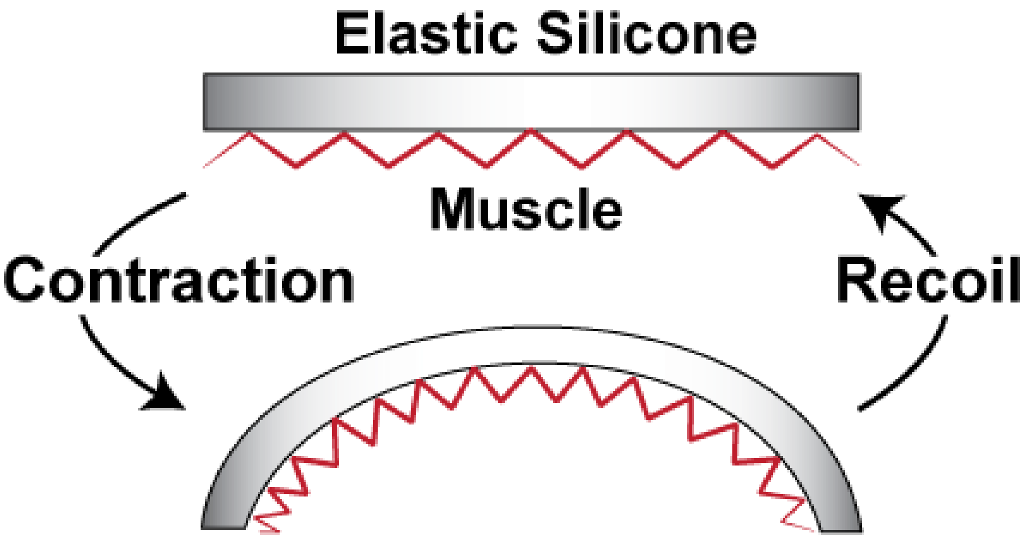


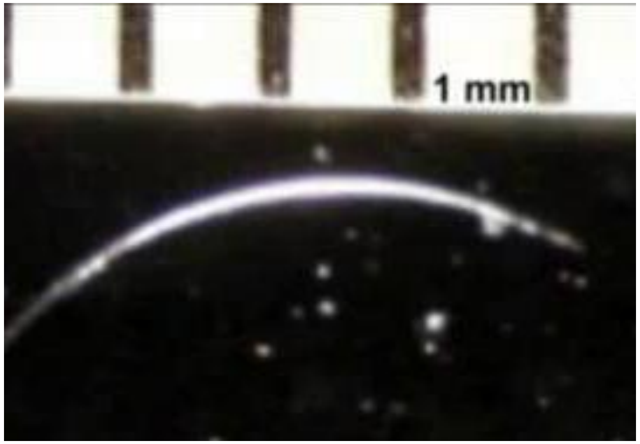
Bell kinematics



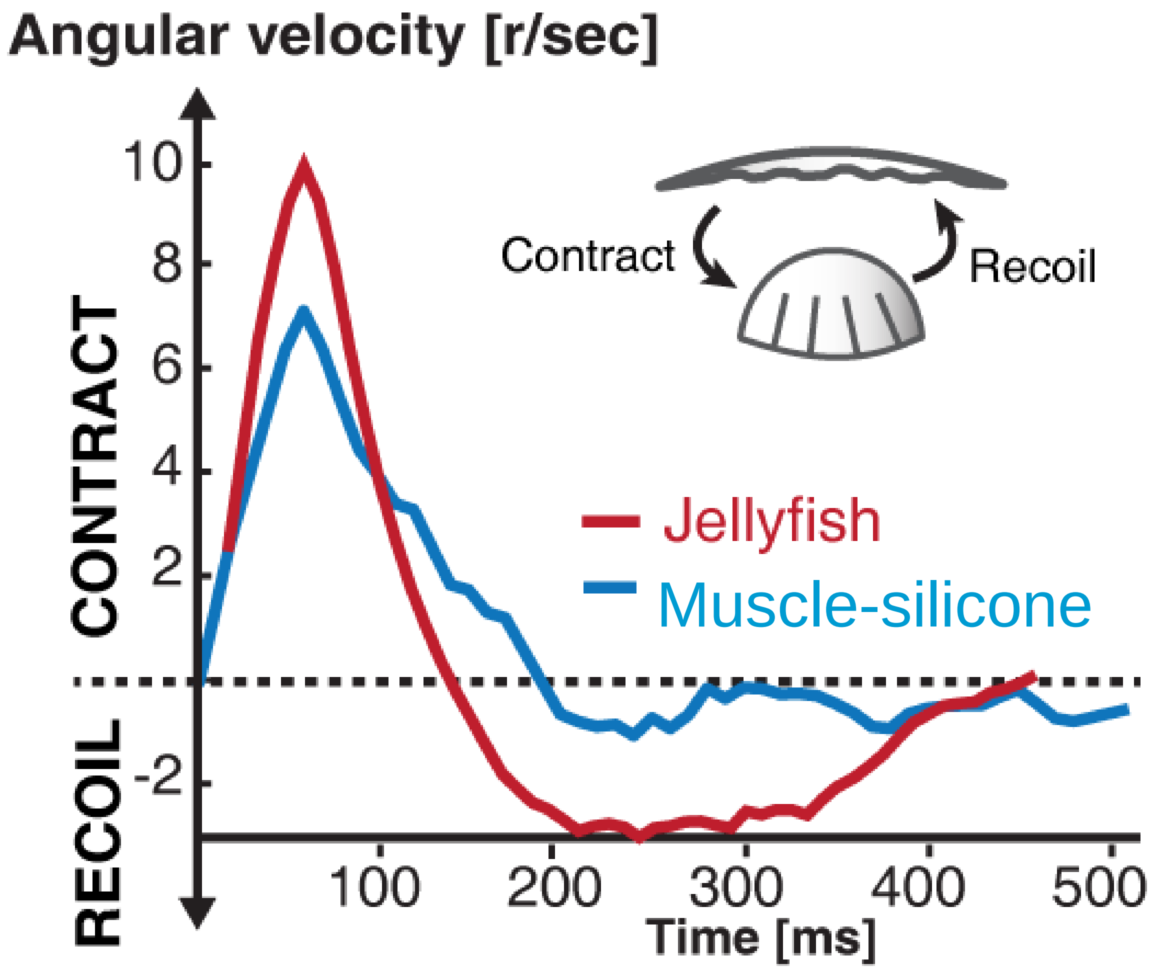
Bell kinematics

Muscle-elastomer composite

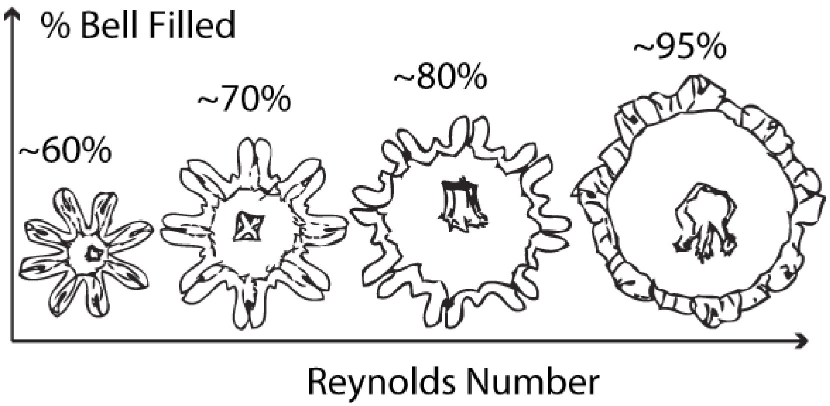




Bell kinematics

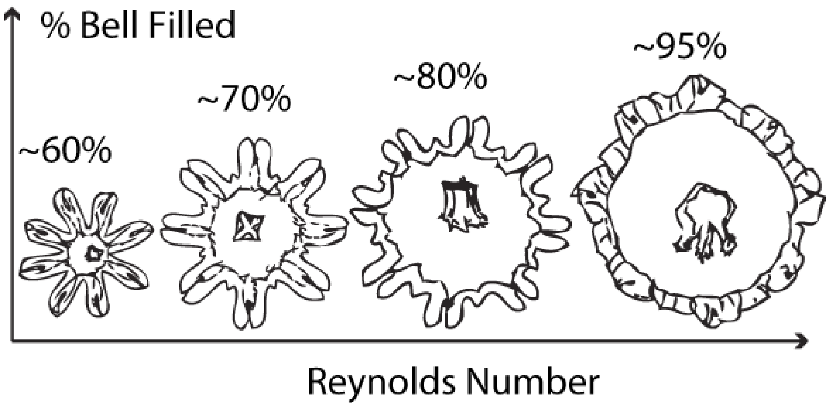


Body geometry



Feitl, 2009; Nawroth, 2010

Body geometry



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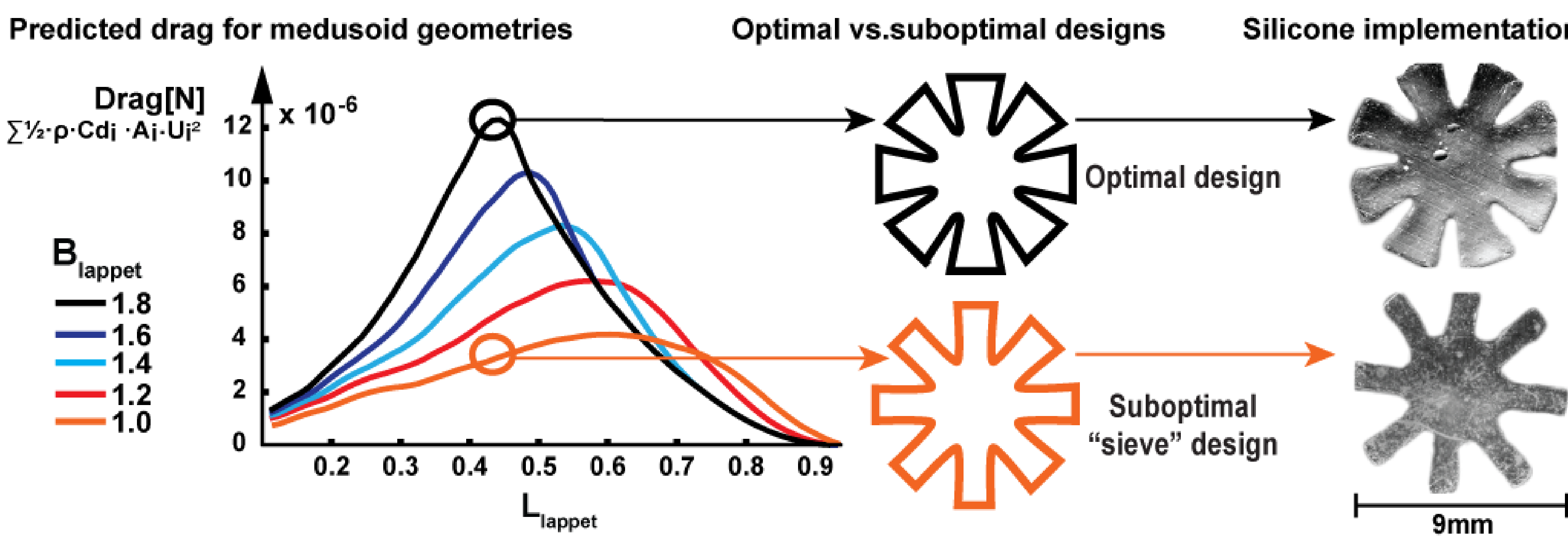
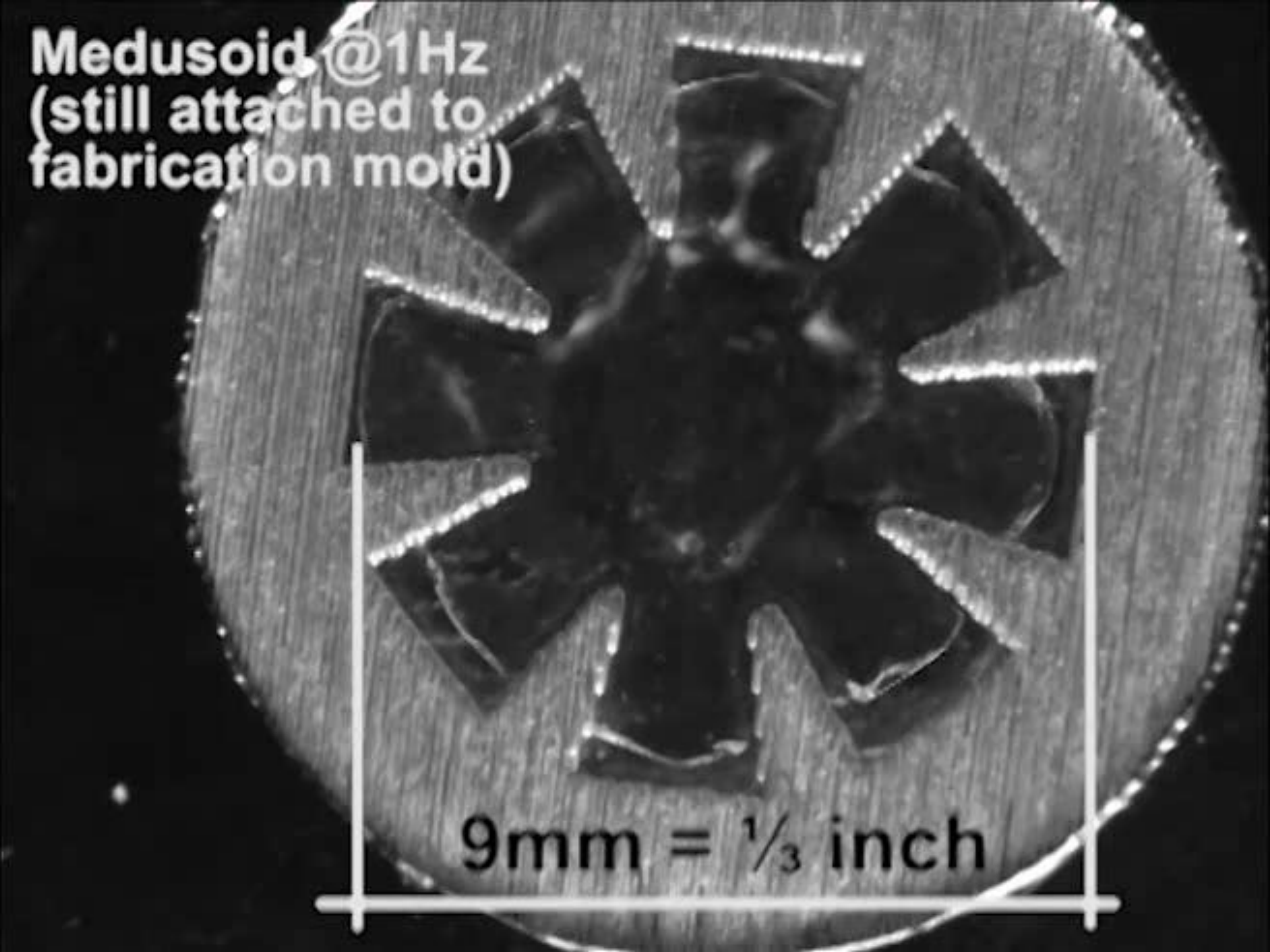
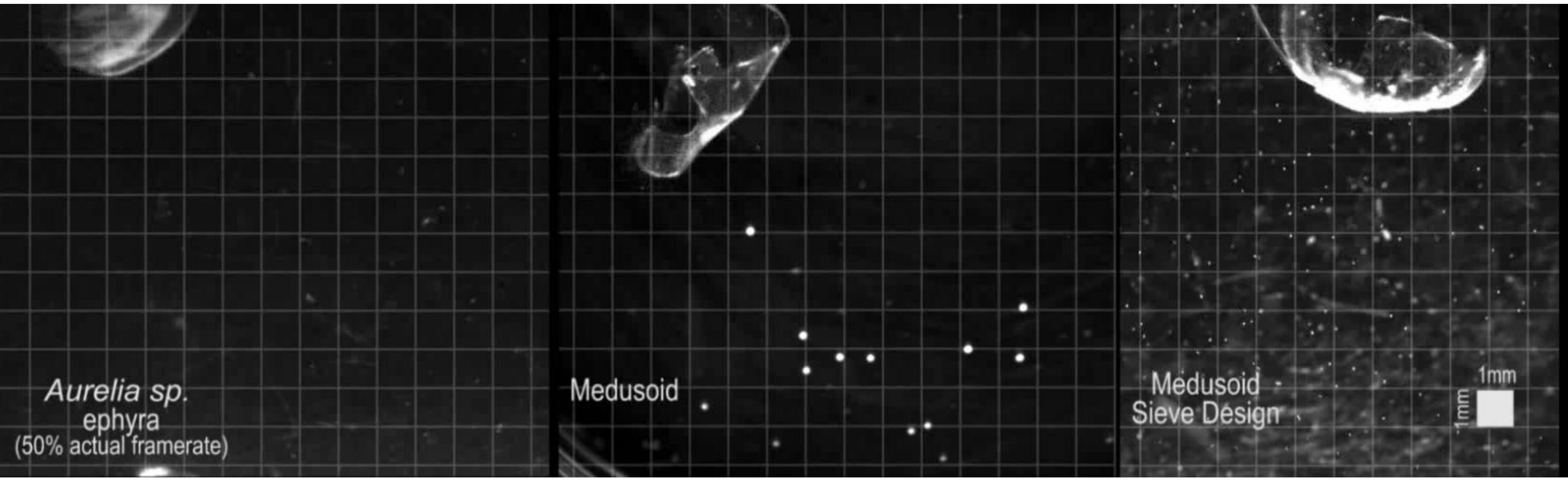



Medusoid @1Hz
(still attached to
fabrication mold)
9mm = ⅓ inch

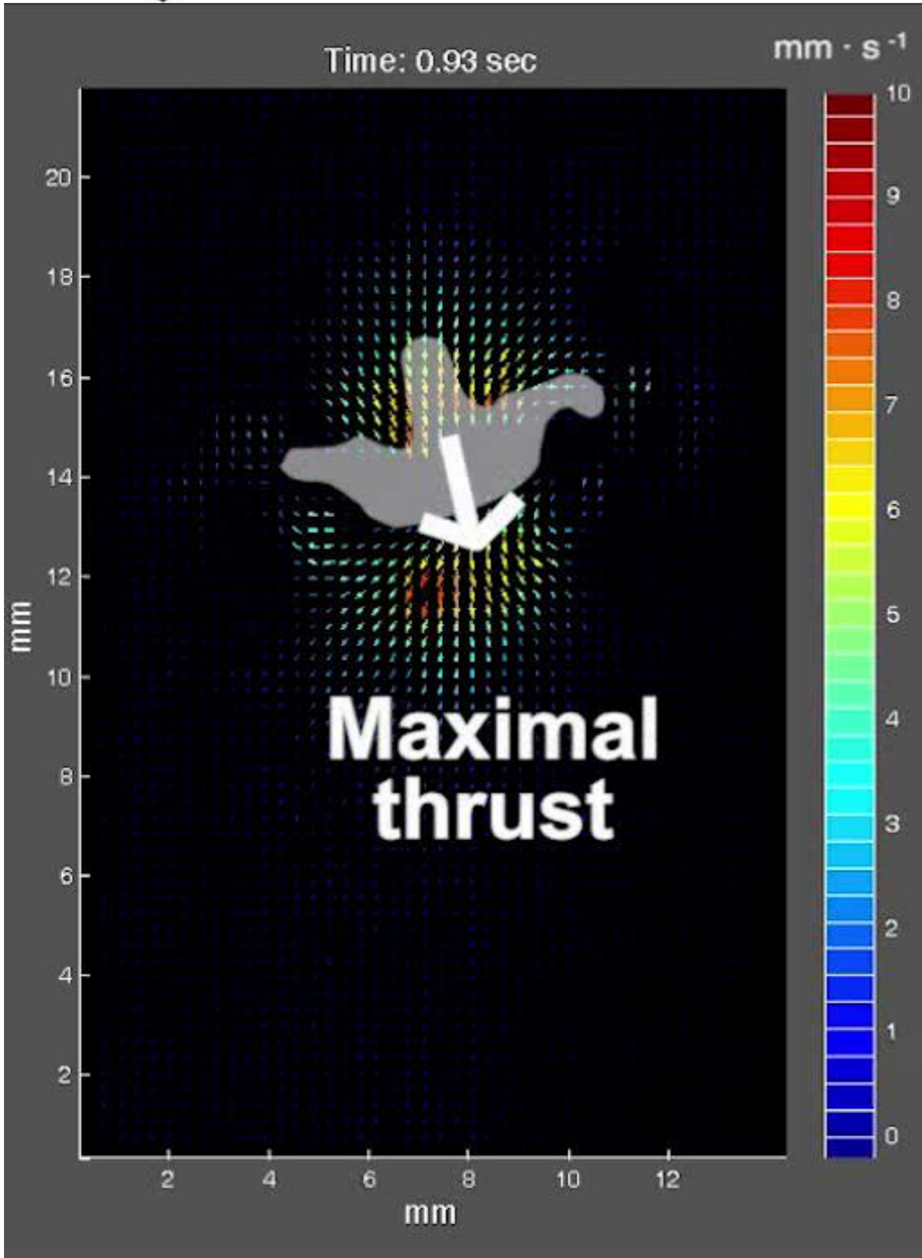
Real and artificial jellyfish propulsion

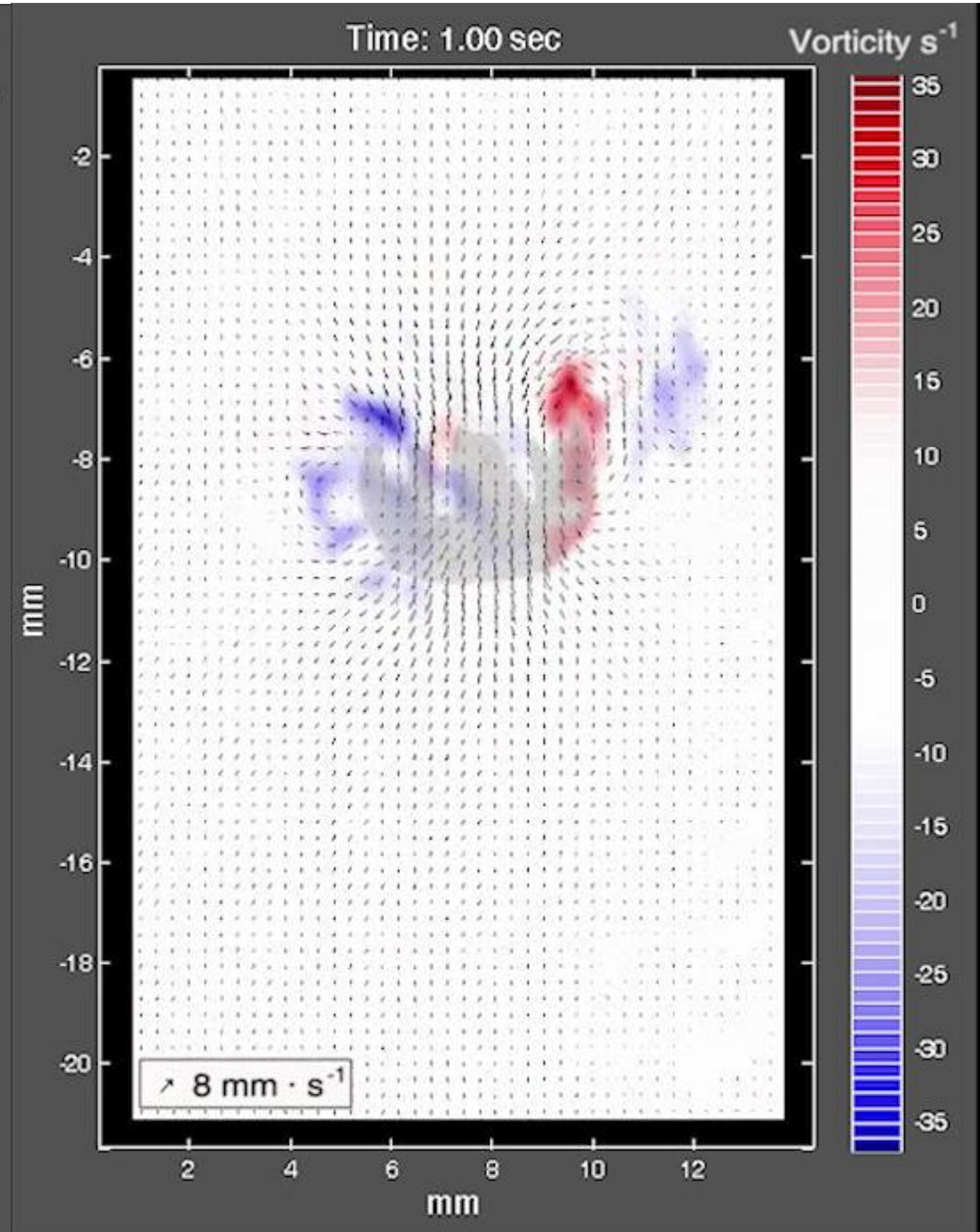
Control: Jellyfish **Optimal design** **Suboptimal design**



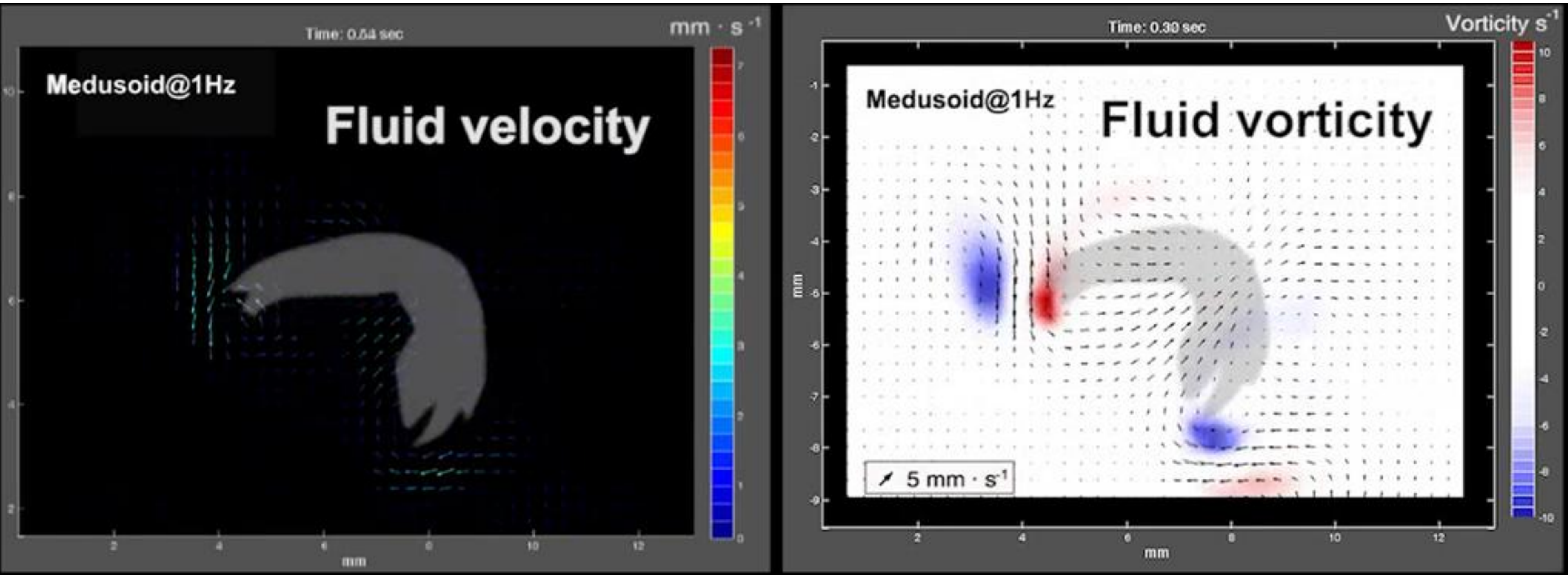
Quantifying feeding and propulsion currents

Control: Flow field in jellyfish

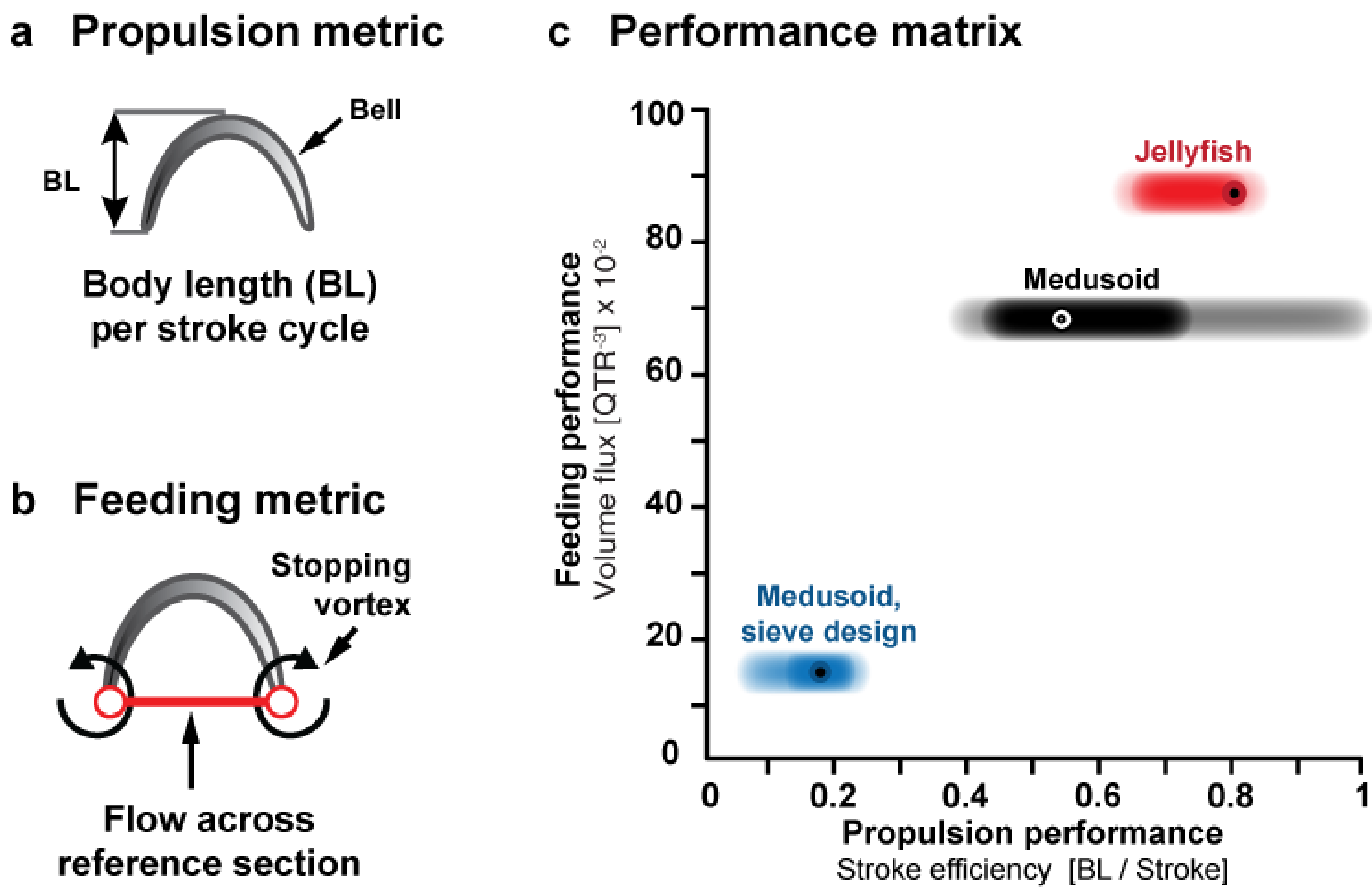




Flow field in optimal Medusoid

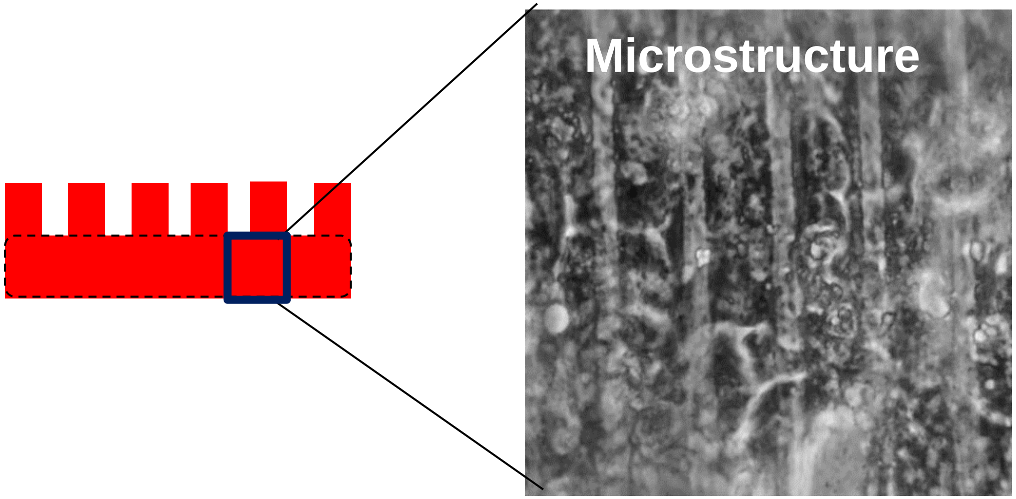


Fitness metrics

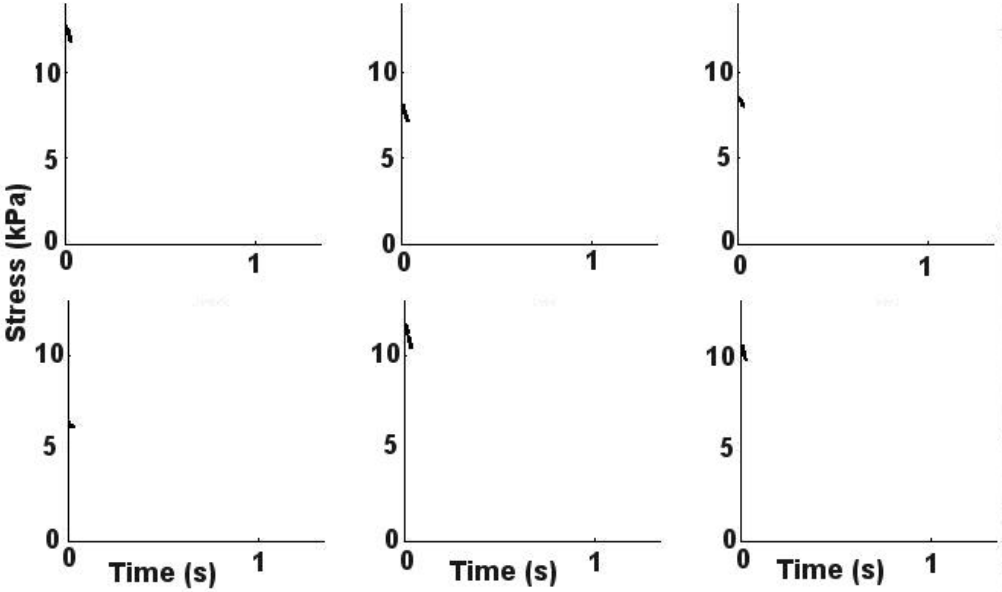


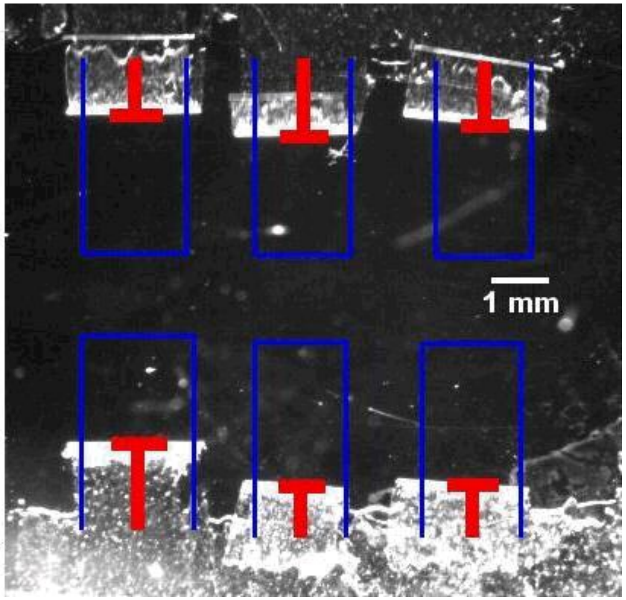
Nawroth JC et al. (2012) "A tissue-engineered jellyfish with biomimetic propulsion"

Heart-on-a-chip: further reduction



Tissue contractile stress

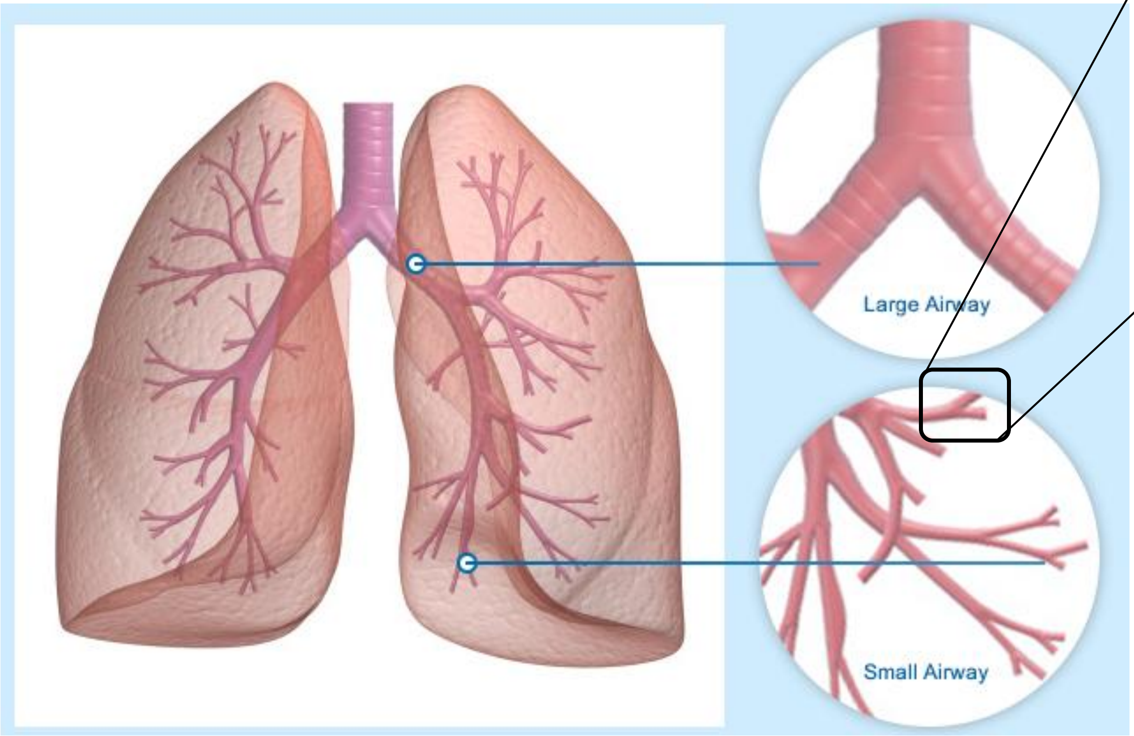


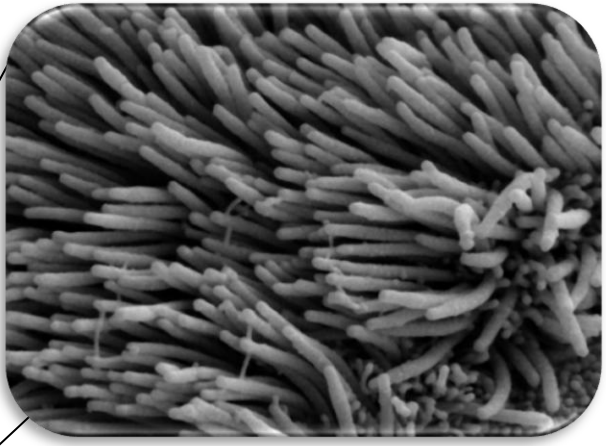


Ref: A. Agarwal *et al*, 2013

Case study: ciliated epithelium

e.g., respiratory epithelium





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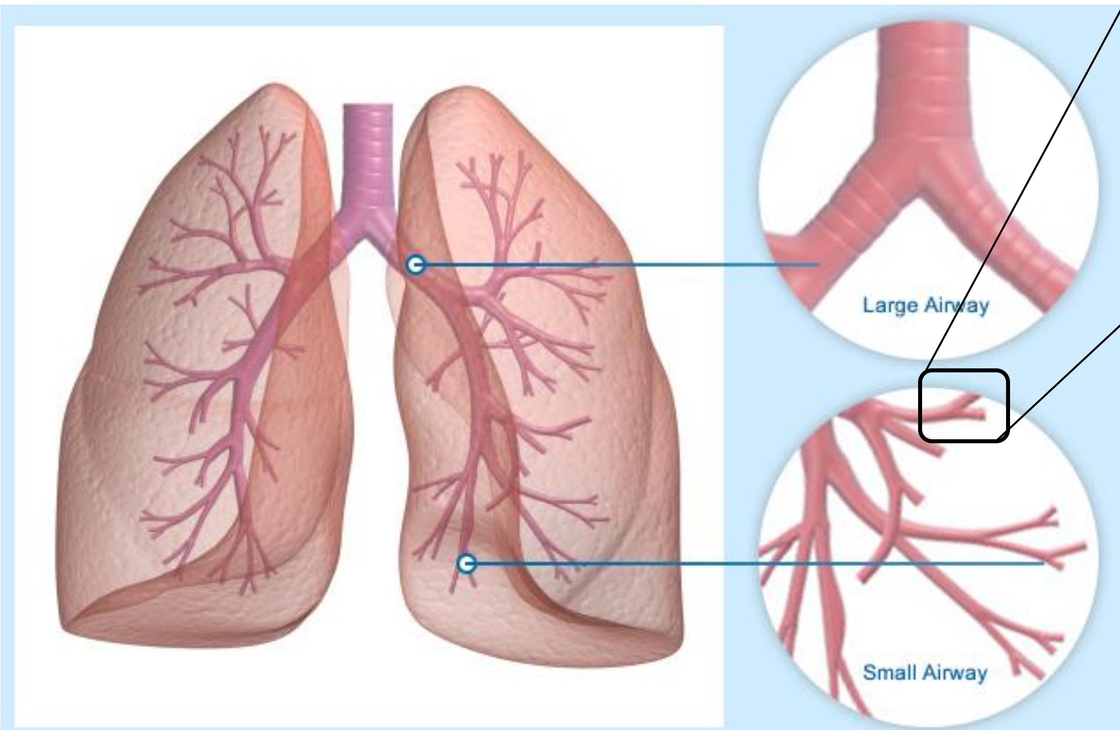
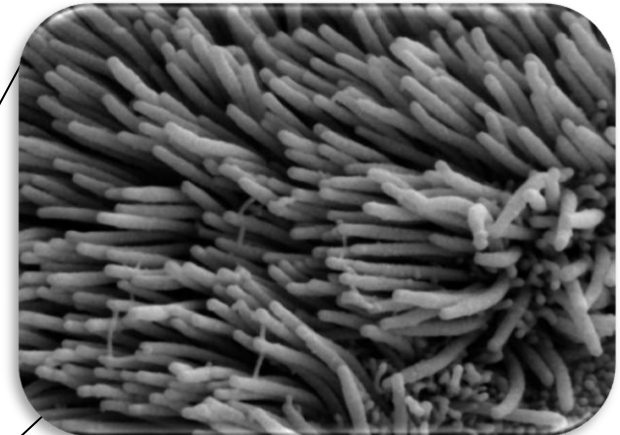
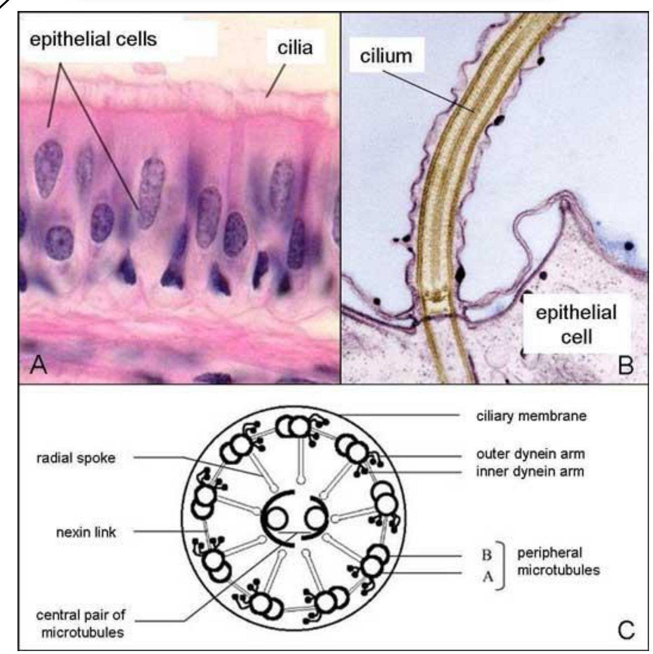
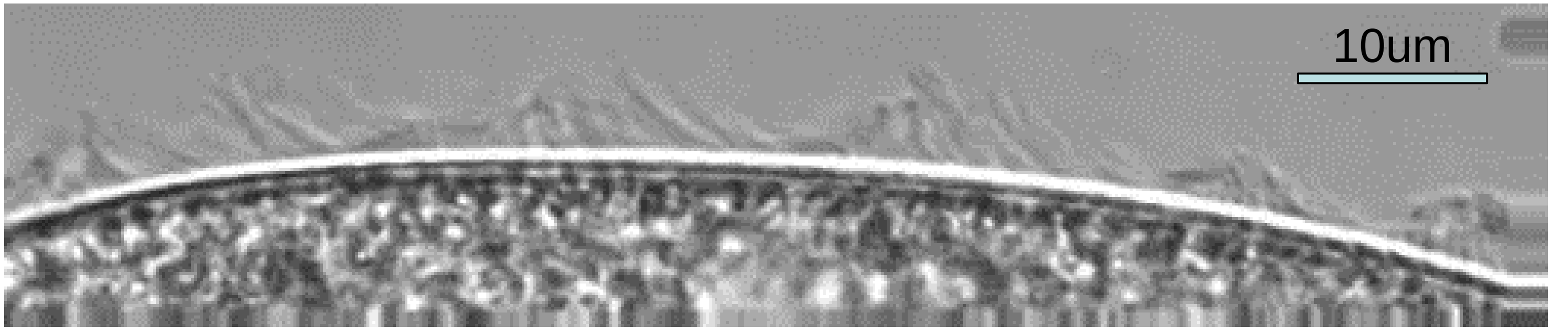


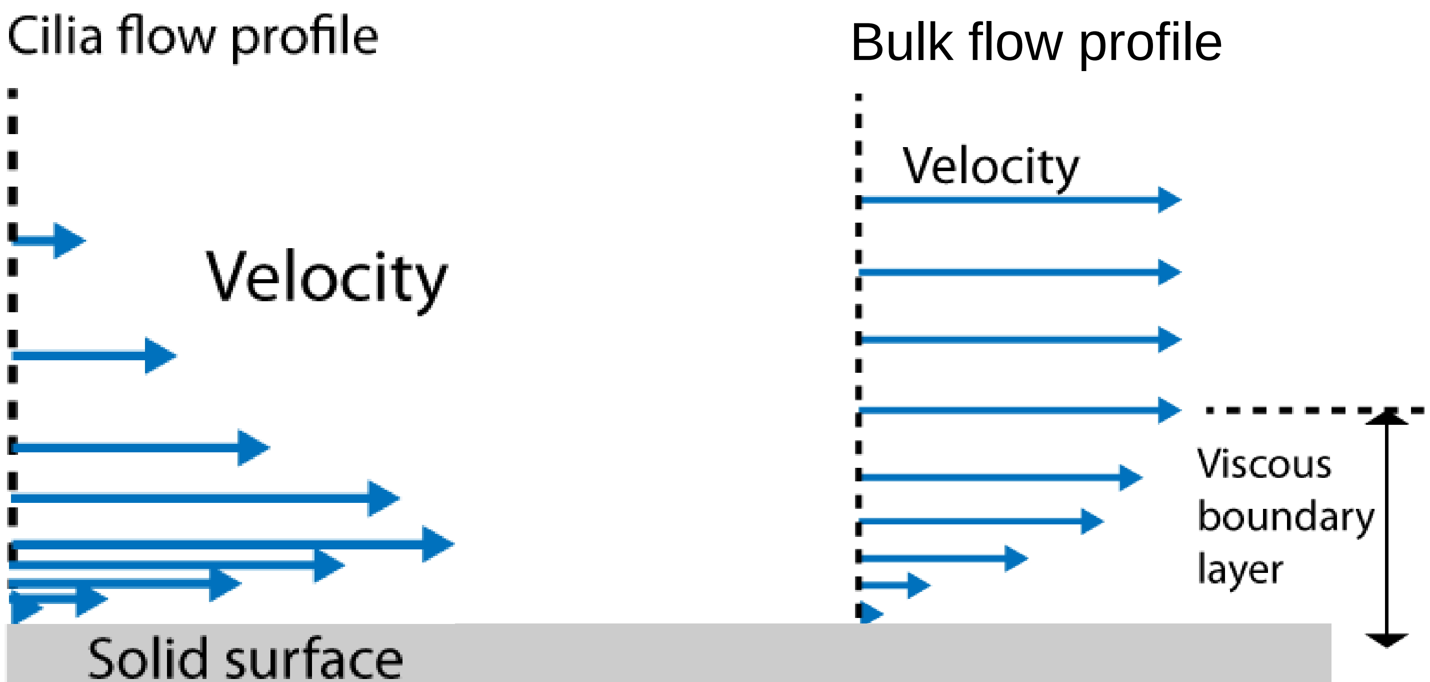




Cilia-powered fluid transport

Ciliated epithelium (Paramecium)





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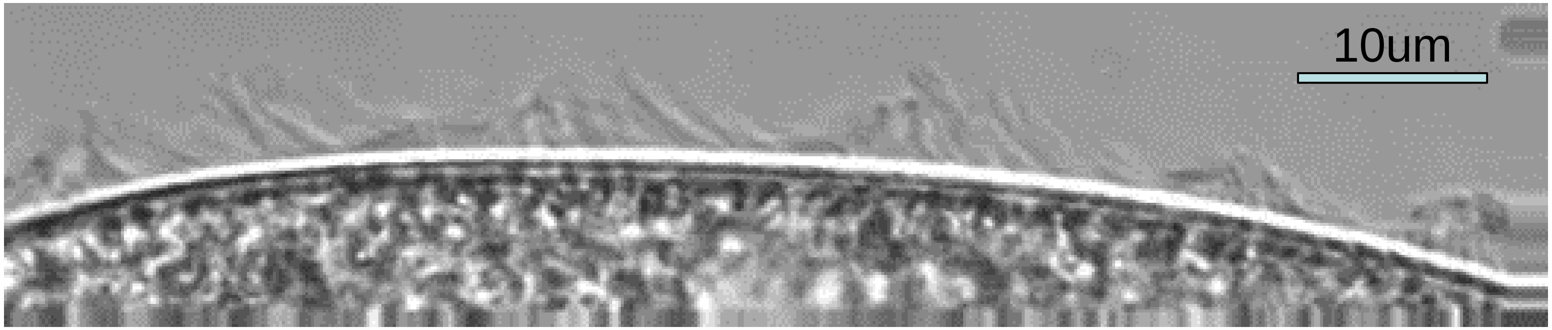
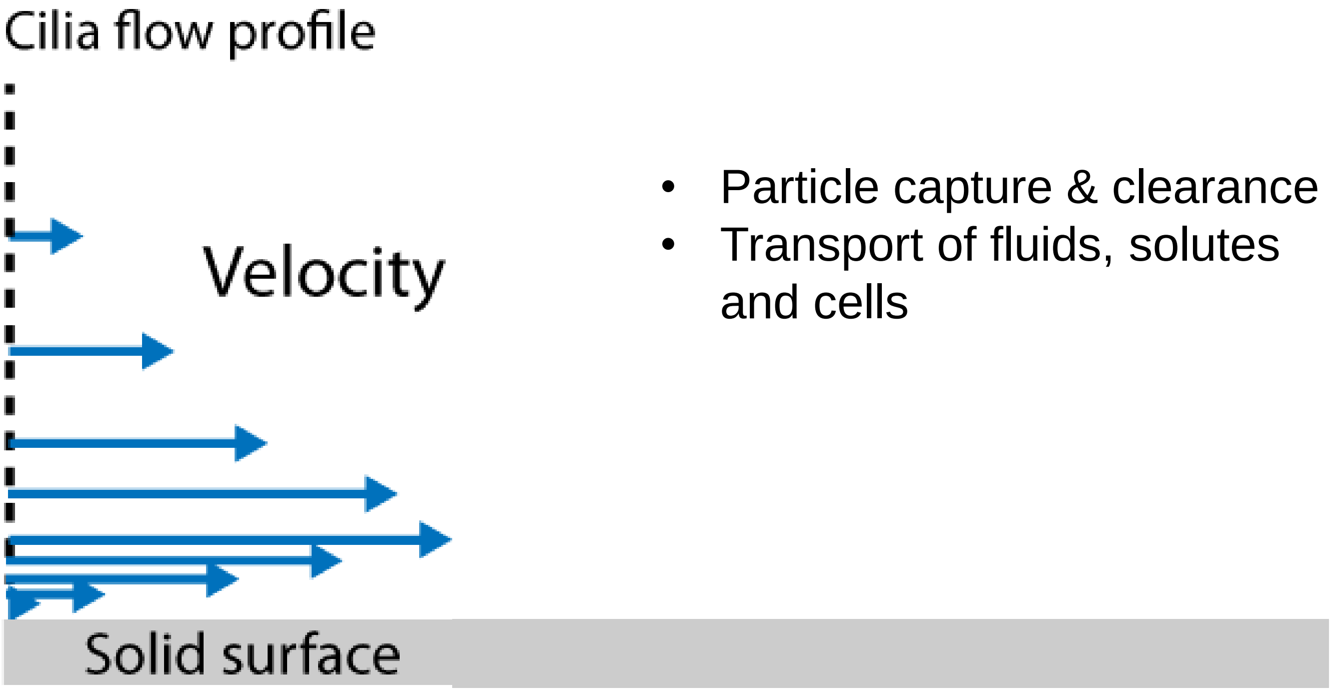
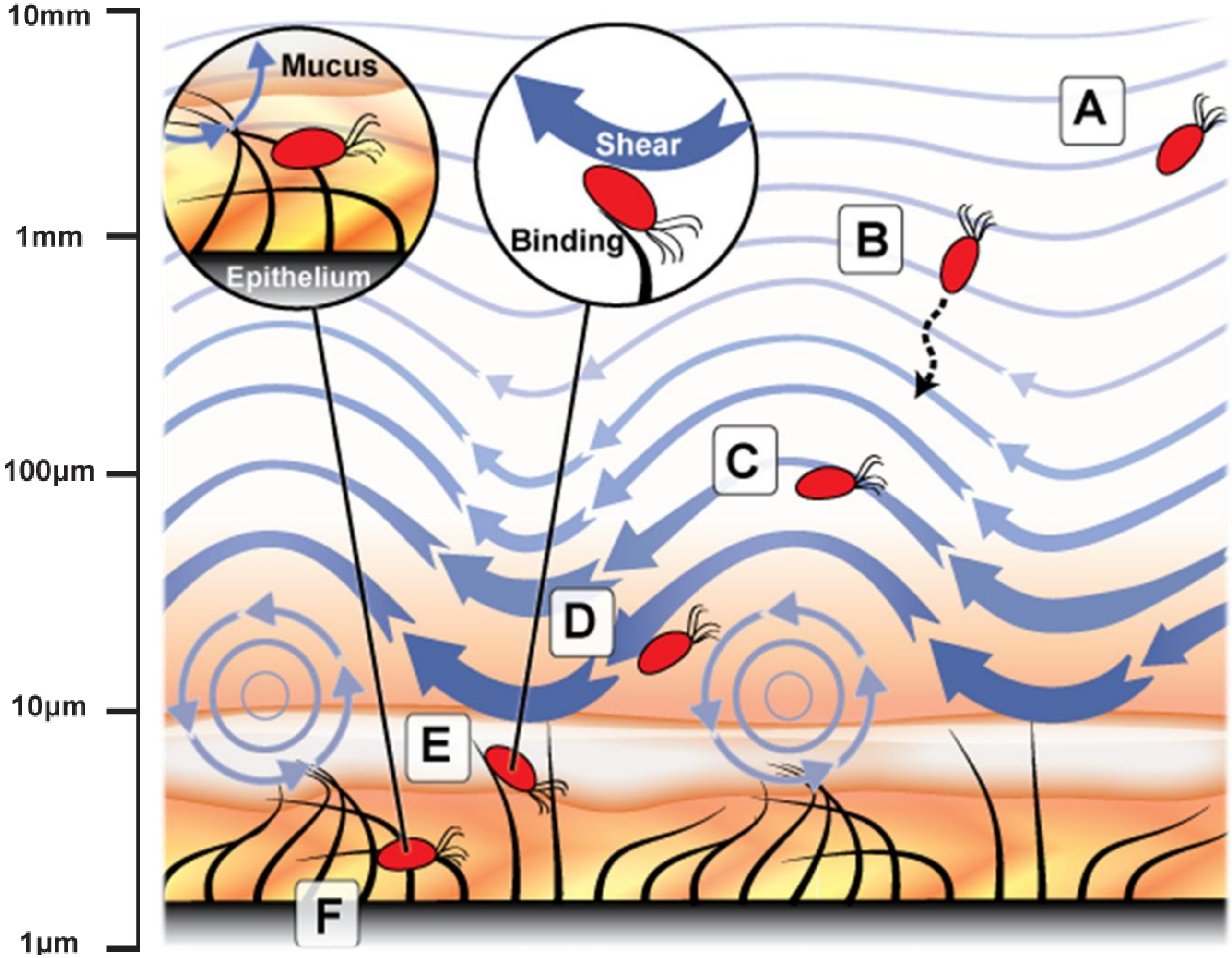




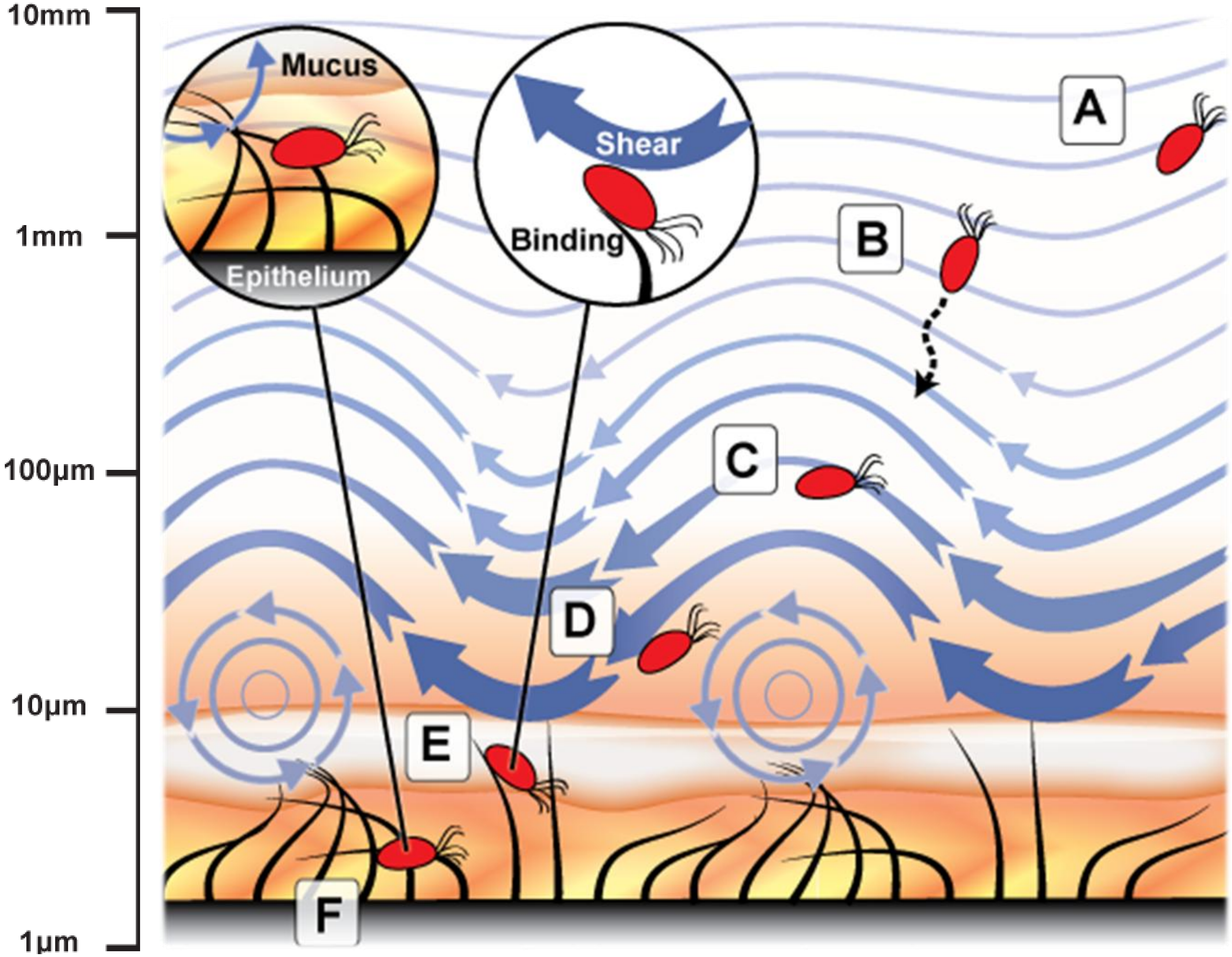
- Particle capture & clearance
- Transport of fluids, solutes and cells

Structure-function relationships of ciliated surfaces



Cilia fitness
Selective bacterial recruitment

Structure-function relationships of ciliated surfaces



Cilia fitness
Selective bacterial recruitment

⬆ ?

Fluid transport and mixing

⬆ ?

Surface geometry

+

Metachronal wave

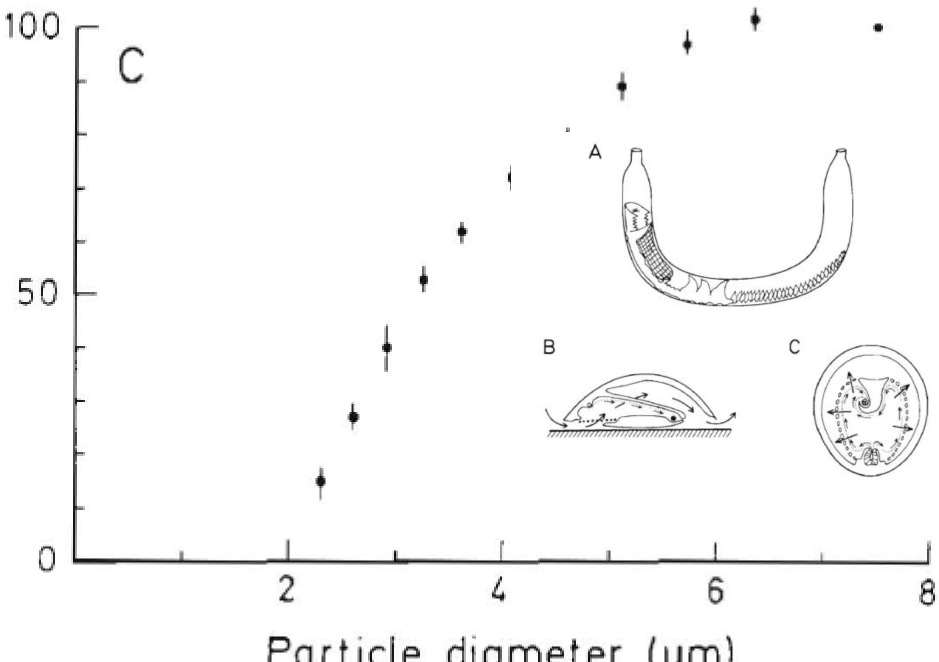
+

Ciliary structure and kinematics

A master of selective bacterial recruitment: The Hawaiian bobtail squid

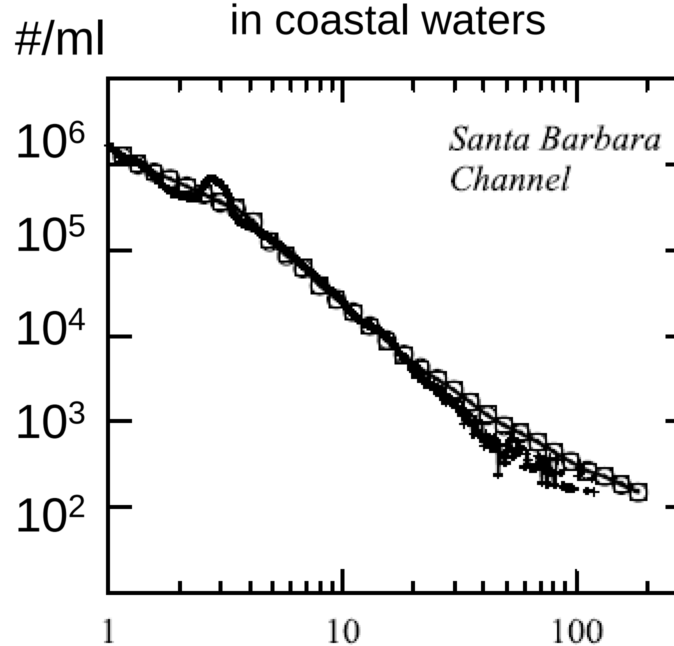
Internal ciliated organ captures 1 µm bacteria species (*Vibrio fischeri*) from huge microbial background (0.5%), and wide range of particle sizes

Retention efficiency in typical ciliary filter feeders



Jorgensen, 1994

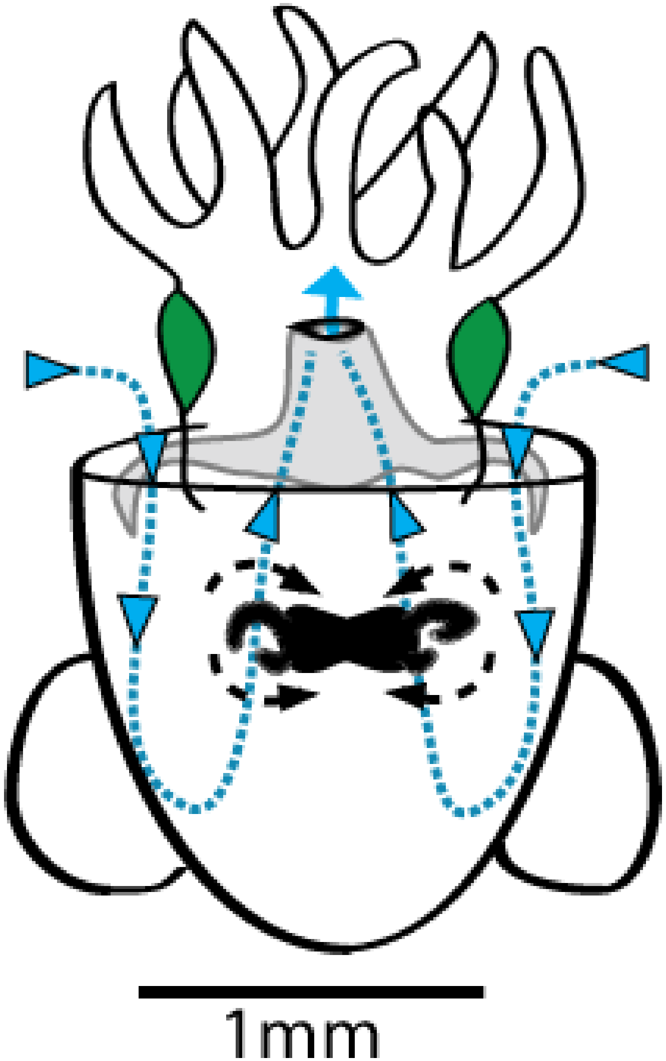
Particle size distribution in coastal waters

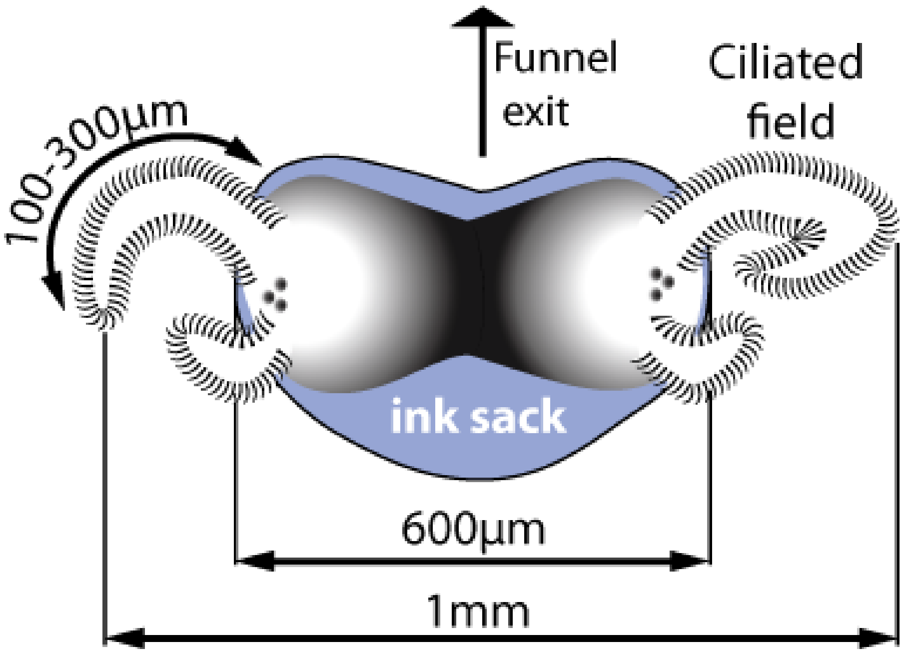


Largest dimension in µm

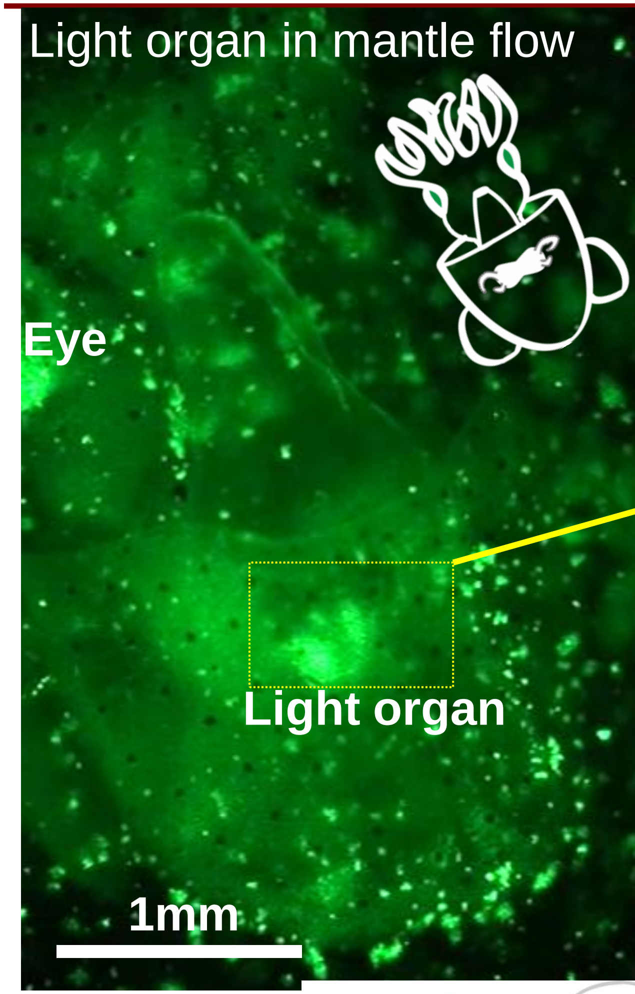
Reynolds et al., 2010

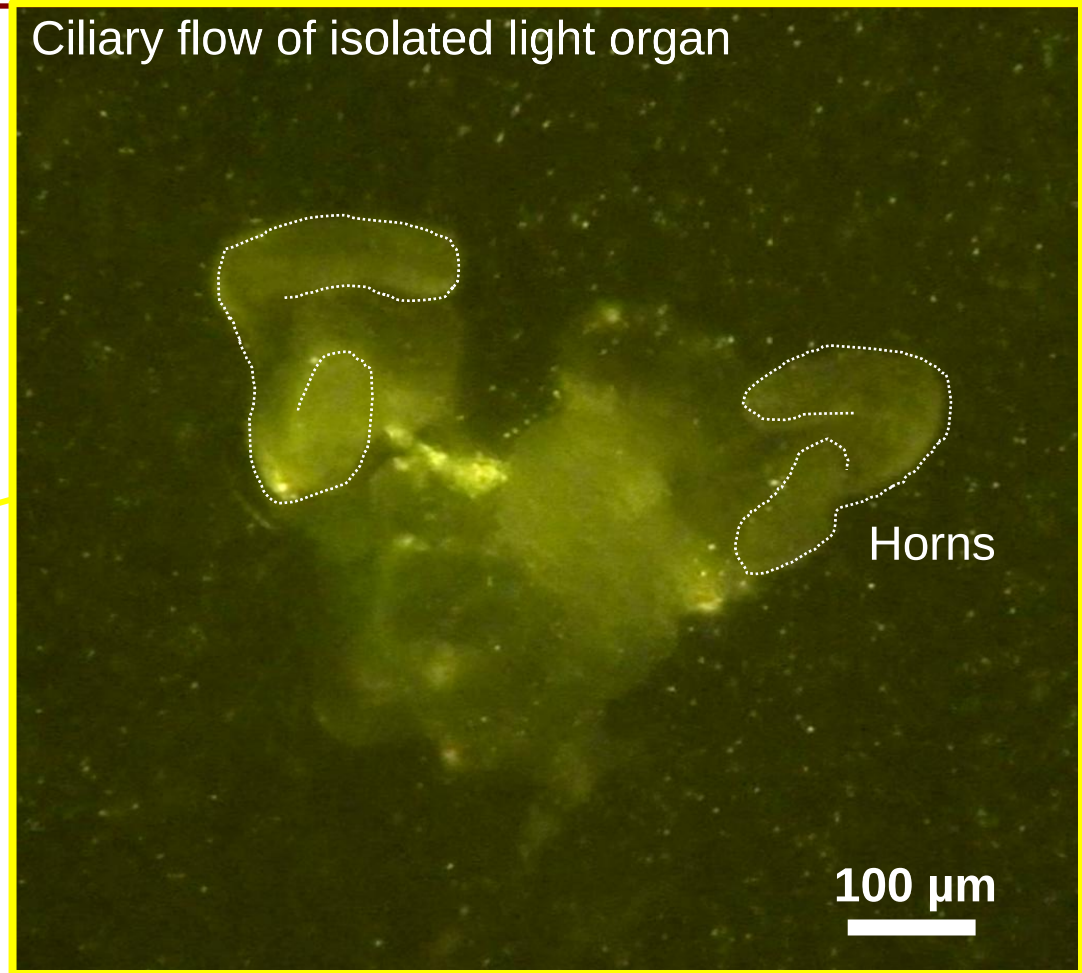
The squid ciliated organ



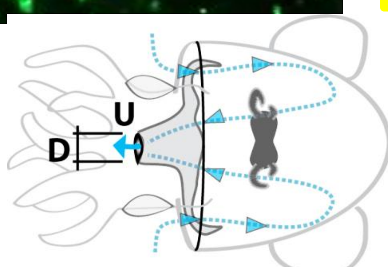


The light organ is subject low Reynolds number flow

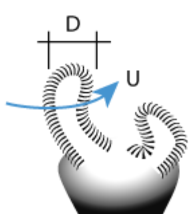




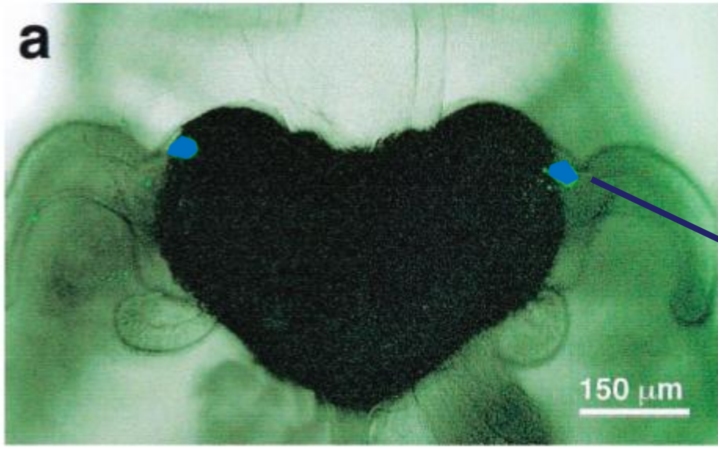
$$Re = \frac{UD}{\nu} = 0.2$$



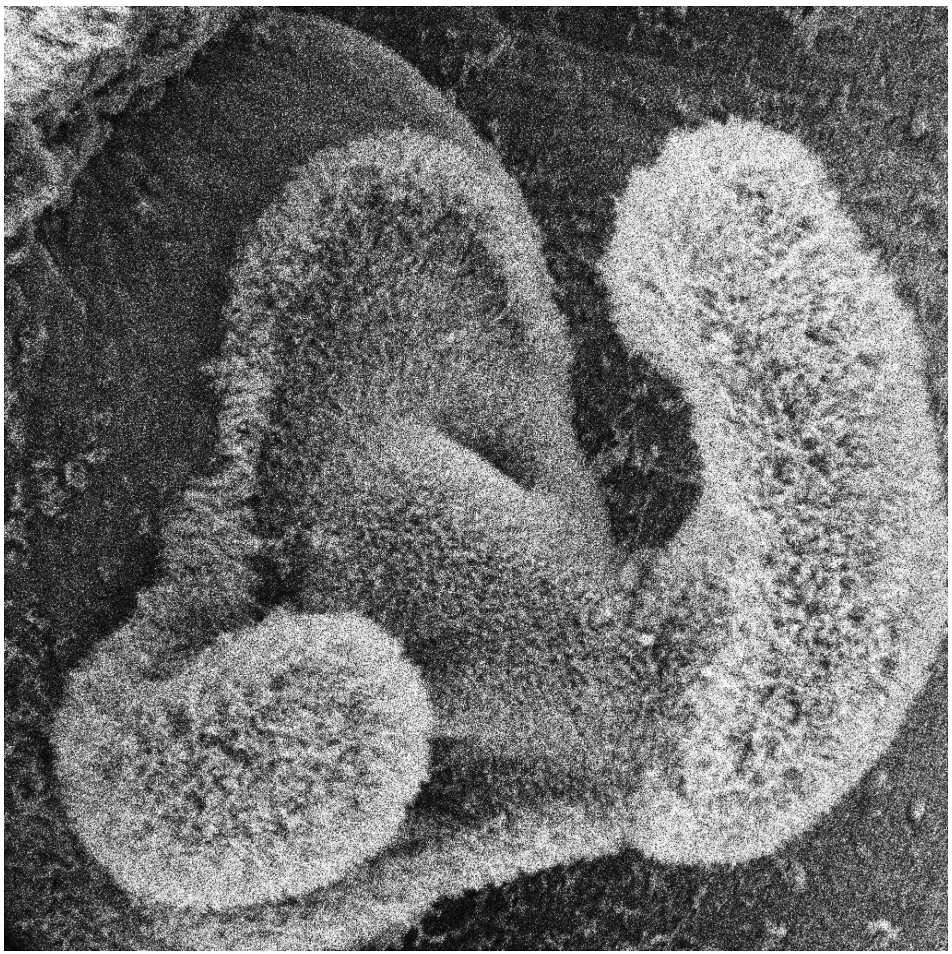
$$Re = \frac{UD}{\nu} = 0.004$$

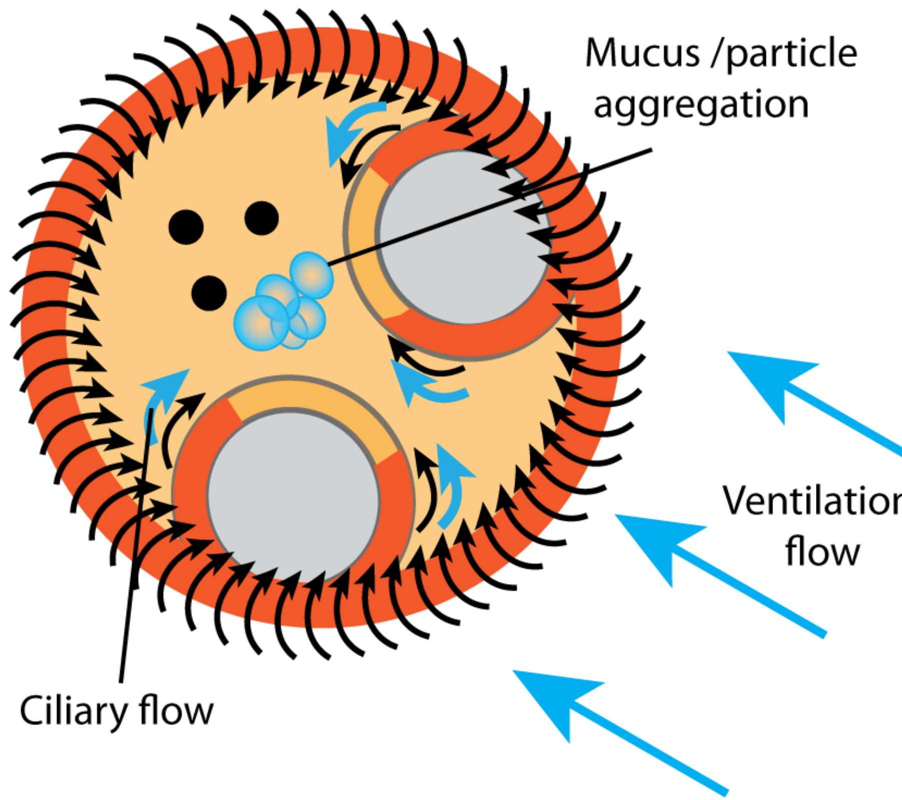


The mucociliary trap

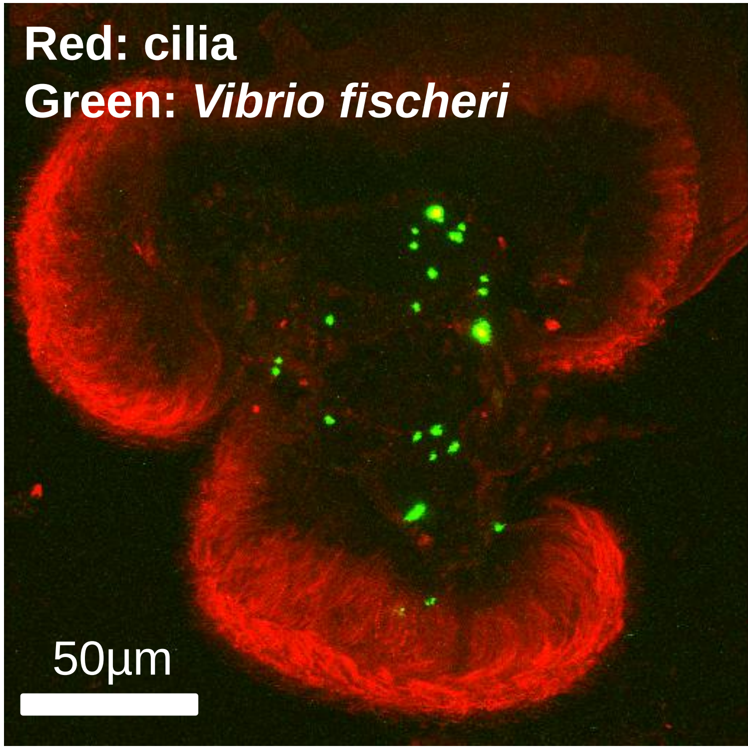


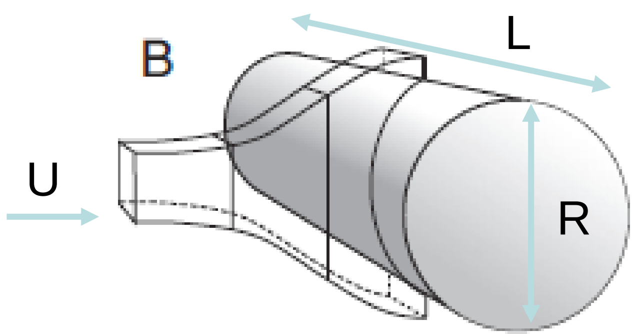
Mucus aggregation



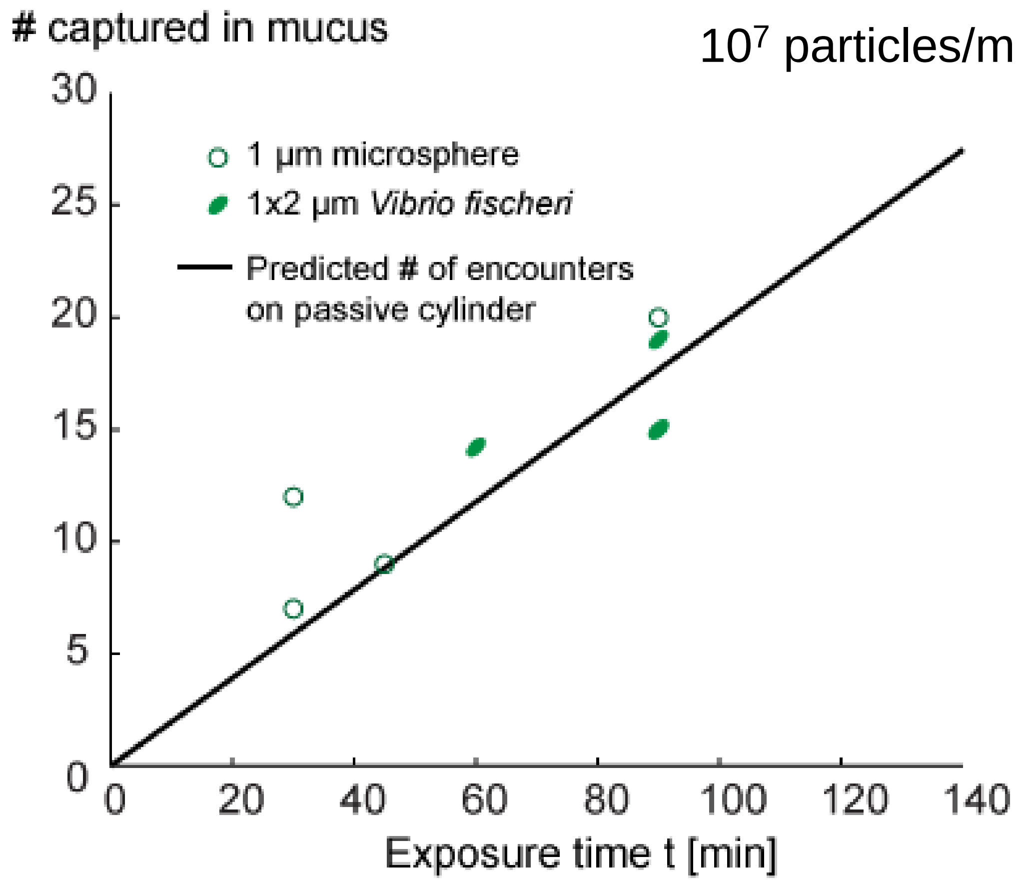


The mucociliary trap: not such a good trap?



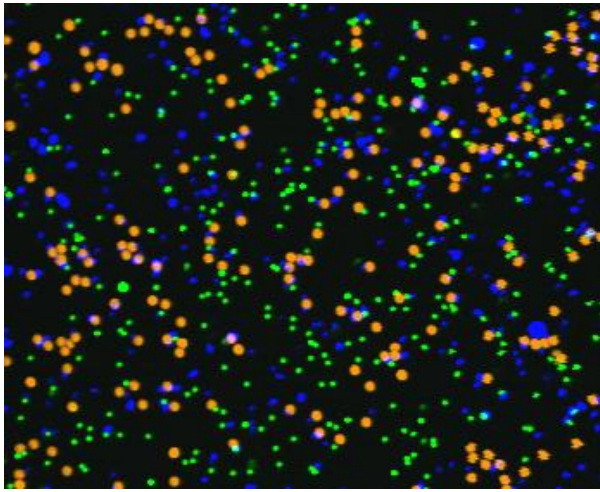


Encounter model for passive cylinder in flow
(Humphries, PNAS, 2009)

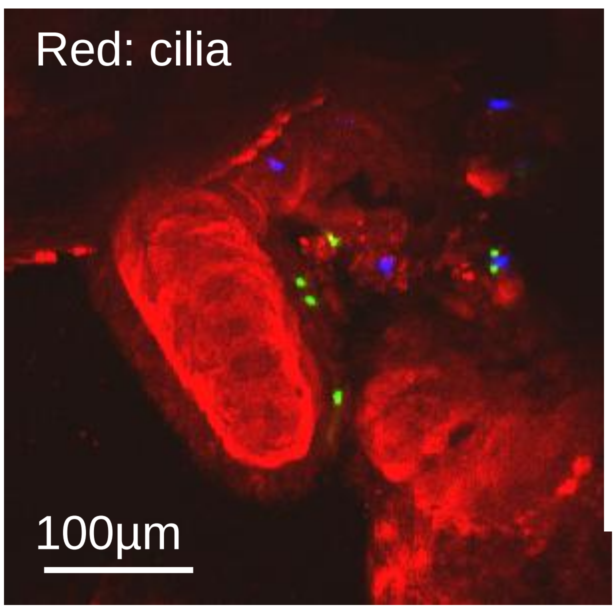


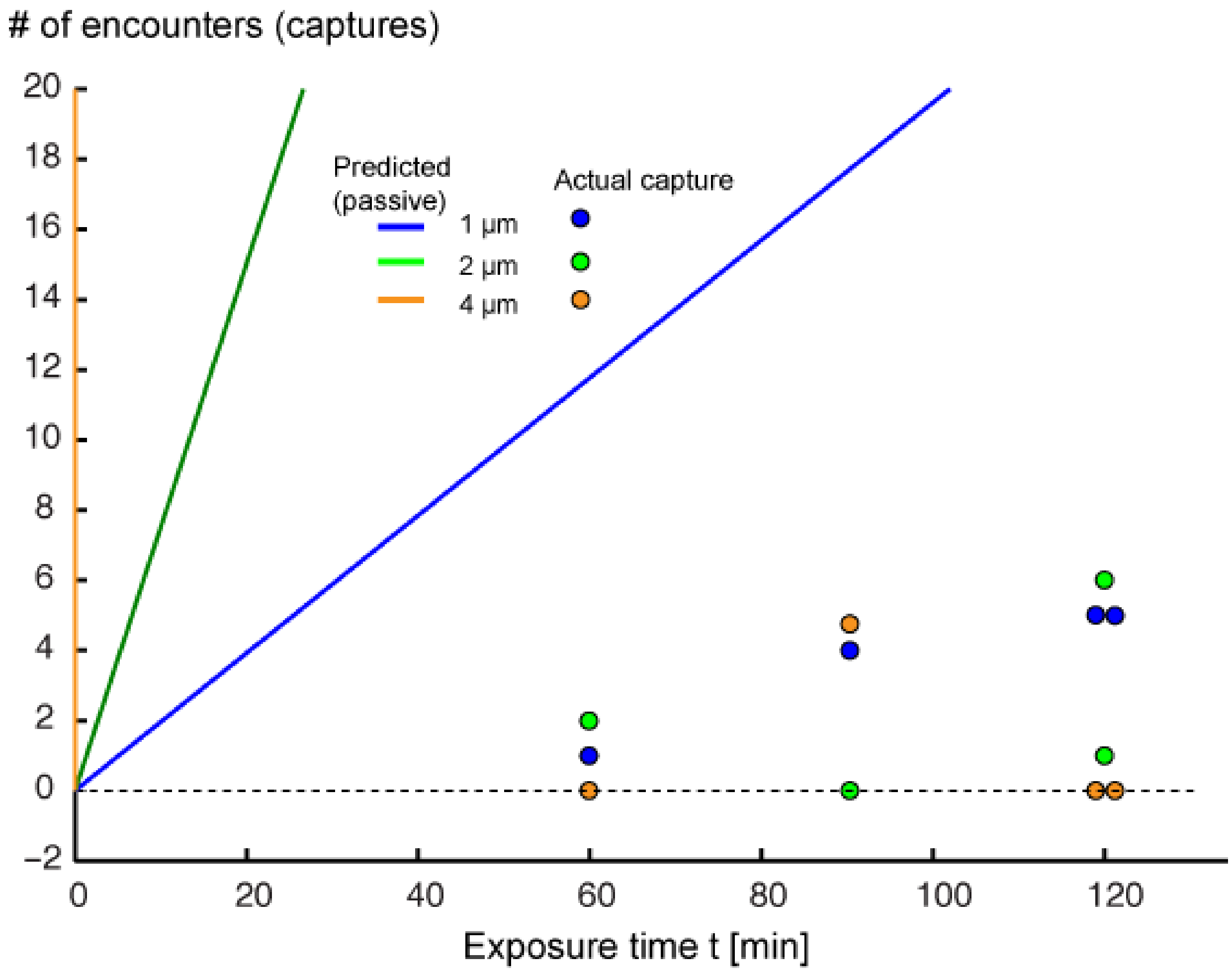
Capture rate similar to predicted encounter rate of passive cylinder in flow
→ No obvious increase in capture rate compared to chance

The mucociliary trap - not for everyone: Evidence for size-biased capture

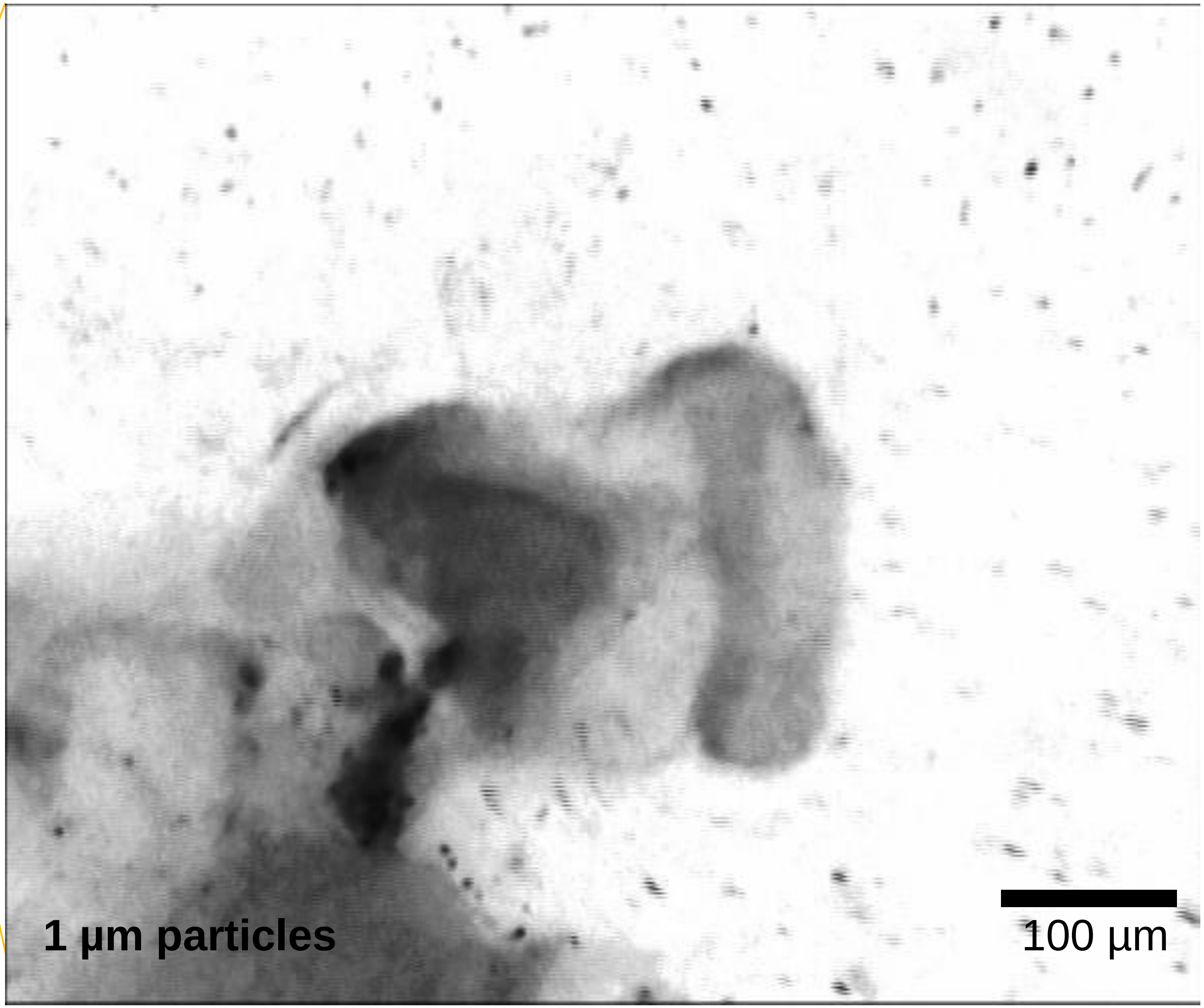


1µm (blue), 2µm (green), 4µm (orange); 10^7particles/ml each

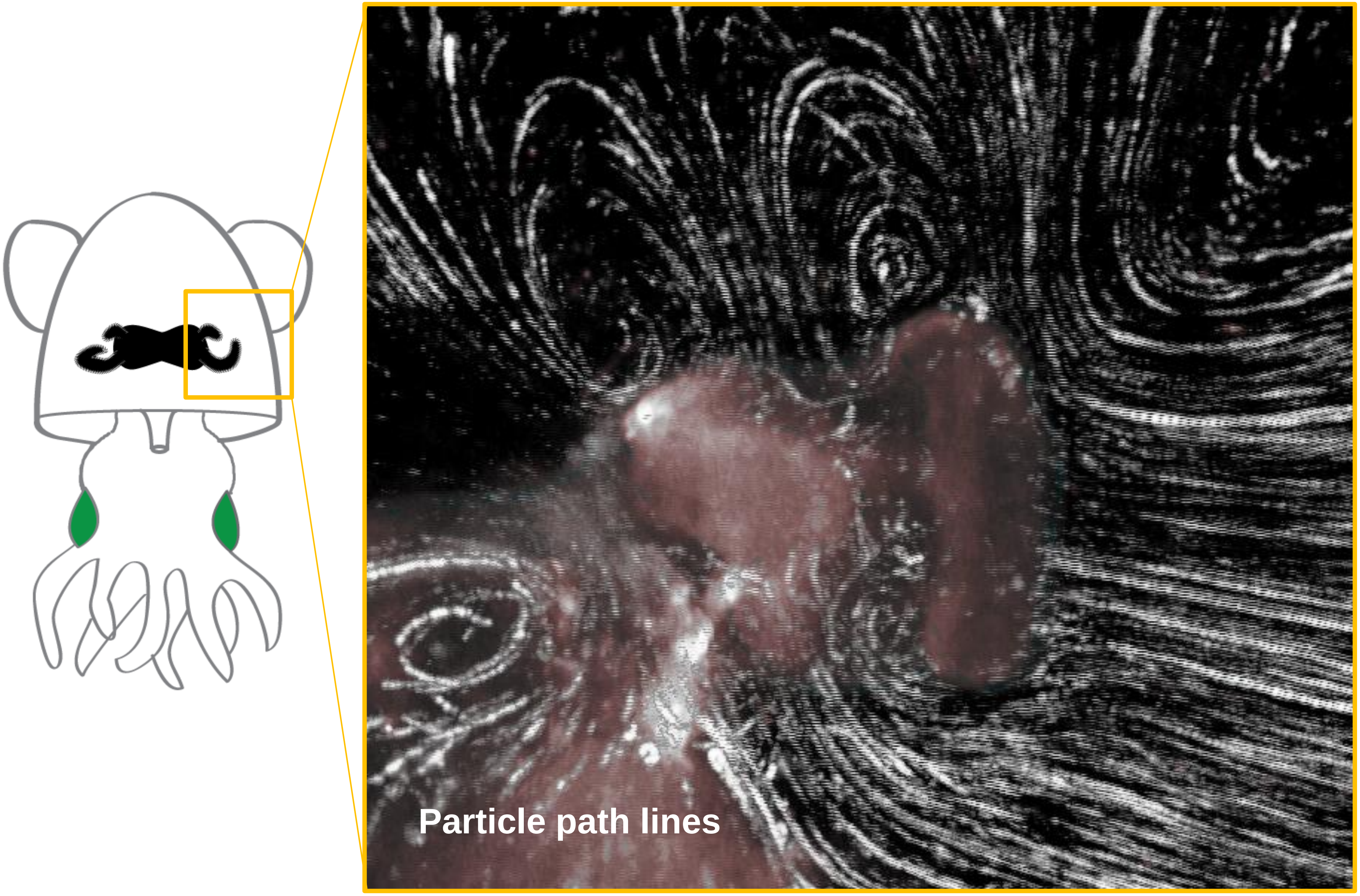




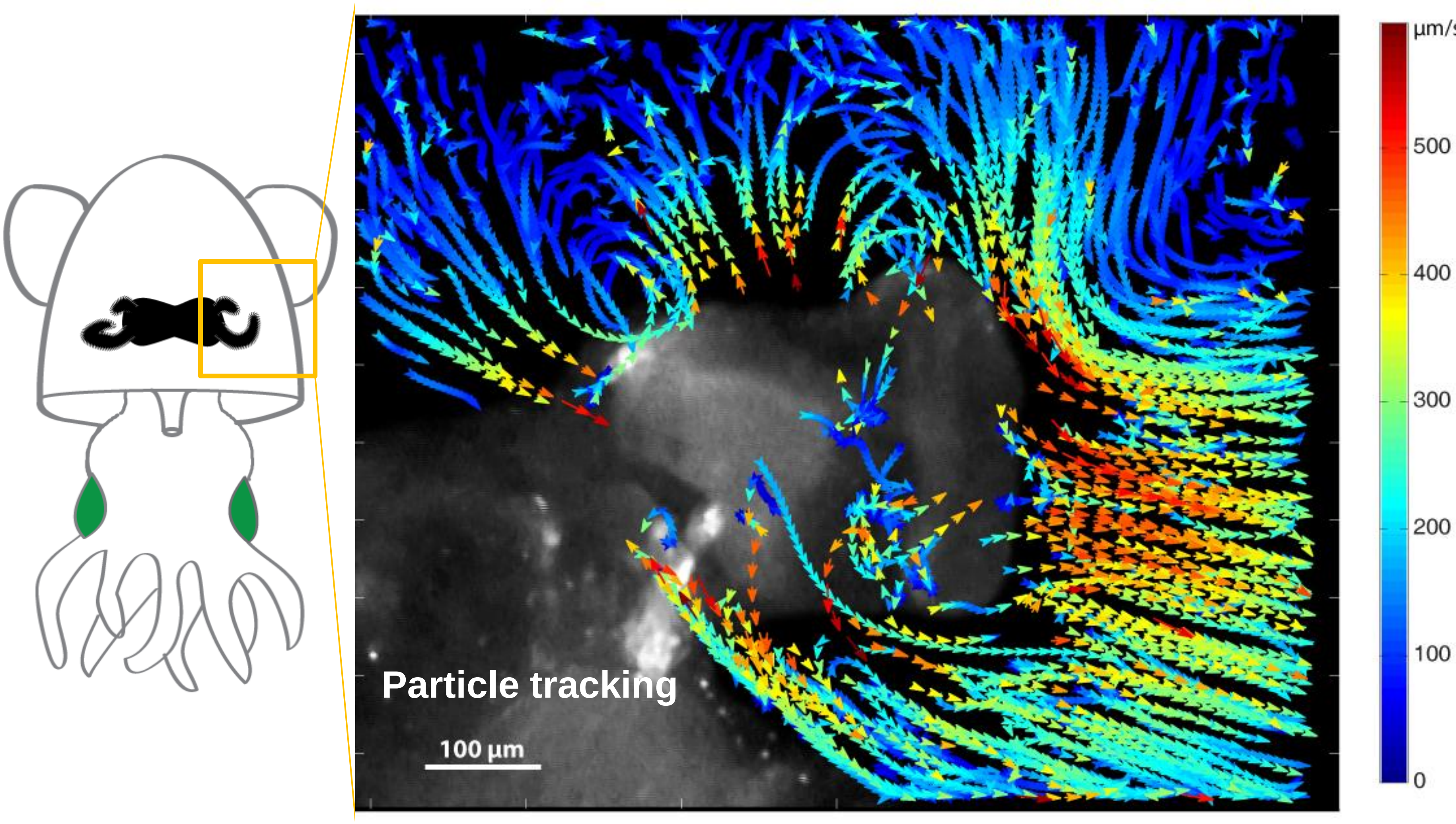
Cilia-generated flow field



Cilia-generated flow field

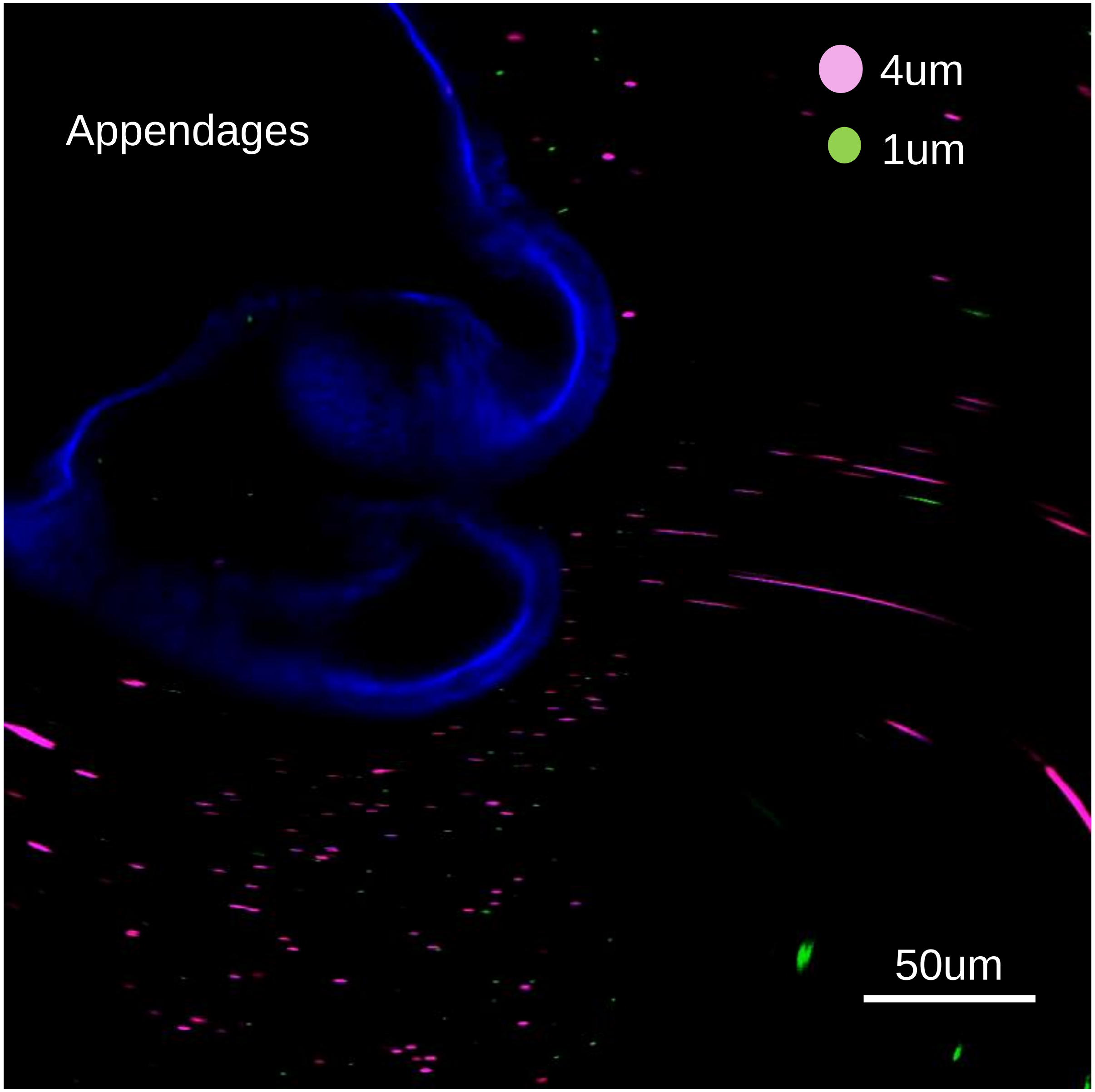


Cilia-generated hydrodynamic sieve

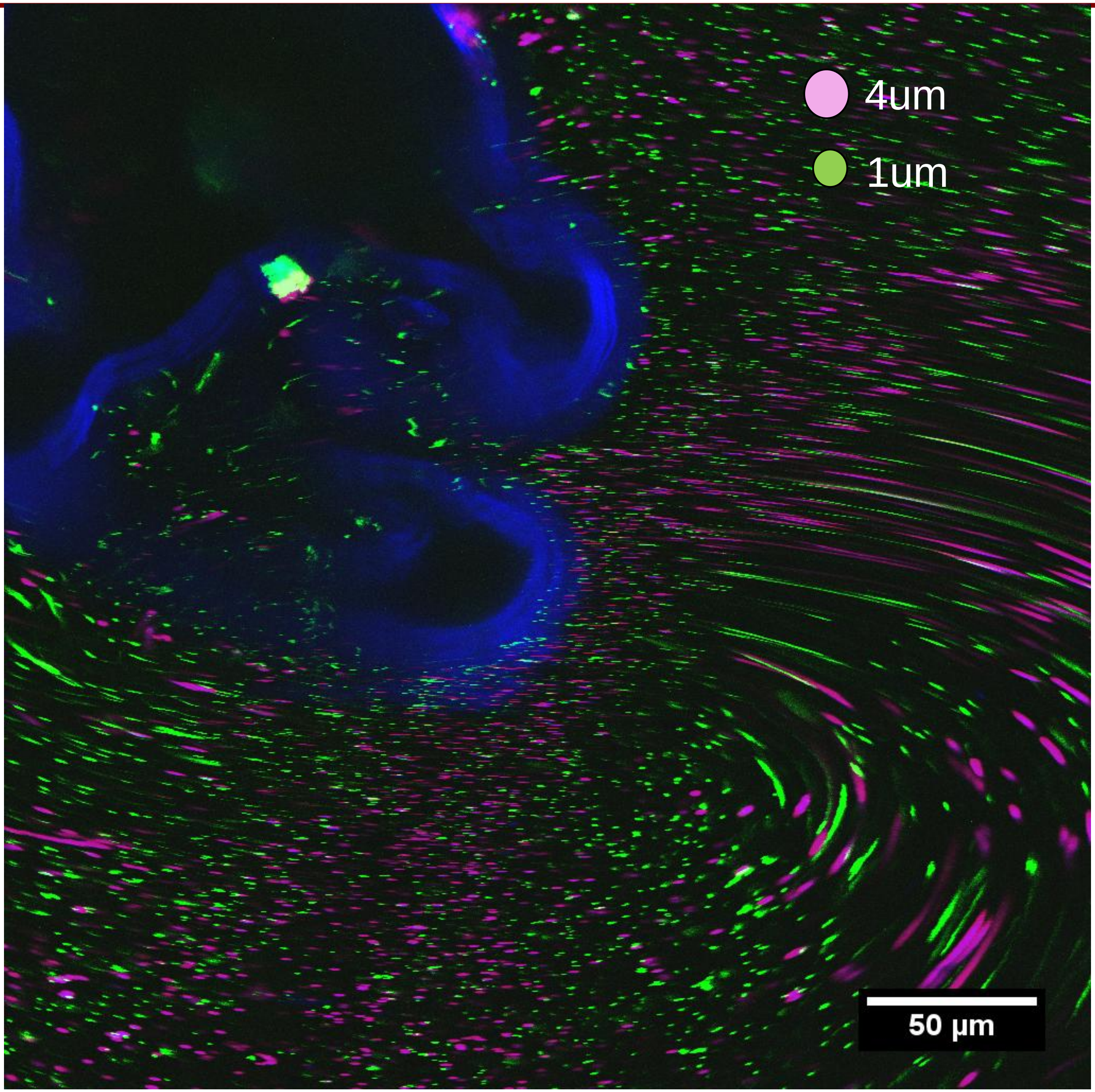


Ratio advected particles:captured particles ≈ 50:1

In vivo capture



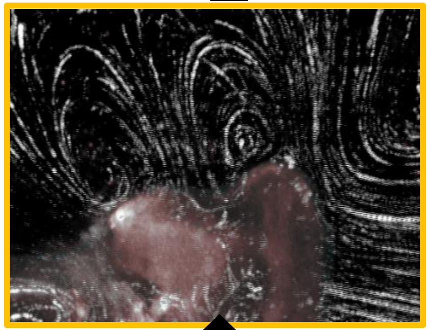
In vivo capture



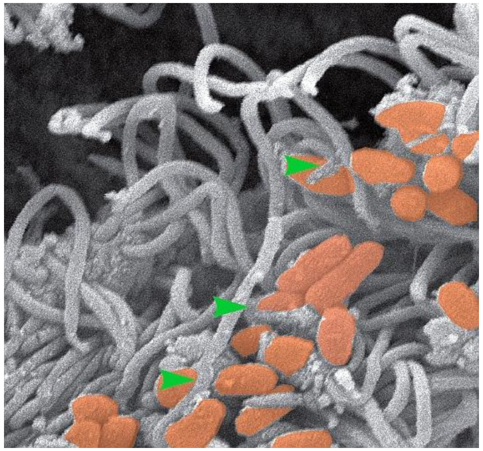
Current work:
Identifying structure-function relationships…

Cilia fitness

Capture and aggregation of bacteria (-sized particles)

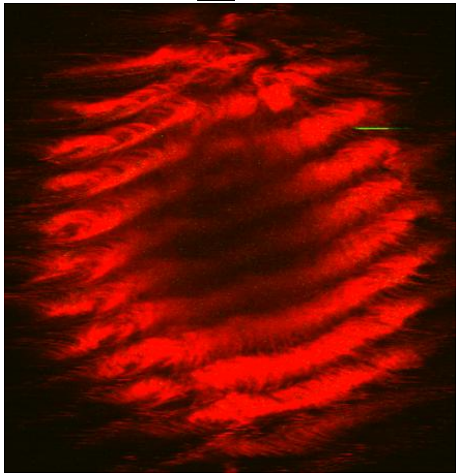


Fluid transport and mixing



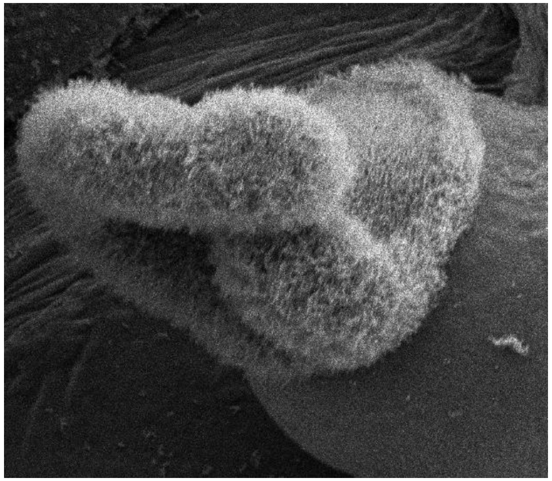
Ciliary structure and kinematics

+



Metachronal wave

+



Surface geometry

Current work:
Identifying structure-function relationships…

…using a variety of methods and approaches