UNIVERSITY OF TWENTE.

USING 3D-PRINTING TO FABRICATE MICROFLUIDIC VASCULAR MODELS TO MIMIC ARTERIAL THROMBOSIS

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BIOS Lab on a Chip group

AST APPLIED STEM CELL TECHNOLOGIES

12 & 13 DECEMBER INTERNATIONAL MICRO NANO CONFERENCE AMSTERDAM 2017

MESA+ INSTITUTE FOR NANOTECHNOLOGY

MIRA BIOMEDICAL TECHNOLOGY AND TECHNICAL MEDICINE

CARDIOVASCULAR DISEASES AND THROMBOSIS

Thrombosis – formation of blood clots inside of blood vessels.

Cardiovascular diseases - 1/3 of all deaths - WHO

- Atherosclerosis, stroke, myocardial infraction
  - Multifactorial
    - Blood-borne factors
    - Vessel wall dysfunction
    - Fluid dynamical effects
    - Genetics

Source: WHO – CVDs factsheet / Obesity Europe Region

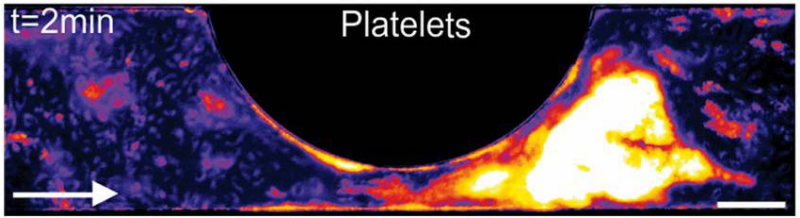
OVERVIEW CURRENT MODELS
ANIMAL & IN VITRO MODELS

Animal models

- Complex nature of cardiovascular diseases
- Does not mimic: human physiology
- Only in large arteries, TNF-α, $FeCl_3$ and heat.
- Unethical

In vitro models

- Human cells
- Lack complexity and systemic effects
- Non realistic flow profiles



E. Westein et al. PNAS 2013;110:1357-1362

Combine complexity of animal models with *in vitro* models

Source: Humane Society International

VISION

- Realistic *in vitro* models for arterial thrombosis
  - CTA-based geometry
  - Human cells
  - Human whole blood

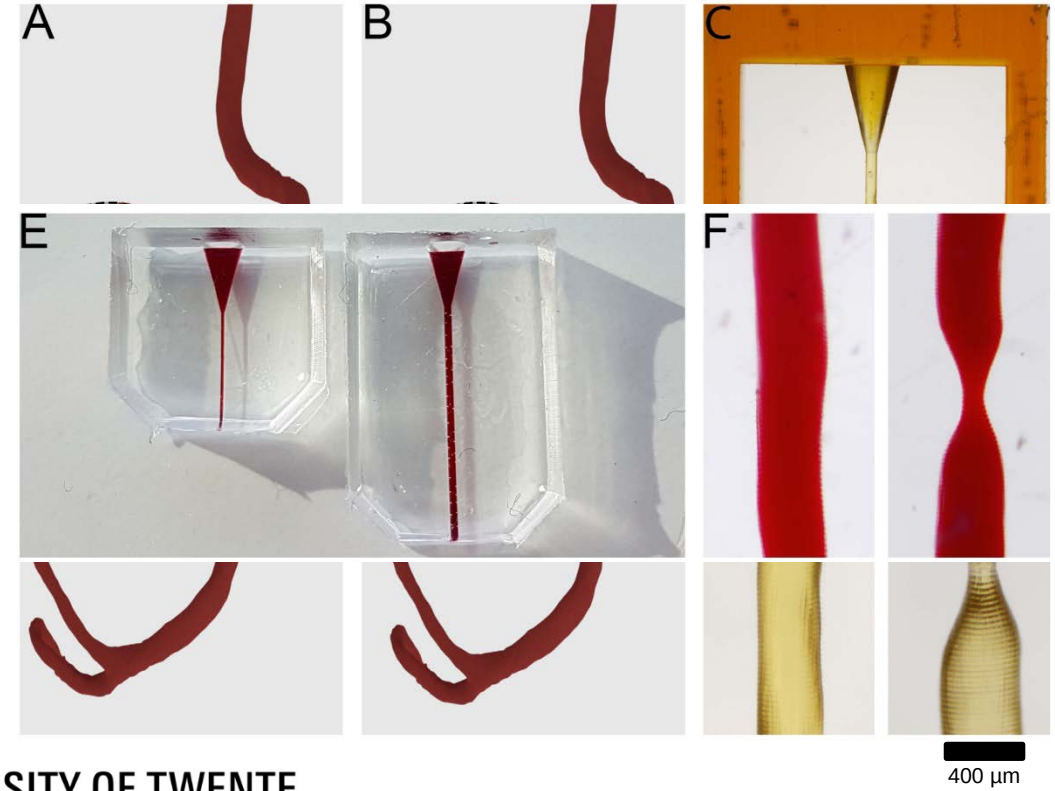
Costa, Pedro F., Albers, Hugo J, Linssen, John EA, et al. "Mimicking arterial thrombosis in a 3D-printed microfluidic in vitro vascular model based on computed tomography angiography data." *Lab on a Chip* 17.16 (2017): 2785-2792

- Complex models
  - Co-culture, inflammatory response & remodeling

- Validation using antiplatelet and anticoagulant therapeutics

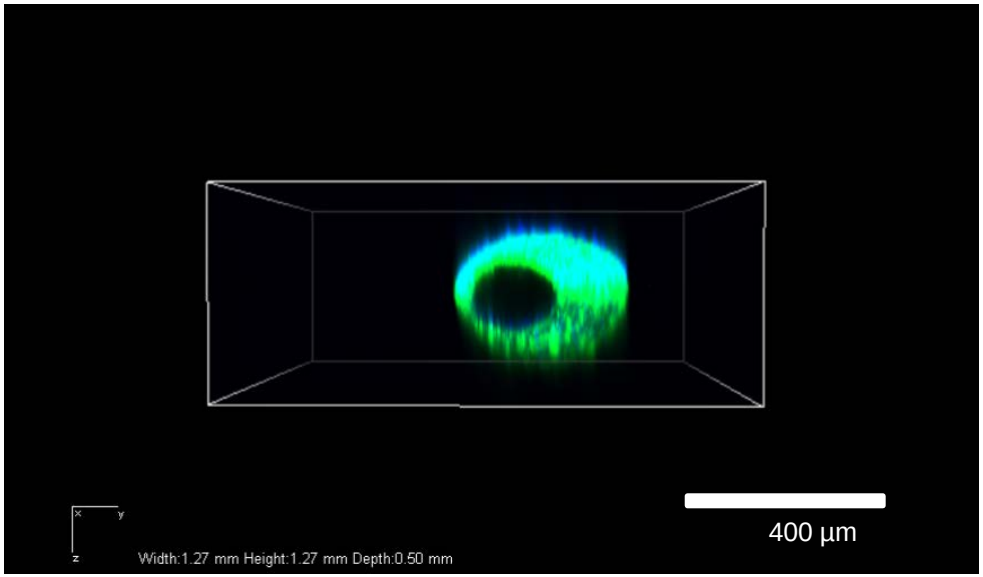
DEVICE FABRICATION

3D-PRINTING

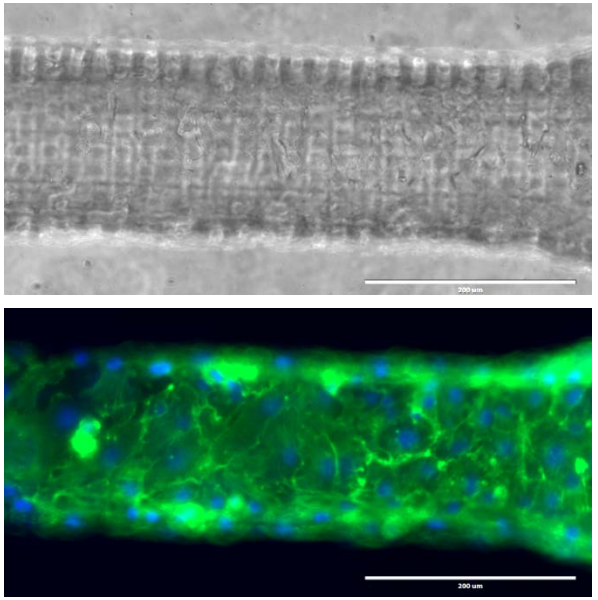


HUVEC CULTURING

HUVEC = Human Umbilical Vein Endothelial Cell

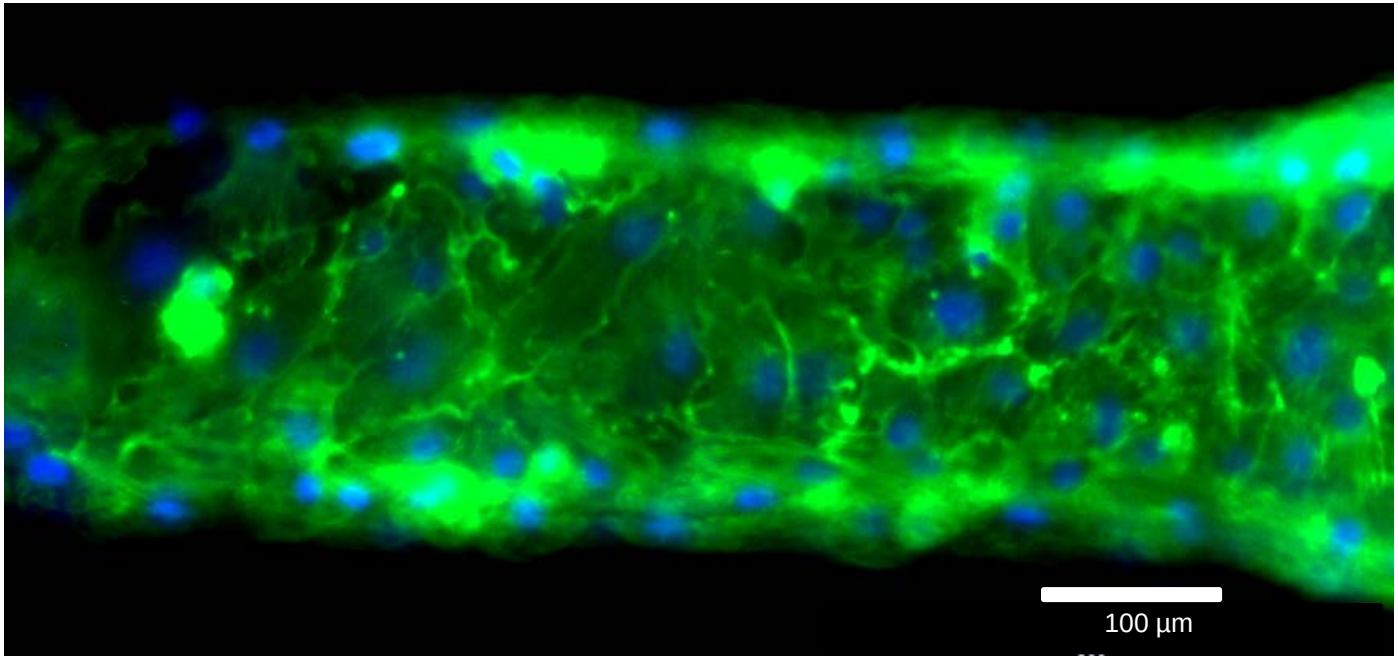


Nuclei & F-Actin



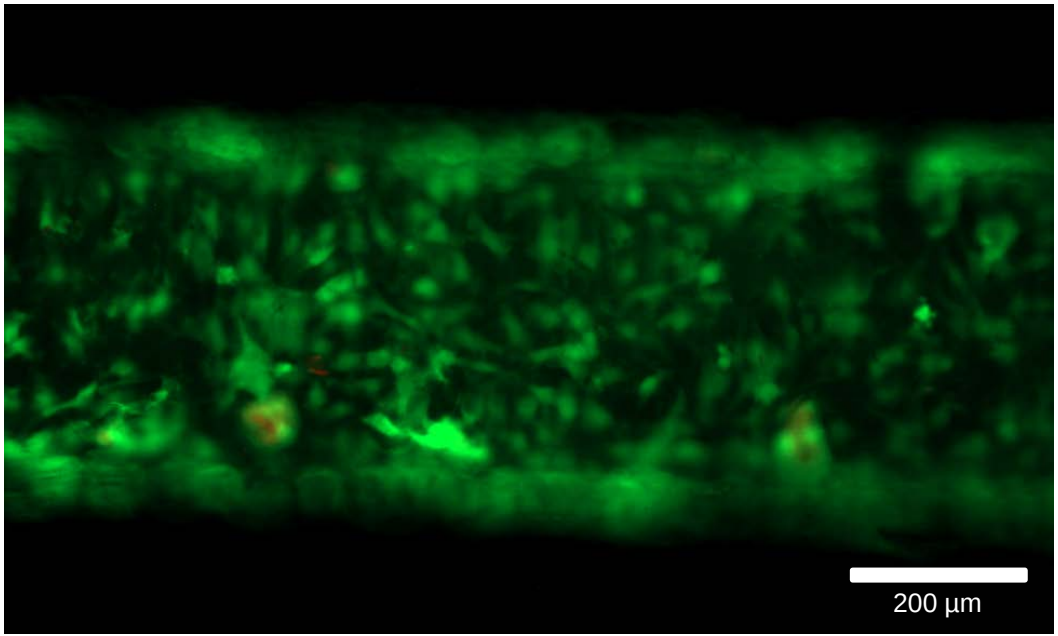
200µm diameter construct – NucBlue & Actin Green

HUVEC CULTURING
MORPHOLOGY



200µm diameter construct – NucBlue & Actin Green

HUVEC CULTURING
LIVE/DEAD STAINING



400µm diameter construct – Live/Dead staining
(Calcein, Ethidium homodimer-1)

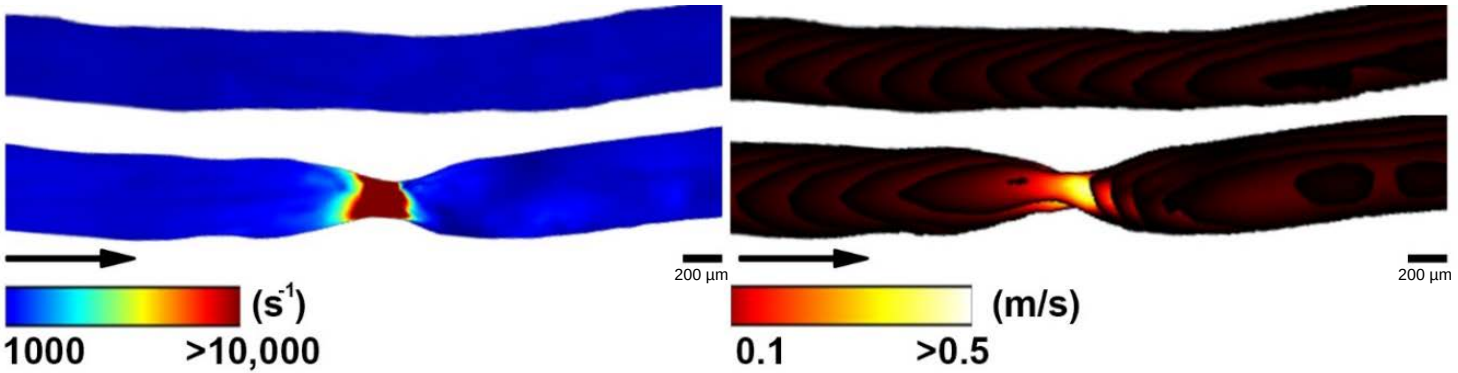
THROMBOSIS-ON-A-CHIP
WHOLE BLOOD PERFUSION

- Next step: Whole blood perfusion in chips lined with HUVECs
  - 2x Control in healthy geometry (no stenosis)
  - 3x Varying stenosis (1000 – 37000 s^{-1})
- Hypothesis:
  - No thrombus formation in healthy channels ~15 min whole blood perfusion
  - Thrombus formation at the apex of stenotic geometry

COMPUTATIONAL FLUID DYNAMICS
SHEAR RATE & FLOW VELOCITY

Shear rate

Flow velocity

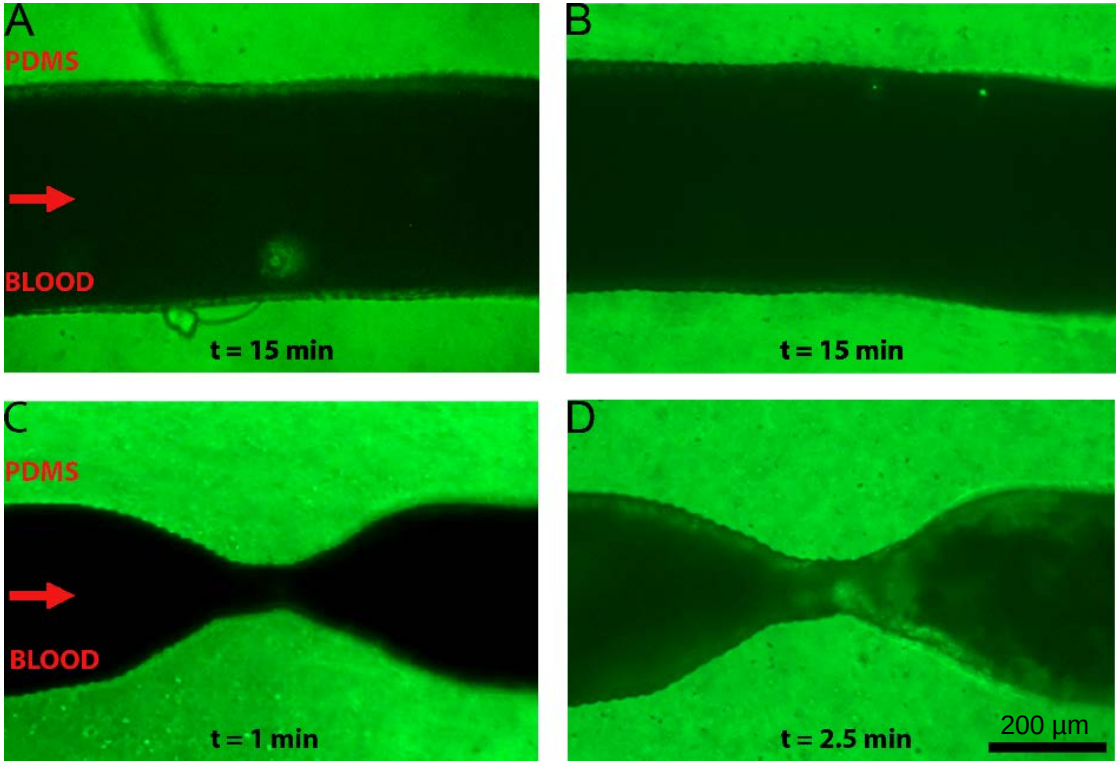


THROMBOSIS-ON-A-CHIP

PROOF OF CONCEPT – LINED WITH HUVECS

Healthy geometry

Stenotic geometry



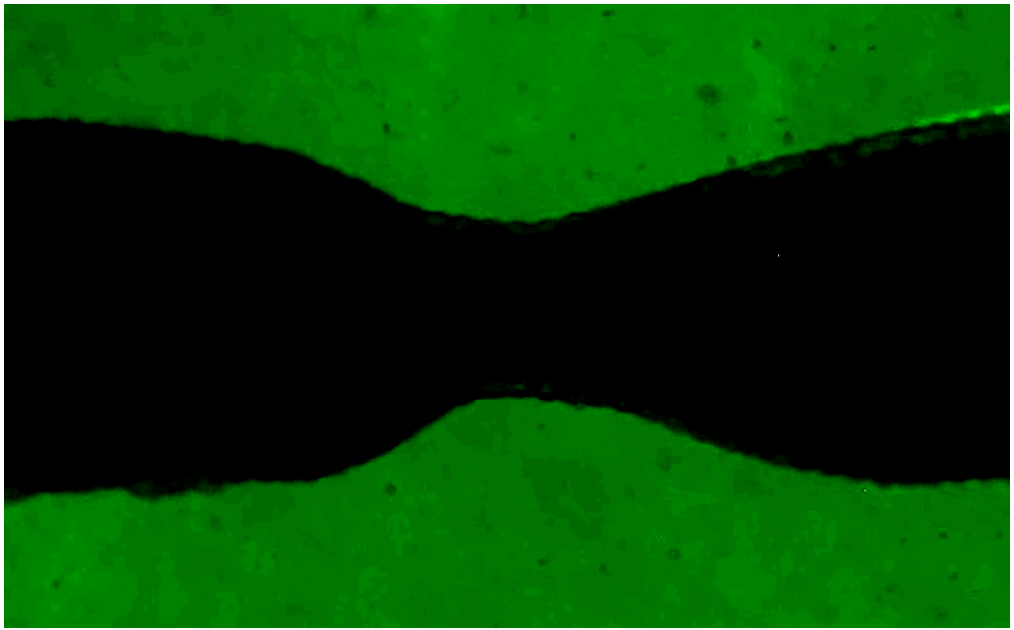
SR = 1000 s^{-1}

Re-calcified citrated whole blood perfused with a 1000 s^{-1} shear rate. Fluorescent platelets ($DiOC_6$)

THROMBOSIS-ON-A-CHIP

PROOF OF CONCEPT – STENOTIC CHIP – LINED WITH HUVECS

Blood flow



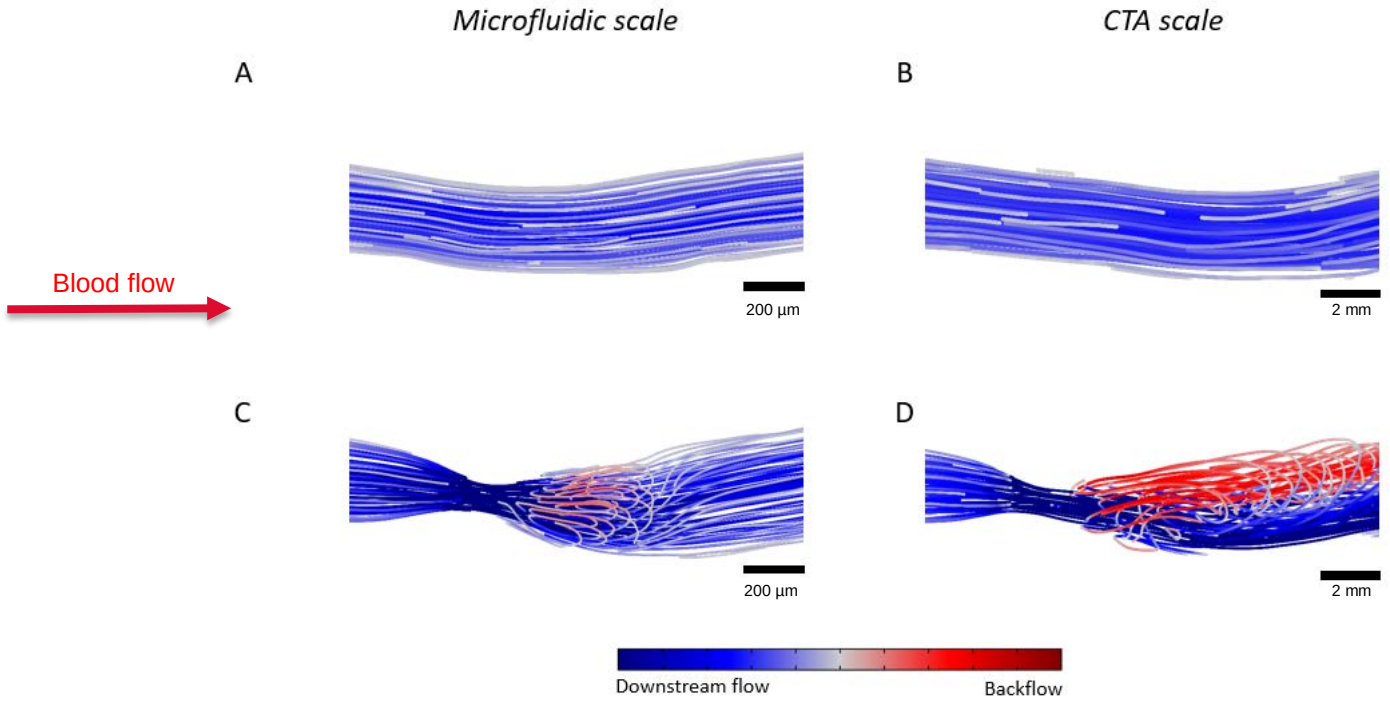
200 µm

8x speed

12 – 14 min

Re-calcified citrated whole blood perfused with a 1000 s^{-1} shear rate. Fluorescent platelets ($DiOC_6$)

COMPUTATIONAL FLUID DYNAMICS
STREAMLINES



CONCLUSIONS

- Successfully printed healthy and stenotic geometries
- Cultured HUVECs for extended periods of time
- Perfused blood at physiologically relevant shear rates:
  - Healthy geometry – no thrombosis
  - Stenotic geometry – thrombosis at apex
- Confirmed hypothesis using CFDs

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QUESTIONS?