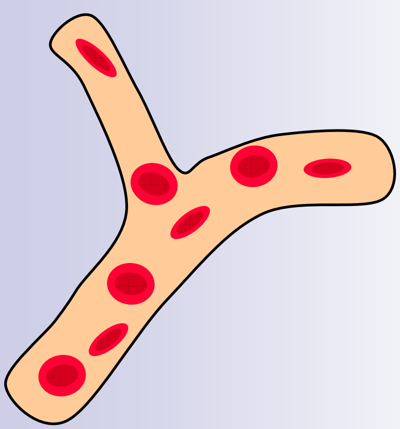
Particle separation in low Re flow conditions:

How do red blood cells decide which branch to take?



Mary D (Molly) Frame, PhD

Department of Biomedical Engineering

Stony Brook University

Overview

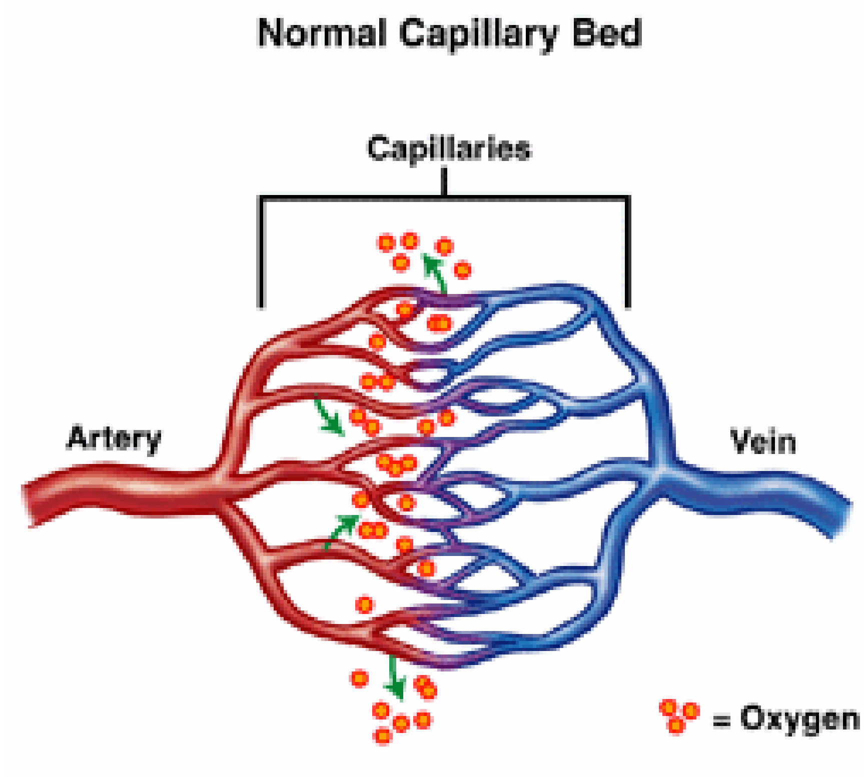
- The microcirculation
  - Oxygen and nutrient delivery to the cells
- Blood: Newtonian fluid?
  - 2- phases: The plasma and the cells
  - Fahraeus Effect: Cells travel in the middle
  - Plasma skimming: Side branches get more plasma
  - Low Reynold's flow: Viscous nature predominates
  - Bifurcation shapes in vivo: RBC filters
- Large Scale Model
- Microchannel Model

Systemic vs. microcirculatory systems

- Systemic circulation
  - >200µm dia.
    - Organ inflow vessels
  - Pressure
    - 120/80 mmHg to 5 mmHg
  - Velocity (aorta)
    - 800 cm/min
  - Shear stress
    - 20 - 50 dyn/cm^2
  - Re >> 1
    - Inertia predominates

Systemic vs. microcirculatory systems

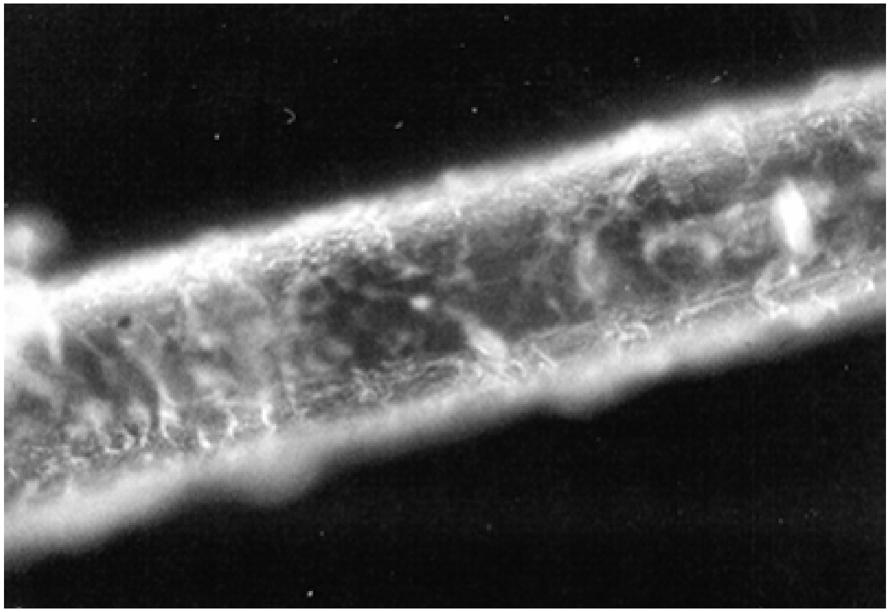
- Microcirculation
  - < 200μm dia.
    - particle to tube dia. ratio
  - Static pressure
    - 50 - 0 mmHg
  - Fluid velocity
    - 0- 6000μm/sec
  - Fluid shear stress
    - 0- 80 dynes/cm^2
  - Re << 1 (Reynolds number)
    - Viscous resistance predominates



neuro.wehealny.org

Human Hair Thickness

- 50 - 200 microns in diameter

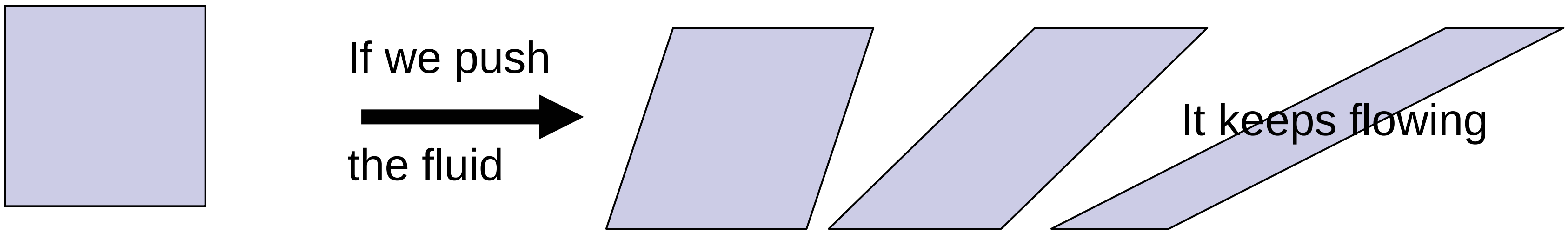


Lab-on-a-chip?

- The principles learned from our studies apply to any microchannel system with particles.
  - Blood analysis chips
  - Bio-hazard detection
- The relative sizes of the tube (channel) and particles are what is important.

Newtonian fluids and the continuum concept

- Newtonian fluids are defined as continuous.
  - Continuum fluid – all of the pieces of the fluid have the same composition and nature
  - Continuum flow – all of the moving streamlines are uniform and seamless

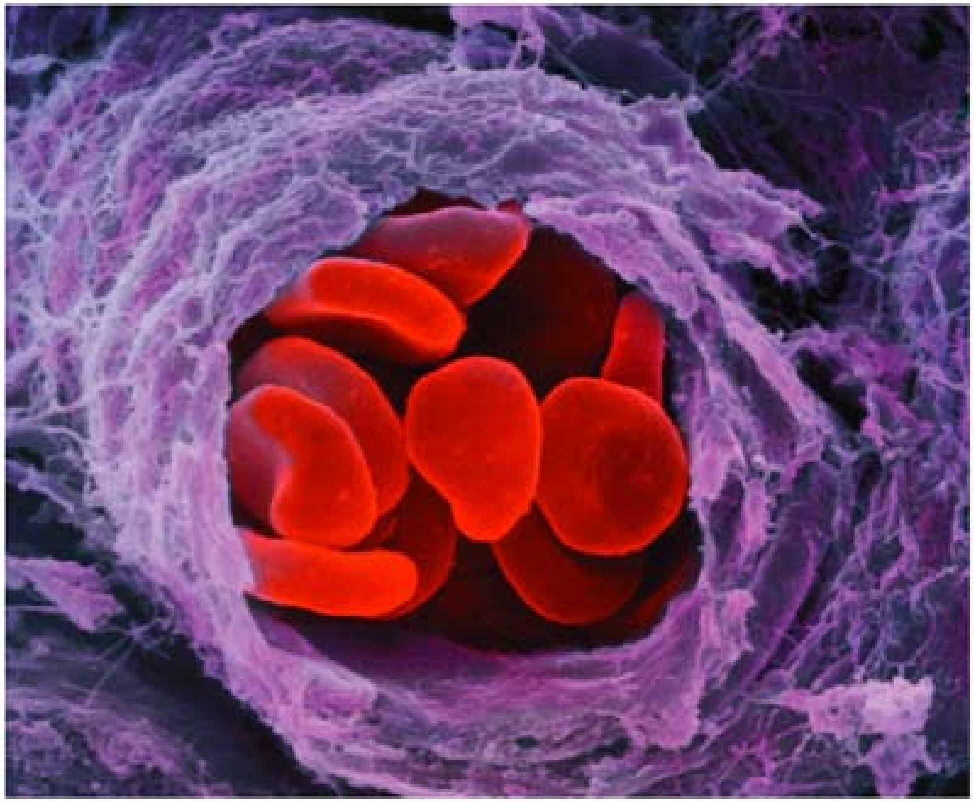


- How small can a volume of blood be and still appear to be continuous?

Blood is a 2-phase fluid:

plasma phase and particle phase

- Hematocrit
  - Red Blood Cells
    - 5µm
    - 30 - 40%
- White Blood Cells
    - 7 - 10µm
- Platelets
    - 1 - 3µm
- Plasma proteins
    - 20 - 80nm

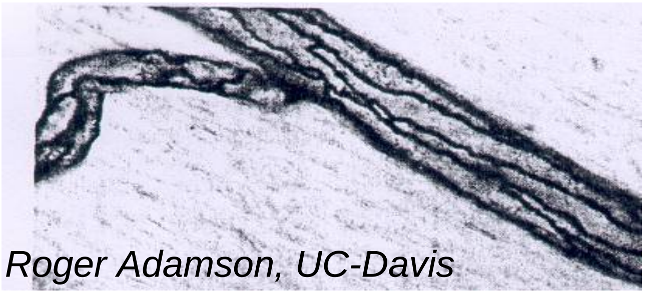


http://www.nature.com/nm/journal/v9/n5/images/nm0503-481-I1.jpg

A note about the 'tube' – the vascular wall

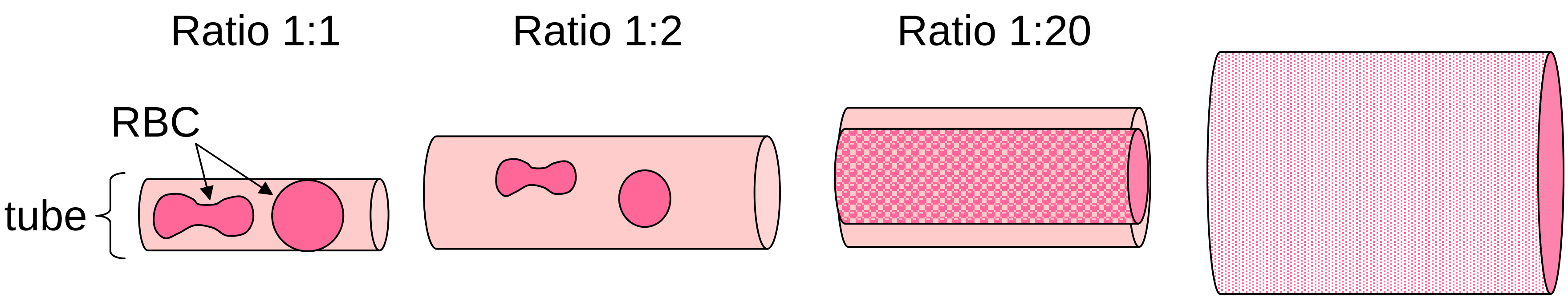
- Endothelial cells form the inside lining.
  - Must withstand fluid shearing forces
- Vascular smooth muscle cells wrap outside.
  - Actively constrict and dilate to change vessel diameter

Endothelial layer



Vascular smooth muscle layer

Tube to particle diameter ratio



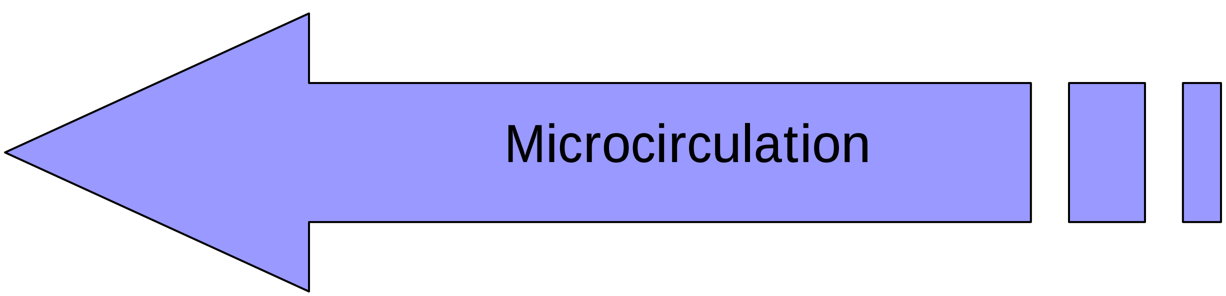
Capillaries
Slug flow

Small arterioles

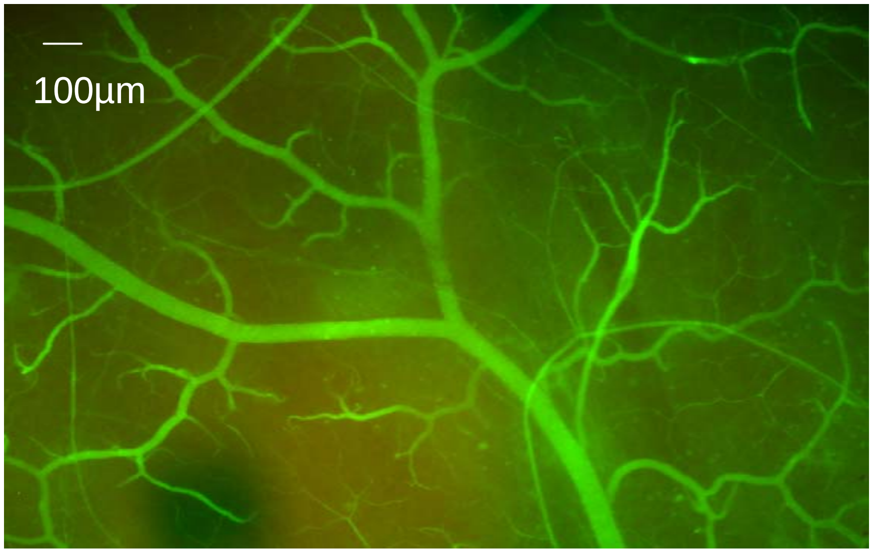
No theory to accurately describe the ‘flow properties.’

50 - 200µm
Bubble flow

Systemic circulation
Newtonian fluid with Newtonian flow properties



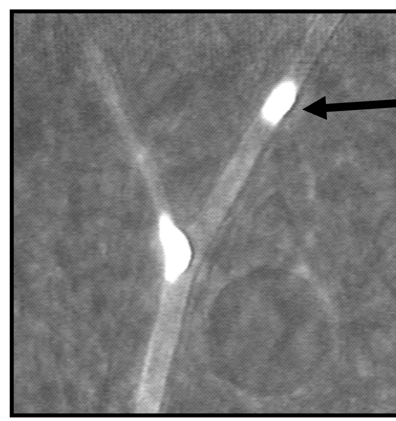
In vivo microvascular networks



Frame Lab: endothelial cells stained with BS-1 lectin

Brightfield and epifluorescence

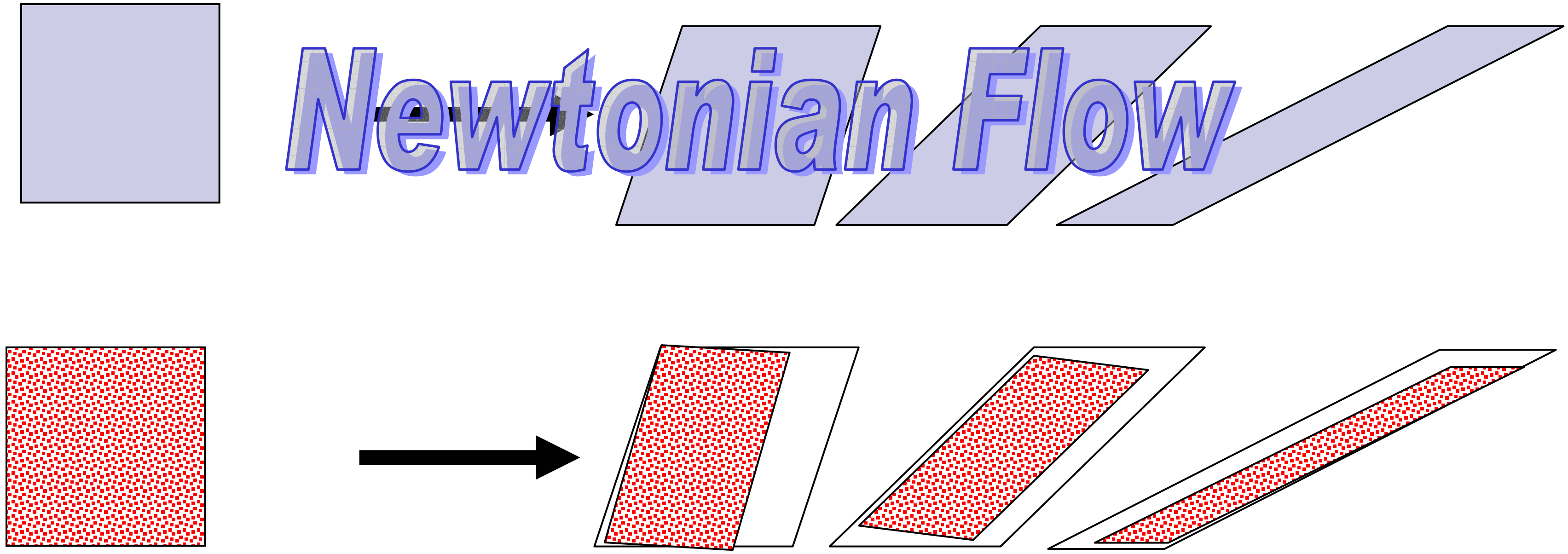
MVR, 1993



XRITC labeled erythrocyte

Non-Newtonian 2-phase flow

- Particles and plasma move differently from each other

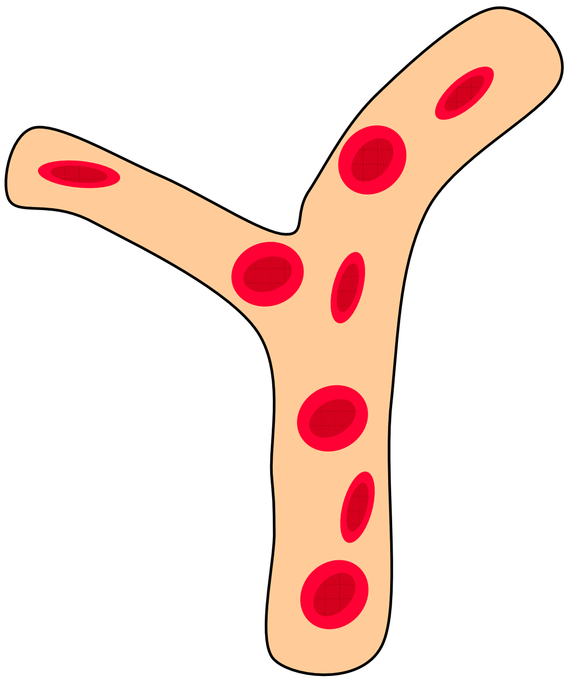


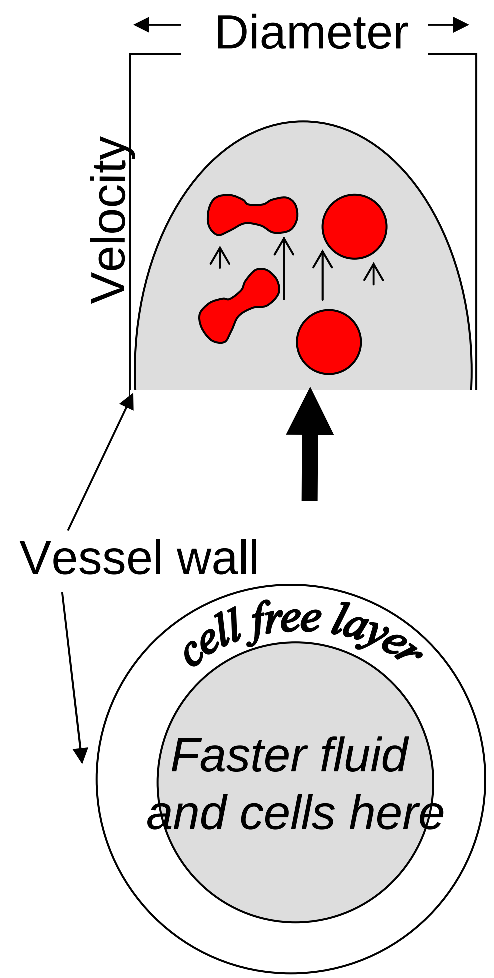
Non-Newtonian 2-phase flow

- Velocity profile
  - Faster flow in the centerline
- RBC travel in faster centerline
  - Cell free zone near the wall
  - RBC move faster than the whole blood

Fahraeus Effect

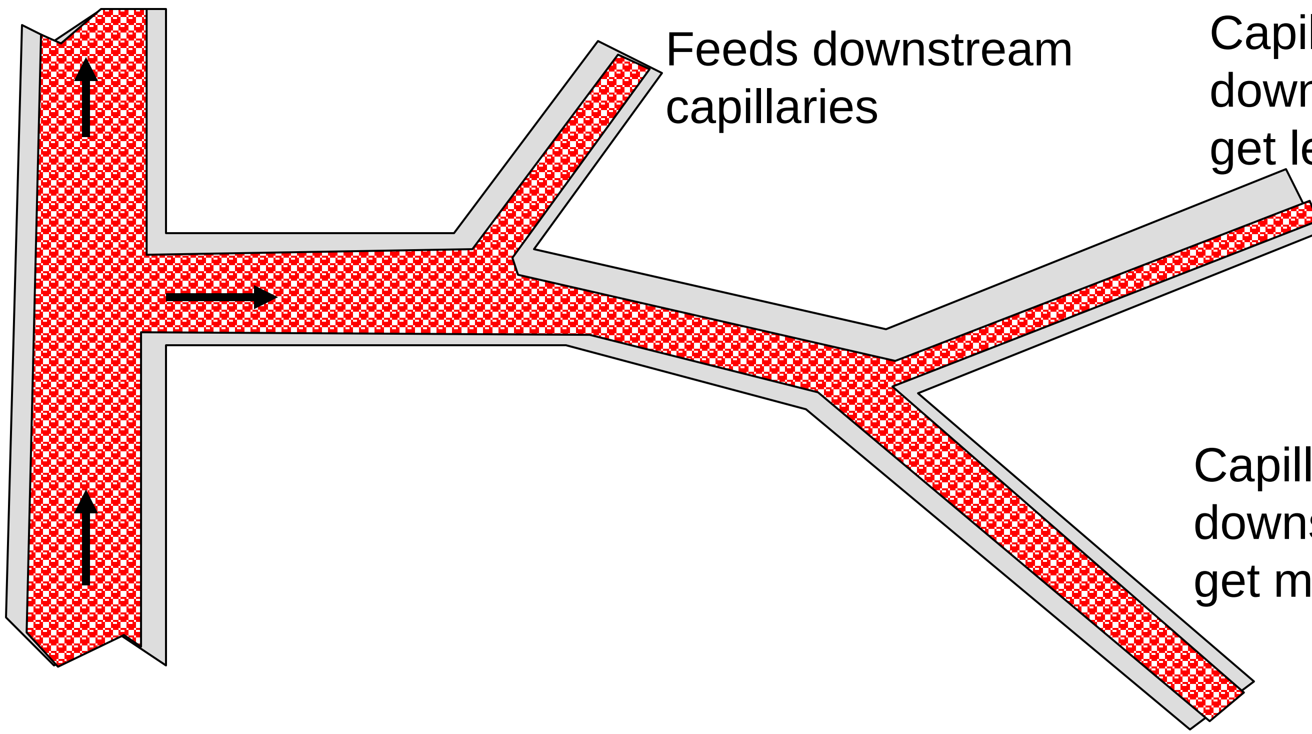
- RBC move faster than the plasma because they are only in the fast streamlines.





Plasma skimming

- At a branch point, if 30% of the flow (volume = nl/min) travels to the branch,
- less than 30% of the RBC (flux = #RBC/time) travel to the branch.



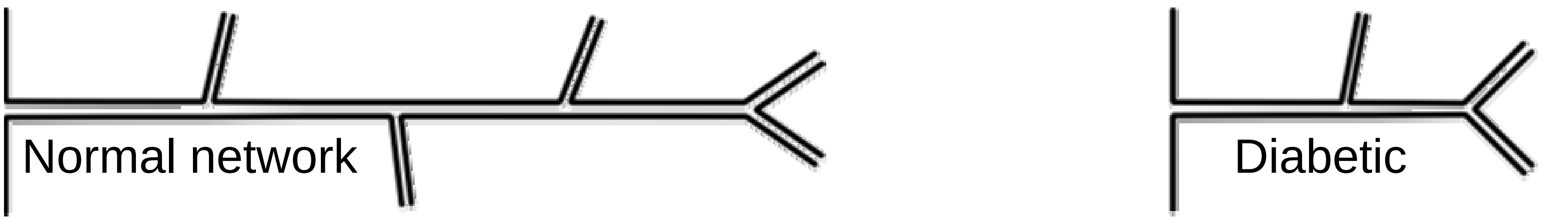
How do the RBCs decide which branch to take?

- Plasma skimming is common knowledge.
- There are no models to accurately predict the degree of skimming that will occur.
- Particle flux (oxygen) distribution is therefore not predictable.
- This severely restricts our ability to understand and treat peripheral vascular disease or damage.

Translational Focus 1: Diabetes

Melissa Georgi, PhD May 2010!!!

- Diabetics have fewer microvessels to begin with.



- Non-uniform oxygen delivery means:
  - Decreased ability to keep up with oxygen demand during exercise
  - Decreased ability to increase oxygen delivery to heal wounds

Translational Focus 2: Wound healing

Anthony Dewar, MS, December 2009!!!

- The key rate limiting step in healing wounds is delivery of enough oxygen to keep up with the increased metabolism

- Both flow through existing microvessels and creation of new microvessels (angiogenesis) are crucial

To understand oxygen delivery we must understand 2-phase particle flow in the microcirculation.

- Particle motion within the tube ✔
  - Consequence for particle flow path
- Inertial forces relative to viscous resistance
  - Consequence for peak shearing forces
- Shape of the branching region (bifurcation)
  - Consequence for particle exclusion

Reynold's number

- Ratio of inertial forces to viscous resistance

$$Re = \frac{\rho \bar{u} D}{\eta}$$

  - ρ, density, gm/cm → assumed constant
  - $\bar{u}$, mean axial fluid velocity, cm/s } together
  - D, tube diameter, cm } shear rate
  - η, viscosity, gm/cm*s

A note about multidisciplinary research: Mechanical Engineers use μ to denote viscosity. For a Chemical Engineer, μ is electrochemical potential; η is viscosity.

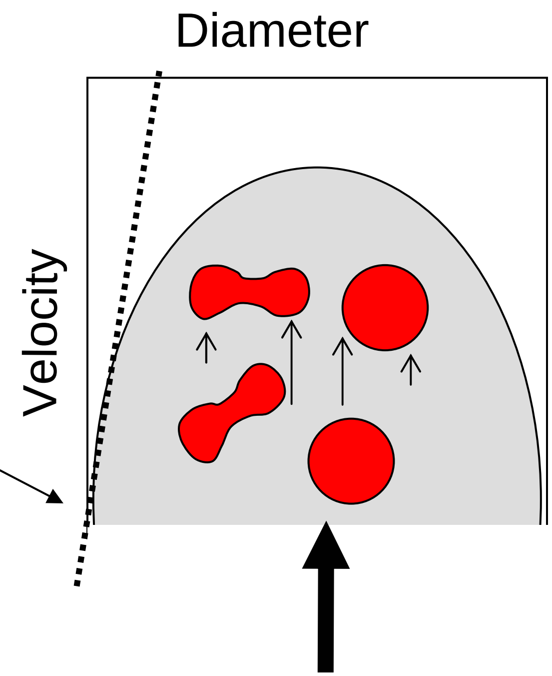
Re - perspective

- Water from a fire hose
  - 110
- Blood from the aorta
  - 3500 → inertia dominates
- Blood in a typical capillary
  - 0.1 to 0.01 → viscosity dominates

Inertial forces: shear rate

- Shear rate, s^{-1}
  - dv/dr, initial slope of velocity profile
- Shear stress, dyn/cm^2
  - $\tau_{\omega} = \eta * dv/dr$

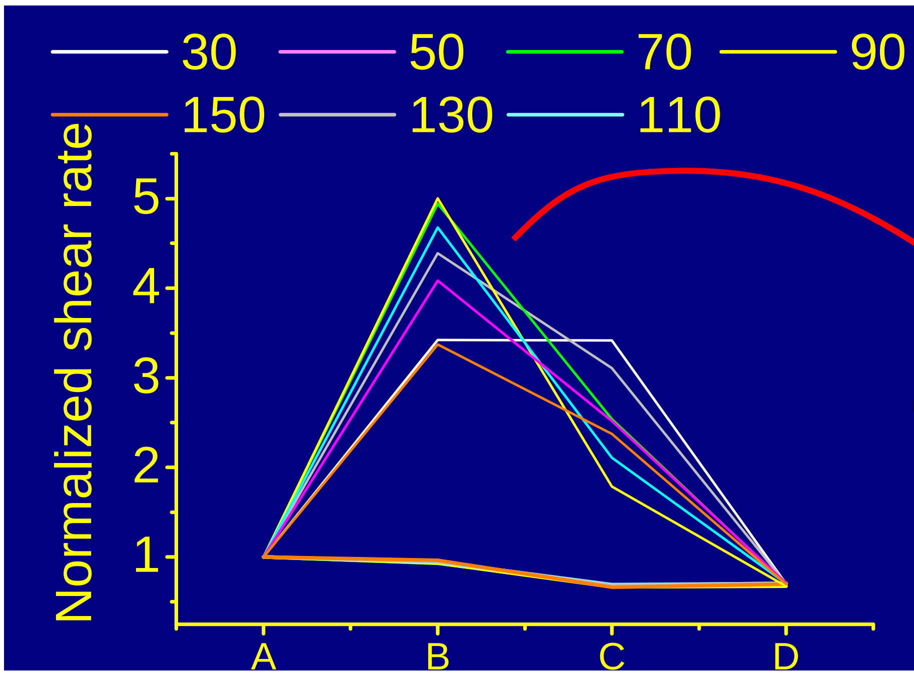
Shear stress = viscosity * shear rate



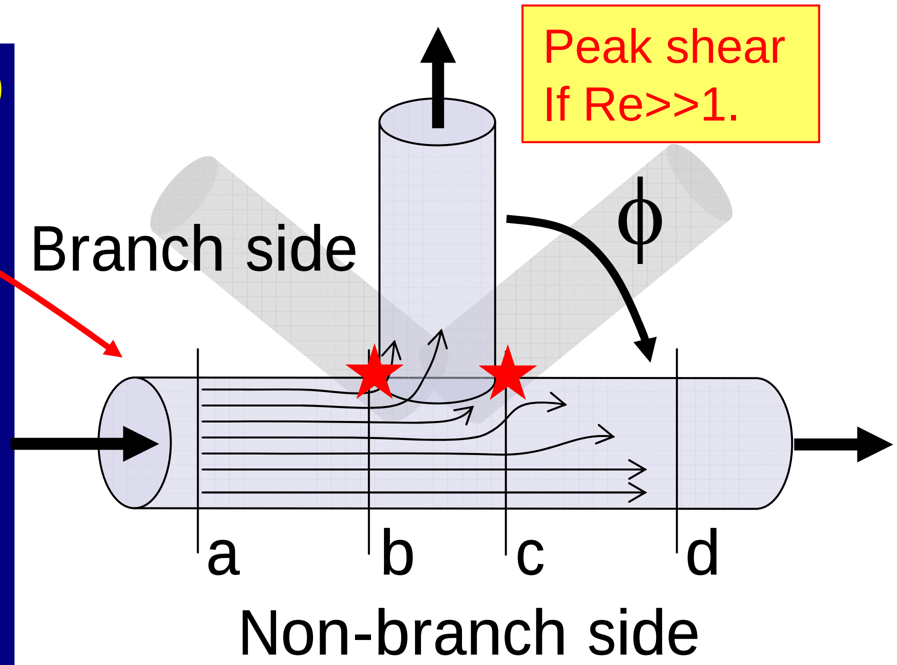
Does the shearing force predict RBC distribution at branches?

For low Re, peak shear is predicted to occur before the branch opening.

Branching angle, ϕ, range from 30 - 150°

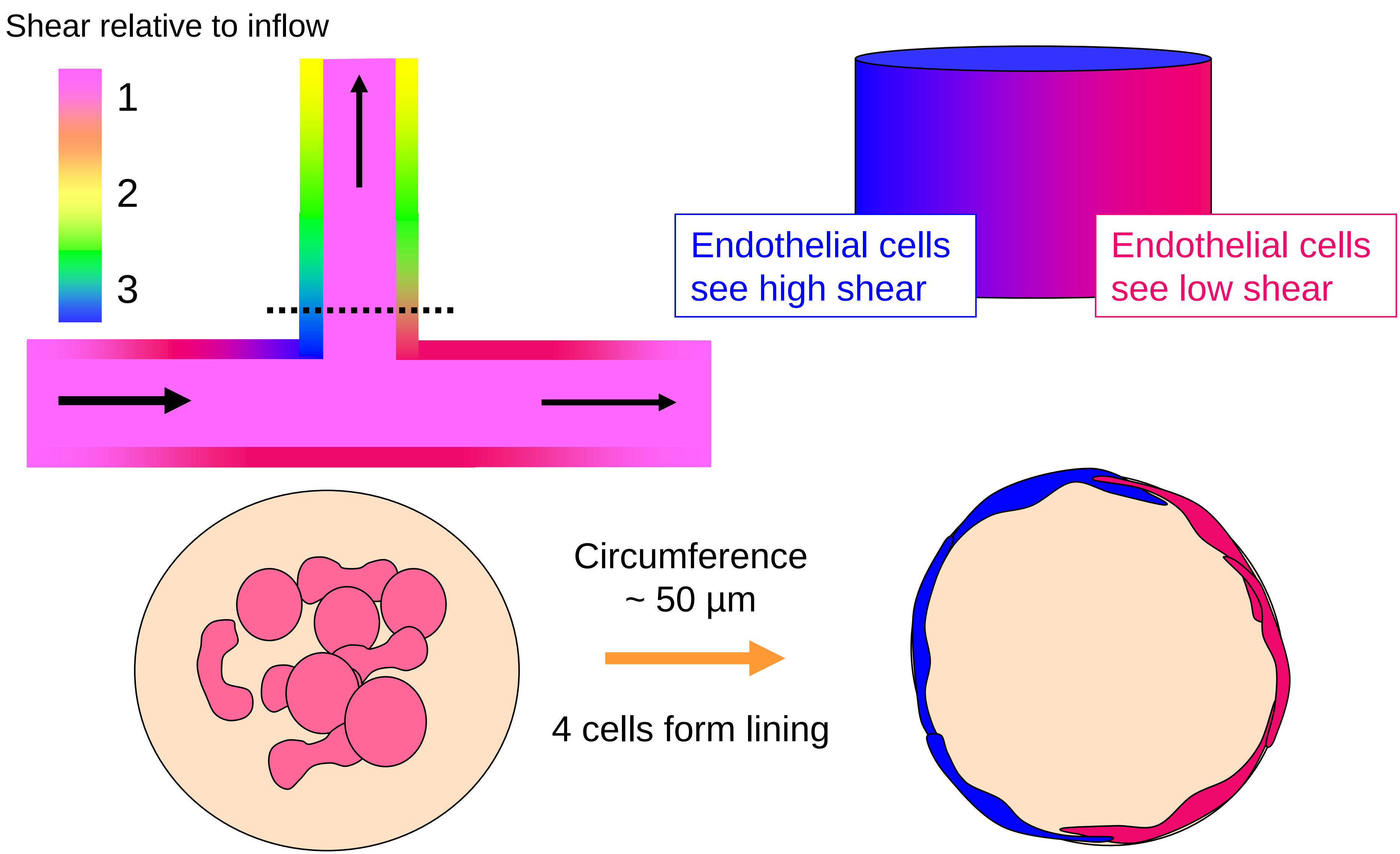


Computational fluid dynamics model



Biorheology, 37: 325-340, 2000

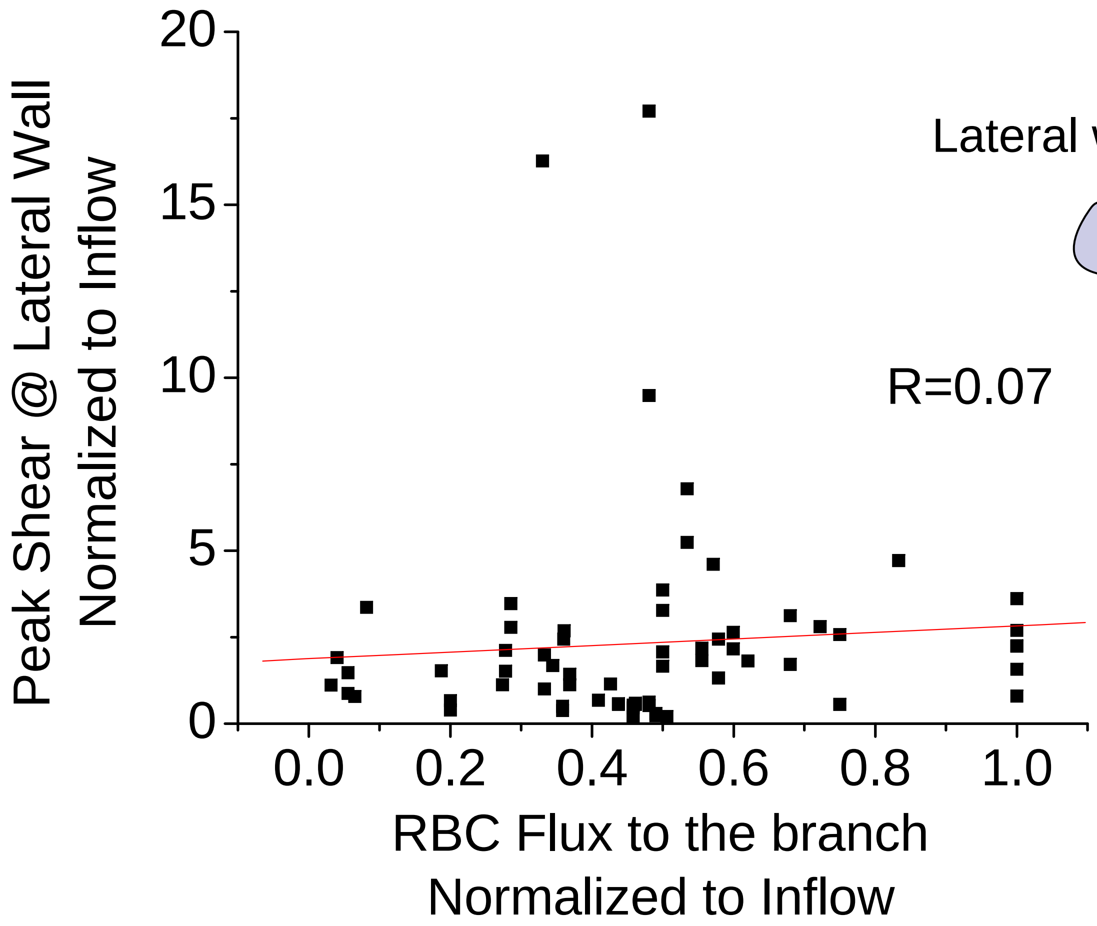
In vivo data: peak shear before branch.

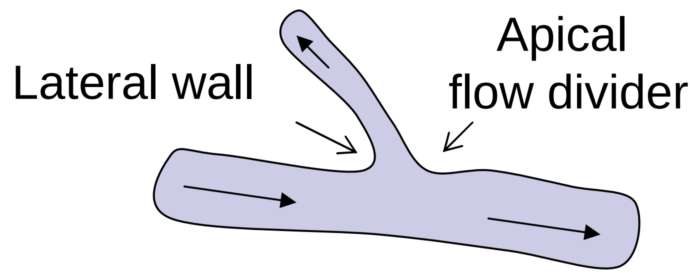


Hypothesis:

- Bifurcations with highest peak shear on the lateral wall will have the highest RBC flux to the branch.

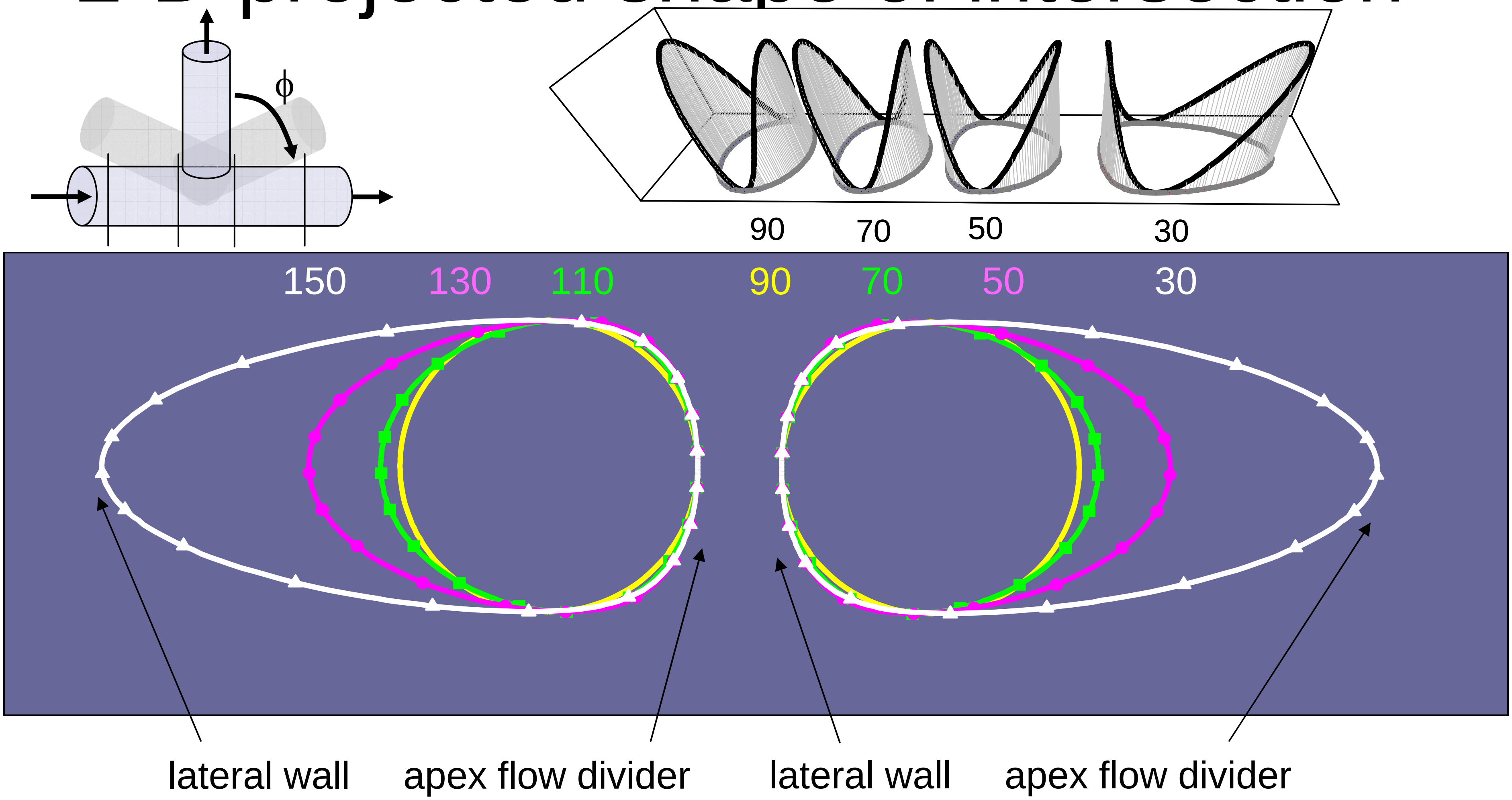
Peak Shear on Lateral Wall is unrelated to RBC flux.





What about the shape of the flow divider?

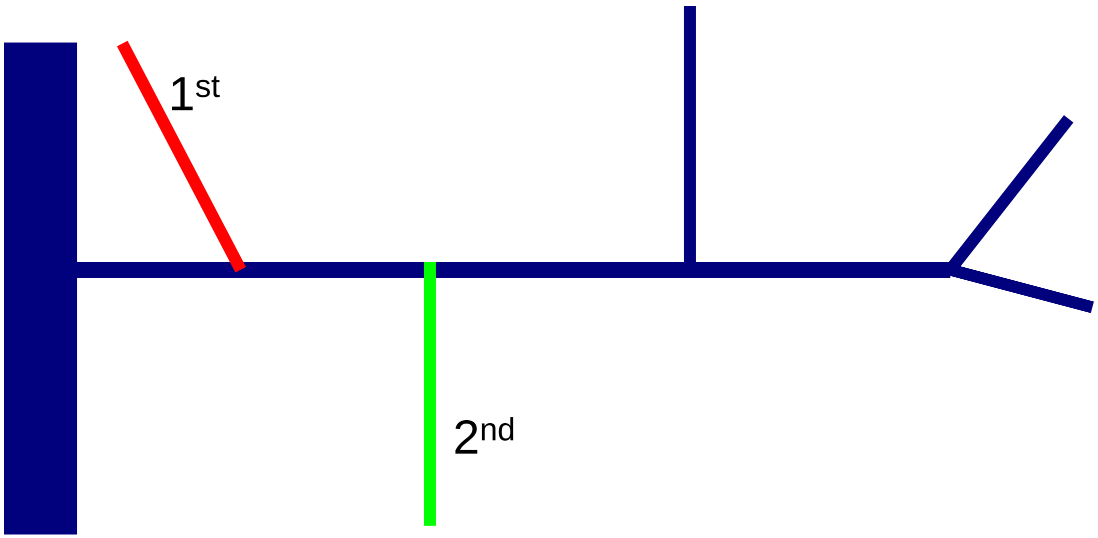
2-D projected shape of intersection



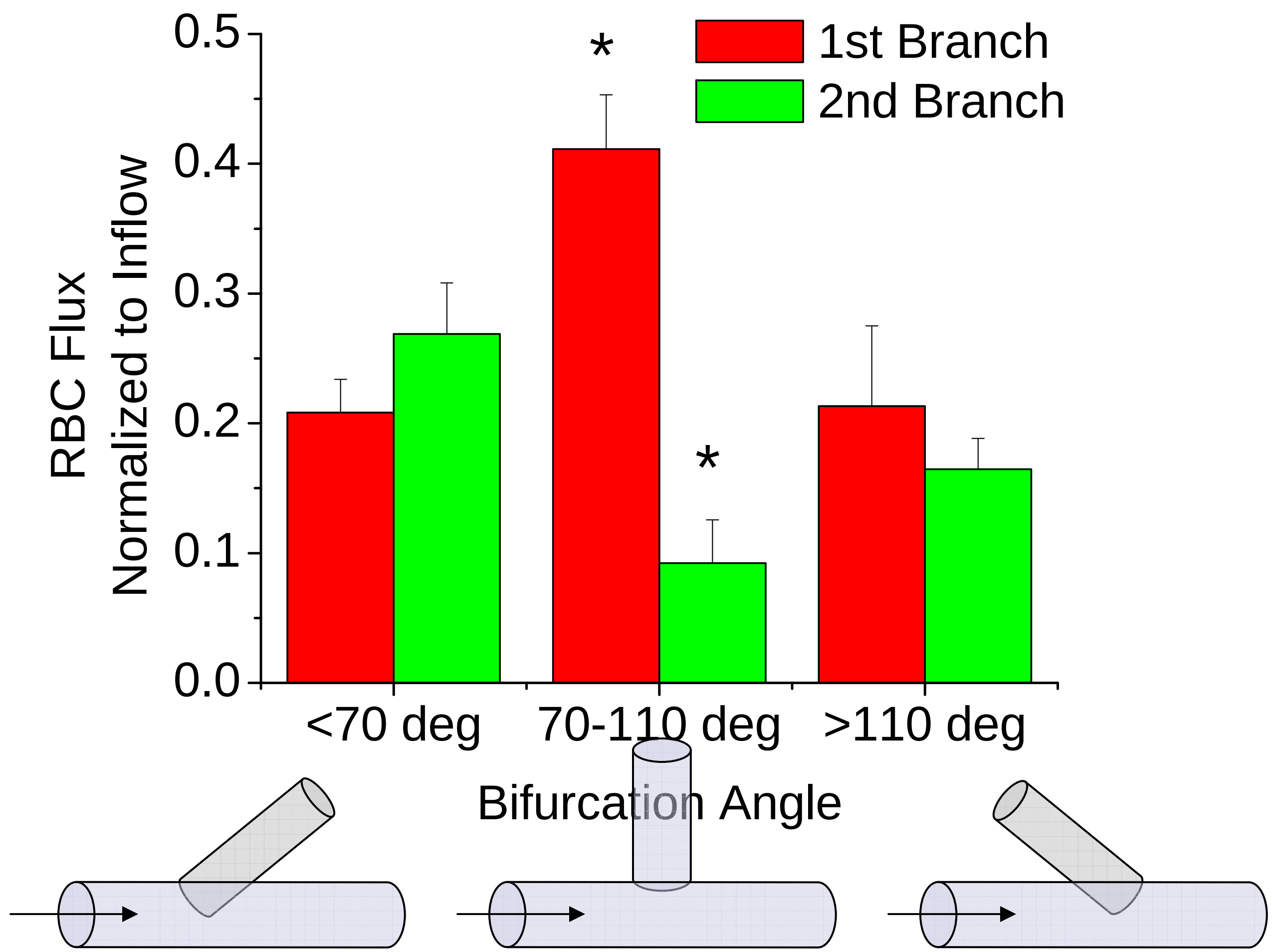
Biorheology, 37: 325-340, 2000

Hypothesis:

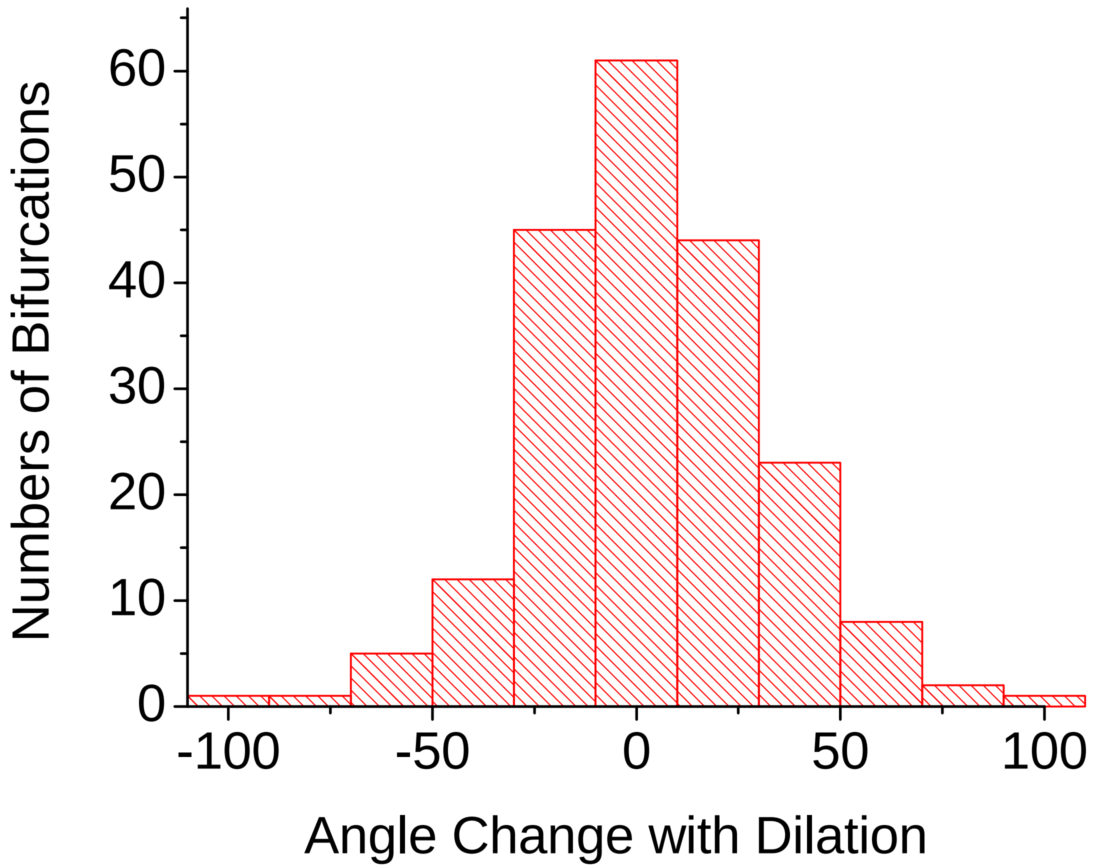
- Bifurcation shape (angle) influences RBC flux to the branch.



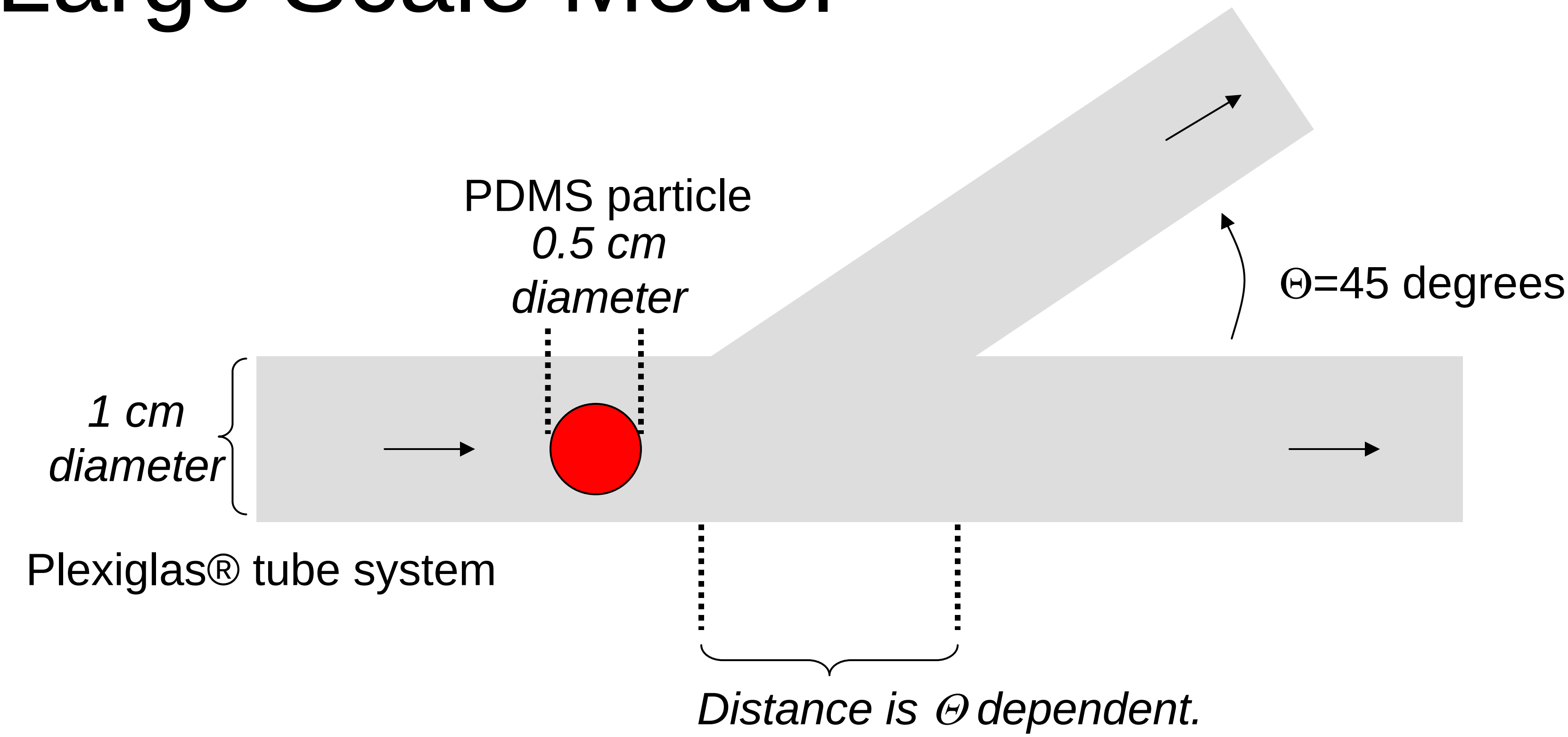
Bifurcation shape and flux are related differently by branch location



Further, bifurcation angles change in vivo with uniform dilation

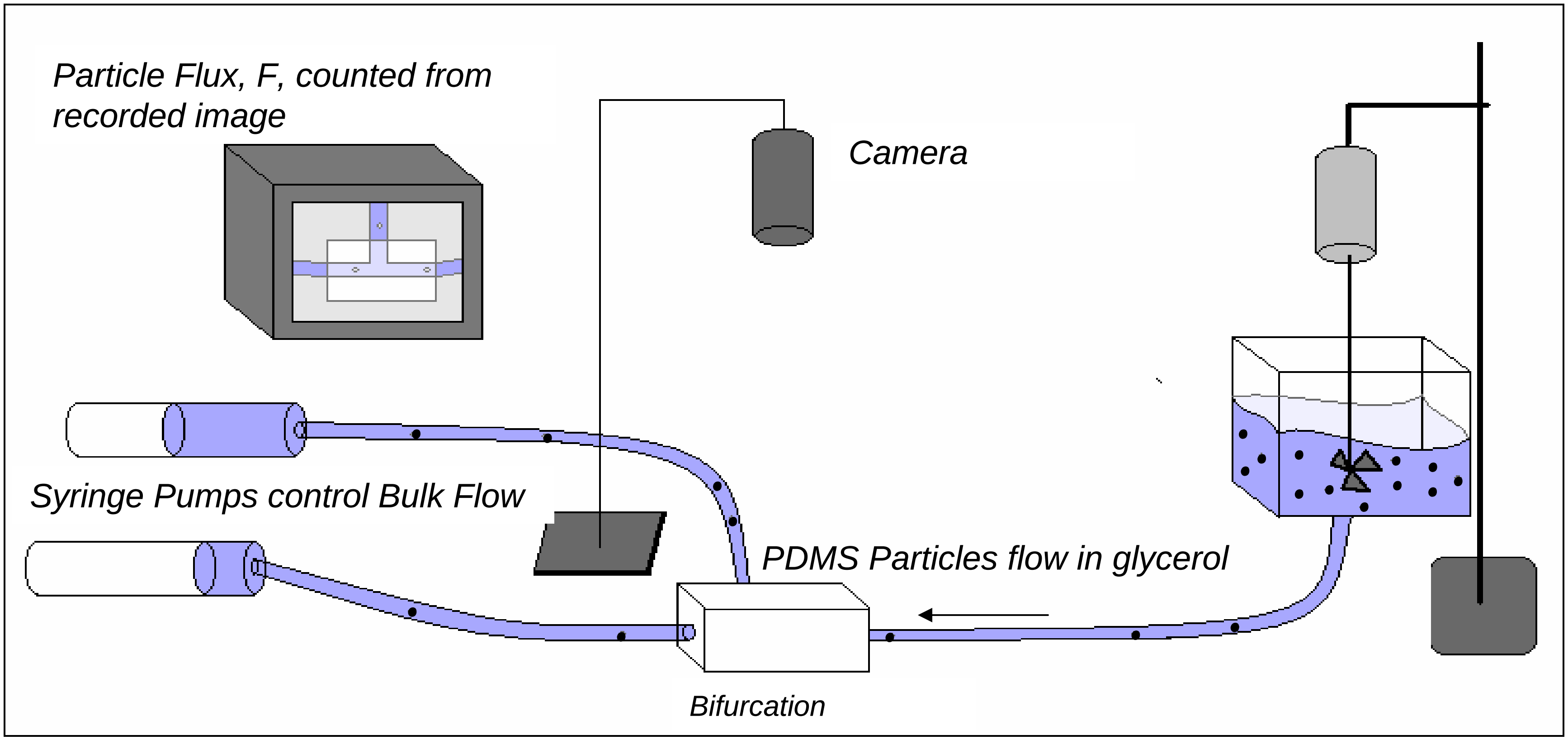


Let's control something – Large Scale Model



Initial thesis project: Aparna Kadam, PhD candidate

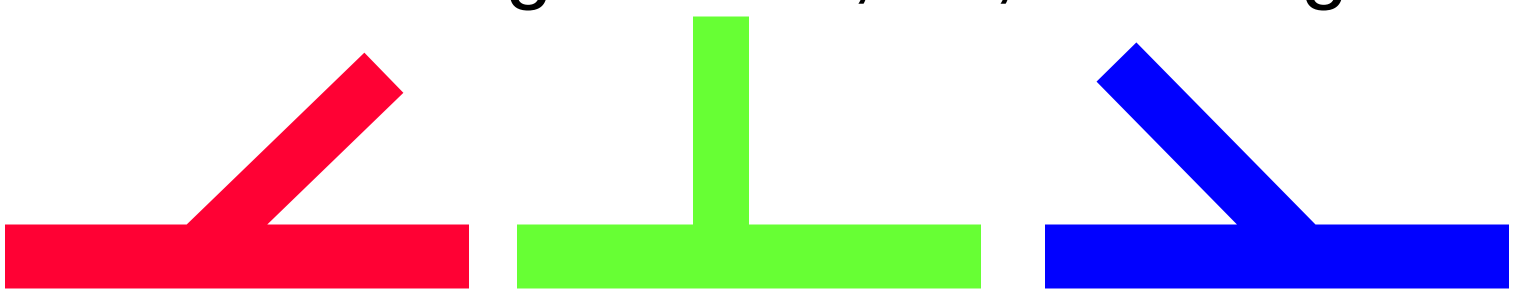
Large Scale Model System



Schematic courtesy of Kathleen Burke

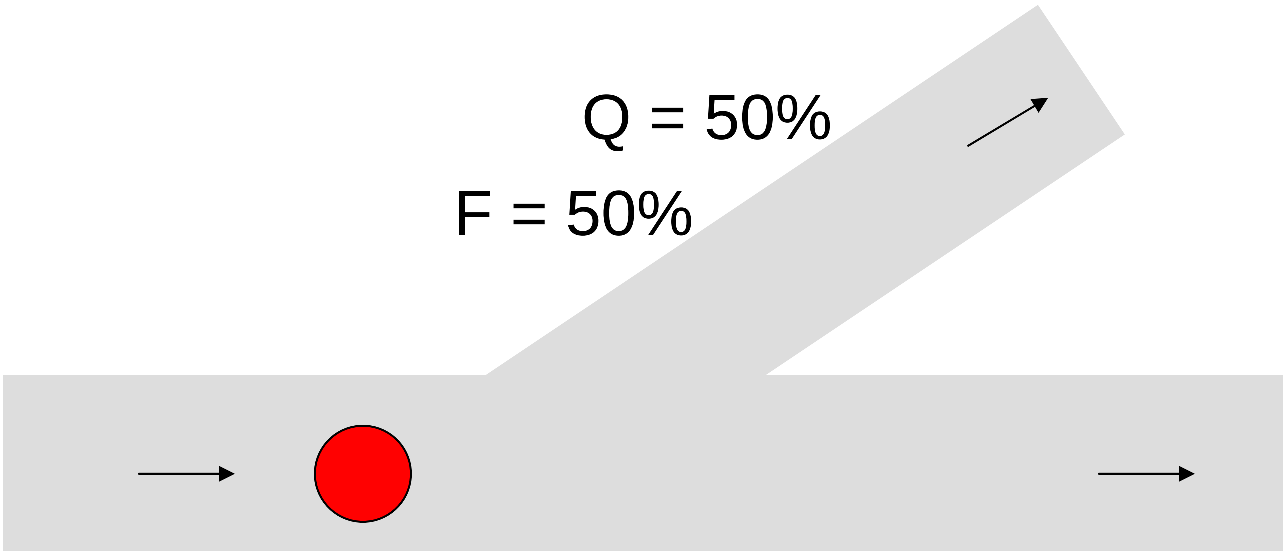
Scaling Up the Relevant Parts

- Re 0.2 to 0.01
  - Controlled by regulating velocity in the feed
- Suspending fluid – glycerol
- RBC – PDMS polymer with correct density
- Bifurcation angles – 45, 90, 135 degrees

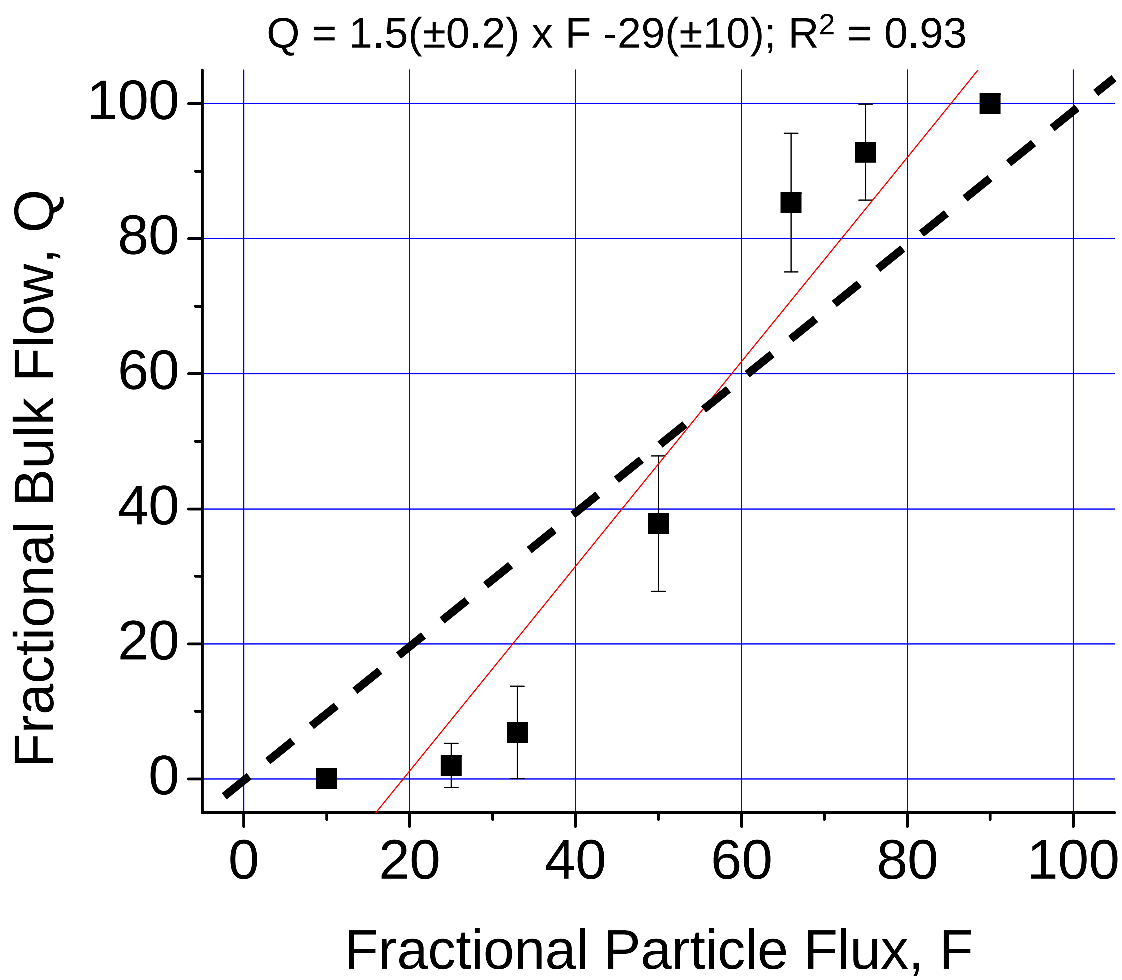


Hypothesis:

- Particle flux (F) to the branch will match Bulk flow (Q) to the branch.

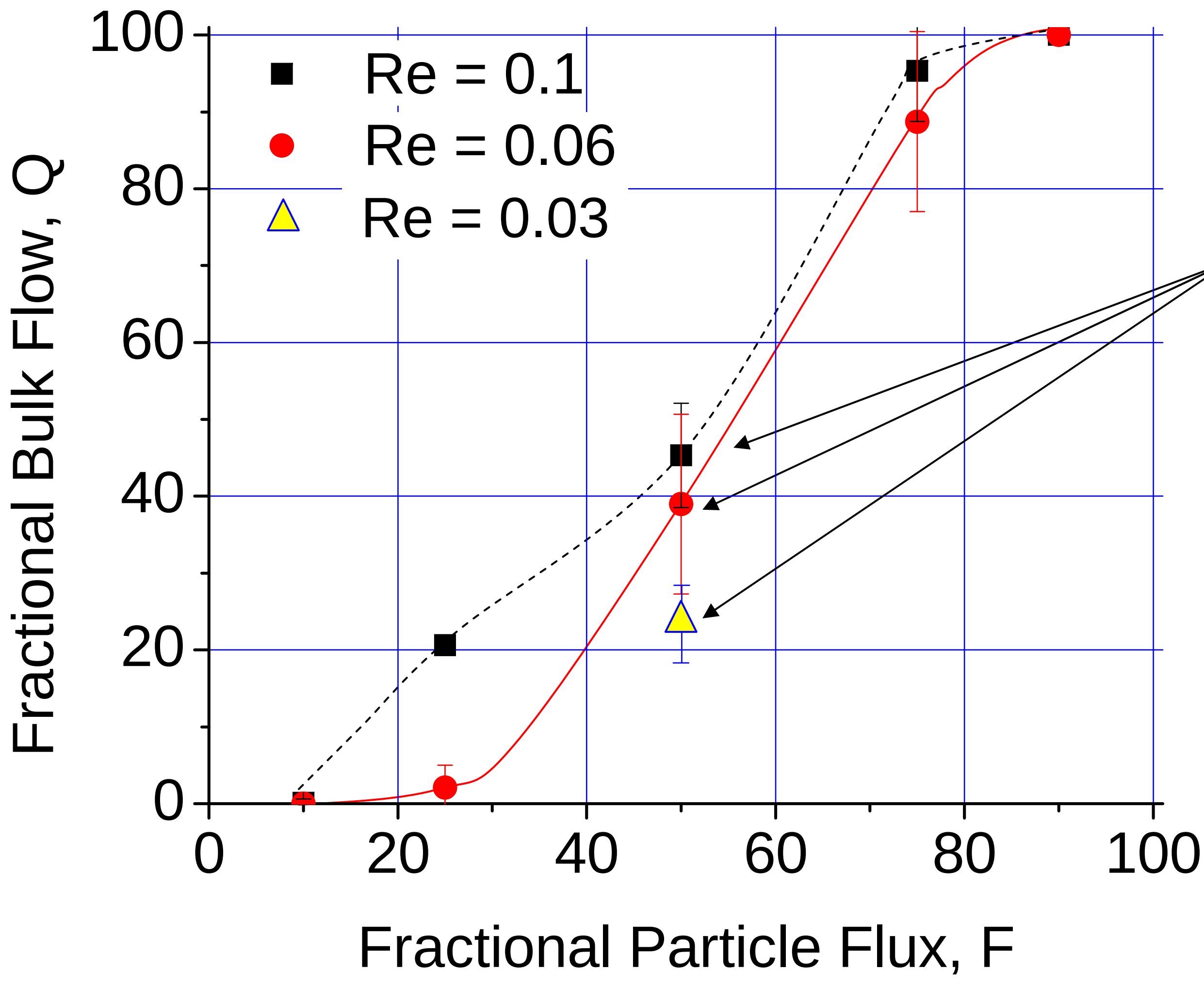


Bulk flow (Q) vs. particle flux (F)



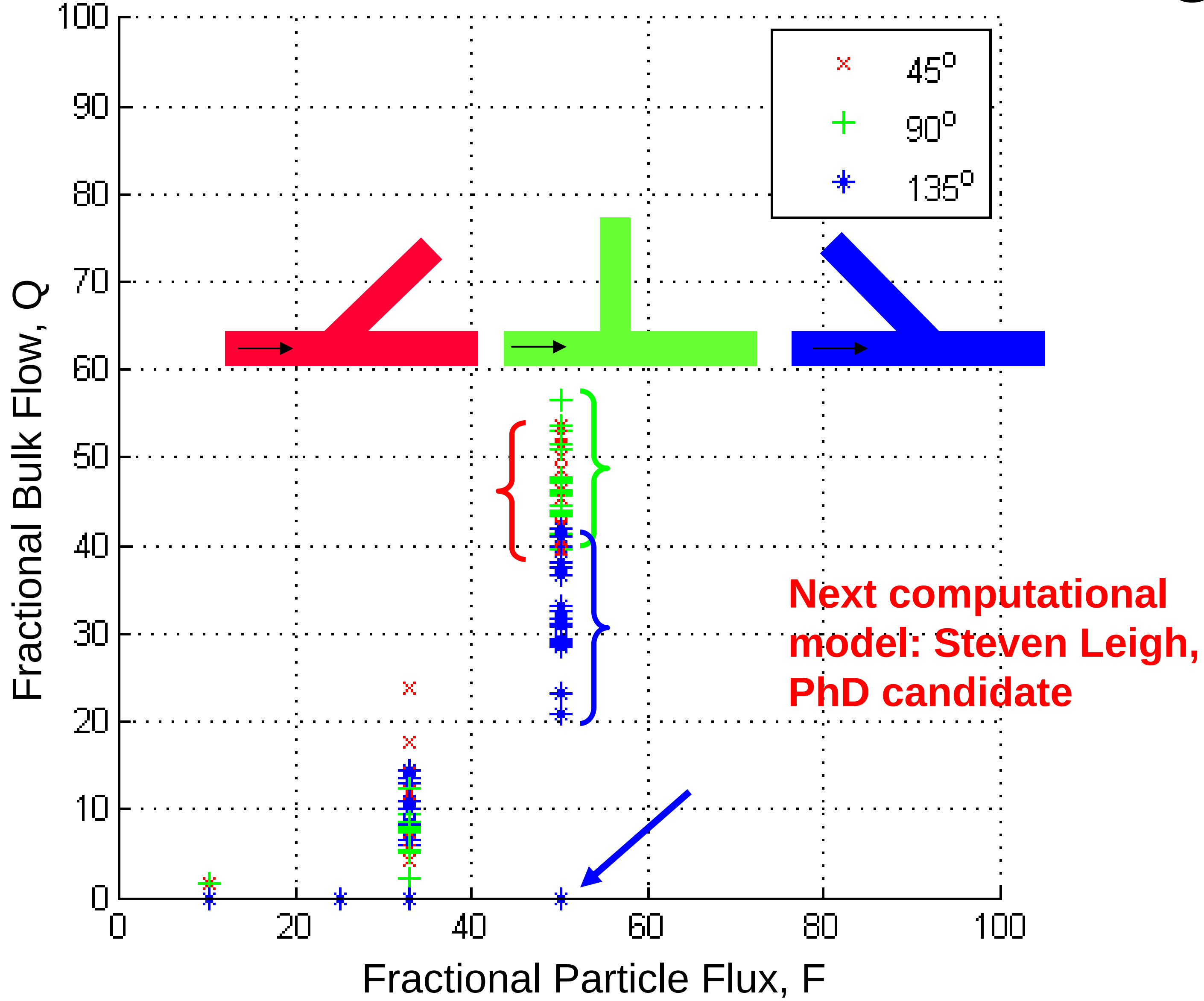
Contributing Undergraduates:
Kathleen Burke, Farha Islam, Hench Wu

Large Scale Model: effect of Re

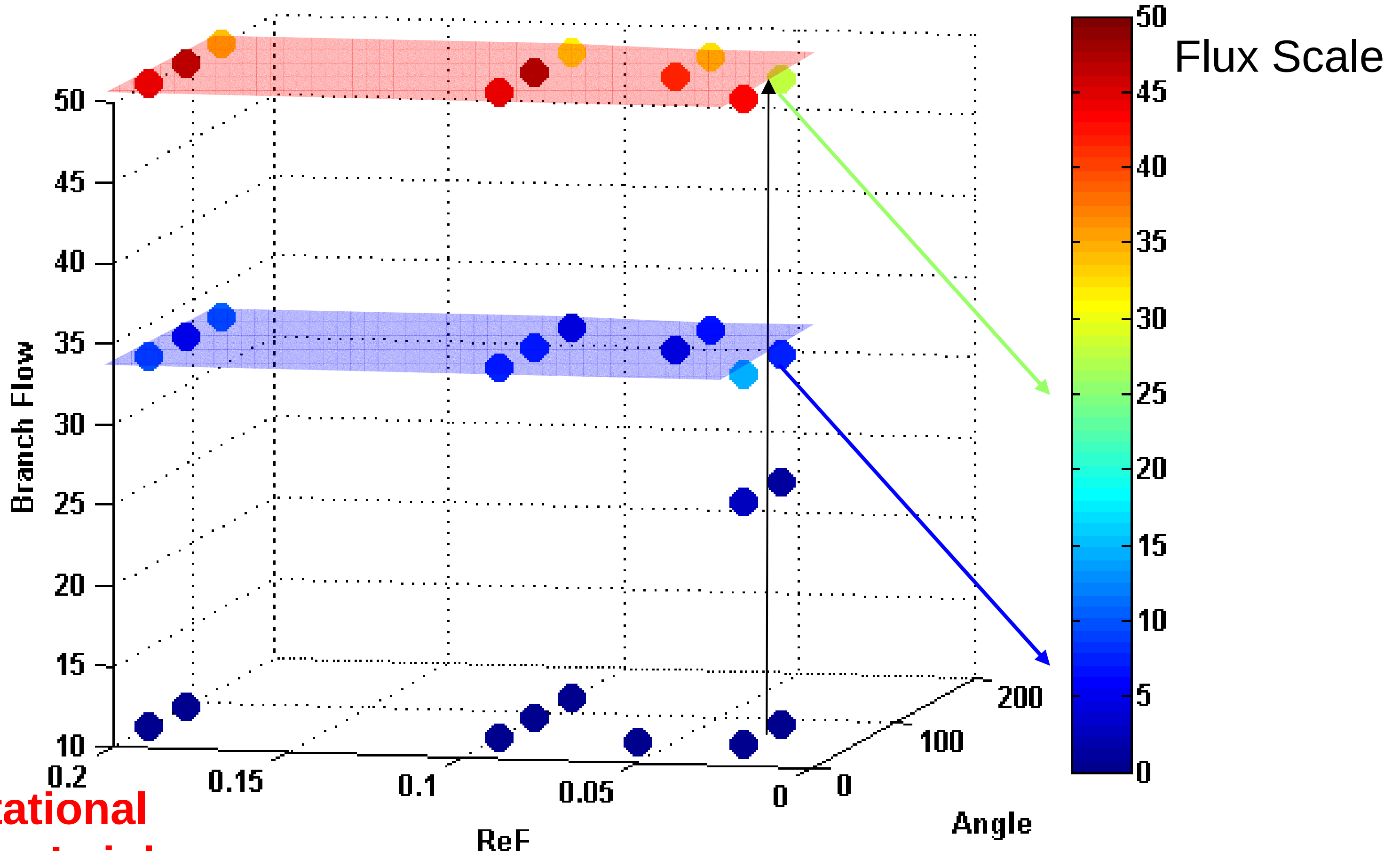


As we lower Re, this disparity is worse.

Large Scale Model: effect of angle



Angle has a larger effect below Re 0.06



Next computational model: Steven Leigh, PhD candidate

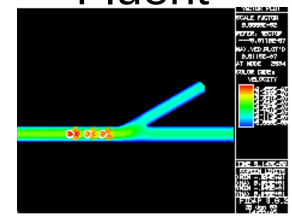
Points to consider

- PDMS particles are more rigid than RBC
- The bifurcation shape is sharp
  - In vivo, radius of curvature is more gradual

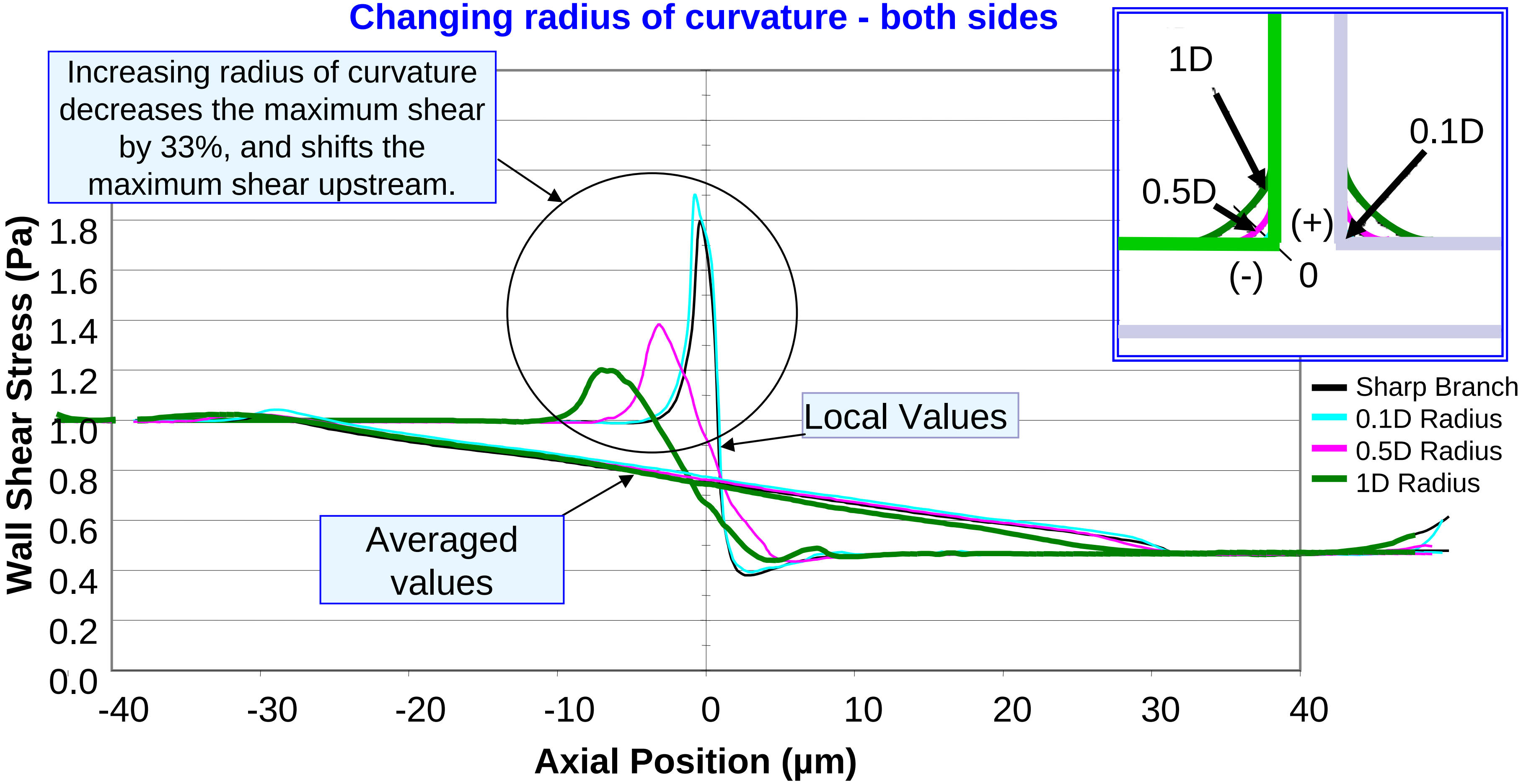
MVR, 1993

2- D Uniform Viscosity Model
Shear Stress Distribution along the Top Wall
Re = 0.01, 10 μm Vessel Diameter

Fluent



90 Degree Bifurcation Angle
Changing radius of curvature - both sides

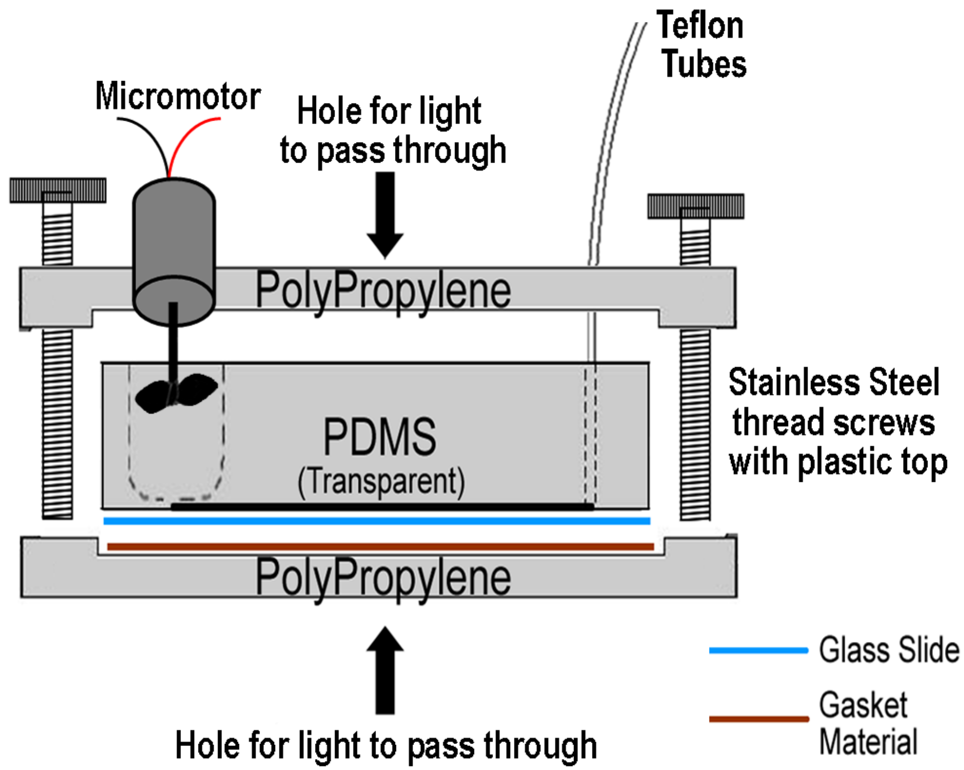


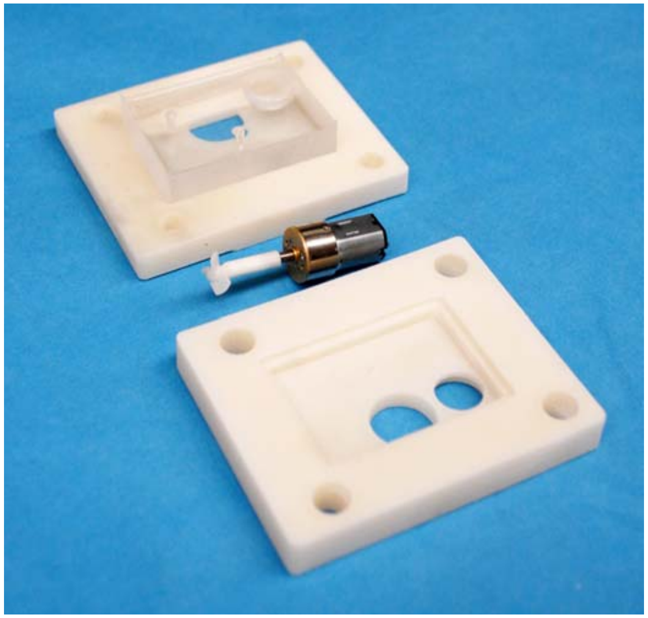
In collaboration with Risa Robinson, PhD, RIT

To-Scale Model

- Microchannels molded from PDMS
  - Prescribe radius of curvature
  - Channel shape is square
- Particles – RBCs

Chamber Mixer Design





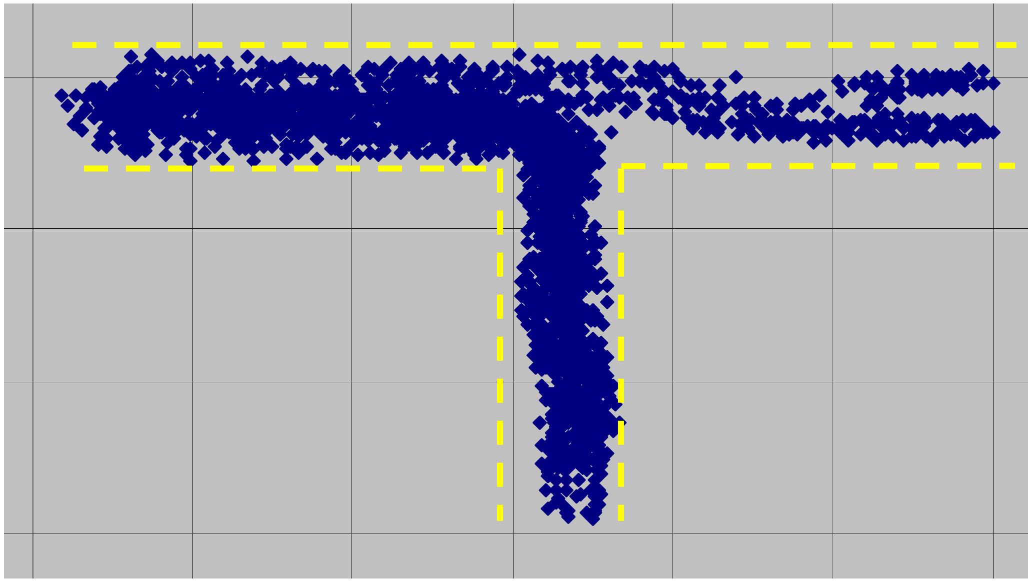
Senior Design Project 2009: Jason Hamilton, Johanna Sisalima

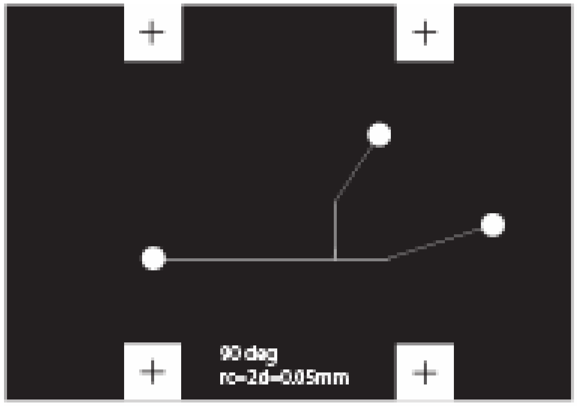
Materials Science and Engineering

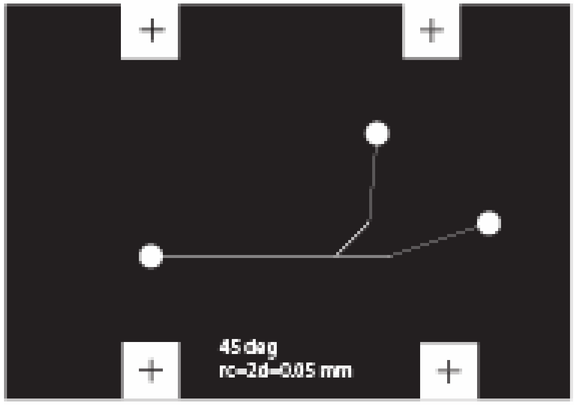
Haema-Mix

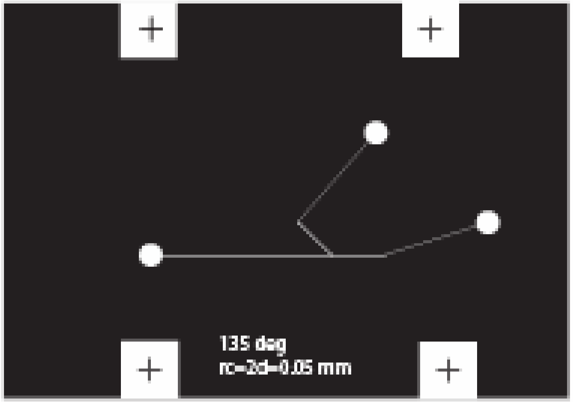
Microchannel Design

- Photolithography
  - SU- 8
- Preliminary data







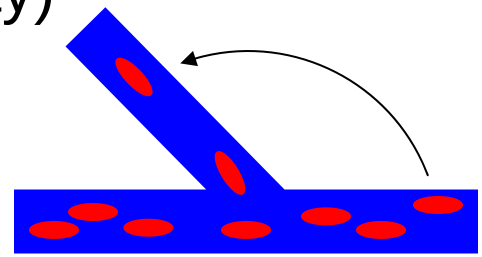


Thesis Project: Aparna Kadam, PhD candidate

In summary…

- What factors control plasma skimming?

- Re < 0.06 → Lower inertia
  - (Higher internal resistance – viscosity)
  - Increased angle to the branch
  - Decreased Flux to the branch



- Angle? Radius of curvature? Particle to tube diameter ratio?

Acknowledgements

- The Frame Lab
  - Melissa Georgi, PhD
  - Anthony Dewar
  - Aparna Kadam
  - Steven Leigh
  - Farha Islam
  - Mohammad Halaibeh
- Our Support