ISB – ISCH

15th international congress of Biorheology

8th international conference on Clinical Hemorheology

KOREA UNIVERSITY

27th May 2015, Hana Square, Seoul - Korea

BLOOD VISCOSITY today

Professor Herbert Meiselman

Professor Philippe Connes

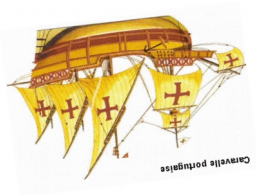
Professor Olivier Greffier

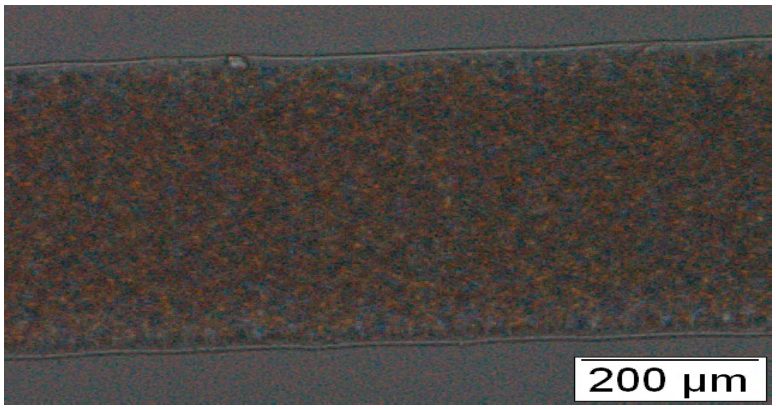
Researcher Alexandre de Tilly

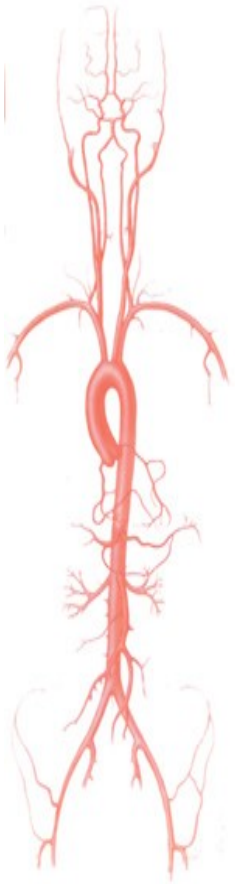
-BLOoDB0W-

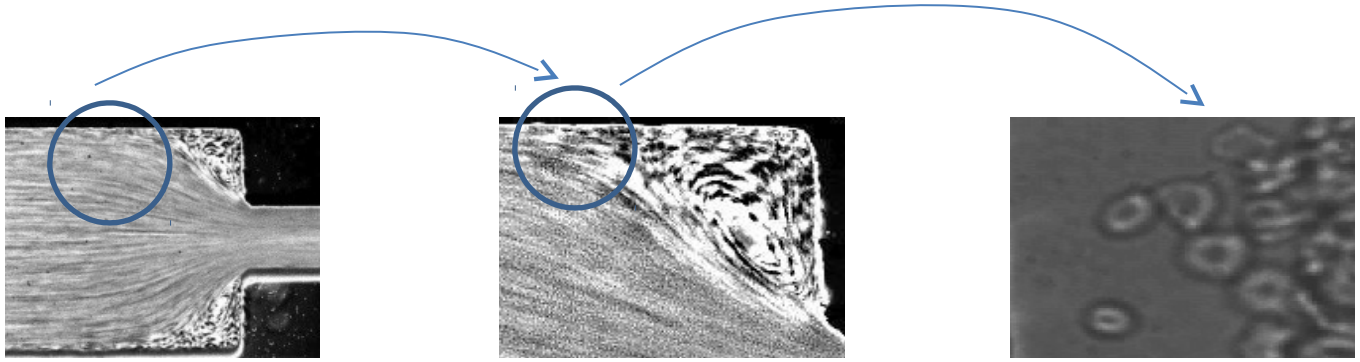
Lab of micro fluidics, and blood dynamic analysis

Faculdade de Medicina Veterinária
Universidade Técnica de Lisboa
Curso de Medicina Veterinária aprovado pela European Association of Establishments for Veterinary Education
Ensino Veterinário desde 1830









PDMS channel fabrication, velocity and pressure measurements, visualizations
Viscosity profiles, pressure loss coefficients, blood fluidity qualification

Literature review

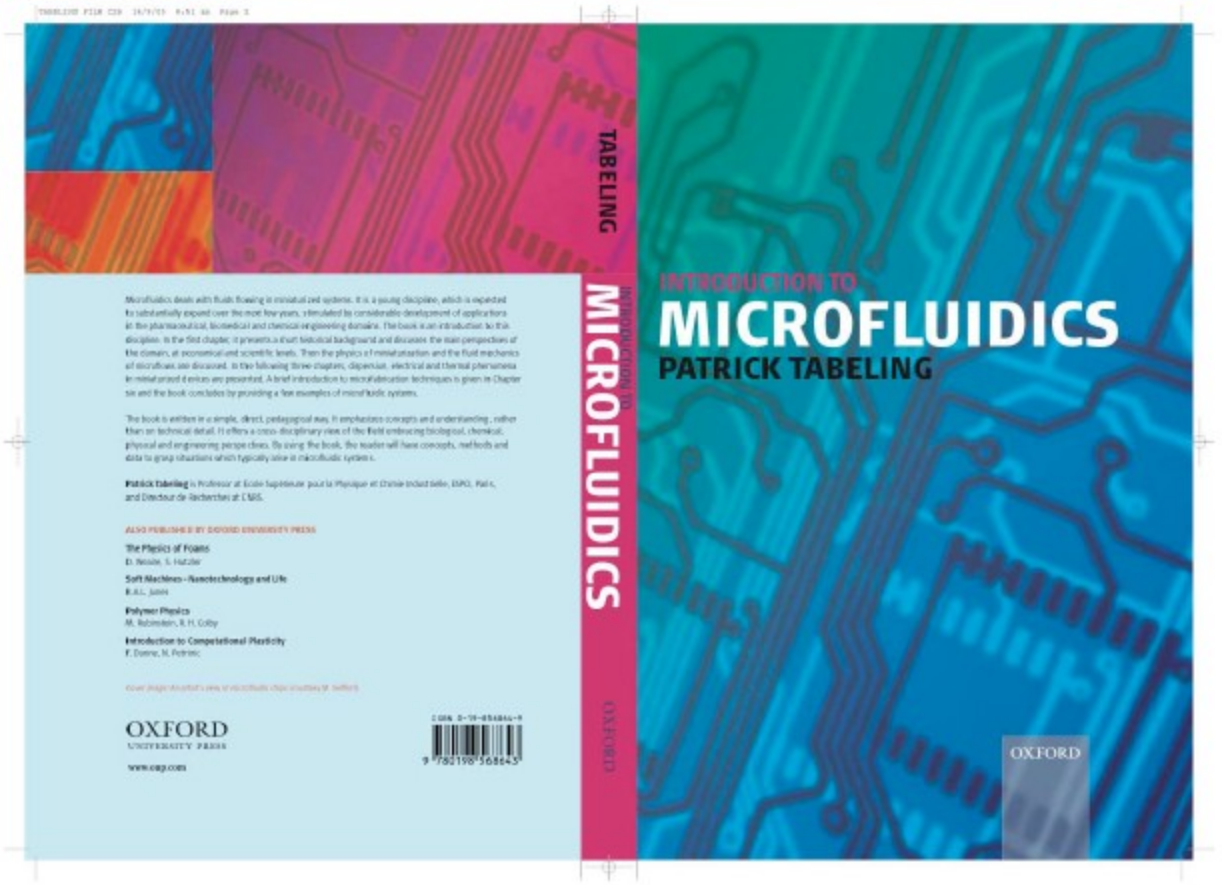
Fluid Mechanics, Engineering, Physics

-C.M.Ho, Y.Tai, Ann.Rev Fluid Mech 30, 579 (1998)

-M. Gad El Hak, Journal of Fluid Engineering, 121, 5 (1999)

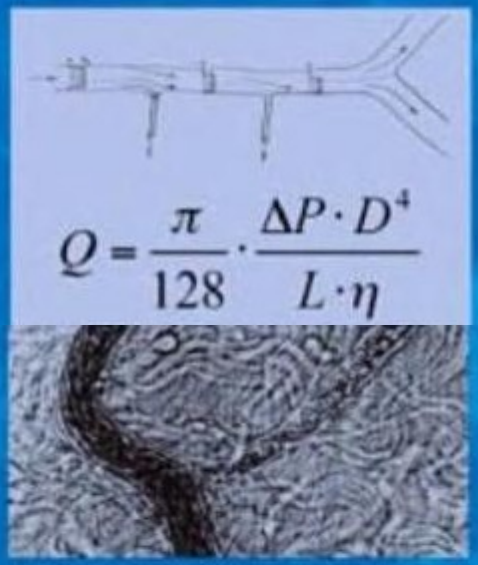
-H.Stone, A.Stroock, A.Ajdari, Ann.Rev.Fluid Mech, 36, 381(2004)

- S.Quake, T.Squire, "Microfluidics : Fluid Physics at the microscale"(2005)



Biomedical and Health Research

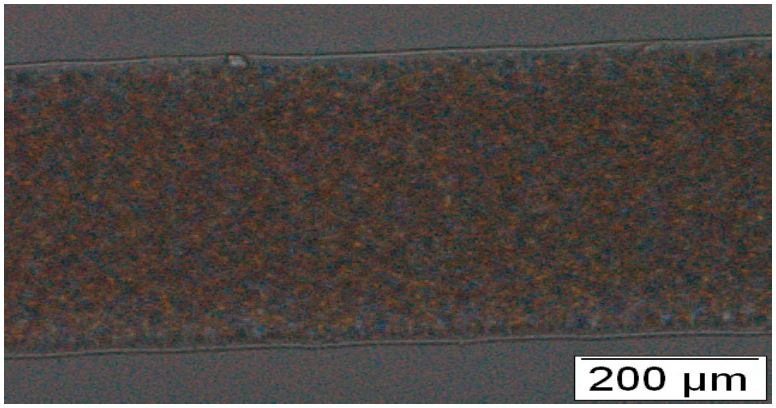
Hemorheology and Hemodynamics

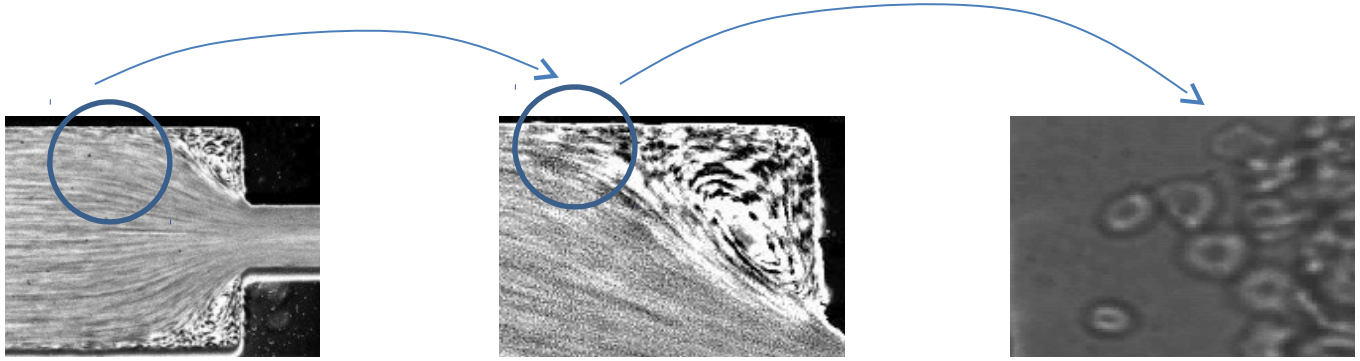


Edited by

Oguz K. Baskurt, Max R. Hardeman,

-Blood viscosity-

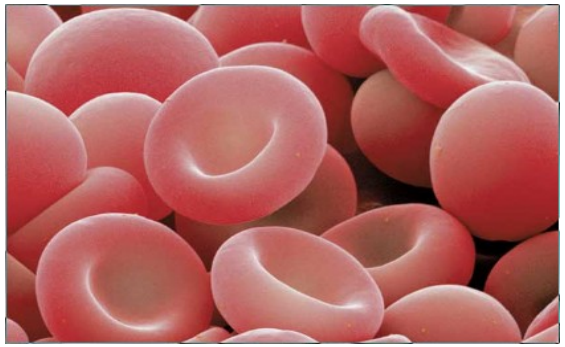


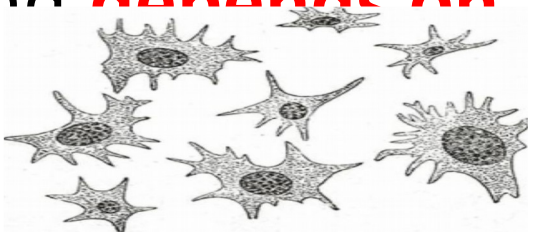


A vessel, velocity and pressure measurements, flow visualizations
Viscosity profiles, pressure loss coefficients, blood organization, blood fluidity qualification

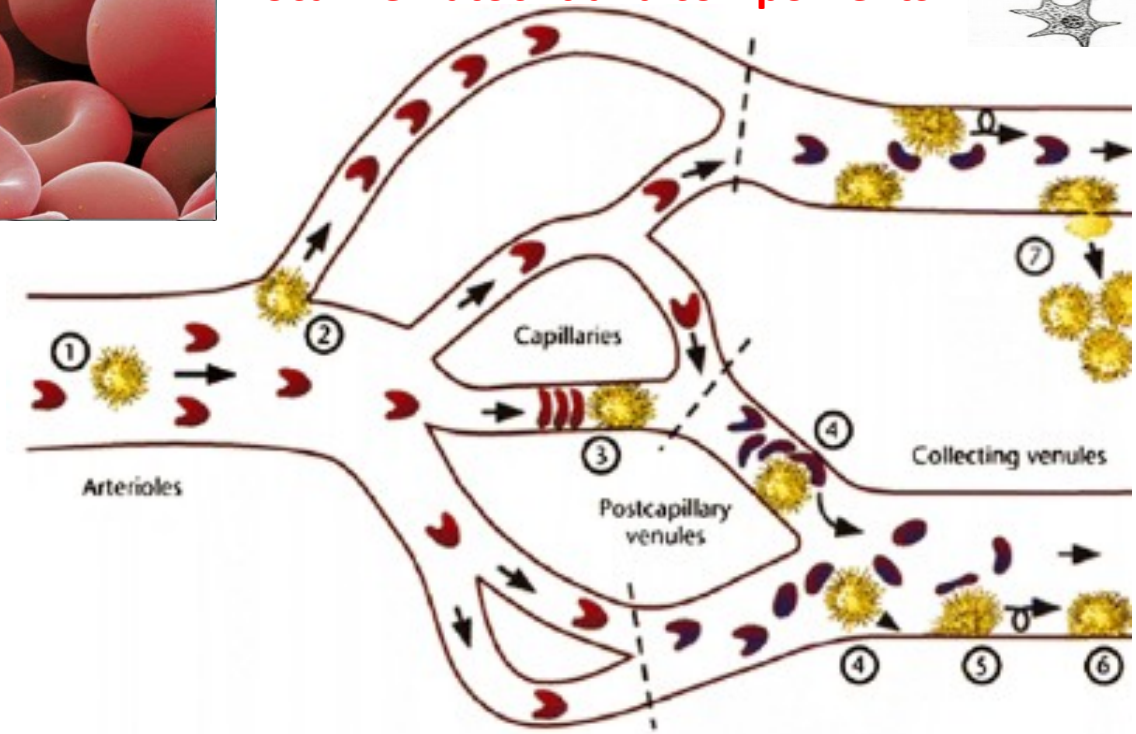
HOW BLOOD ORDONATES IN A FLOW REQUIRE ENERGY
FRICION BETWEEN ELEMENTS REQUIRES ENERGY
SHOCKS BETWEEN BLOOD COMPONENTS REQUIRES ENERGY

Fluidity or viscosity is ability to flow and depends on

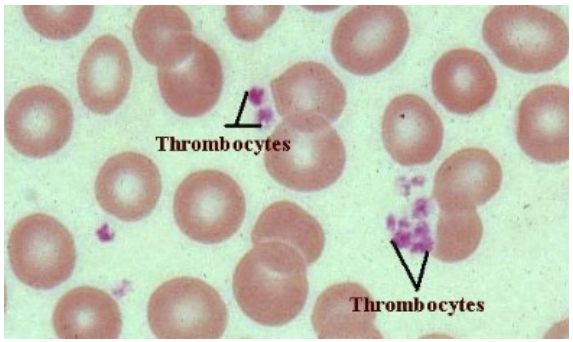




Local hematocrit and compoments

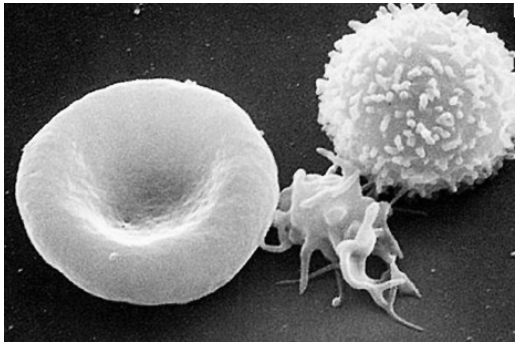


Size of the vessel
Deformability
Pressure
velocity



Labile components

Molecule friction, plasma



PATICIPANTS TO THIS BLOOD RHEOLOGY

- BOWLTD
  - Georges de Tilly
- IDMEC – IST, LISBOA
  - Viriato SEMIAO, Joao MELO DE SOUSA, MOTA SOARES
  - Students: David Alexandre, Cesar Aguiar, Carlos Completo, Antonio SImioes
- FACULDADE DE VETERINARIA, LISBOA
  - Belmira CARRAPICO, Teresa BRITO
- FACULDADE DE FARMACOLOGIA, Lisboa
  - Olga SILVA
- IMM, Hopital Santa Maria de Lisboa
  - Carlota SALDANHA, Ana SILVA
- LMM, ESPCI-PARIS
  - Patrick TABELING, Magalie Faivre
- CHR, EFS, NANCY
  - JF STOLTZ, Fabienne PAULY
- X, CNRS, France
  - Hervé WILLAIME
- LEADING PERSONS IN THE STORY OF BLOOD RHEOLOGY
  - Léandre Pourcelot, inventor of echography
  - Michel René Boisseaux, an encyclopedy of blood rheoogy Bordeaux
  - Jean Frédéric BRUN, Blood of sportives
- LPM, Metz, SPECIALISTS IN RHEOLOGY : viscosity, elasticity, birefringence, scatterng light
  - Olivier Greffier
  - Jean Paul Decruppe
- Koç University, blood rheology, Oguz Baskurt lab
  - Ozlem Yalcin

Blood viscosity presentation acts

- 1 Basics used for this study
- 2 Construction of devices of experimental studies of blood flow

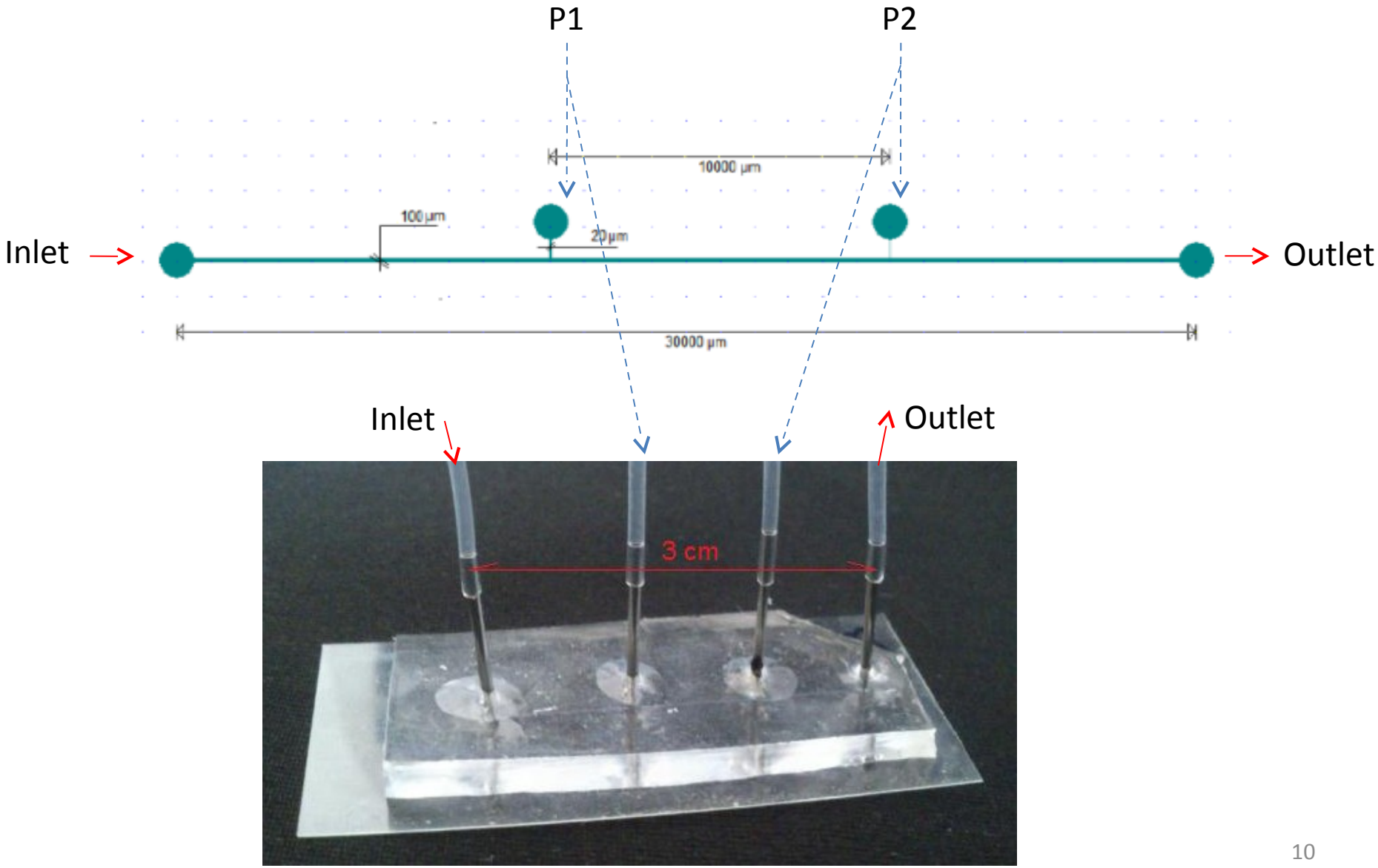
  A few illustration results
- 3 A few important results in the literature

  Consistent and contradictory
- 4 Aim at studying blood fluidity
  - Hyothesis, state of art
- 5 A hypothetic Blood flow result : Constant resistance of the flow, Index of blood viscosity

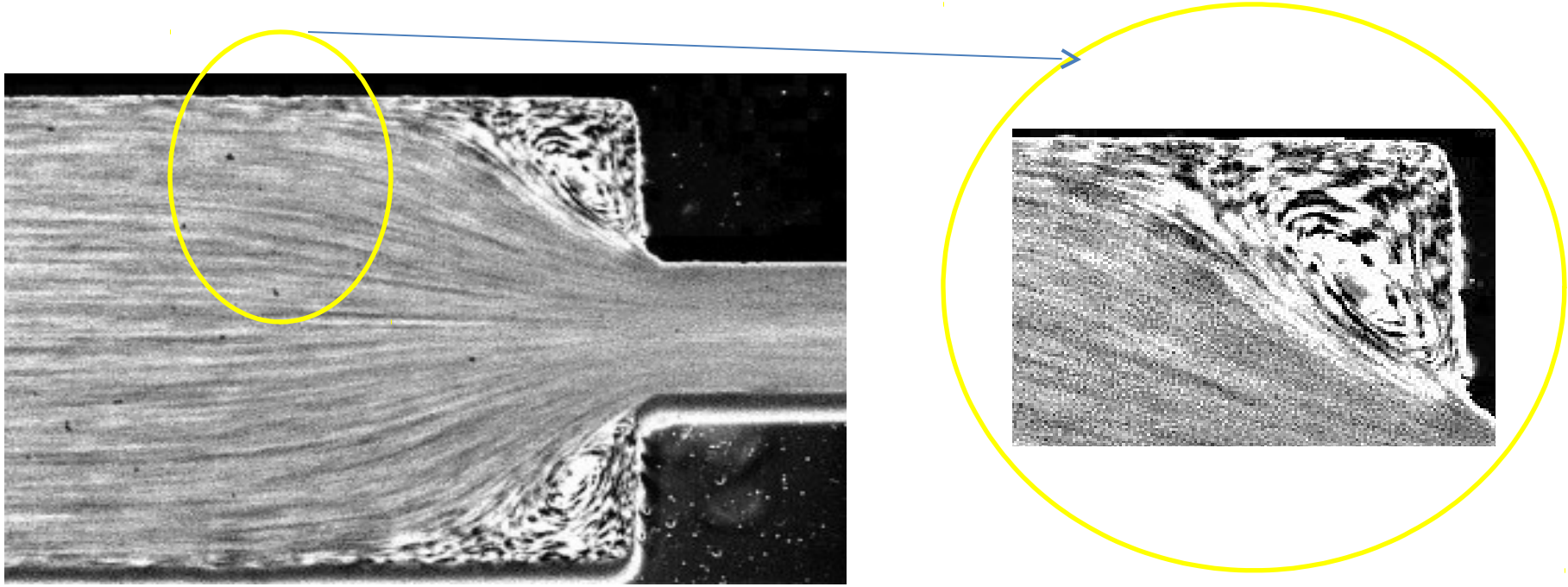
REQUIREMENTS

- Defining proper blood viscosity for comparisons and help for diagnostics:
  - A measure propper to blood
  - DEPENDANCE :
    - BLOOD COMPONENTS
    - Influence of speed, pressure, vessel size
  - ELIMINATE VARIABILITY CAUSES OT PROPPER TO BLOOD VISCOSITY
  - Temperature is constant
  - MEASURES DEVICES SHOULD BE STANDARD

MODEL OF THE STUDY
perfect channels, controlled pressre and speed

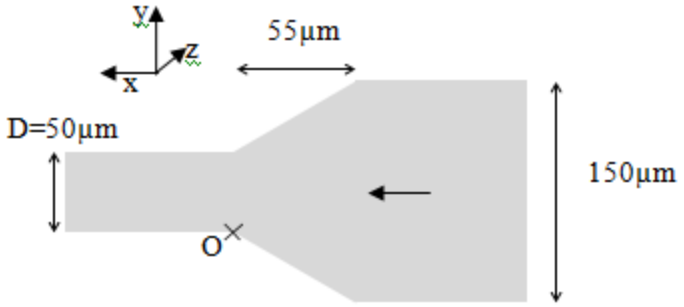


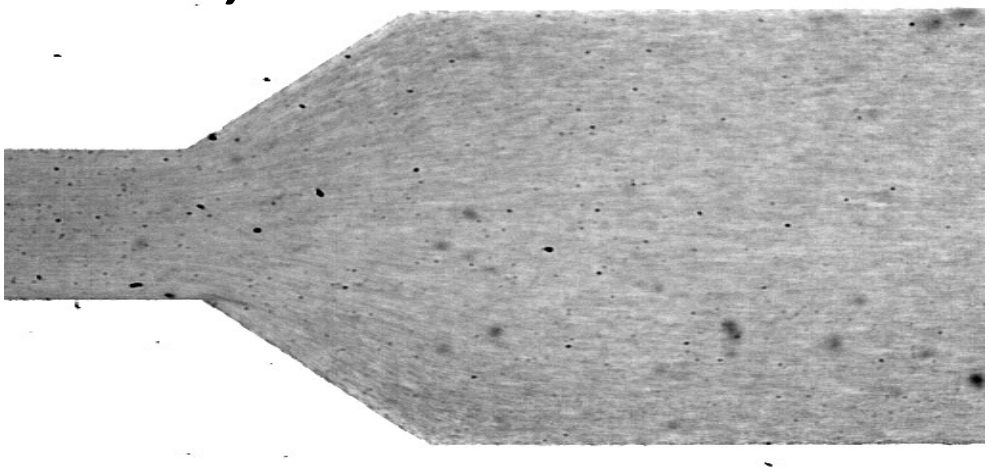
Visualization of a straight contraction with a swirl

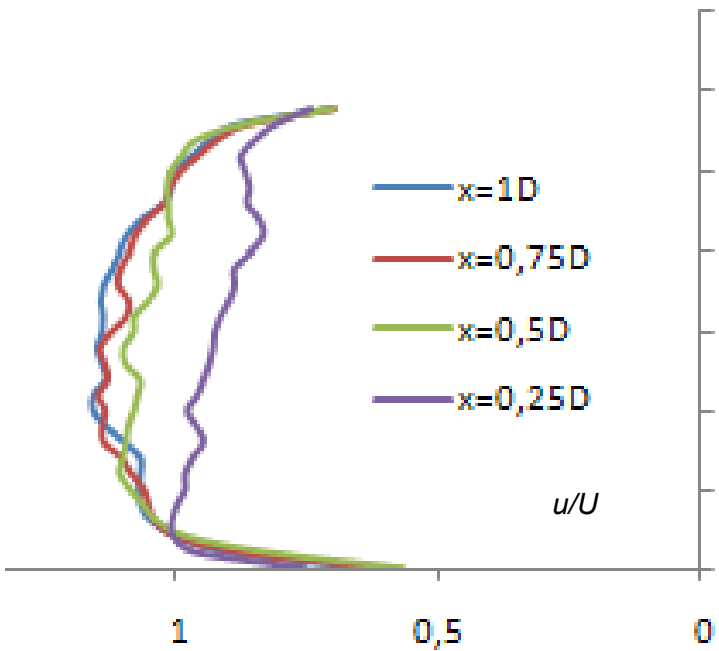


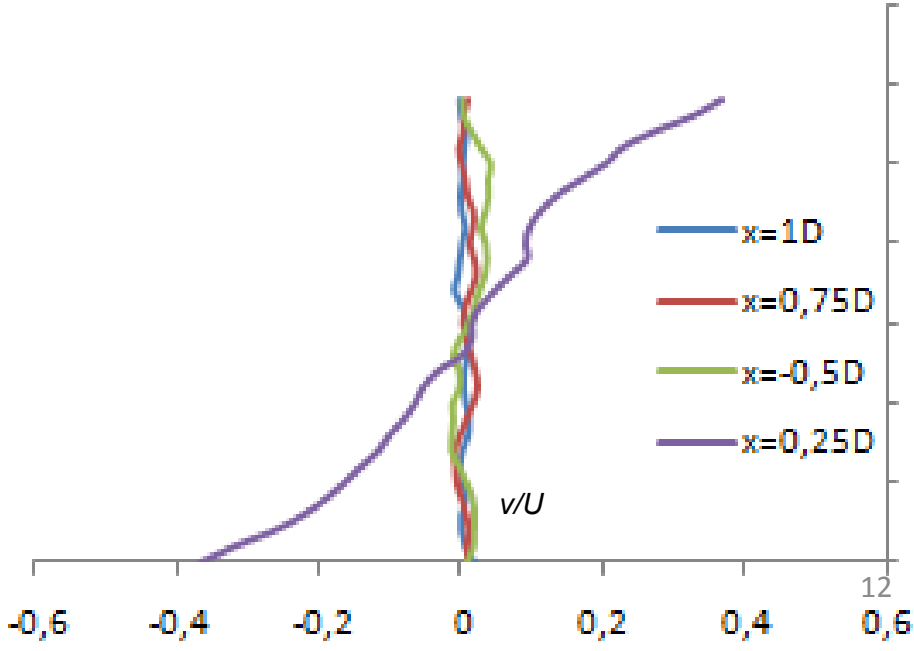
Blood is not transparent
⇒ strong enlightening source
⇒ small material thickness

Sweet contraction, no more swirl





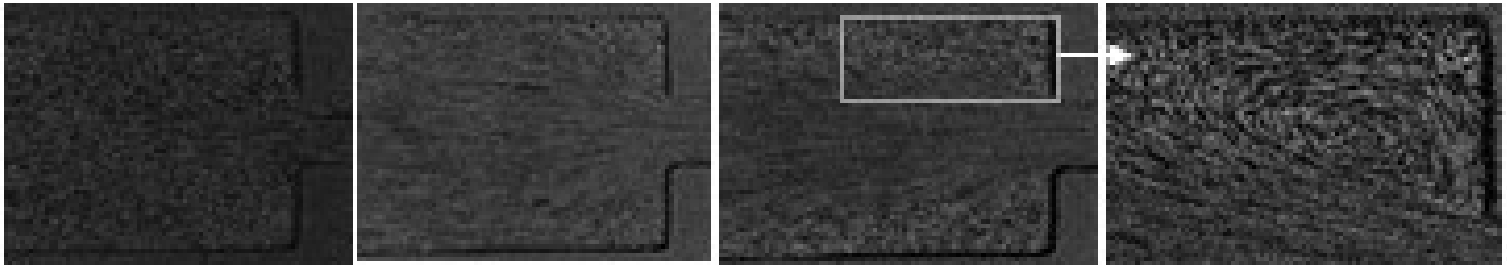




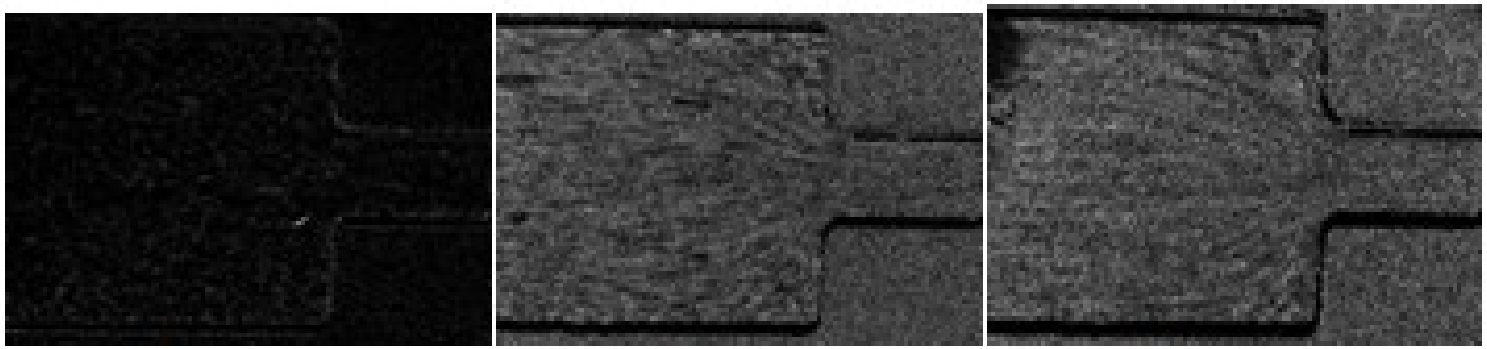
Effects of increasing velocity and changing fluid

Flow rate = 0.4, 1.2, 3.6 mL/h

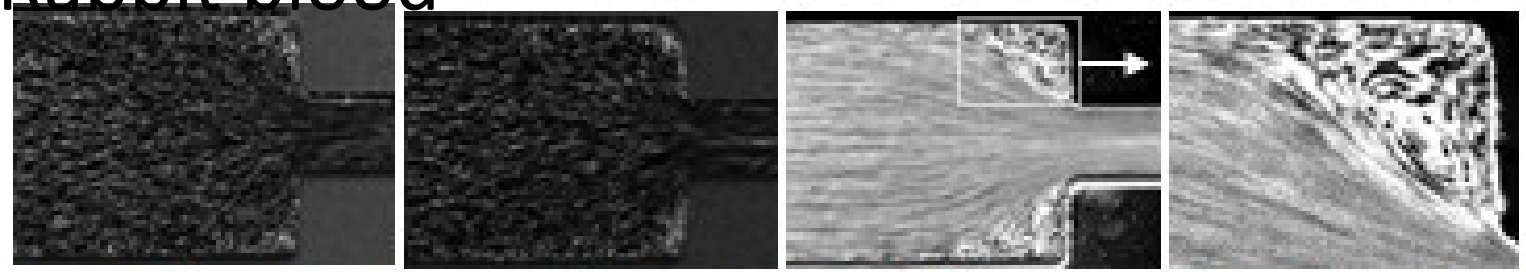
water



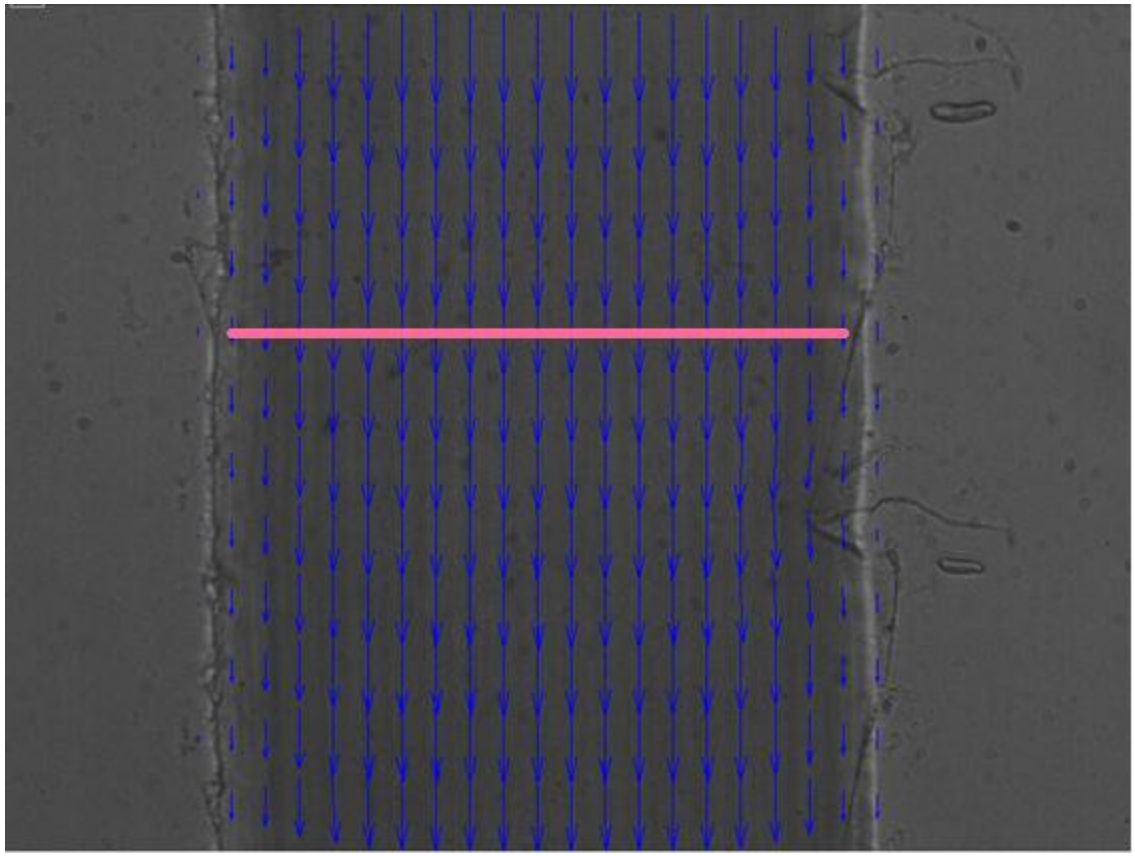
Glycerin/xanthan similitude fluid for rabbit blood



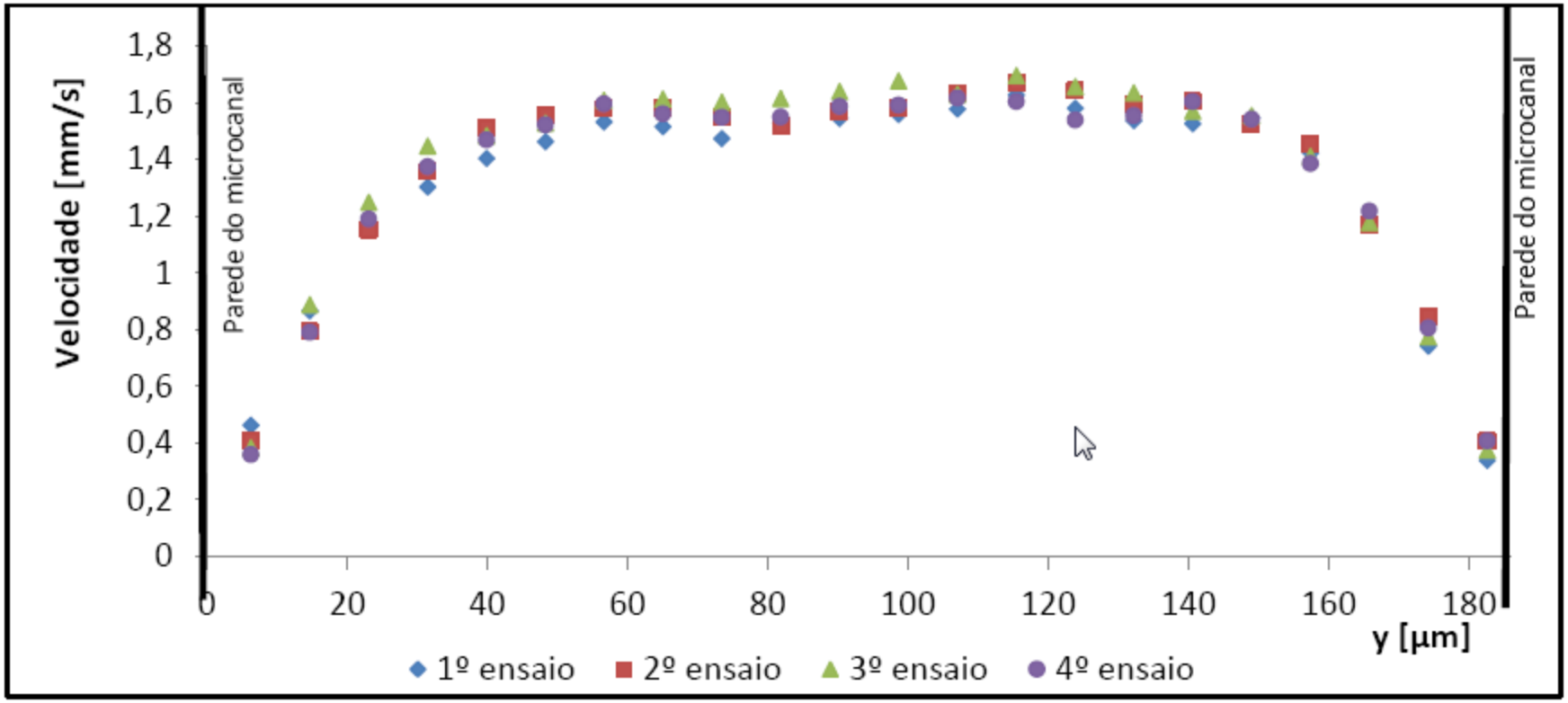
Rabbit blood



Micro PIV result in s straight square channel



VELOCITY PROFILE



- A few results of literature : consistence, contradiction

- Viscosity is for fluids, local and global has to be the same :
  - viscosity = shear stress / shear rate
  - – shear stress = grad (V)
  - – – shear stress = friction force

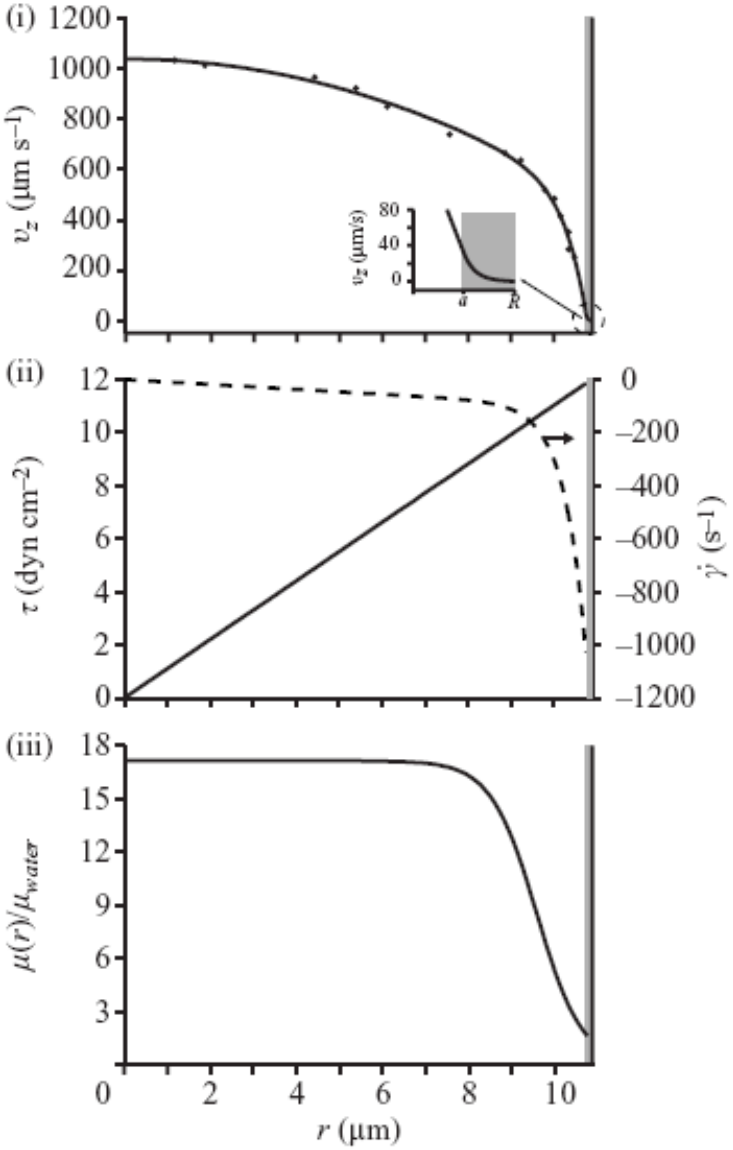
- Fluid has to be homogeneous : density, form, organization

  A FLUID IS CONNEX !!!!! Simply

  STOKES Hypothesis is respected

- Question : is blood a fluid ? Non Newtonian, characteristics, physically
  - - blood is a COMPLEX LIQUID
  - -- blood holds several phases : gas dissolute, heterogeneous RBCs, other cells, molecules, etc…
  - --- blood is a different complex liquid in the different points of space : a suspension

VISCOSITY VARIATIONS IN A VESSEL



Estimation of viscosity profiles using velocimetry data from parallel flows of linearly viscous fluids: application to microvascular haemodynamics

By E. R. DAMIANO[1], D. S. LONG[1] AND M. L. SMITH[2]

[1]Department of Mechanical and Industrial Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA

[2]Department of Biomedical Engineering, University of Virginia Health Science Center, Charlottesville, VA 22908, USA

(Received 22 August 2003 and in revised form 24 November 2003)

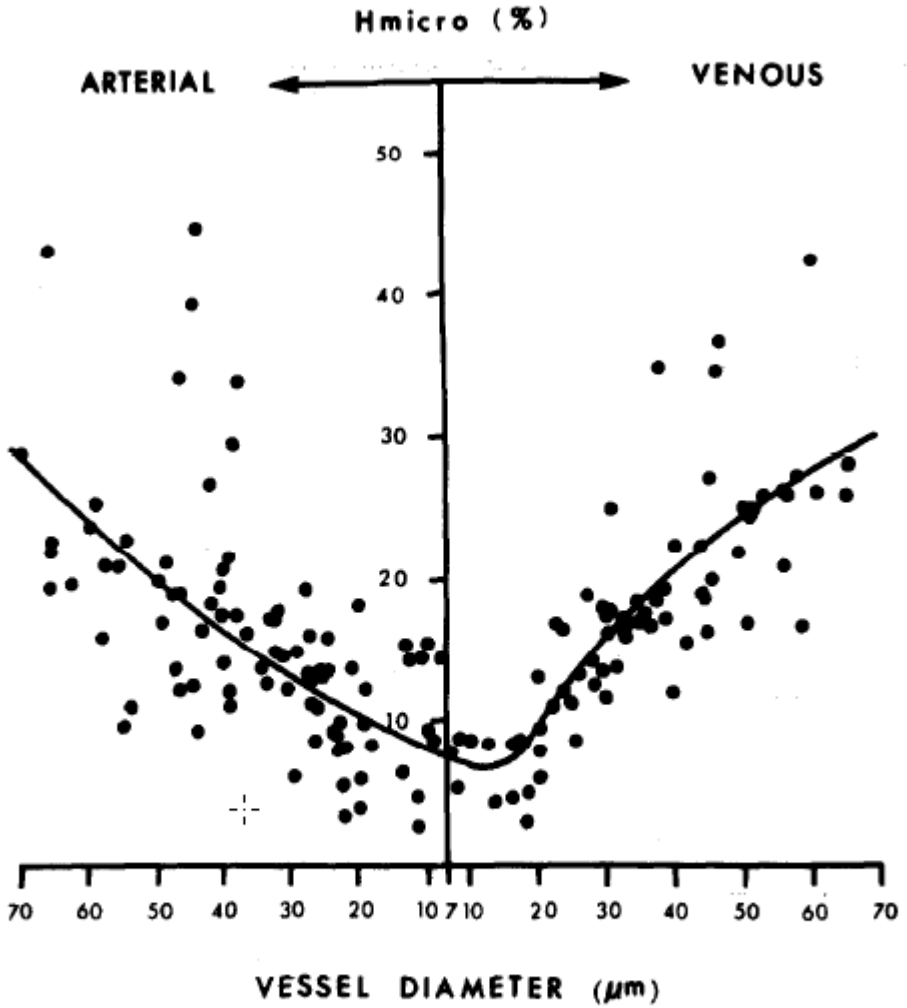


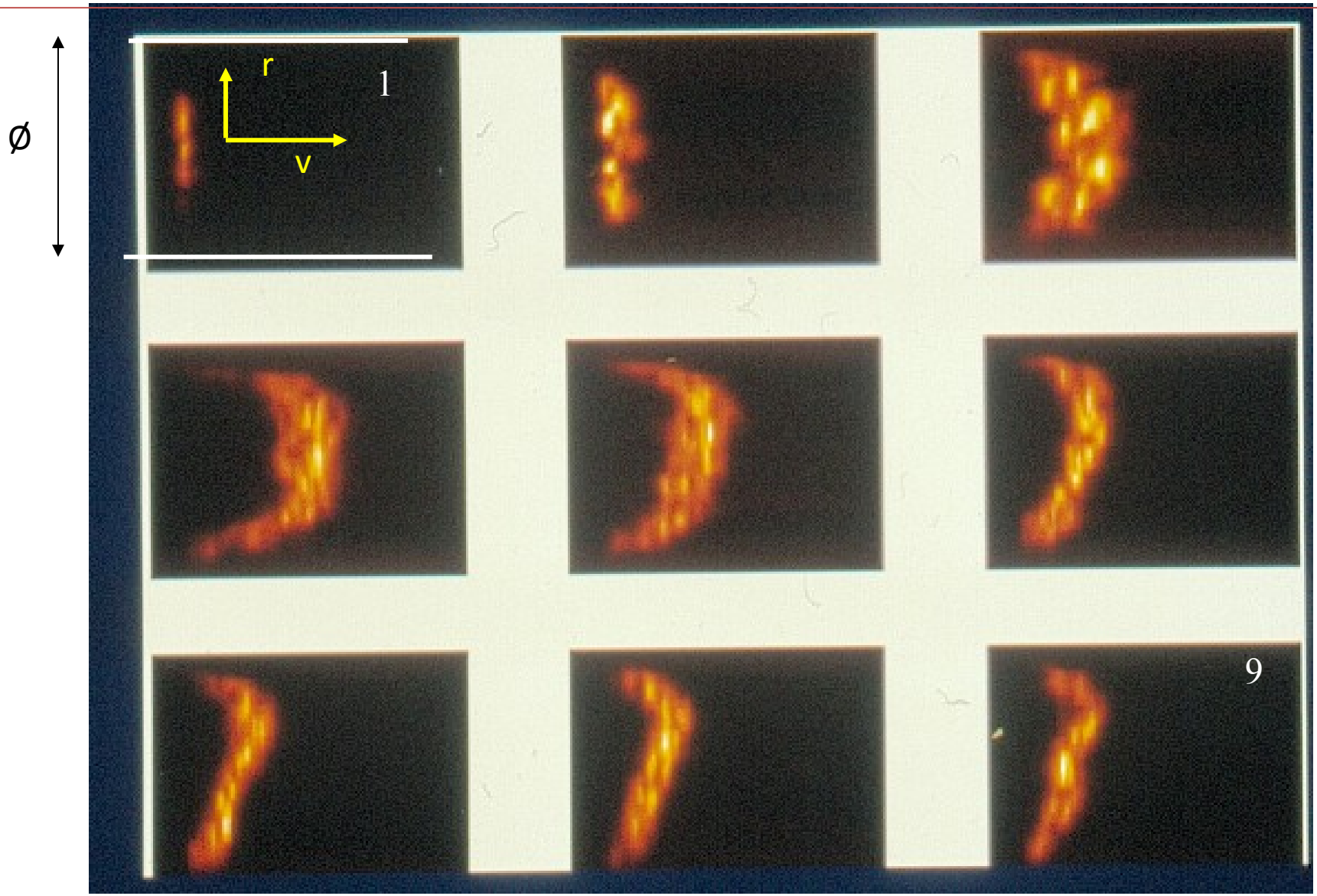
FIG. 3. Arteriovenous distribution of microvessel hematocrit (H_{micro}). The solid curve is a piecewise cubic spline fit of the data. For microvessels larger than 20 μm in diameter, H_{micro} was determined by the optical density method. In smaller microvessels ($\leq$20 μm), H_{micro} was determined by microocclusion.

- *Pries AR**, Neuhaus D, and Gaehtgens P.** Blood viscosity in tube flow: dependence on diameter and hematocrit. Am J Physiol Heart Circ Physiol 263: H1770–H1778, 1992.*
- presence of a thick endothelial surface layer (ESL)
  - **Microvascular blood viscosity in vivo and the endothelial surface layer**

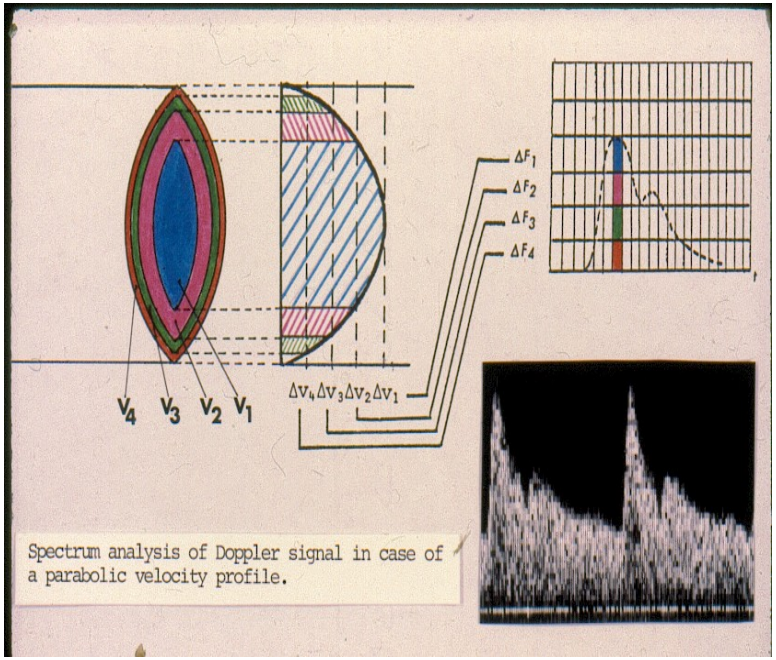
  A. R. Pries1,2 and T. W. Secomb3

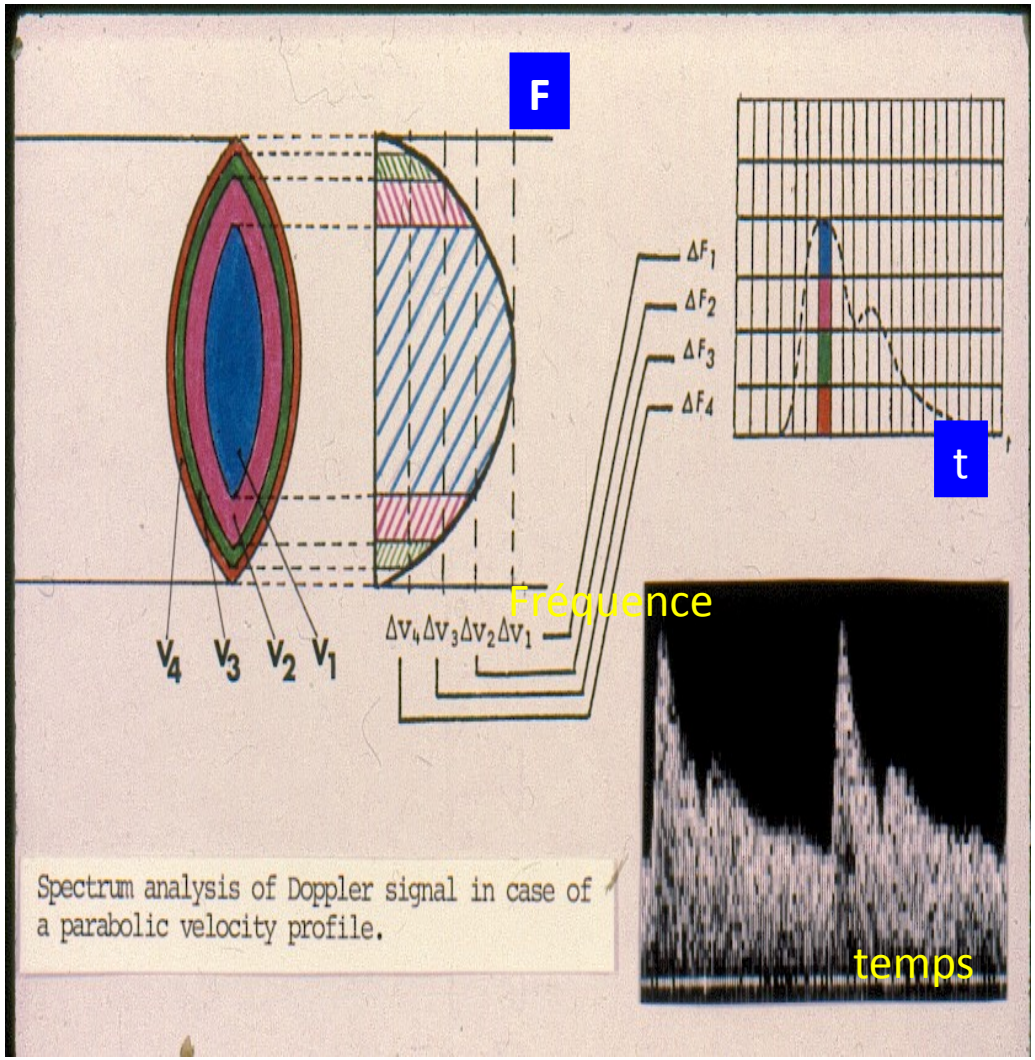
- Professor George B. Thurston, of the University of Texas, first presented the idea of blood being viscoelastic in 1972

Evolution du profil de vitesse au cours d'un cycle cardiaque, L. Pourcelot (Doppler, echography)



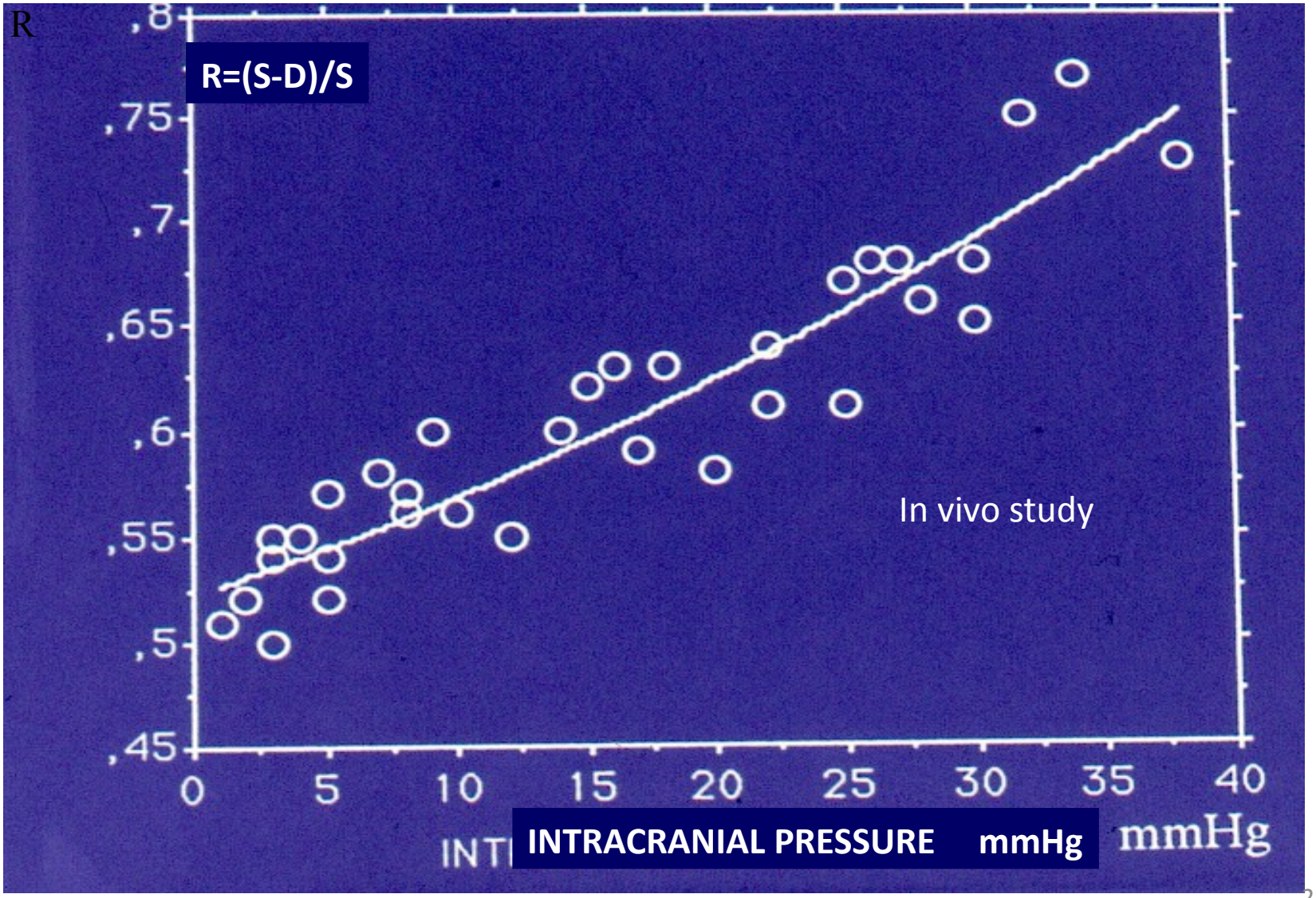
Distribution locale des vitesses: analyse spectrale des signaux Doppler





Problem of utting poiseuille profile in vivo???

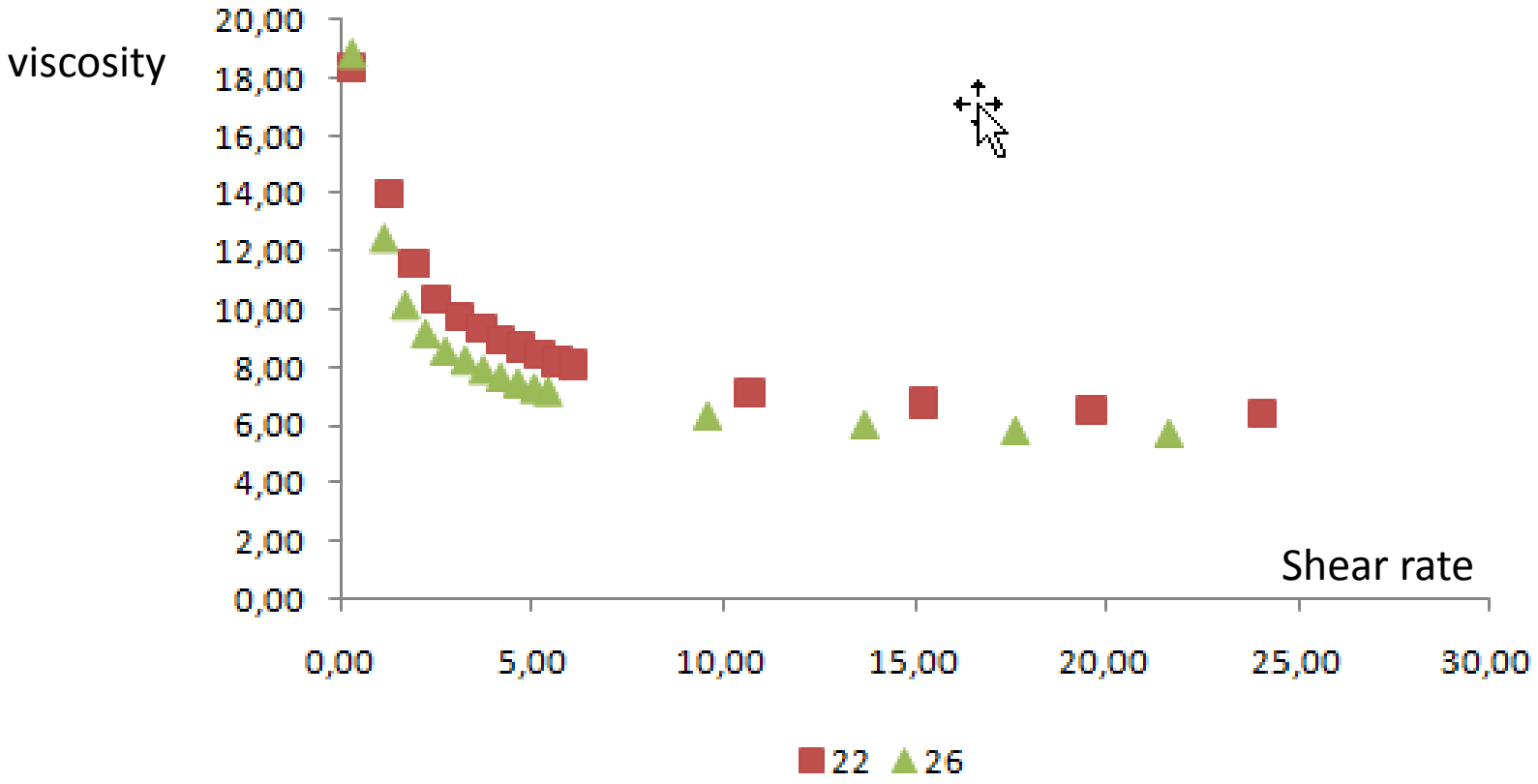
Resistive index and IC Pressure



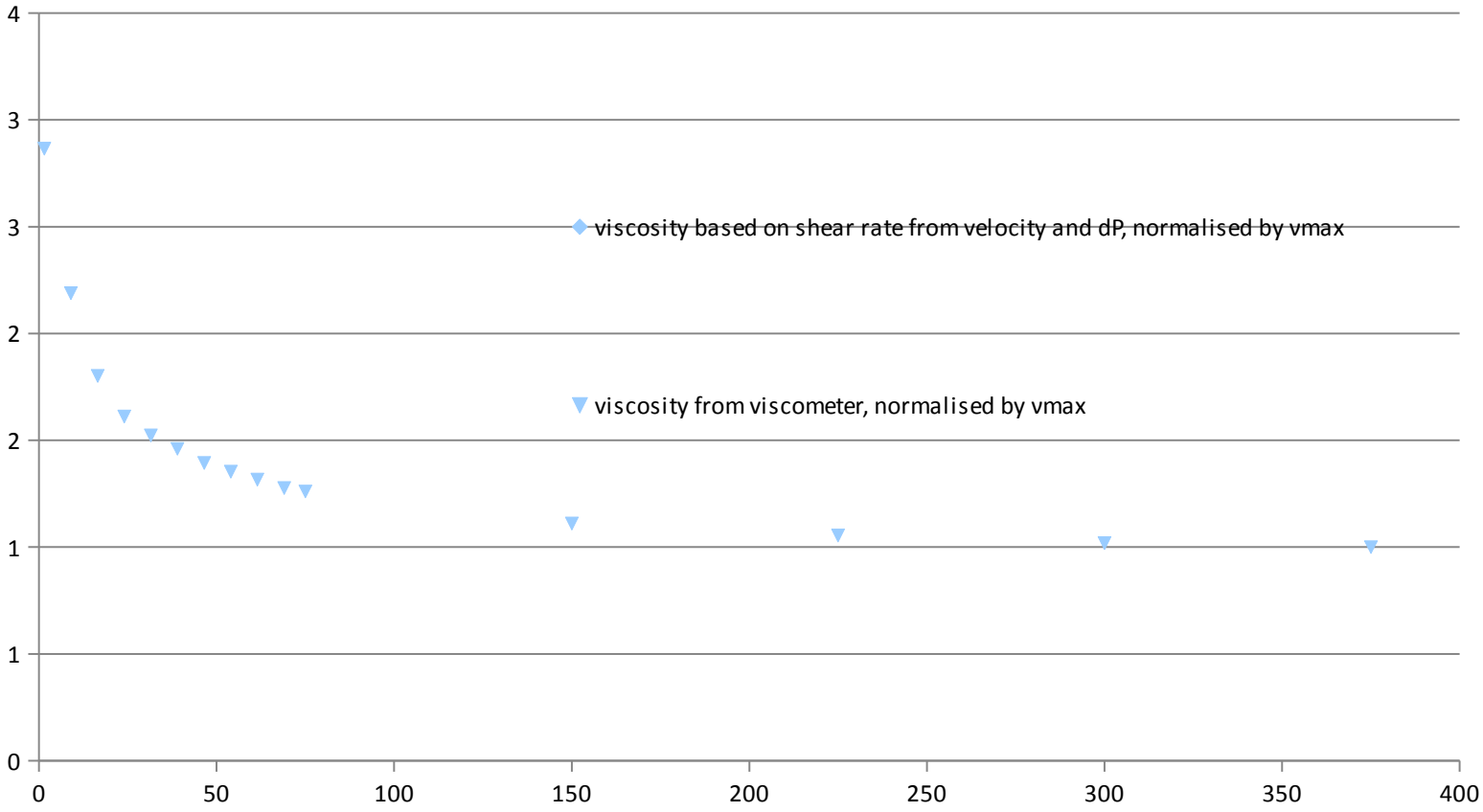
Unsatisfying operating viscosity

- *Pries AR**, Secomb TW, Gessner T, Sperandio MB, Gross JF, and Gaehtgens P.** Resistance to blood flow in microvessels in vivo. Circ Res 75: 904–915, 1994.*
- Abstract/FREE Full Text
- one-third of the observed pressure drop could be explained on the basis of blood viscosity as measured in vitro. On the basis of the comparison of the measured flow distribution with predictions of a mathematical flow simulation, the authors derived a viscosity relation that exhibited a substantially attenuated Fåhraeus-Lindqvist effect and much higher effective viscosities in smaller vessels. However, this relation was not based on a physical model for the causes of the increased effective viscosity.
- In the last decade, the experimental evidence for the presence of a comparatively thick layer on the endothelial surface [endothelial surface layer (ESL)] has expanded substantially (30). In addition to indirect evidence from measurements of hematocrit (6, 15) and flow resistance (32, 33), the layer and its modification by physiological and pathophysiological stimuli have been visualized (49, 50). A number of theoretical approaches have been proposed to analyze the mechanical properties of the ESL and its impact on blood rheology and exchange between the blood and the tissue

Viscosity of blood vs shear rate
temperature 22ºC (more viscous in brown) and 26ºC measured (more fluid in green) in a Couette cell

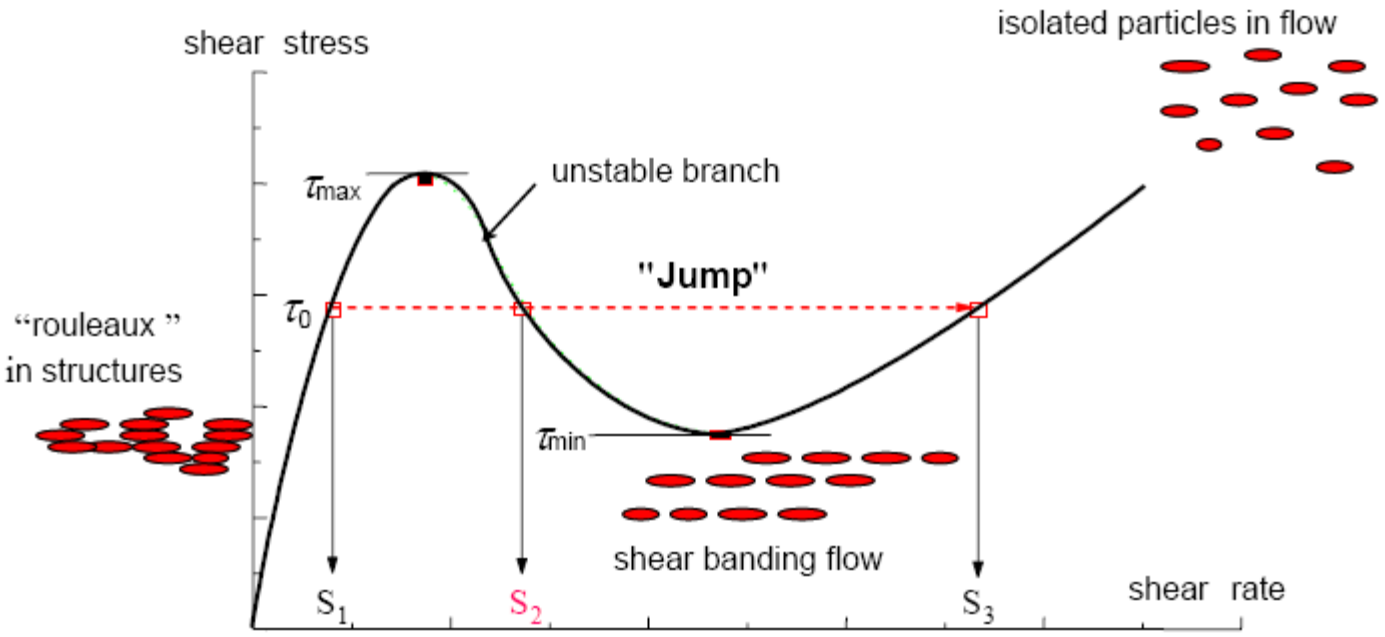


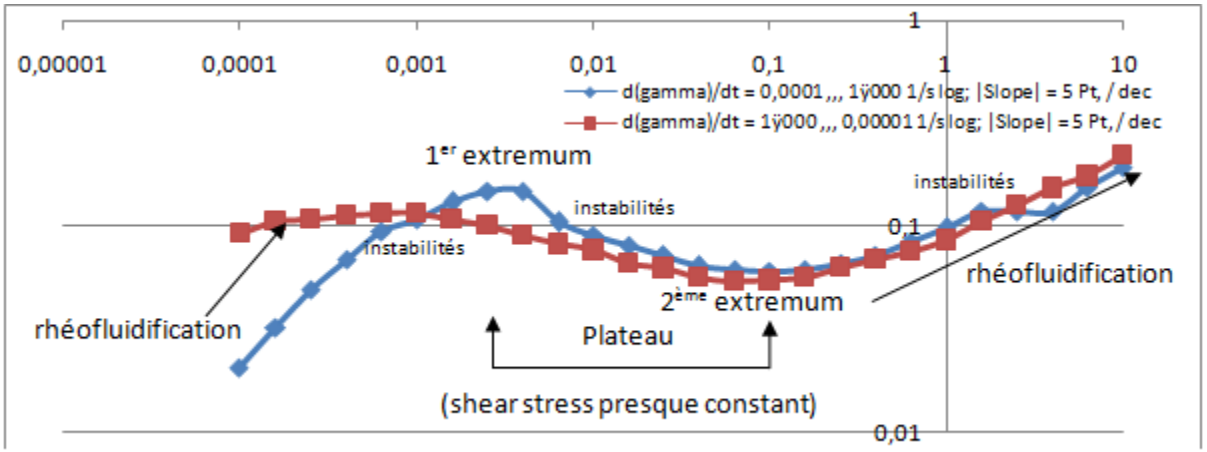
For numerical simulation : comparison between the Couette and Poiseuille



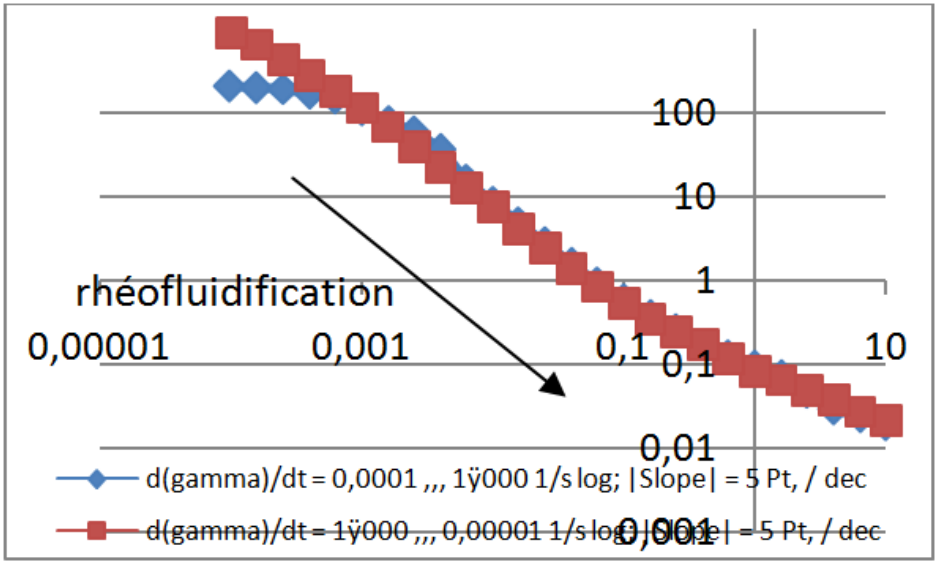
- Problems of Couette
  - Rotating flow : migration in 2 directions
    - Axial
    - Radial
  - Depends on
    - Temperature
    - Volume of measure
    - SIZE, Distance between cone and plan
  - Based on fluid characteristics : homogeneity, shear rate equally distributed, BUT BLOOD IS NOT A FLUID
- Rheological behavior non conform to blood flow
  - Necessary calibration for a large range of viscosities : diagrams
  - No transposition between velocity profile in vessel and viscosity value of viscometer

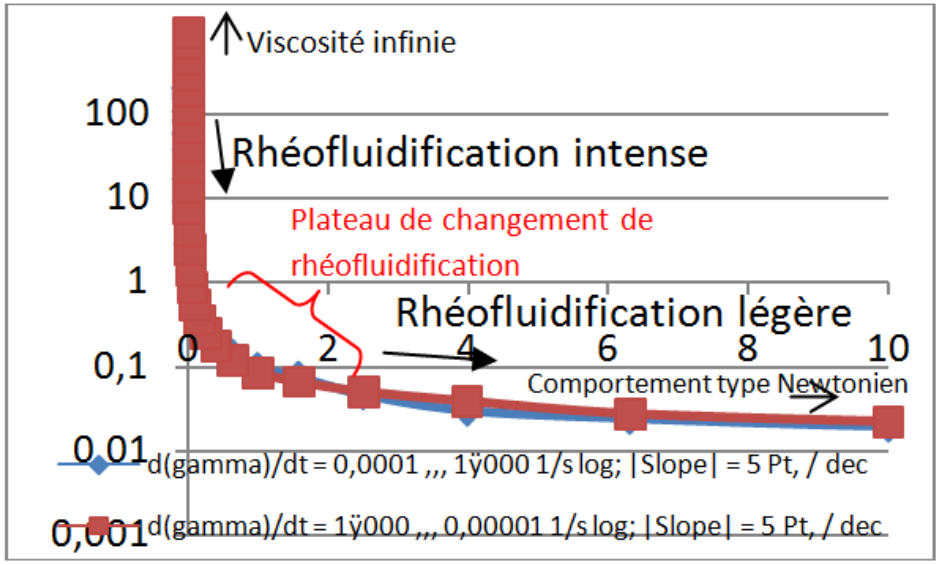
Instable blood flow





Shear stress versus shear rate





- Blood is not the same flow when driven by pressure or imposed velocity
- Hysteresis
- Instabilities (plateaux)
- Threshold values to initiate blood flow

(dernières expériences avec Jean Paul, see report)

- Aims at studying flowing blood in a channel
  - Routine
  - Reproducible
  - Consistent

- **Contribution to blood**
  - **Analysis complementary of the Haemogram**
  - **Qualification in general for the body health information or in particular cases to follow the effect of diseases or treatments**

- **More specifically, we aim at generalizing the use of an**

  index to qualify blood fluidity I_{fs} usable for quality control

- *In reality, the state of art is more than requesting : viscometers or other classical fluids mechanics tools, based on linear analysis, are not used by praticians… the calculations of mass flow rates even suggest that the blood velocity profile is not known, because approximations are too elevated, the similitude to in vivo cases is wrong, and the boundaries are not satisfyingly controlled in both applications*

Some medical specific cases subjected to fluidity

- Blood fluidity is affected by many factors
  - Hematocrit
  - Thrombos
  - Pressure, blood flow rate
  - Vascular surface
  - …

- Blood fluidity is affected by many diseases:
  - **Leukemia**
  - ***Leishmania***
  - Diabetes
  - Obesity
  - Cholesterol
  - …

- Blood fluidity can indicate different problems, thus can be used as a diagnoses tool to detect
  - Stenosis
  - Aggregation
  - Coagulation
  - risk factors for vascular disease like high cholesterol, high blood pressure
  - ….

BACK TO THE ROOTS

- ETYMOLOGY
  - Viscosity : viscum

    mistletoo : GUI (French)

  - VISCUM : VISCOUS : fish : Pitch : DROPET SIZE due vicosity

In French : Poix

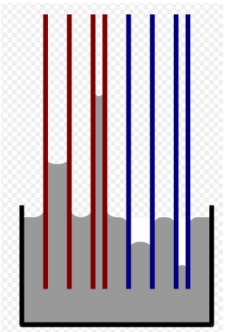
Units : Poise : Poiseuille

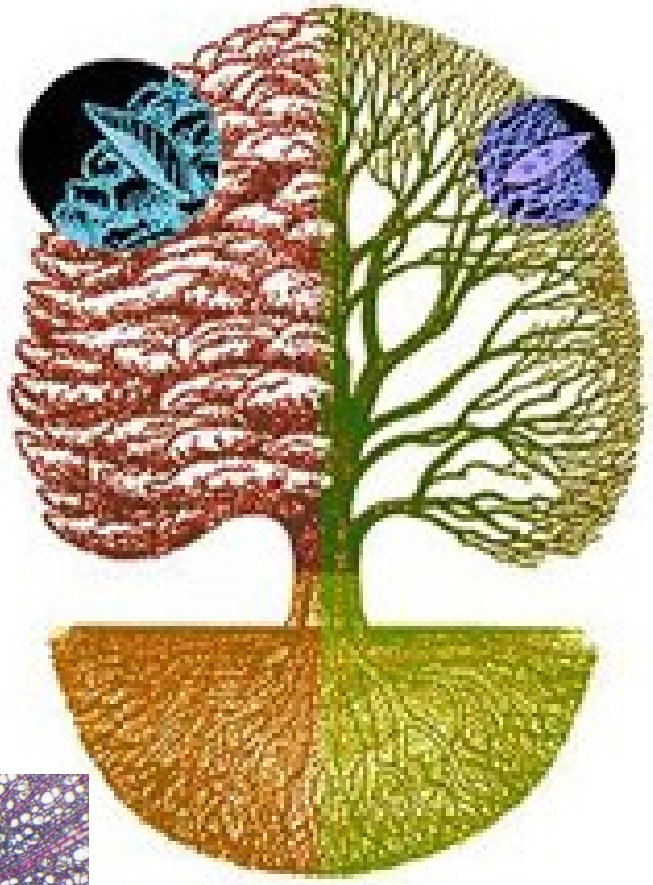
BACK TO THE ROOTS

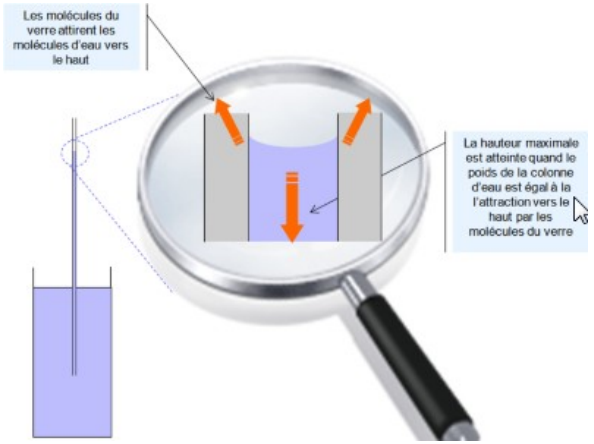
- Physics, Euristics

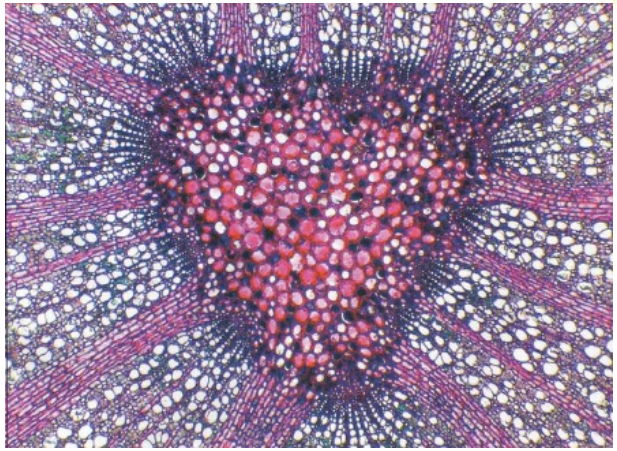
- Viscous is qualifying was keeps atched in the flow
  - Recipients droplets
  - Size of rain drops
  - Glue
  - Seve
- Viscosity is what makes the material elements stick :
  - Fibers
  - Fluids viscosity
  - Cells
- Viscosity is small geometries :
  - Wall is a small pertubation
  - Nutch, cut
  - Adhesion
  - Surace tension

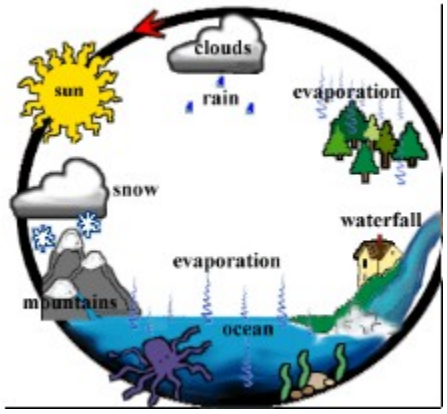
Surface tension, interface energy



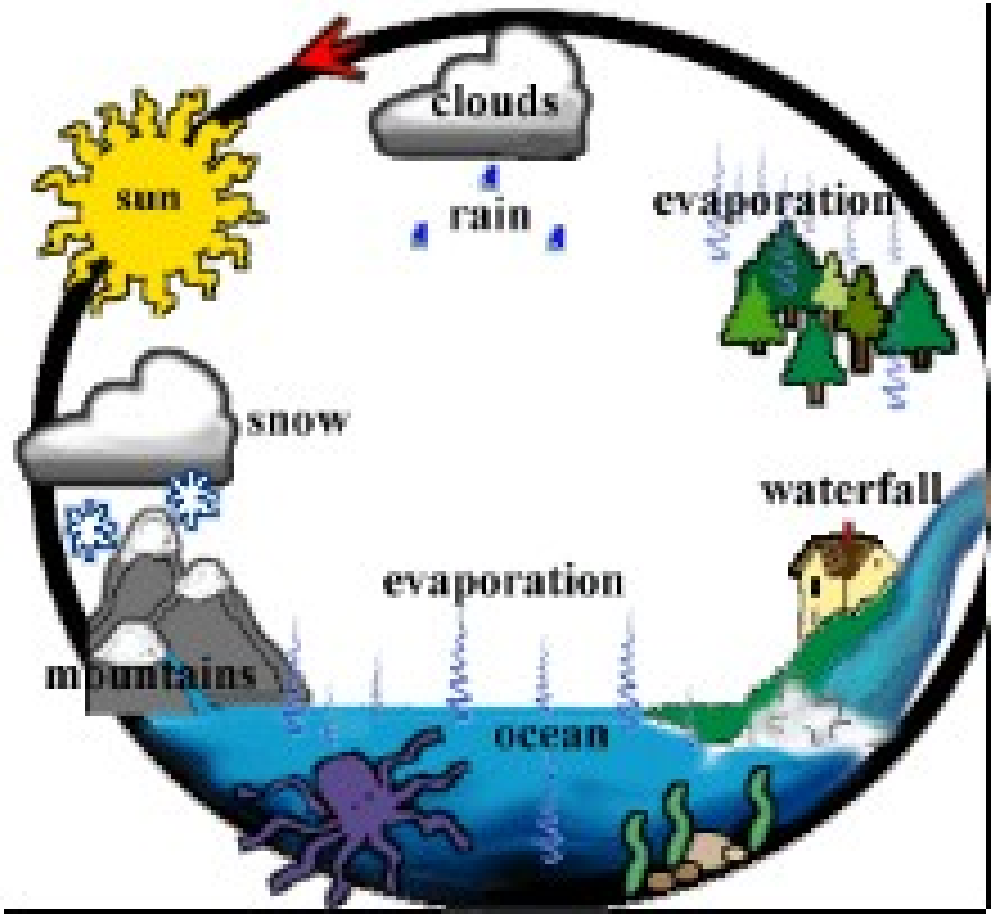


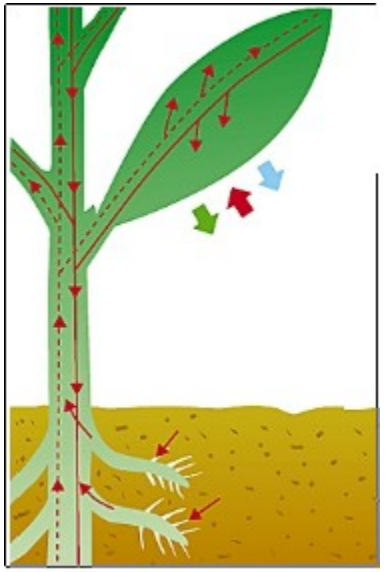






Aunt, droplet
Water droplet on a leaf
Tree sap (botany)
Mist, contact with the windshield





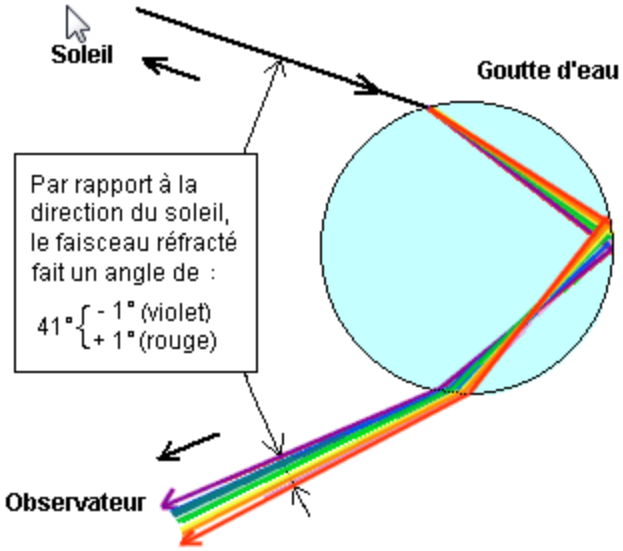
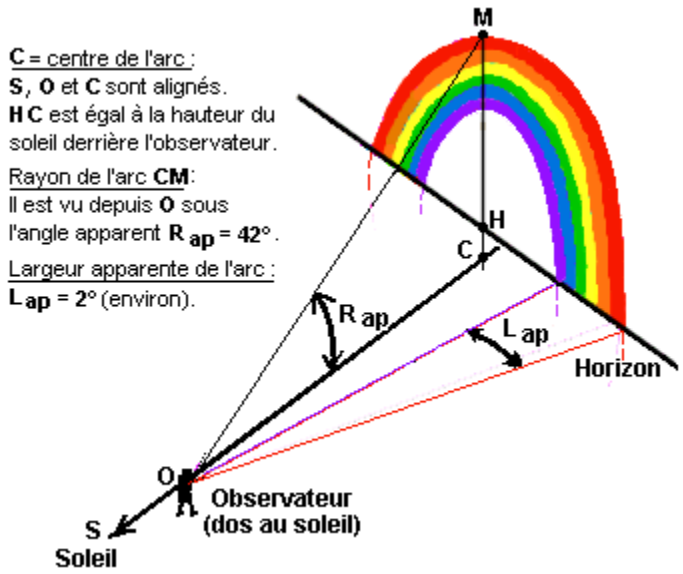
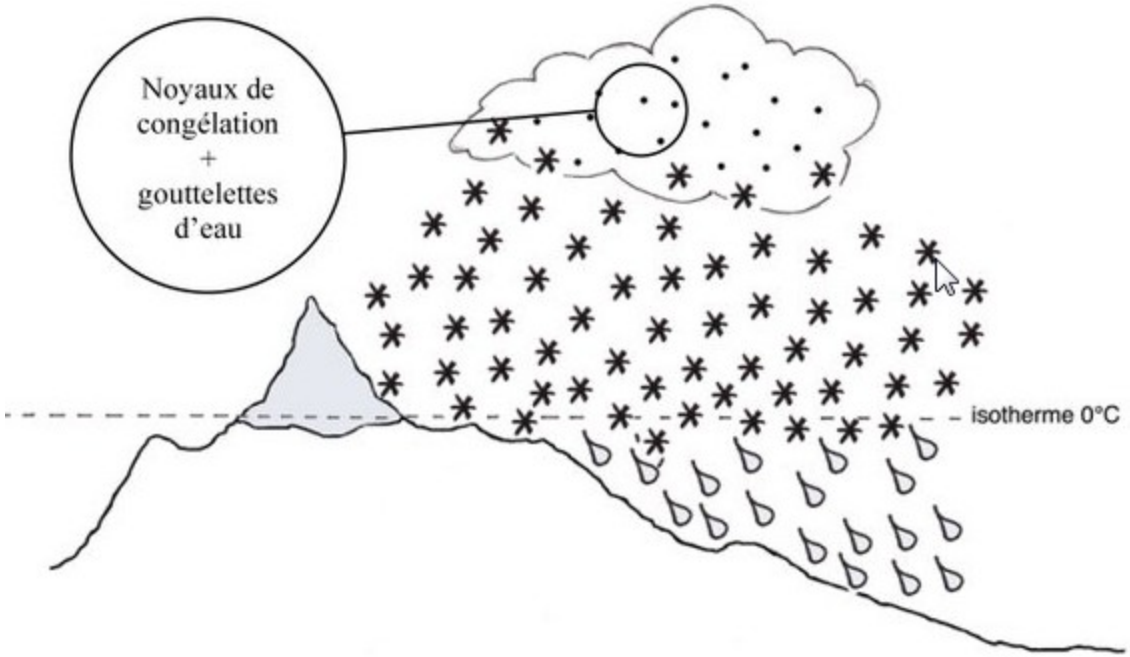
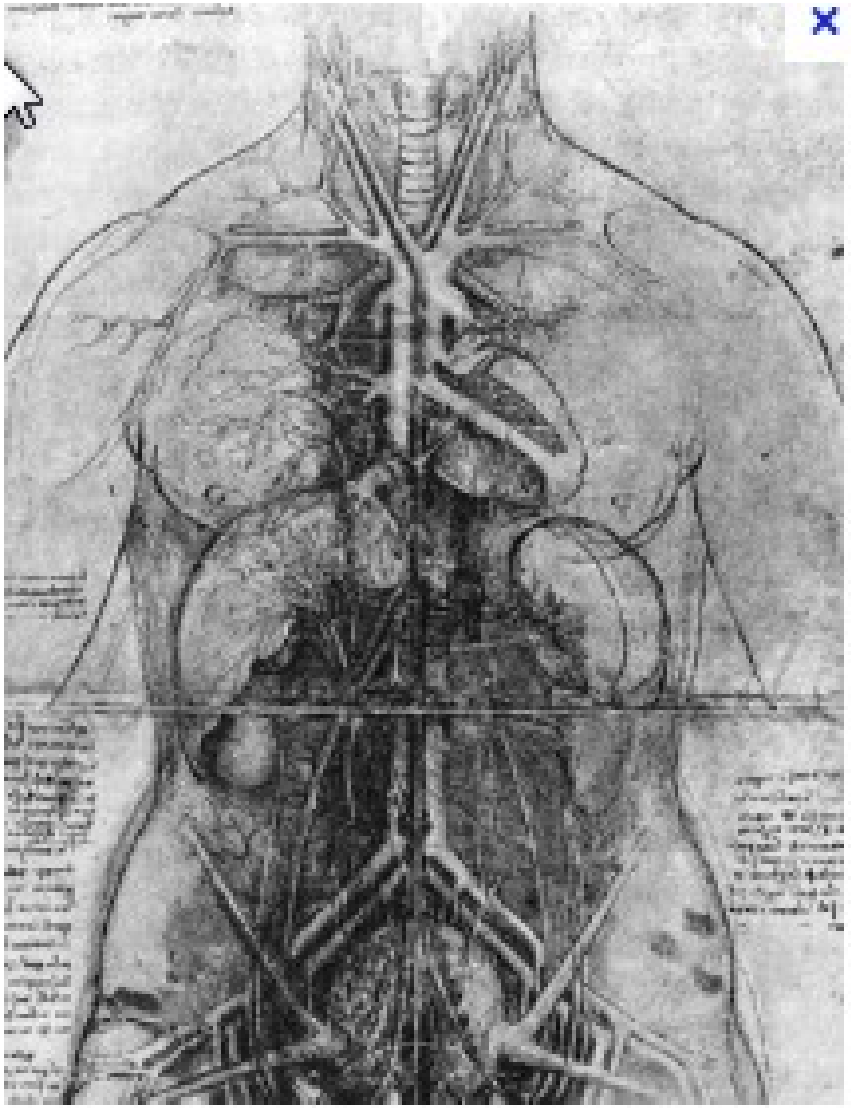
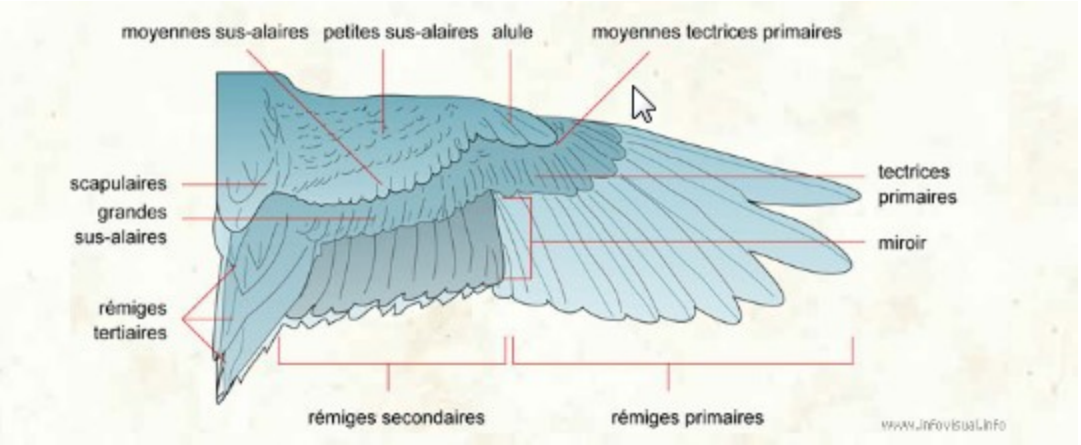


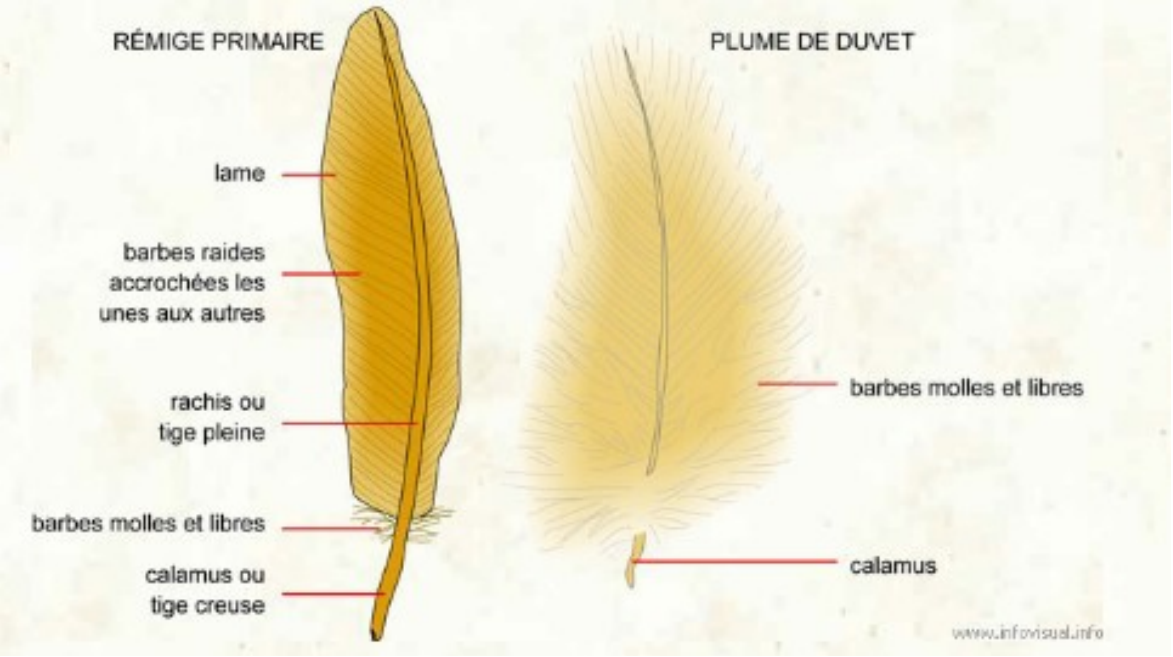
Fig. 1 - Réflexion et réfraction par une goutte d'eau

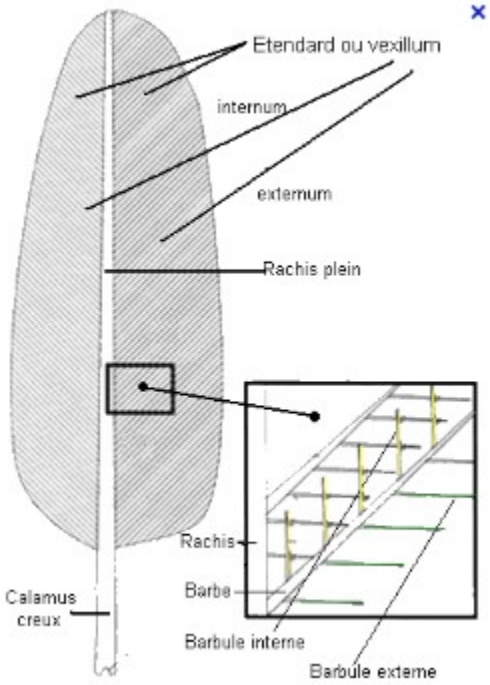



Noyaux de
congélation
+
gouttelettes
d'eau
isotherme 0°C

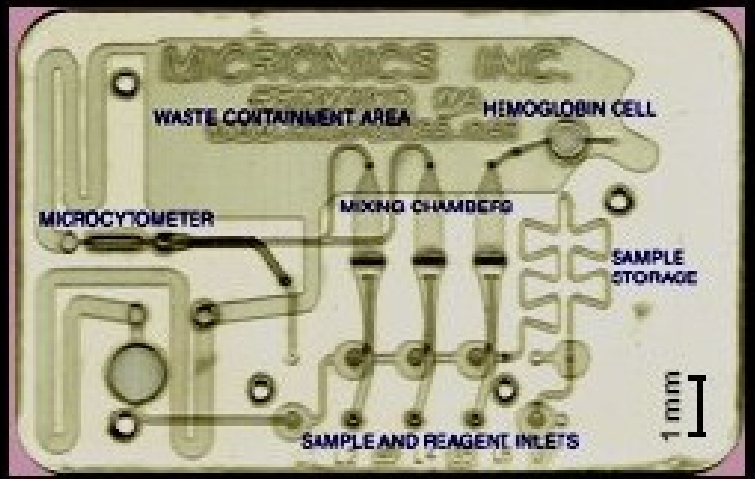



moyennes sus-alaires
petites sus-alaires
alule
moyennes tectrices primaires
scapulaires
grandes sus-alaires
rémiges tertiaires
tectrices primaires
miroir
rémiges secondaires
rémiges primaires
www.infovisual.info


RÉMIGE PRIMAIRE
lame
barbes raides accrochées les unes aux autres
rachis ou tige pleine
barbes molles et libres
calamus ou tige creuse
PLUME DE DUVET
barbes molles et libres
calamus
www.infovisual.info


Etendard ou vexillum
internum
externum
Rachis plein
Rachis
Barbe
Barbule interne
Barbule externe
Calamus creux

DISCRETE/DIGITAL MICROFLUIDICS for LAB-ON-A-CHIP TECHNOLOGIES



A few milestones

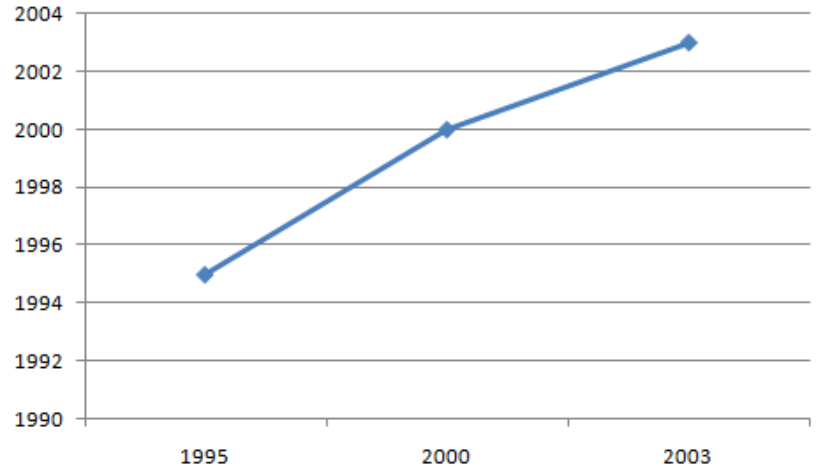
Before 1970´s : nothing

1976 : FIRST Inkjet printer

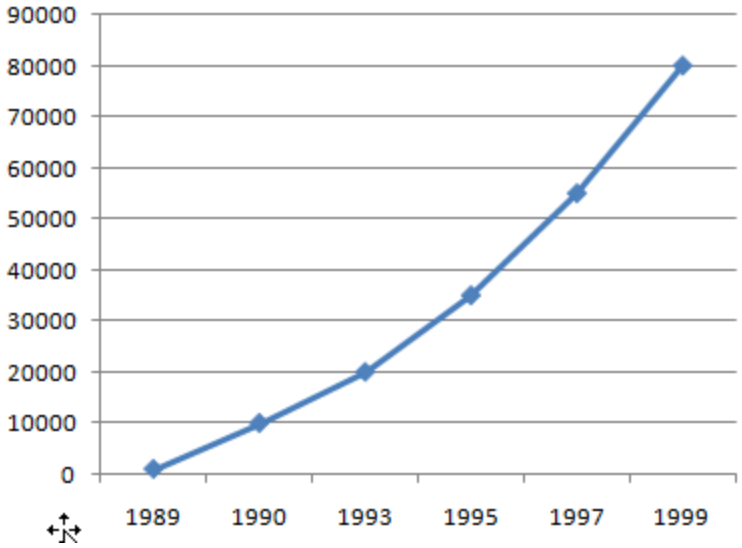
1990 : first liquid chromatograph (Manz et al, Manz, Graber, Widmer, *Sens.Actuator, 1991)*

1990 **-1998** : FIRST micro systems in microfluidics (micromixers, microreactors, separation systems...)

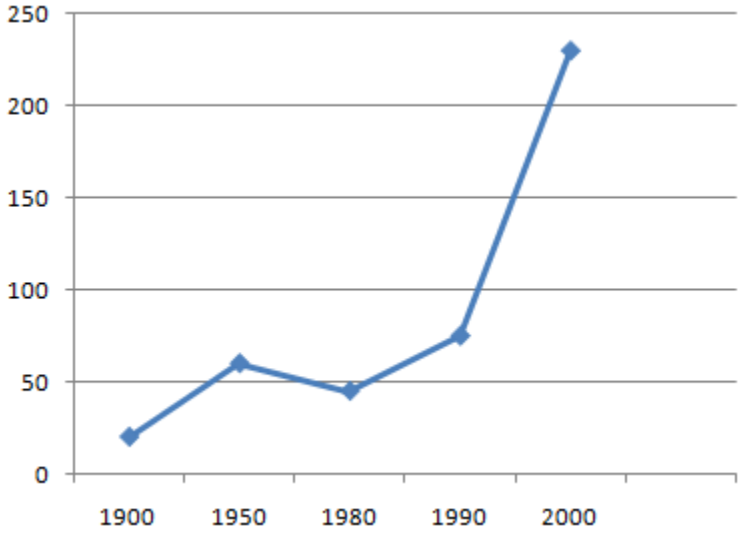
1998-2004 : Apparition of « soft lithography technology », that really contributed to increase this industry (different systems and technologies)



patents / year



Publications cumulated



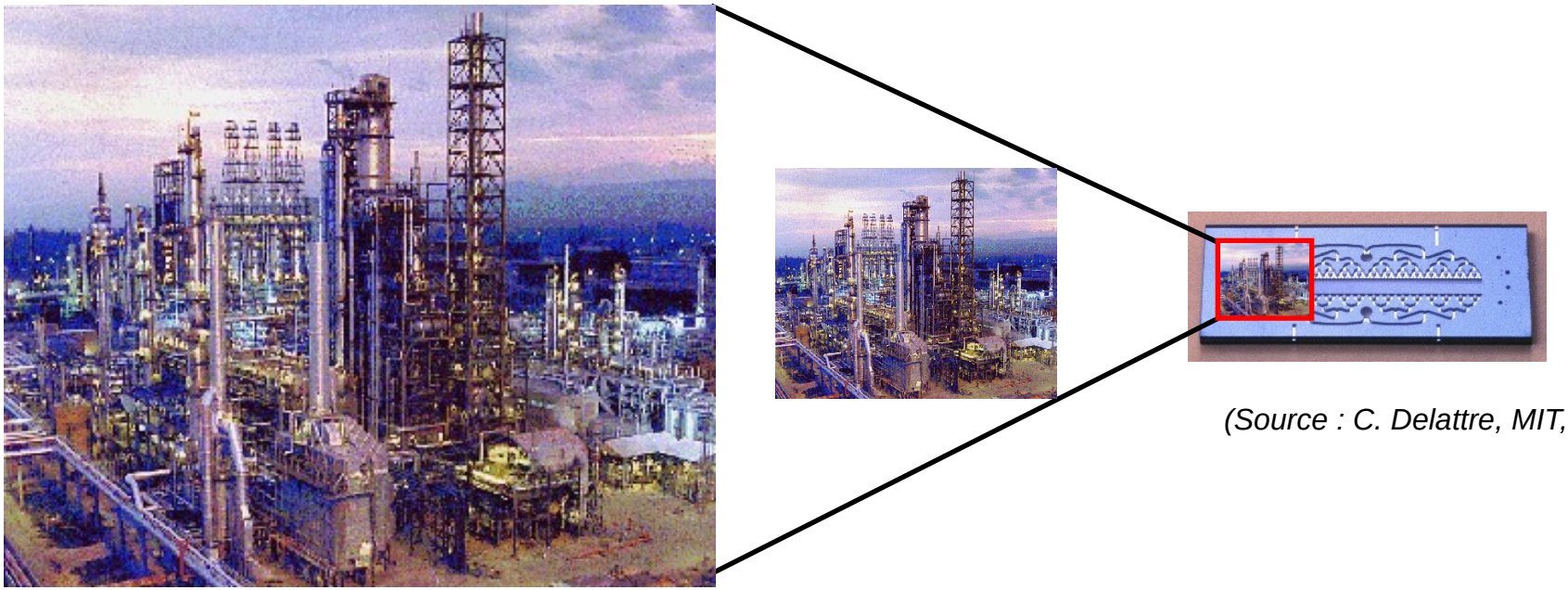
Companies created along the time (years)

Microfluics is then used in lots of areas:

- *Alimentary industry*
- *chemistry*
- *Biotechnology*
- *Petrol industry*
- *…*

Looking forward a great evolution in microsystems

Transfers in chemical reactions

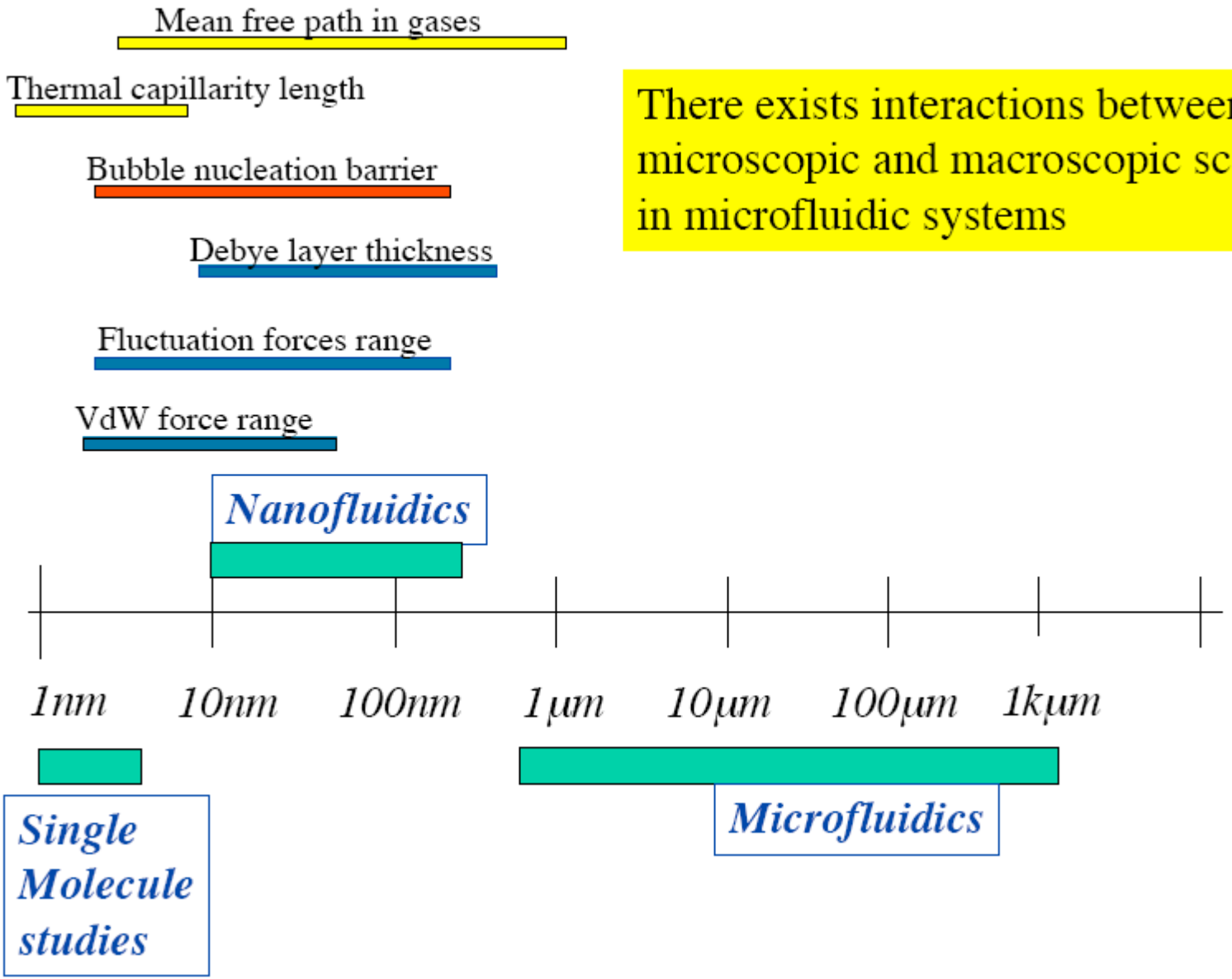


(Source : C. Delattre, MIT, MTL)

Heat transfers are much easier in micro systems
and
selectivity of processes is much more accurate and better

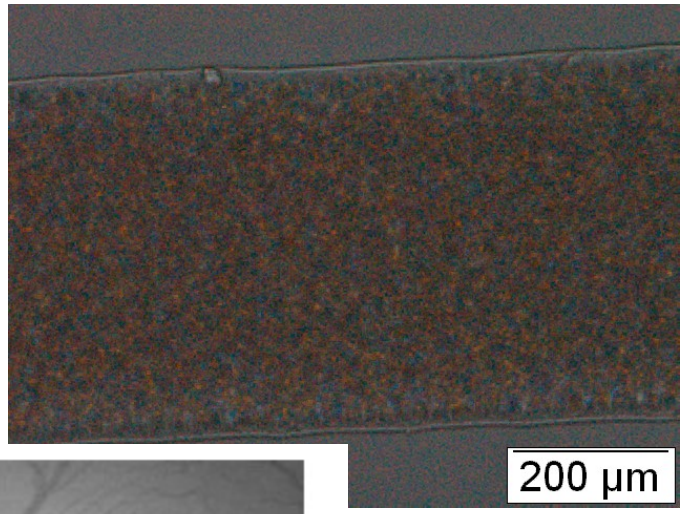
Before making a study of complex micro liquid flows like blood, we should think about :

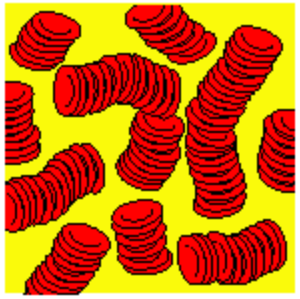
Quantity	Scaling law
Intermolecular Van der Waals force	l^{-7}
Density of Van der Waals force between interfaces	l^{-3}
time	l^{0}
Capillary force	l^{1}
distance	l^{1}
Flow velocity	l^{1}
Thermal power transferred by conduction	l^{1}
Electrostatic force	l^{2}
Diffusion time	l^{2}
Volume	l^{3}
Mass	l^{3}
Force of gravity	l^{3}
Magnetic force with an exterior field	l^{3}
Magnetic force magnétique without an exterior field	l^{4}
Electrical motive power	l^{3}
Force centrifuge	l^{4}

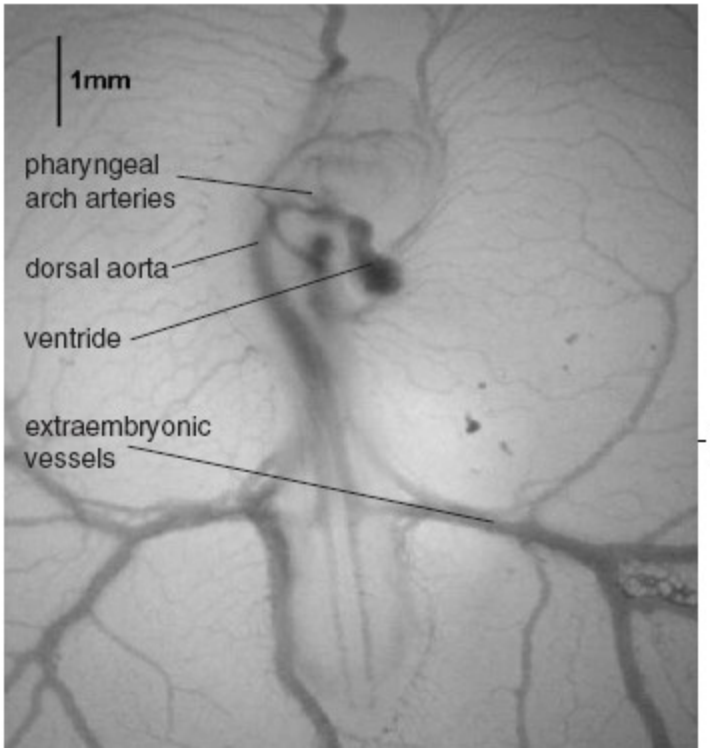


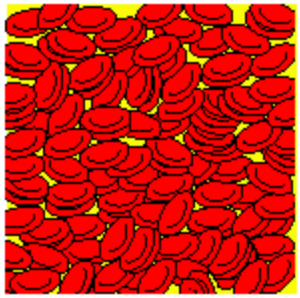
There exists interactions between microscopic and macroscopic scales in microfluidic systems

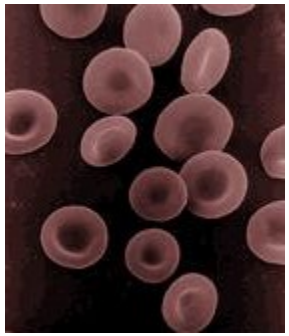
Remarquable example of micro flow : Blood flow in the body

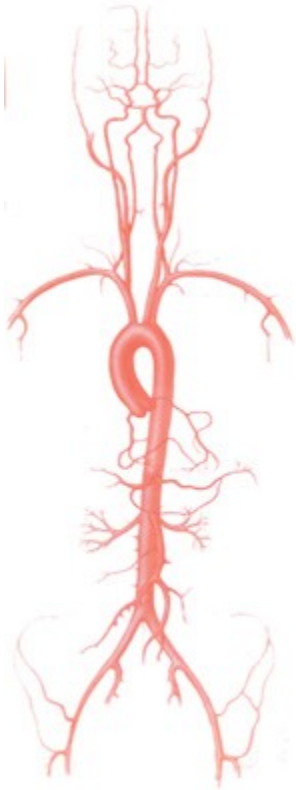


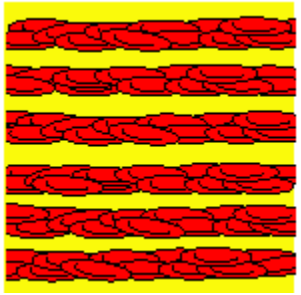












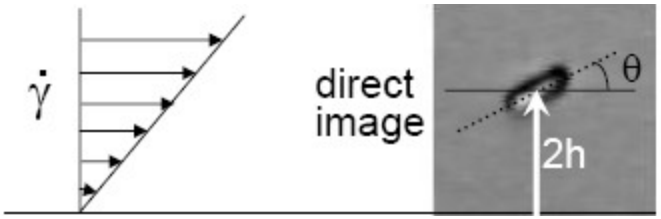
Blood is a complex fluid

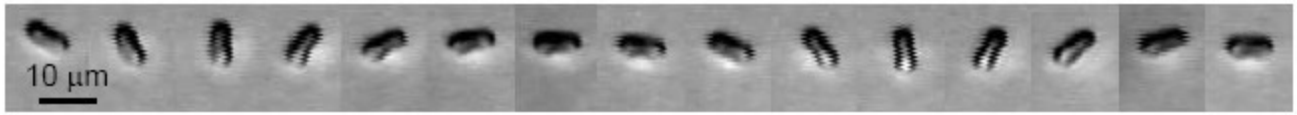
Non Newtonian fluid, non transparent

- Blood accounts for 7% of the human body weight, with an average density of approximately 1060 kg/m^3, very close to pure water's density of 1000 kg/m^3.
- The average adult has a blood volume of roughly 5 liters
  - Plasma 54.3% (by volume)
  - Erythrocytes, deformable (red blood cells) 45%
  - leukocytes (white blood cells) 0.7%

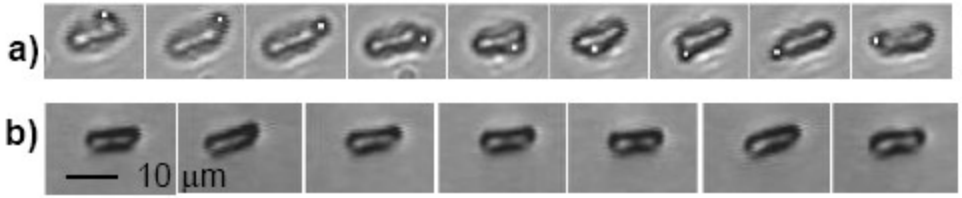
Red cell single behavior in a longitudinal pressure gradient flow

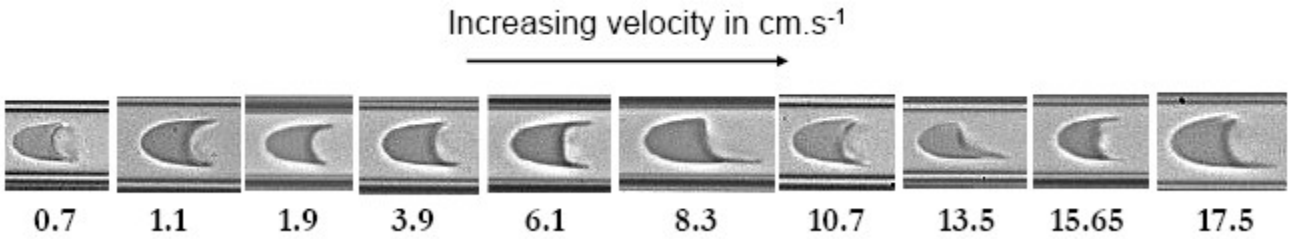
- Red cells :
  - Physical description
  - Physical parameters
  - Solid like motion, the tumbling



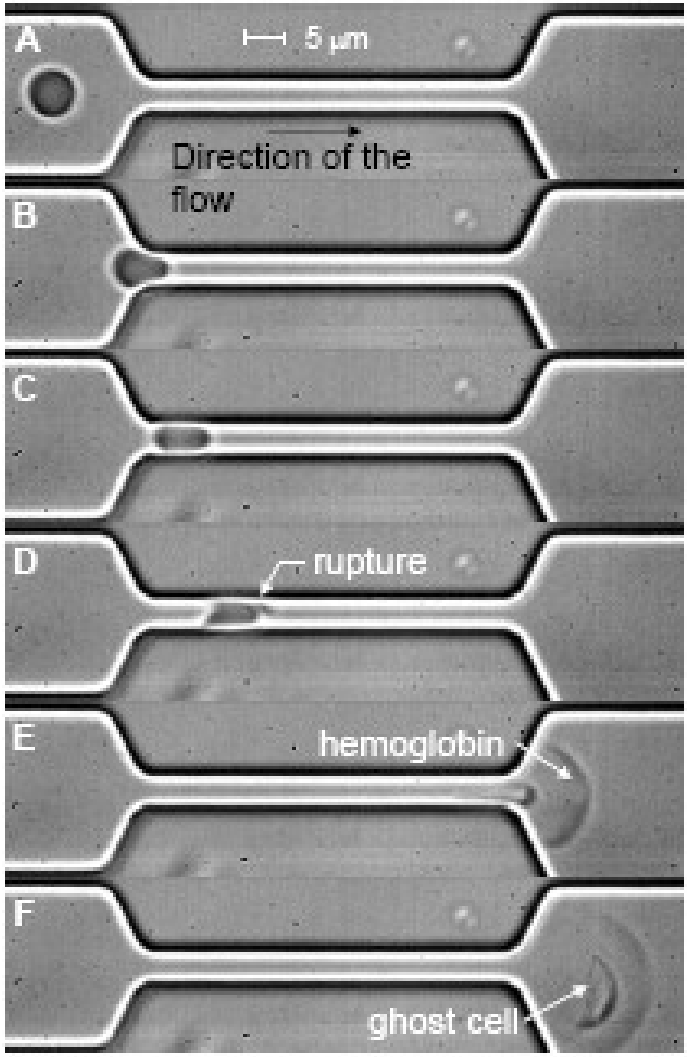


  - Swing motion, oscillation of the cell

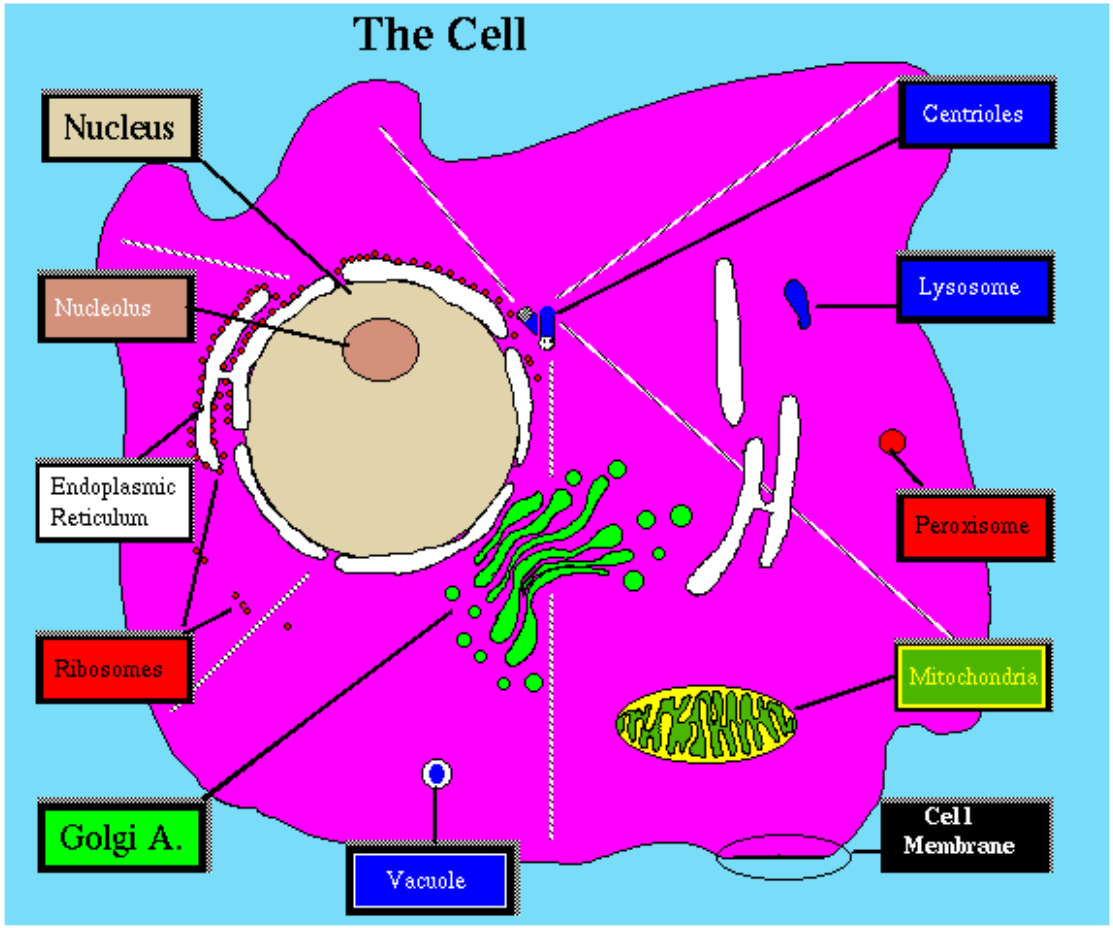




Influence of the vertical pressure gradients due to geometrical variations along a longitudinal flow



Small structures carriage : cells, DNA, molecules



Cells : mm → µm

millions of cells of 25 micrometers can tighten into a cube of 1 cm caracteristical length

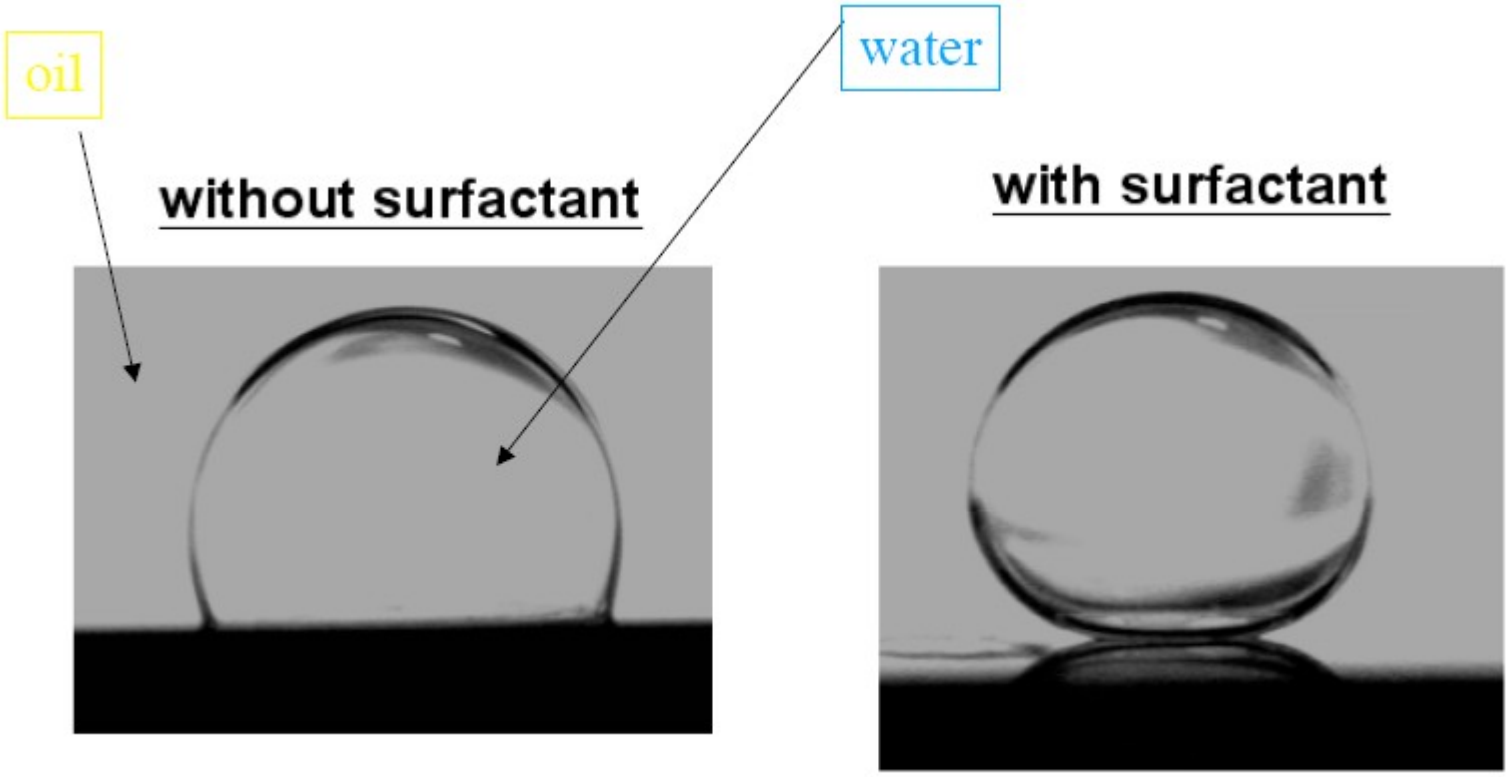
Blood components make it hard to be modellised as a fluid, even as a suspension

Einstein law does not work for complex bodies in a fluid :

LE MOUVEMENT BROWNIEN ET LA FORMULE D'EINSTEIN Par M. J. DUCLAUX.
REVUE LE RADIUM, 1940

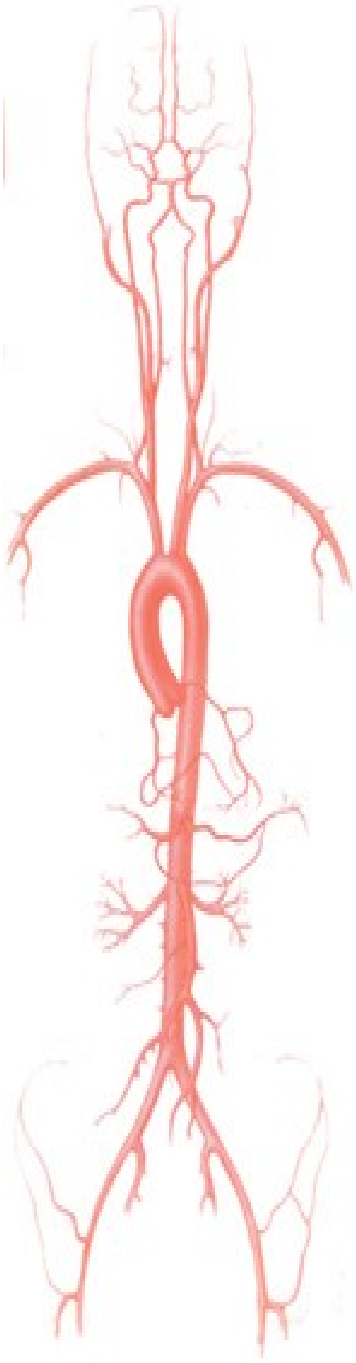
Examples of micro flows phenomena

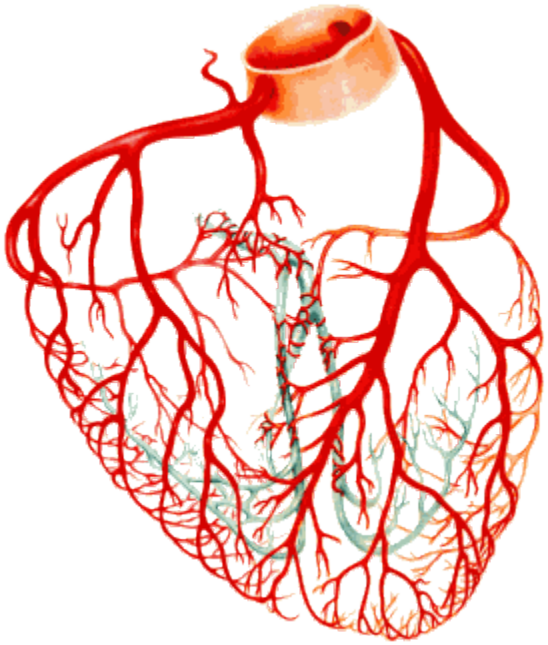
- Droplets



Droplet dynamics

- Initial micro-PIV results.flv
- PIV of Splashing Droplets.flv
- Water droplet impinging on an isothermal surface.flv



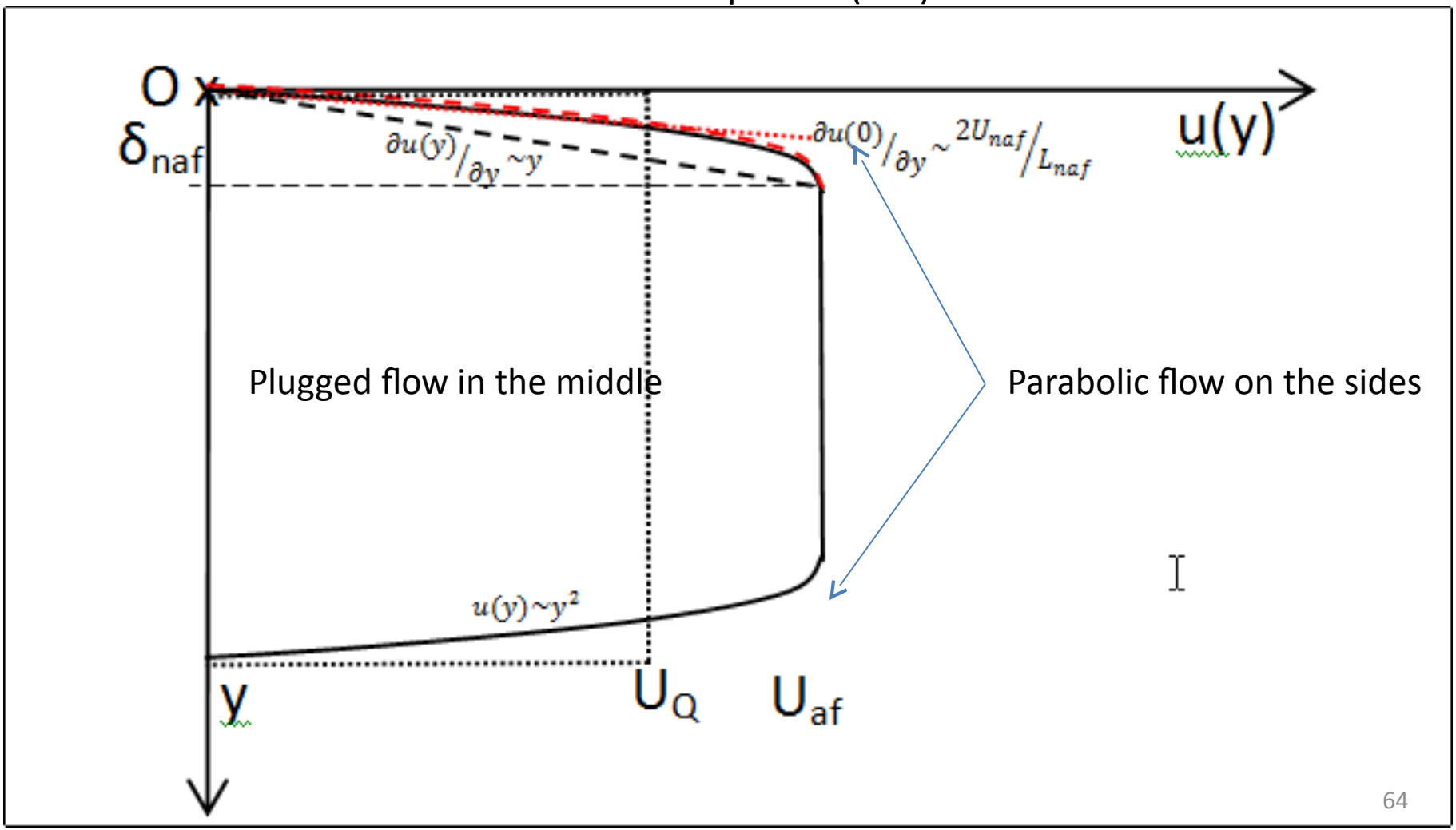


BLOOD VISCOSITY STUDY

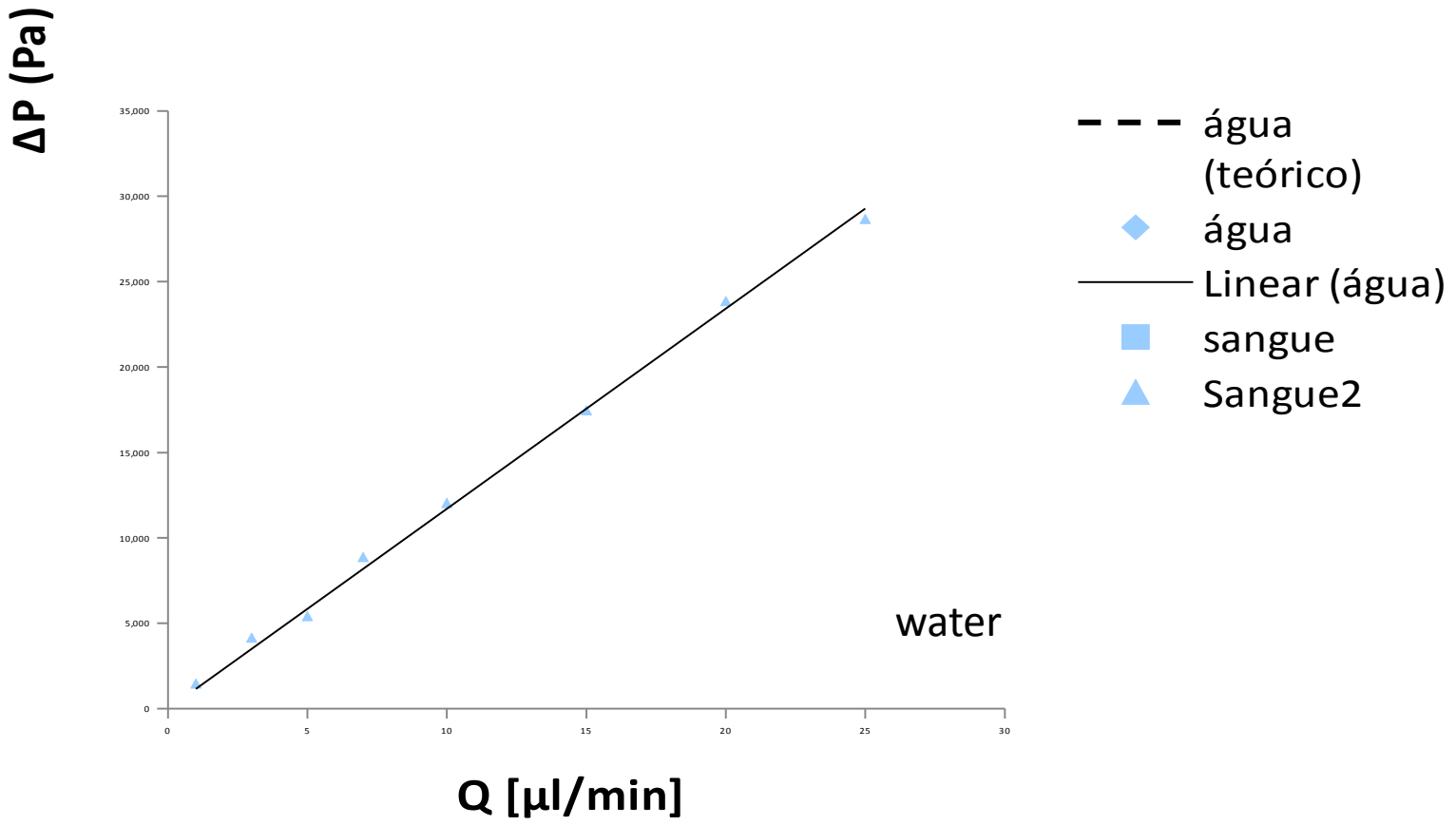
- In a straight channel
- Influence of the wall, friction, viscosity
- Organization

Schematics principle of blood flow in a Poiseuille channel

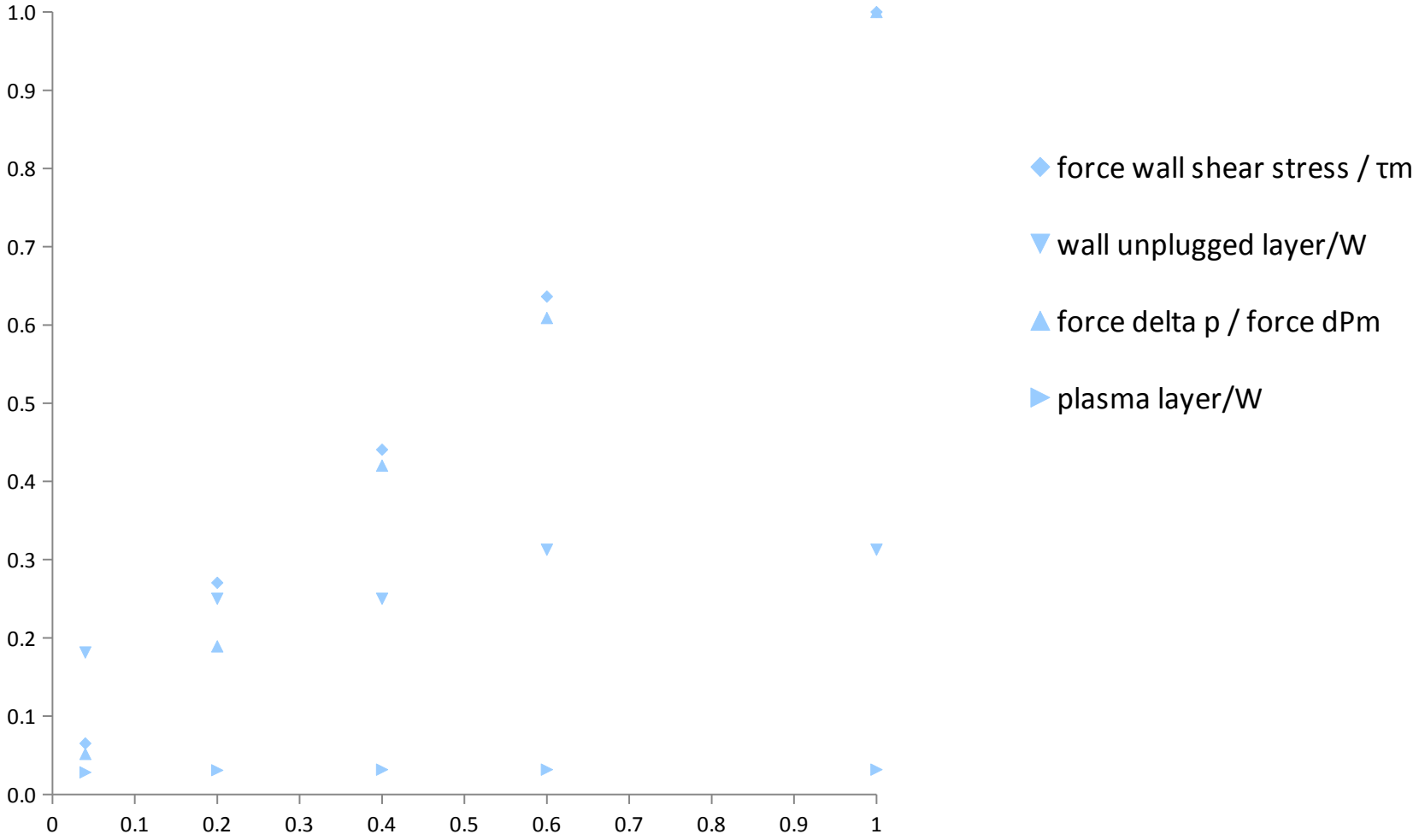
In the wall layer, δ_{naf}, the flow is not plugged and follows experimentally a Parabolic profile (PIV)



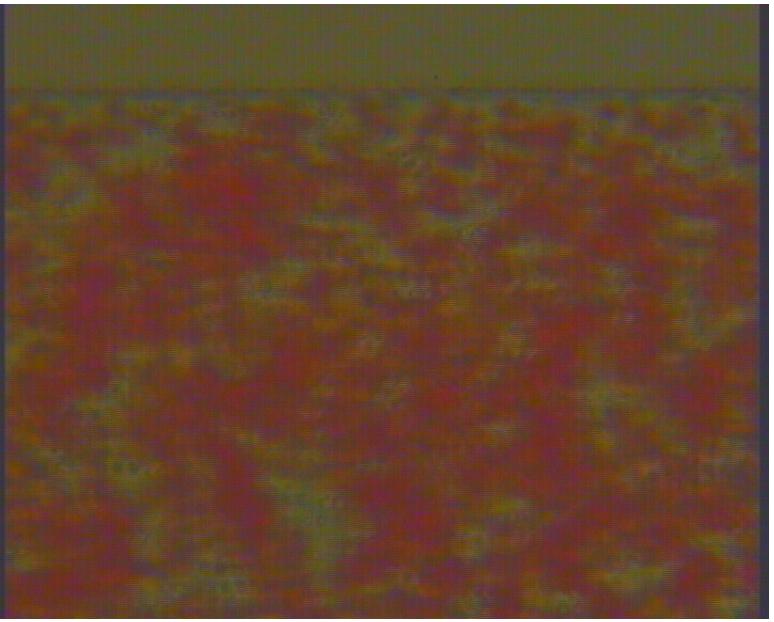
Pressure drop coefficient K is constant, and the geometrical factor G fits for the water case (viscosity constant).

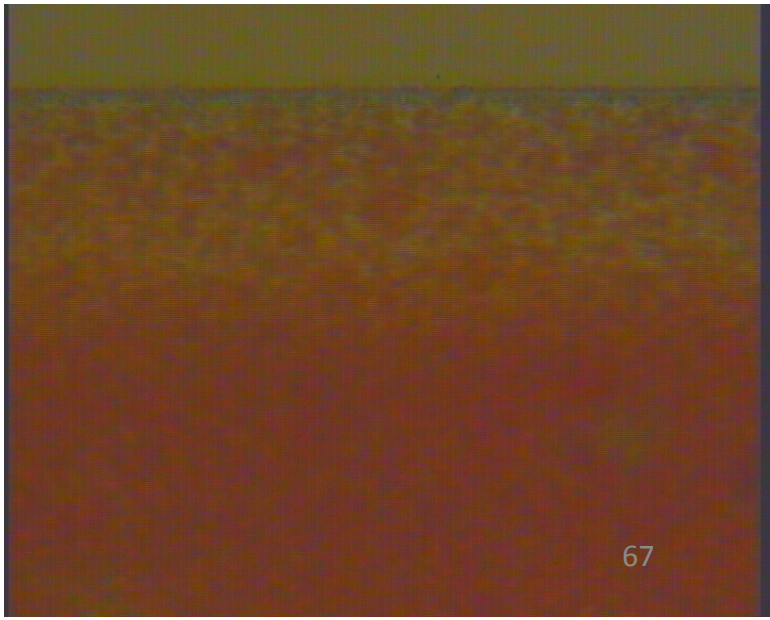


- This gives the three different values of I_{fs} measured for these three fluids, easy to compare and to appreciate for fluidity estimation

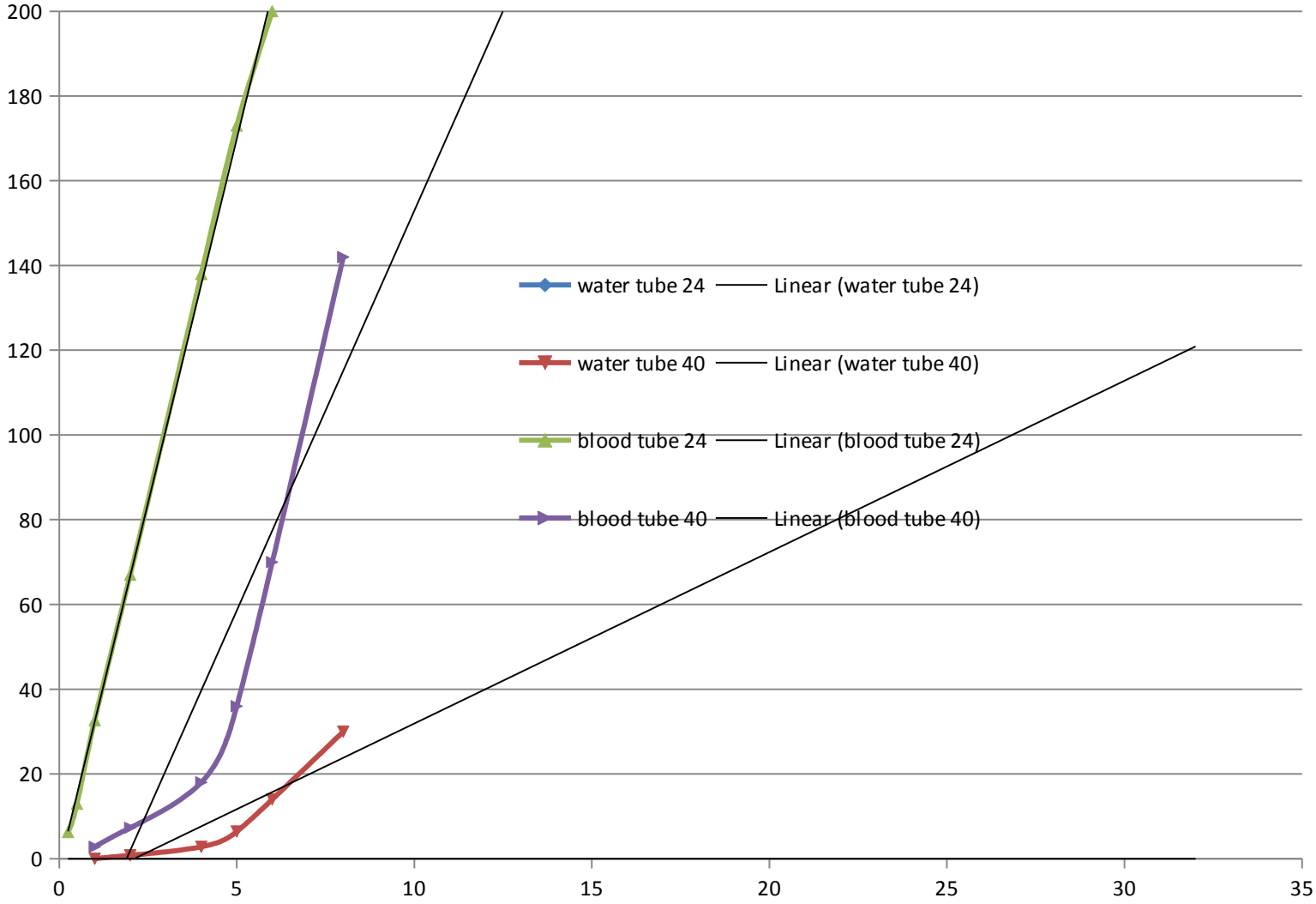

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
force wall shear stress / τm
wall unplugged layer/W
force delta p / force dPm
plasma layer/W

Movies, shear banding 1- 2- 4 - 8 mm/s

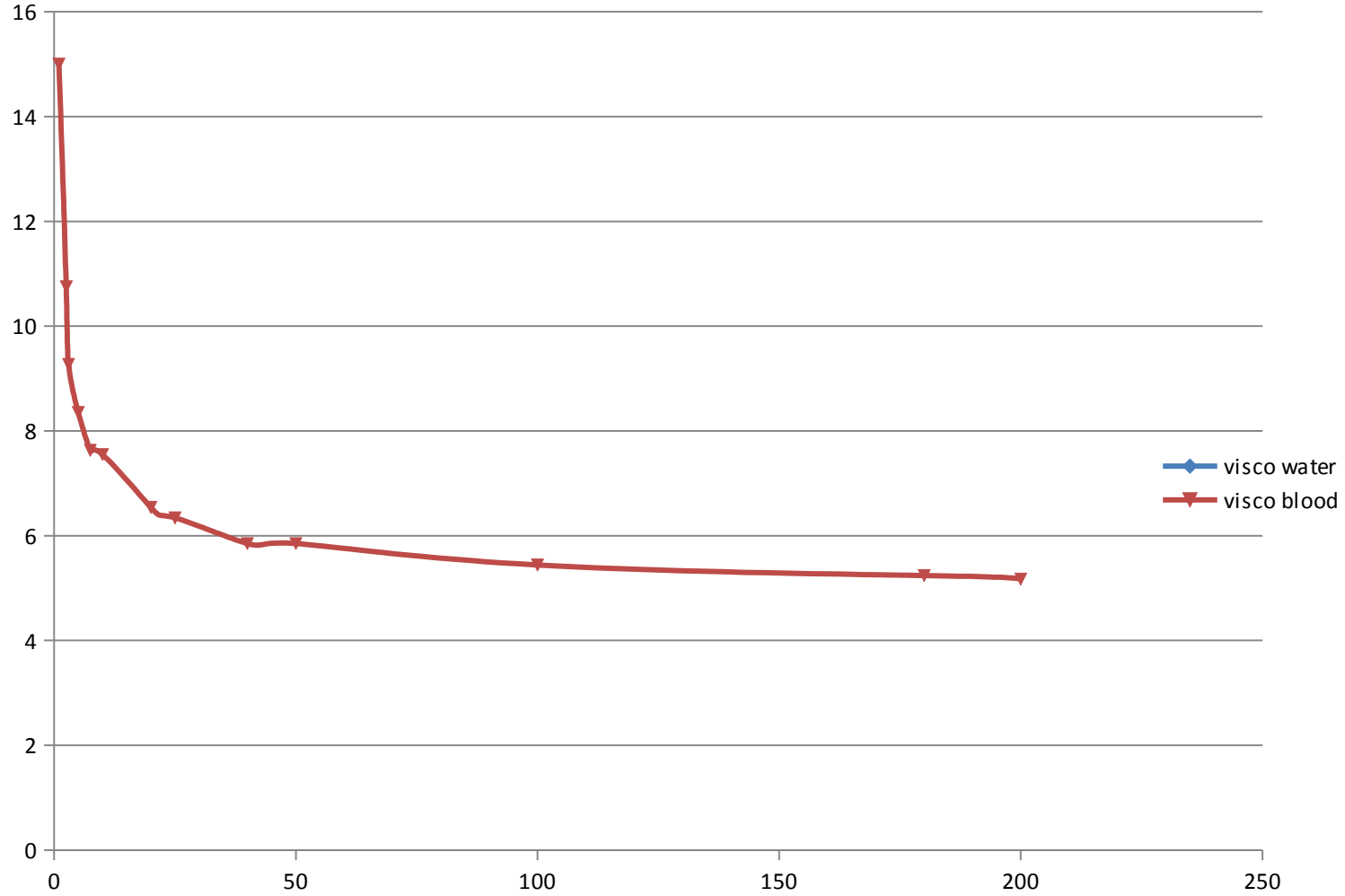




HAD TO CHECK IT IN TUBES
Human blood, Koç University Baskurt



Viscometer Couette, Koç University



Many other results :

- Blood cells in phisiological is less viscous than plasma and than total blood, work to be published soon from experiments in Metz
- Plasma is non newtonian
- Sepsis cases (A B C) show that decreasing haematocrite increases viscosity, Fluid resuscitation ???
- Plasma viscosity is higher than total blood, work to published soon from experiments in LMM (Carlota Saldanha)

BUT

We never had the possibility to have a complete haemogram to study paradoxes, intercorrelations etc…

For example : albumine, Igs, White cell, Von Willebrandt factor, …

- Constant Index is viscosity * D / Lnaf
  - Viscosity of blood
  - D size of channel
  - Lnaf size of attached flow
- Application to blood devices design
- Bio marker
- A parameter to study CVDs

Measures, controls :

- dP
- L
- Q
- Dh
- Lnaf

In the end, a unique viscosity index explaining :

the friction at the wall, the dissipation in the flow, the ability of blood to flow

- Next
  - Database of this index
  - Have a table of values depending on haemogram
  - Correlation to known diseases
- Potential
  - Replace old viscometers
  - Homologation for suitable blood treatment
    - In vivo
    - Ex vivo
    - In vitro (manipulations)

- Organization
  - Equipment
  - Measurements
  - Data treatment
  - Diagnostics
  - Research projects
- Strategy
  - Blood
  - Complex liquids
- Flowmeters to be put in hospitals, labs, and for sell

SUMMARY : WE HAVE AN ABSOLUTE VALUE OF VISCOSITY

- THE PROJECT IS TO DEVELOP A NEW SCIENTIFIC INSTRUMENT TO MEASURE BLOOD VISCOSITY
- BASED ON A NOVEL, TESTED AND DEMONSTRATED PATENTED TECHNOLOGY owned by BOW
- BRINGS ACCURACY, SPEED OF MEASUREMENT, REPRODUCIBILITY AND SCIENTIFIC RIGOR

- THE MEASURE IS COST COMPETITIVE COMPARED TO CURRENT STATE OF THE ART EQUIPMENT
- THE MEASURE IS A UNIQUE VALUE OF A NEW VISCOSITY INDEX
- **THE MEASURE IS OBTAINED IN A FEW SECONDS**

- CURRENT STATE OF THE ART PROVIDES non realistic VISCOSITY DIAGRAMs HARD TO INTERPRET for blood circulation
- CURRENT STATE OF THE ART REQUIRED SEVERAL minutes/hours TO PRODUCE THE DIAGRAMs for a range of shear rates from 0 to 200 s-1 which should all be calibrated. A single rotative machine is traditionally used which requires strong clean between measurements
- CURRENT STATE OF THE ART IS NOT ACCURATELY REPRODUCIBLE THEREFORE COMPARABLE between different machines and blood samples. Blood is not a fluid and the low shear rates present different blood organization and initial conditions. Low shear rates correspond to low speeds in viscometers but in in vivo circulation, low shear rates correspond to high speed flow and another organization of the red cells.
- CURRENT STATE OF ART RESULTS ARE NOT VISCOSITY VALUES OF BLOOD, they are related to it

SUMMARY

- THE AIM IS TO ONE METHODOLOGY TO MEASURE BLOOD VISCOSITY
- WE NEED ASTANDARD MEASUREMENT IN HEALTH CARE AND BIO-PHARMA R&D

- TO BUILD AROUND THIS NEW INSTRUMENT:
- Data base for everybody : research, doctors, patients (who eat snaks)
- Help on CVDs or related to viscosity diseases

THE SUCCESSFUL COMPLETION OF THIS FIRST PHASE MAY LEAD TO THE A NEW DIAGNOSTIC WITH A VERY LARGE MARKET AND SIMILARLY VAST BUSINESS POTENTIAL

TECHNOLOGY

BOW Ltd and Mechatronics NV collaborate on a mechanical key parameter.

This new methodology utilizes a new formula to measure a unique Viscosity Index (VI) in Complex Liquids (CL) of which whole blood is a strong model as it contains nearly 50% solid and shows a stable and known velocity profile in a stabilized vessel type flow.

The accuracy of the methodology has been tested in various university laboratories and the underlying formula demonstrated mathematically.

A number of leading scientists doing research on blood viscosity, how it relates to a patient's health as well as the resulting effect of a range of stimuli on viscosity have expressed an interest in using this new methodology. Initially to validate its advantage over current measuring devices which do not provide accurate measurements for Complex Liquids like whole blood.

FUTURE of TODAY : Centralized database

That’s it