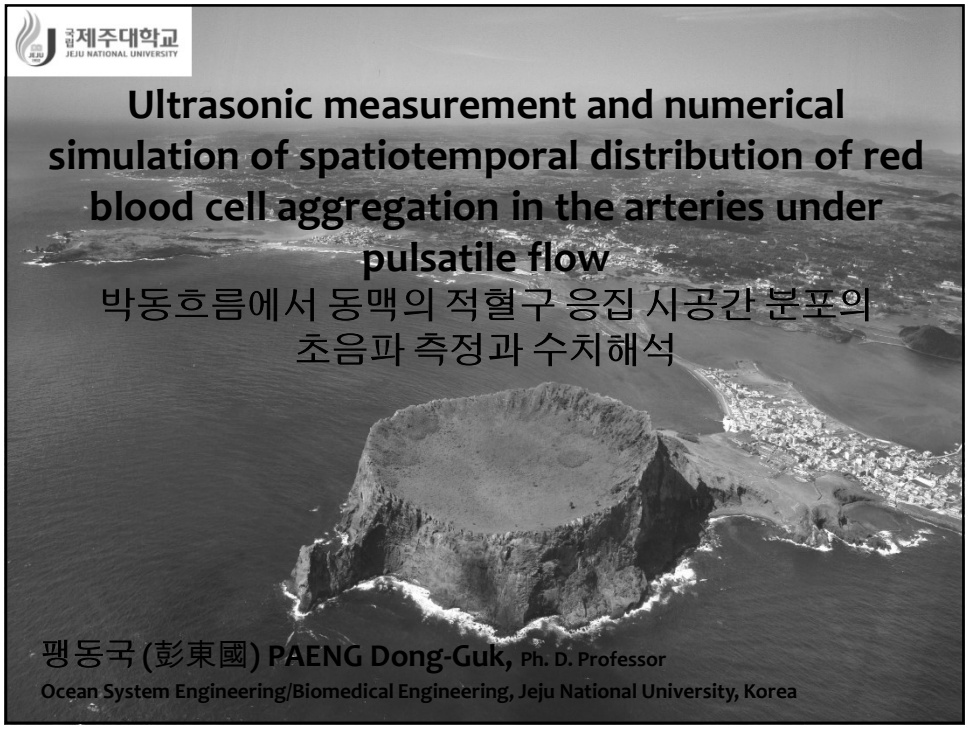
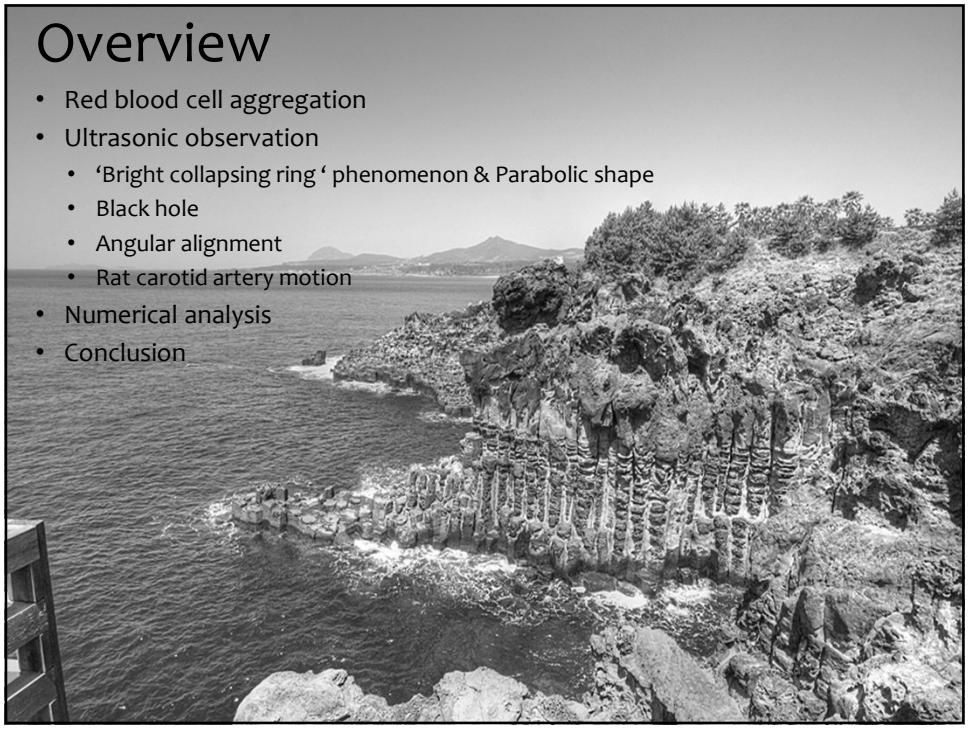
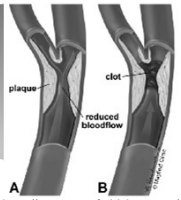

제주대학교
JEJU NATIONAL UNIVERSITY
Ultrasonic measurement and numerical simulation of spatiotemporal distribution of red blood cell aggregation in the arteries under pulsatile flow
박동흐름에서 동맥의 적혈구 응집 시공간 분포의 초음파 측정과 수치해석
팽동국 (彭東國) PAENG Dong-Guk, Ph. D. Professor
Ocean System Engineering/Biomedical Engineering, Jeju National University, Korea


Overview
• Red blood cell aggregation
• Ultrasonic observation
• 'Bright collapsing ring ' phenomenon & Parabolic shape
• Black hole
• Angular alignment
• Rat carotid artery motion
• Numerical analysis
• Conclusion

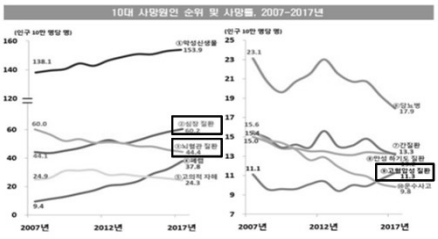
Vascular diseases



http://www.mayfieldclinic.com/PE-CarotidStenosis.htm

→ Vascular dieses: Sudden and unpredictable

- Stroke and heart disease in America
  - Stroke attacks ~800,000 Americans and kills ~140,000 victims each year; one in every 20 deaths, every 4 minutes.
  - Stroke is a leading cause of serious long-term disability, with an estimated annual cost of $34 billion each year
  - Ischemic strokes~ **87%**, when blood flow is blocked.
  - Heart disease (which includes Heart Disease, Stroke and other Cardiovascular Diseases) is the No. 1 cause of death in the United States, killing nearly 787,000 people in 2011.
    https://www.cdc.gov/mmwr/volumes/66/wr/mm6635e1.htm?s_cid=mm6635e1_w
- In Korea, 538,000 patients
  - 3.2 % increase and 29.6% increase in expense (1,684.7 billion KRW) in 2015, 77.8% over 60 years old



2017년 사망원인 통계, 2018년 9월 19일 보도

Non-invasive Imaging of Blood & Vessel

	CT imaging	MR imaging	Ultrasound (US) imaging
Real time	no	no	high frame rate
Cost	high	high	relatively low
Resolution	high	high	relatively low
Limitation	ionizing radiation	injection of contrast dye	small window operator dependency
Blood properties	no	no	yes

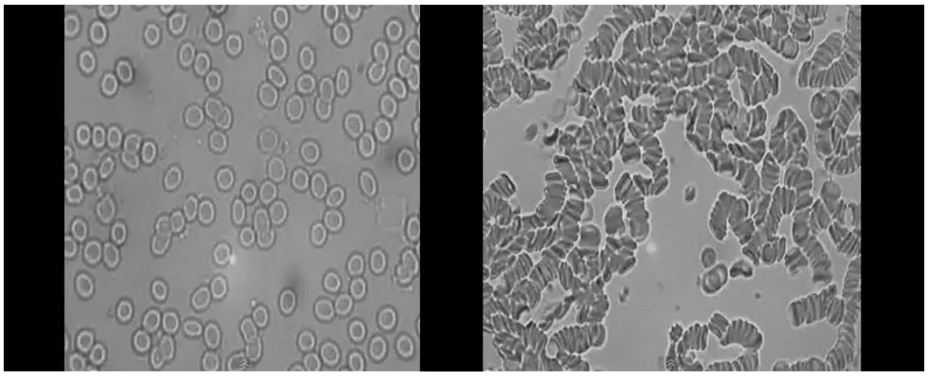
Ultrasound Blood Imaging

- Doppler imaging for blood flow speed
  - Doppler spectrum: spectrum at a position
  - Color Doppler: mapping in 2-D space
  - Power Doppler: vessel visualization in 2-D
- IntraVascular US (IVUS) imaging
  - Vessel wall and plague imaging
- Others
  - Speckle image velocimetry (SIV) or Echo-PIV Imaging
  - B-flow imaging: B-mode + Blood echogenicity by GE
- B-mode
  - *In vitro* B-mode imaging of blood & vessel
- Harmonic imaging
  - *In vivo* imaging of large human vessels & blood

Red Blood Cell (RBC) aggregation

Non-aggregating blood

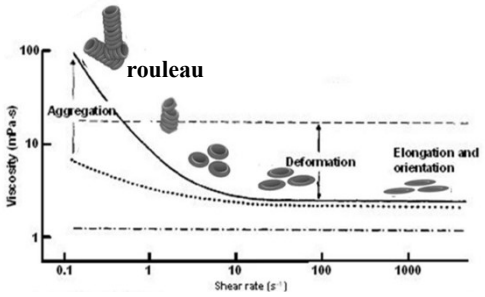
Aggregating blood



https://www.youtube.com/watch?v=nfUQNJWDFqQ

RBC aggregation

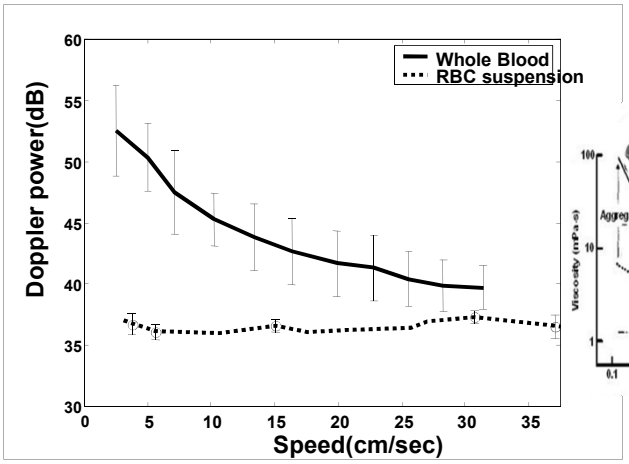
- Red Blood Cell (RBC) Aggregation
  - Importance in affecting blood viscosity & blood flow
  - Pathological importance: thrombus formation, hyper-lipidemea, atherosclerosis, chronic atrial arrythmia, diabetes, inflammation, etc.
- Ultrasound (US) imaging
  - Real time monitoring
  - Noninvasive technique

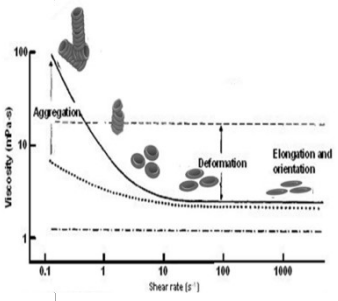


Rampling MW. Red cell aggregation and yield stress in Clinical blood rheology. Vol I edited by Lowe, GDO. CRC Press, 1988;45-64

Hemodynamics ←→ RBC aggregation ←→ US

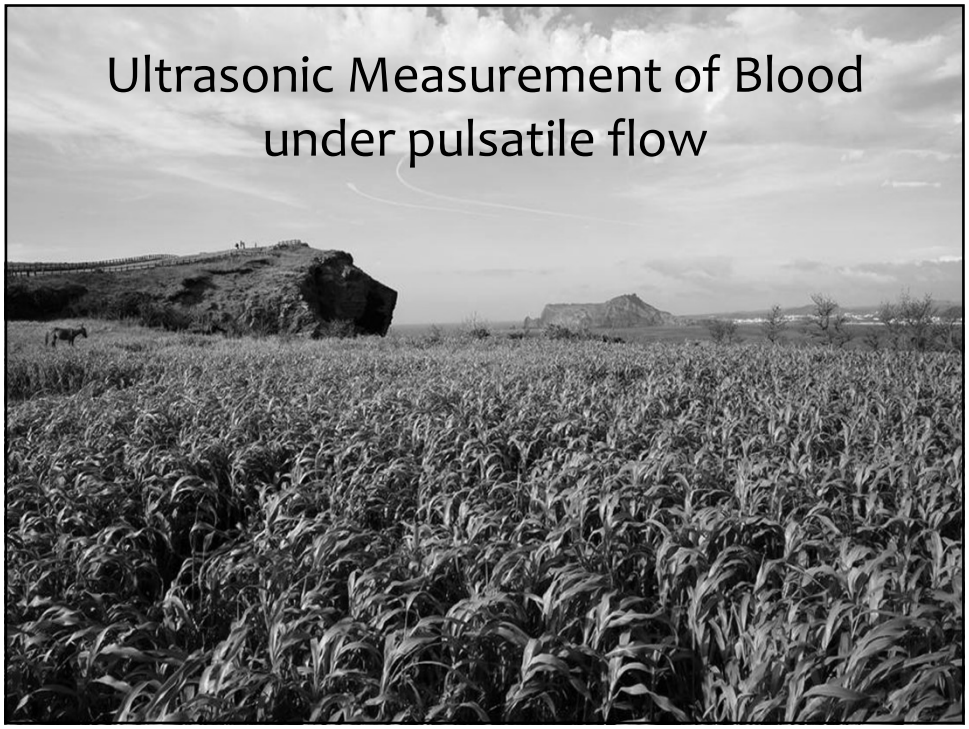
Steady Flow: Porcine Blood



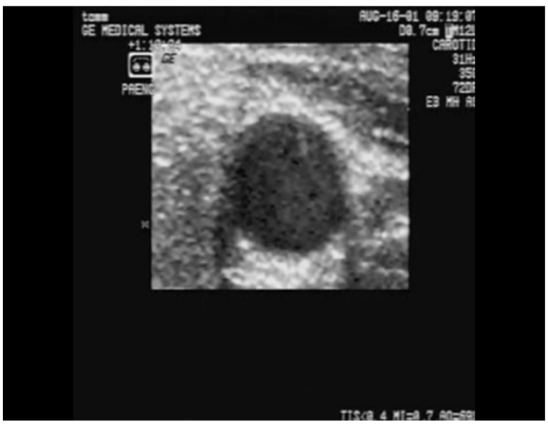


D.-G. Paeng et al., UMB, 2001, 27(9) 1245-1254

Ultrasonic Measurement of Blood under pulsatile flow

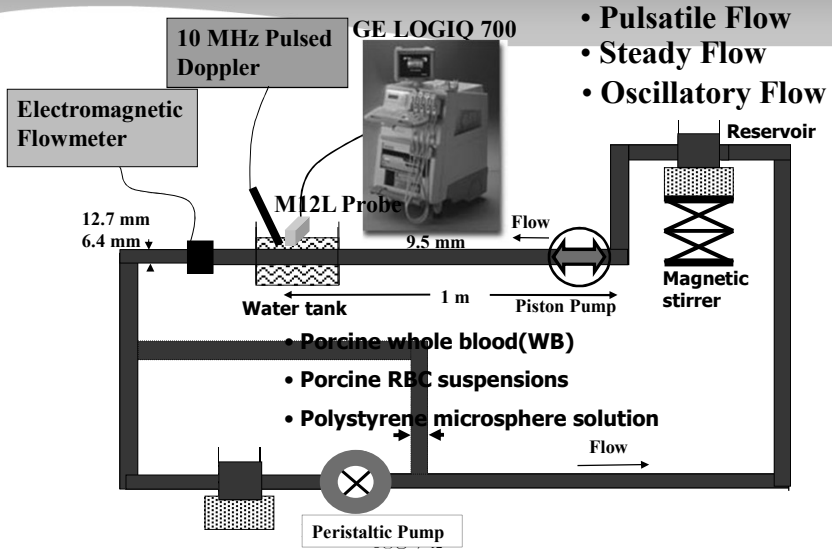


In vivo Dynamic Blood Imaging from Human Carotid Artery



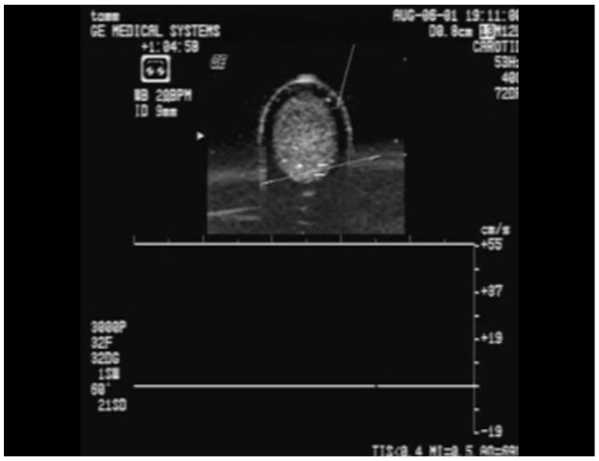
- GE LOGIQ 700 Expert System with an M12L probe of 13 MHz
- Observed only in harmonic images due to smaller echogenicity contrast between tissue and blood

In Vitro Experimental Setups



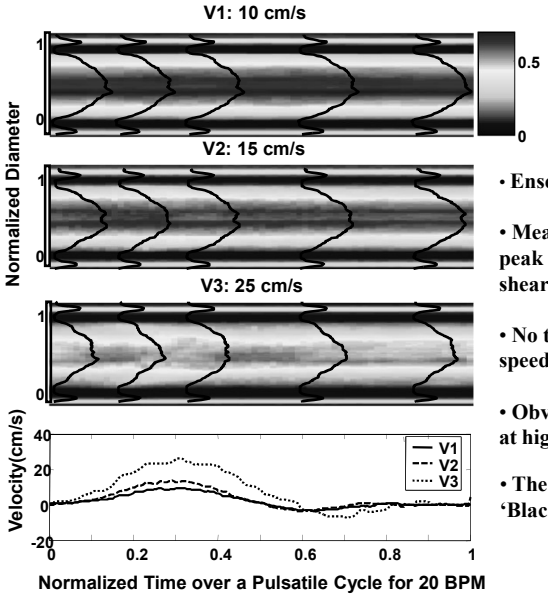
- Pulsatile Flow
- Steady Flow
- Oscillatory Flow

In vitro Dynamic Blood Imaging



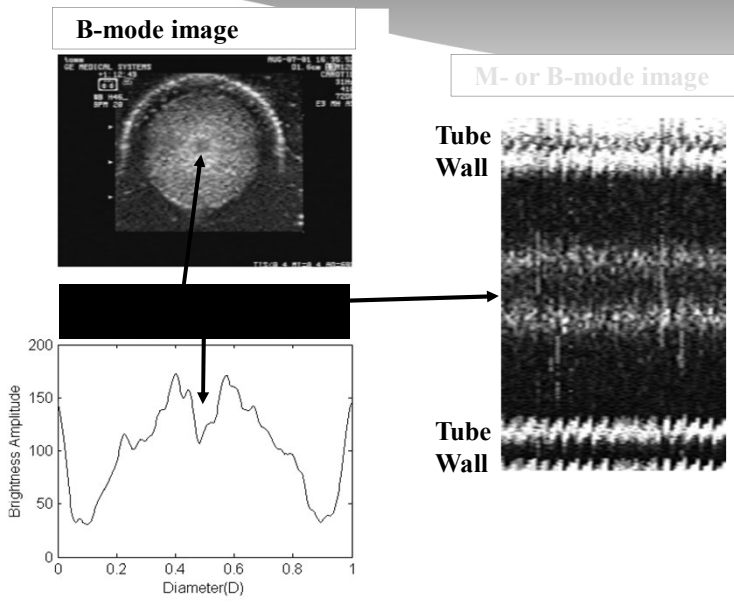
- **GE LOGIQ 700 Expert System**
- **M12L probe: 13 MHz**
- **B-mode cross sectional images**
- **Porcine whole blood**
- **Hematocrit: 40%, 12 ~ 46%**
- **Tube: ID 9.5 mm**
- **'Bright Collapsing Ring'**

Cyclic & Radial Variation of Echogenicity

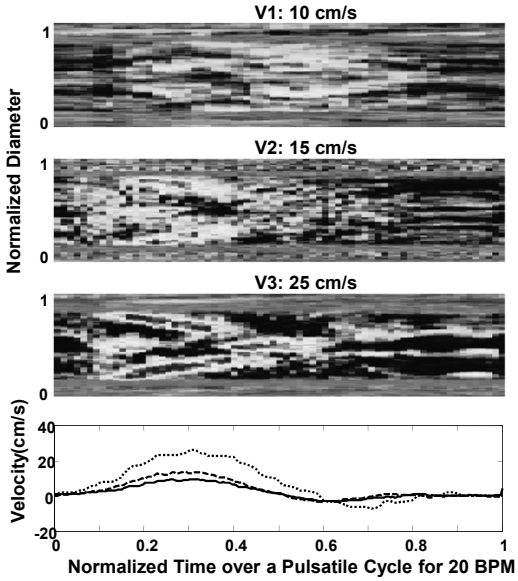


- **Ensemble averaged over 10 cycles**
- **Mean echogenicity decreased as peak speed increased since mean shear rate increased**
- **No temporal variation at lower speed**
- **Obvious variation during systole at higher peak speed**
- **The cyclic variation of the 'Black Hole' phenomenon**

'Black Hole' Phenomenon



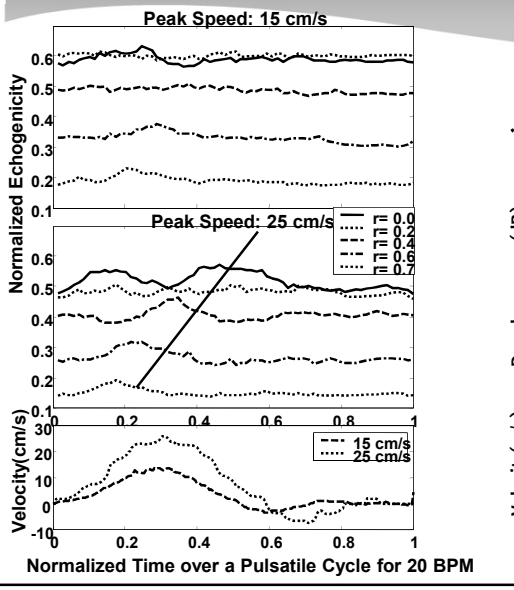
Velocity Dependence

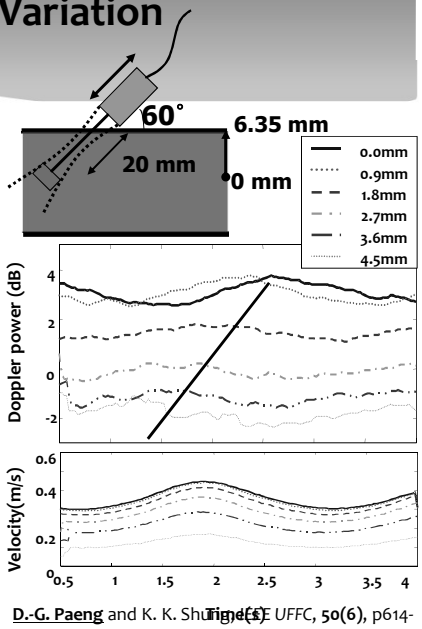


- No temporal variation at 10 cm/s peak speed
- 'Bright Collapsing Ring' phenomenon at higher peak speed
- Higher echogenicity during systole -> cannot be explained by shear rate
- Acceleration may enhance aggregation

D.-G. Paeng, R. Y. Chiao and K. K. Shung, *UMB*, **30(1)**, p45-55, 2004

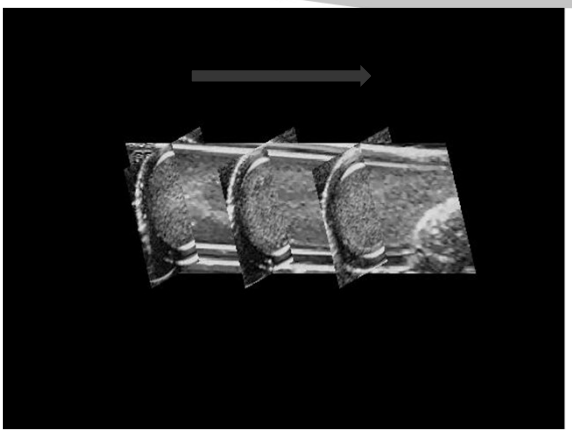
Radial & Temporal Variation





D.-G. Paeng and K. K. Shung, *IEEE UFFC*, **50(6)**, p614-22, 2003

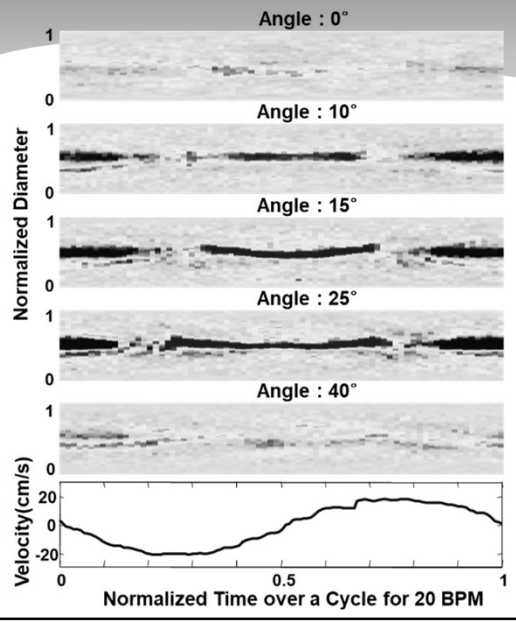
3-D 'Bright Ring' from Stenosis



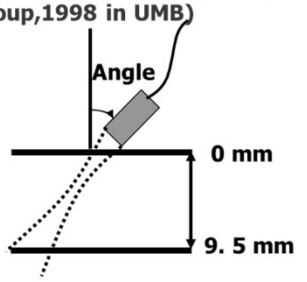
- Systole : The size of rouleaux is bigger at tube center
- Diastole : RBC rouleaux accumulation around the flow margin

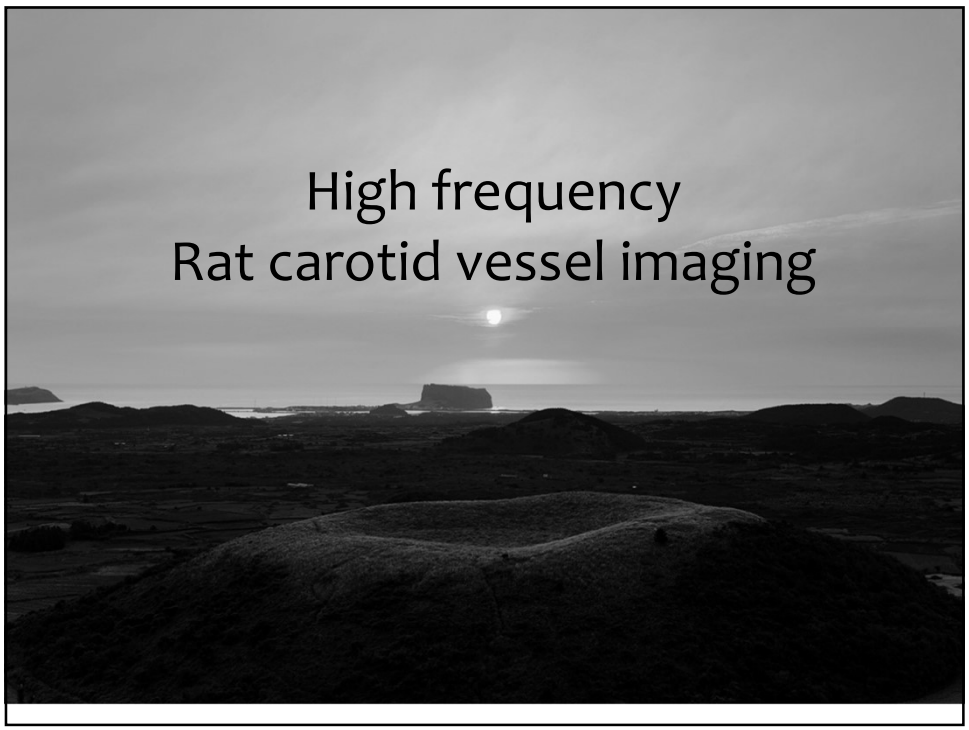
D.-G. Paeng, K.H. Nam, M.J. Choi and K.K. Shung, *IEEE UFFC*, **56(4)**, p880-5, 2009

Angle dependence



- Minimum cyclic variation at lower and higher angles
- Max variation at 25° of angle
- Radial distribution of rouleaux during acceleration (Cloutier group,1998 in UMB)

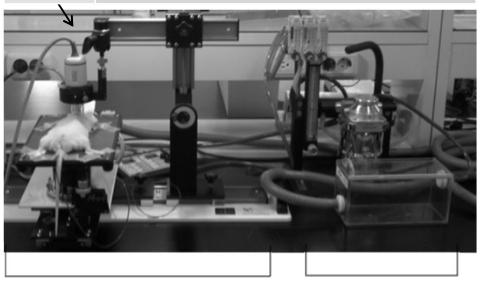




Experimental setup

Vevo 770
: High-frequency ultrasound imager

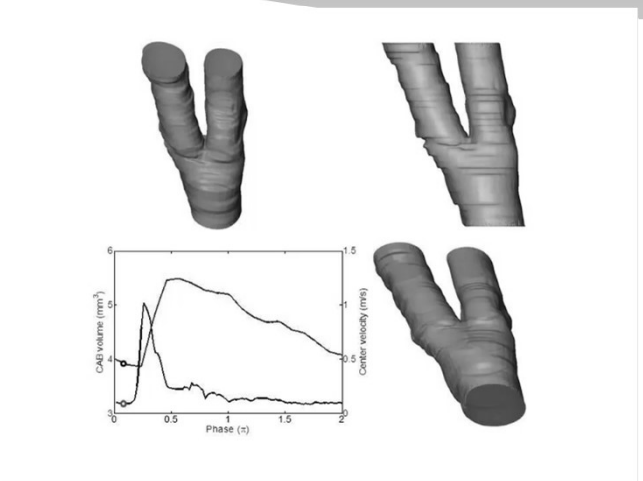
Probe	Center freq./axial res/ lateral res/focal length/depth of field
RMV 704	$40MHz$-$40\mu m$-$80\mu m$-$6mm$-$1.5mm$



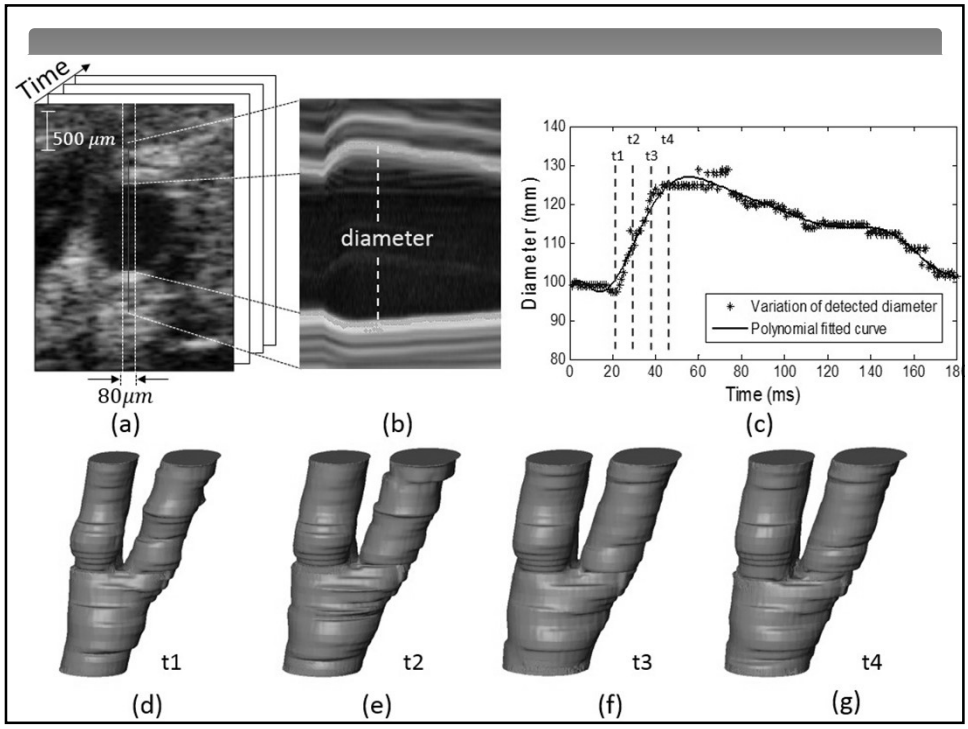
Animal stage
: ECG, XYZ positioner, temperature controller

Anesthesia system
: isoflurane inhalation

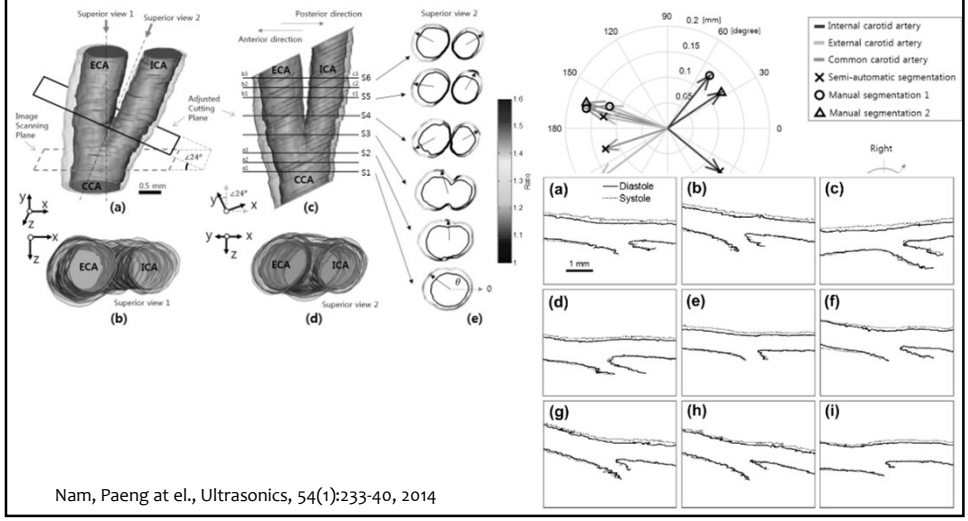
Rat Carotid Artery



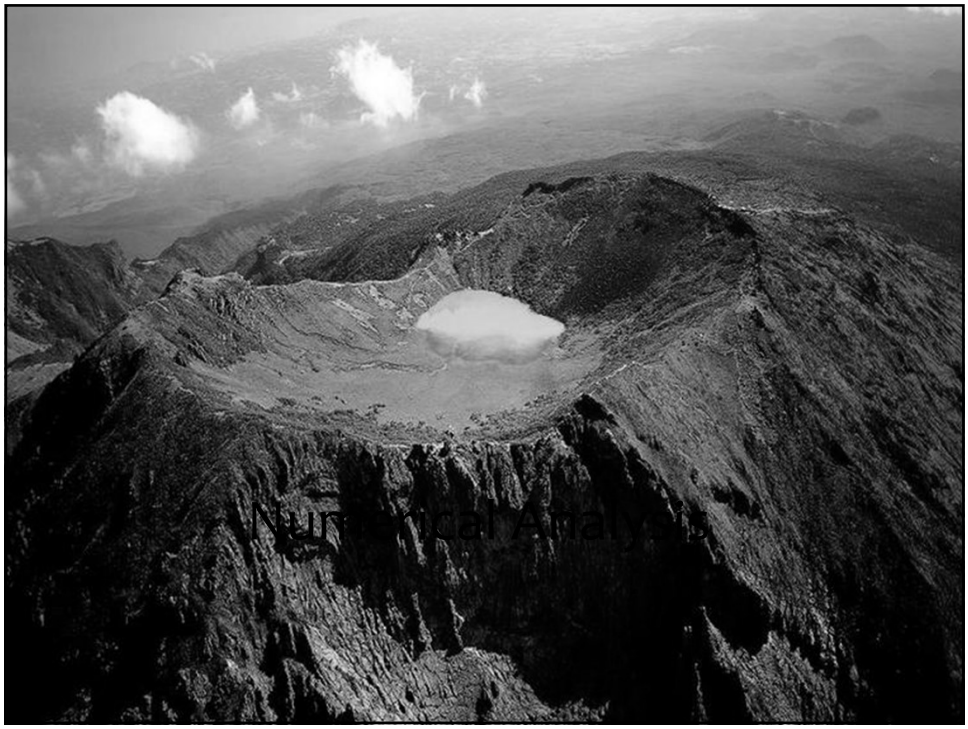
Jin, Nam & Paeng, Int J Cardiovasc imaging 2016



Asymmetric Expansion



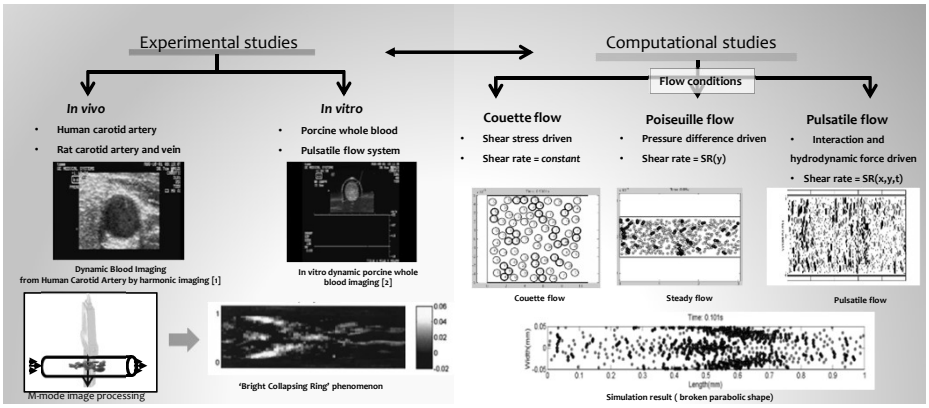
Nam, Paeng at el., Ultrasonics, 54(1):233-40, 2014



Literature review

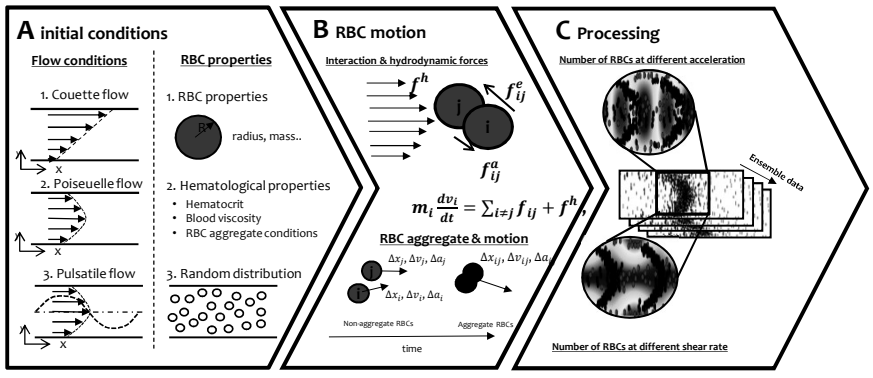
Approach	Flow type	Observation	Studies
Experiment	Steady flow	Microscopic	Reinke W, Gaehtgens P et al. American Jornal .1987 HL Goldsmith et al. Microvascular research, 1984 HL Goldsmith, T Karino Annals of the New York Academy of Sciences, 1977 Hudetz, Antal G. Microcirculation 4.2 ,1997
		Ultrasound	Y.W. Yuan and K.K.Sung, ASA, 1988 H L Goldsmith et al ,Circulation Research,1991 Louis Allard et al, IEEE, 1996 Yaling Liu, Wing Kam Liu, Science Direct, 2006
	Pulsatile flow	Microscopic	-
		Ultrasound	Cloutier G, Shung,KK,IEEE,1993 Paeng D et al, UMB, 2003 C.C. Huang, IEEE,2009
Simulation	Steady flow	-	Fenech M et al, Ann Biomed Eng ,2009 Lim, Brian, Peter AJ Bascom et al. Biorheology, 1779 Zhang, Junfeng, Paul C. et al, ournal of biomechanics, 2008
	Pulsatile flow		LEE CA, KONG.Q, Paeng DG, Biorheology ,2018

Experimental and Numerical Studies



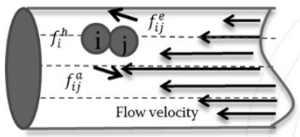
[1] Cyclic and radial variation of the echogenicity of blood in human carotid arteries observed by harmonic imaging (Dong_Guk Paeng et al. UMB, 2010)
[2] Echogenicity variations from porcine blood :"the bright collapsing ring" under pulsatile flow (Dong-Guk Paeng et al, UMB,2003)
[3] Depletion-model-based numerical simulation of the kinetics of red blood cell aggregation under sinusoidal pulsatile flow (CheognAh Lee, et al, biorheology , 2018)

Simulation methods



Depletion-model-based numerical simulation of the kinetics of red blood cell aggregation under sinusoidal pulsatile flow

Mechanical Model



Aggregation Force

The 2nd Newton's law:

$$m_i \frac{dv_i}{dt} = \sum_{i \neq j} f_{ij}^e + f_{ij}^a + f_i^h$$

Elastic Force

Hemo-dynamic Force

TABLE 1. Constitutive parameters for three selected aggregation forces.

	Agg^-	Agg^+	$Agg^+_{s.n}$
δ_0: Zero-force length (nm)	11	11	11
DA: Energy (J)	10^{-25}	10^{-24}	2×10^{-24}
B: Scaling factor (m^{-1})	10^7	10^7	5×10^6

$$f_{ij}^a = -\frac{\partial \Phi_{ij}}{\partial \delta_{ij}} A = 2DAB\left(e^{2B(\delta_0-\delta_1)} - e^{B(\delta_0-\delta_1)}\right)\mathbf{n}$$

Φ_{ij}=D $\left(e^{2B(\delta_0-\delta_1)} - 2e^{B(\delta_0-\delta_1)}\right)$, *Morse* potential

DA--- Energy, B---Scaling factor

$$\boldsymbol{f_{ij}^e = k(2R-d)^{\frac{2}{3}}\mathbf{n} \quad if\ d < 2R \qquad = 0 \quad otherwise}$$

$$f_i^h(t) = -6\pi\mu R U_p - 6\pi\mu R\left(\frac{a^2}{\pi\nu}\right)^{\frac{1}{2}} \int_{-\infty}^{t} \frac{\dot{U}_p(s)ds}{(t-s)^{\frac{1}{2}}} - \frac{2}{3}\pi\rho R^3 \dot{U}_p(t)$$

Drag force | Basset force | Added mass force

Fenech, M. Annals of Biomedical Engineering 37(11): 2299-2309. 2009.

29

Steady Flow Results

(1) Steady flow condition

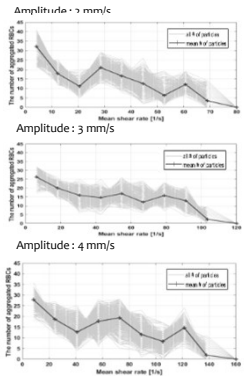
Velocity :

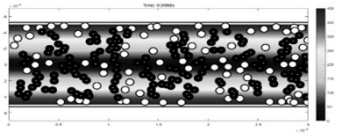
$u(y) = A_f\left(1 - \frac{4y^2}{h^2}\right)$ [m/s]

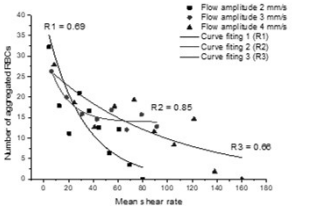
Shear rate :

$SR(y) == A_f\left(\frac{8y}{h^2}\right)$ [1/s]

- Amplitude : 2 mm/s
- Amplitude : 3 mm/s
- Amplitude : 4 mm/s

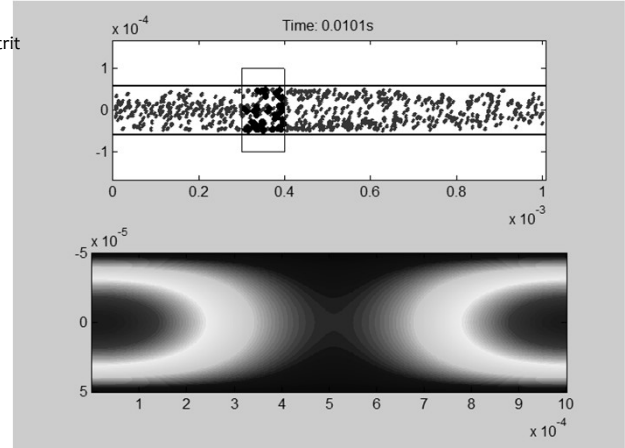






Particle Model Simulation

Condition:
Particles: 596 of 40% hematocrit
Velocity: 0.5 cm/s – 3.5 cm/s
Stroke rate: 60 bpm

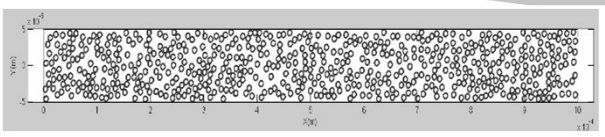


$v(t,x,y) = v_o(t,x)*\{1-(2y/h)^2\}$
$v_o(t,x) = A*\sin(\omega t-kx+\varphi) + B$

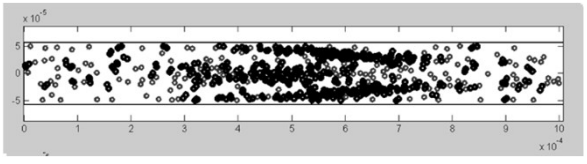
x-direction velocity

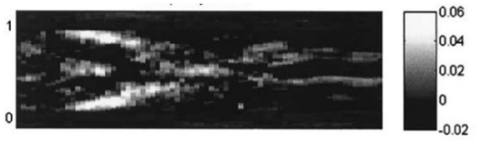
Simulation vs Experiments

T=0s



T=0.01s, 0.05s, 0.1s



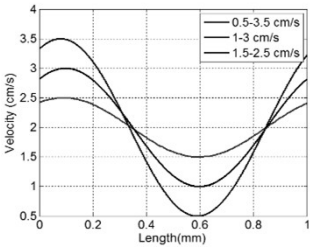


RBC number: 596
X_boundary=1mm
Y_boundary=0.1mm
Hematocrit: 30%

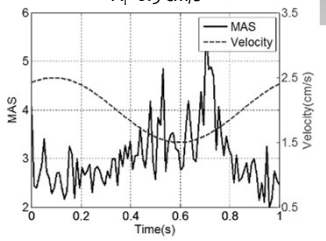
'Bright Collapsing Ring'

Paeng, D. and R. Y. Chiao, et al. "Echogenicity variations from porcine blood I: the "bright collapsing ring" under pulsatile flow." Ultrasound in Medicine & Biology 30(1): 45-55. 2004.

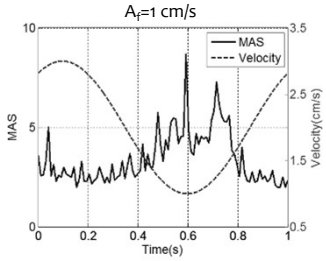
Velocity amplitude A



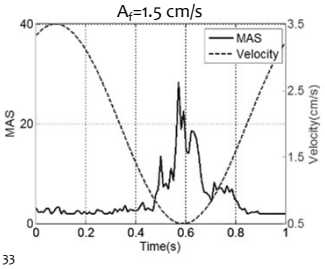
A_f=0.5 cm/s



A_f=1 cm/s



A_f=1.5 cm/s



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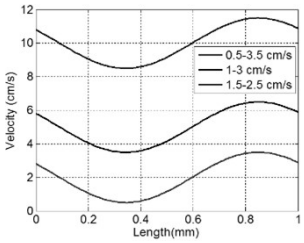
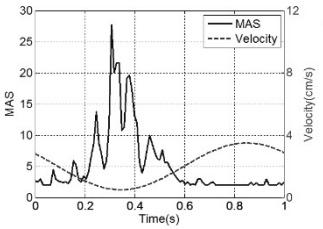
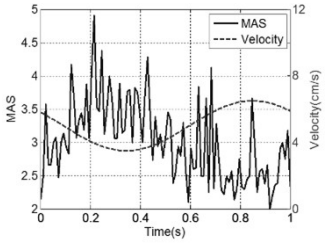
Mean flow velocity B

B_f = 2 cm/s

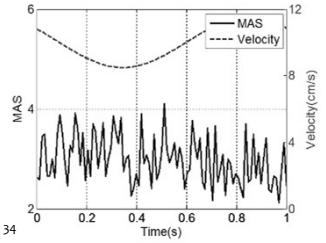




B_f = 6 cm/s



B_f = 10 cm/s



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Summary

- Ultrasonic observation of RBC aggregation
  - ‘Bright collapsing ring’ in cross sectional view
  - Parabolic shape in longitudinal view
  - ‘Black hole’ phenomenon
  - Angular dependence
  - Asymmetric rat artery expansion
- Numerical analysis
  - Validation of shear rate dependence under steady flow
  - Parabolic shape formation during a pulsatile cycle