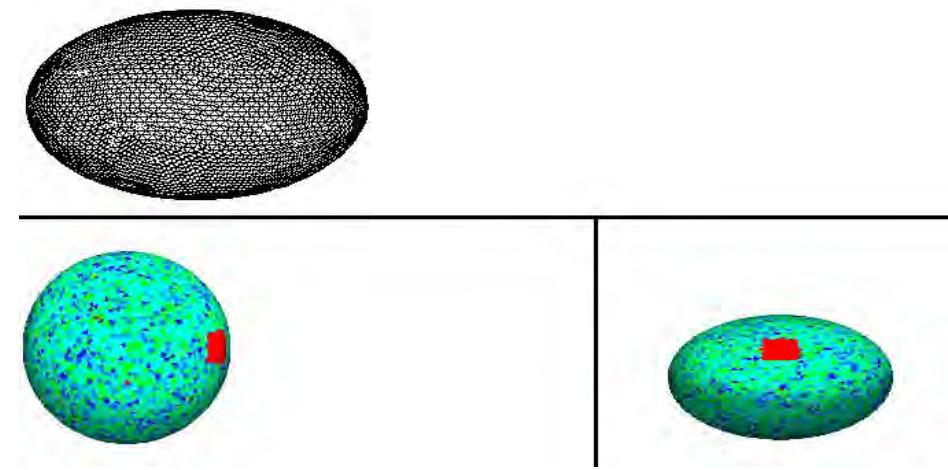
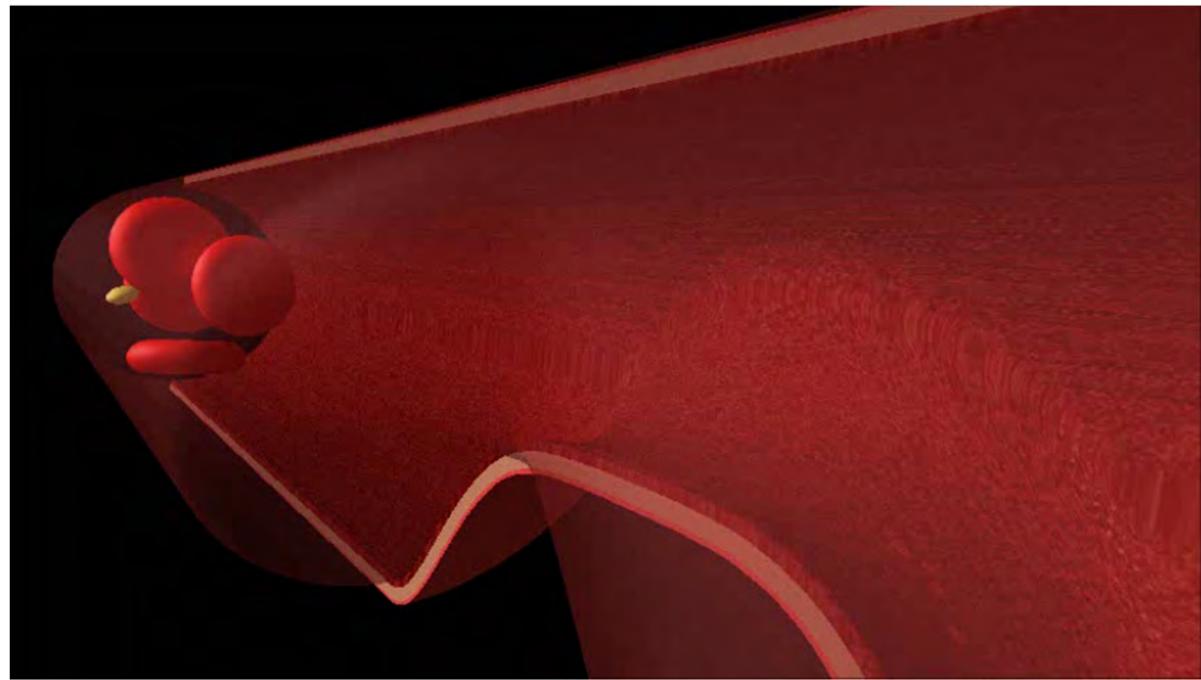
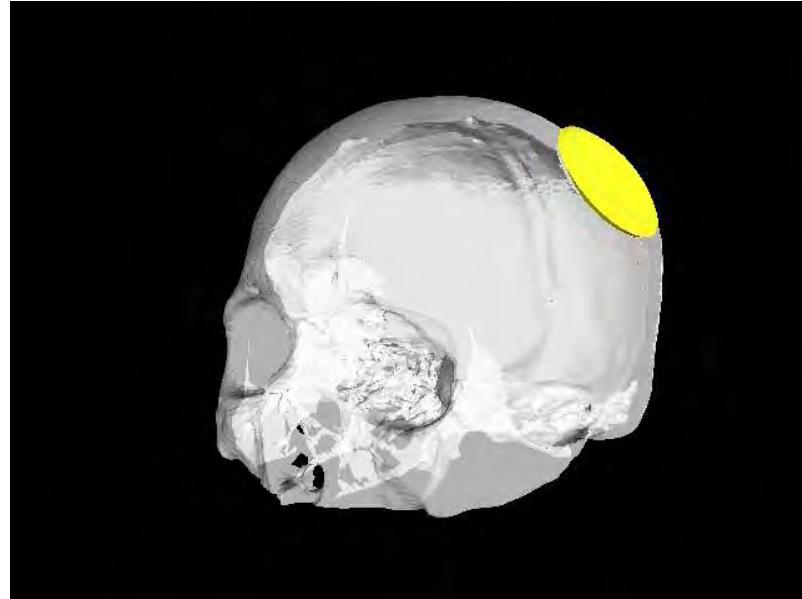


# 予測医療に向けた階層統合シミュレーション

東京大学 大学院工学系研究科  
機械工学専攻 & バイオエンジニアリング専攻  
高木 周



# 階層統合生体力学シミュレーションとその医療応用

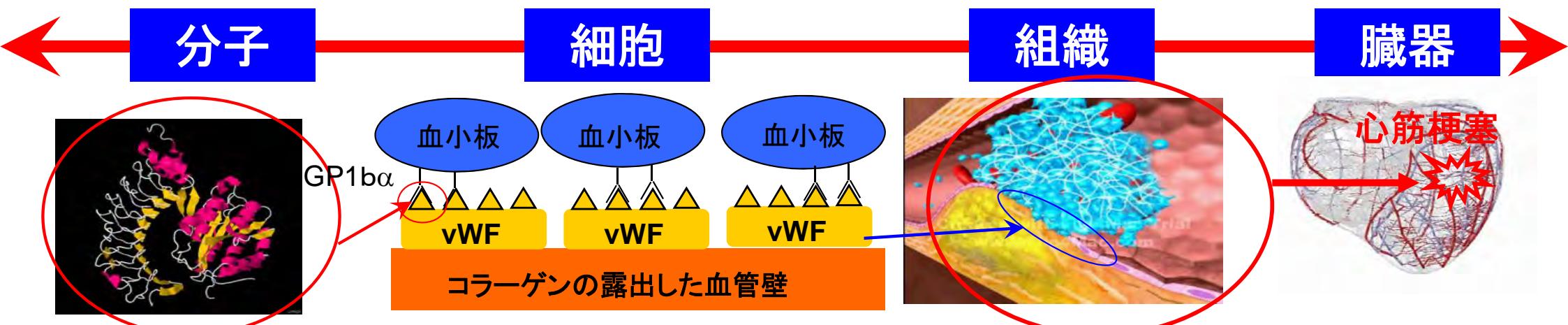
## シミュレーションによる病態予測と治療支援

方針:

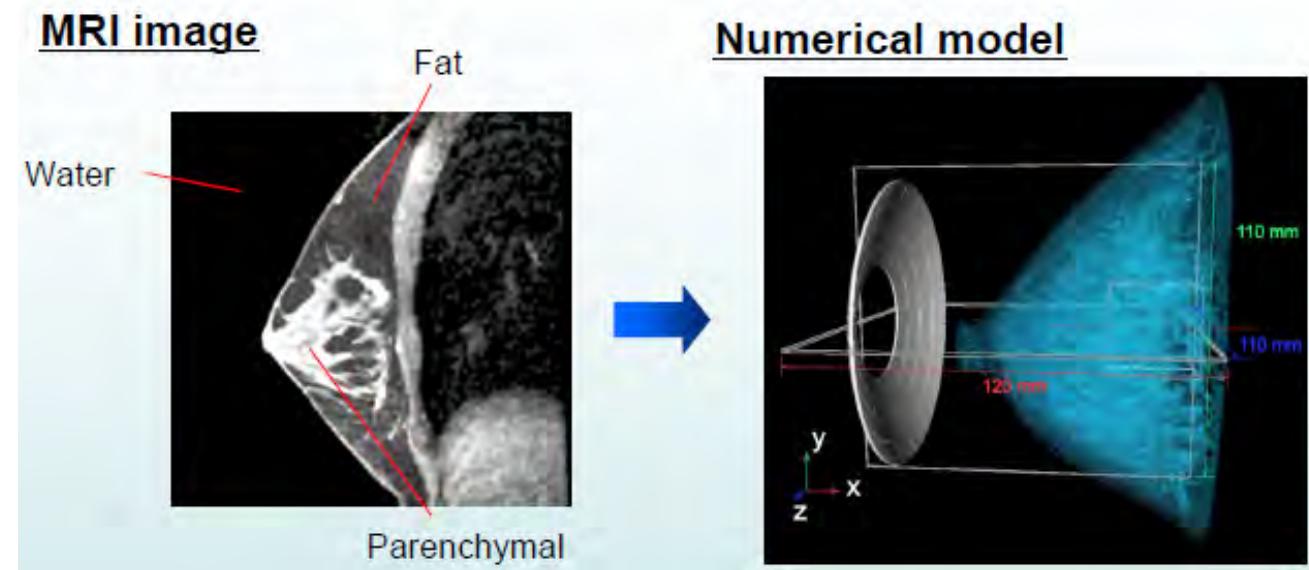
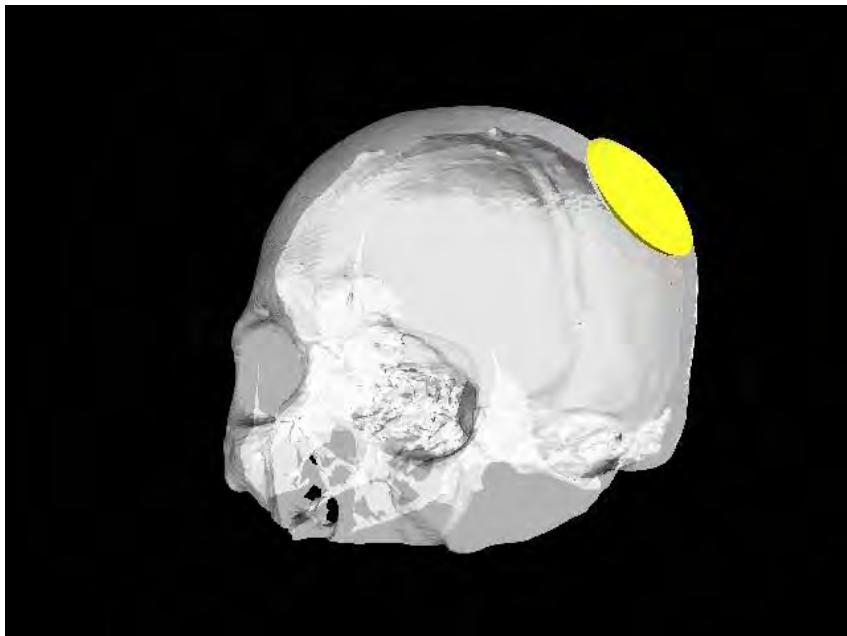
- ・ミクロ(分子生物学, 細胞動態)とマクロ(病態予測, 治療法検討)を結びつける.
- ・マクロ(病態)からミクロ(分子)へトップダウンのアプローチ.  
(病態をシミュレートしながら, ミクロ因子の影響を調べる)



### 階層統合シミュレーションによる新しい予測医療の構築

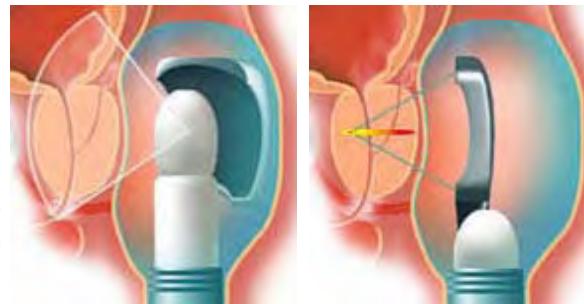


# For the Design and Development of High Intensity Focused Ultrasound Therapy (HIFU) Device



# High Intensity Focused Ultrasound therapy

- Prostate cancer
- Breast cancer

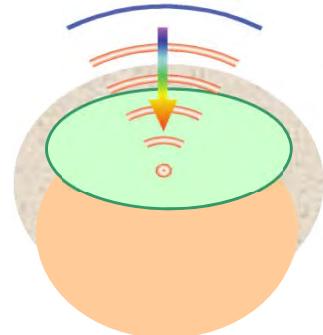


<http://www.prostatecancercentre.co.uk/treatments/hifu.html>

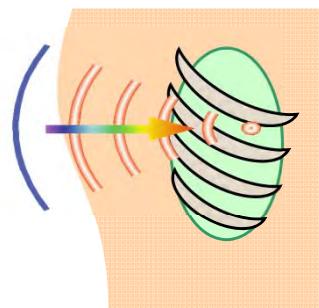


HIFU therapy has been developed for the treatment of deeply-placed cancer.

Brain cancer



Liver cancer



Displacement of focal point due to the reflection and refraction of ultrasound at the interfaces of bones



<http://www.imasonic.com/>

Control of the focal point by an array transducer

# Recent Development of HIFU Device

## Products

(1) InSightec(GE) : Exablate 4000

Brain Treatment, Phase Control by Array Transducer

(1024 elements),

MR-Guided, (MR-ARFI under development)



(1) InSightec: Exablate 4000

(2) Phillips: Treatment of uterus myoma,

MR-Guided

(3) Siemens: collaborating with

Chongqing(重慶) HIFU, MR-Guided

(4) Supersonic Imaging: collaborating

with Prof. Fink (Inserm), MR-ARFI

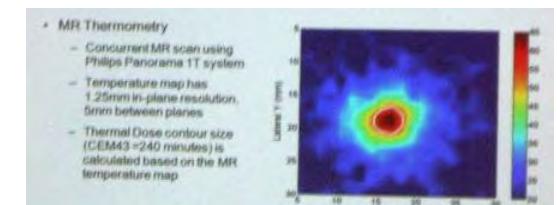


(4) 256 Channels

(5) University of Michigan, Profs, C. Cain, B. Fowlkes, Z. Xu

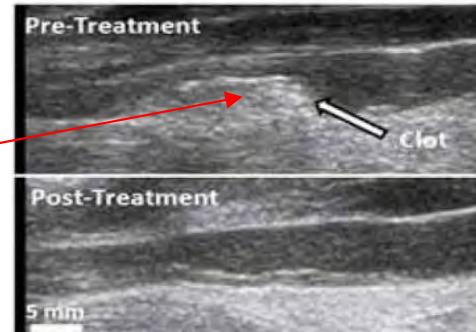
**Histotripsy** (**Cavitation** induced Treatment)

Utilization of Cavitation, to Control the Focused Area



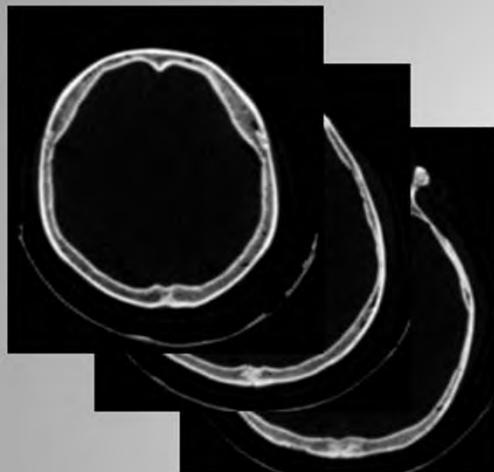
(2) Phillips; Temperature Monitoring by MRI

(5) Plaque:  
blown away

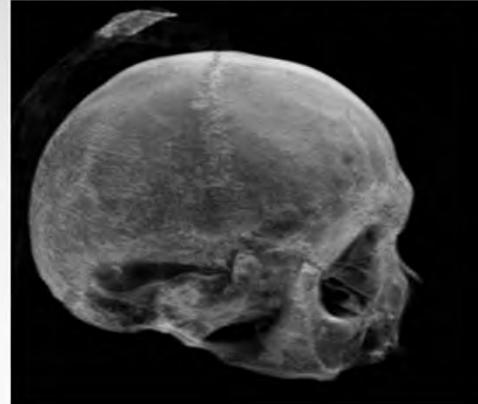


# HIFU simulator

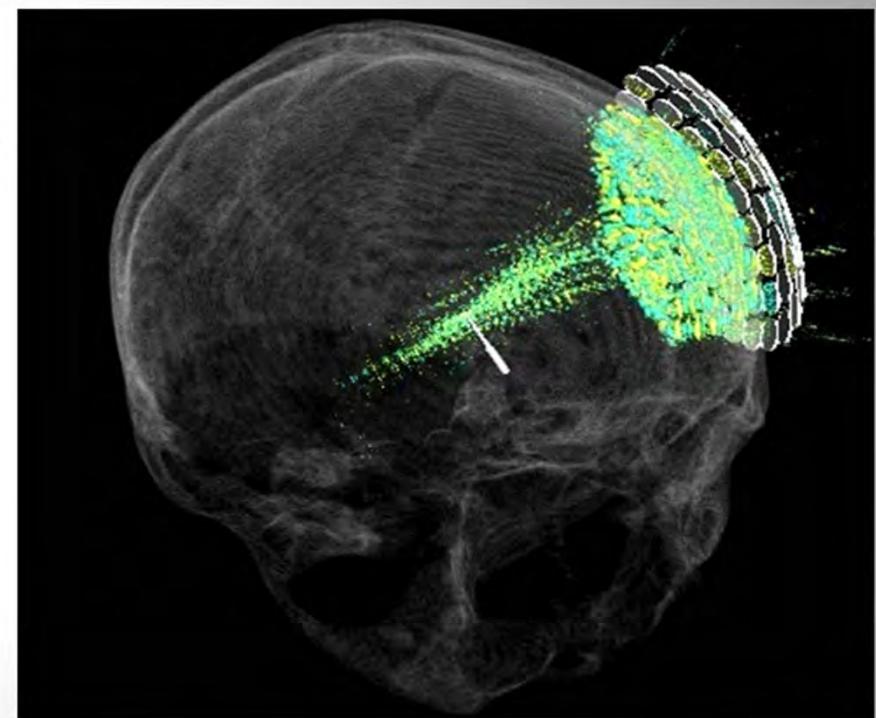
CT/MRI



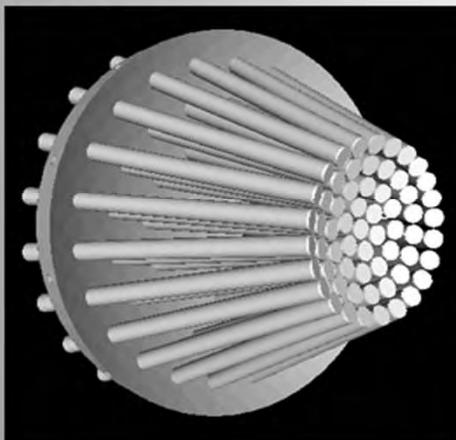
Voxel Phantom



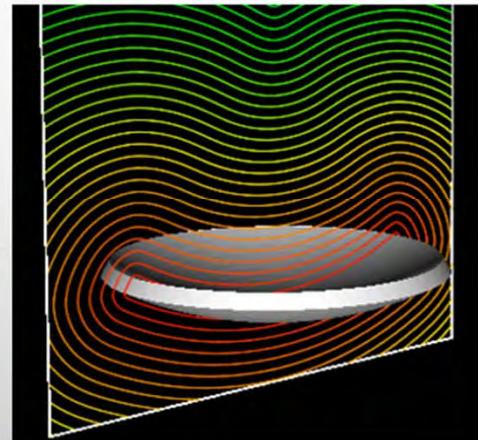
HIFU Simulation



CAD

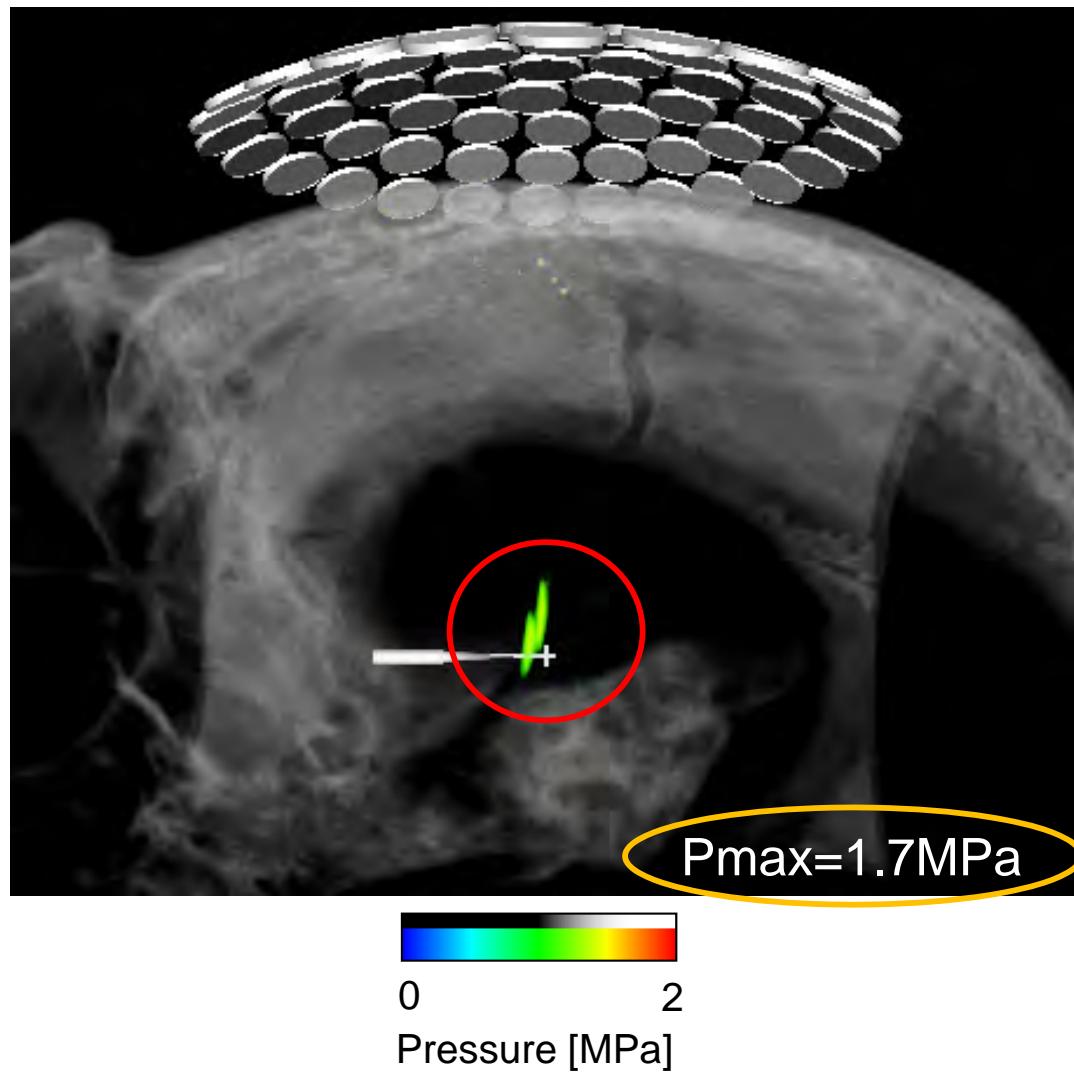


SDF

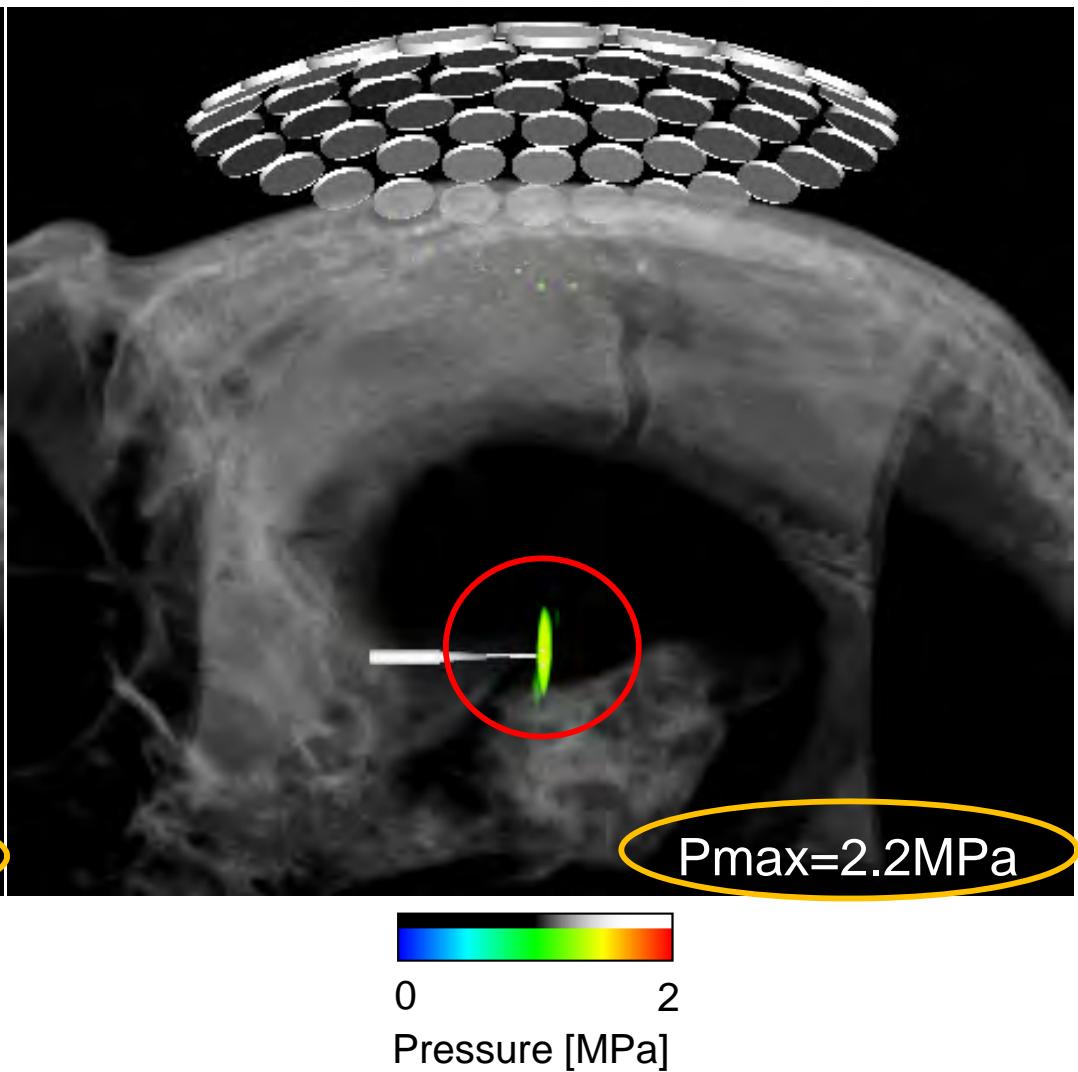


# Comparison of the focal point

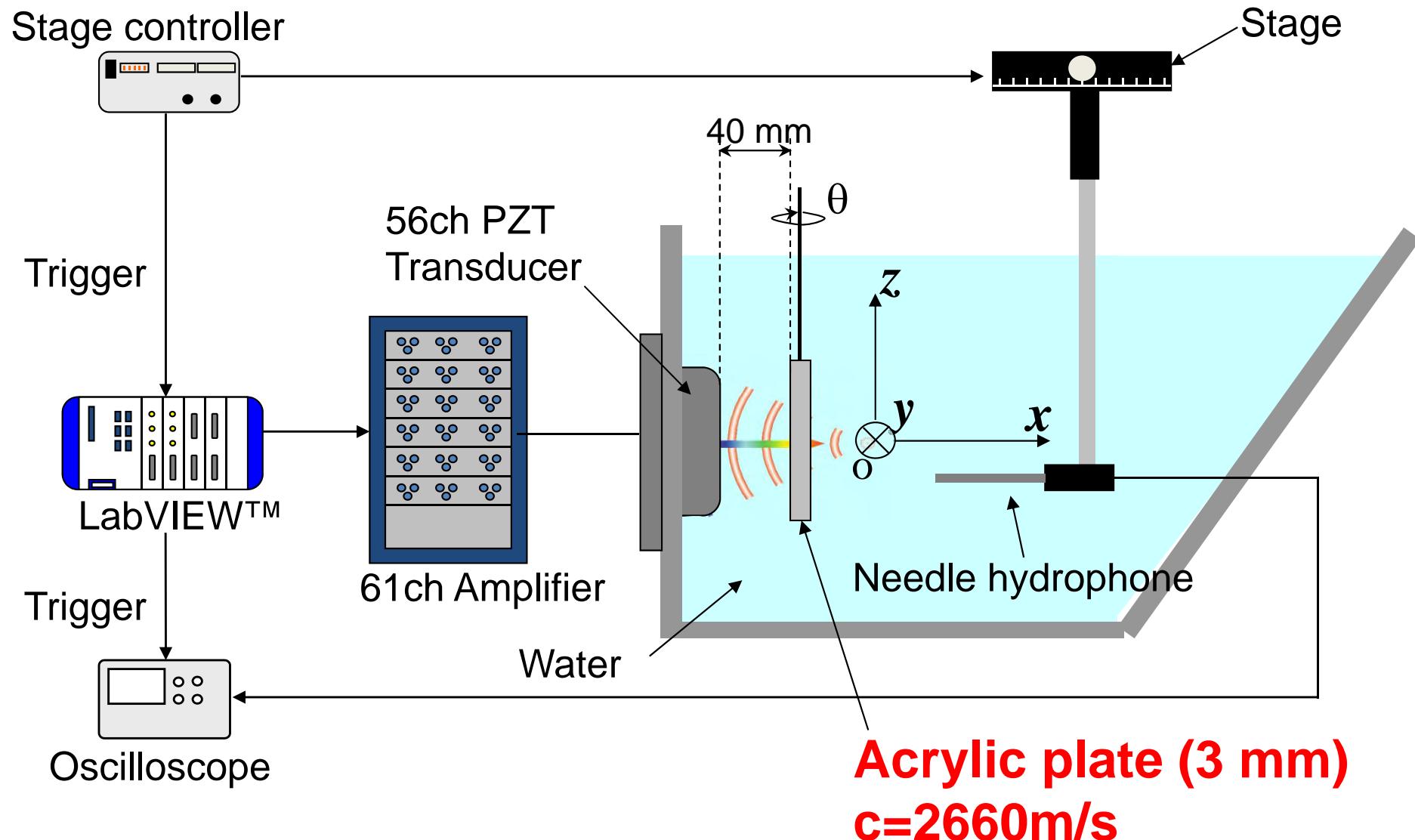
Without phase delay



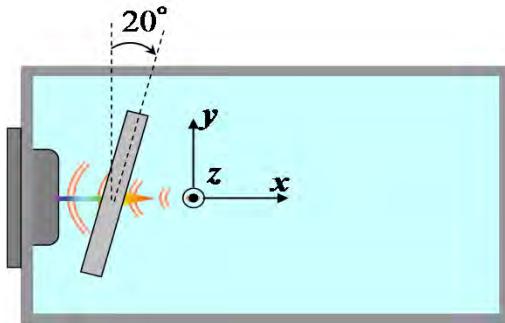
With phase delay



# Experimental Apparatus



# Ultrasound through acrylic plate (20deg)

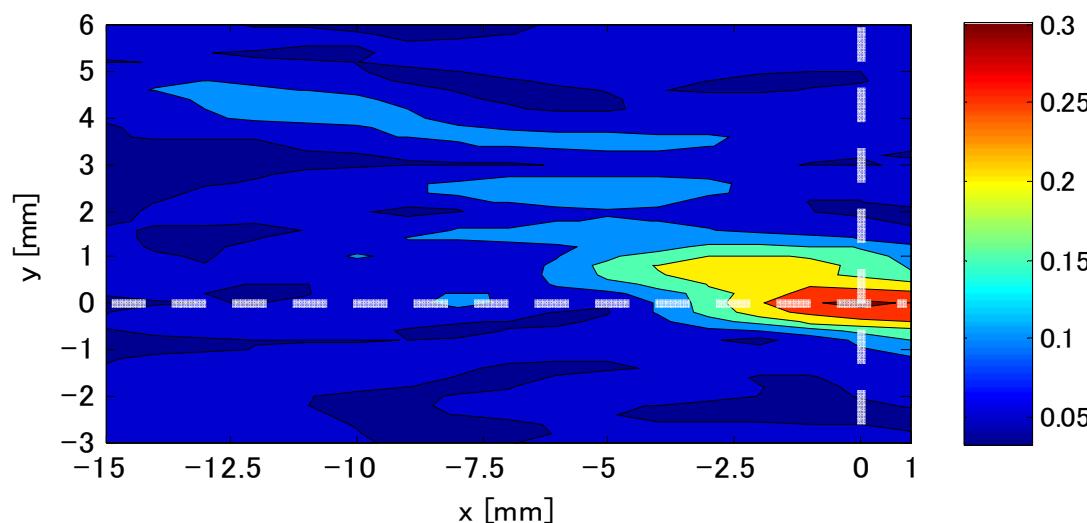
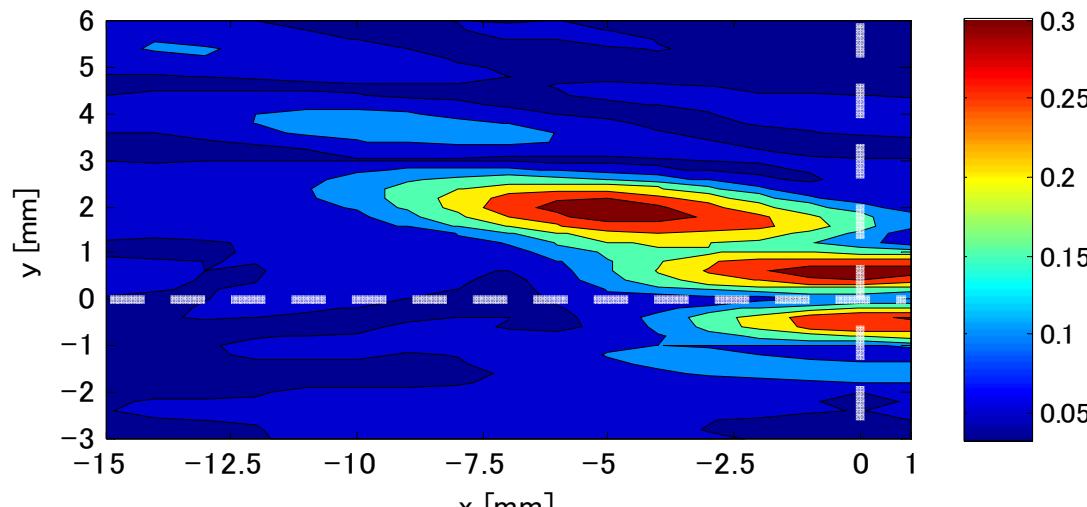


w/o phase shift



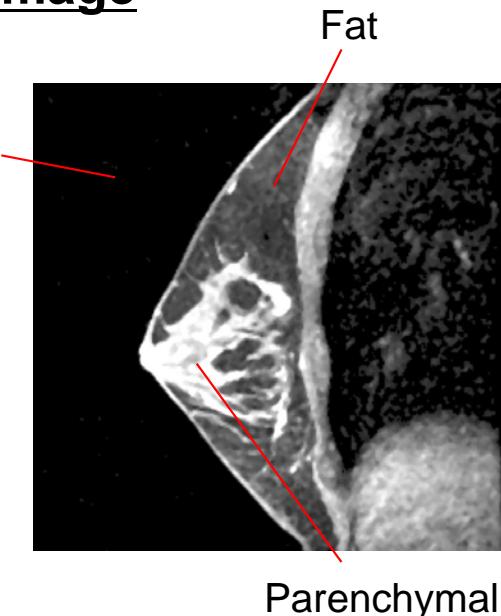
w/ phase shift

Acrylic plate is arranged with the angle of 20 degrees.

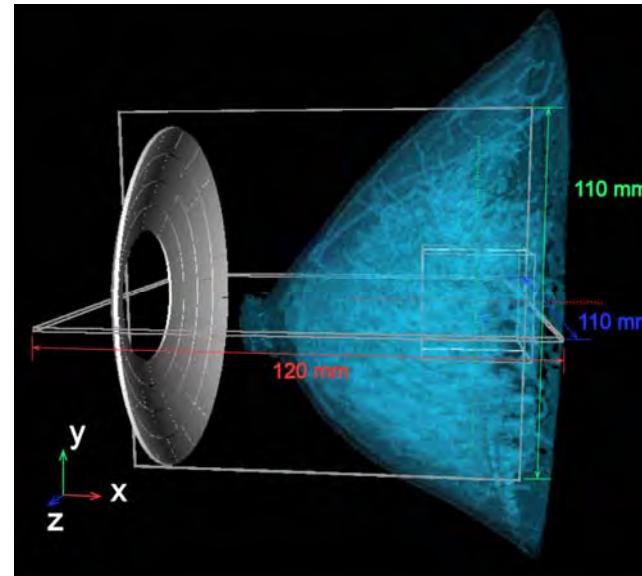


# HIFU Simulation for Focus Control for Breast Cancer using MRI data

## MRI image



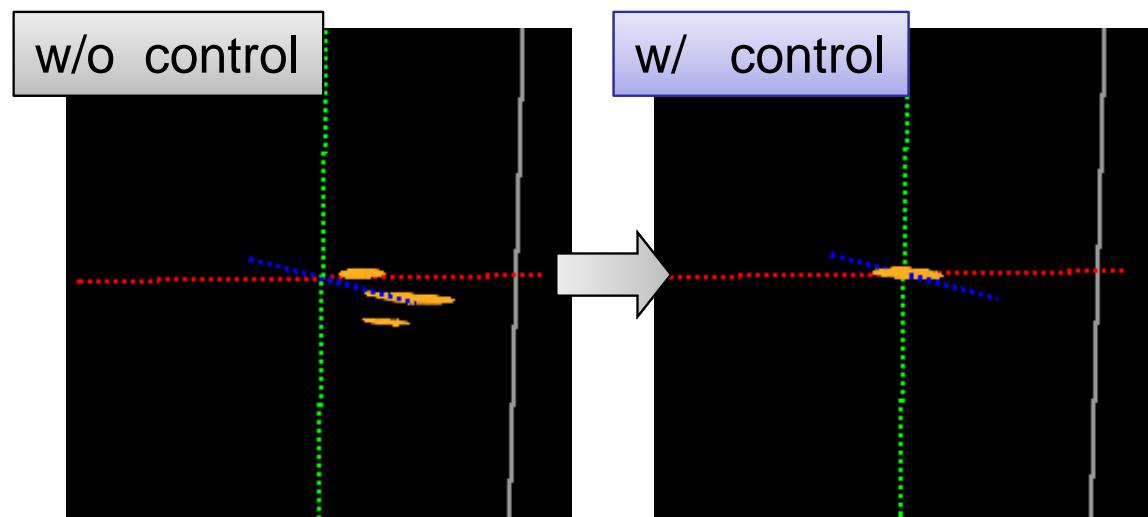
## Numerical model



- 56ch transducer
- Focal distance 100 mm
- Frequency 2 MH
- 3D orthogonal mesh
- Size 120x110x110 mm
- 1200x1100x1100 grid
- 8x4x4 sub domains

	Speed of Sound [m/s]	Density [kg/m <sup>3</sup> ]
Fat	1465 <sup>[1]</sup>	985 <sup>[1]</sup>
lacteal gland	1547 <sup>[2]</sup>	1032 <sup>[2]</sup>
connective tissue	1615 <sup>[1]</sup>	1090 <sup>[1]</sup>

[1] ICU REPORT 61, [2] T. D. Mast,, 2000



# **Parkinson's Disease Simulation**

**Close collaboration among teams of**  
**K. Doya(OIST),**  
**Y. Nakamura(Univ. Tokyo),**  
**T. Nomura(Osaka Univ.),**  
**and S. Takagi (Univ. Tokyo)**

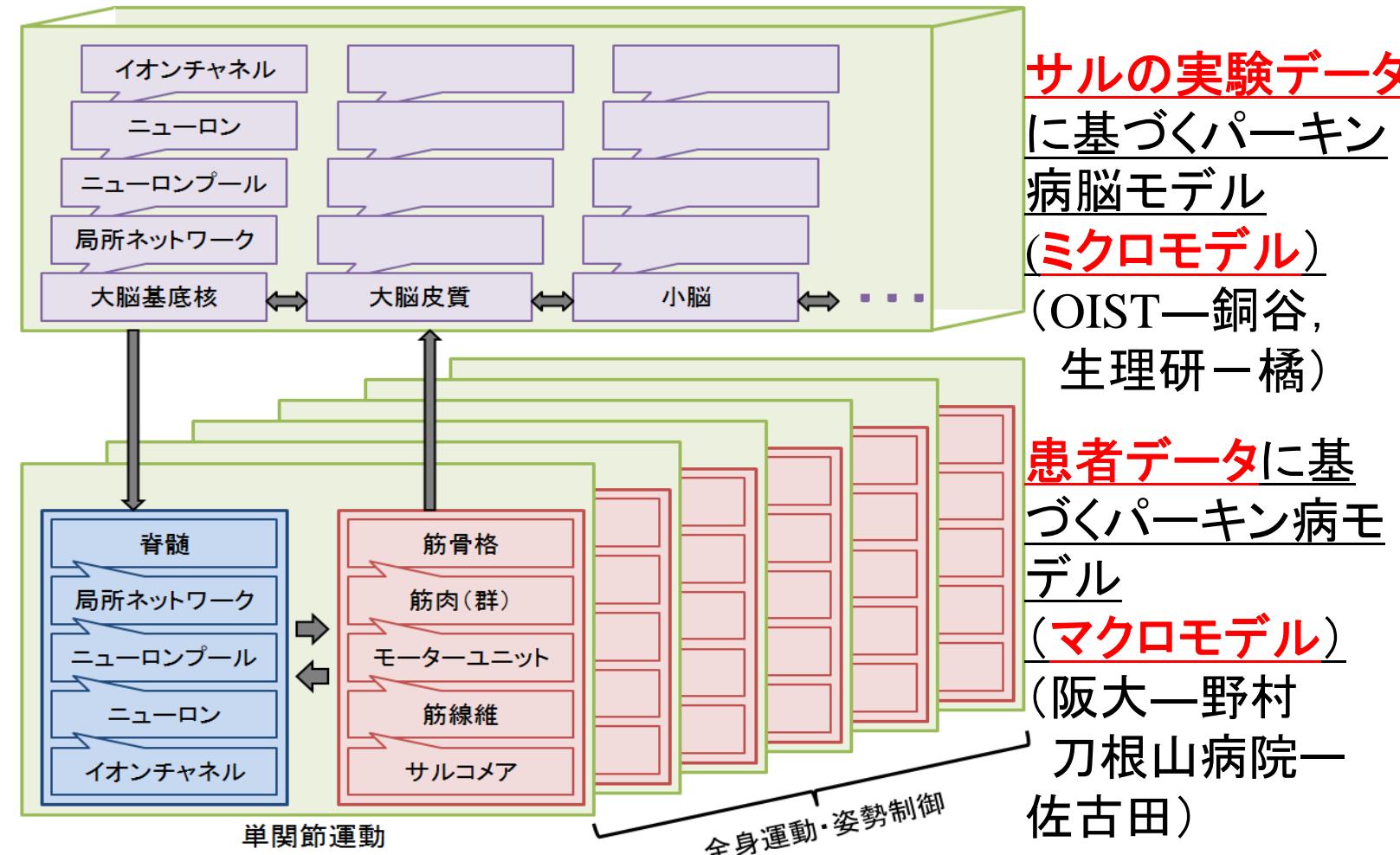
# 研究実施体制 (筋骨格-脳神経系 階層統合シミュレーション)

パーキンソン病の階層統合シミュレーションによる病態理解と  
治療応答予測および運動と脳の関係のモデル化

大脳基底核-皮質  
-小脳神経回路  
大規模シミュレーション  
(OIST-銅谷)

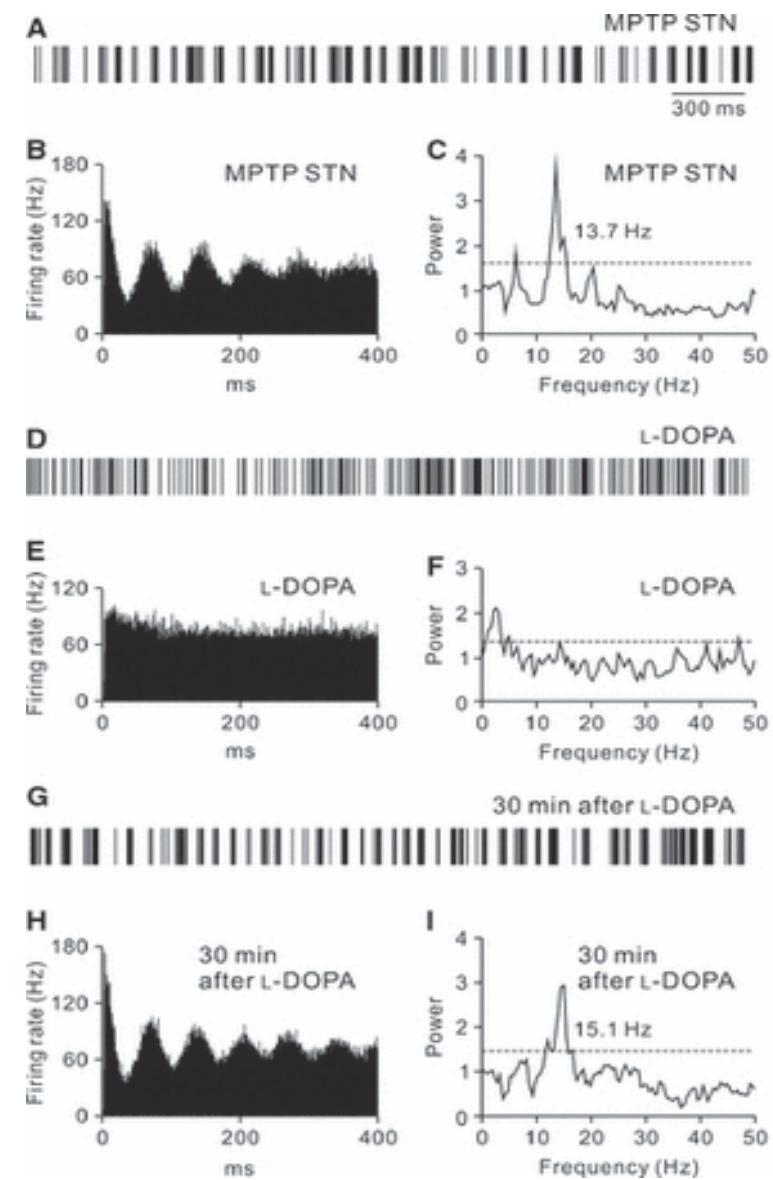
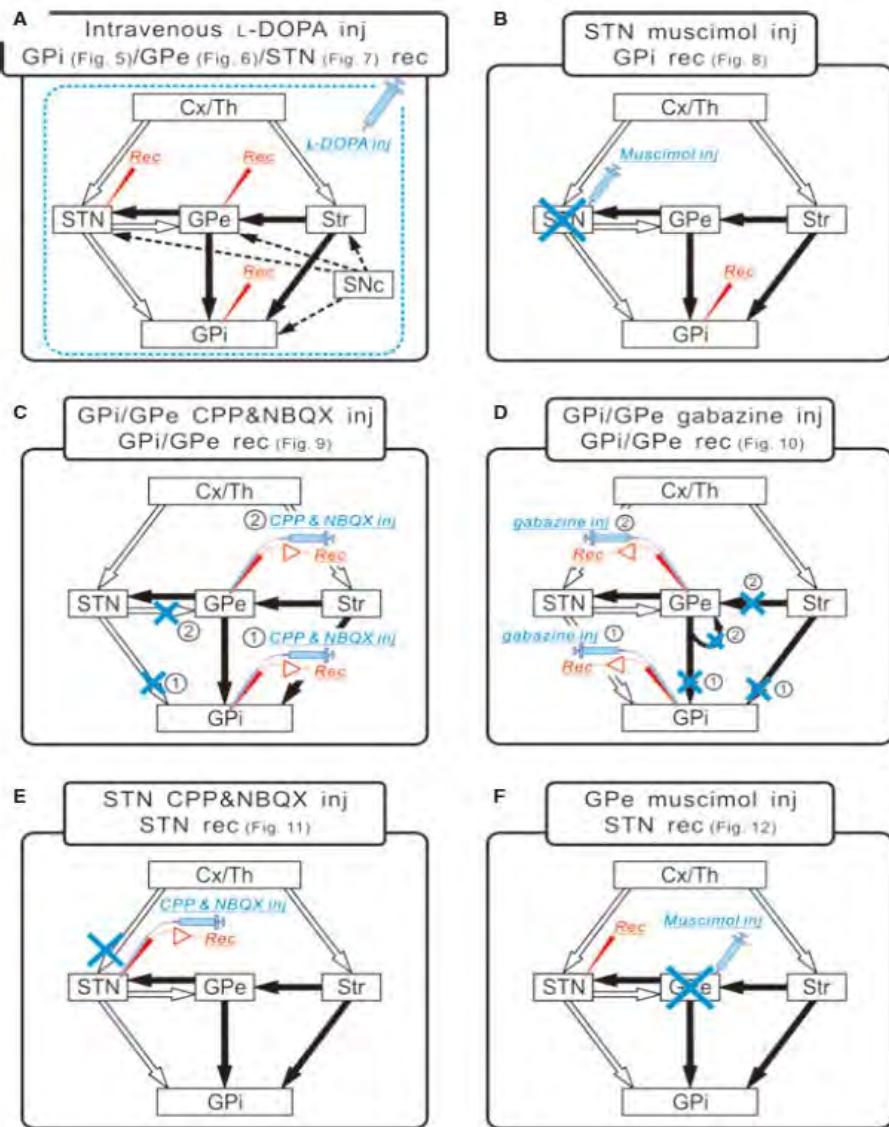
脊髄反射の  
神経回路モデル  
(東大-中村, 高木)

筋繊維レベルからの  
筋収縮の有限要素解析  
(東大-高木)



全身の分布質量筋モデルによる姿勢制御予測(東大-中村)

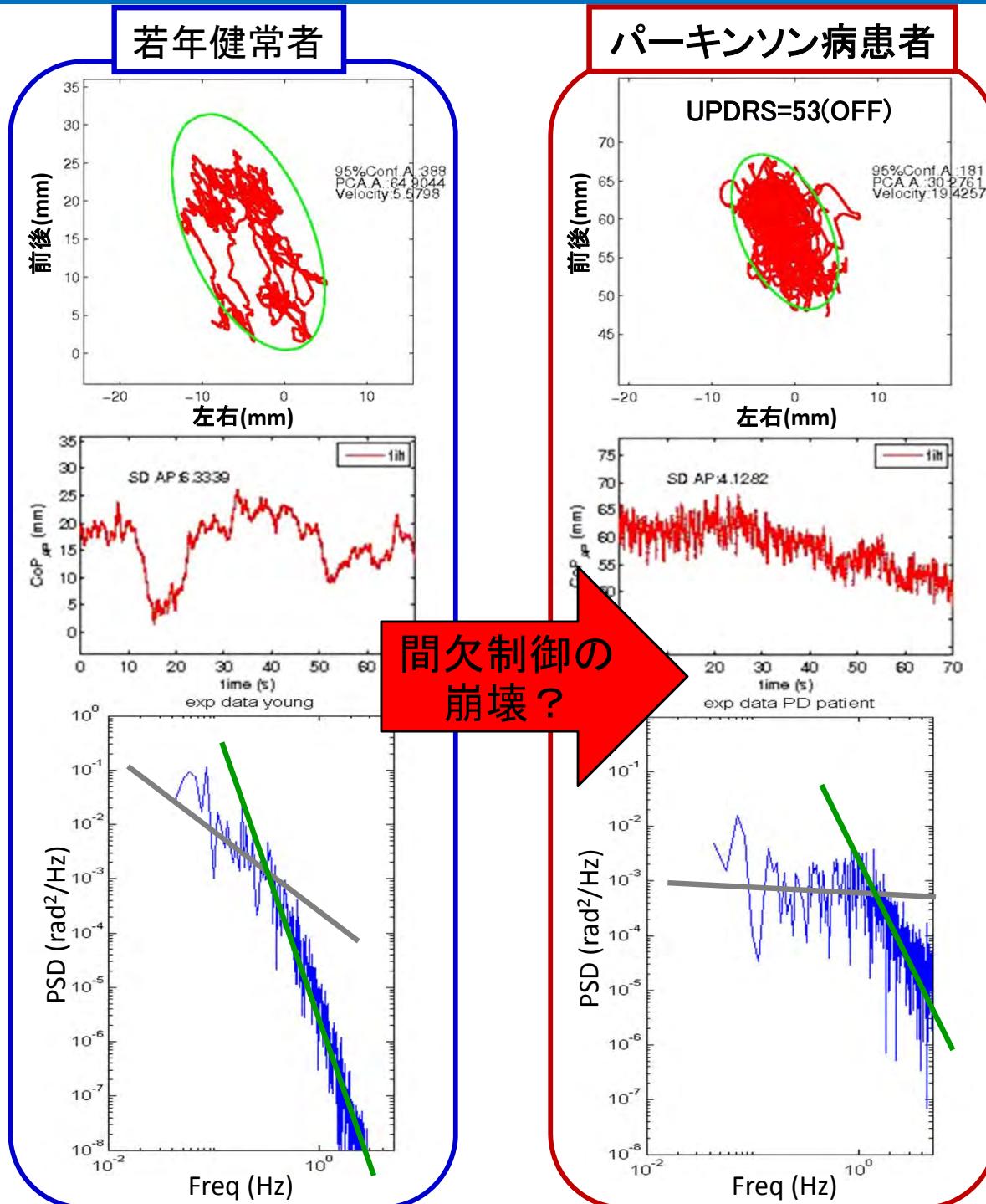
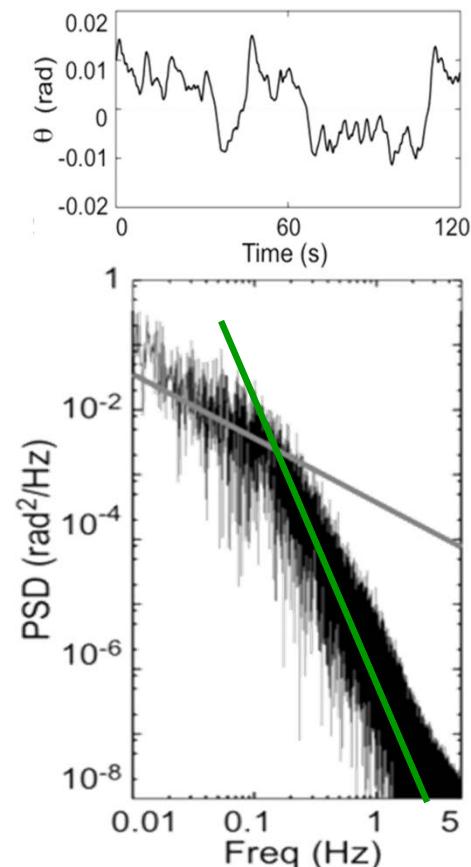
# ミクロスケール実験データ: パーキンソン病モデルサルの脳シグナル (Tachibana et al. (2011))



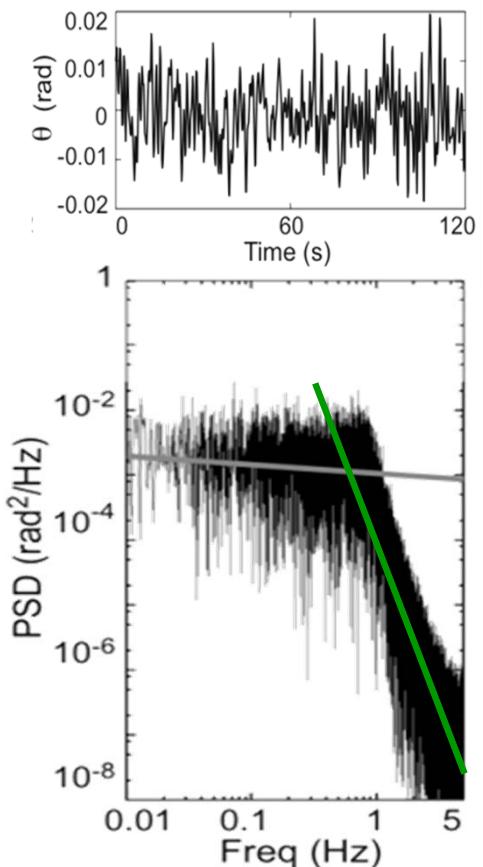
# マクロスケール実験データ: パーキンソン病における姿勢反射障害発生機序の仮説モデル (野村(阪大))

- PLoS One (2009)
- Hum Mov Sci (2008)
- J Theor Biol (2012)
- Math Biosci (2013)

**新しい仮説  
間欠制御モデル  
(シミュレーション)  
適切なタイミングで  
制御OFF  
柔かな運動**



**従来仮説  
連続的制御モデル  
(シミュレーション)  
常に制御ON  
高ゲインで安定化  
硬い運動**



## 今までの実施状況1(脳神経系シミュレーション)(2011-2014年度)

Diesmann (ユーリッヒ研究所), 五十嵐(OIST銅谷チーム)ら  
2013年7月, ISLiMで開発された脳神経系 シミュレータ NESTを  
用いて、「京」上で, 10兆個の結合を持つ大脳皮  
質局所神経回路のシミュレーションに成功

### －世界最大の脳神経シミュレーション－

- ・ 17億3,000万個の神経細胞
- ・ 10兆4,000億個のシナプス結合



マーモセットなどの小型霊長類の全脳規模に匹敵  
ヒトの脳機能解明に向けた第一歩

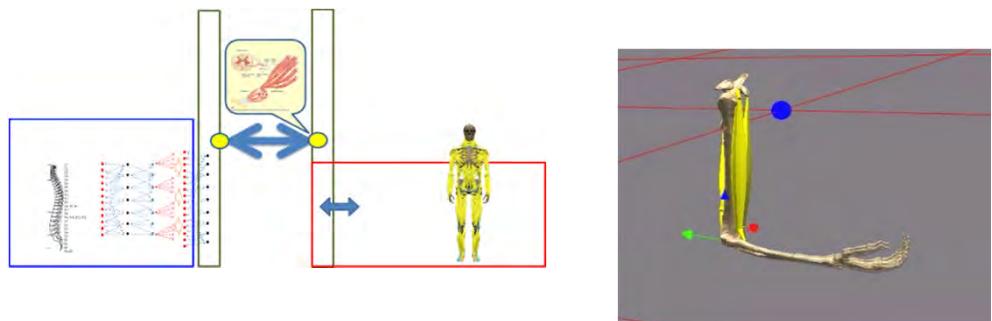
プレスリリース [http://www.riken.jp/pr/topics/2013/20130802\\_2/](http://www.riken.jp/pr/topics/2013/20130802_2/)

# 今までの実施状況2 (2011-2014年度)

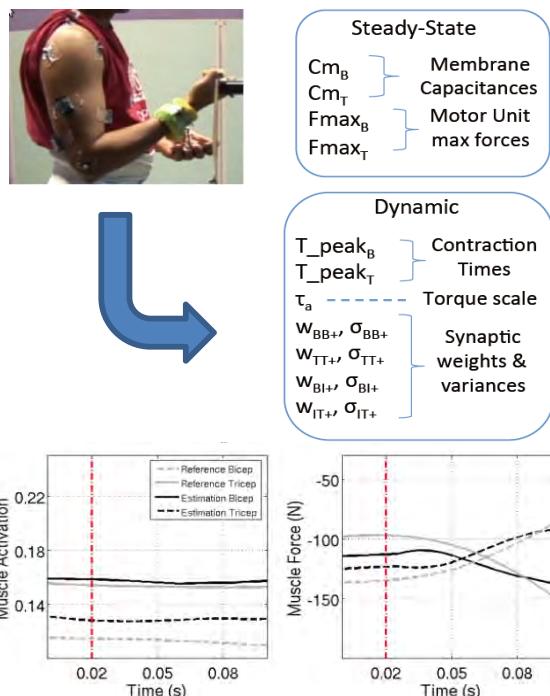
## 筋骨格-神経系階層統合シミュレーション (中村, 高木, 銅谷)

### (1) PyNEST + MUSIC + K-Body

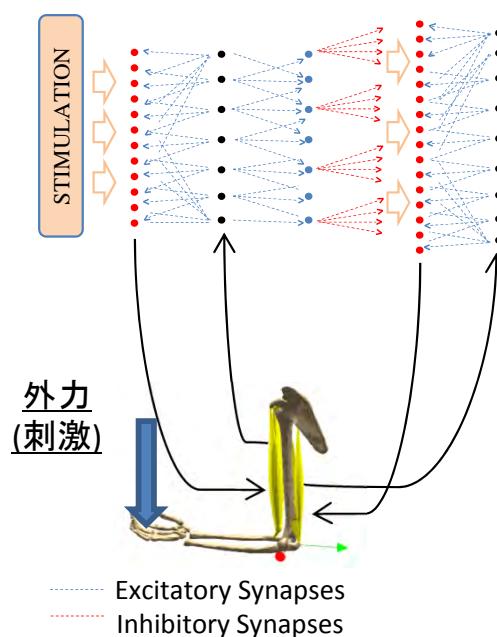
脊髄神経モデルと筋骨格ワイヤモデルの接続



実験データを用いた筋・神経の  
モデルパラメータの同定

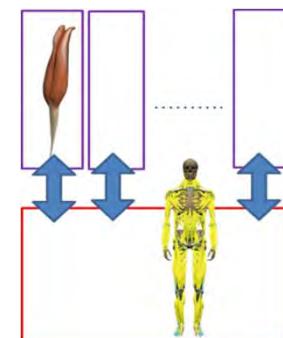


### 伸張反射 シミュレーション

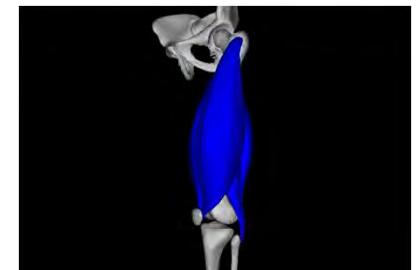
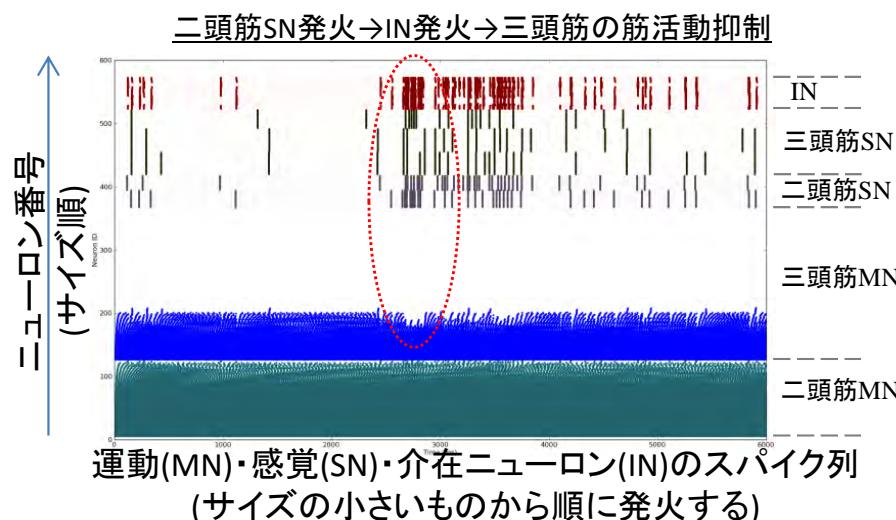
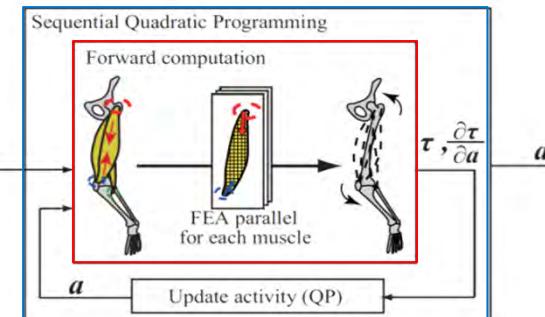


### (2) K-Body+HI-Muscle

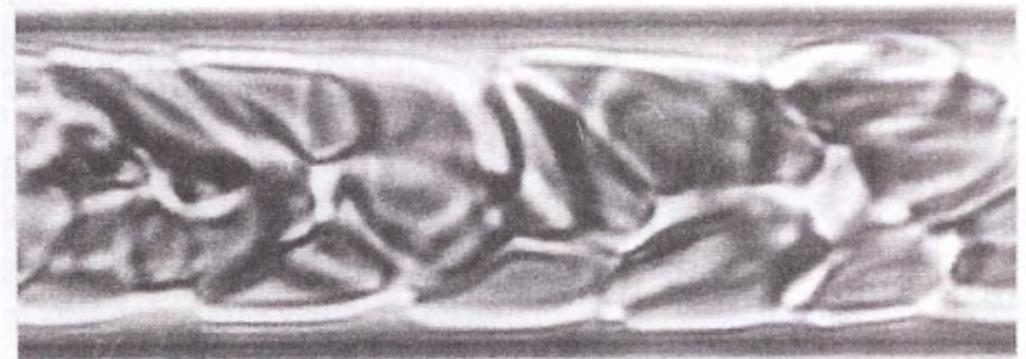
全身骨格モデルと  
筋有限要素モデルの接続



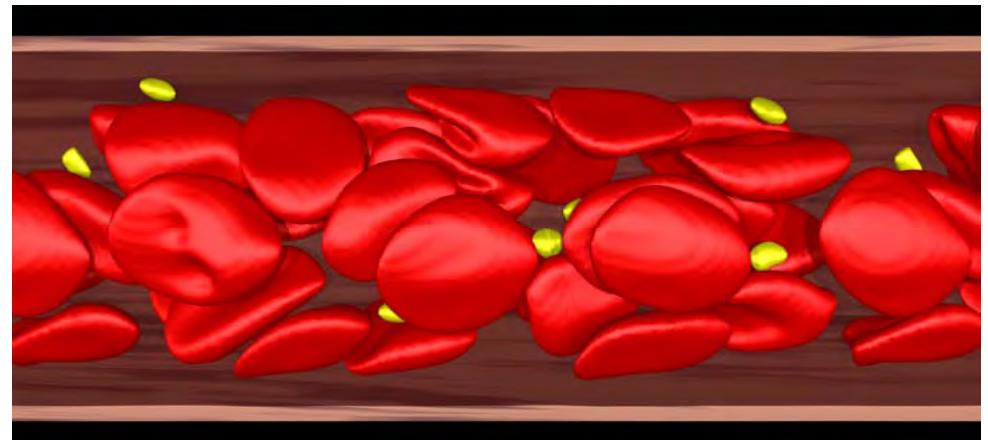
### 下肢の筋活動度推定計算



# Numerical Method Suitable for Medical Image Data (Full Eulerian FSI simulations)



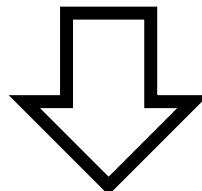
Gaehtgens *et al.*(1980) *Blood Cells.*, **6**, 799.



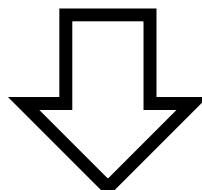
# Background

## Fluid-Structure coupling analysis of living body

Diagnostic image (CT, MRI)

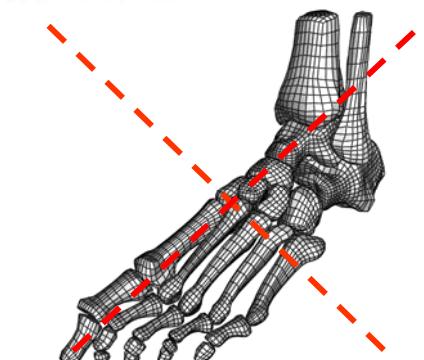
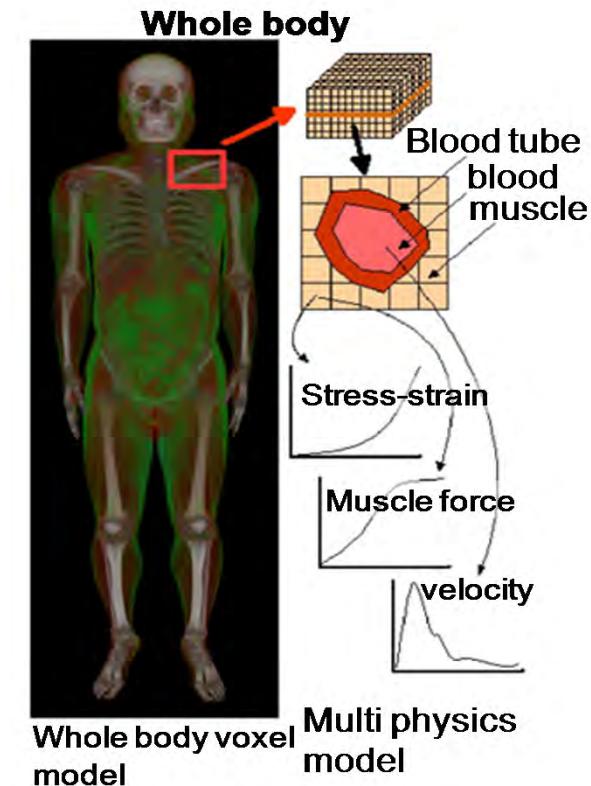


Voxel data (**Volume Fraction of Constituents**)  
representing multi-component geometry



**without Mesh Generation**

(Finite-Difference or Finite-Element) Simulation  
on **Eulerian** frame



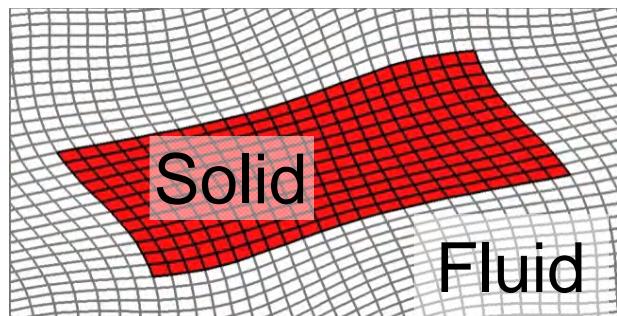
# Full Eulerian approach for Fluid-Structure Interactions

Lagrangian

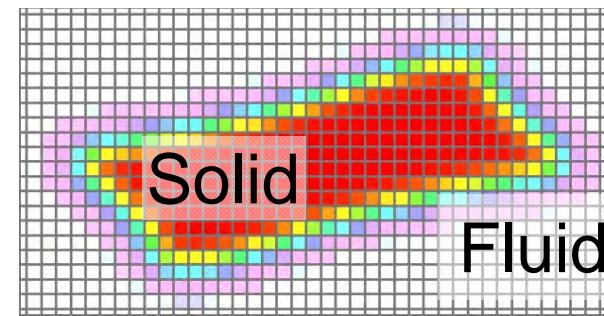
vs.

Eulerian

How is the two-phase distinguished ?

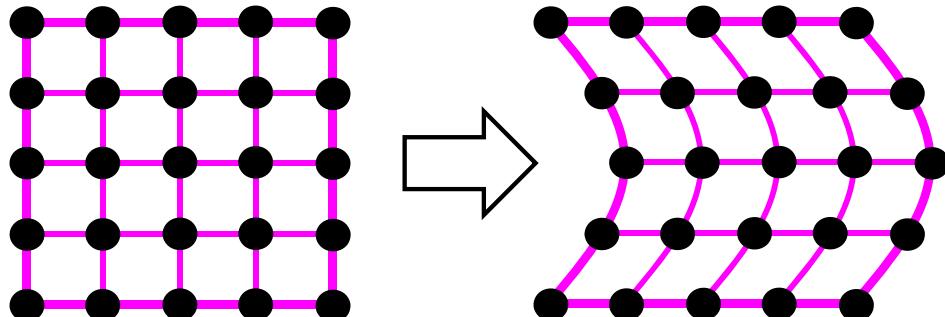


by the boundary of mesh

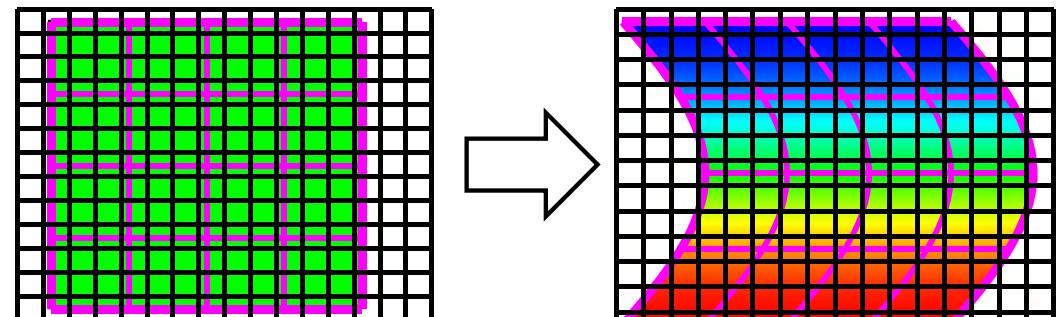


by **solid volume fraction**

How is the solid deformation described?



by the displacement of  
material points themselves



by **left Cauchy-Green  
deformation tensor**

- Sugiyama, Ii *et al.* (2011) *J. Comput. Phys.*, **230**, 596.
- Ii, Sugiyama *et al.* (2011) *Int. J. Numer. Meth. Fluids*, **65**, 150.

# Basic equations for conservation and constitutive law

$$\nabla \cdot \mathbf{v} = 0, \quad \rho_m (\partial_t \mathbf{v} + (\mathbf{v} \cdot \nabla) \mathbf{v}) = -\nabla p + \nabla \cdot \boldsymbol{\sigma}'_m,$$

**Cauchy's stress tensor in mixture form**

$$\boldsymbol{\sigma}'_m = (1 - \phi_s) \boldsymbol{\sigma}'_f + \phi_s \boldsymbol{\sigma}'_s,$$

**solid volume fraction**

**fluid (Newtonian):**

$$\boldsymbol{\sigma}'_f = 2\mu_f \mathbf{D}',$$

$$\mathbf{D} = \frac{1}{2} (\nabla \mathbf{v} + \nabla \mathbf{v}^T),$$

↑  
strain rate

**solid (visco-hyperelasto):**

Mooney-Rivlin model:

$$\boldsymbol{\sigma}'_s = 2c_1 \mathbf{B}' + 2c_2 (\text{tr}(\mathbf{B}) \mathbf{B} - \mathbf{B} \cdot \mathbf{B})' + 2\mu_s \mathbf{D}'.$$

↑

**left Cauchy-Green deformation**

$$\mathbf{B} = \mathbf{F} \cdot \mathbf{F}^T, \quad F_{ij} = \frac{\partial x_i}{\partial X_j},$$

- Sugiyama, Ii *et al.* (2011) *J. Comput. Phys.*, **230**, 596.

# Basic equations for kinematics of solid motion

**solid volume fraction**

$$\partial_t \phi_s + (\mathbf{v} \cdot \nabla) \phi_s = 0,$$

**left Cauchy-Green deformation tensor**

$$\partial_t \mathbf{B} + (\mathbf{v} \cdot \nabla) \mathbf{B} = \mathbf{L} \cdot \mathbf{B} + \mathbf{B} \cdot \mathbf{L}^T,$$

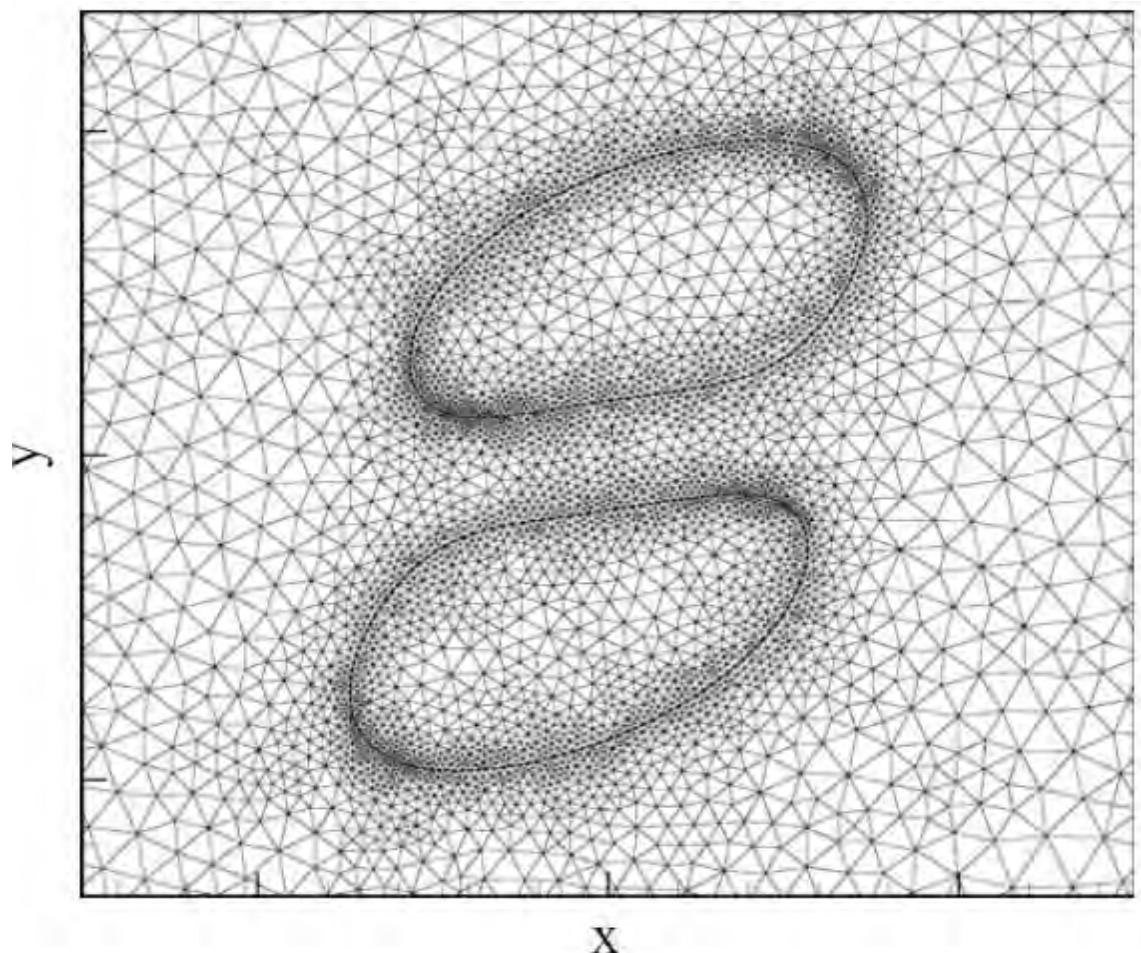
$$\text{where } \mathbf{L} = \nabla \mathbf{v}^T.$$

- Sugiyama, Ii *et al.* (2011) *J. Comput. Phys.*, **230**, 596.

# Validation I

## Comparison with available numerical data

Gao & Hu (2009)  
*J. Comput. Phys.* **228**, 2132.  
particle-particle interactions  
in a shear flow  
full Lagrangian



# Particle-particle interactions in a shear flow

(roll-over and bounce-back modes)

Movie

$$\rho_s = \rho_f = 1, L_x = 8, L_y = 4, \mu = 20, C_1 = 0, C_0 = 80$$

$$V_{\text{top}} = 1$$



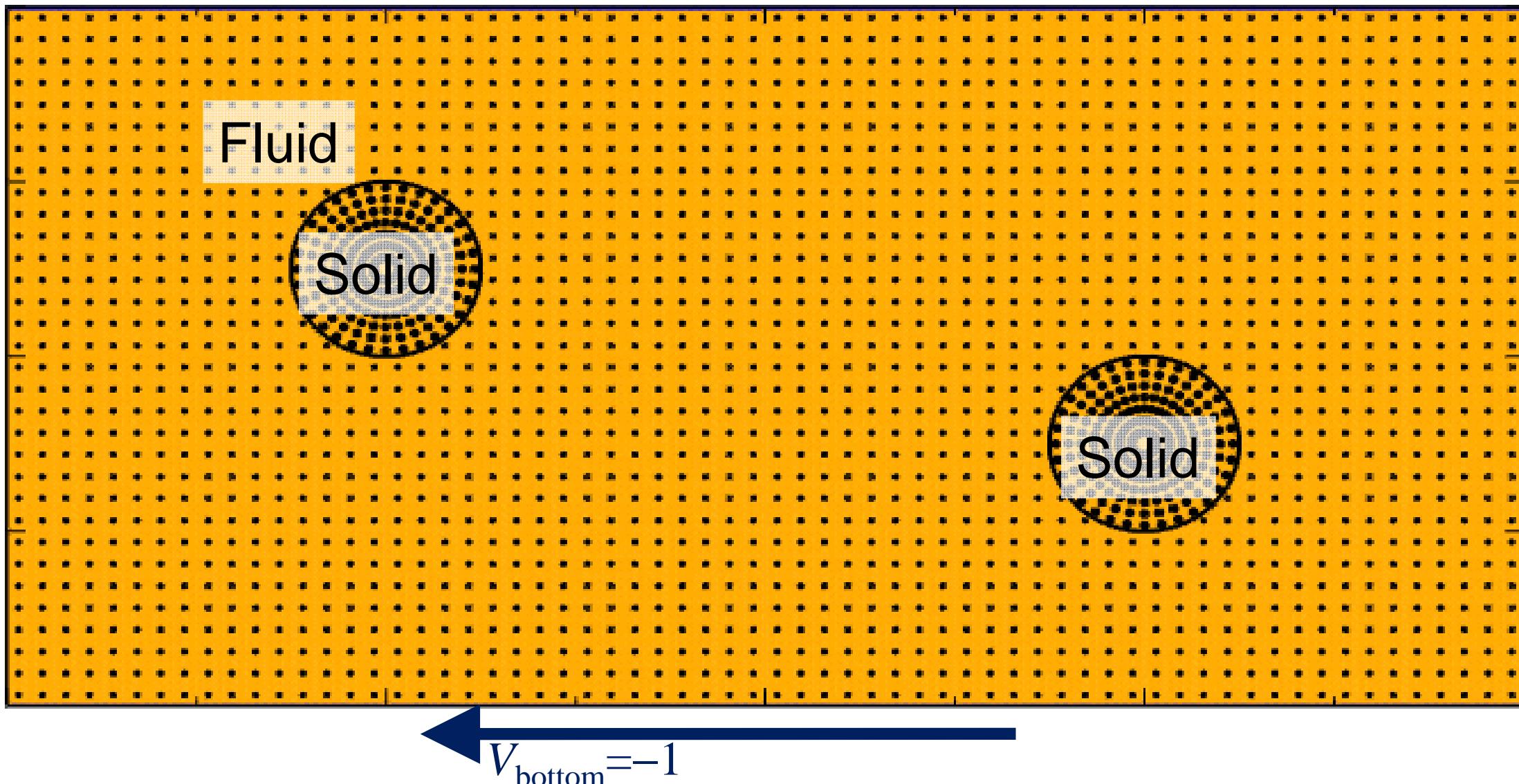
● material points (tracers)

contour: vorticity (spin)



-3

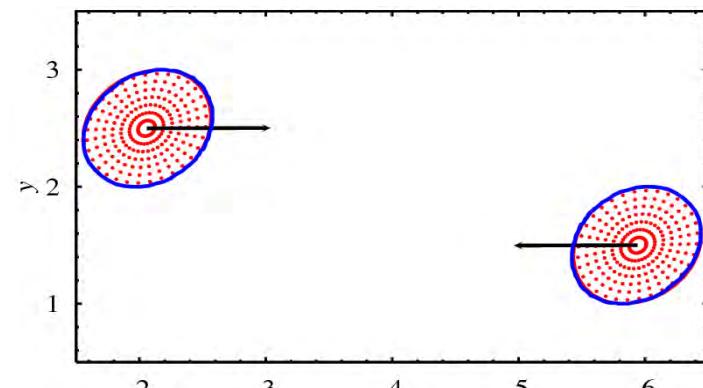
1



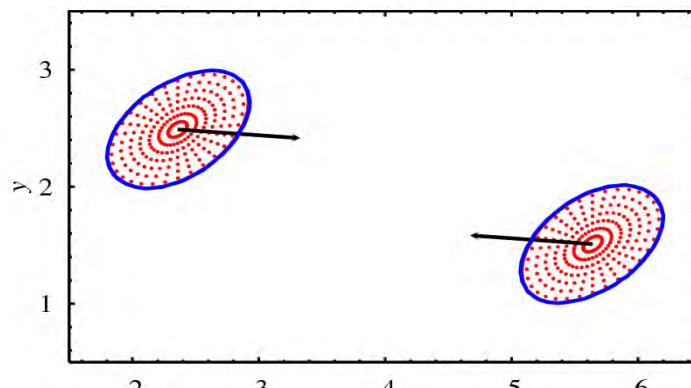
# Comparison with Gao & Hu (JCP2009)'s results

- Gao & Hu (full Lagrangian)
- Present (full Eulerian)

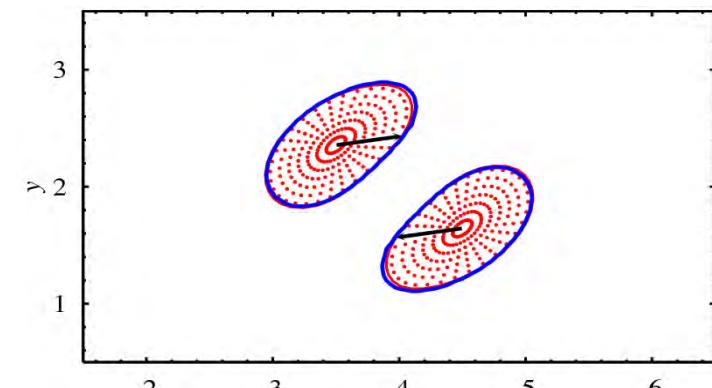
$N_x \times N_y = 1024 \times 512$



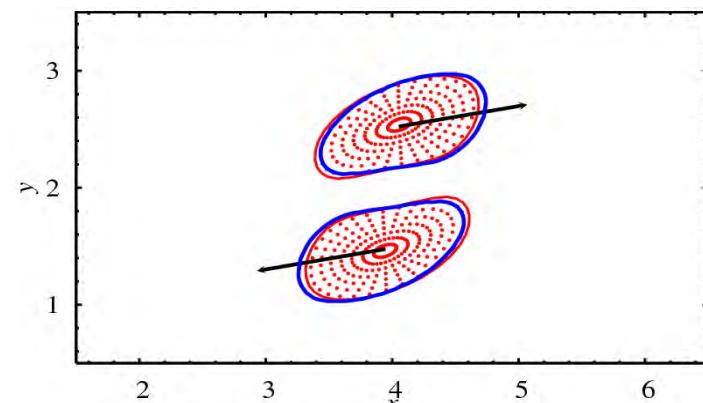
$t=0.2$



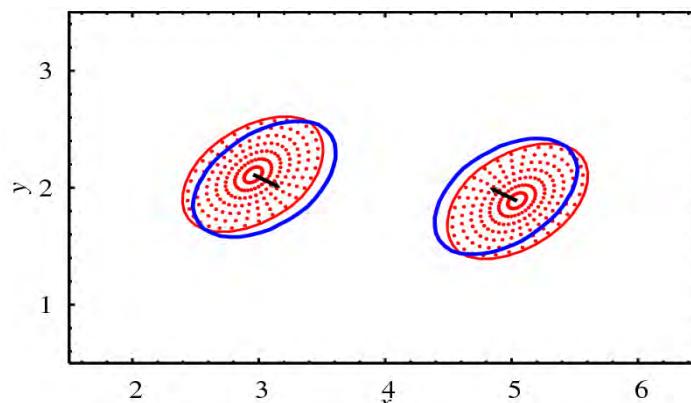
$t=0.8$



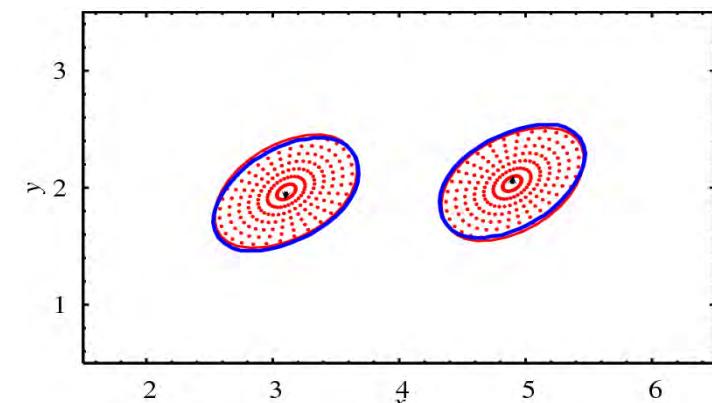
$t=4.0$



$t=5.6$



$t=30.0$



$t=33.2$

# Extension to 10-particle system

Movie

$$\rho_s = \rho_f = 1, L_x = 8, L_y = 4, \mu = 20, C_1 = 0, C_0 = 80$$

$$V_{\text{top}} = 1$$

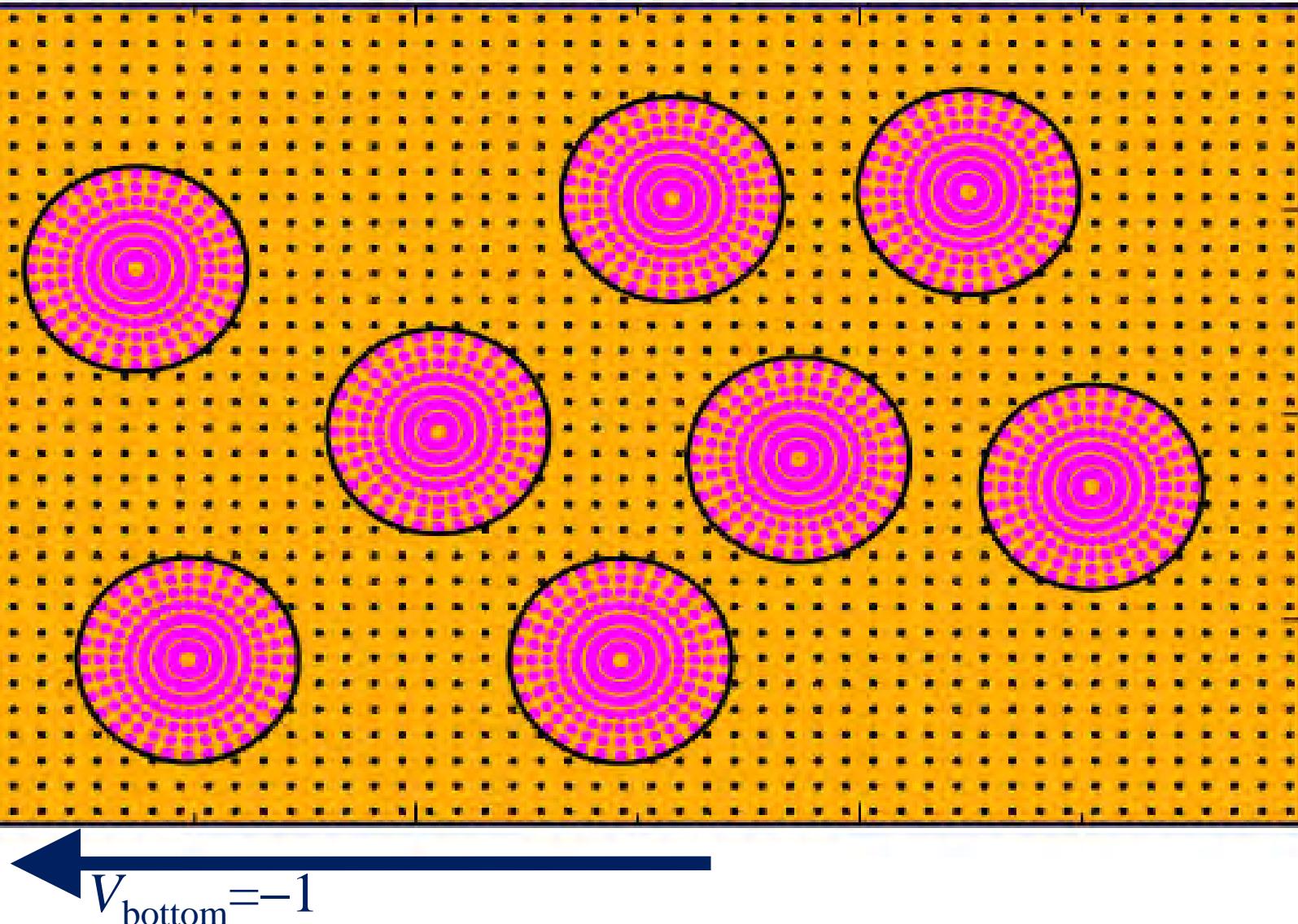
● material points (tracers)

contour: vorticity (spin)



1

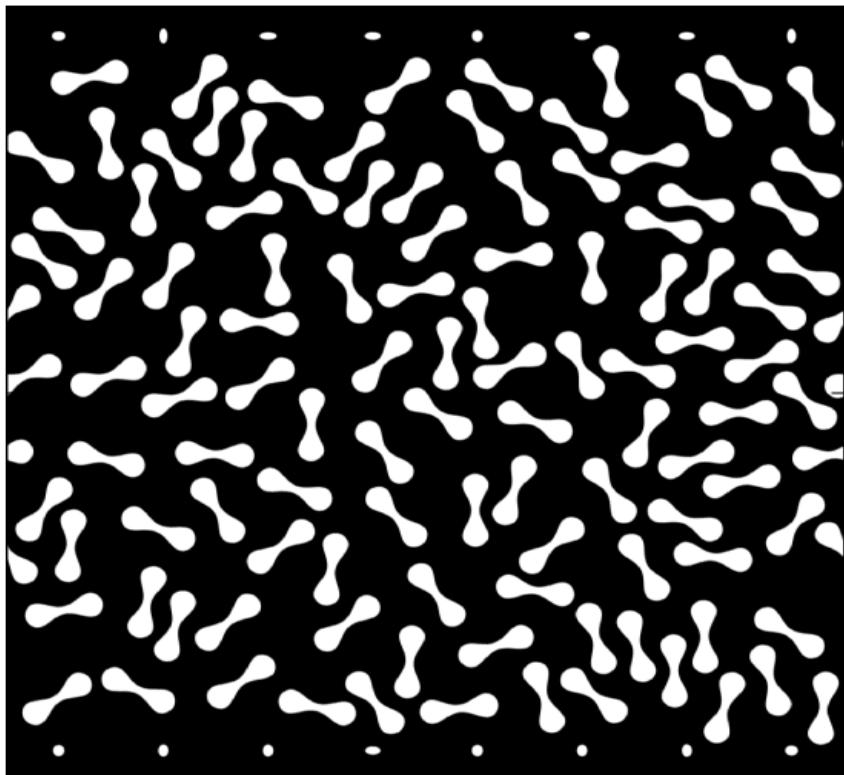
-3



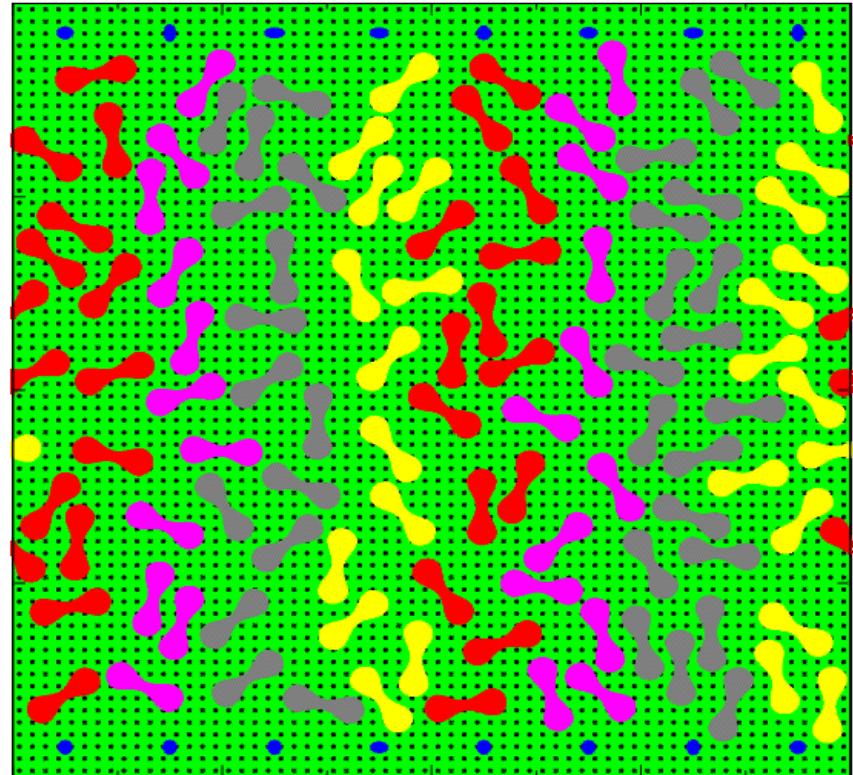
# Feature: full Eulerian approach

- makes it easily possible to perform FSI simulations with complex geometry

Initial voxel data



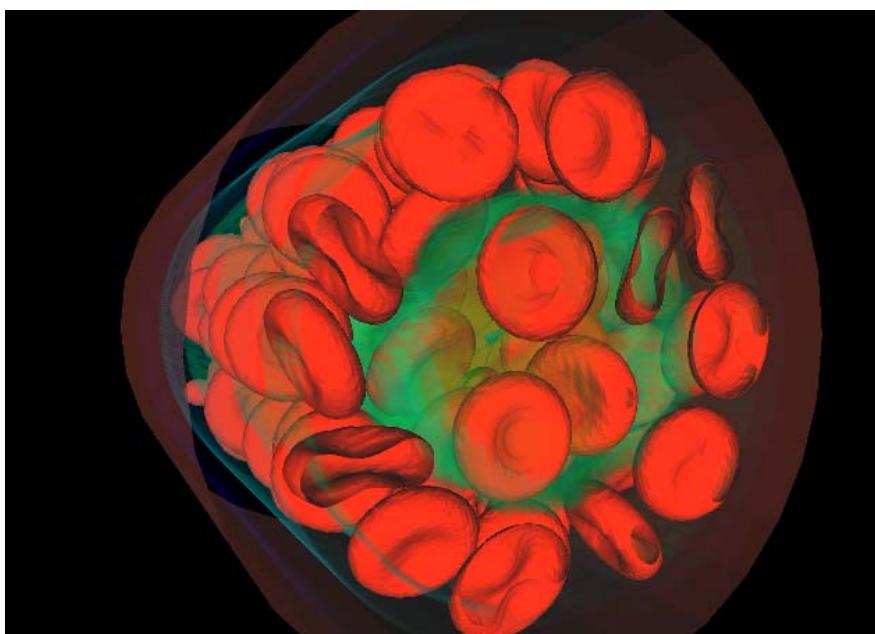
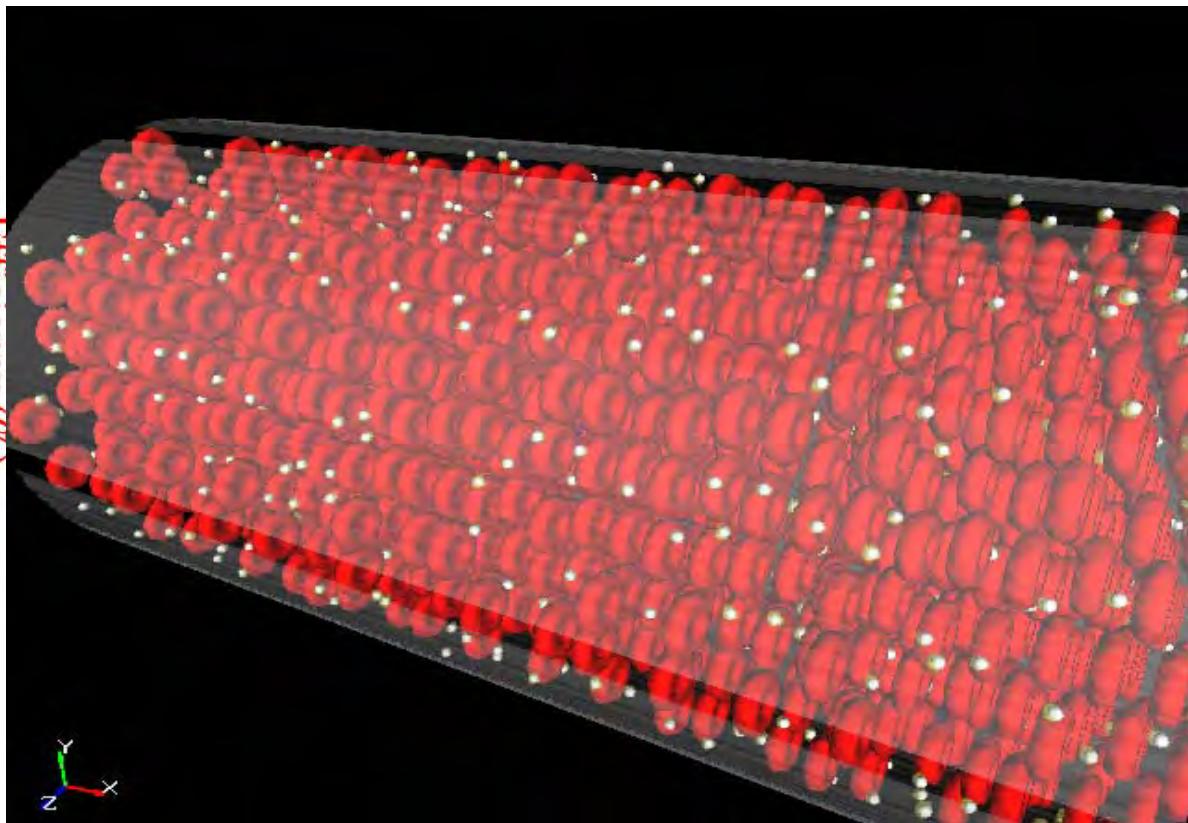
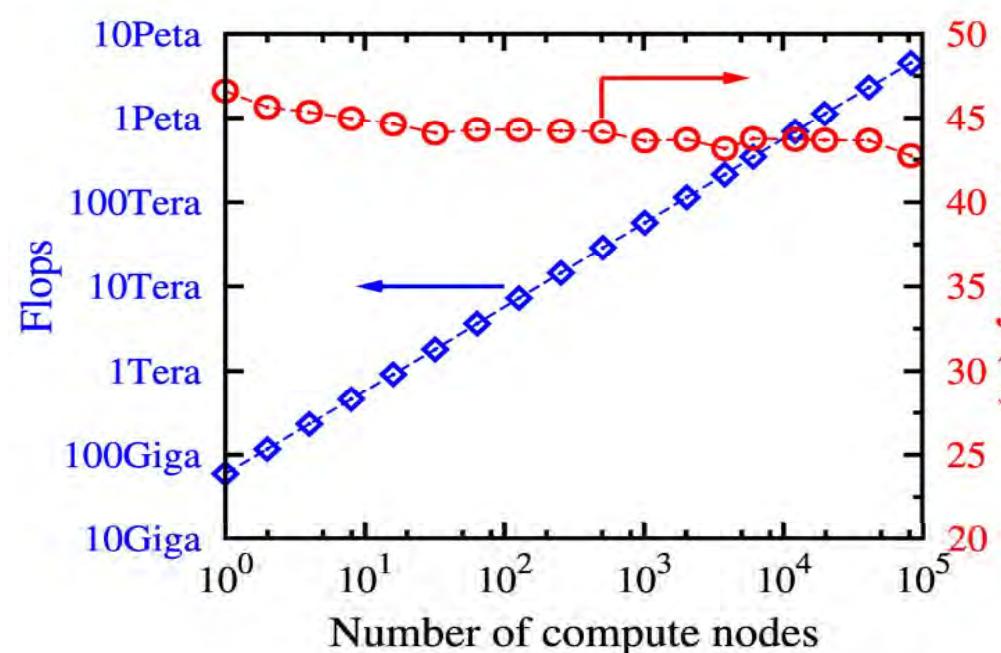
FSI simulation



without mesh generation/reconstruction

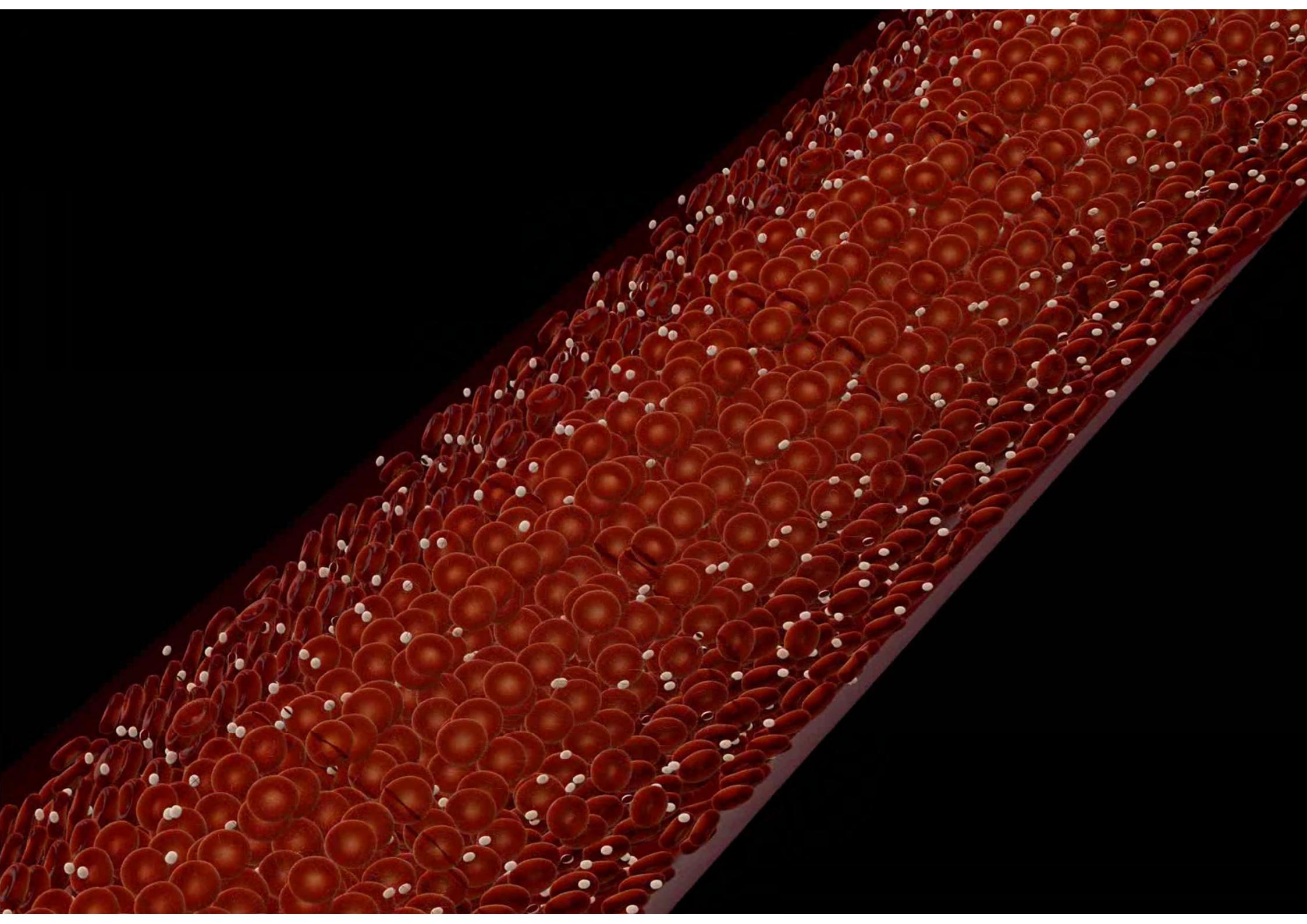
- Sugiyama, Ii *et al.* (2010) *Comput . Mech.*, **46**, 147.
- Nagano, Sugiyama *et al.* (2010) *J. Fluid Sci. Tech.*, **5**, 475.
- Takagi, Sugiyama *et al.* (2012) *J. Appl. Mech.*, **79**, 010911.

# The Super-Fast FSI Solver: ZZ-EFSI

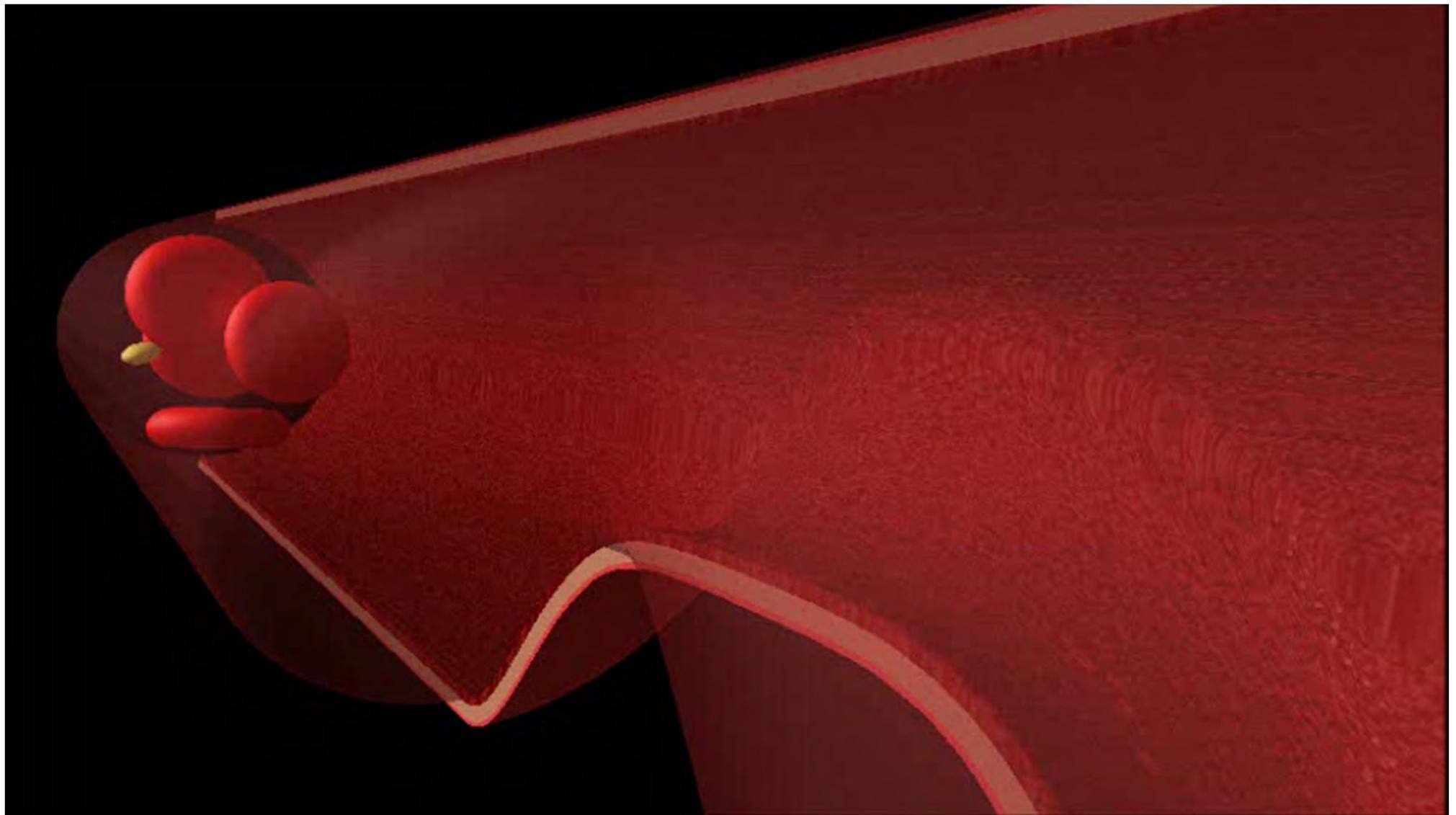


ZZ-EFSI achieved the actual speed of **4.5 PETA FLOPS!!!**

Software available at  
[http://www.islim.org/islim-dl\\_e.html](http://www.islim.org/islim-dl_e.html)

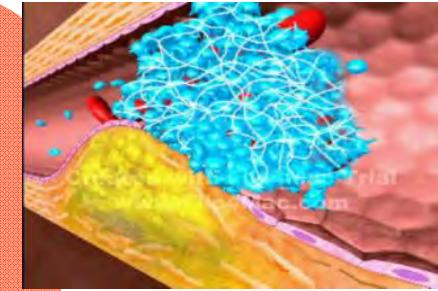
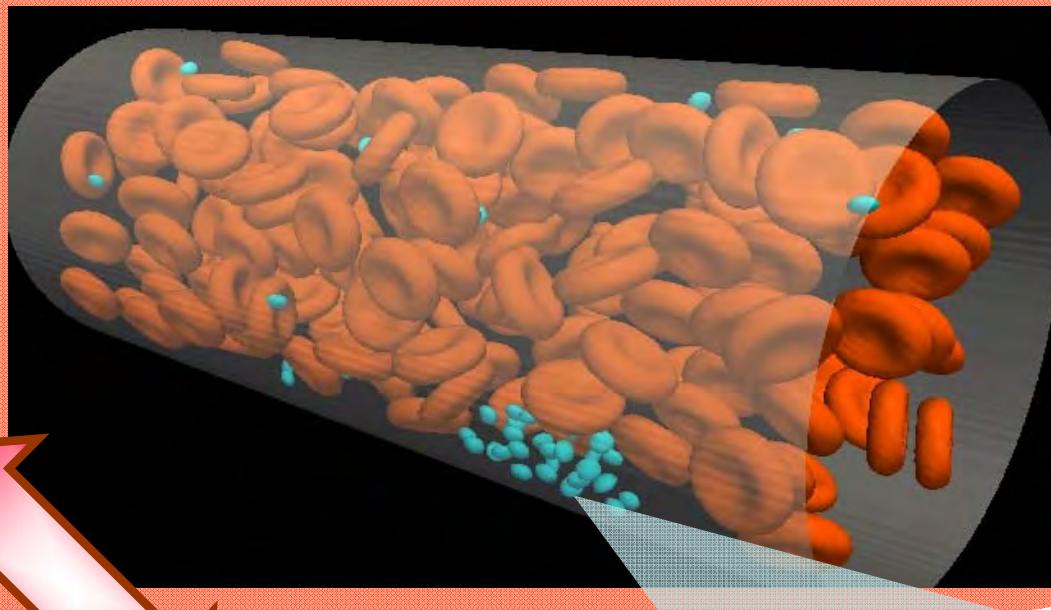


# Development of Multiscale Thrombosis Simulator

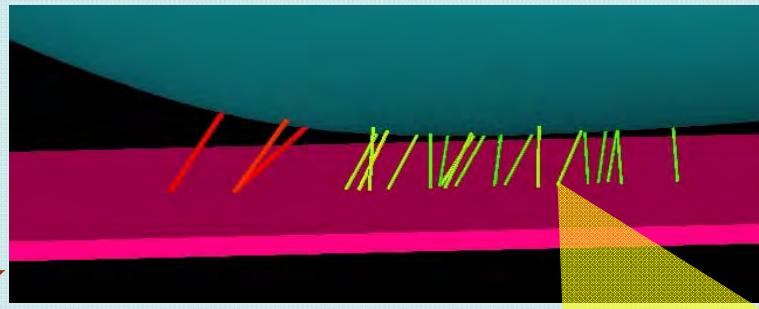


# Multiscale modeling of initial stage of thrombosis

Blood flow  
(continuum mechanics)

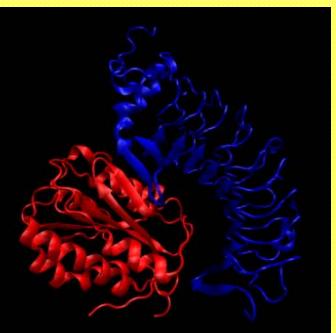


Protein(wWF)-Protein  
(GP1b $\alpha$ ) binding  
(stochastic process)



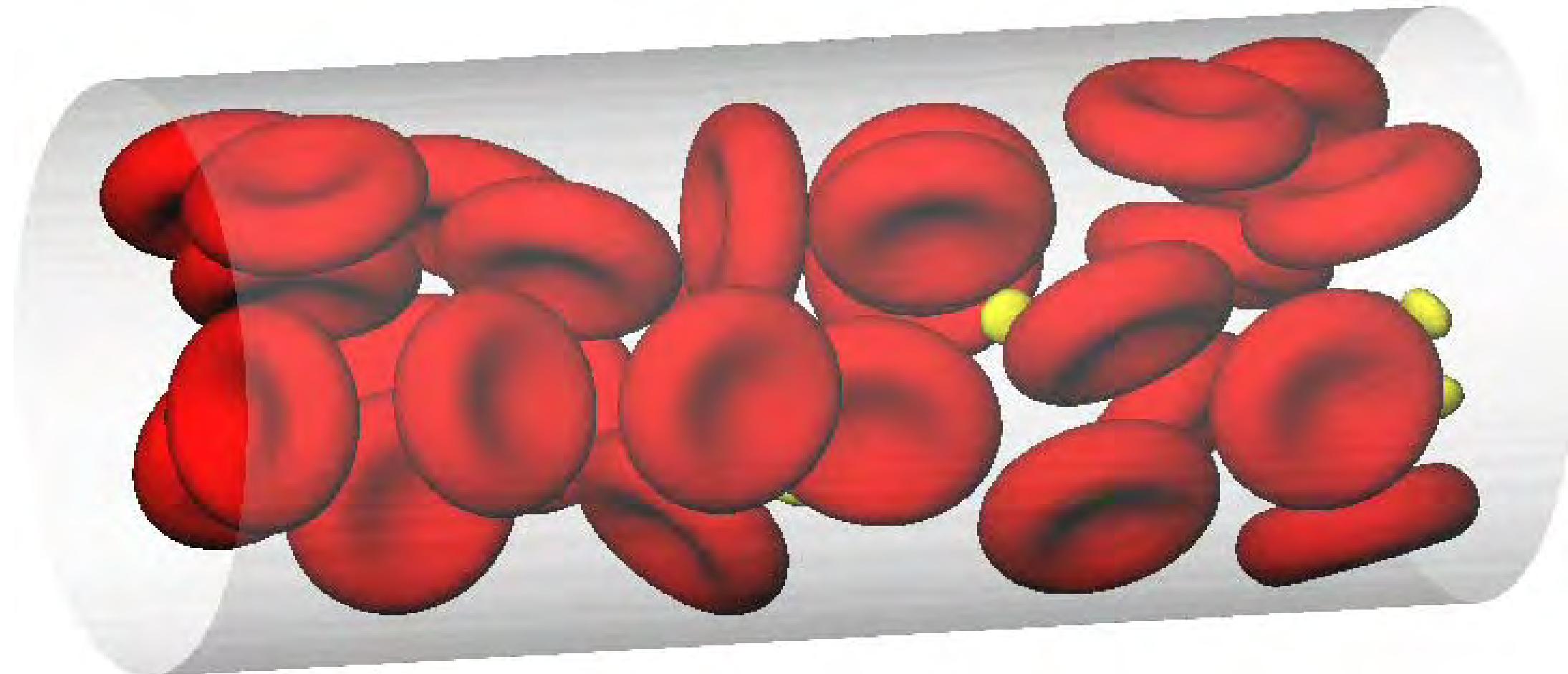
- Substance diffusion
- Metabolic reaction and activation
- Morphology change

Molecular interaction  
(molecular dynamics)



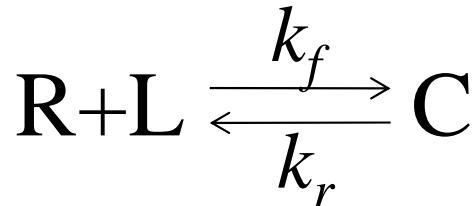
# Blood flow simulation

- $[0,44] \times [0,22] \times [0,22]$  [ $\mu\text{m}$ ],  $D=20$  [ $\mu\text{m}$ ],
- 30 RBCs, 10 platelets ( $Ht \approx 20$  [%])
- $\langle u \rangle \approx 2$  [mm/s]                                    320x160x160 mesh, MPC-RICC at RIKEN (256 cores)



- Ii, Sugiyama *et al.* (2012) *J. Biomech. Sci. Eng.*, 7, 72.

# Stochastic Monte Carlo Simulation of Cell adhesion on vessel wall



R: Receptor

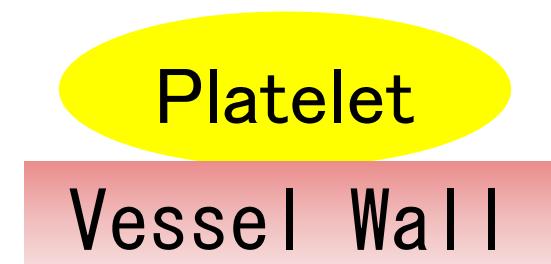
L: Ligand

C: R-L complex

$k_f$ : Binding React. Rate Cnst.

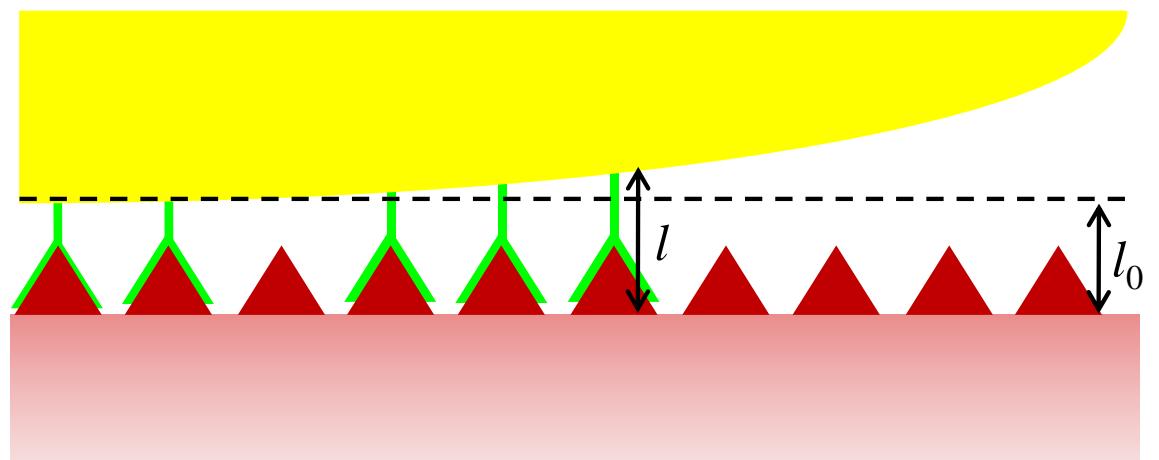
$k_r$ : Dissosc. React. Rate Cnst.

Jianrong Li, et. al(2009)



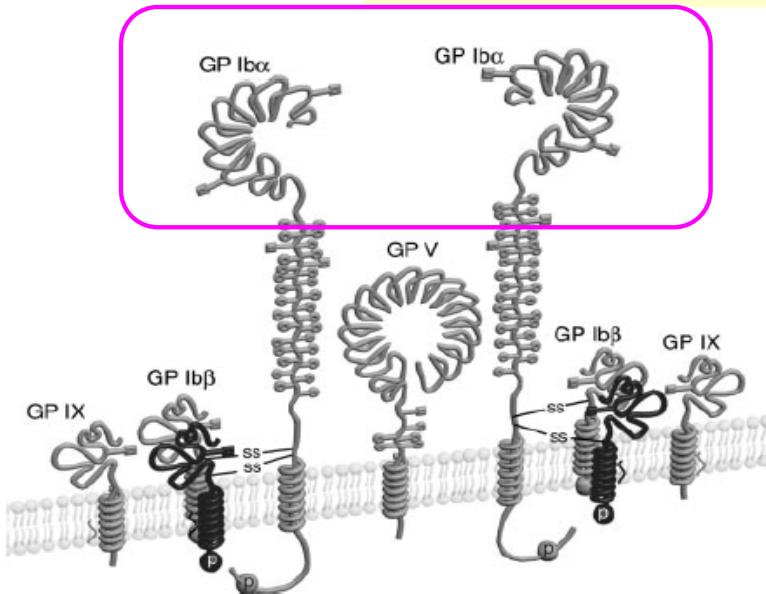
Receptor—Ligand Bind. Force

$f_b = \text{Function of } (l - l_0)$



# Ligand-Receptor Binding Model

## Stochastic model with energetic elasticity



Luo *et al.* (2007) *Blood*, **109**, 603.

forward reaction rate

$$k_f(l) = k_{f0} \exp\left(-\sigma_{ts} \frac{(l - l_0)^2}{2k_b T}\right)$$

Formation

reverse reaction rate

$$k_r(l) = k_{r0} \exp\left((\sigma_p - \sigma_{ts}) \frac{(l - l_0)^2}{2k_b T}\right)$$

Breakage

Eyring (1935) *J. Chem. Phys.*, **3**, 107.

Bell (1978) *Science*, **200**, 618.

Dembo (1988) *Proc. R. Soc. Lond. B*, **234**, 55.

Hammer & Apte (1992) *Biophys. J.*, **63**, 35.

$$P_f = 1 - \exp(-k_f \Delta t) \geq R_f \rightarrow \text{formation}$$

$$P_r = 1 - \exp(-k_r \Delta t) \geq R_r \rightarrow \text{breakage}$$

( $R_f, R_r \in [0,1]$  : Random numbers)

$$f = \sigma_p (l - l_0)$$

Model Parameter

$$\sigma_p = 10^{-4} \text{ [N/m]}, \quad \sigma_{ts} = 0.9\sigma_p \text{ [N/m]}$$

$$l_0 = 60 \text{ [nm]}, \quad k_{r0} = 3 \text{ [s}^{-1}\text{]}$$

Fox *et al.* (1988) *J. Biol. Chem.*, **263**, 4882.

Arya *et al.* (2005) *Biophys. J.*, **88**, 4391.

Kim *et al.* (2010) *Nature*, **466**, 992.

# Motion of an adhering platelet

dimensionless time:  $t^* = \gamma t$

$\gamma = 1000 \text{ (1/s)}$



$\gamma = 3000 \text{ (1/s)}$



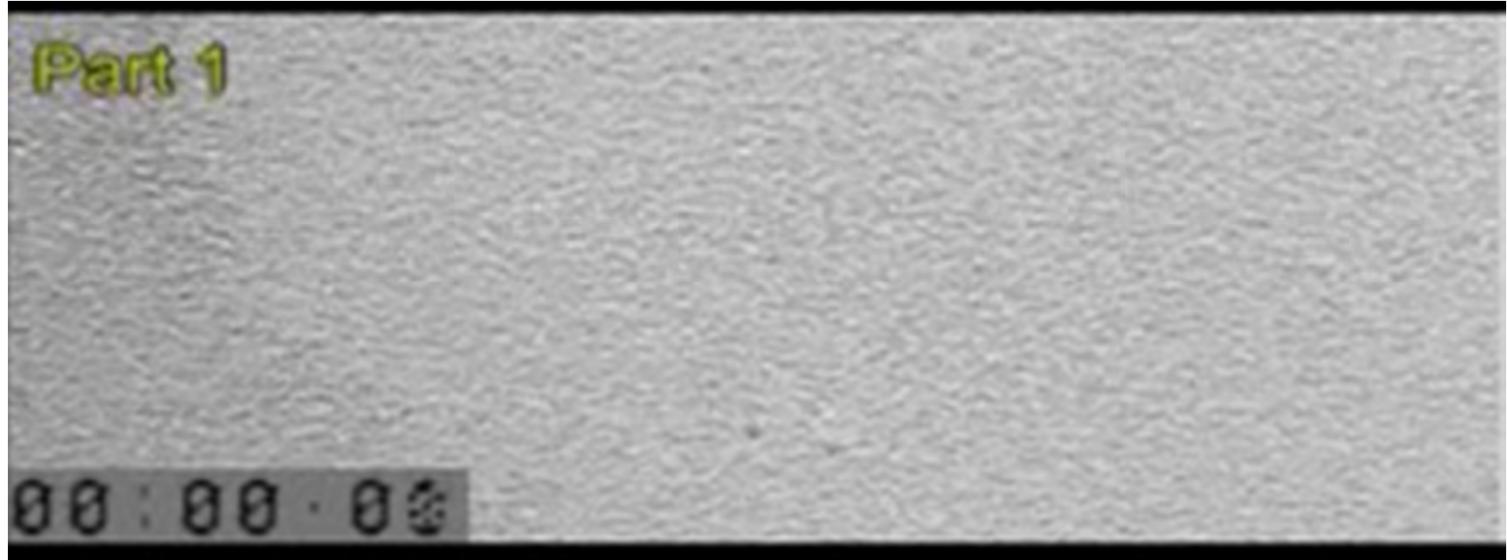
$\gamma = 6000 \text{ (1/s)}$



# Simulated Example : Wall-Adhering Platelet moving in Shear Flow

## Experiment

Reininger *et al.*, *blood*, 107  
(2006) 3537



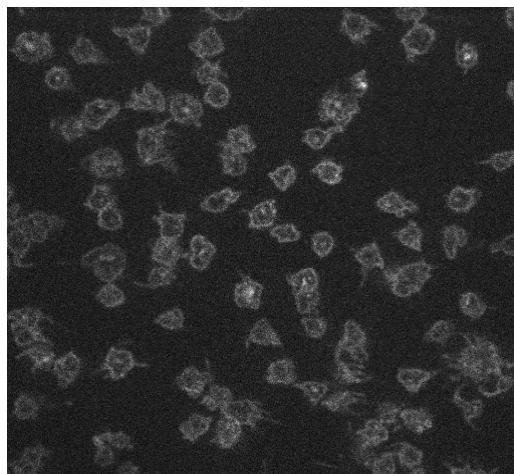
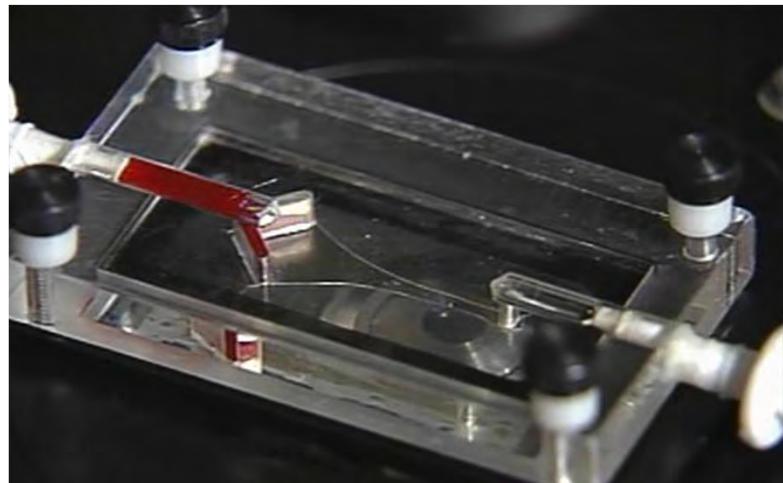
## Simulation

( $\gamma = 3000 \text{ s}^{-1}$ )

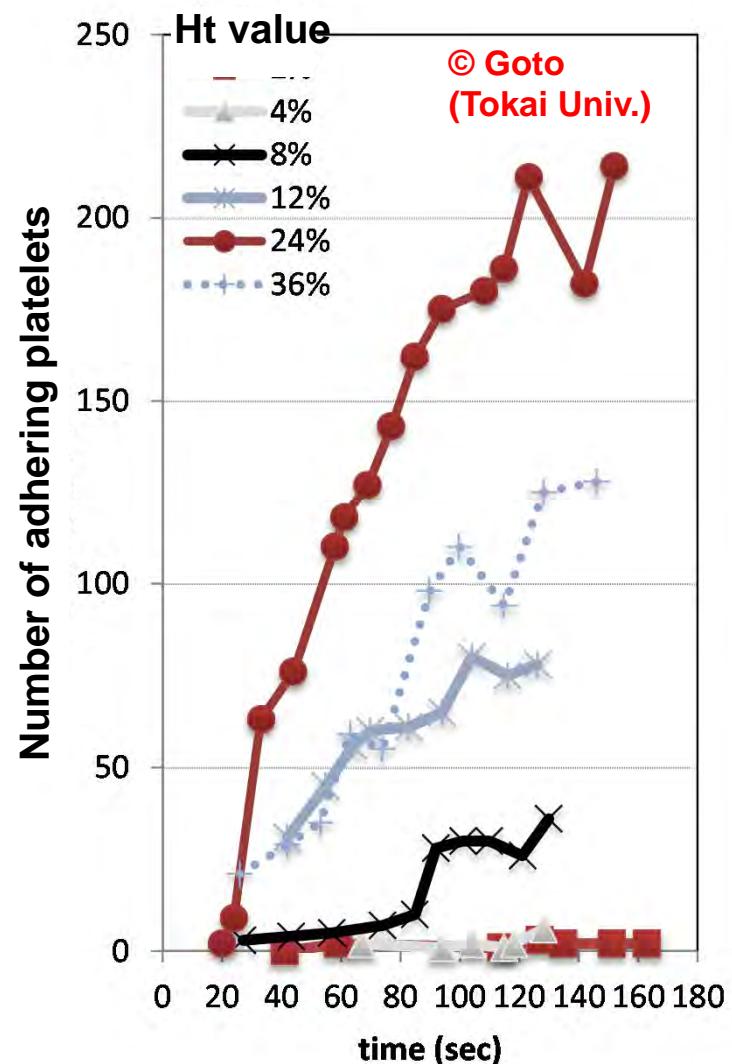


# シミュレーションモデル構築のための実験 (後藤信哉(東海大)より提供)

シミュレーション用データ取得のための  
フローチャンバーを用いた実験



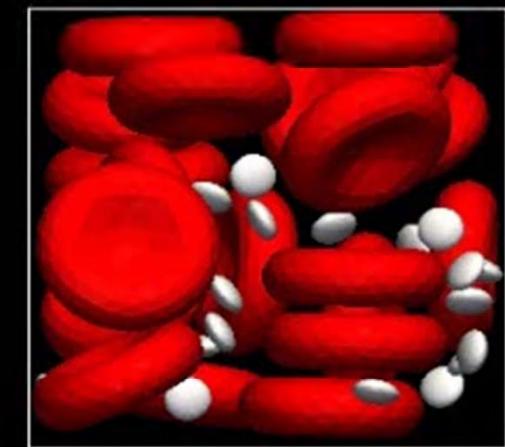
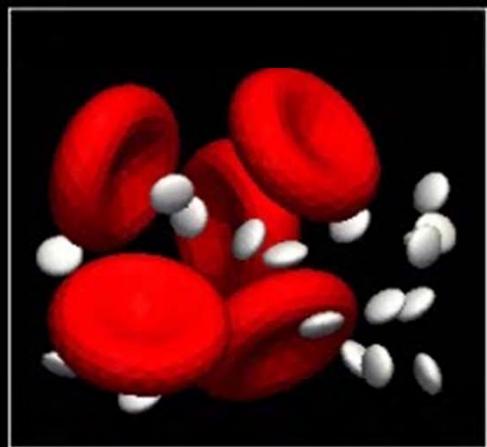
血小板粘着に対する赤血球の影響に関する実験データ  
(後藤(東海大)ら 2012)



Experimental data by Goto & Tamura.

# Adhesion of Platelets in a Shear Flow

$\gamma = 800 \text{ (s}^{-1}\text{)}$     $t \leq 200 \text{ (ms)}$



Ht = 5.5 %

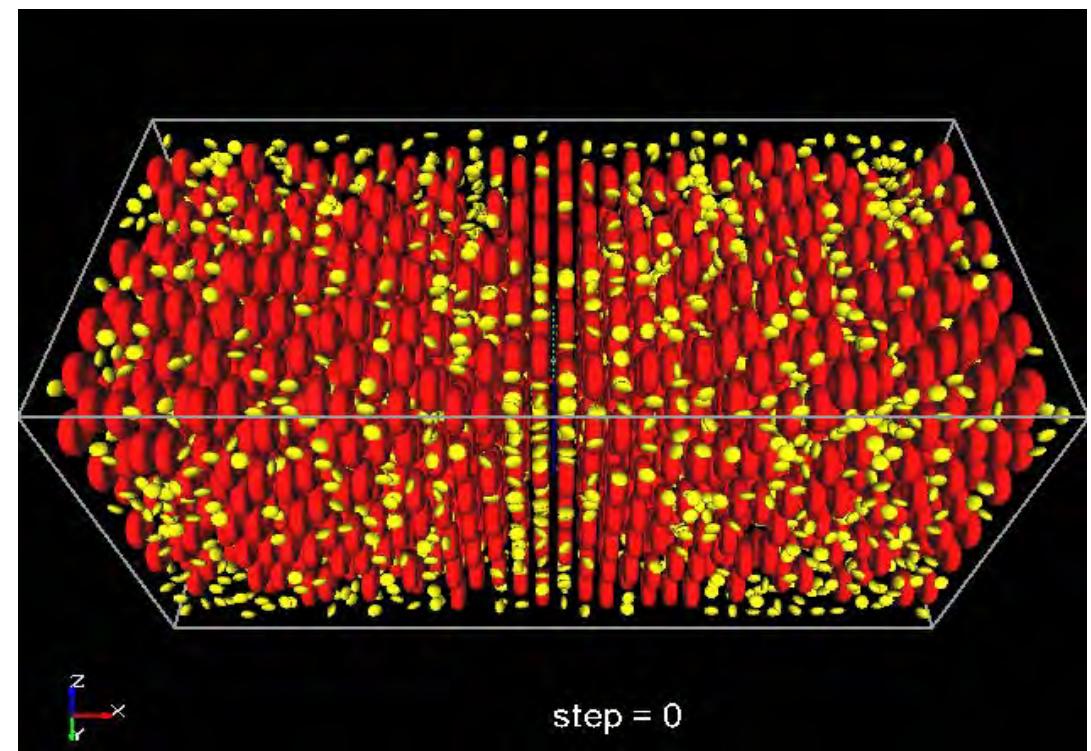
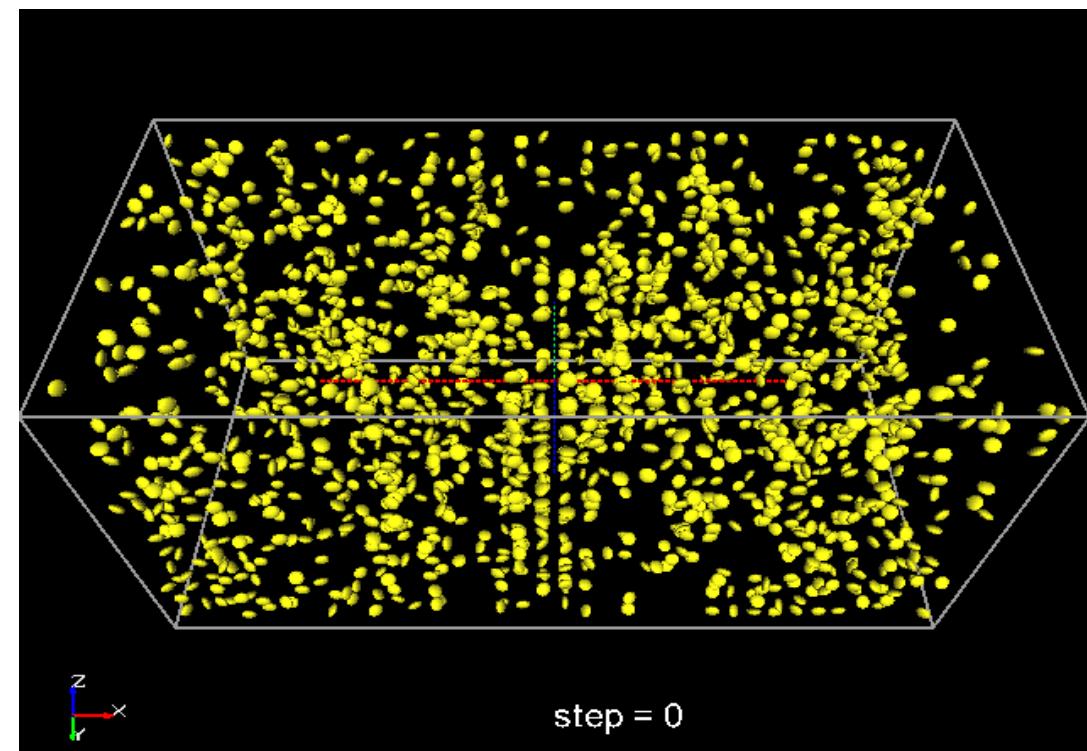
Ht = 15.3 %

Ht = 21.9 %

# Numerical Simulations for the Experiment by Goto et al.

$Ht = 0\%$

$Ht = 20\%$



Domain Size:  $144\mu\text{m} \times 72\mu\text{m} \times 72\mu\text{m}$   
# of grid points:  $480 \times 240 \times 24$

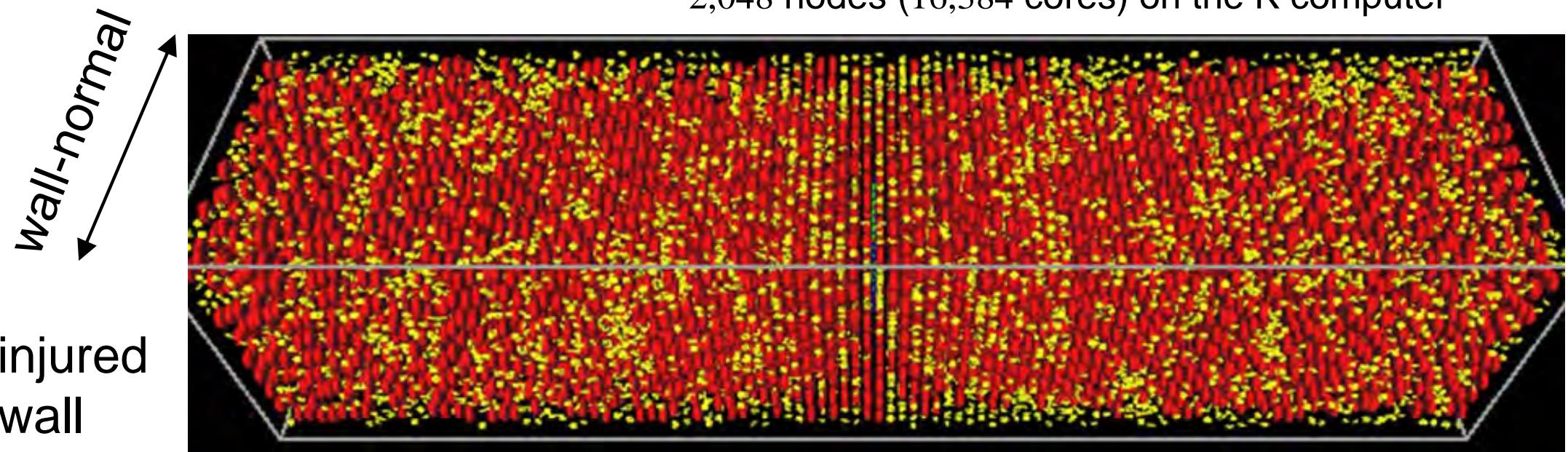
# 本年度: 実験系と同じ流路サイズのシミュレーション

$Ht = 20\%$

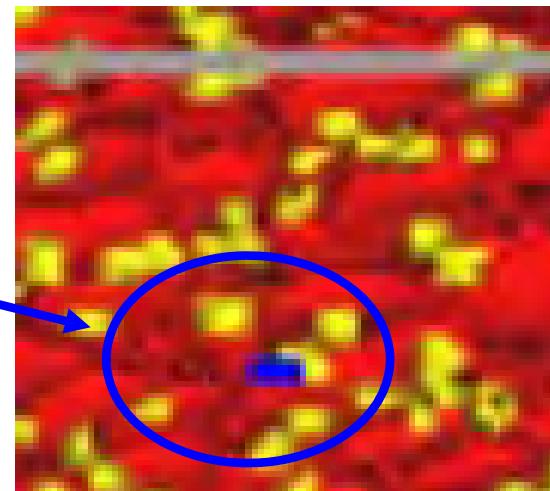
Comp. extent:  $400\mu\text{m} \times 100\mu\text{m} \times 100\mu\text{m}$

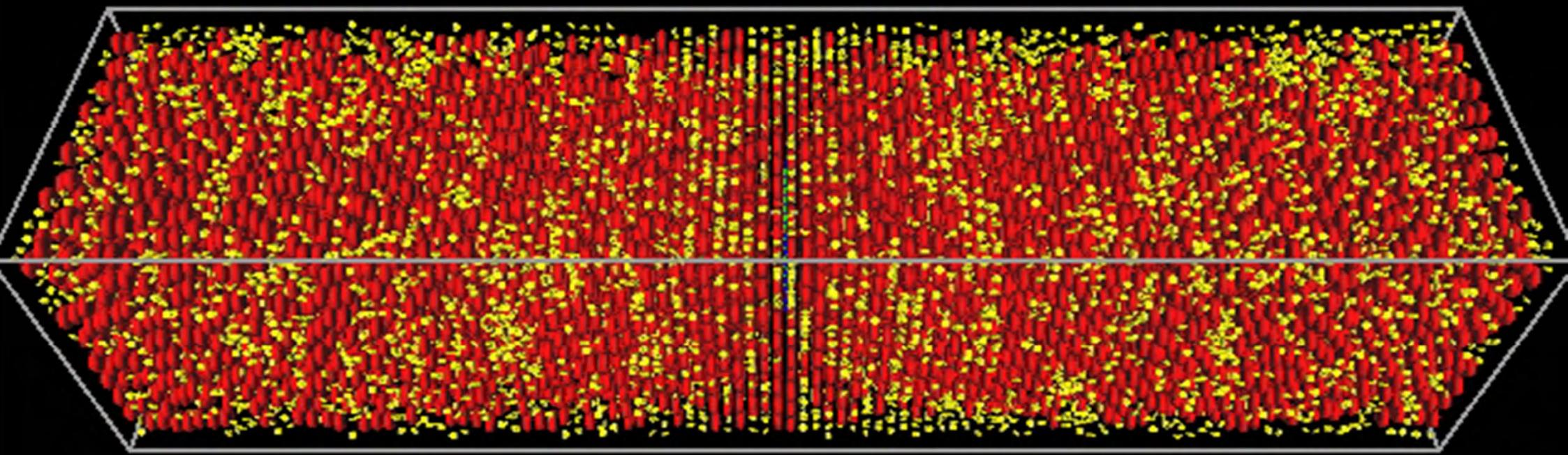
Num. grid points:  $2,048 \times 512 \times 512$

2,048 nodes (16,384 cores) on the K computer

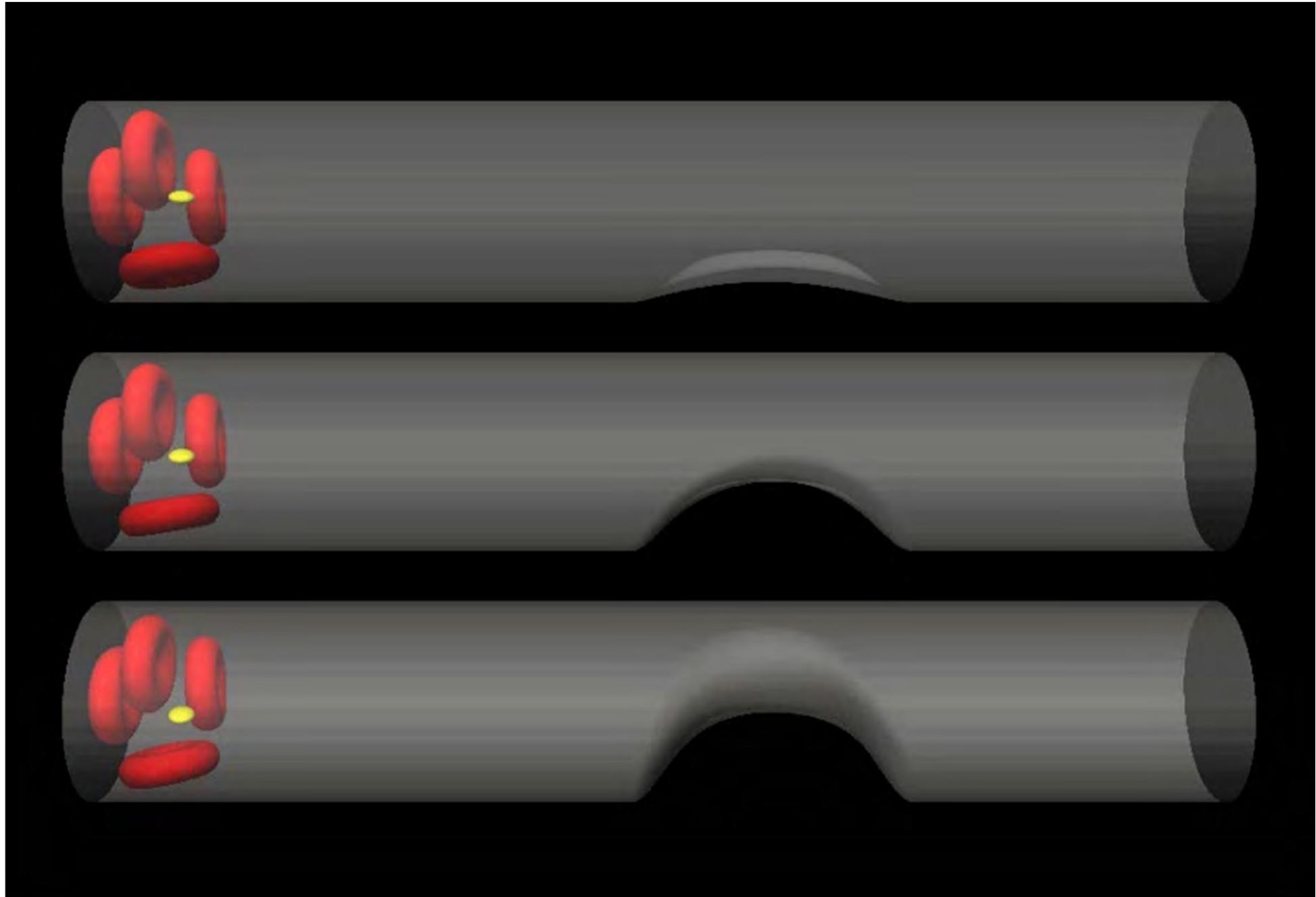


platelet adhesion

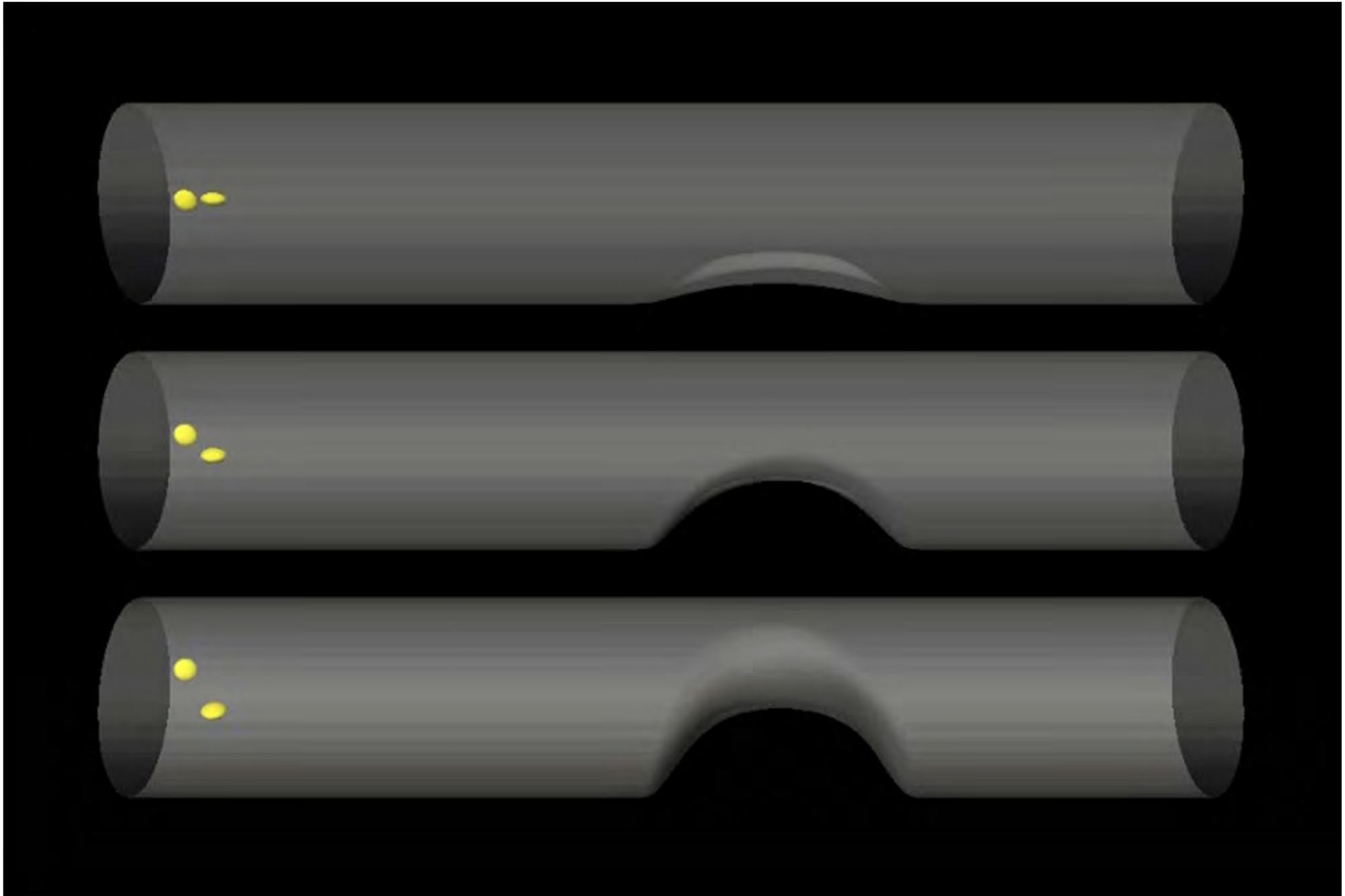




# Effect of arteriosclerosis size ( Hematocrit Value: 20% )



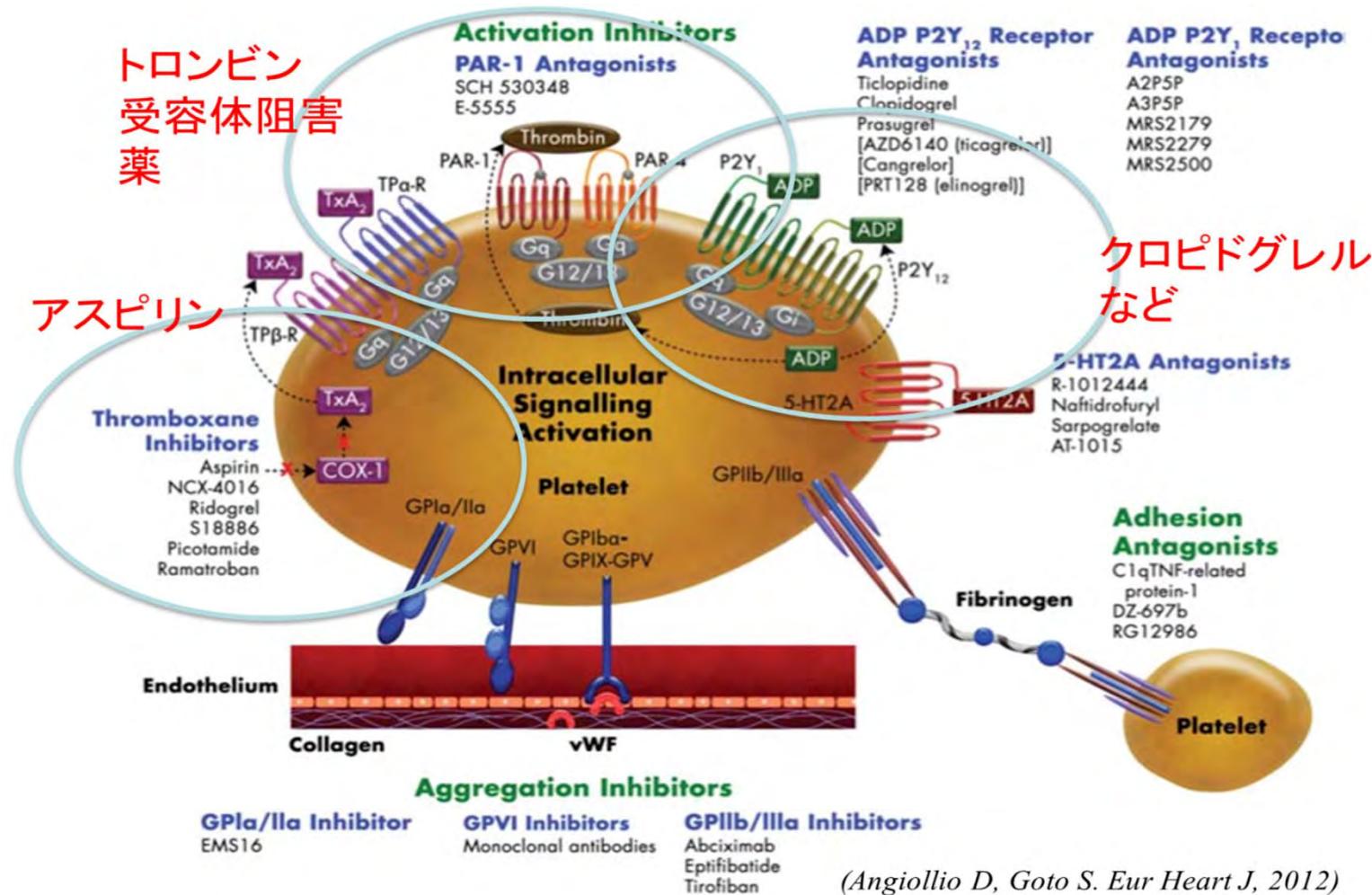
# Effect of arteriosclerosis size ( Hematocrit Value: 0% )



# 抗血小板薬のモデリング

## 循環器系

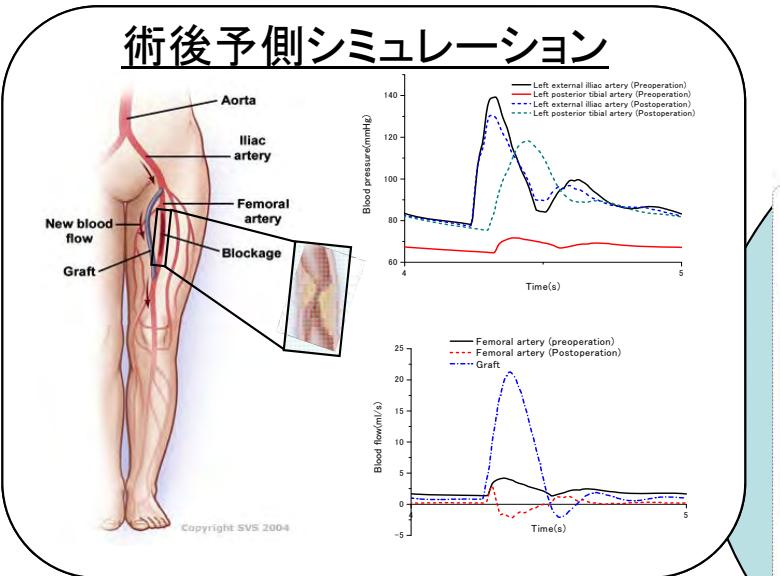
- ・ 抗血小板薬の薬効再現のためのモデリングとシミュレーション



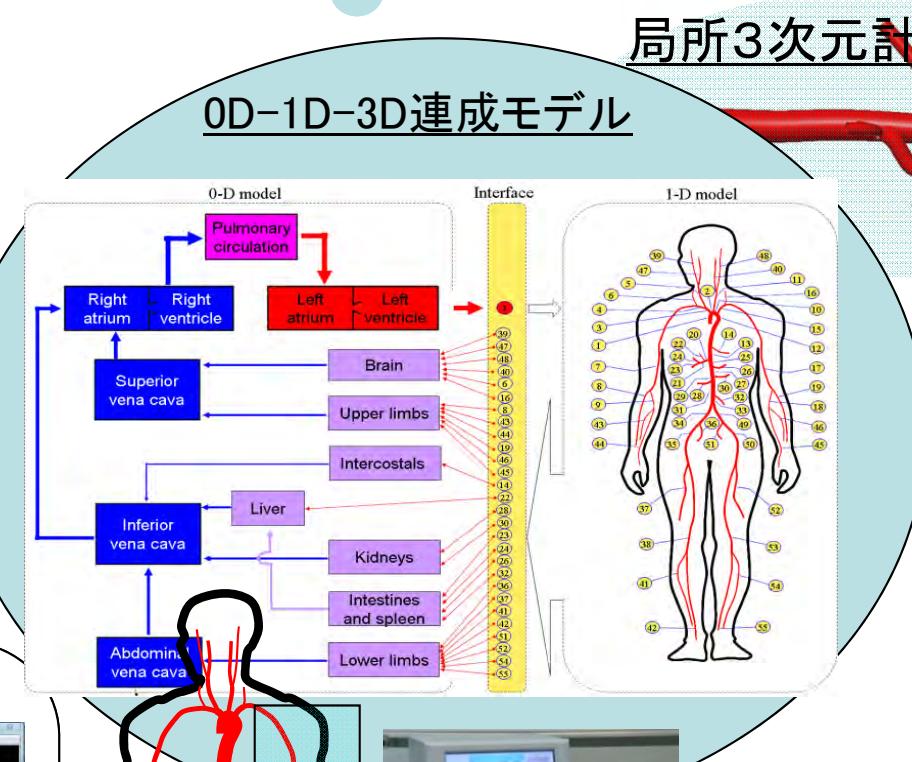
(Angiolillo D, Goto S. Eur Heart J, 2012)

# 実測データを用いた循環器系統合シミュレーション

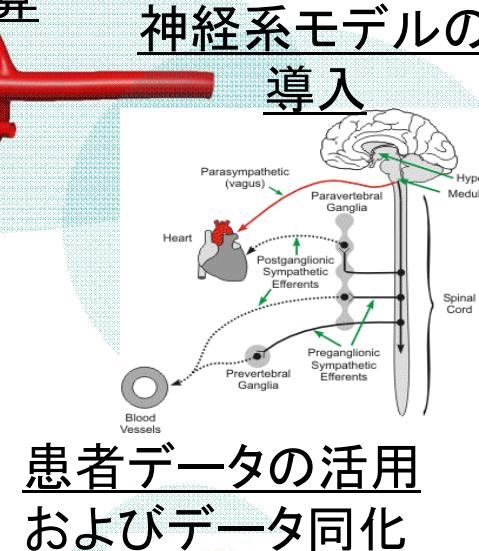
開発済み



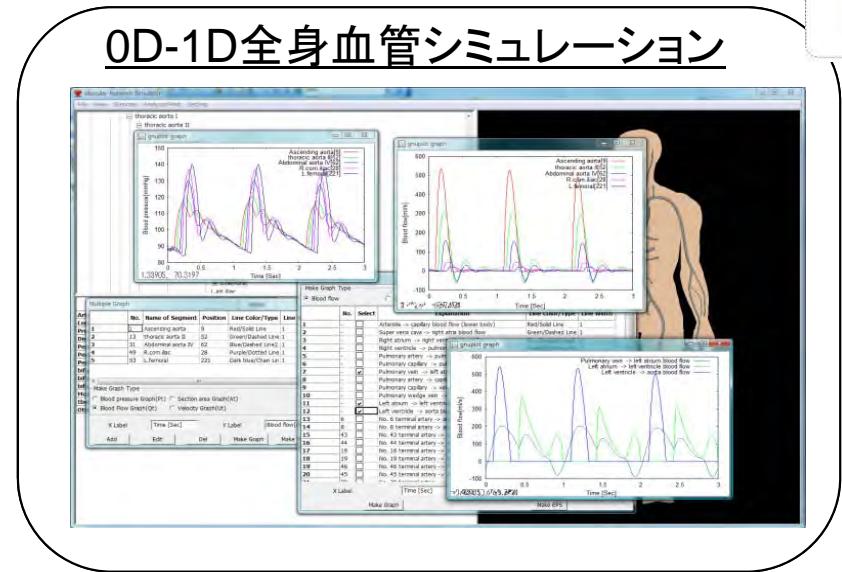
開発中



神経系モデルの導入



患者データの活用  
およびデータ同化



# まとめ

## 現状

- ・医療応用に向けてソフトウェアの準備ができ、本格計算が始まったところ
- ・真の意味での医療応用はこれからが勝負。

→ 医学・医療さらには看護に対して何を創出できるか。

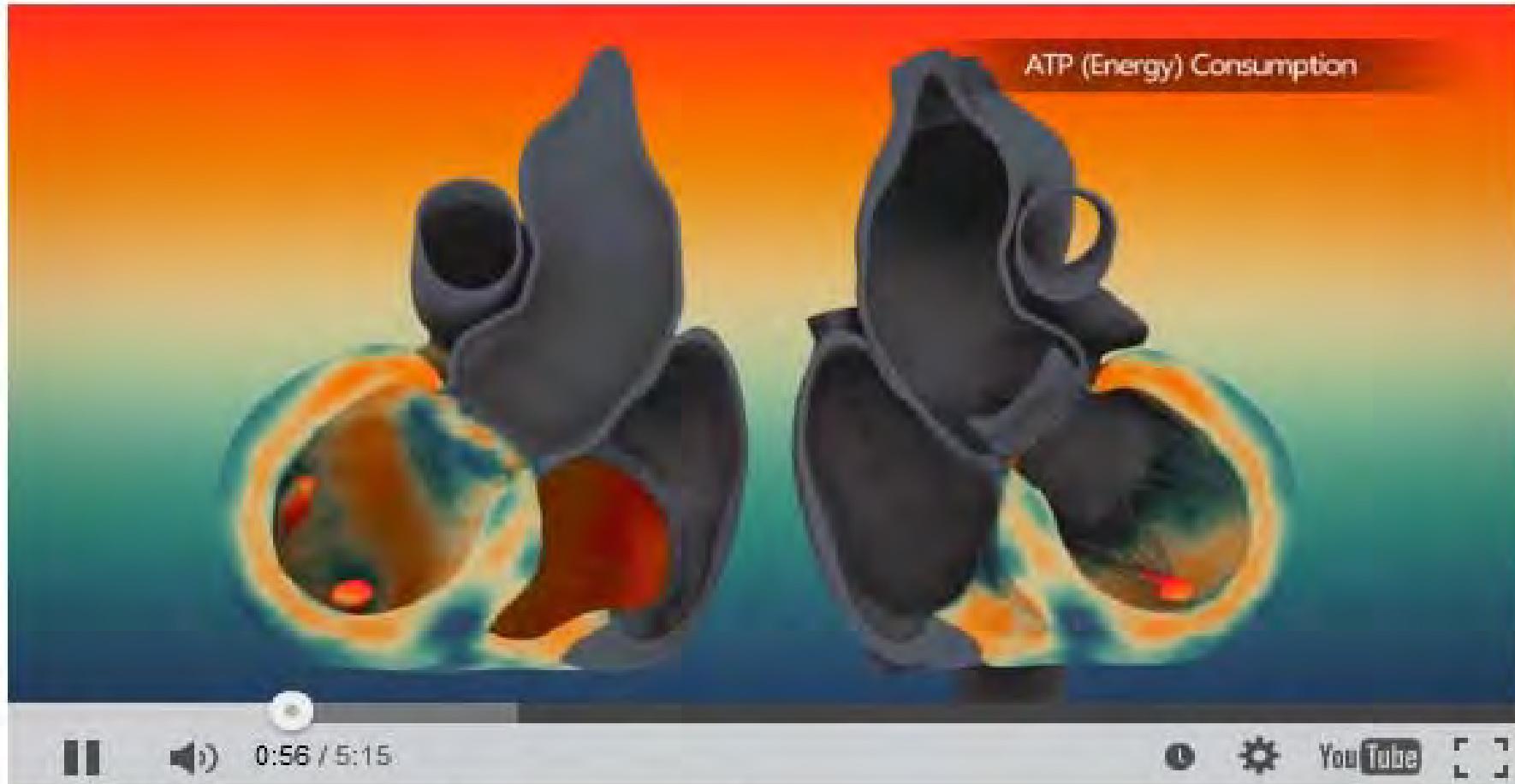
## 今後の予定

- ・超音波診断・治療器設計に向けた計算
- ・血栓シミュレータによる血小板粘着過程の再現と抗血小板薬の薬効評価(P2Y12阻害薬他)
- ・脳神経系と筋骨格系の統合シミュレーション(パーキンソン病の再現)

→ シミュレーションが支援する新しい医学・医療の創出へ.....

Research Achievement (2015)

# Won a Distinguished Simulation Award!!!



Multi-scale Multi-physics Heart Simulator UT-Heart



Win an Award for the 42nd annual Computer Animation Festival, SIGGRAPH 2015

The category: BEST VISUALIZATION OR SIMULATION

**UT-Heart (Hisada et al.)**

# 謝辞

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