

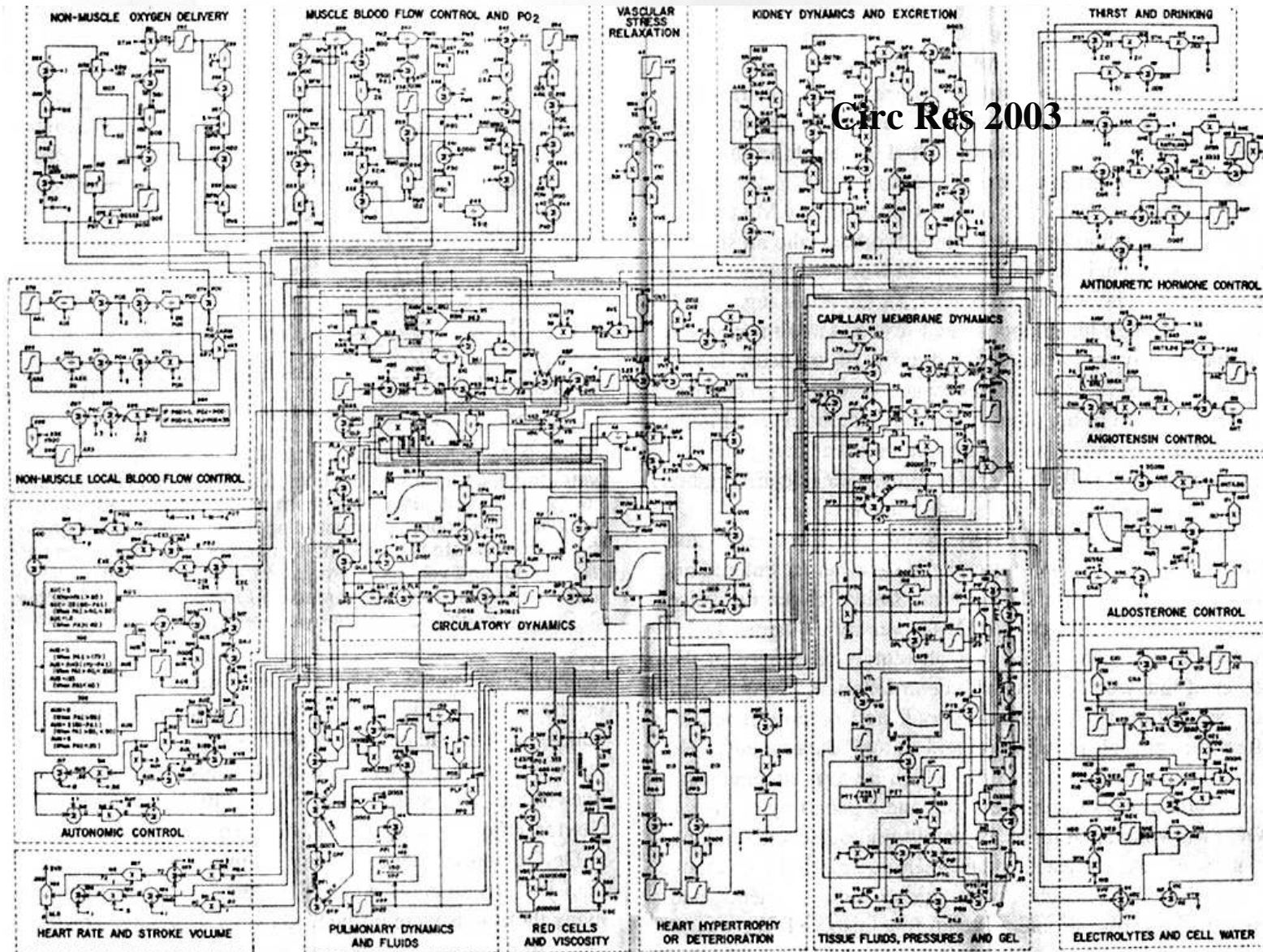
バイオスーパーコンピューティング研究会 (BSCRC) 第二回総会・講演会
2010.10.15 14:35 - 15:25

U-T Heart, テーラーメイド医療への の応用を目指したマルチスケール、マルチ フィジックス心臓シミュレータ

杉浦 清了, 岡田 純一, 鷲尾巧, 渡邊浩志, 久田俊明

東京大学大学院新領域創成科学研究科

循環器領域では早くから シミュレーションの有用性が認識されていた



Circ Res 2003

マクロの指標に基づくシミュレーションは病態を明解に説明できる。

しかし一方で.....

- 薬のターゲットは分子
- 疾患と遺伝子異常の **関係** — **病因?**

Ex.

家族性肥大型心筋症



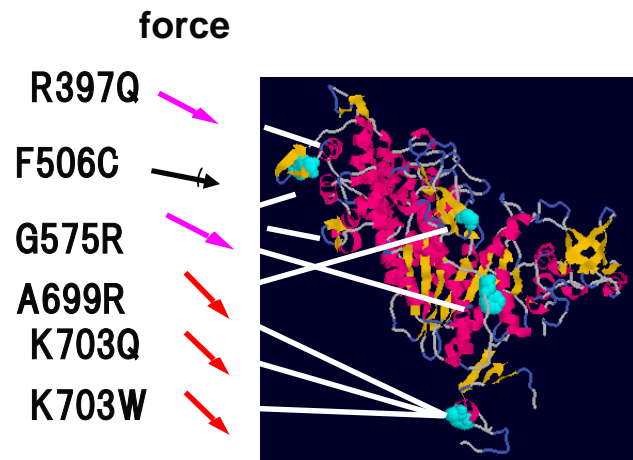
原因不明の心肥大
若年での突然死

Linkage analysis



収縮タンパク
ミオシンの点突然変異

これらの変異はタンパクの機能低下を来す!



Fujita et al. 1996

しかし...



心肥大
突然死

全て説明できるわけではない。

At the bench



Gene



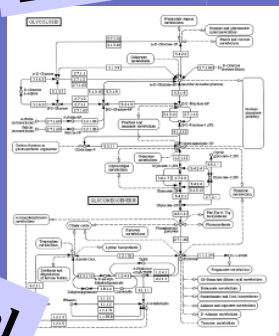
Gapを埋めるシミュレーションを

Gap

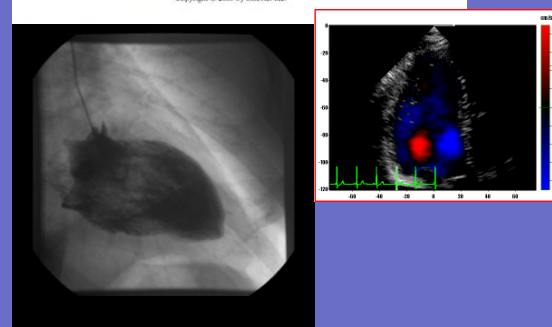
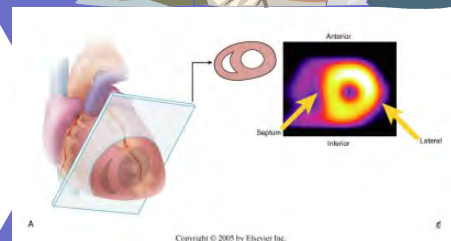
pathway



Transcriptional factor

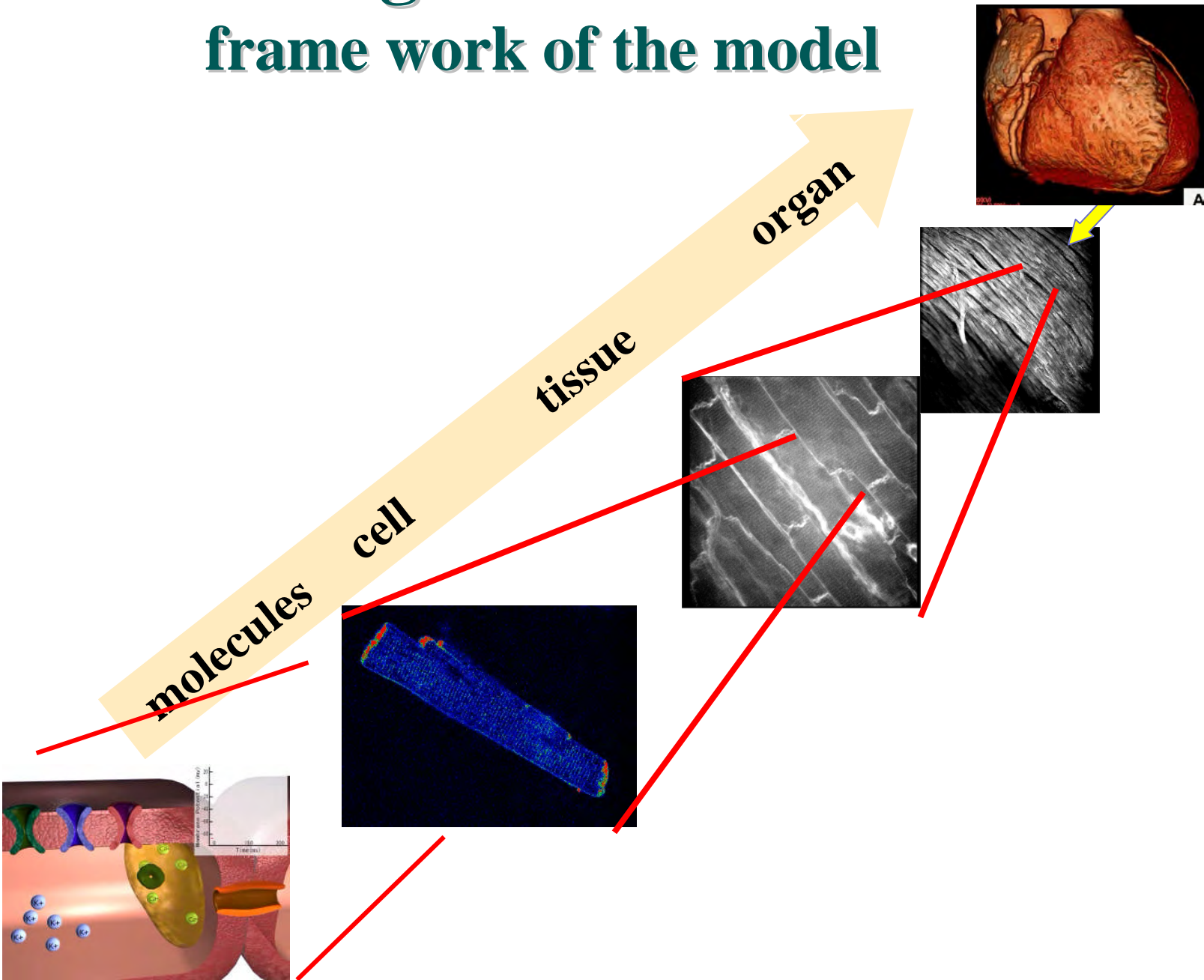


At the bedside



Creating the heart *in silico*

frame work of the model



Electrophysiology model for excitation

TenTusscher K.H.W.J. et al Am J Physiol 2003

Courtemanche M. et al Am J Physiol 1998

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa}$$

$$I_{Na} = G_{Na} m^3 \cdot h \cdot j \cdot (V - E_{Na})$$

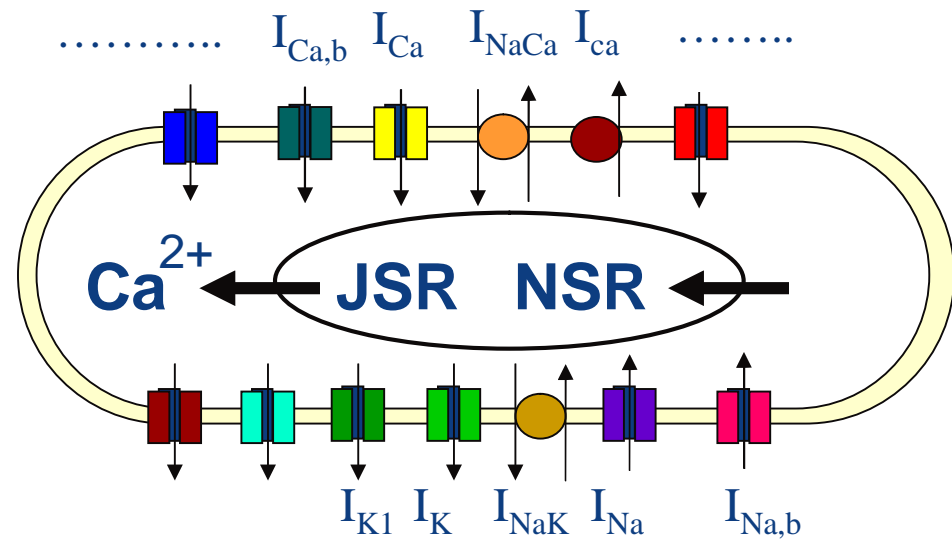
.....

$$I_{leak} = V_{leak} (Ca_{sr} - Ca_i)$$

$$I_{up} = \frac{V_{max\ up}}{1 + \frac{K_{up}^2}{Ca_i^2}}$$

$$I_{rel} = \left(a_{rel} \frac{Ca_{sr}^2}{b_{rel}^2 + Ca_{sr}^2} + c_{rel} \right) dg$$

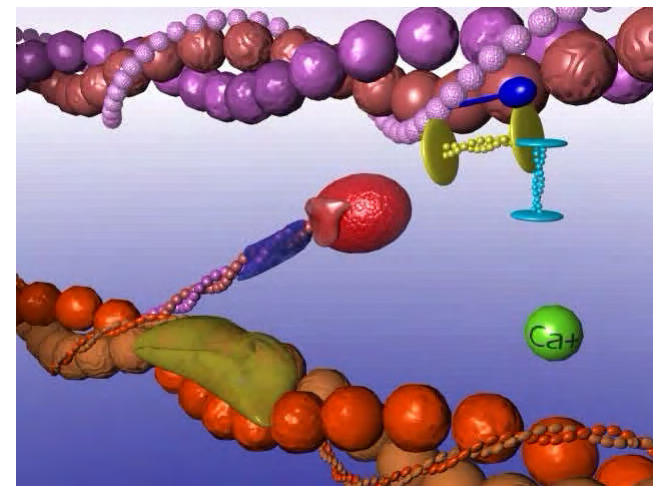
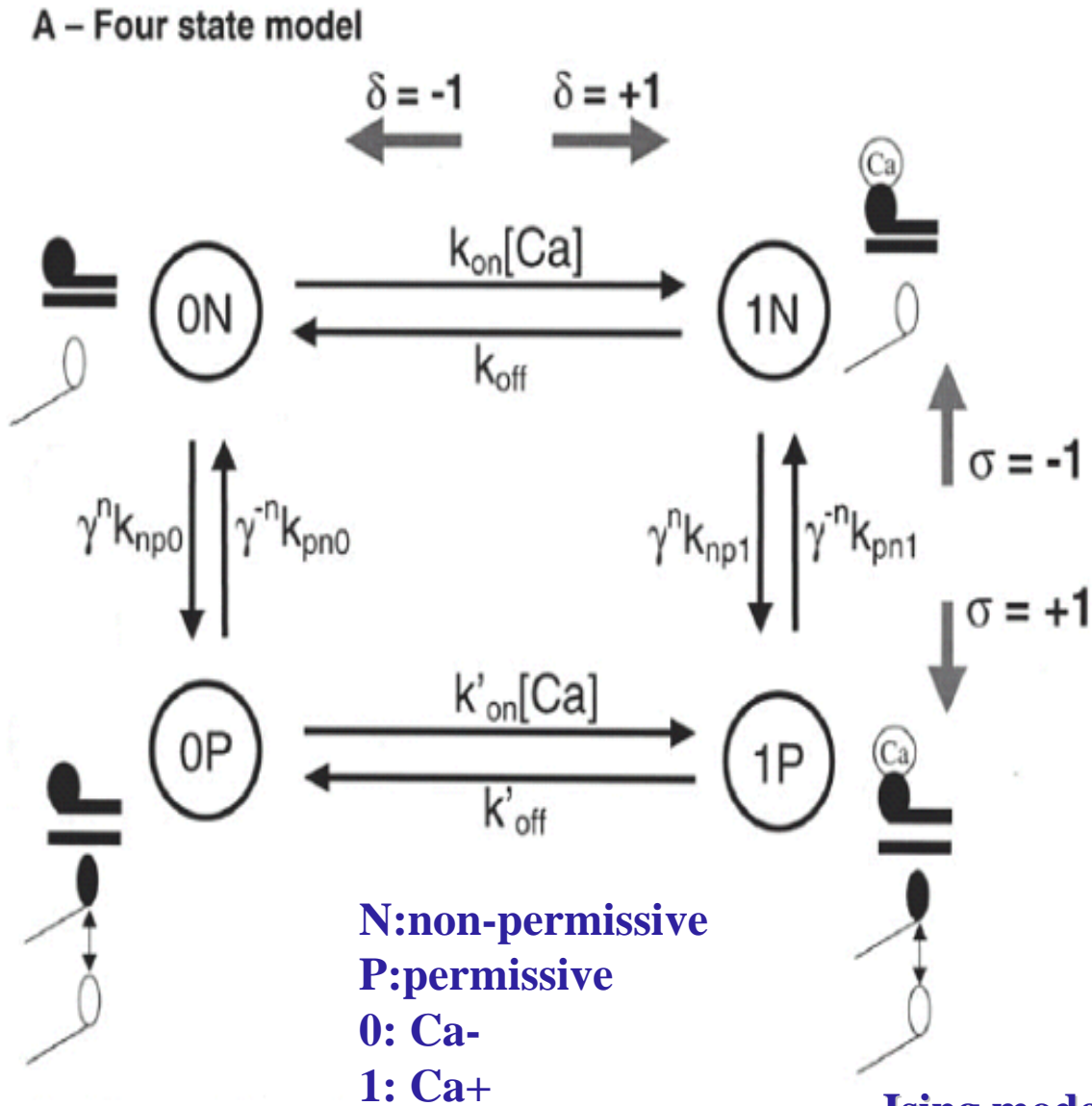
$$\frac{dV}{dt} = \frac{I_{ion} + I_{stim}}{C_m}$$



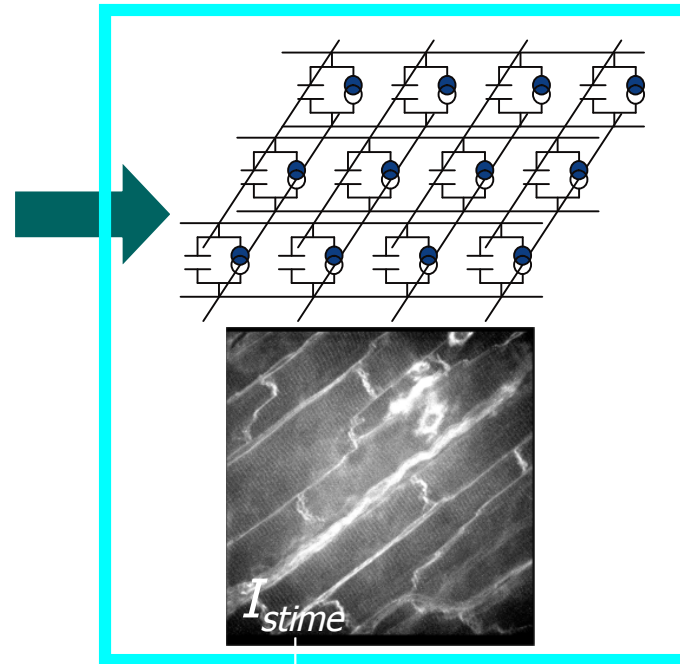
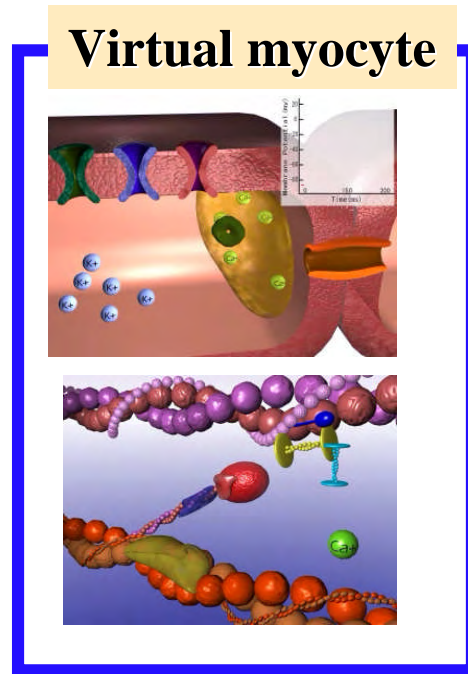
I_{rel}  Contraction model



Sarcomere dynamics model for contraction



Virtual myocytes are coupled to build the tissue structure



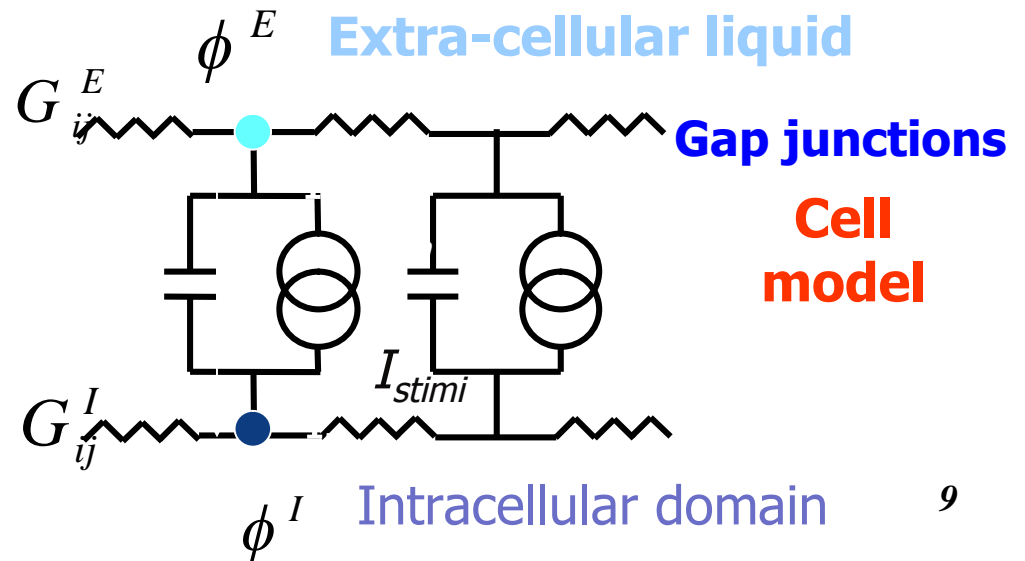
Bidomain model

$$\beta \left(C_m \frac{\partial V}{\partial t} + I_{ion} \right) = I_{stim} - \frac{\partial}{\partial x_i} \left(G_{ij}^E \frac{\partial \phi^E}{\partial x_j} \right)$$

$$V = \phi^I - \phi^E$$

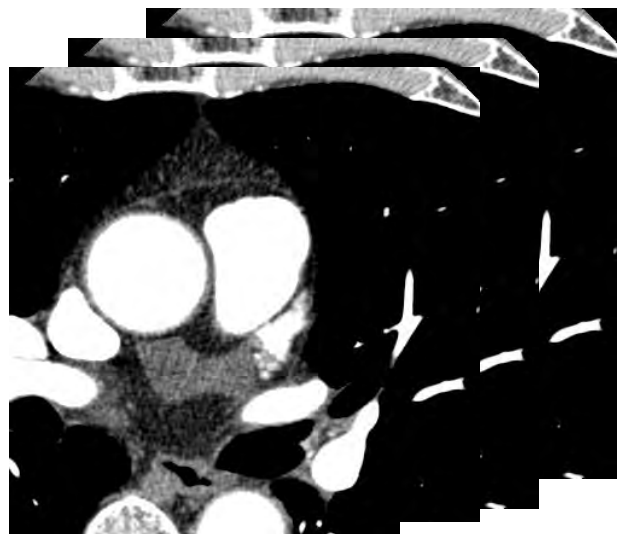
$$\beta \left(C_m \frac{\partial V}{\partial t} + I_{ion} \right) = I_{stim} + \frac{\partial}{\partial x_i} \left(G_{ij}^I \frac{\partial \phi^I}{\partial x_j} \right)$$

Monodomain model

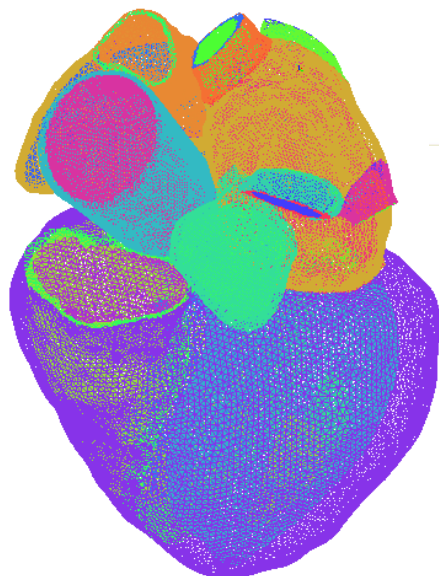
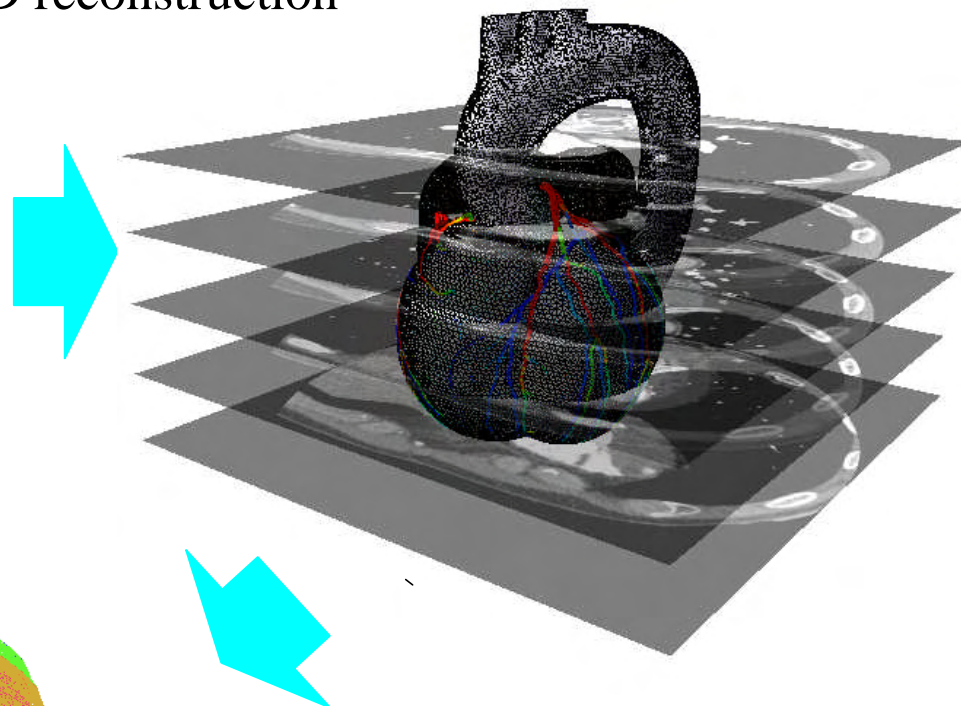


CT画像に基づいた心臓有限要素法モデル

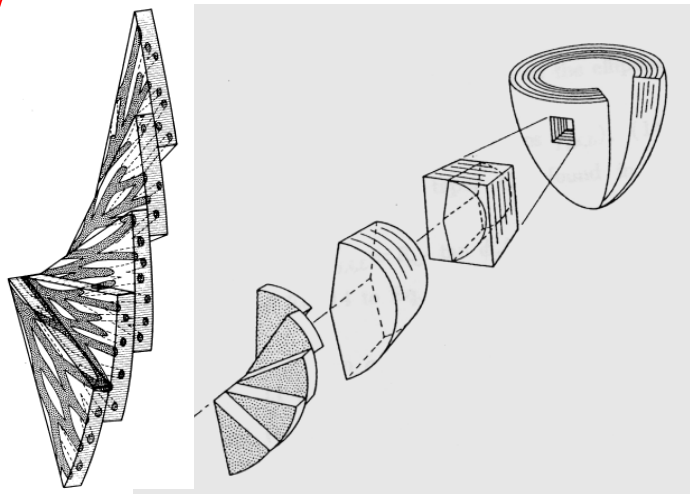
CT images



3D reconstruction



心筋の線維方向とシート構造のモデル化

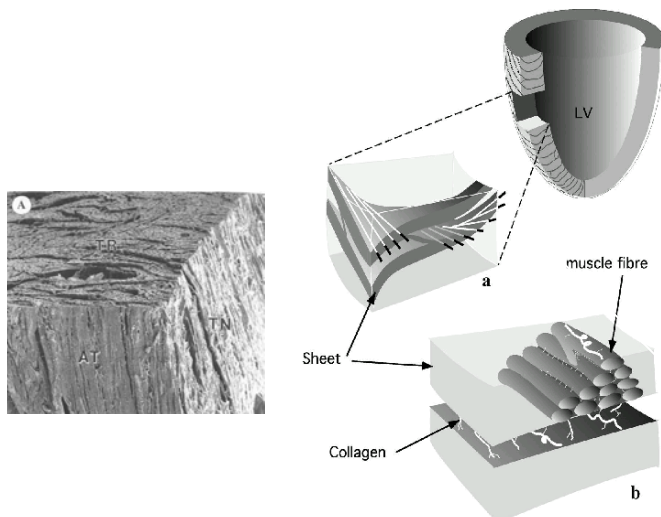
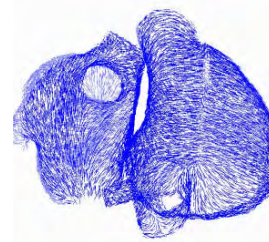


Streeter DD et al, *Circ Res* 1969;24:339
Streeter DD et al, *Circ Res* 1973;33:656

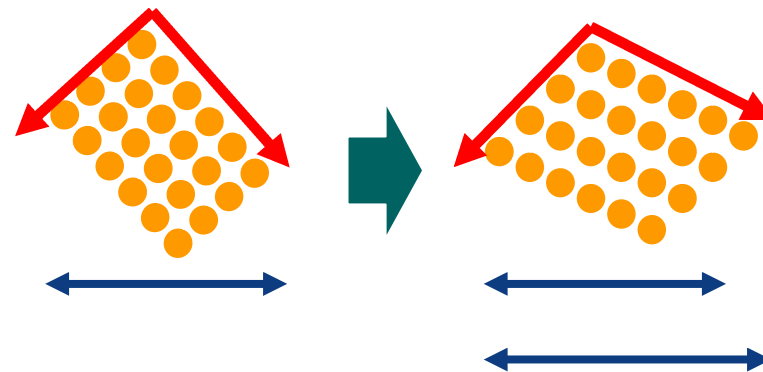
心室



心房



LeGrice, Hunter, P. J. et al. *AJP* .1995.



Costa K D, et al, *AJP* 1999

刺激伝導系



Tawara



One-dimensional Finite Element Network was constructed based on anatomical data.

Cell model: DeFrancesco and Noble, 1985

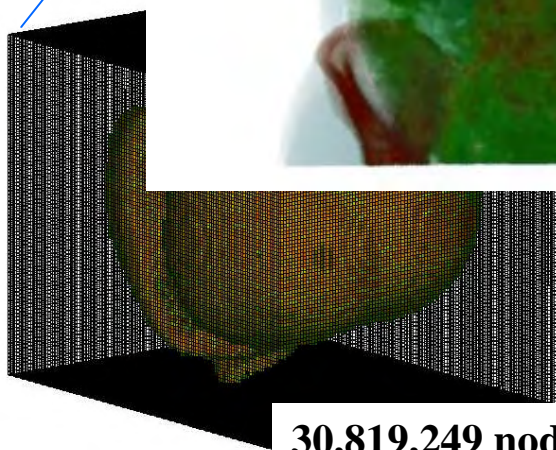
興奮伝播解析用voxel model

Torso



主要臓器 (電気伝導度)

Heart

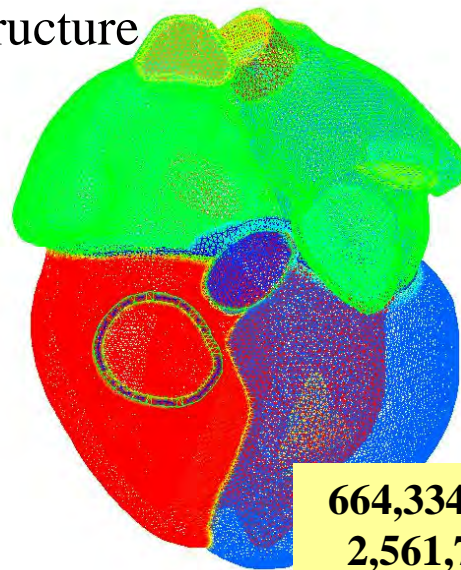


30,819,249 nodes

(Total 49,425,860 nodes)

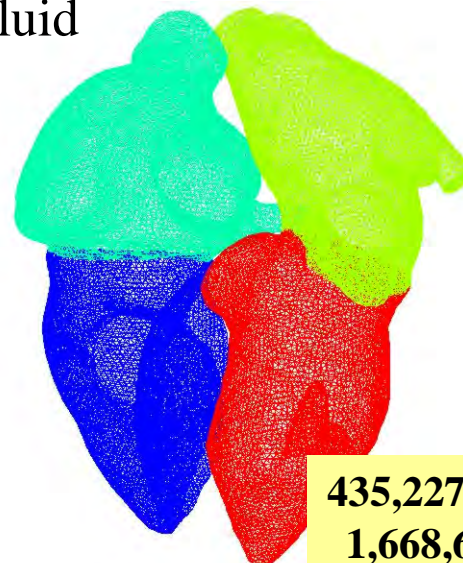
力学解析用Tetrahedral FEM model

structure



664,334 elements
2,561,750 DOF

fluid

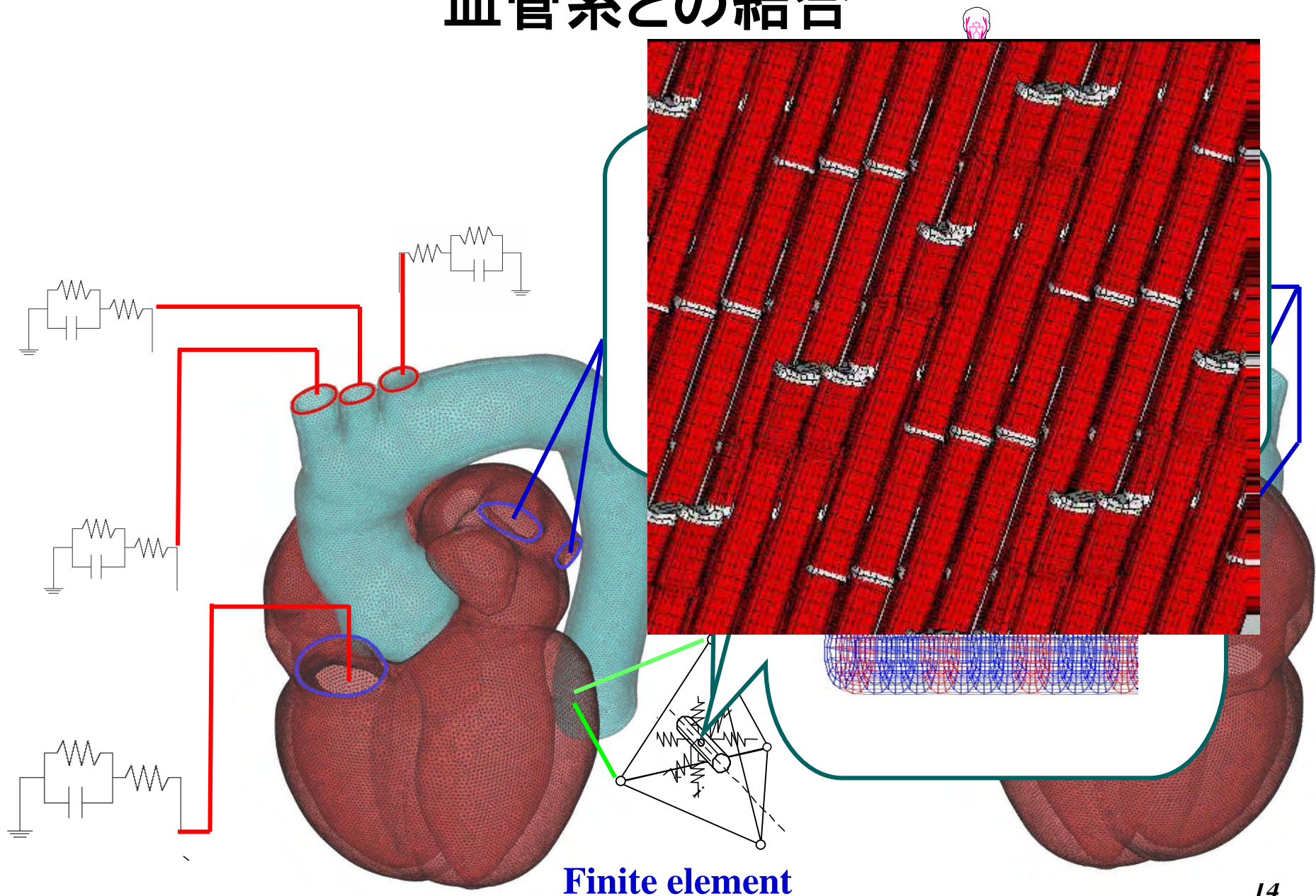


435,227 elements
1,668,669 DOF



(total ~4.2 million DOF)

血管系との結合



興奮伝播

房室結節

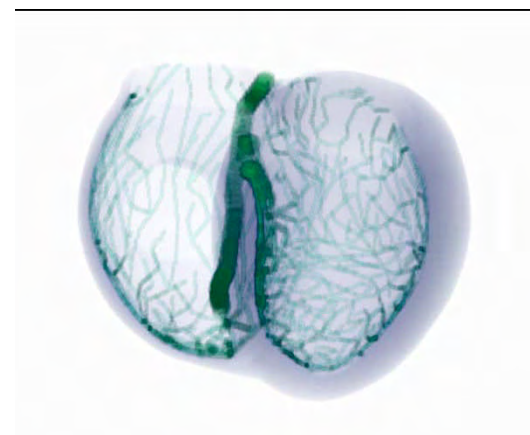
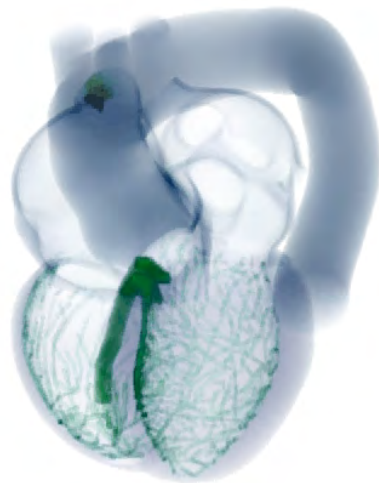
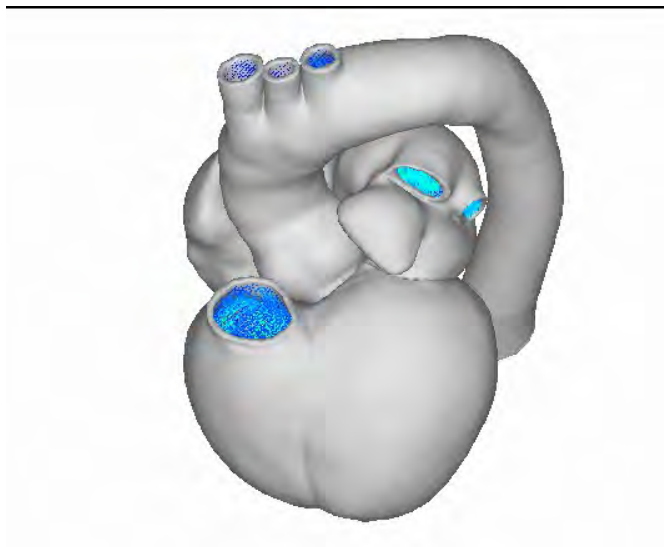
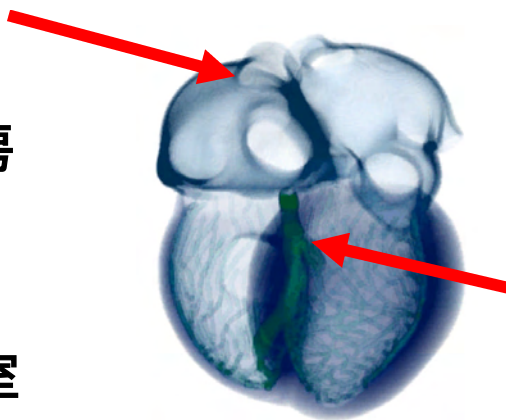
右心房

右心室

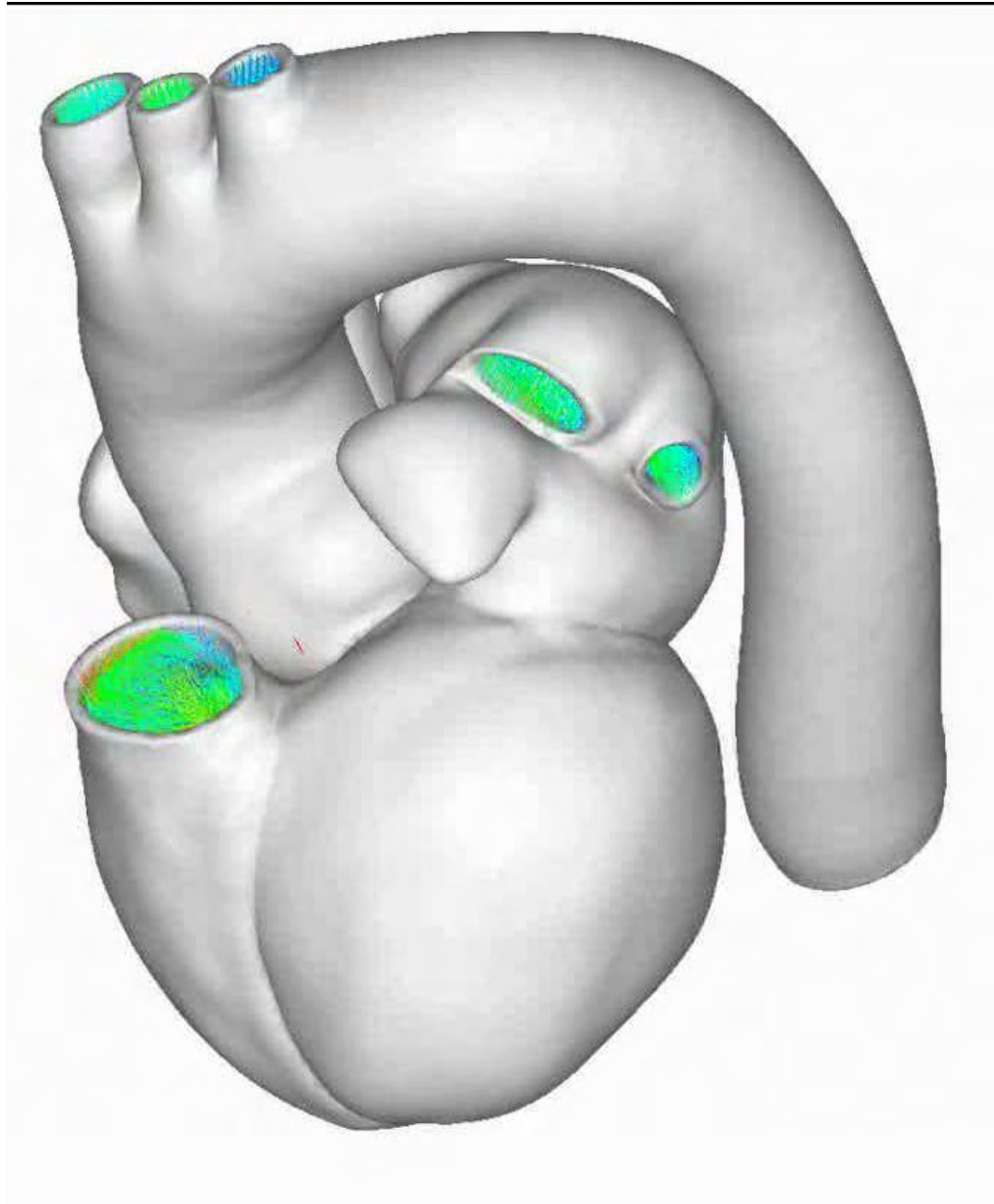
左心房

プルキンエ線維

左心室

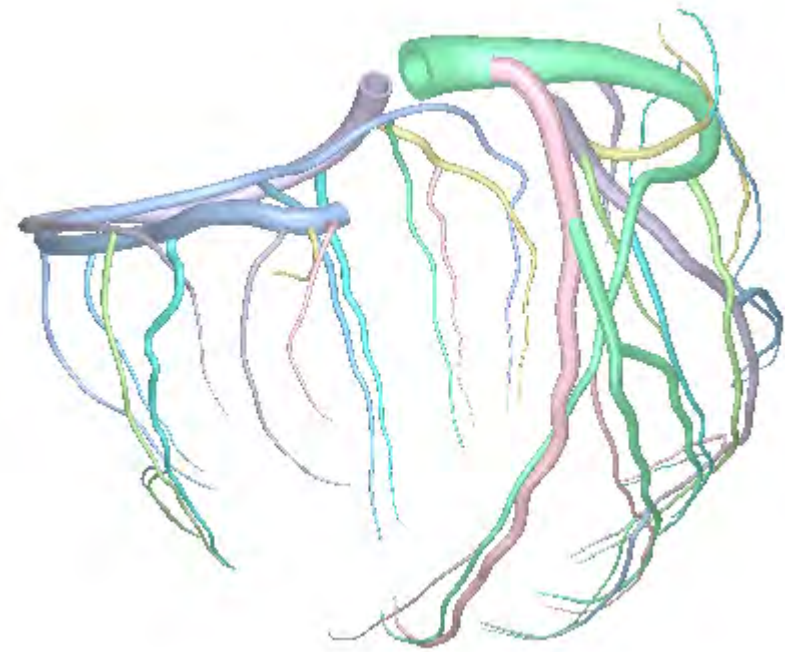


slow motion 15

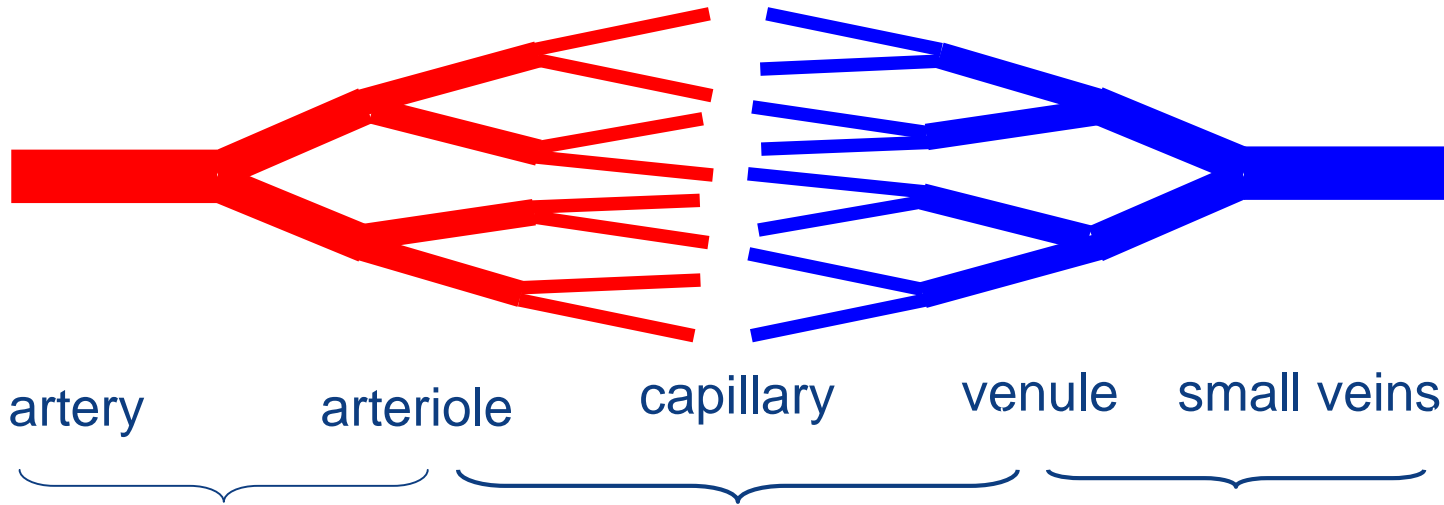


冠循環のモデル化

1. 心表面の血管 (artery and vein)



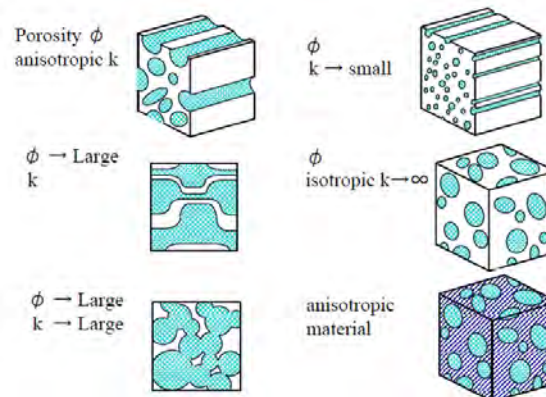
2. 小血管 & 微小循環



network model

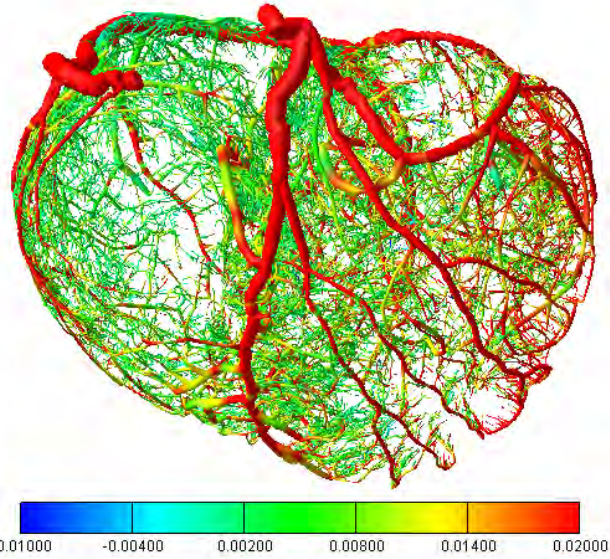
porous medium

network model

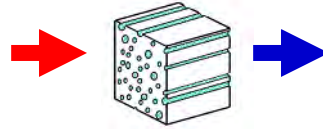


Biphasic theory

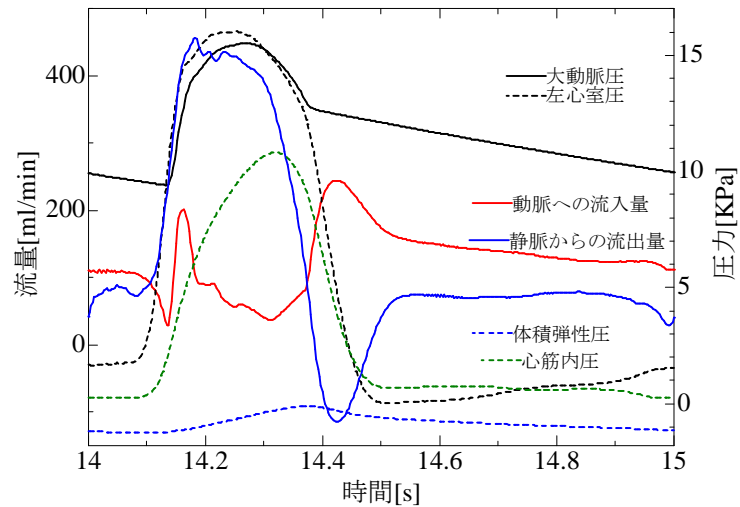
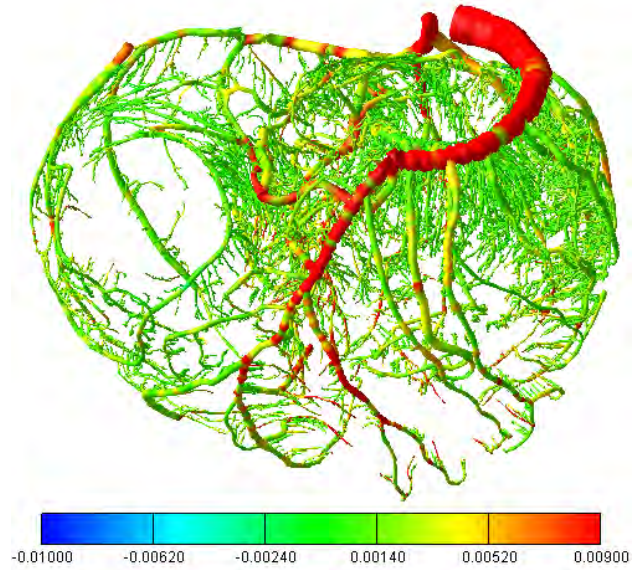
動脈(6+1 levels)



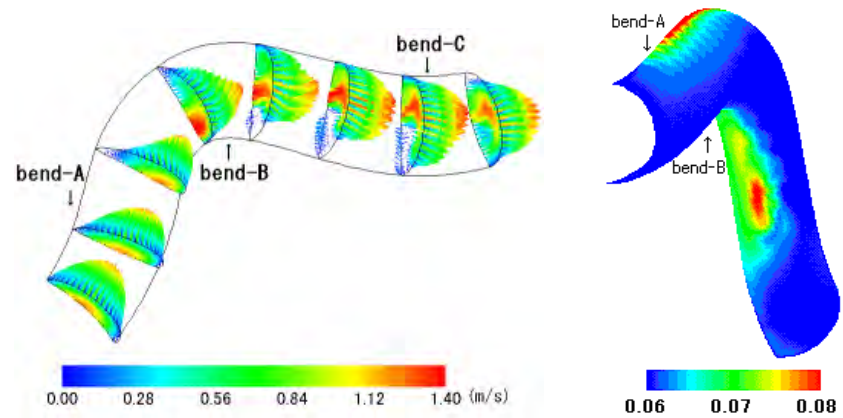
微小循環

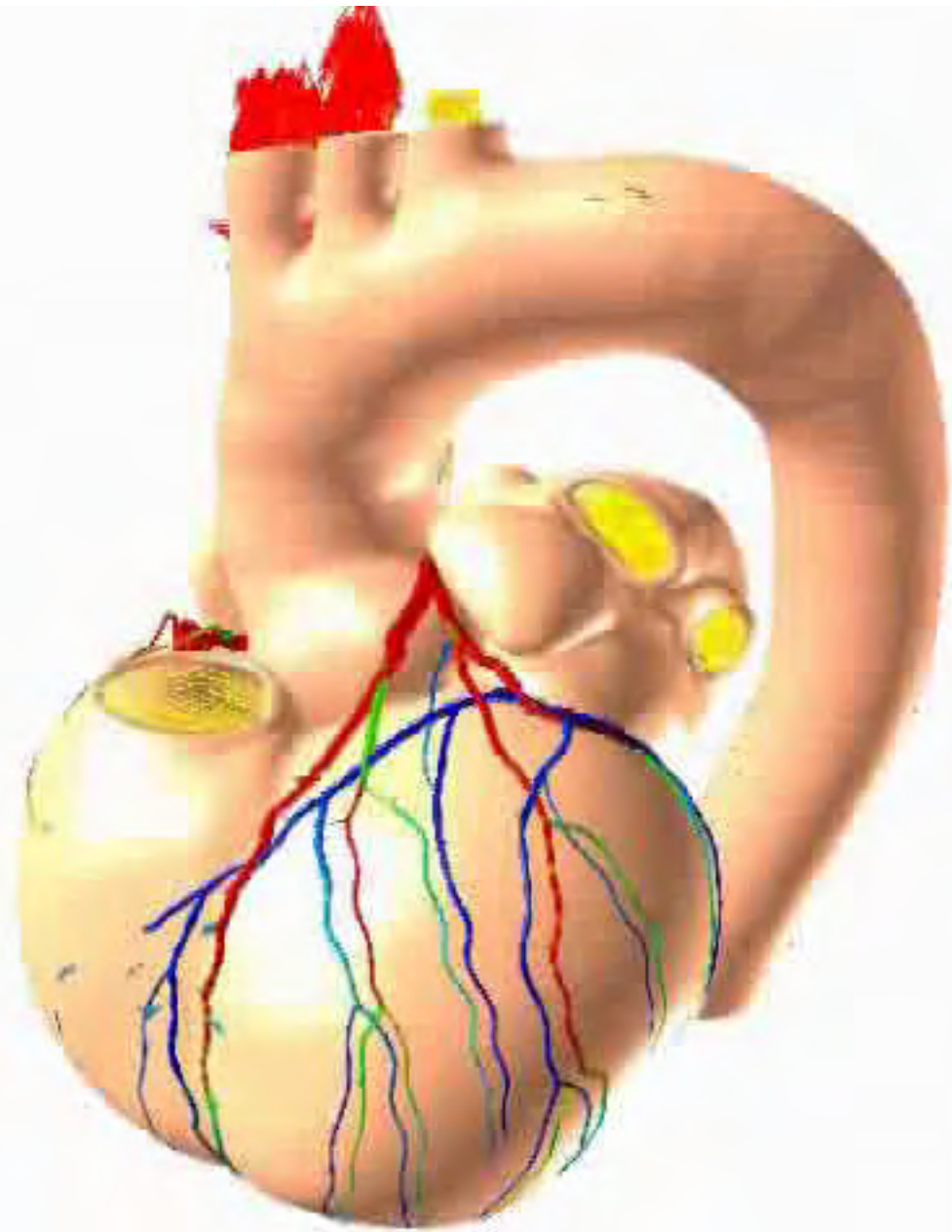


静脈(6+1 levels)



右冠動脈・血管壁内におけるLDL蓄積



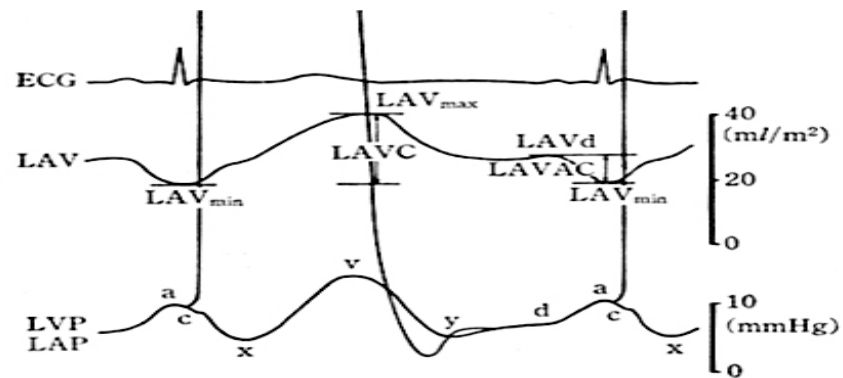
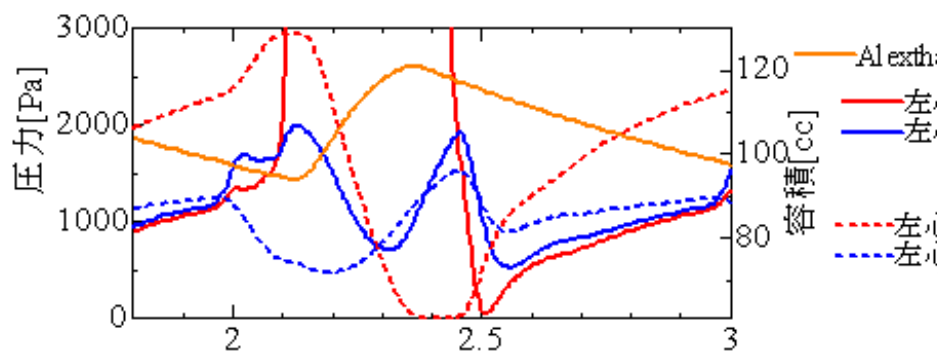
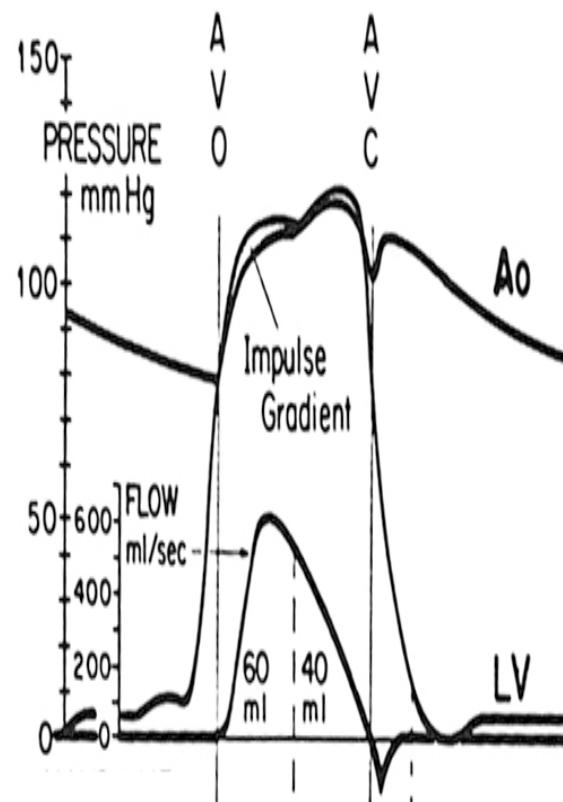
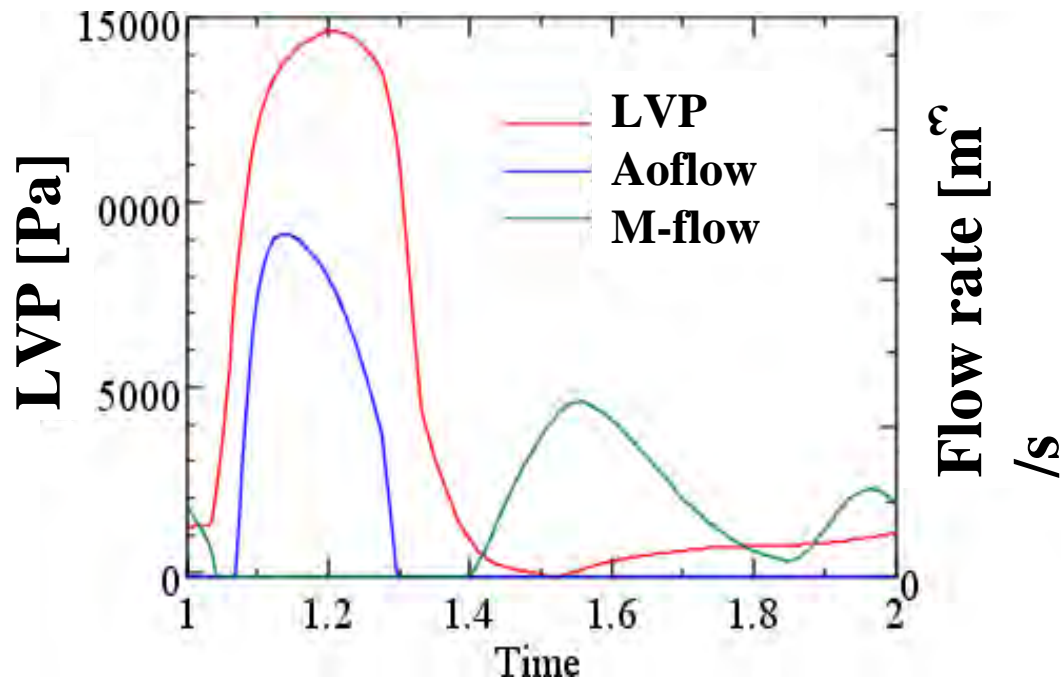


In silico 診断 & 治療

-- Clinical application and verification --

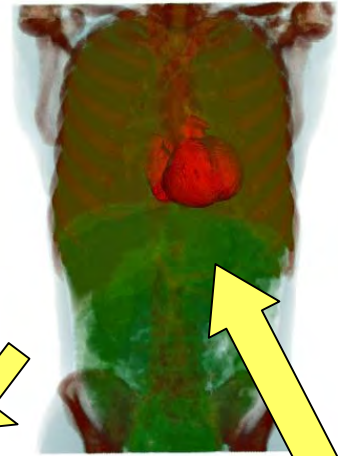


1. 血行動態



In silico 診断

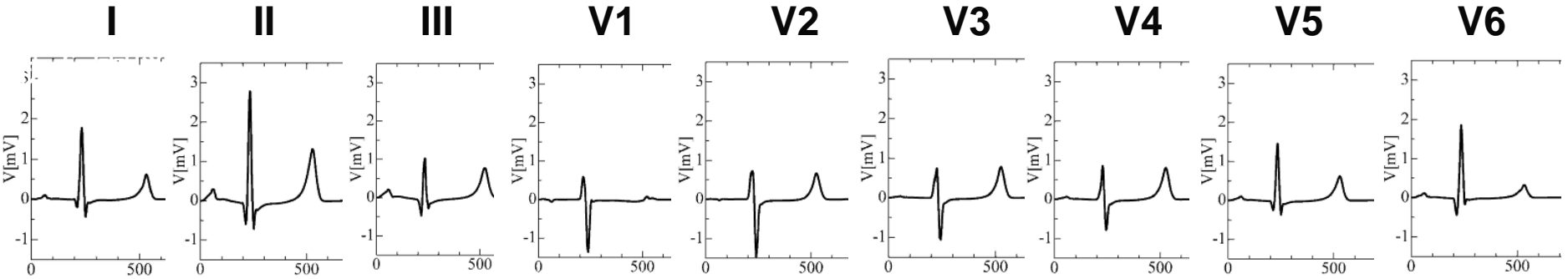
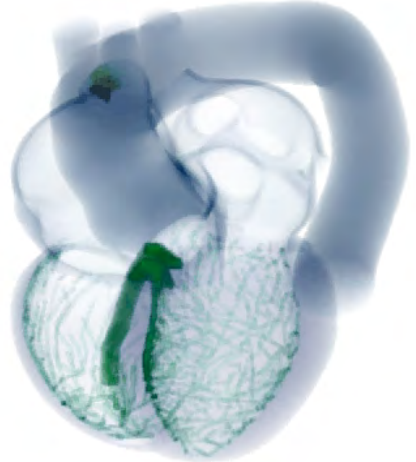
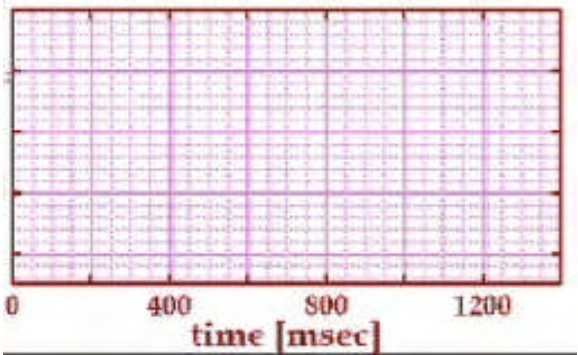
2. 心電図



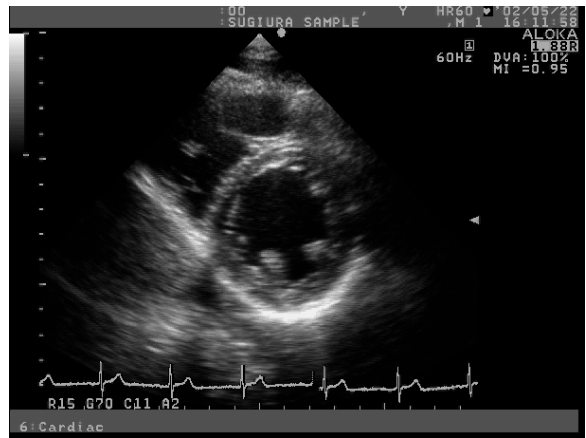
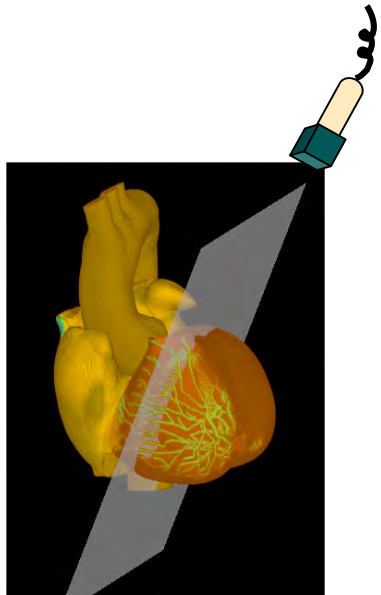
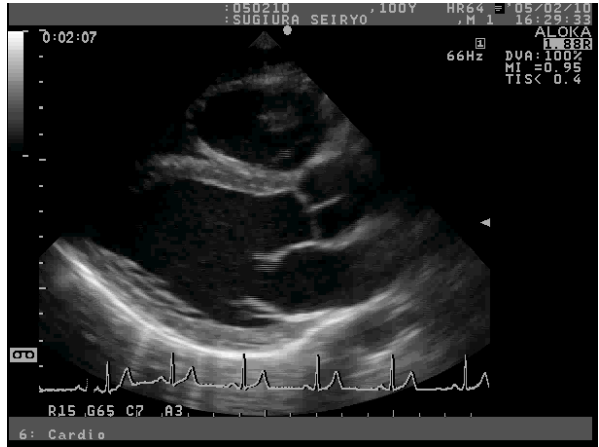
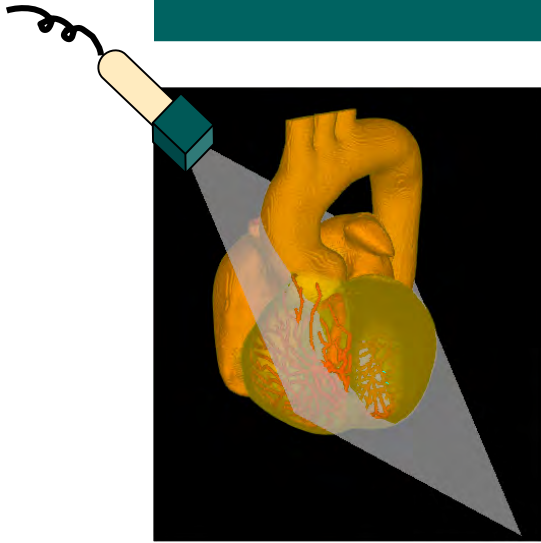
膜電位

体表面電位

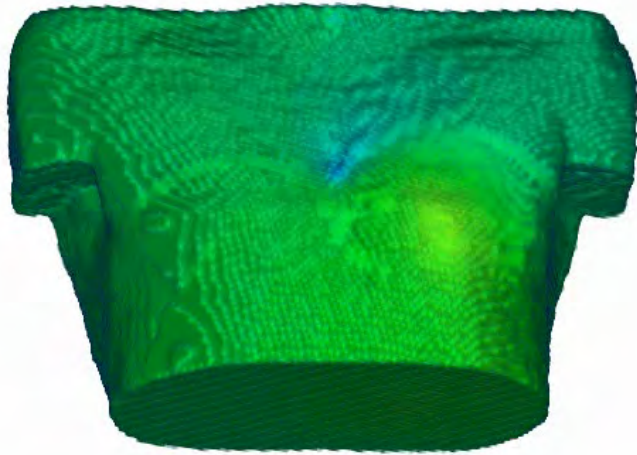
第二誘導



3. 心エコー



心室細動 Ventricular fibrillation (VF)

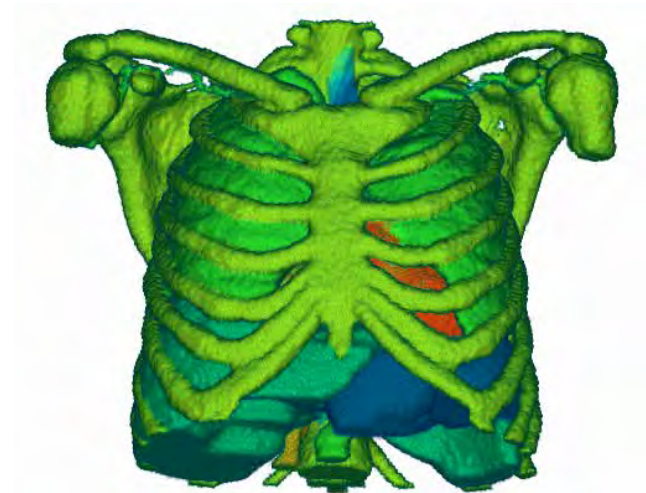
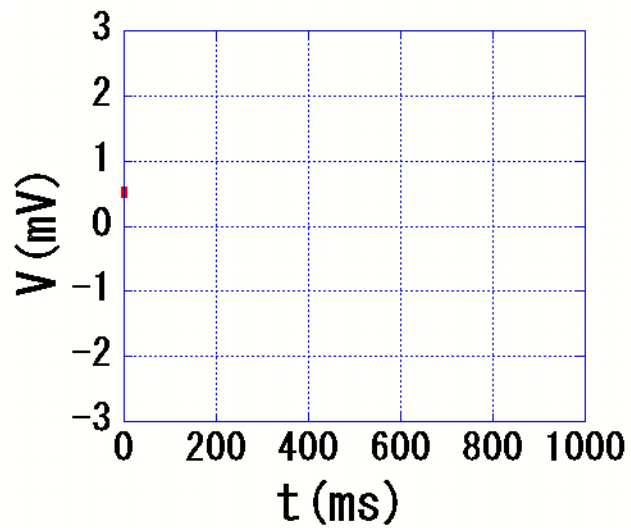


Body surface map



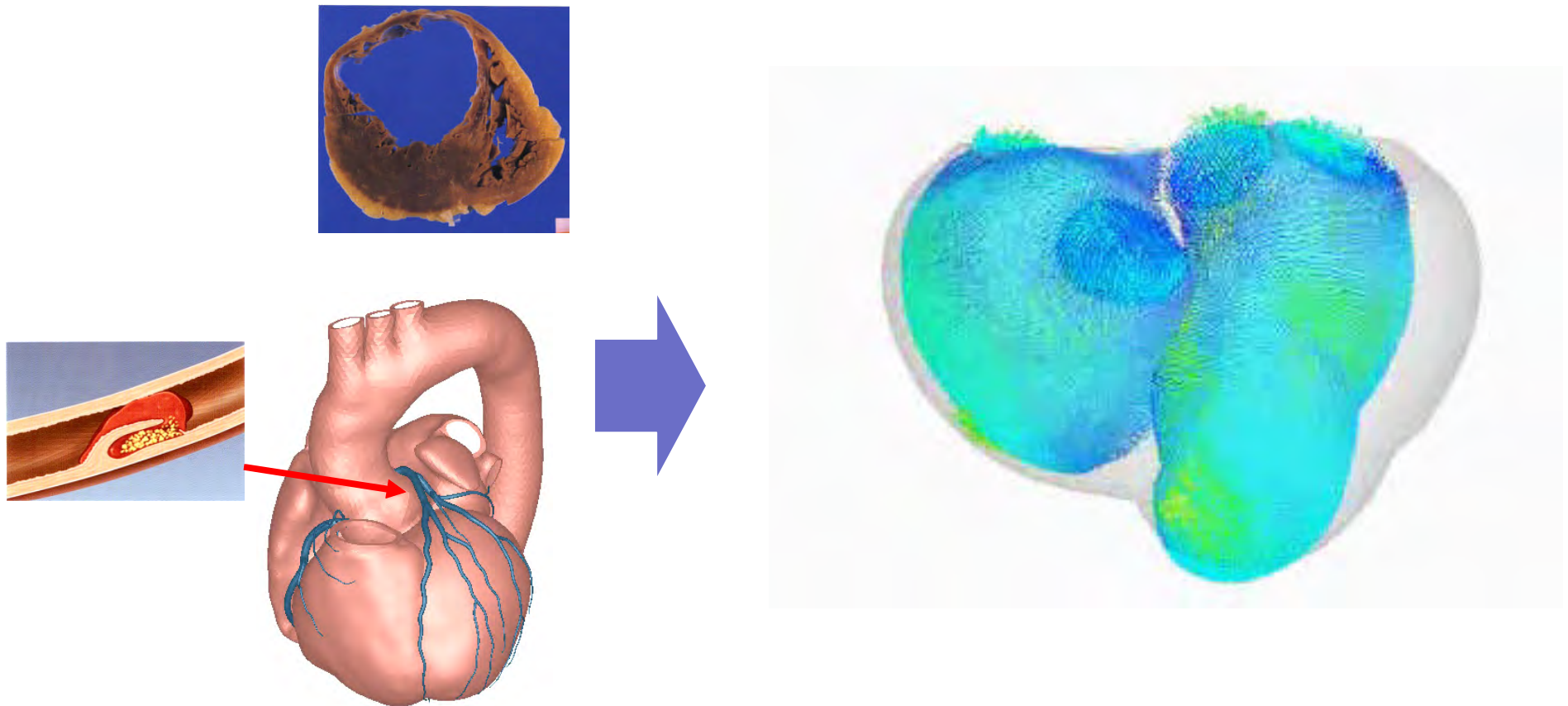
Membrane potential

II lead



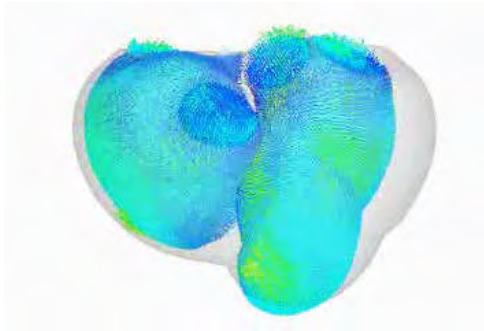
バーチャル心臓手術

Case#: 梗塞後の心室瘤



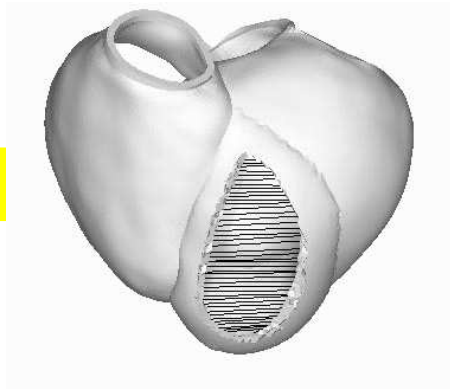
左室瘤

術前



①

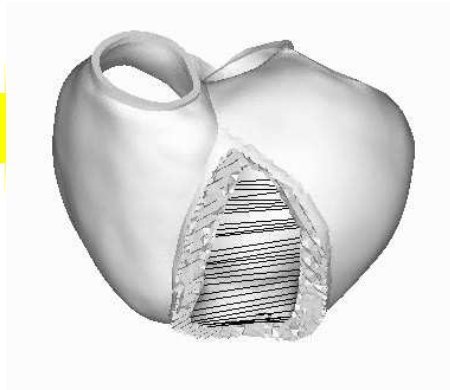
modest



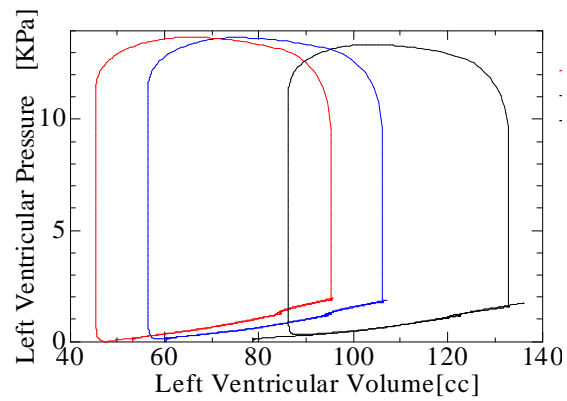
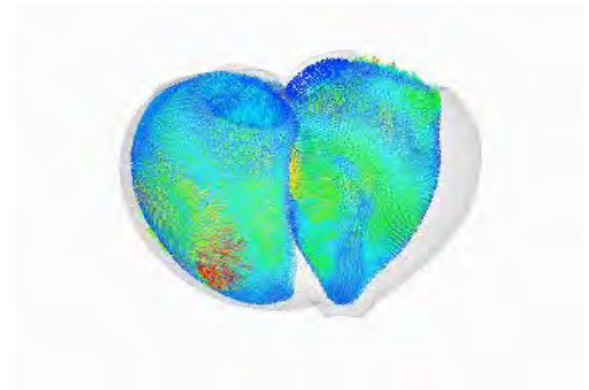
②



radical

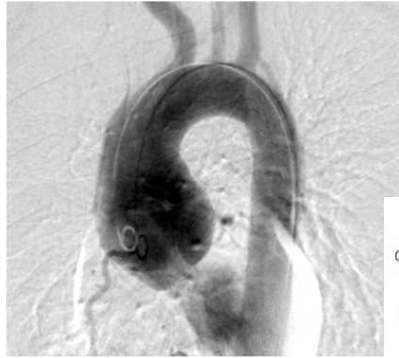


③

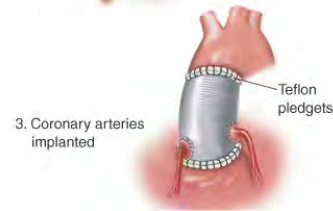
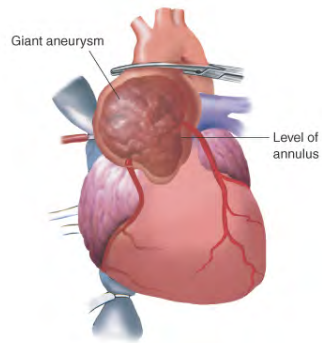
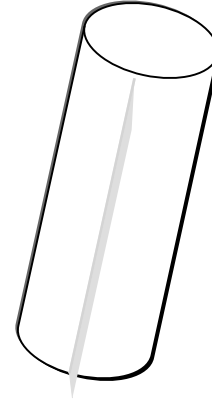
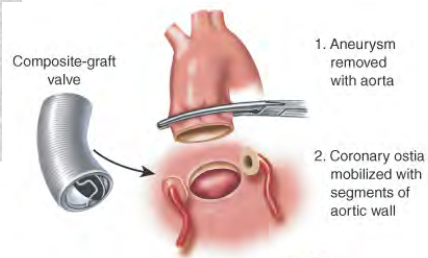


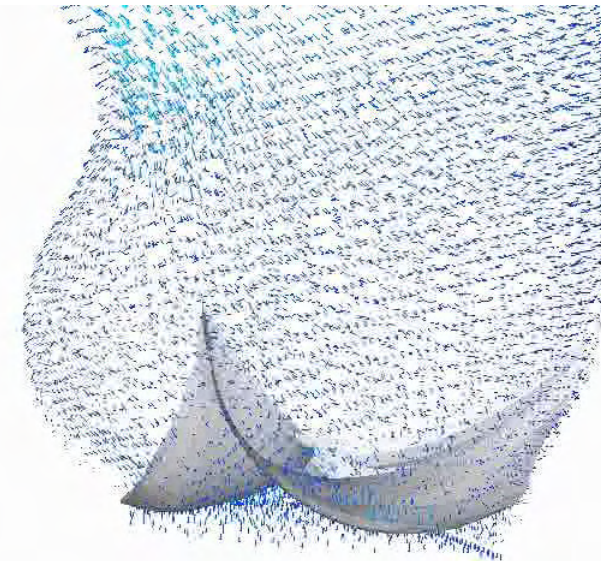
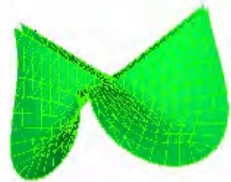
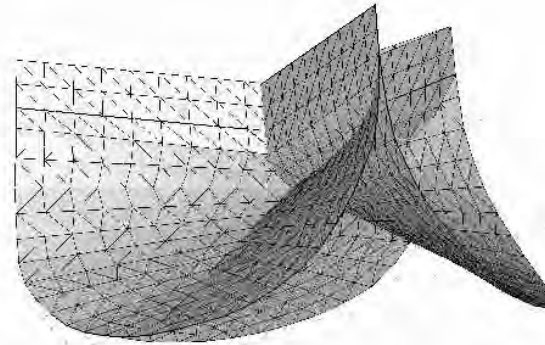
	EF
①	34.9
②	46.6
③	50.9

Optimal design of the graft



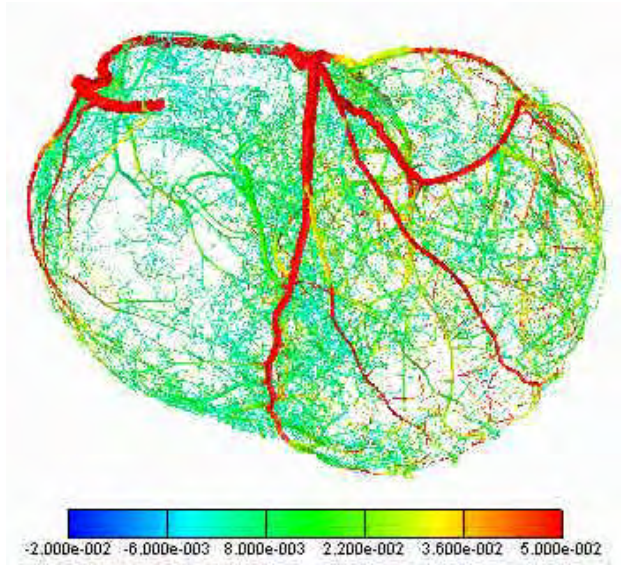
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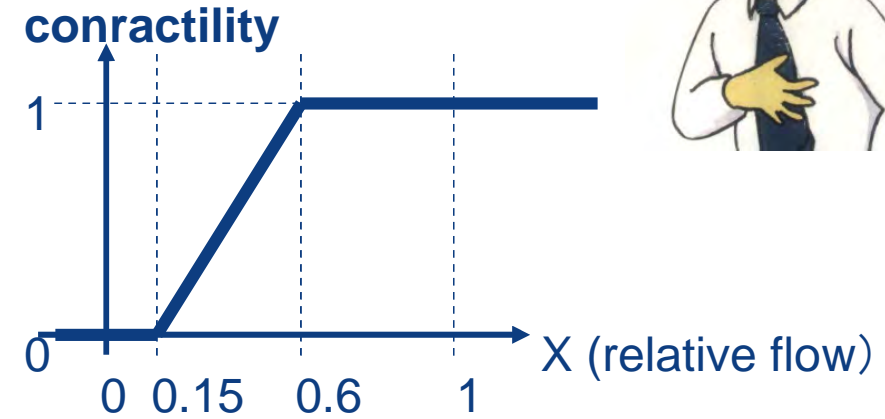
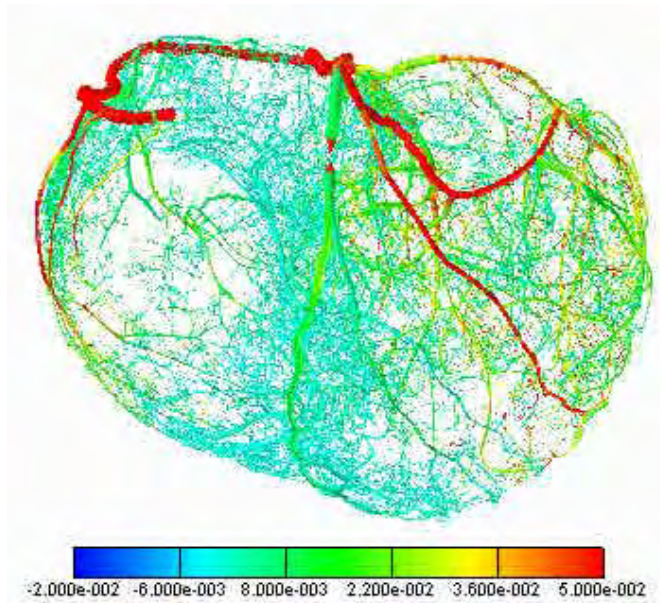


冠動脈狹窄： 流量

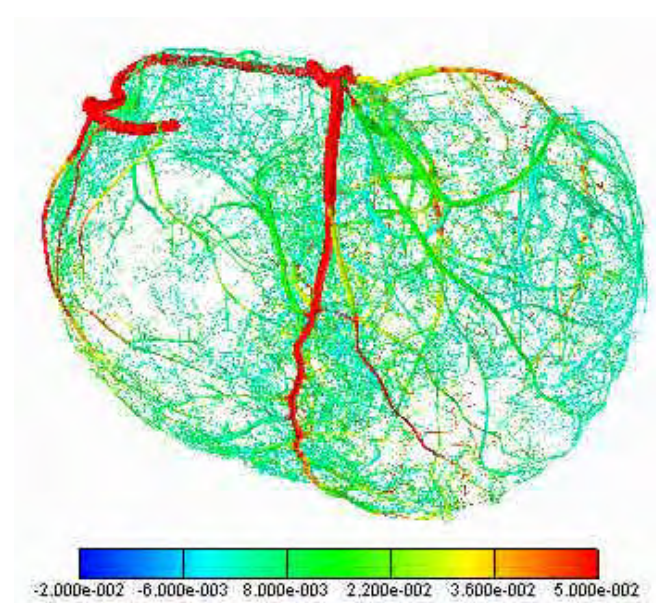
Normal



LAD stenosis

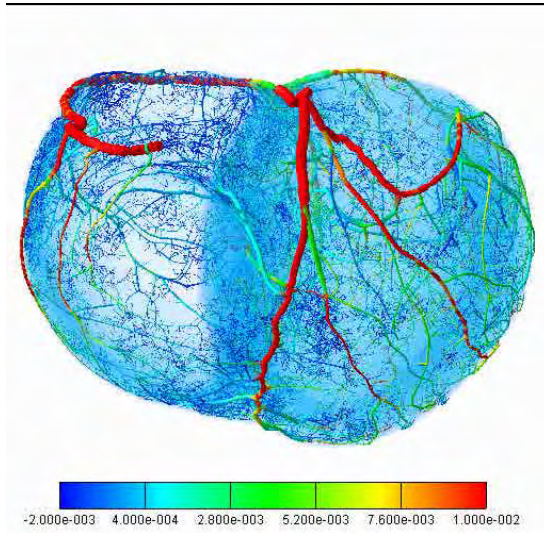


LCX stenosis

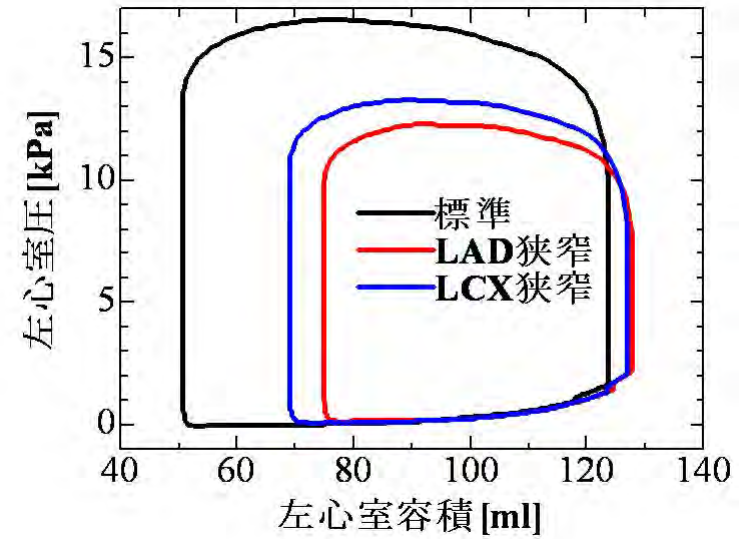


局所仕事

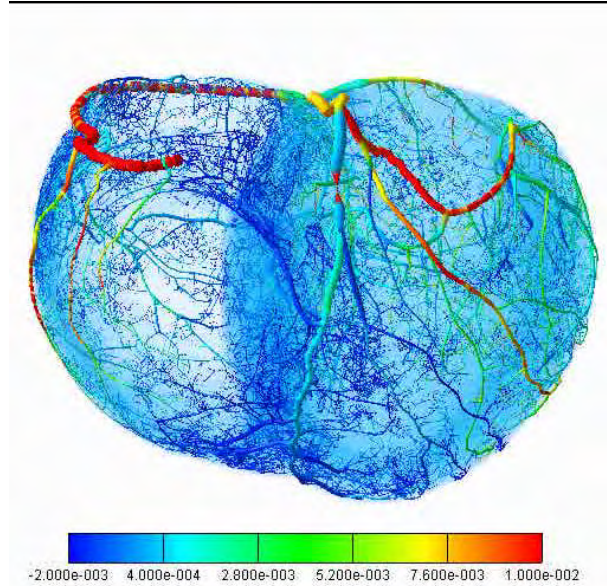
Normal



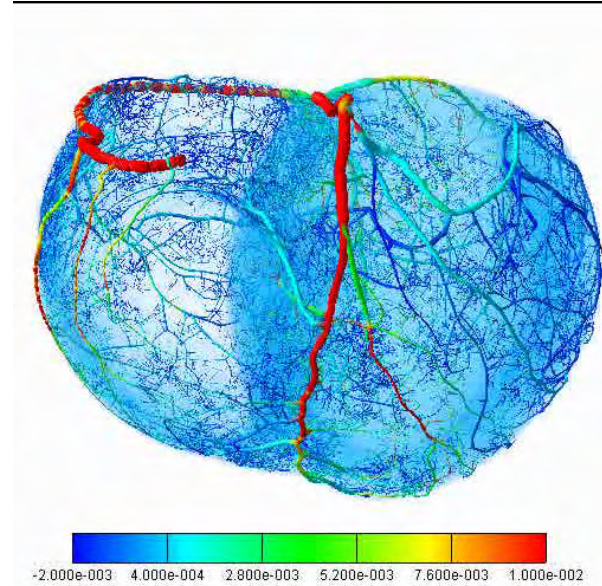
EF 59%



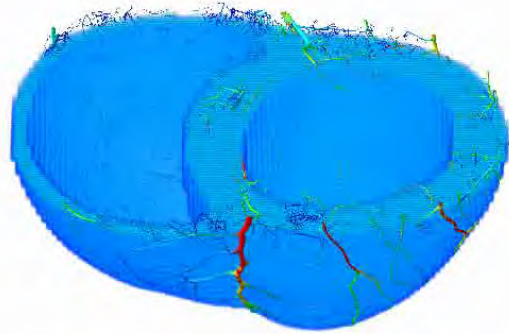
LAD stenosis (EF 41%)



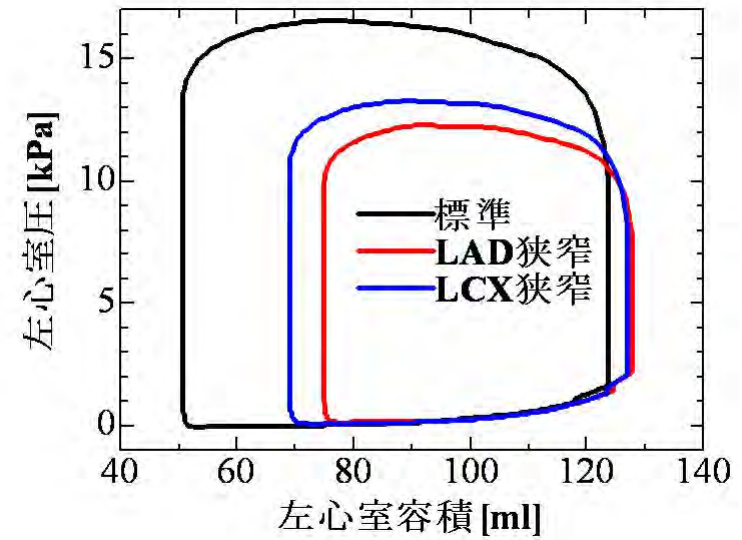
LCX stenosis (EF 46%)



局所仕事 2

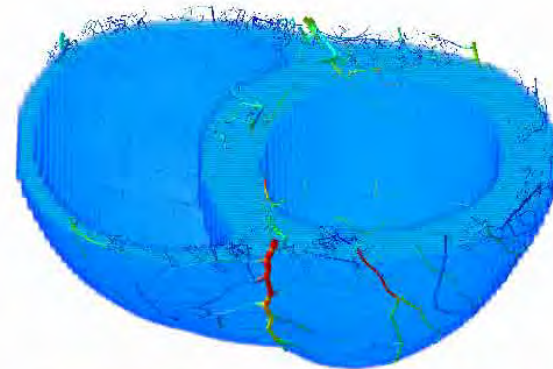
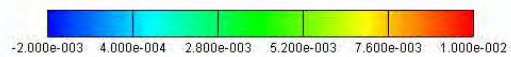
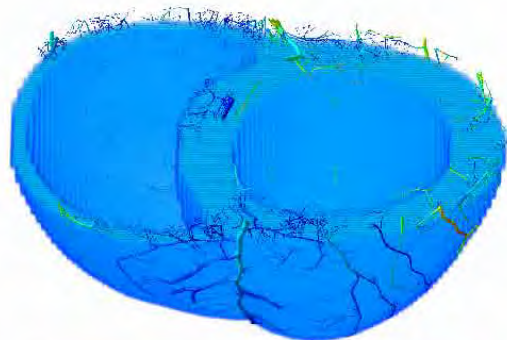


Normal
EF 59%

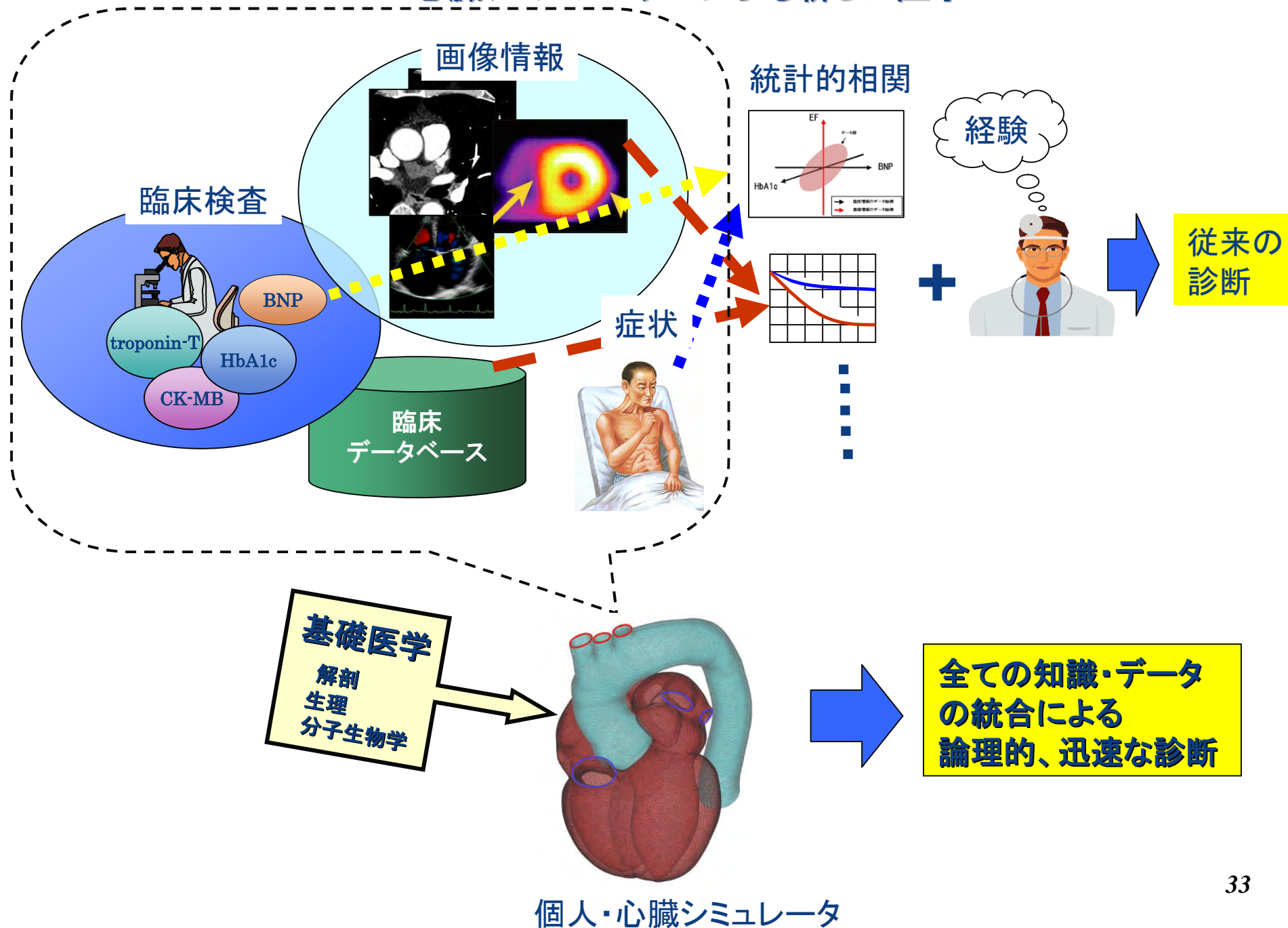


LAD stenosis (EF 41%)

LCX stenosis (EF 46%)



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