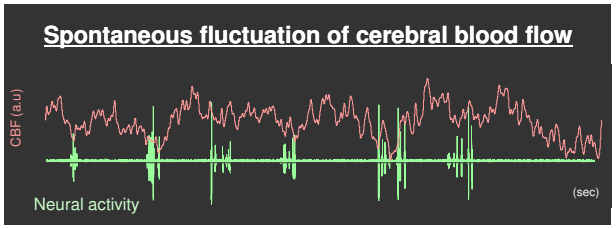
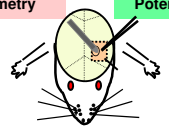
# 脳機能イメージングと脳微小循環計測

正本 和人[1,2,3]
[1]電気通信大学 先端領域教育研究センター 特任准教授
[2]放射線医学総合研究所 分子イメージング研究センター
客員協力研究員
[3]慶應義塾大学 医学部 神経内科 訪問助教

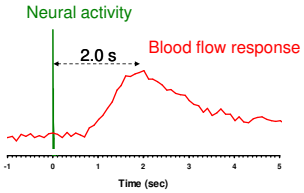
## Spontaneous fluctuation of cerebral blood flow




Laser-Doppler flowmetry | Local Field Potential

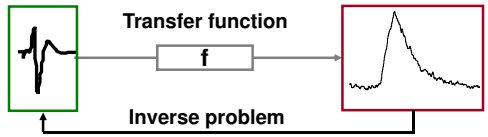


Somatosensory cortex in anesthetized rats




## Physiological coupling of Neural and Vascular activities

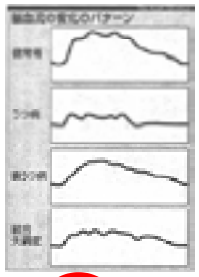
Neural activity → Vascular response




**We can see brain functions noninvasively by measuring vascular responses (not electrical activity!)**

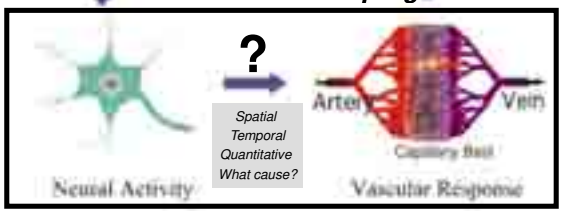
## Optical imaging of human brain function

(Hasegawa and Sato, 2007)

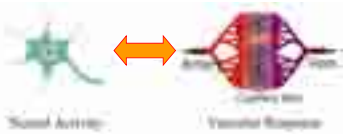




***Neuro-vascular coupling*** ?




## Understanding of Neuro-Vascular interactions



**1. Spatiotemporal accuracy (時間空間的特異性)**

How accurate blood vessels respond to neural activity?

**2. Quantitative relationship (定量性)**

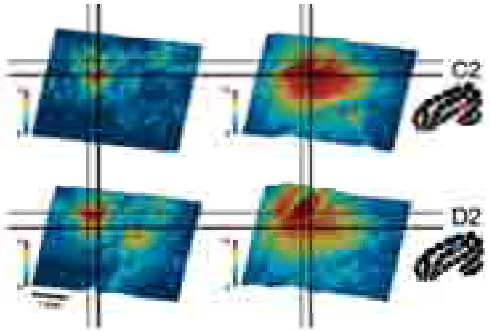
Larger vascular response means stronger neural activity?

**3. Physiologic mechanism (生理学的機構)**

How can we interpret the vascular signals in terms of neural functions?

## *Spatial specificity of metabolic and hemodynamic signals*

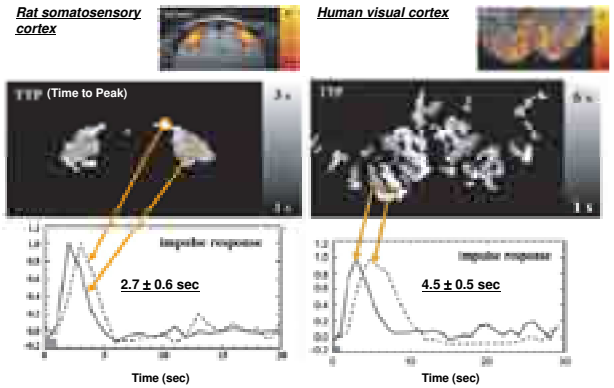
Auto fluorescence image (Metabolic origin) | Laser speckle imaging (Hemodynamic origin)



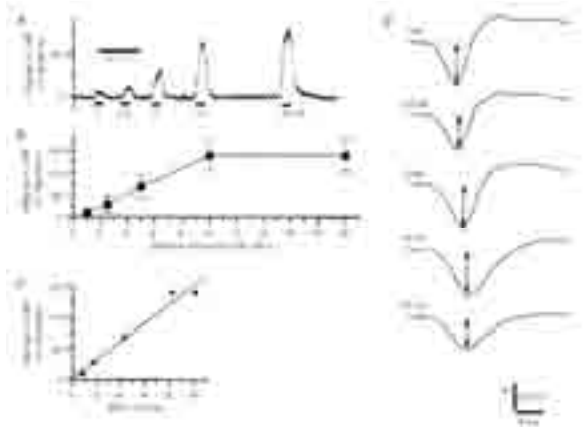

(Webner et al., 2004)

## *Species differences in hemodynamic response function*

*Rat somatosensory cortex* | *Human visual cortex*



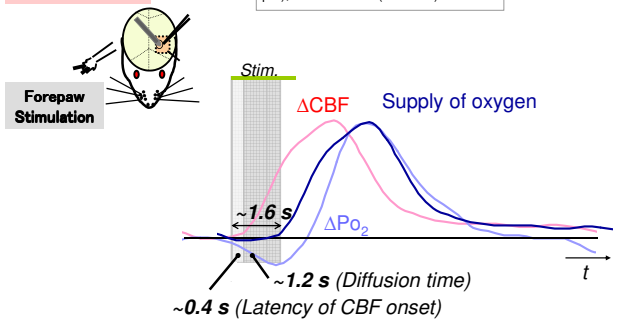

(de Zwart et al., 2005)



(Mathiesen et al., 1998)

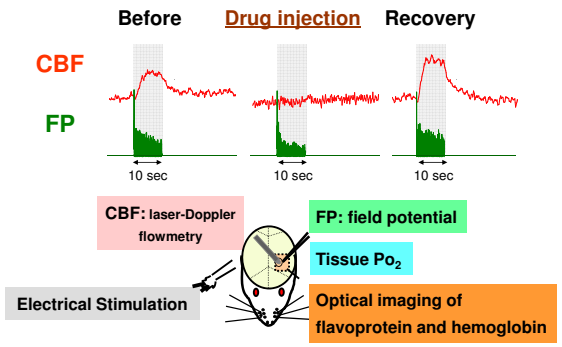
## Lags behind Demand due to Diffusion Time for Oxygen

CBF: laser–Doppler flowmetry | Tissue $Po_2$ | Oxygen microsensor (tip diameter: ~10 μm), time-constant (~0.2 sec)



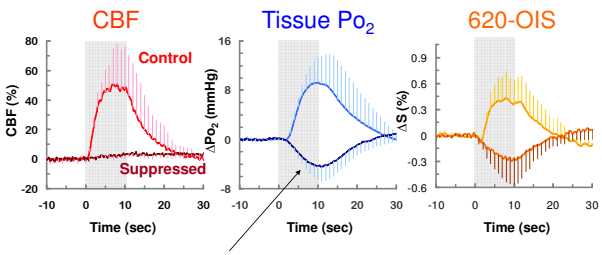

(Masamoto et al., JAP 2007)

## Suppressed vascular response experiment




*(Masamoto et al., 2007)*

## Decrease in oxygen tension due to CMRO2 increase




**Tissue and blood Po2 decrease due to an increase in oxygen consumption (CMRO2)**

(Masamoto et al., NeuroImage 2007)

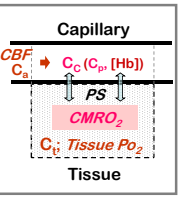
## Dynamic $CMRO_2$ with Oxygen Exchange Model

$$V_c \frac{dC_c(t)}{dt} = \underbrace{2CBF(t)(C_a - C_c(t))}_{\text{Supply}} - \underbrace{PS(C_p(t) - C_t(t))}_{\text{Exchange}}$$

$$V_t \frac{dC_t(t)}{dt} = \underbrace{PS(C_p(t) - C_t(t))}_{\text{Exchange}} - \underbrace{CMRO_2(t)}_{\text{Demand}}$$

$$C_c(t) = C_p(t) + \frac{4[Hb]}{1 + \left(\frac{\alpha P_{50}}{C_p(t)}\right)^{hill}}$$

Plasma ($C_p$) and hemoglobin-binding oxygen




**Constant:**

$V_c$ = 1 mL/100 g (capillary)
$V_t$ = 97 mL/100 g (tissue)
α = 0.00139 mmol/L/mmHg
$P_{50}$ = 38 mmHg, hill = 2.73
PS = 7000 mL/min/100g
CBF = 150 mL/min/100 g*
(*ASL- MRI technique)

**Measured:**

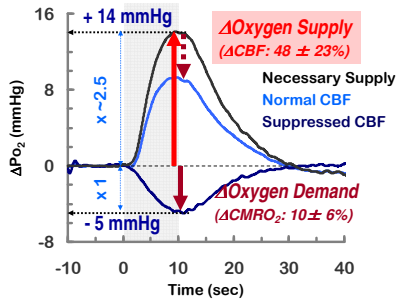
CBF (t): LDF (t) x CBF
$C_t$(t): tissue $Po_2$
$C_a$, [Hb]: systemic arterial blood

**Variable:**

$CMRO_2$ (t) (mL/min/100 g)
$C_c$ (t): capillary oxygen concentration

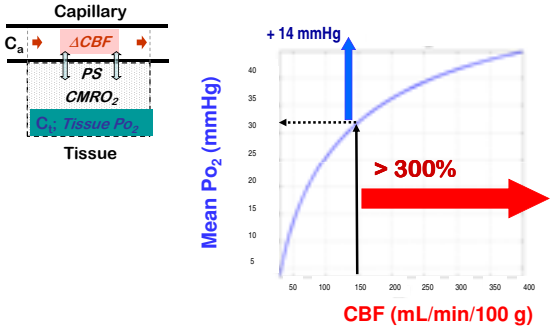
(Modified from Valabrègue et al., JCBFM 2003)

## 2.5 Times Higher Supply Relative to Demand

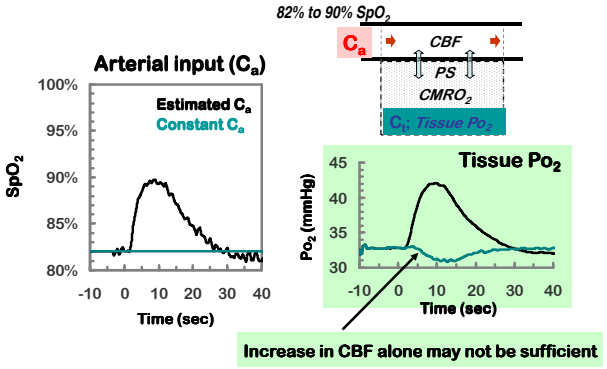



(Masamoto et al., 2007)

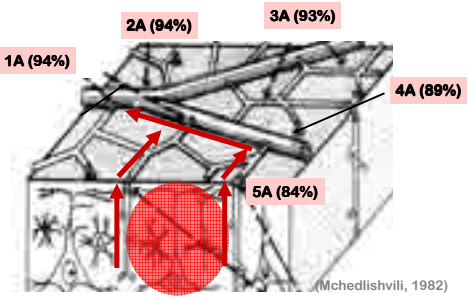
## Po2 increase is not explainable by the change in CBF alone




## Dynamic changes in arterial oxygenation level



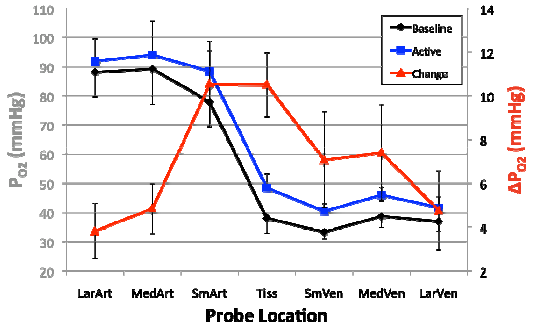

## Recruitment of upstream arterial blood



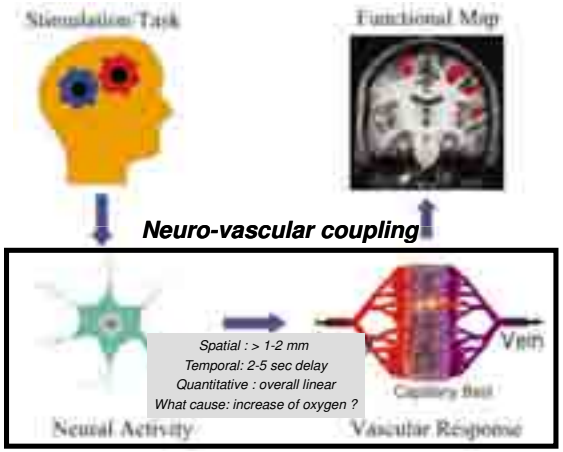

| Branching | 1A | 2A | 3A | 4A | 5A |
|---|---|---|---|---|---|
| Blood $Po_2$ ($SpO_2$) | 81 mmHg (94%) | 79 mmHg (94%) | 76 mmHg (93%) | 68 mmHg (89%) | 62 mmHg (84%) |

($Po_2$ and $SpO_2$ data from Vovenko, 1999)

## PO2 Changes in vascular and tissue compartment




(Vazquez et al., JCBFM 2010)




## テニュア・トラックにおける研究提案

（検討項目）
1. 血流反応の時間空間的特異性
2. 神経ー血流反応の定量性
3. 血管反応のメカニズム（神経科学的解釈）

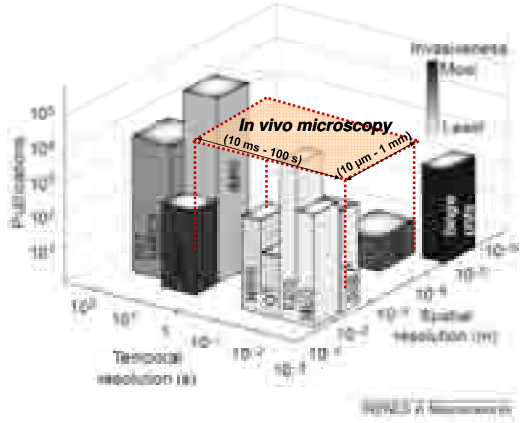
（具体的アプローチ）

① 動物実験モデルの構築
長期に渡り継続観察可能なマウス・ラットを用いた動物実験モデルの構築

② 可視化手法の確立
脳血管形態を可視化するための光イメージング手法の確立
脳内環境（酸素・グルコース）の光イメージング手法の確立

③ 生体活動の計測
脳神経活動に対する血管反応の領域・大きさに関する検討
様々な神経活動に対するエネルギ代謝・血管反応の計測

## *Comparison of functional brain imaging tools*




## Two-Photon Laser Scanning Fluorescence Microscopy

1. Deep penetration
2. Less photobleaching and photodamages

Near infrared laser (700-1000 nm wavelength)

Excitation

Agar (2.0%) with fluorescent micro-beads (1 μm)

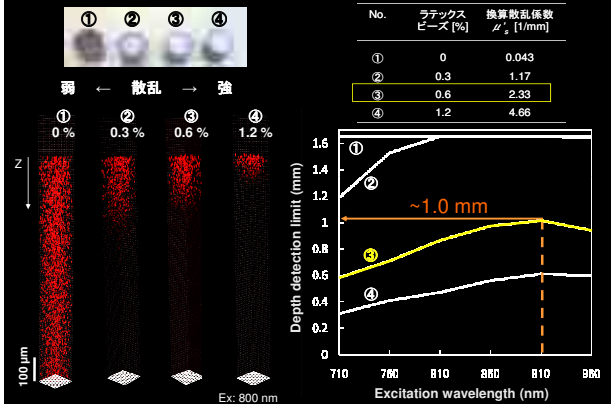
Detection with PMT

Emission

(Raster scanning)

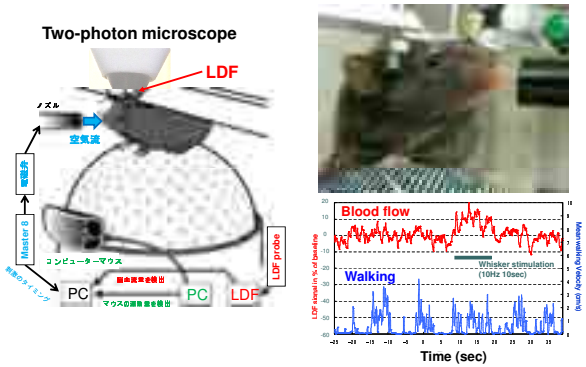
| 16,000 lines/sec |
|---|
| 30 fps (512 x 512) |
| 60 fps (512 x 256) |
| 100 fps (512 x 128) |
| 200 fps (512 x 64) |

## Tissue Scattering Effect on Depth Detection Limit




| No. | ラテックスビーズ [%] | 換算散乱係数 $\mu_s'$ [1/mm] |
|---|---|---|
| ① | 0 | 0.043 |
| ② | 0.3 | 1.17 |
| ③ | 0.6 | 2.33 |
| ④ | 1.2 | 4.66 |

## Dynamic CBF measurements in awake mice



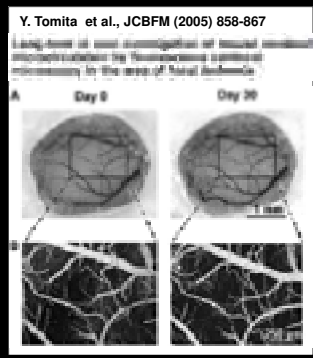

(Takuwa et al., submitted)

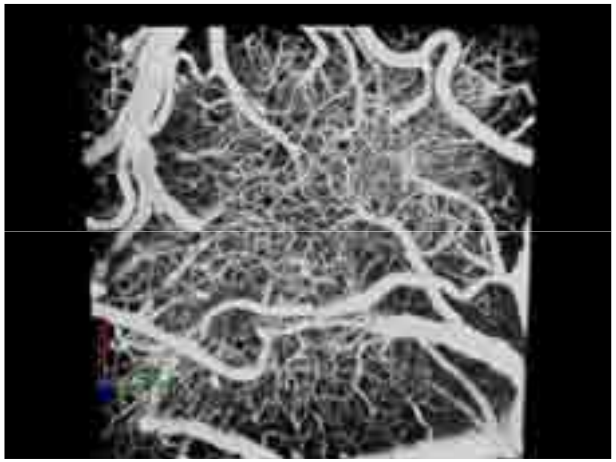
## Two-photon imaging through a closed cranial window

C57BL/6J mice (20-30 g)
Isoflurane (1%) or awake
Closed cranial window: open skull (3 mm in diameter), dura intact
Fluorescent dye: Sulforhodamine 101 (5-10 mM in saline, 8 ml/kg)

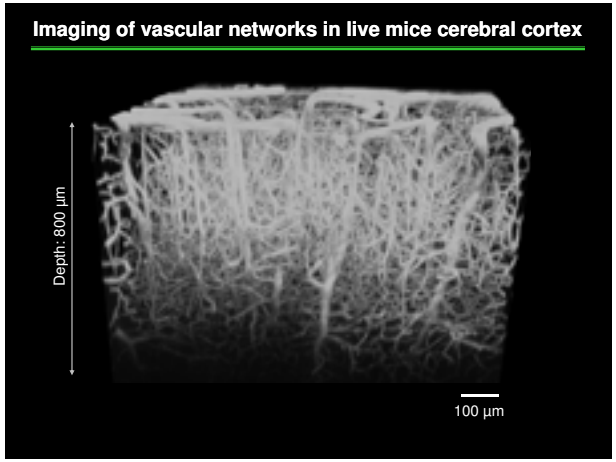
Experimental arrangement

Y. Tomita et al., JCBFM (2005) 858-867

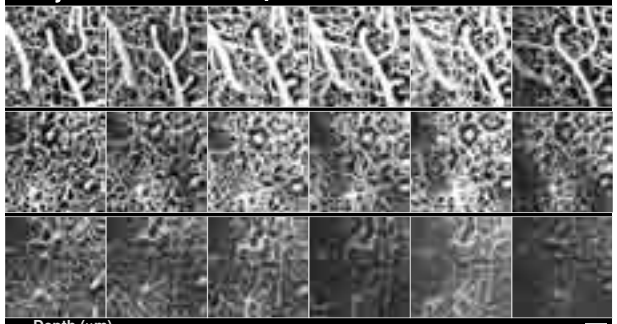


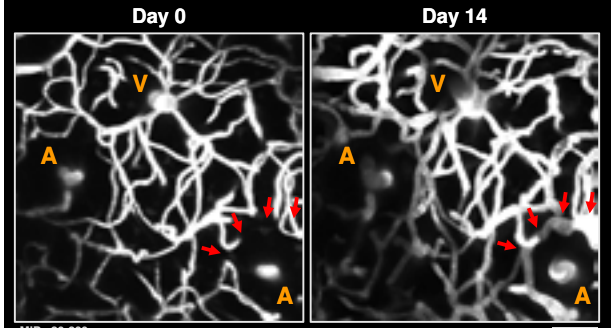
## Imaging of vascular networks in live mice cerebral cortex



## Cerebrovasculature changes during chronic hypoxia

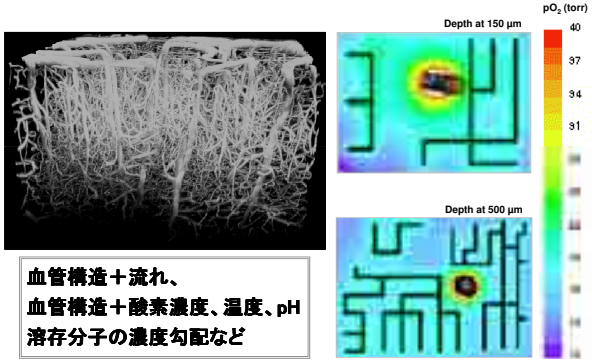



## New vessel formed between capillaries




## 2011年度の予定(1)

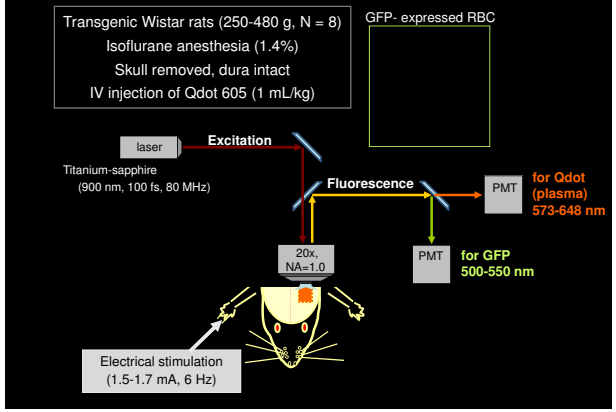
### (1) 形態→形態＋付加情報のイメージングへ



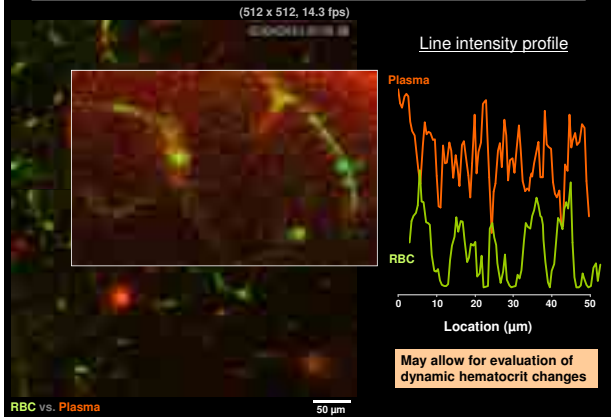

血管構造＋流れ、
血管構造＋酸素濃度、温度、pH
溶存分子の濃度勾配など

## 3D volume imaging of GFP-expressed rat cortex

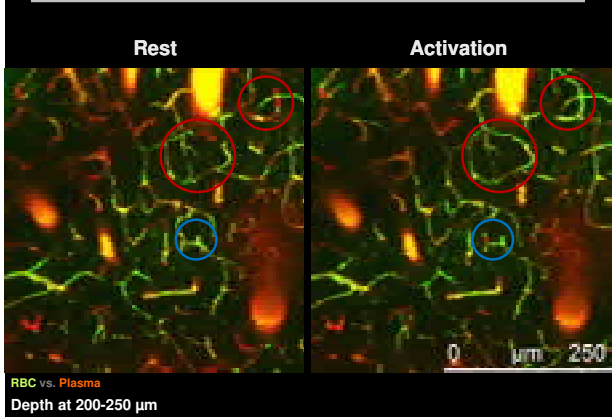
Transgenic Wistar rats (250-480 g, N = 8)
Isoflurane anesthesia (1.4%)
Skull removed, dura intact
IV injection of Qdot 605 (1 mL/kg)



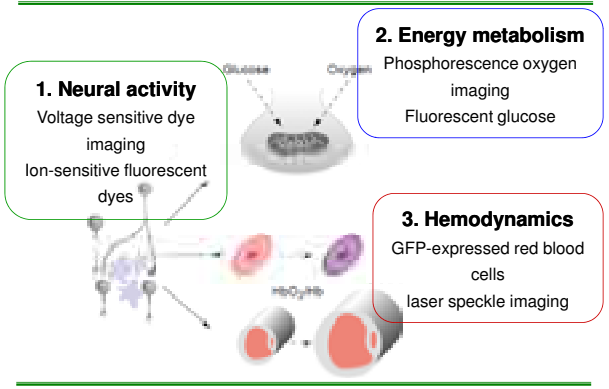

## RBC vs. plasma flow in parenchyma capillaries



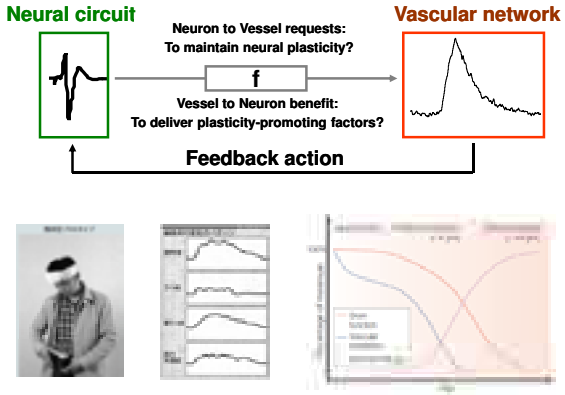

## RBC and plasma distribution in the capillary networks




## Optical imaging of neural, metabolic, and vascular activities




## Current hypothesis on neurovascular coupling




## 謝 辞

（敬称略）


電気通信大学 知能機械工学科
教授　山田幸生
助教　大川晋平
吉原光一

慶應義塾大学 システムデザイン工学科
教授　谷下一夫
米家一洋
関口悠太

（独）放射線医学総合研究所
先端生体計測研究グループ
菅野巌
田桑弘之
川口拓之
山崎享子

慶應義塾大学 医学部神経内科
教授　鈴木則宏
冨田裕
畝川美悠紀
鳥海春樹

（米国）ピッツバーグ大学 放射線科
Prof. Seong-Gi Kim
Mitsuhiro Fukuda
Tae Kim
Vazquez Alberto

（株）日立製作所　基礎研究所
牧　敦