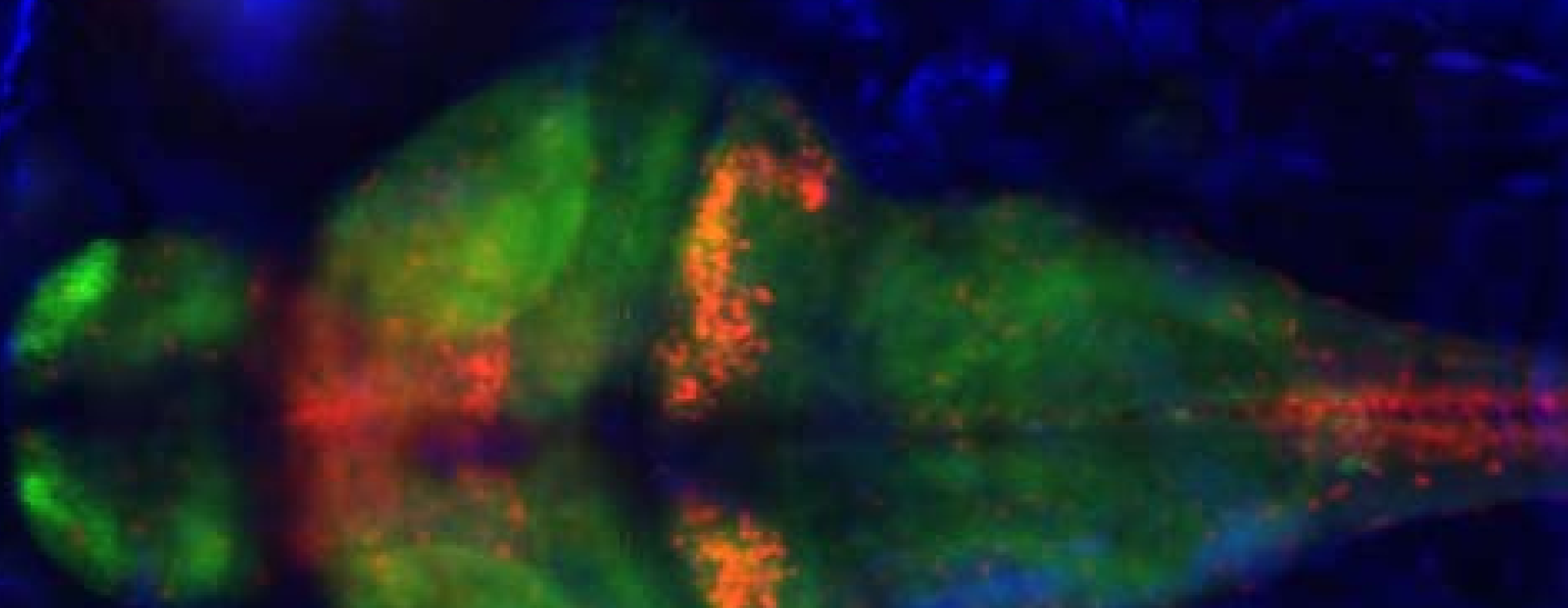
Systems Neuroscience Modeling
系统神经生物学模拟



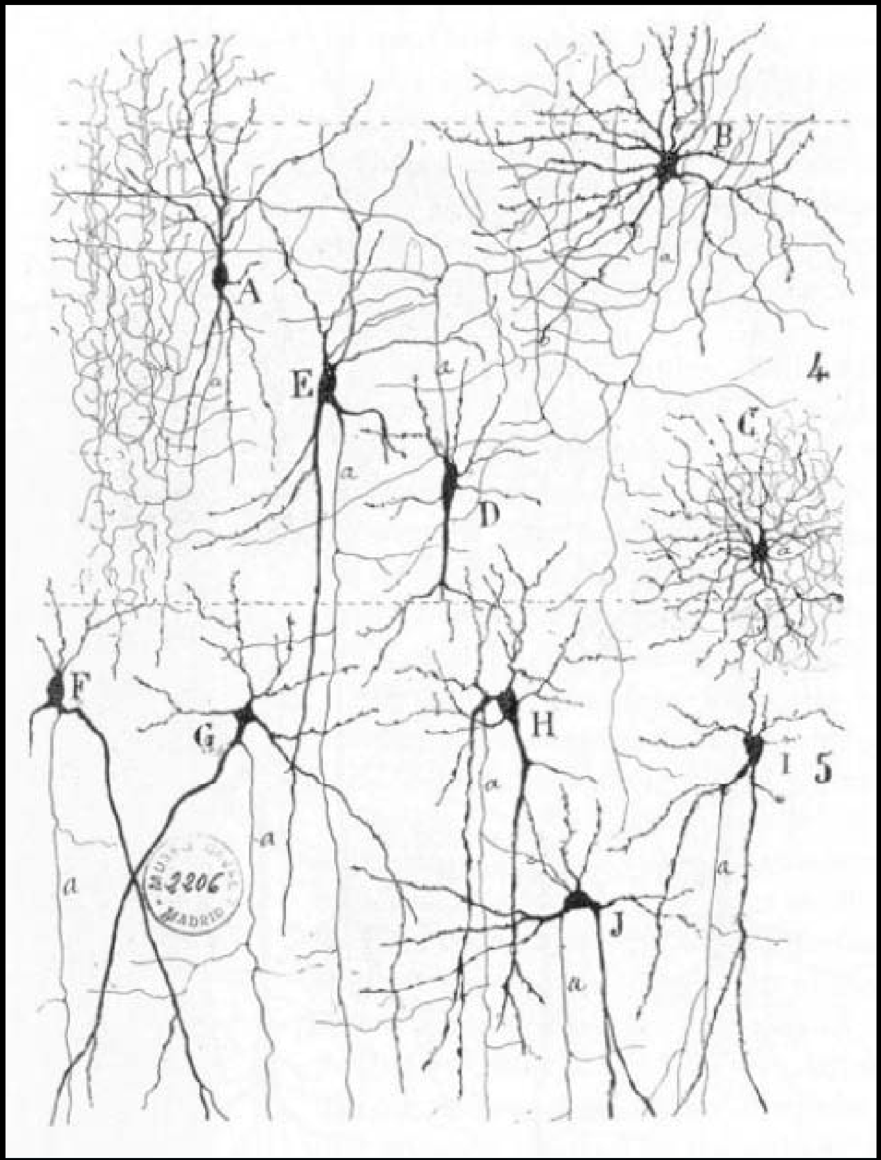
陶乐天 北京大学生命科学学院 生物信息中心
Louis Tao, Center for Bioinformatics, College of Life Sciences, PKU

Beijing, 29 March 2011

Neuronal Networks Are Complex

~10^{11} neurons & 10^{15} connections

10^4 cells & 1,000 m wiring in 1 mm^3 of cortex



From "Texture of the Nervous System of Man and the Vertebrates" by Santiago Ramón y Cajal.

Neurons 神经元

- Information processing units 信息处理/加工单元
- 哺乳动物大脑：10^{10}-10^{13} neurons in mammalian brains
- 10^4 cell bodies and roughly 10^3 m of 'wiring' per mm^3
- Different shapes, sizes, functions, … 不同形状、大小、功能
- *Spiking* vs. *Analog* neurons 锋电位（动作电位）vs.
  e.g., bipolar and amacrine cells in retina, sensory-motor neurons of invertebrates, …
  视网膜里的双极细胞与无长突细胞，无脊椎动物的感觉−运动神经元，等…
- Many other cells (e.g., glia cells 胶质细胞) in cortex: to supply energy, to provide structural stability, …, and not directly involved in information processing

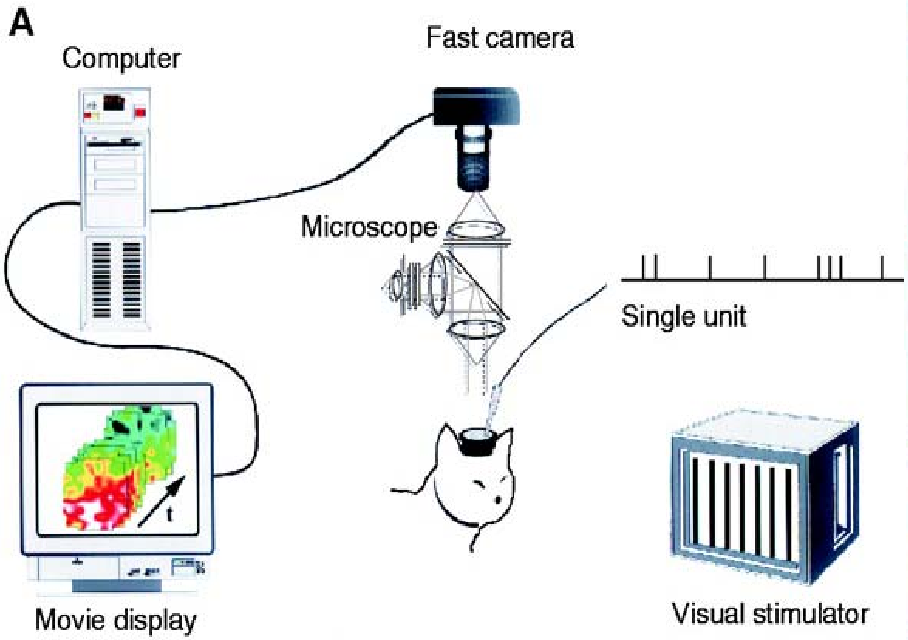
系统神经生物学的研究

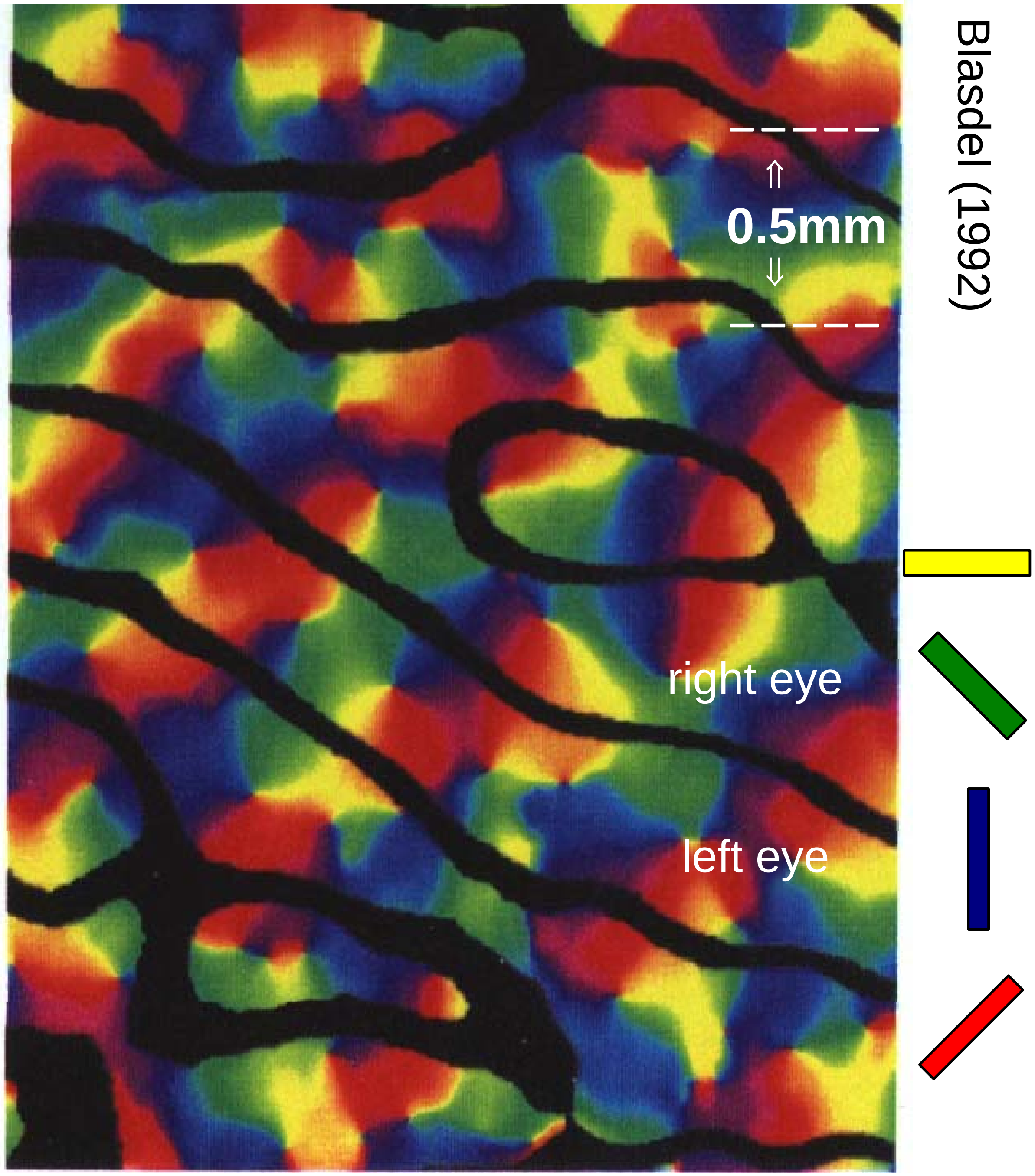
1. 数据分析：神经元活性 与 刺激/行为 的 相关性

2. 编码机制：动作电位频率(rate coding)
   动作电位时间(temporal coding)
   神经元群(Population coding)
   吸引子 / 瞬变动态 (attractor/transient coding)

3. 数学模拟：以神经元模型为单元的网络动力系统

Cortical Map of Orientation Preference
朝向/方向选择





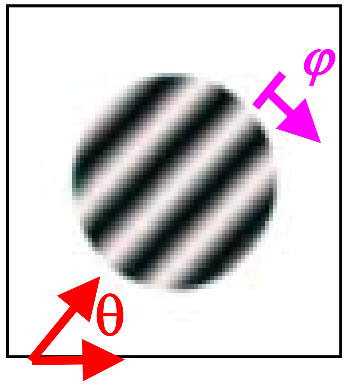
Typical experimental setup for optical imaging

(above figure taken from Tsodyks et al 1999)

Show Larry’s Movie

2. 编码机制

初级视觉皮层的朝向选择性

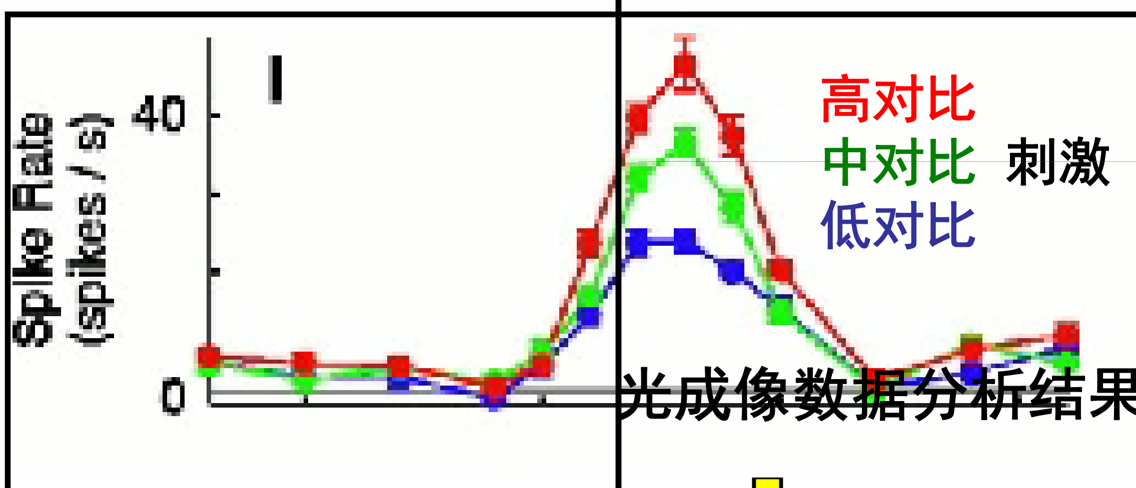


视觉刺激：光栅

$$I(\vec{x},t)=I_0\left[1+\varepsilon\sin(\omega t+\vec{k}\cdot\vec{x}-\varphi)\right]$$

$$\vec{k}=\left(k\cos\theta,k\sin\theta\right),\quad k=\left|\vec{k}\right|$$

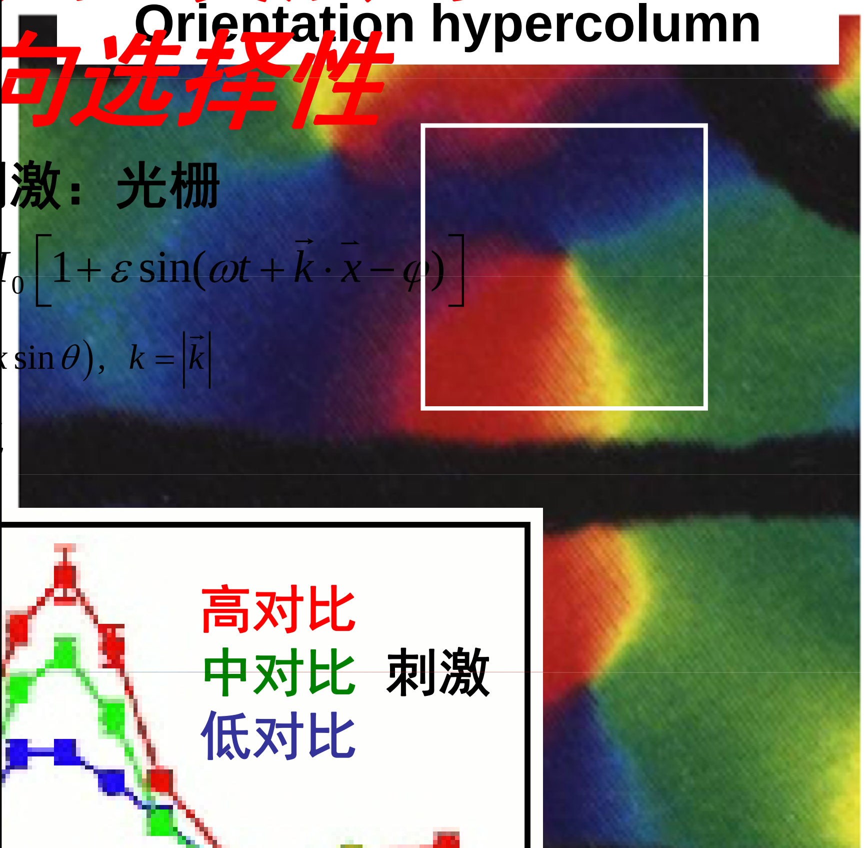
ε 对比



Anderson et al, Science 2000

朝向柱

Orientation hypercolumn



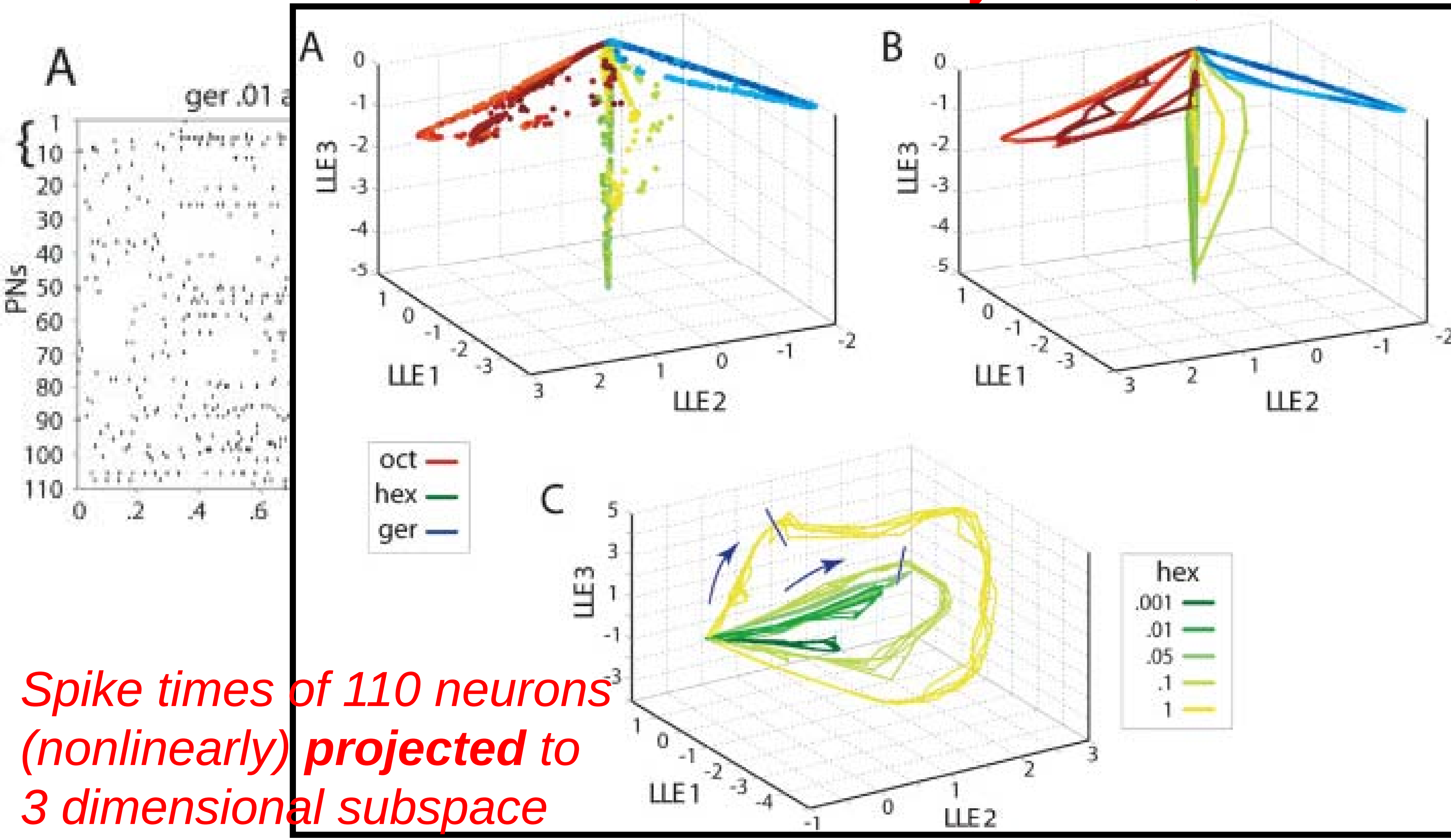
光成像数据分析结果

Blasdel 1992

Rate coding, population & 'space' coding

2. 编码机制

蝗虫天线叶 (antenna lobe)
Transient dynamics 瞬变动态

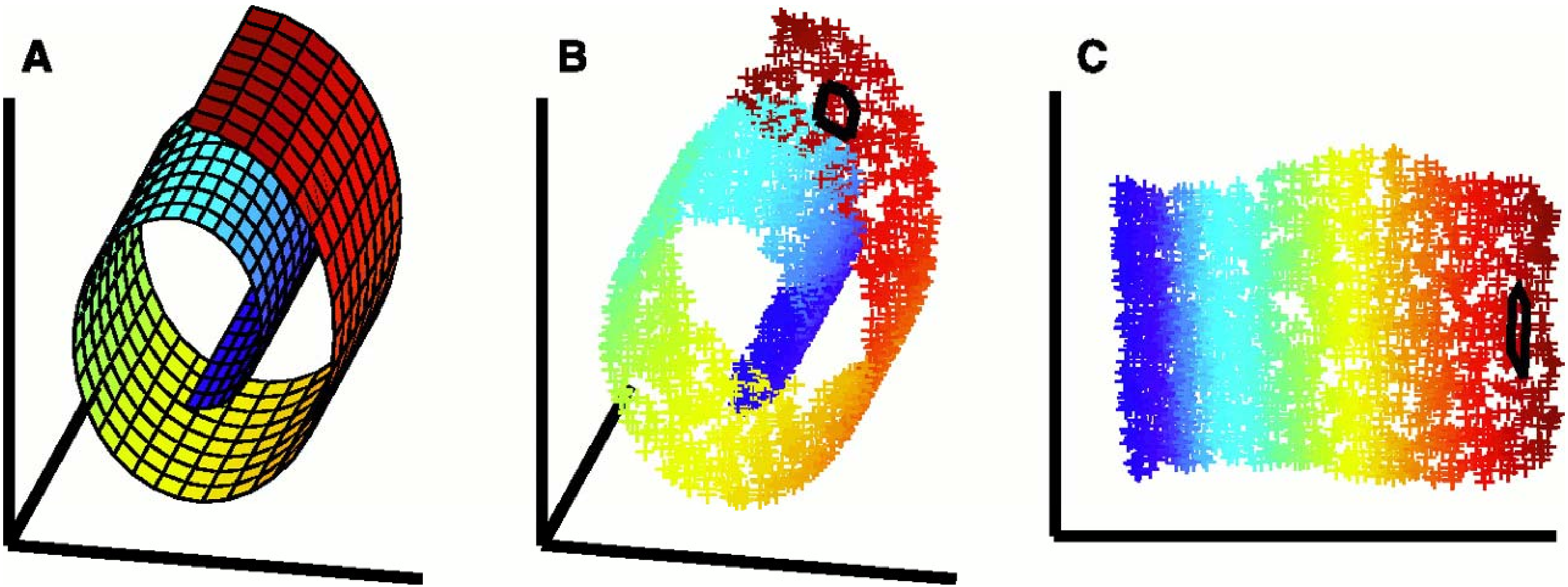


Spike times of 110 neurons (nonlinearly) ***projected*** *to 3 dimensional subspace*

Stopfer et al, Neuron 2003
(Gilles Laurent 实验室)

Locally Linear Embedding (Roweis & Saul, *Science* 2000)

局部线形嵌入 Locally Linear Embedding

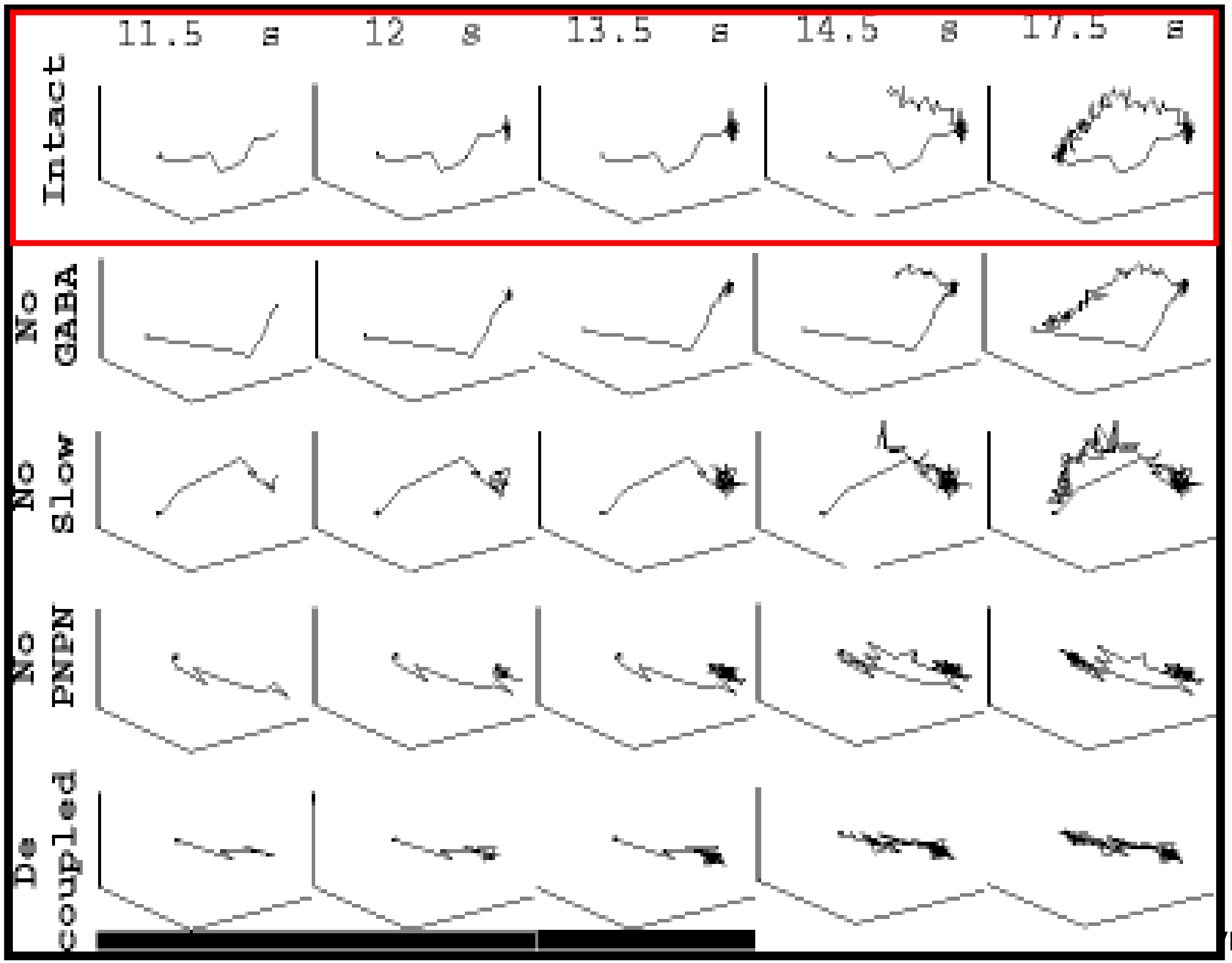


- Roweis & Saul, Science 2000
- Modern Problem: *How to find low dimensional subspace in high dimensional data?*

3. 数学模拟:神经元网络模型

蝗虫的嗅觉系统 --- 天线叶 (antenna lobe)

~ 90 PN projection neuron（兴奋性）
~ 30 LN local neuron (抑制性)
稀疏的网络连接性 (sparse connectivity)



数学模型
数值仿真

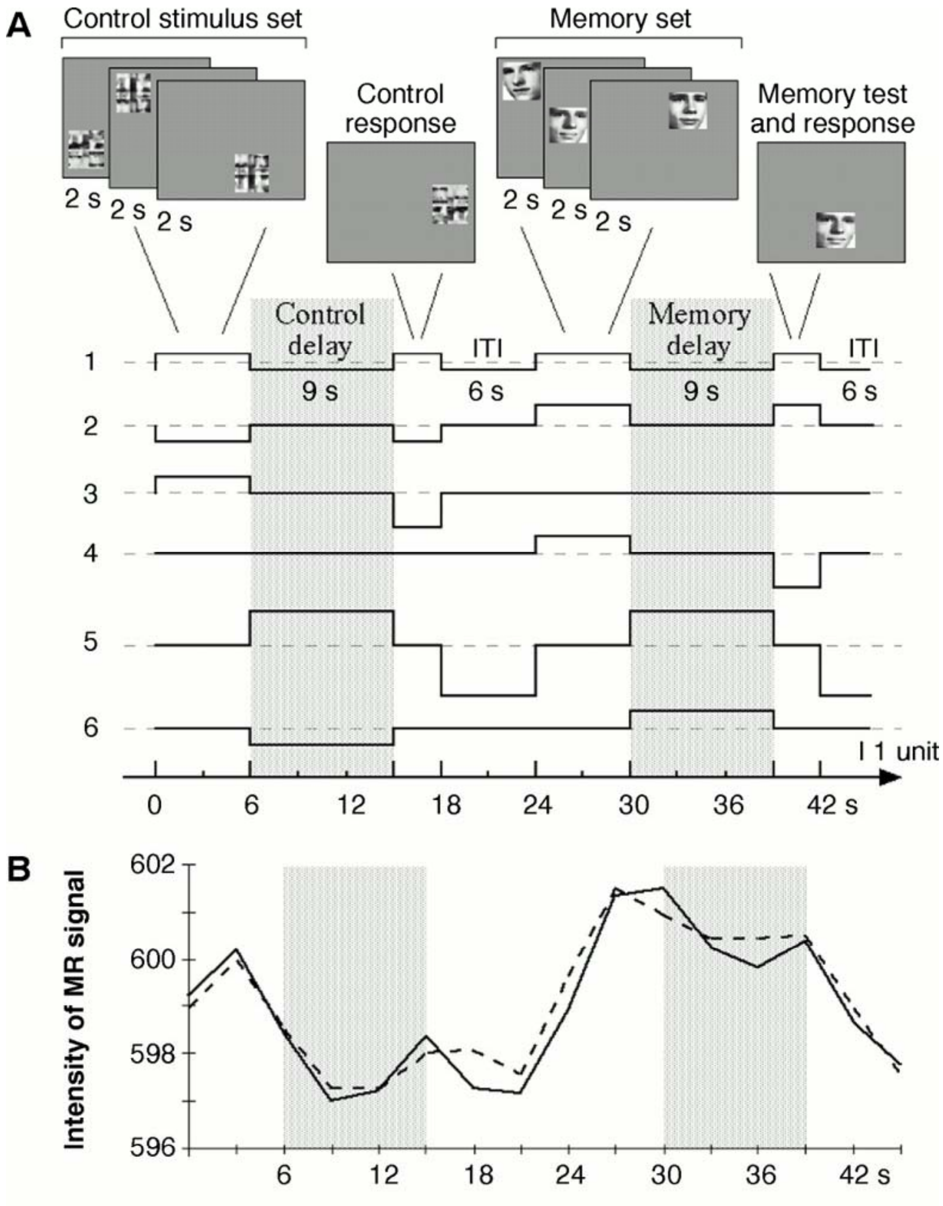
1）系统分析

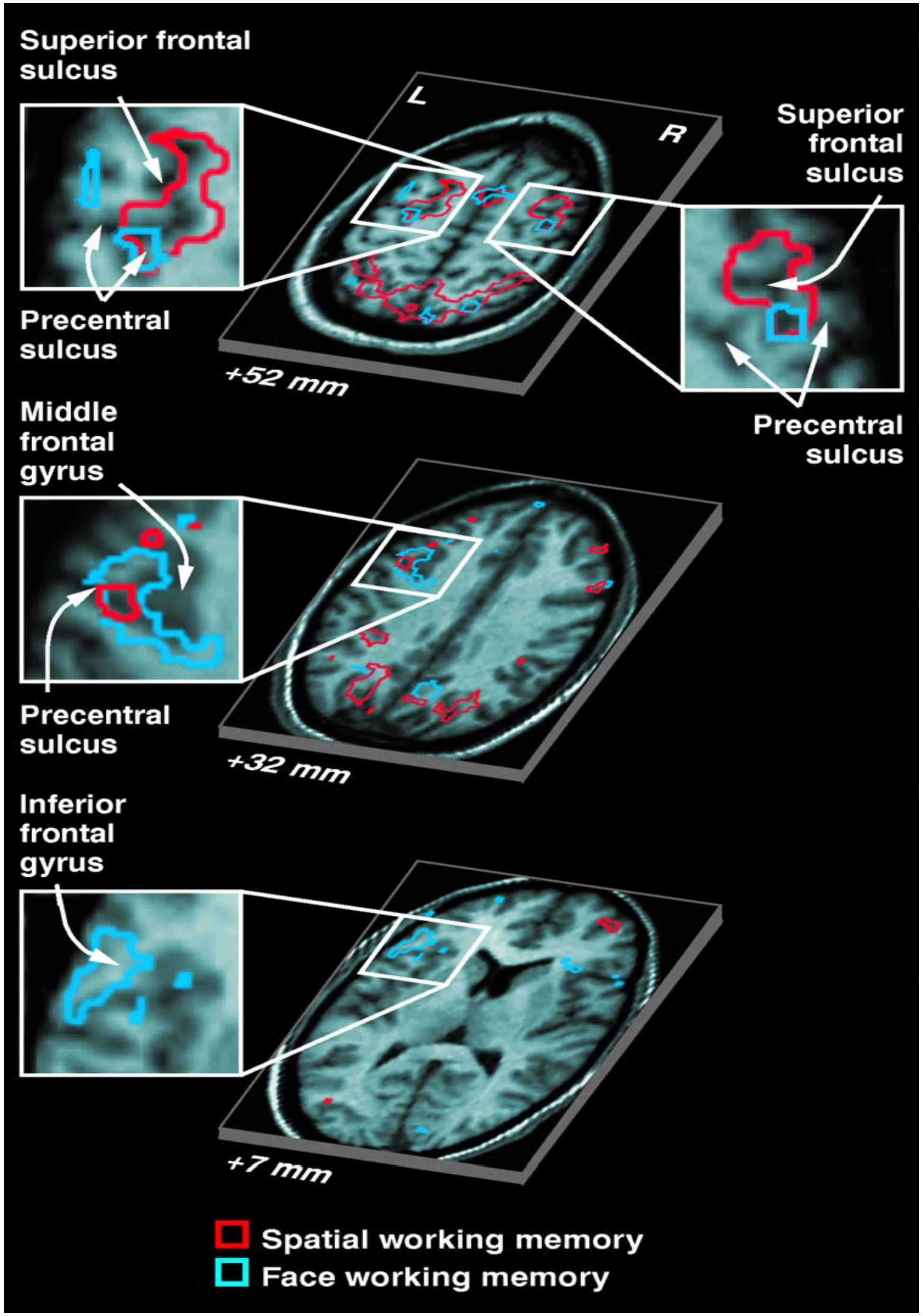
2）了解机制

（左：Patel, Rangan & Cai, *J. Comput. Neurosci.*, ’09)

What is "cognitive function" at the neural level?
如何研究认知功能？

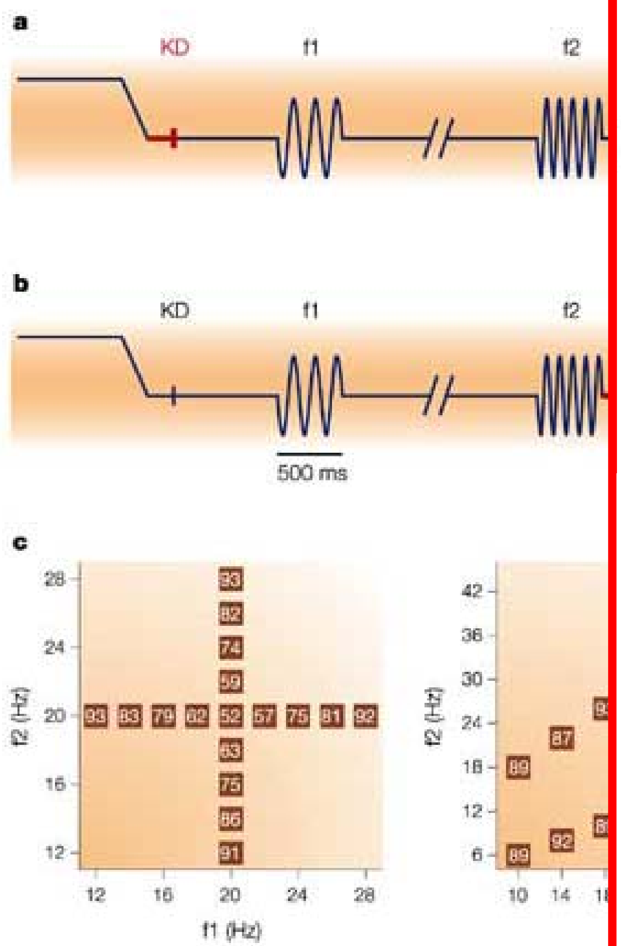
fMRI: Functional Magnetic Resonance Imaging

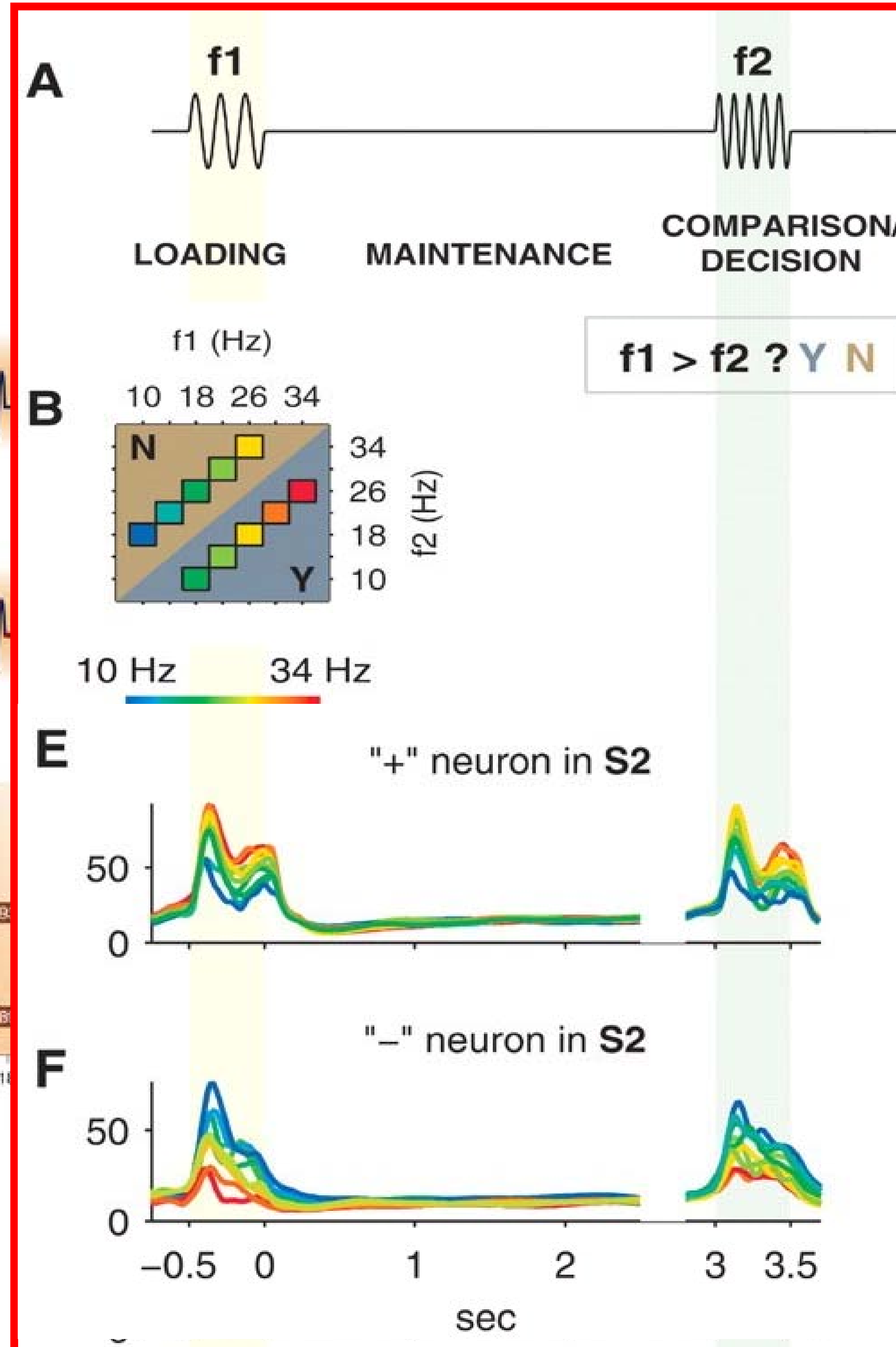




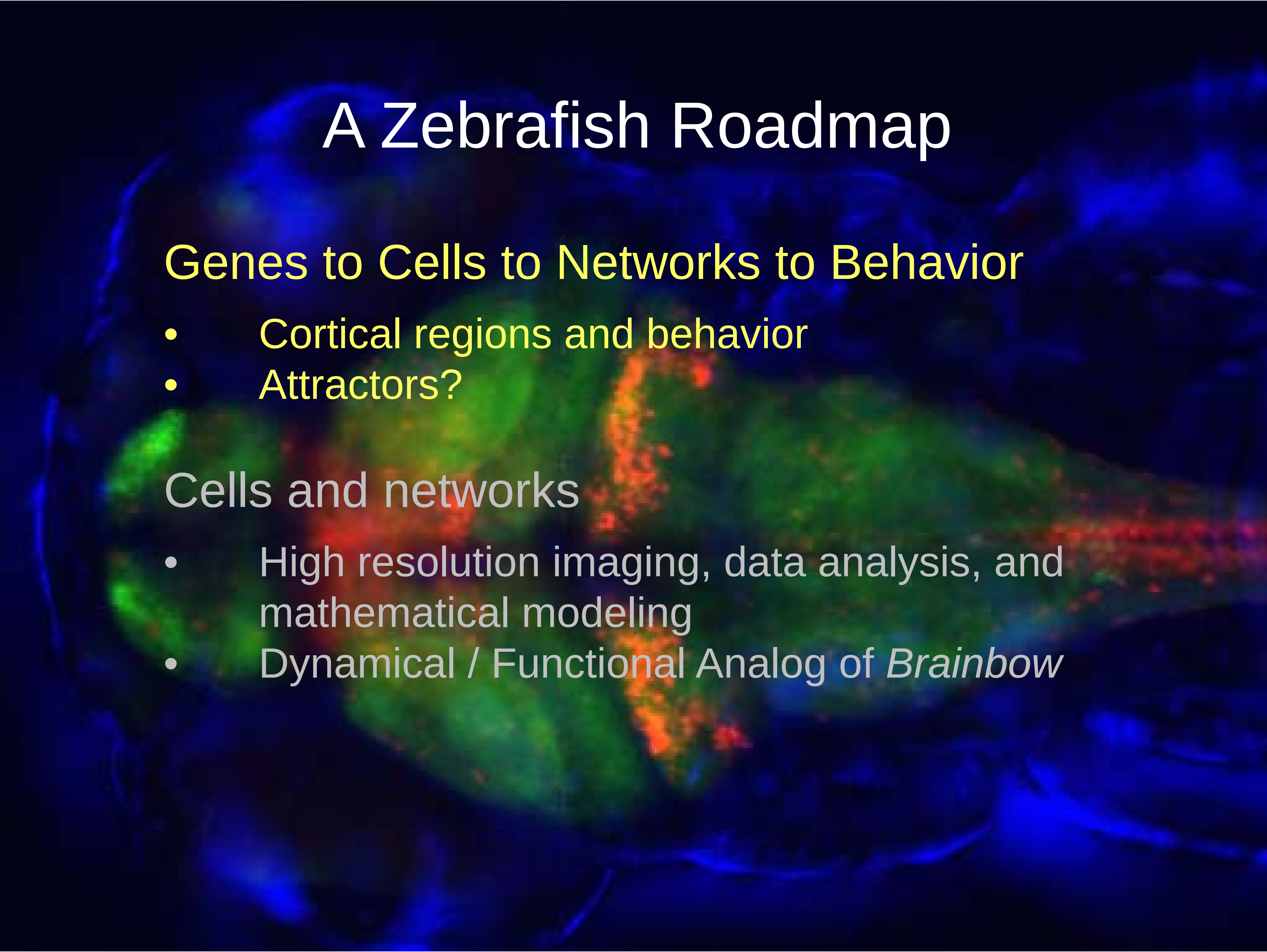
Courtney et al, Science, 1999

Neuro-/Electro-physiology





Romo & Salinas Nat Rev Neurosci 2003
Machens et al Science 2005



A Zebrafish Roadmap

Genes to Cells to Networks to Behavior

- Cortical regions and behavior
- Attractors?

Cells and networks

- High resolution imaging, data analysis, and mathematical modeling
- Dynamical / Functional Analog of *Brainbow*

A Zebrafish Roadmap

从 <u>基因</u> 到 <u>细胞</u> 到 <u>网络</u> 到 <u>行为</u>

- 大脑区域与行为
- 吸引子 / Attractor

从 <u>神经元</u> 到 <u>网络</u>

- 高分辨率的光学成像、数据分析、数学模型
- 有‘功能’、动态的*Brainbow*

吸引子 / Attractor

- Point 点
- Line 线
- Circle or Ellipse 圆圈/椭圆 (limit cycle, planetary orbits, …)
- Higher & non-integer (fractal) dimensional geometric objects / chaotic dynamical system 混沌动力学

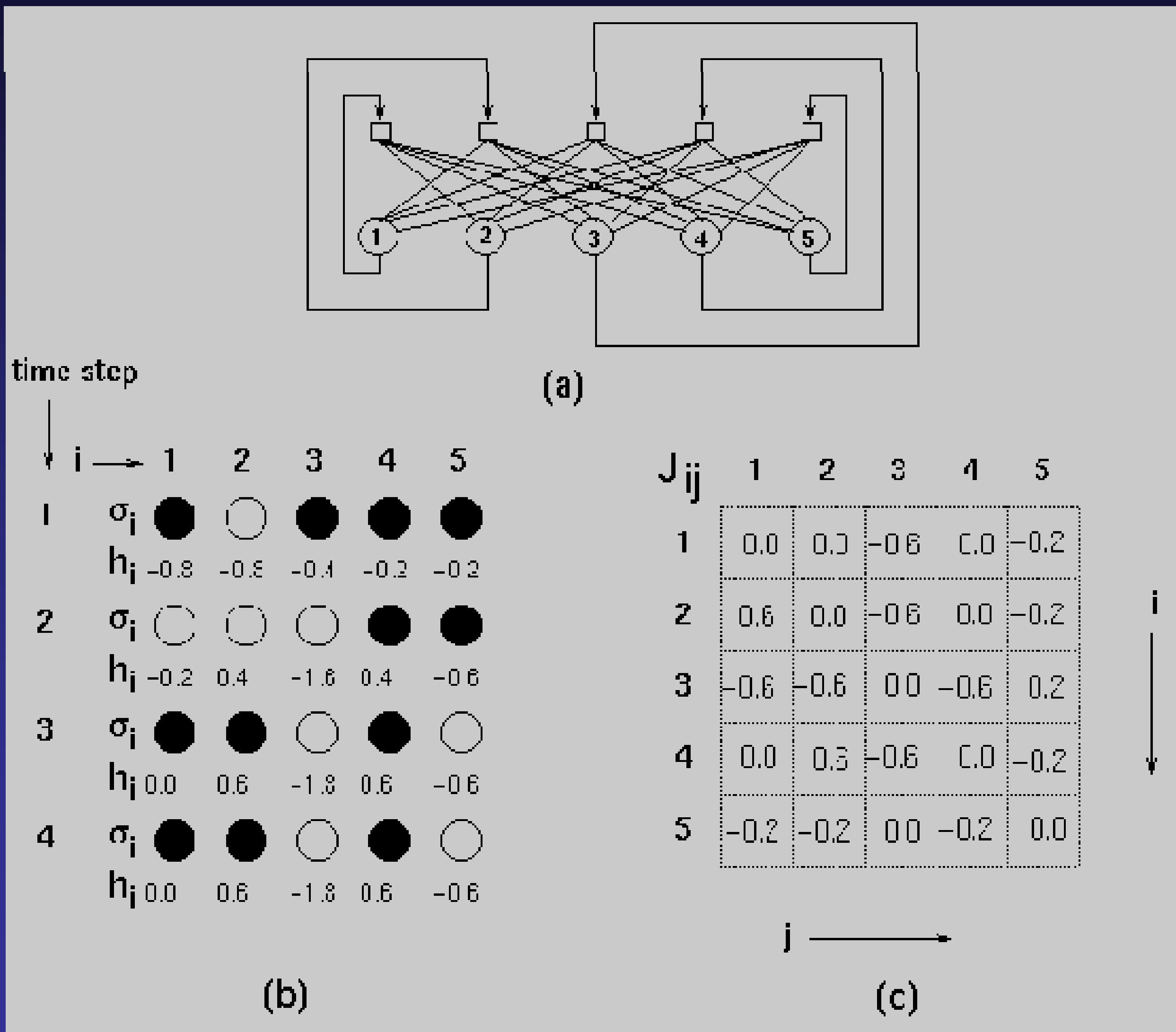
$$\frac{dx}{dt} = \sigma(y - x)$$

$$\frac{dy}{dt} = x(\rho - z) - y$$

$$\frac{dz}{dt} = xy - \beta z$$

Wikipedia，Lorenz_attractor_yb.svg

‘吸引子’神经网络



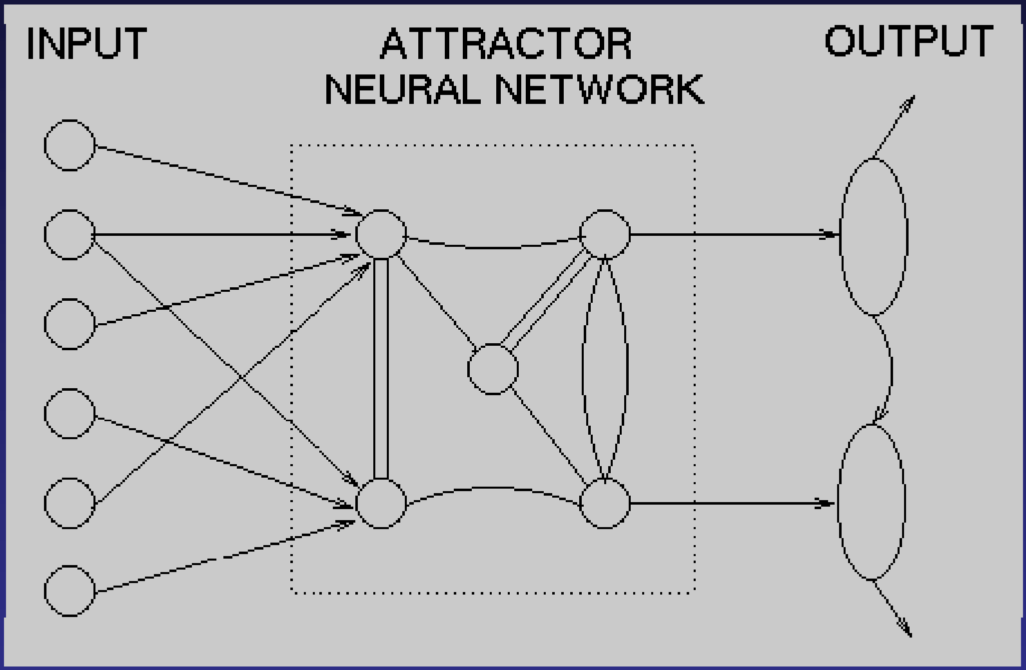
J_{ij}	1	2	3	4	5
1	0.0	0.3	−0.6	0.0	−0.2
2	0.6	0.0	−0.6	0.0	−0.2
3	−0.6	−0.6	0.0	−0.6	0.2
4	0.0	0.3	−0.6	0.0	−0.2
5	−0.2	−0.2	0.0	−0.2	0.0

An attractor for the network exists if from any initial configuration of network states the network evolves in time until:

- A given configuration of network states repeats itself (point attractor).
- A given sequence of network states repeats itself (limit cycle attractor).
- The network states evolve non-periodically

D J Amit. Modelling Brain Function: The World of Attractor Neural Nets. Cambridge University Press, New York, 1989.

吸引子与记忆



D J Amit. Modelling Brain Function: The World of Attractor Neural Nets. Cambridge University Press, New York, 1989.

Basic tenants of attractor network theory as applied to memory:

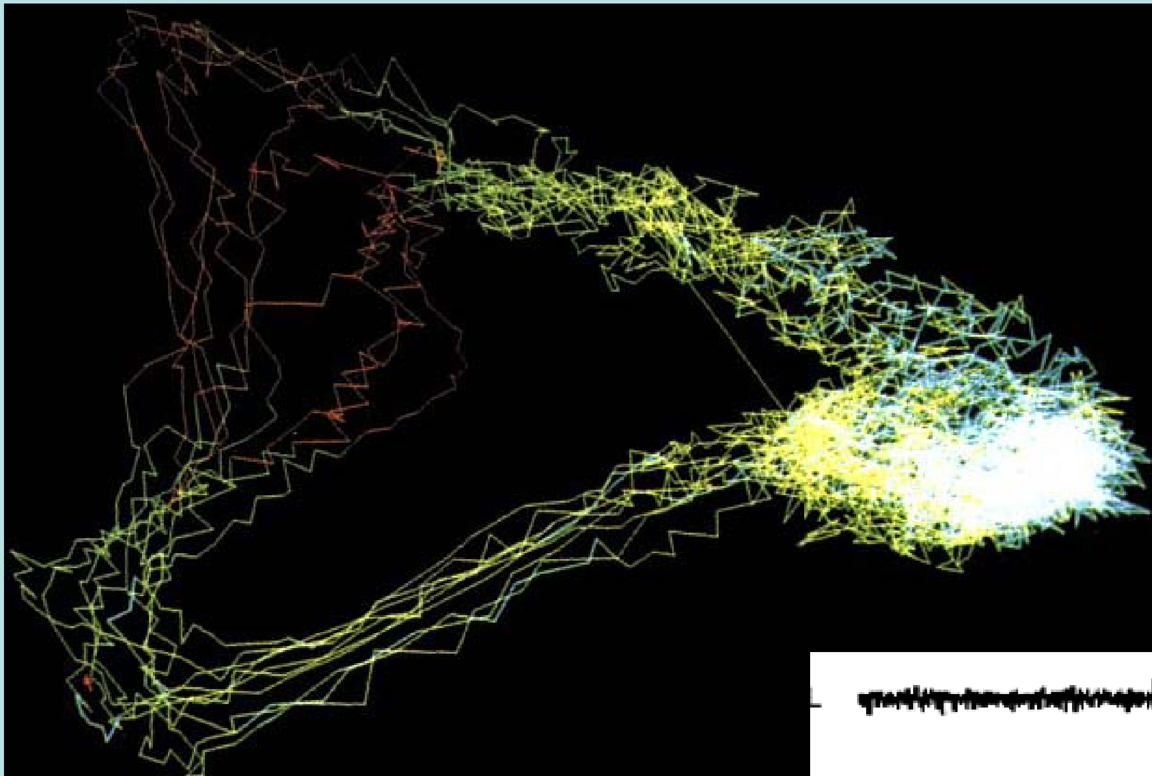
1. Memories reside in specialized recurrent neural networks as specific patterns of neuronal activity.

2. Memory states are imprinted in the network by modifications of recurrent synaptic connections.

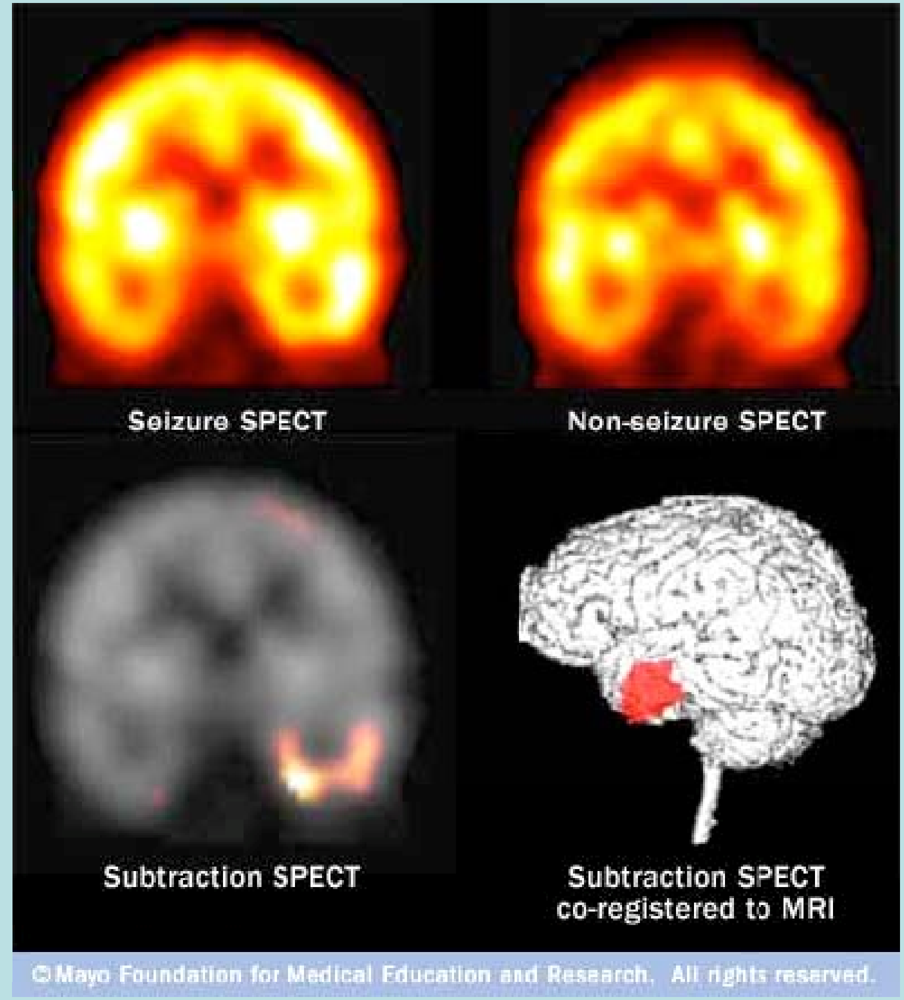
3. As a result of synaptic modifications, memory states can be retrieved through input of partial cues and persist due to recurrent self-excitation (turn into attractor states of the network).

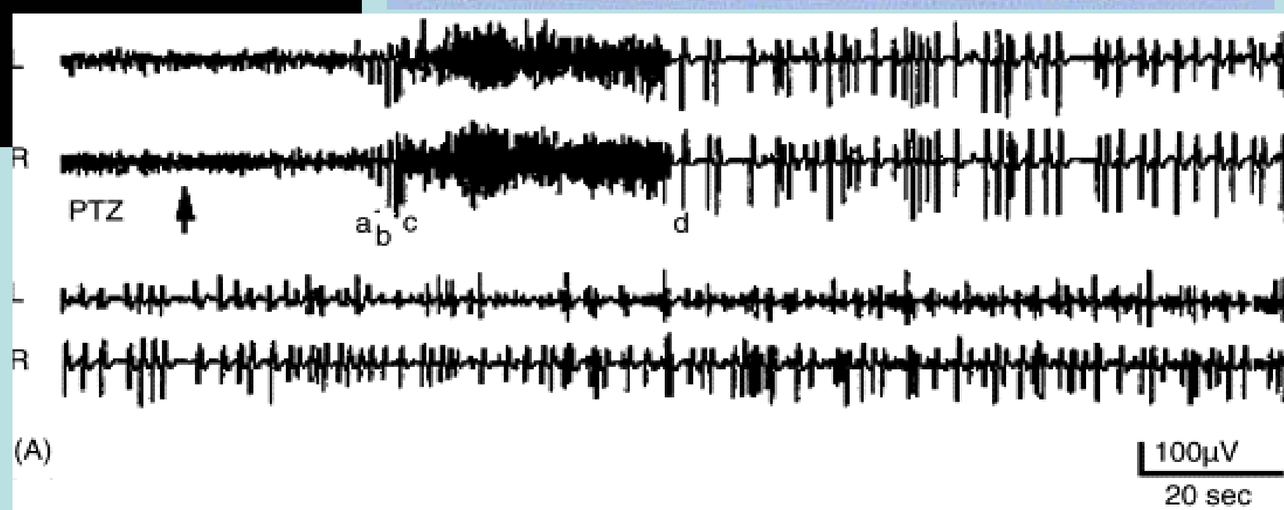
John J. Hopfield. PNAS, 1982
Misha Tsodyks. Neuron, 2005

吸引子与癫痫
seizure / epilepsy



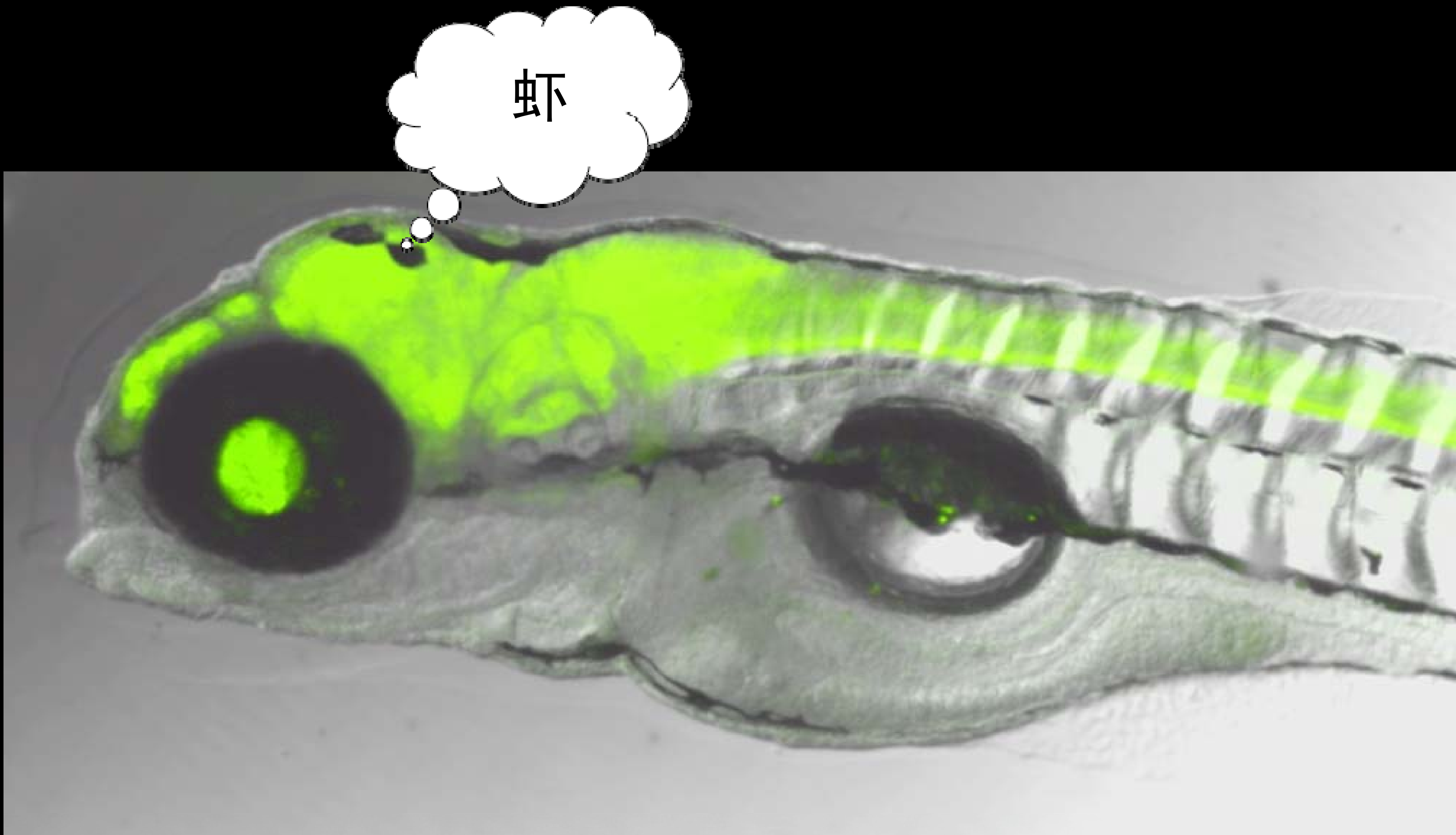
W. J. Freeman. IEEE Transactions on Circuits and Systems 35 (7), 1988





Keogh et al Epilepsy Research 66:75-90, 2005

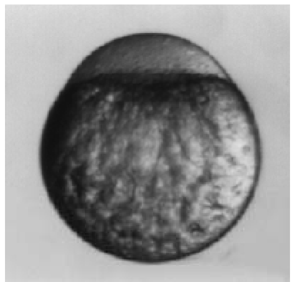
利用光学成像技术来研究认知功能



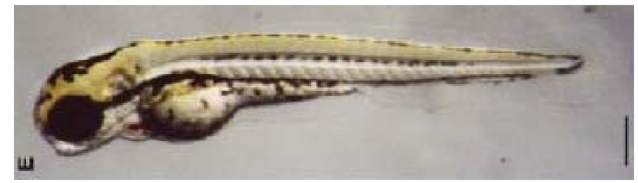
Tg(HuC:cameleon)

斑马鱼 发育生物学的模式动物

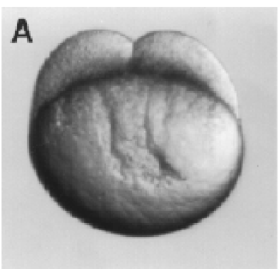
3 months



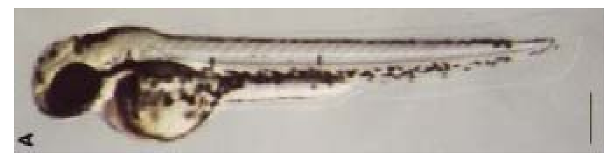
10 min



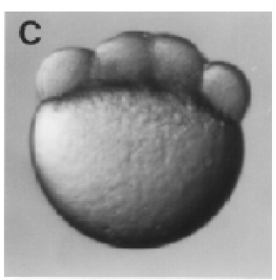
3 days



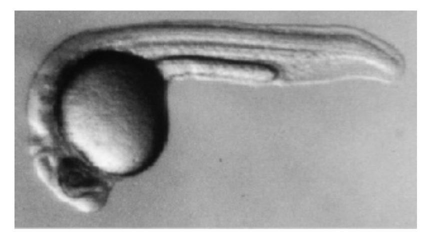
45 min



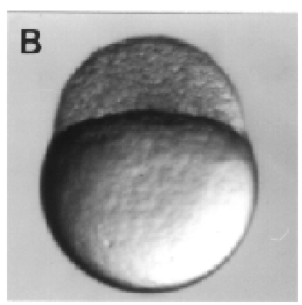
2 days



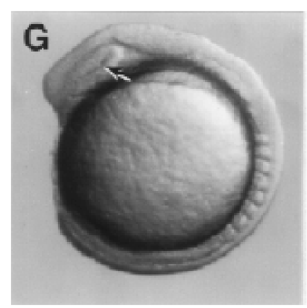
~ 1 hour



1 day

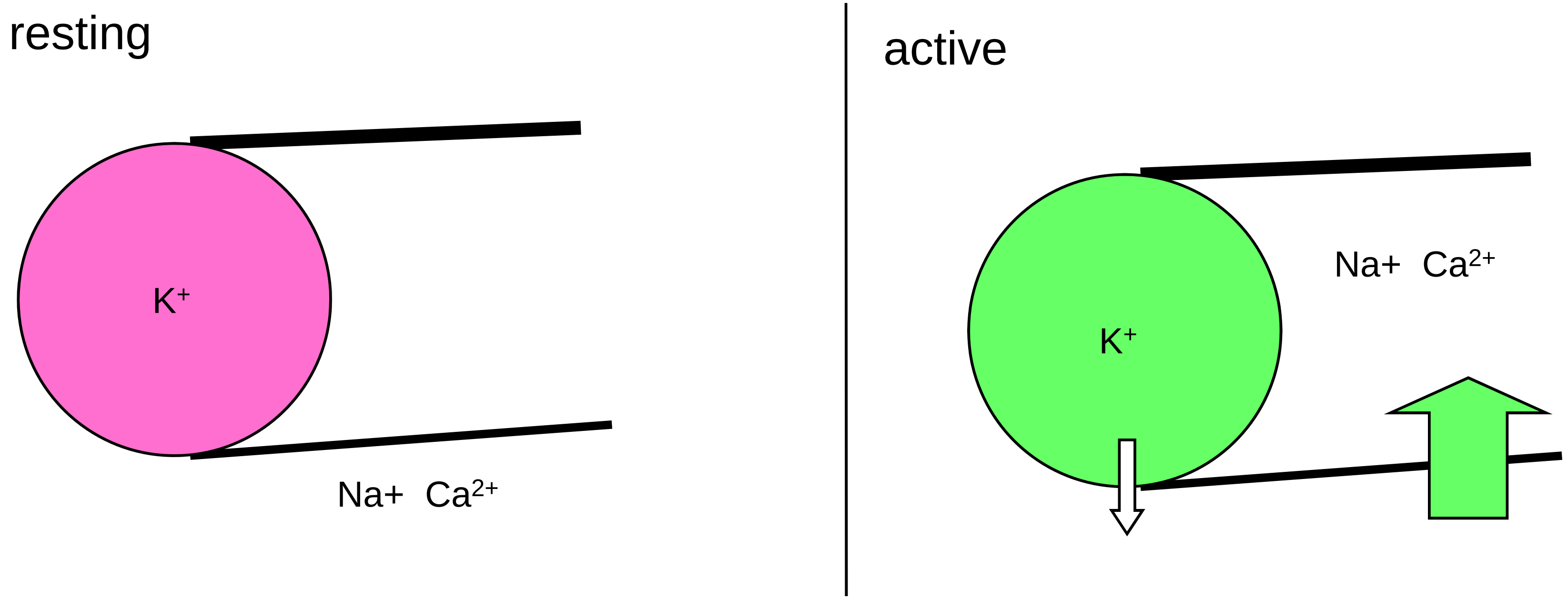


~ 3.5 hours



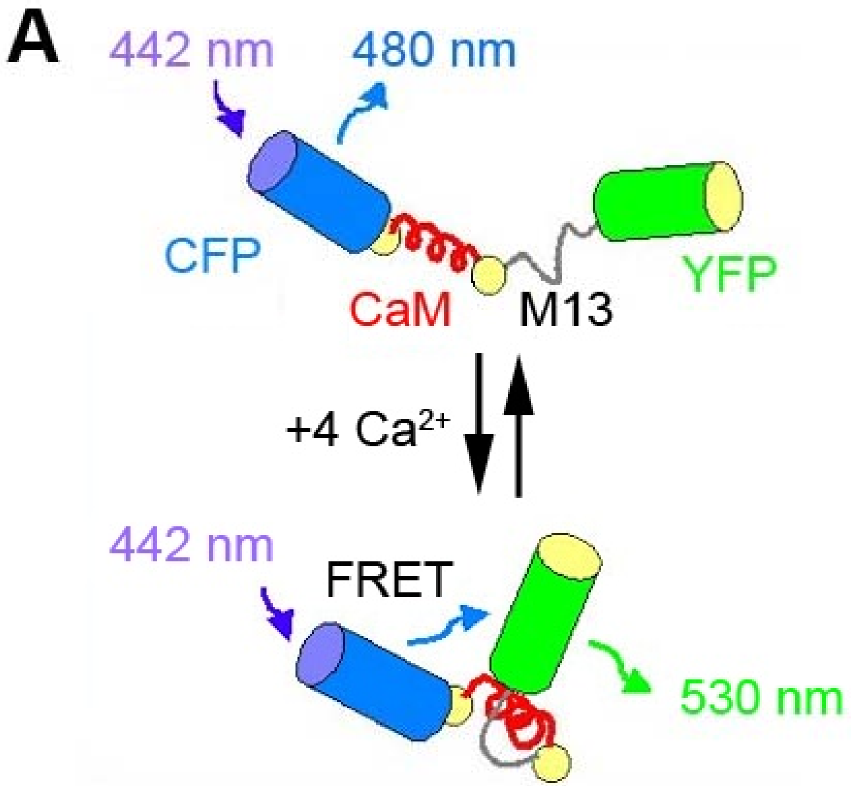
13 hours

钙浓度代表神经元活跃性

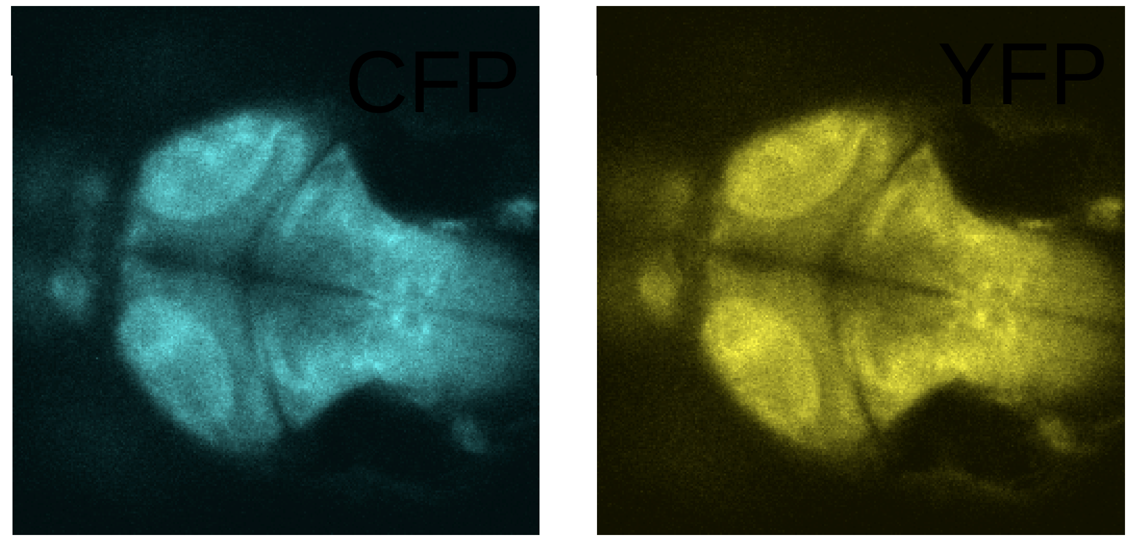


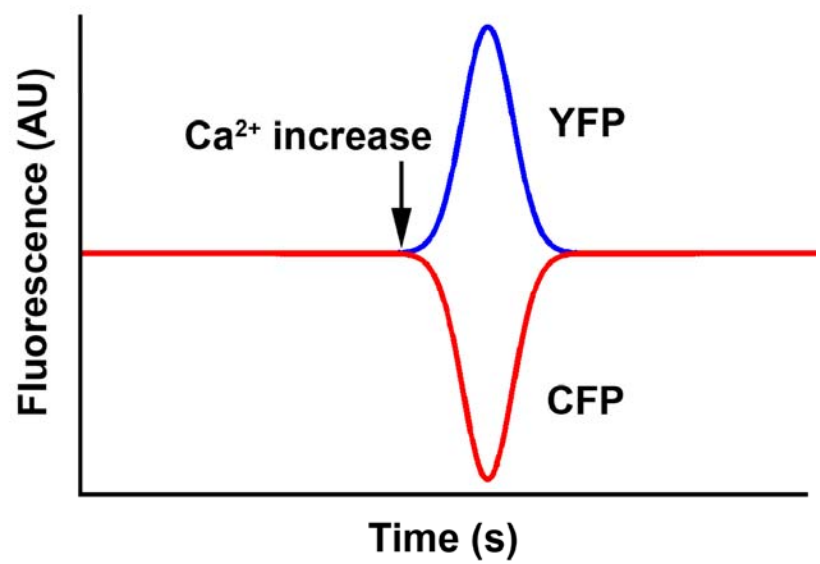
Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out : In	E_{ion} (at 37° C)
K^+	5	100	1:20	-80 mV
Na^+	150	15	10:1	62 mV
Ca^{2+}	2	0.002	10,000:1	123 mV
Cl^-	150	13	11.5:1	-65 mV

FRET指示钙离子浓度的原理



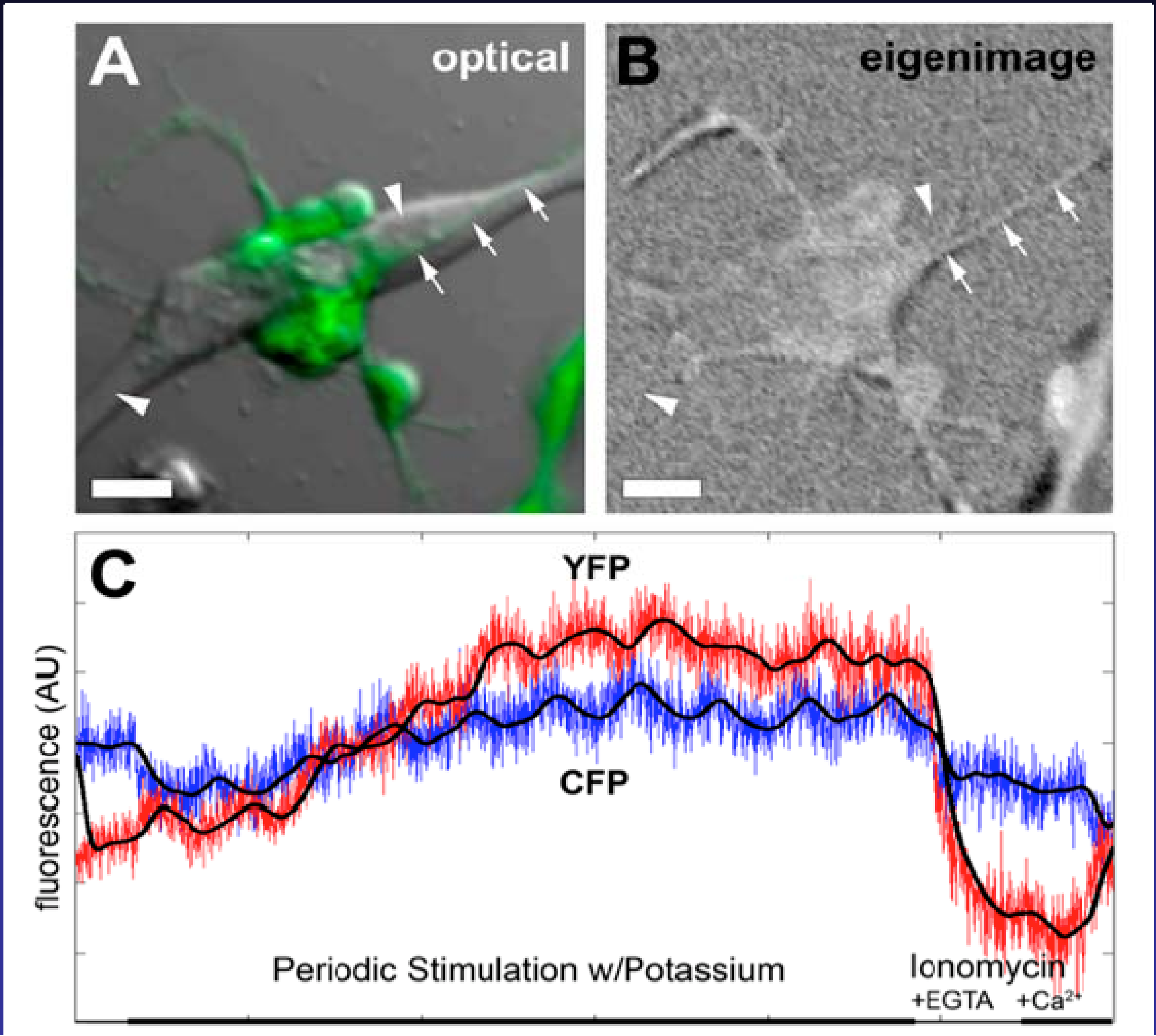
Miyawaki et al., Nature 388:882-887, 1997





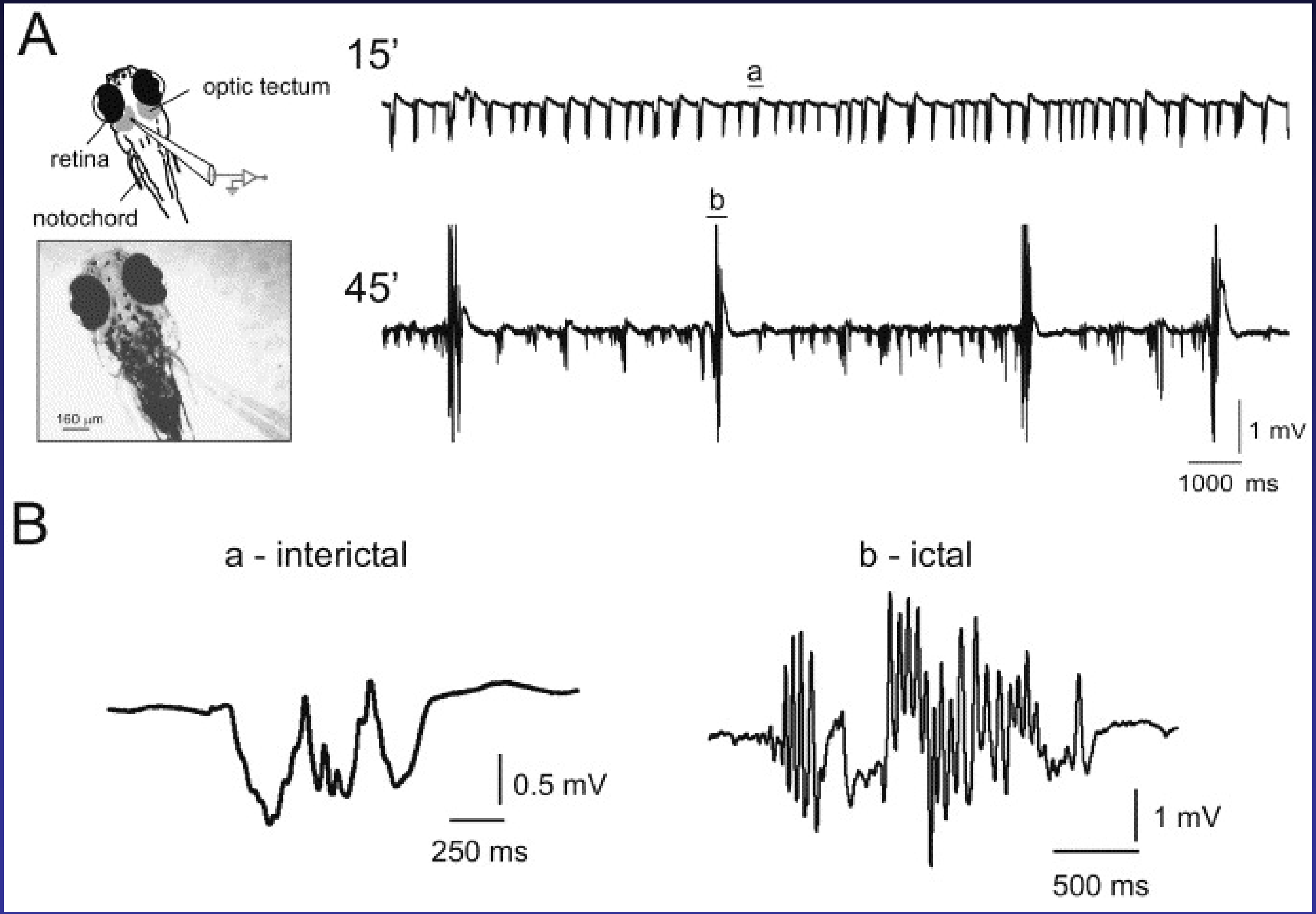
Multi-photon/Confocal Fluorescence Imaging

Detection of the FRET response of cameleon-expressing neurons to stimulation



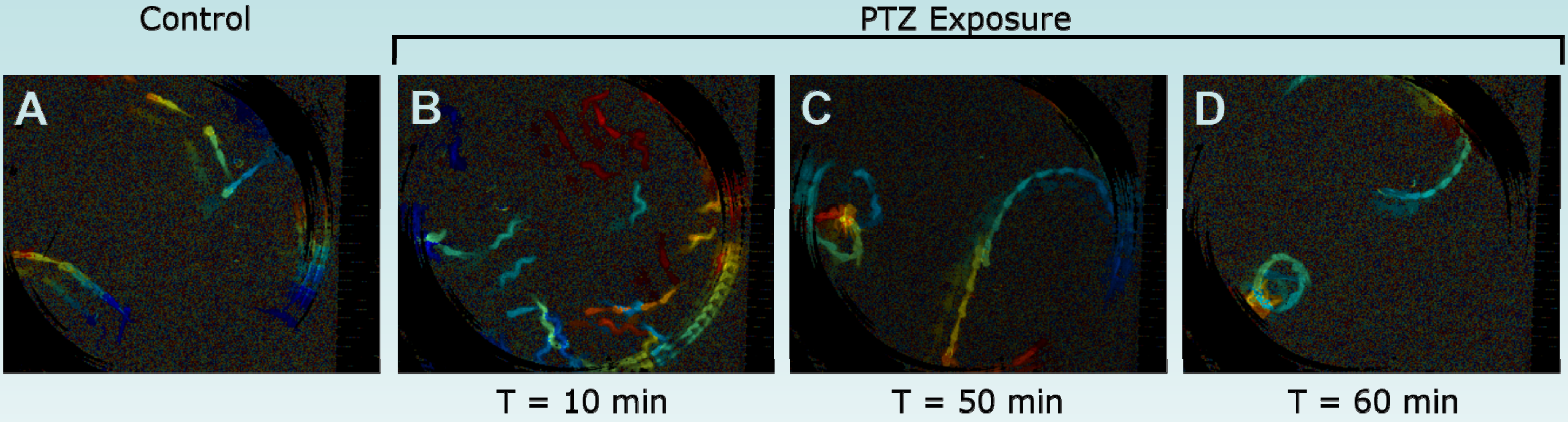
Fan et al., J Biomed Optics 12(3), 030417 (2007)

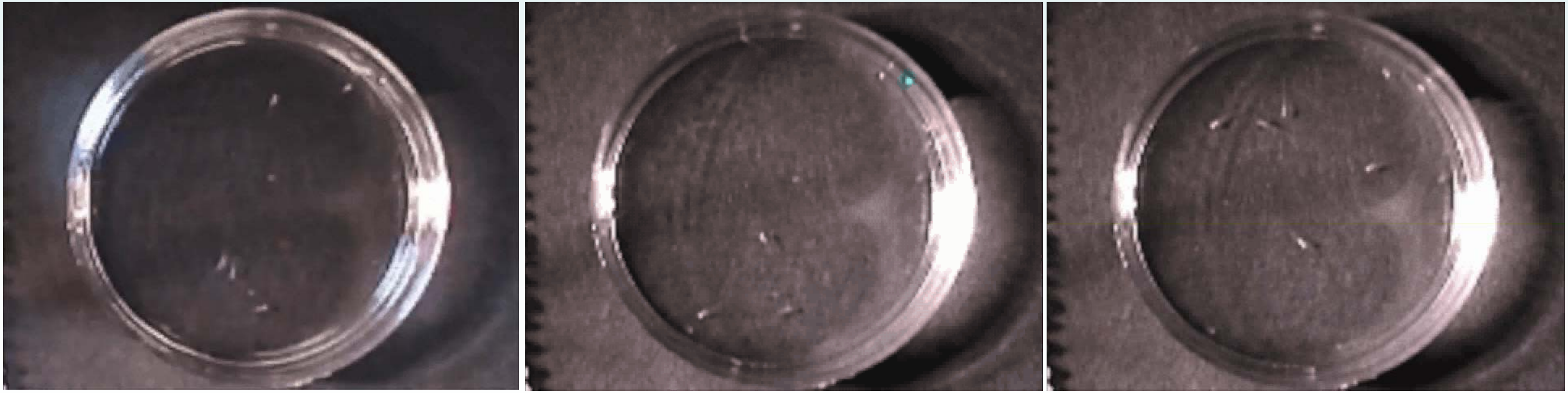
PTZ induces epileptiform-like electrographic activity in zebrafish larvae



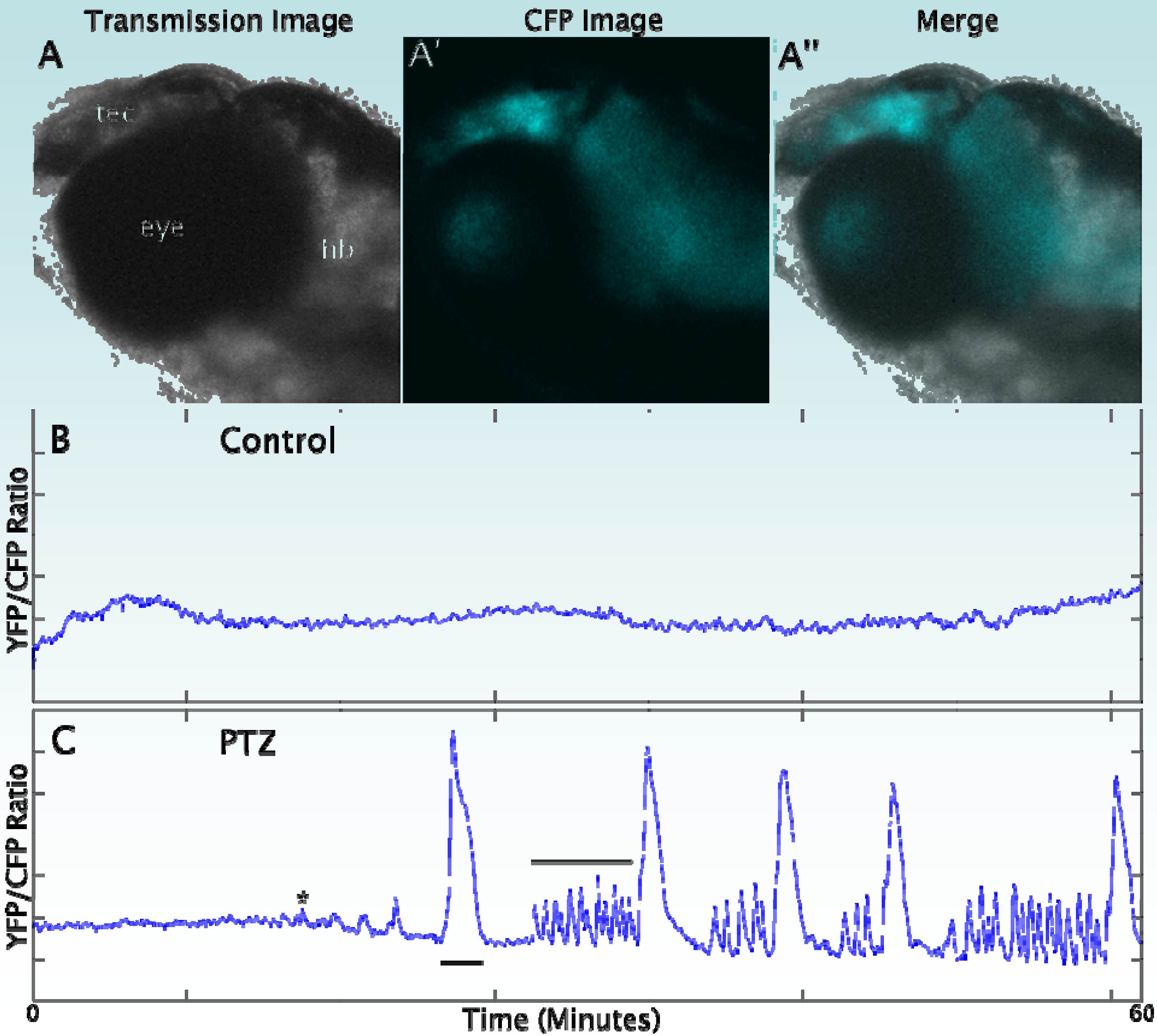
Baraban et al. Neuroscience 131: 759-768, 2005

PTZ induces characteristic behaviors in zebrafish larvae





PTZ与神经元内钙浓度的变化

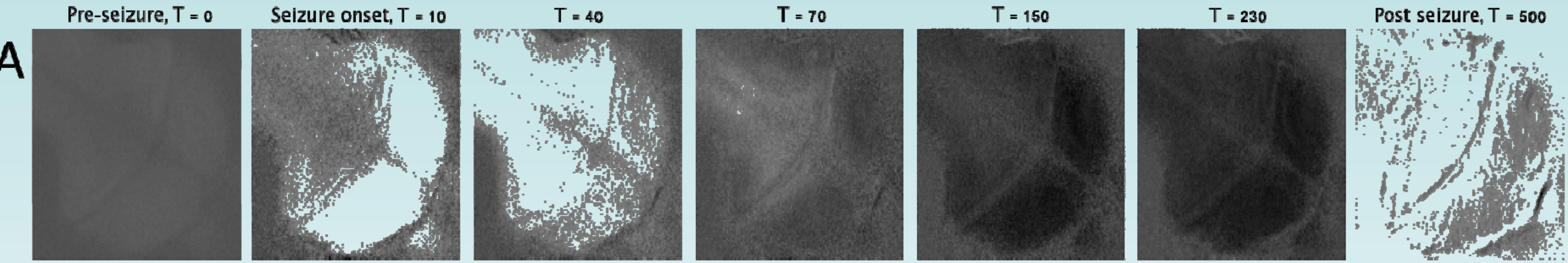


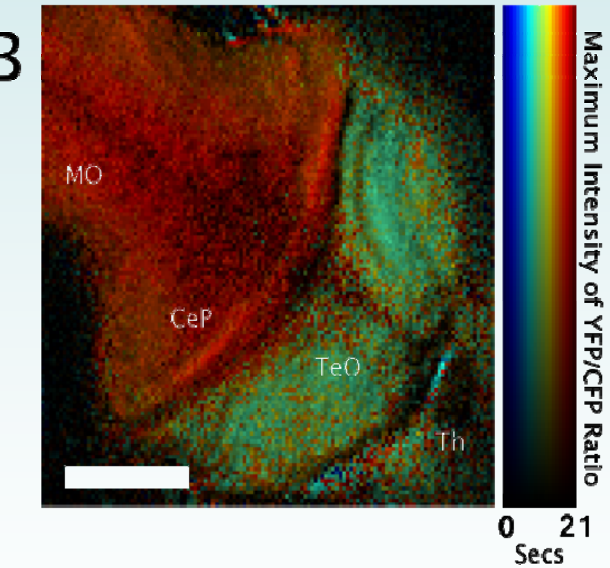
7 dpf

Srinivasamoorthy et al.

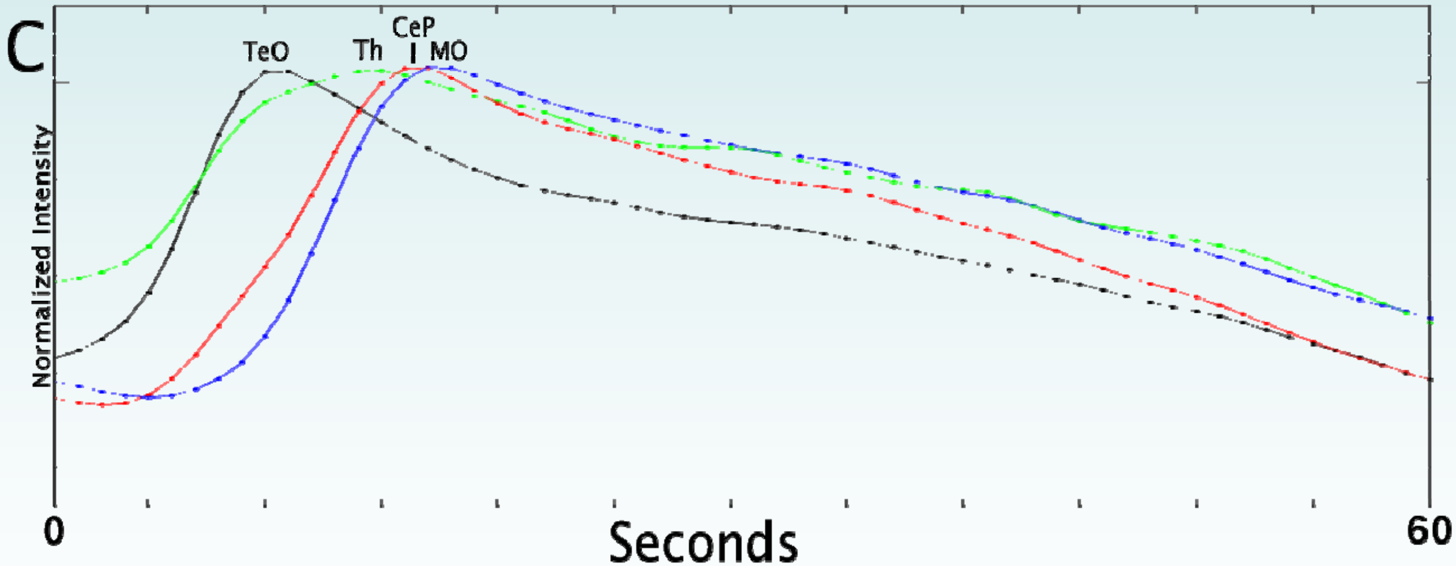
PTZ与神经元内钙浓度的变化

Spatial Characteristics of Seizure





Phase-Intensity Plot

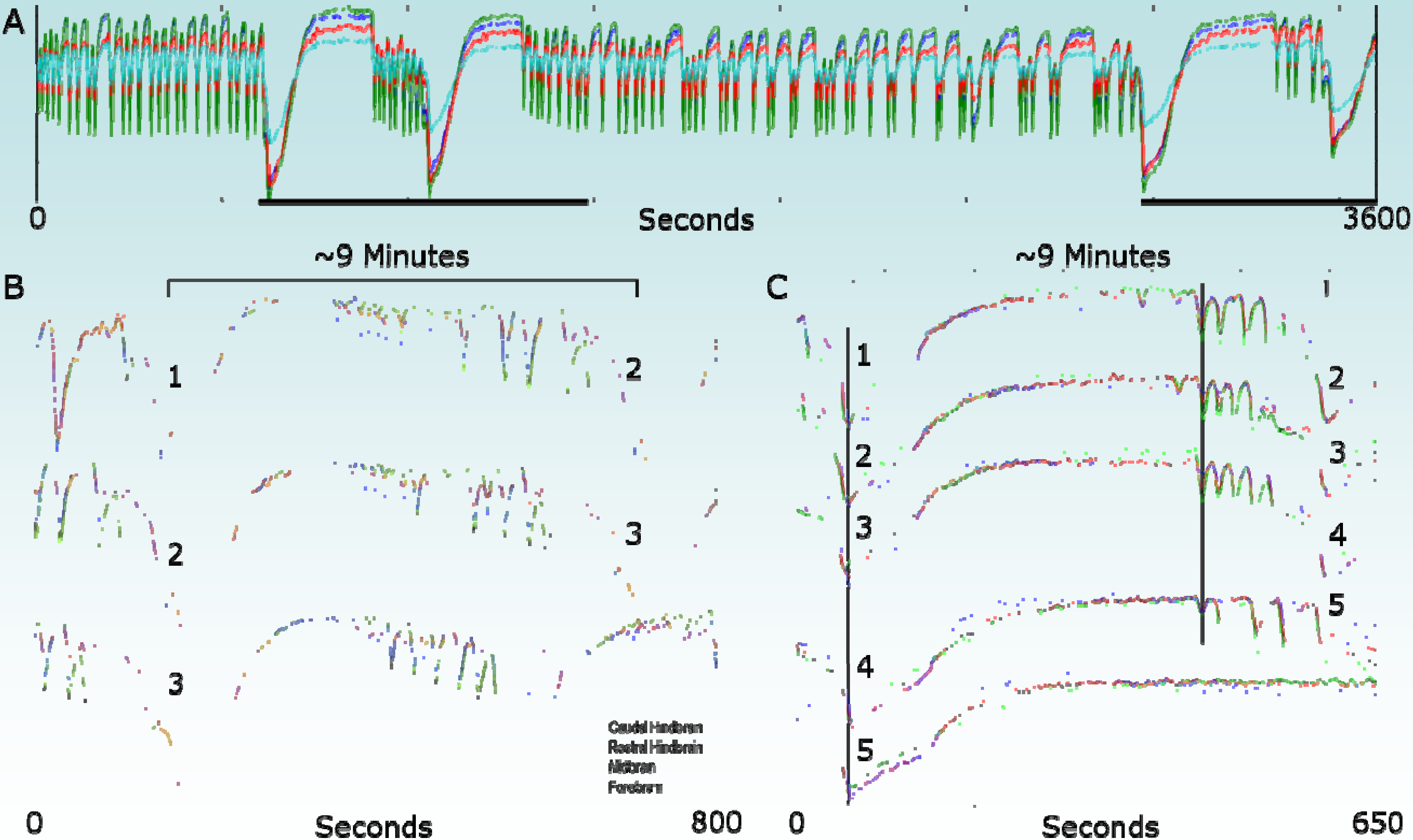


Evolution of Calcium Activity as a Function of Compartment

TeO: optic tectum; Th: thalamus; CeP: cerebellar plate;
MO: medulla oblongata

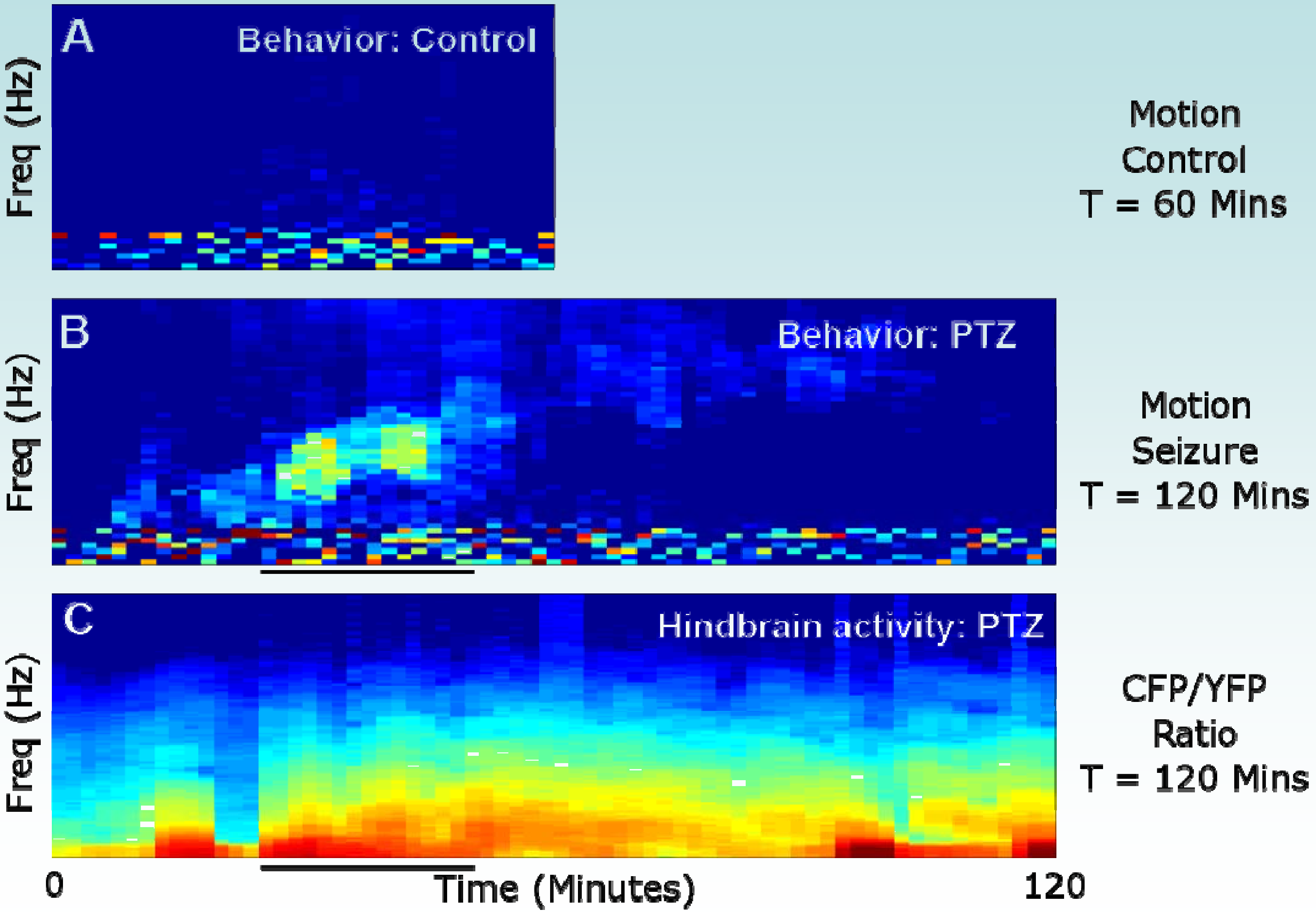
Srinivasamoorthy et al. in revision

吸引子？



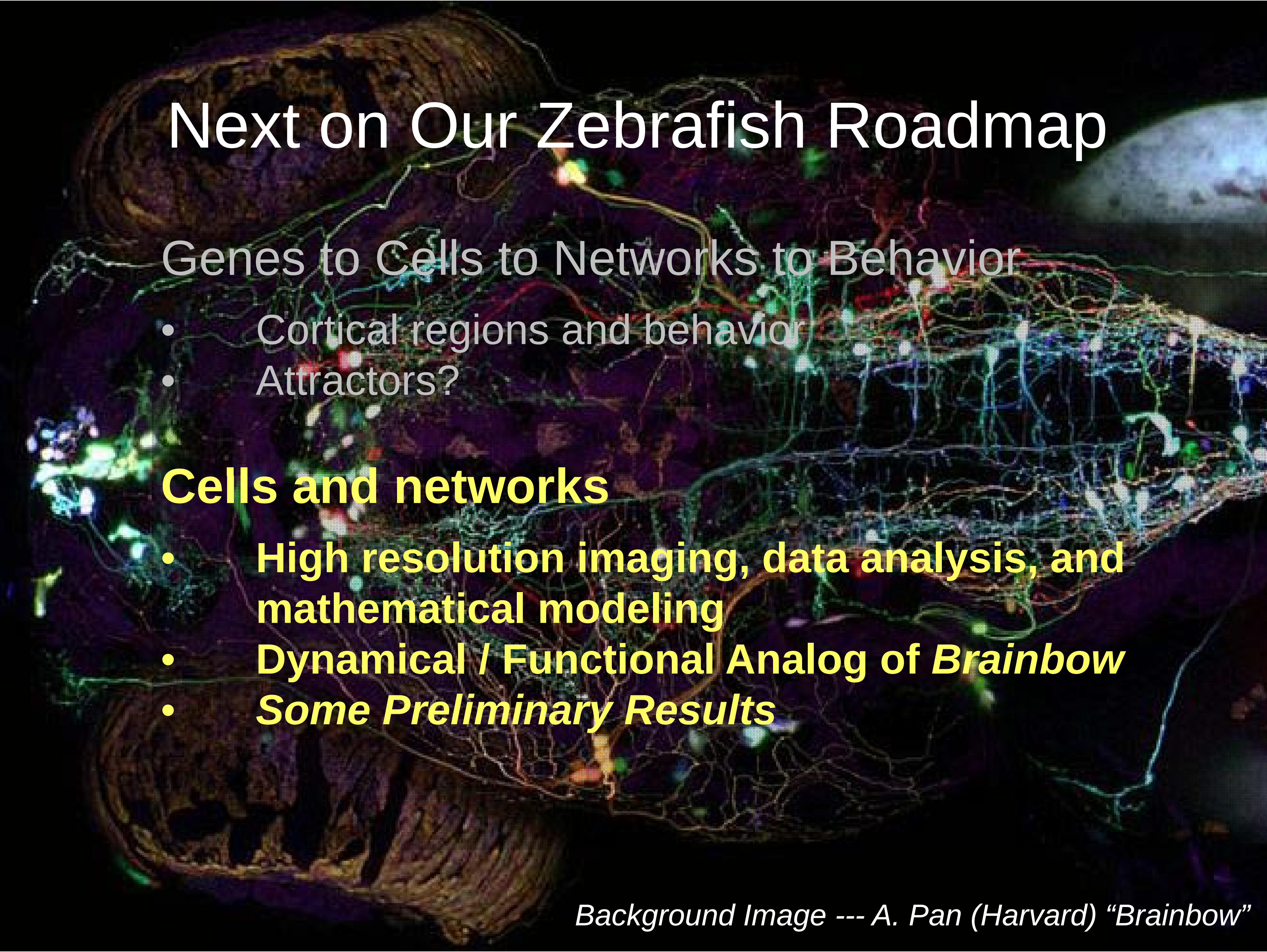
Srinivasamoorthy et al. in revision

Relating Calcium Activity and Behavior



Srinivasamoorthy et al. in revision

Next on Our Zebrafish Roadmap



Genes to Cells to Networks to Behavior

- Cortical regions and behavior
- Attractors?

Cells and networks

- **High resolution imaging, data analysis, and mathematical modeling**
- **Dynamical / Functional Analog of *Brainbow***
- ***Some Preliminary Results***

Background Image --- A. Pan (Harvard) "Brainbow"

电生理与神经功能网络分析

荧光钙离子指示剂

↓

神经元细胞内钙浓度

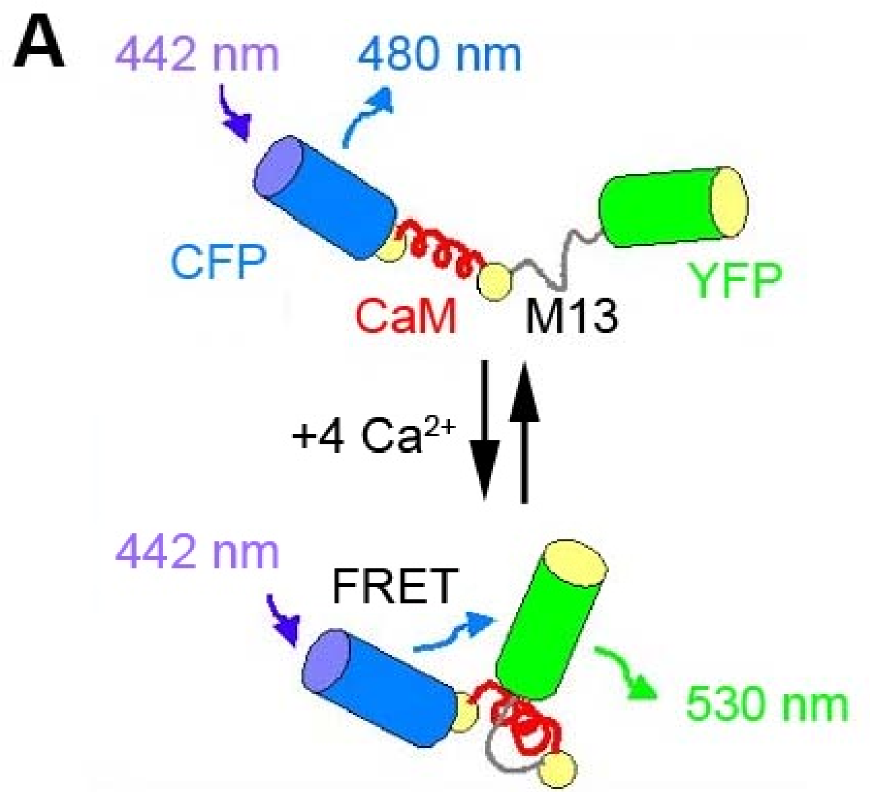
↓

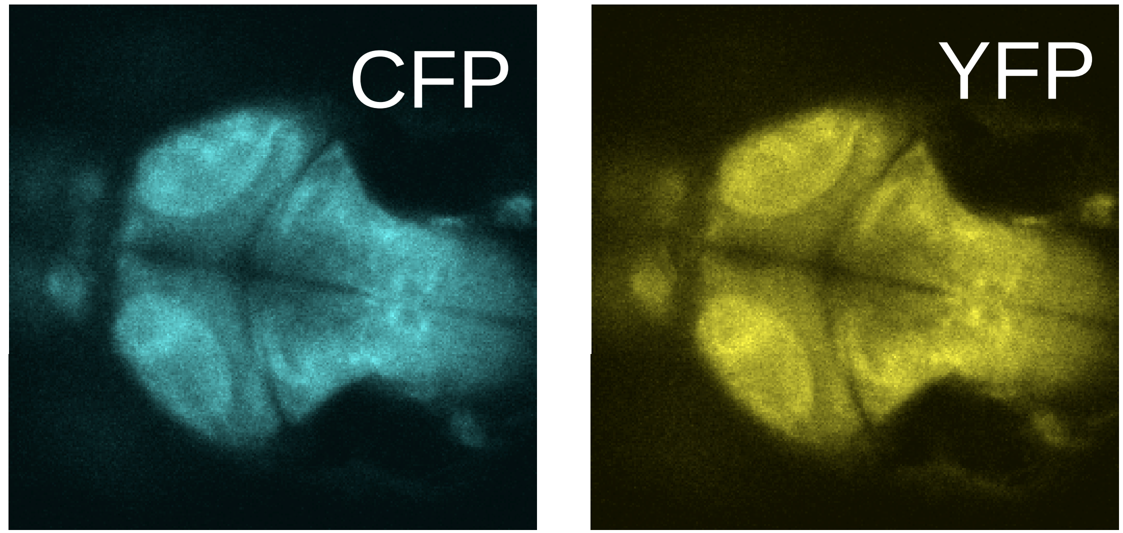
神经元动作电位时间/频率

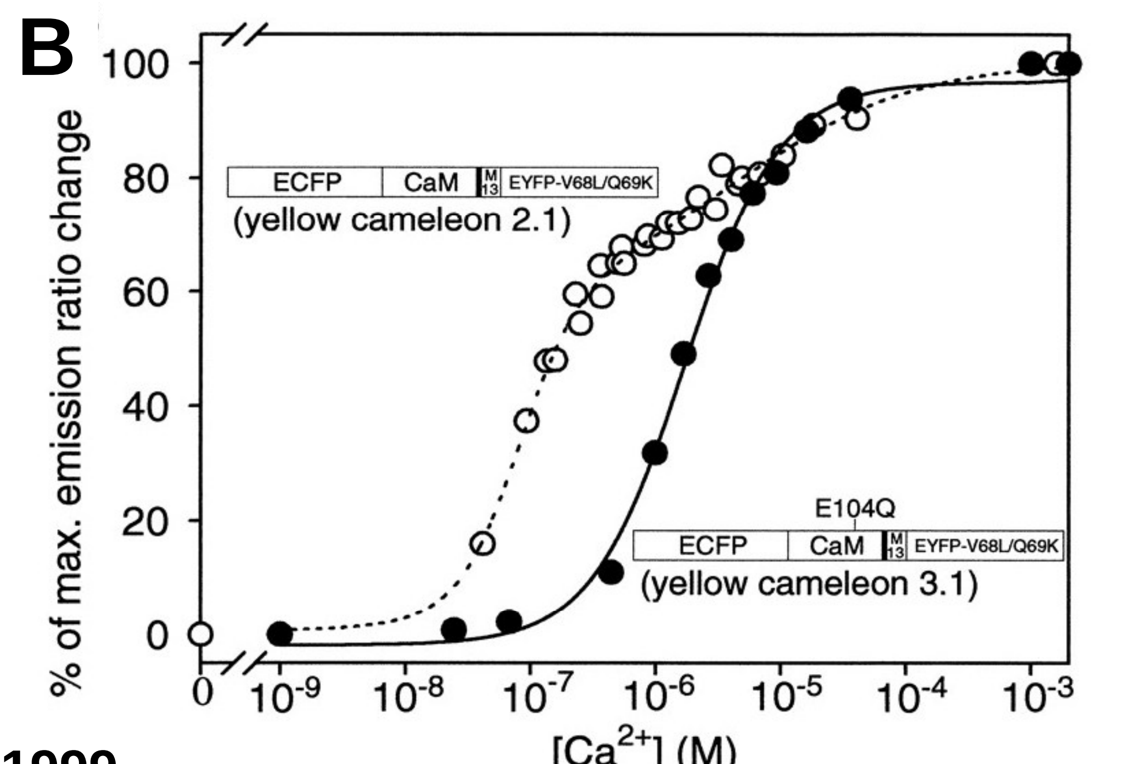
↓

神经元功能网络与模型

FRET指示钙离子浓度的原理







Miyawaki et al., PNAS 96:2135-2140, 1999

钙浓度与神经元
动作电位时间/频率

动作电位
时间序列

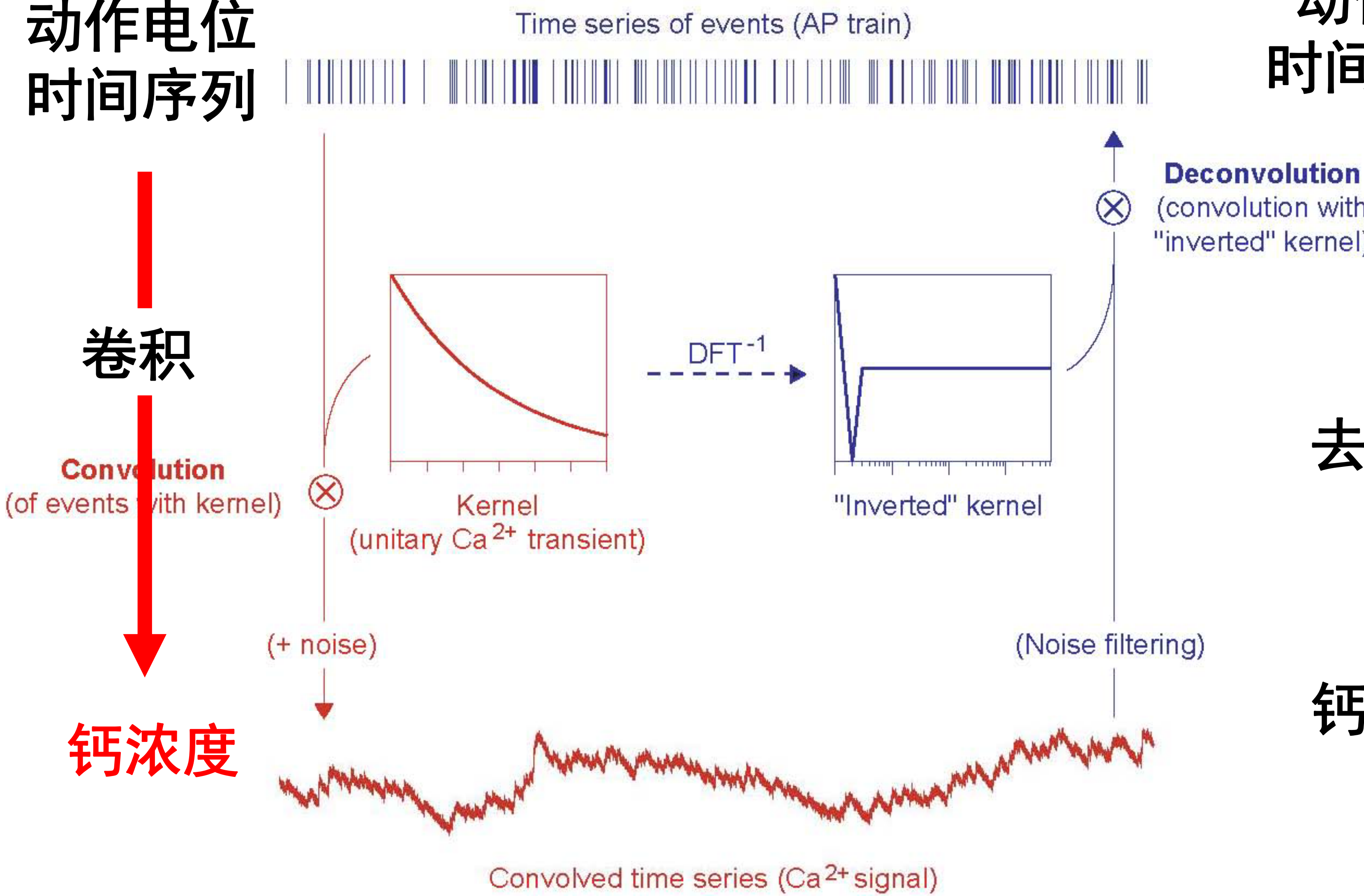
卷积

钙浓度

动作电位
时间或频率

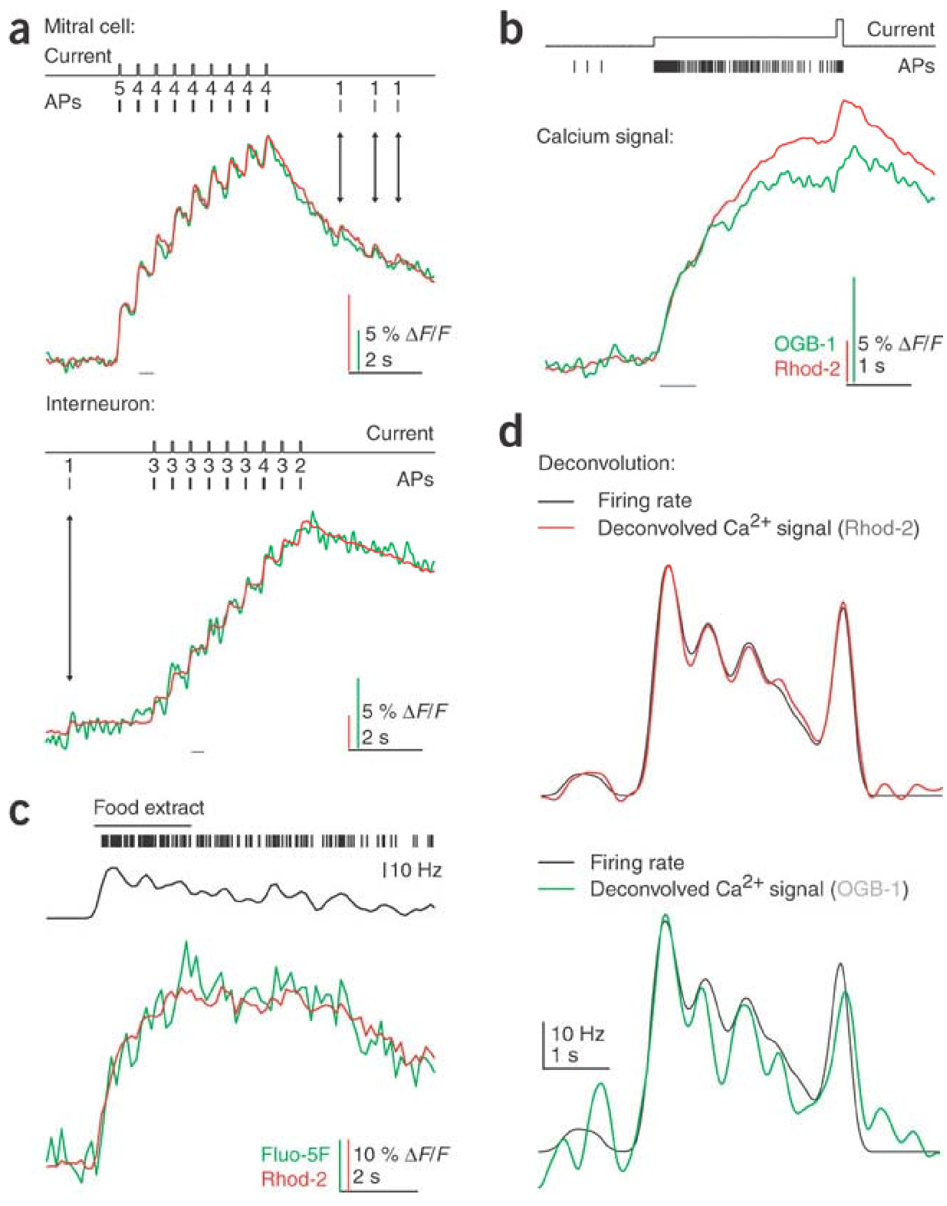
去卷积

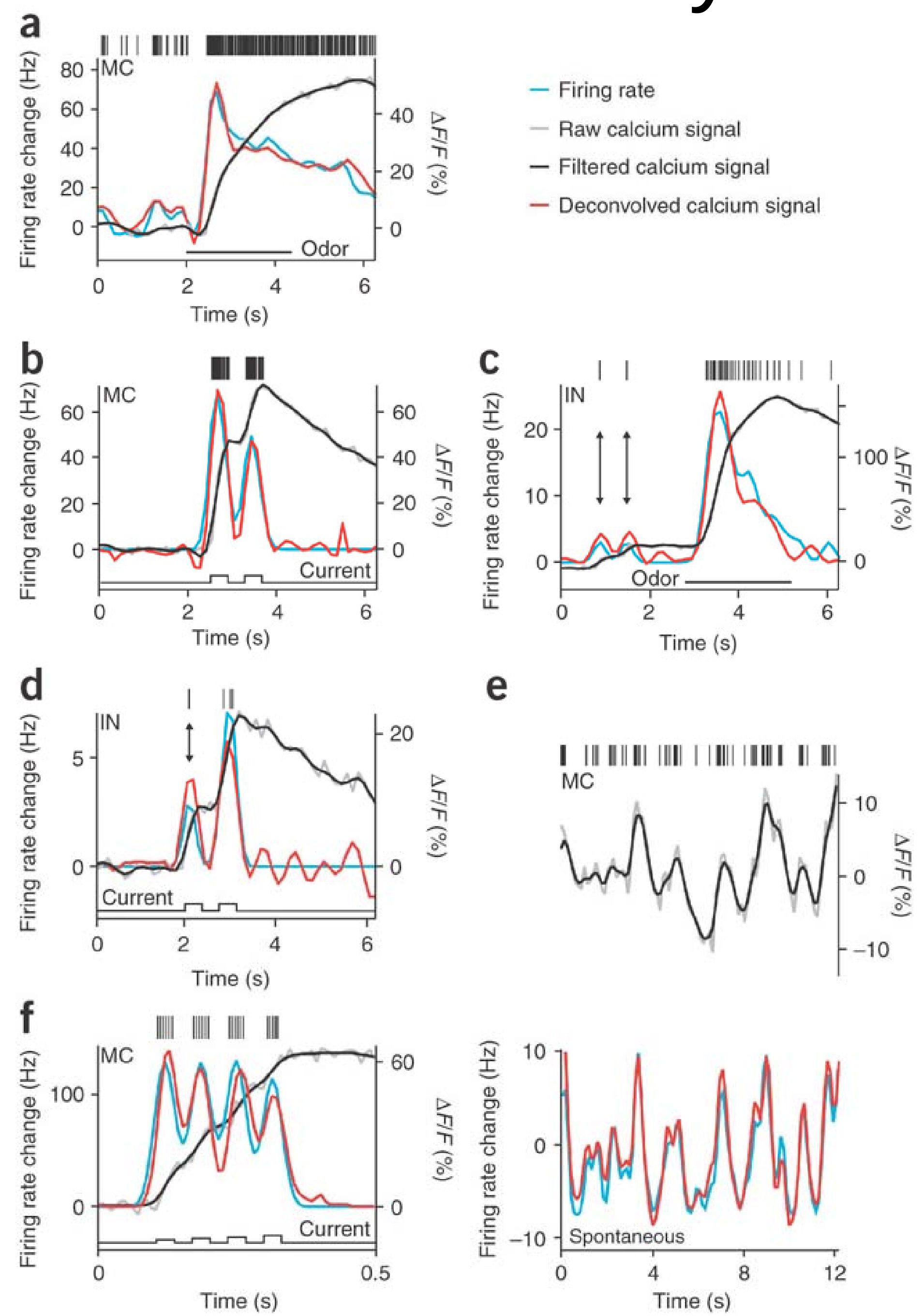
钙浓度



Yaksi & Friedrich, Nature Methods 2006

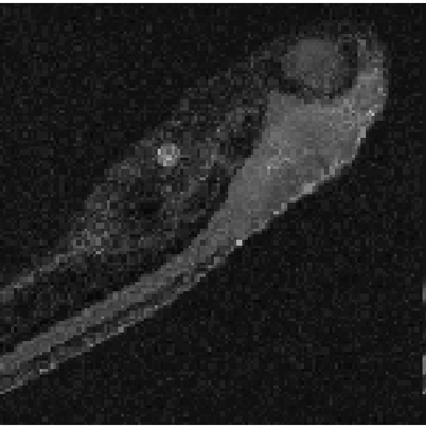
Ca^{2+} Concentration & Neuronal Activity



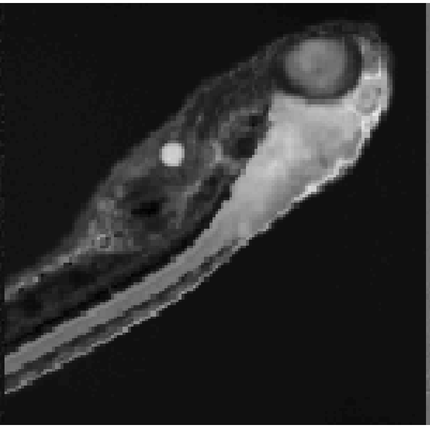


Yaksi & Friedrich, Nature Methods 2006

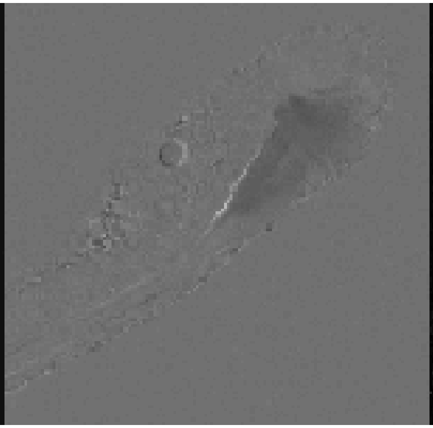
荧光钙离子指示剂 → 钙浓度 → 神经元动作电位频率 → 神经元功能网络



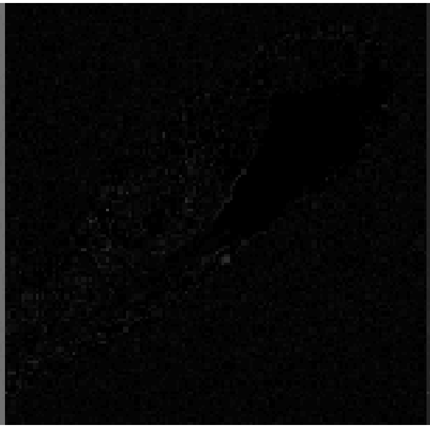
Y/CFP FRET Ratio
钙离子指示剂（荧光亮度）



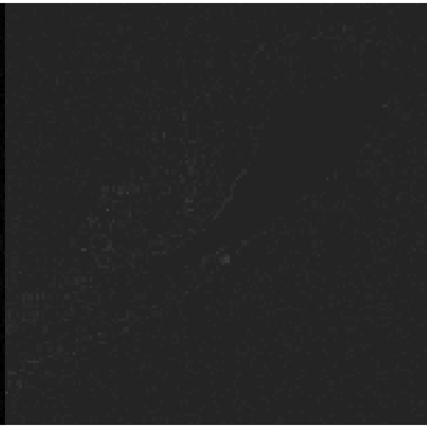
SVD-Based Multivariate Data Analysis
基于主成分分析的多元数据分析



Signal (Background Subtracted)
信号（除背景）



Calcium Concentration
钙离子浓度

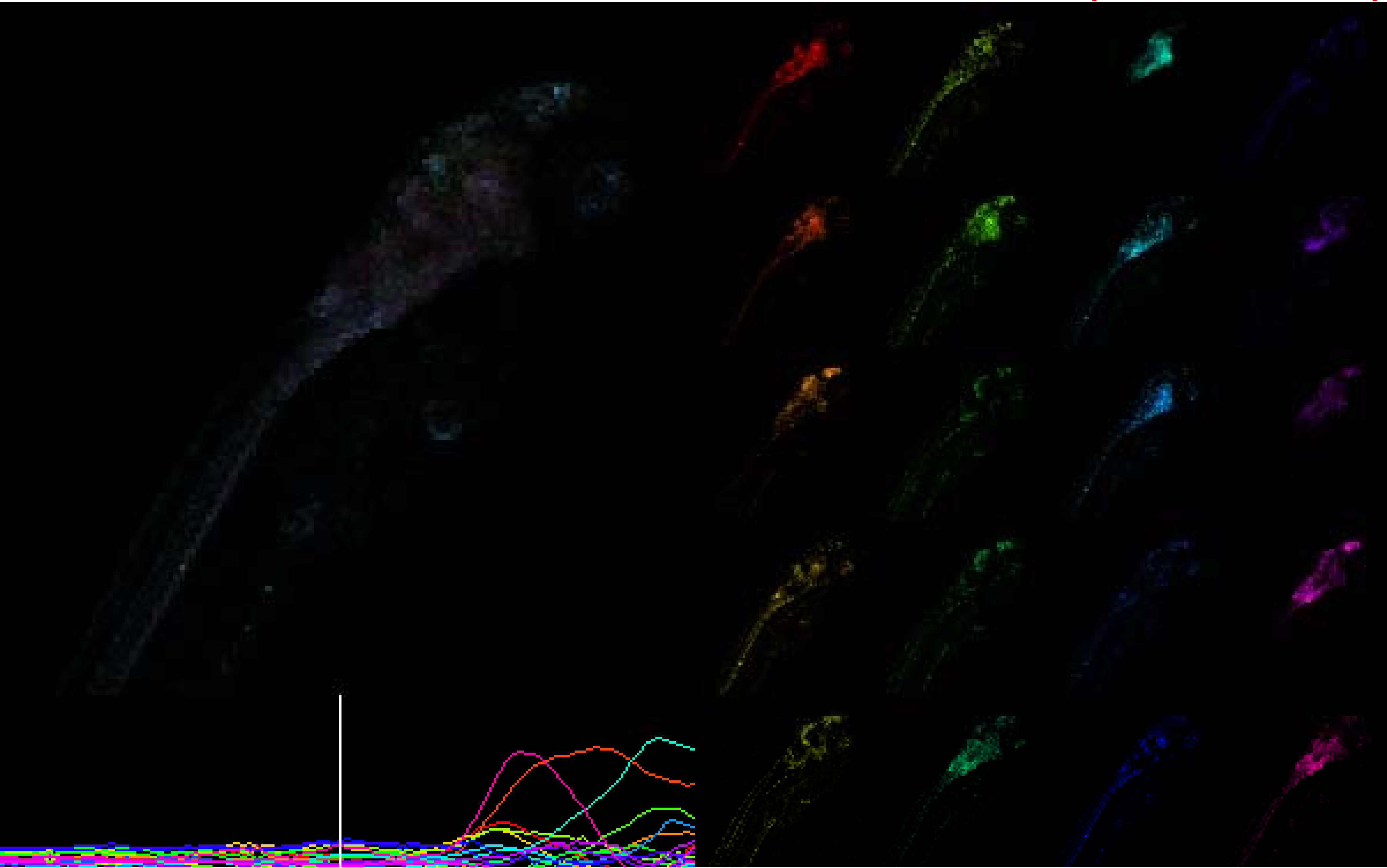


Neuronal Activity
神经元动作电位频率

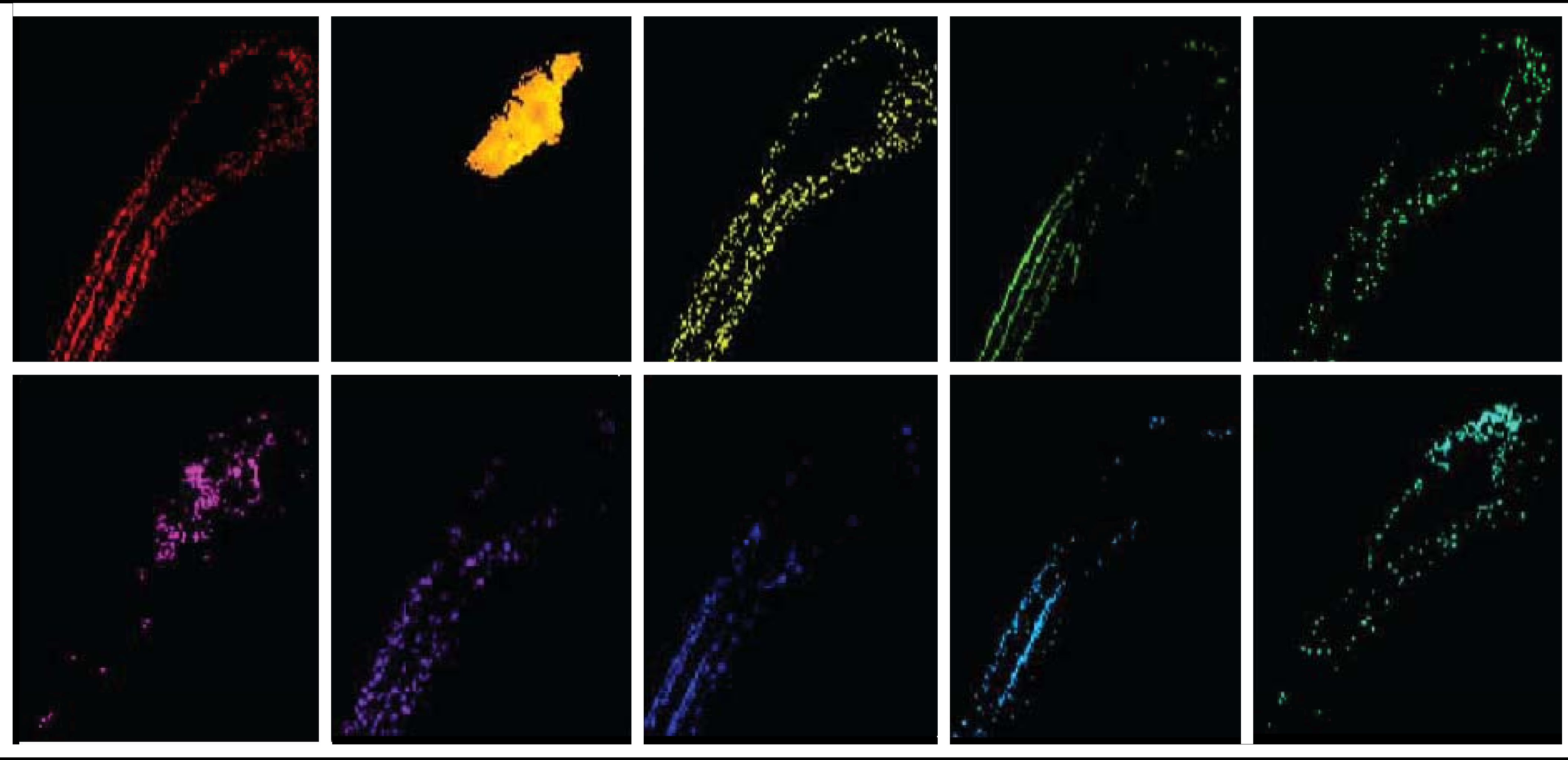
Sornborger & Lauderdale (U Georgia)
斑马鱼荧光成像数据 (unpublished)
Tao et al 分析方法 (in revision)

利用数学模型寻找合理的神经元群动力系统

(Tao et al, in revisn.)



非负矩阵分析结果：神经元群的分布



(Tao et al, in revision)

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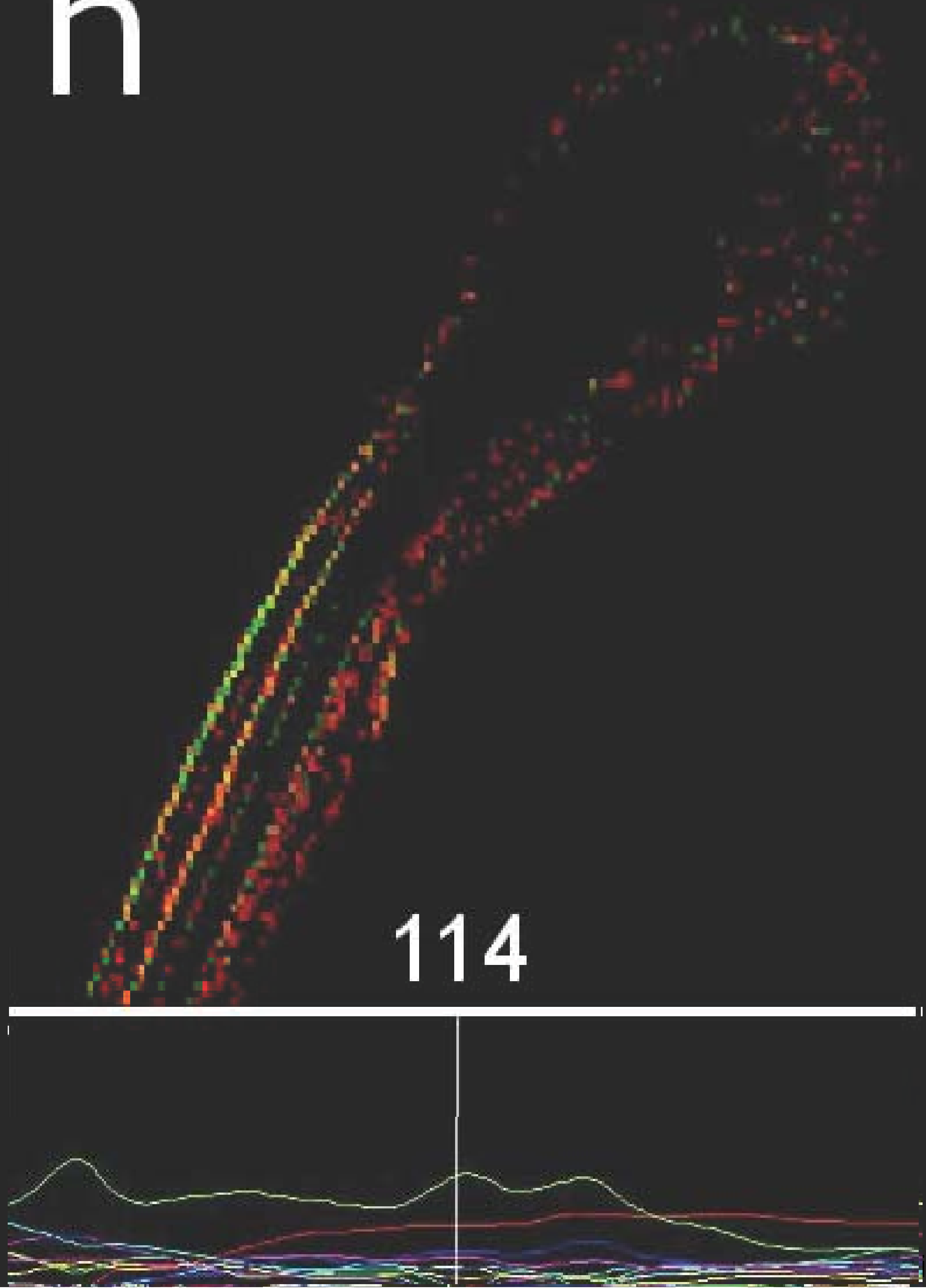
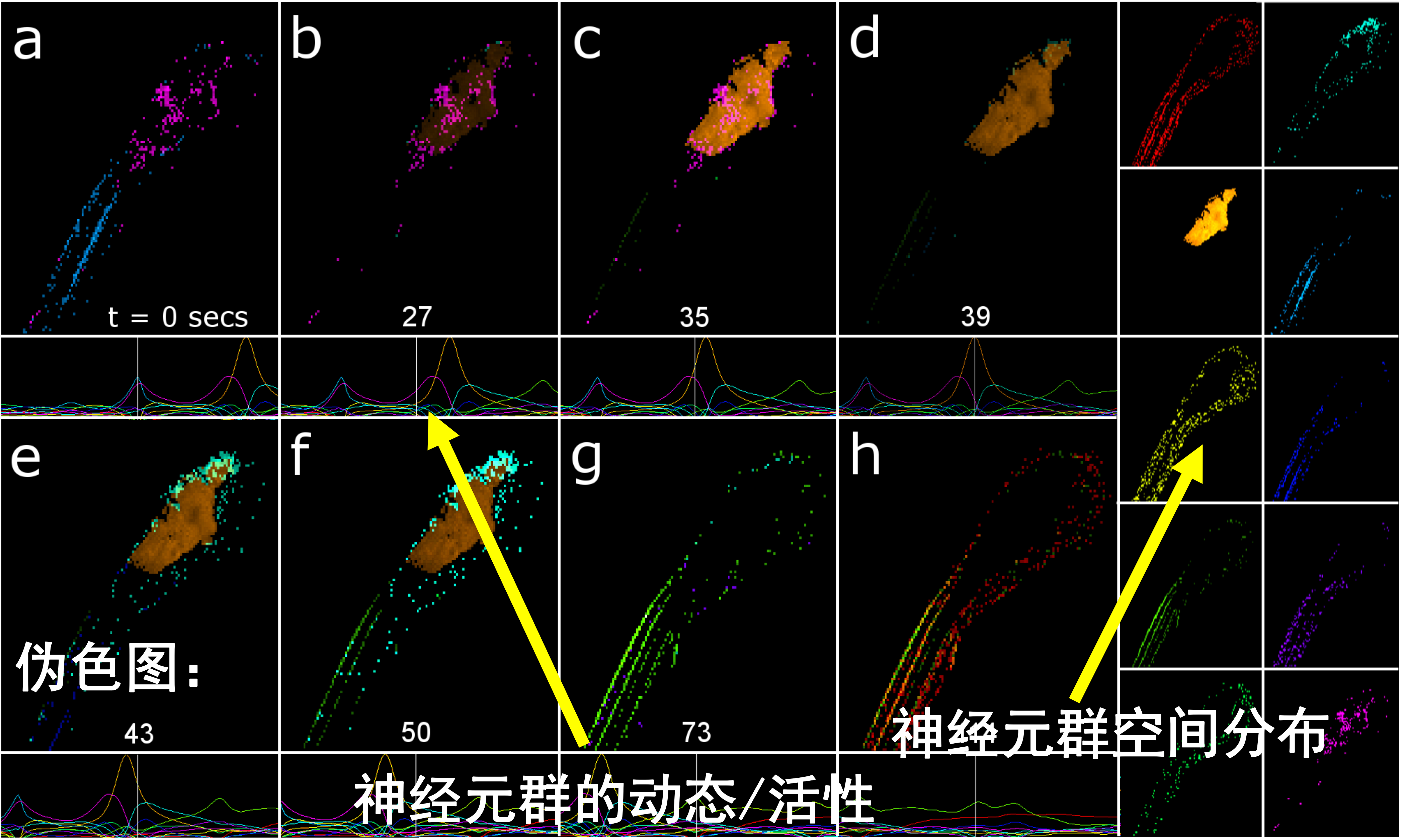


非负矩阵分析结果：神经元群的动态



(Tao et al, in revision)

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<u>*D. rerio* seizure model</u>
<u>@ U Georgia</u>

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Wang Cong 王聪

<u>Math @ PKU</u>

Jiang Ming 姜明

<u>*C. elegans* & *D. rerio* @ PKU</u>

Liu Dong 刘东

<u>Visual behavior in</u>
<u>*D. melanogastor* @ IBP ?</u>

Zhu Yan 朱岩

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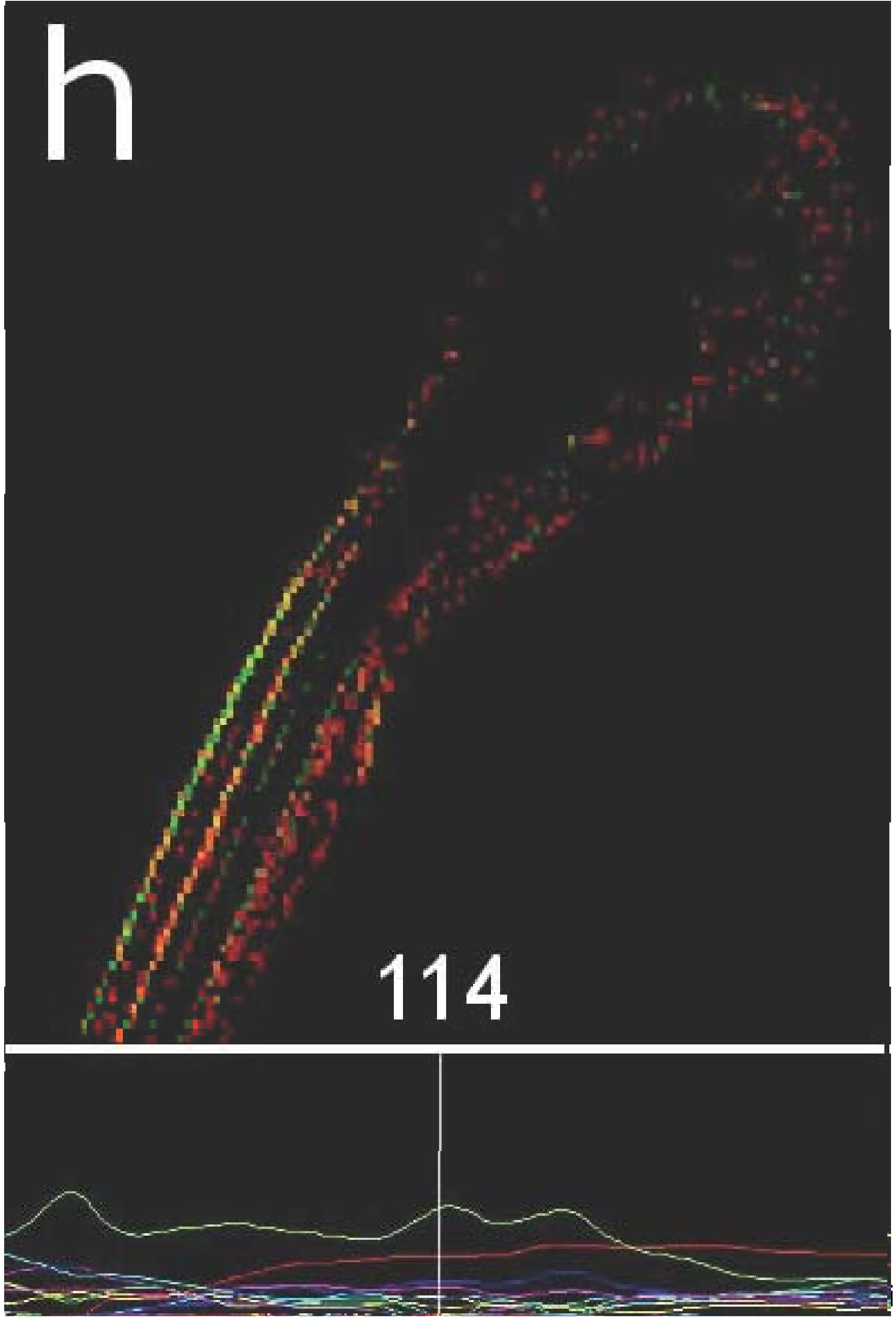
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Questions?