e-Scientific Reconstruction of Cardiac Systems @ Manchester

– combined approaches of simulation and electrophysiology

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Reconstruction of the cardiac pacemaker and conduction system (sinoatrial node and atrioventricular node)

Funding bodies: BHF & BBSRC

Teams

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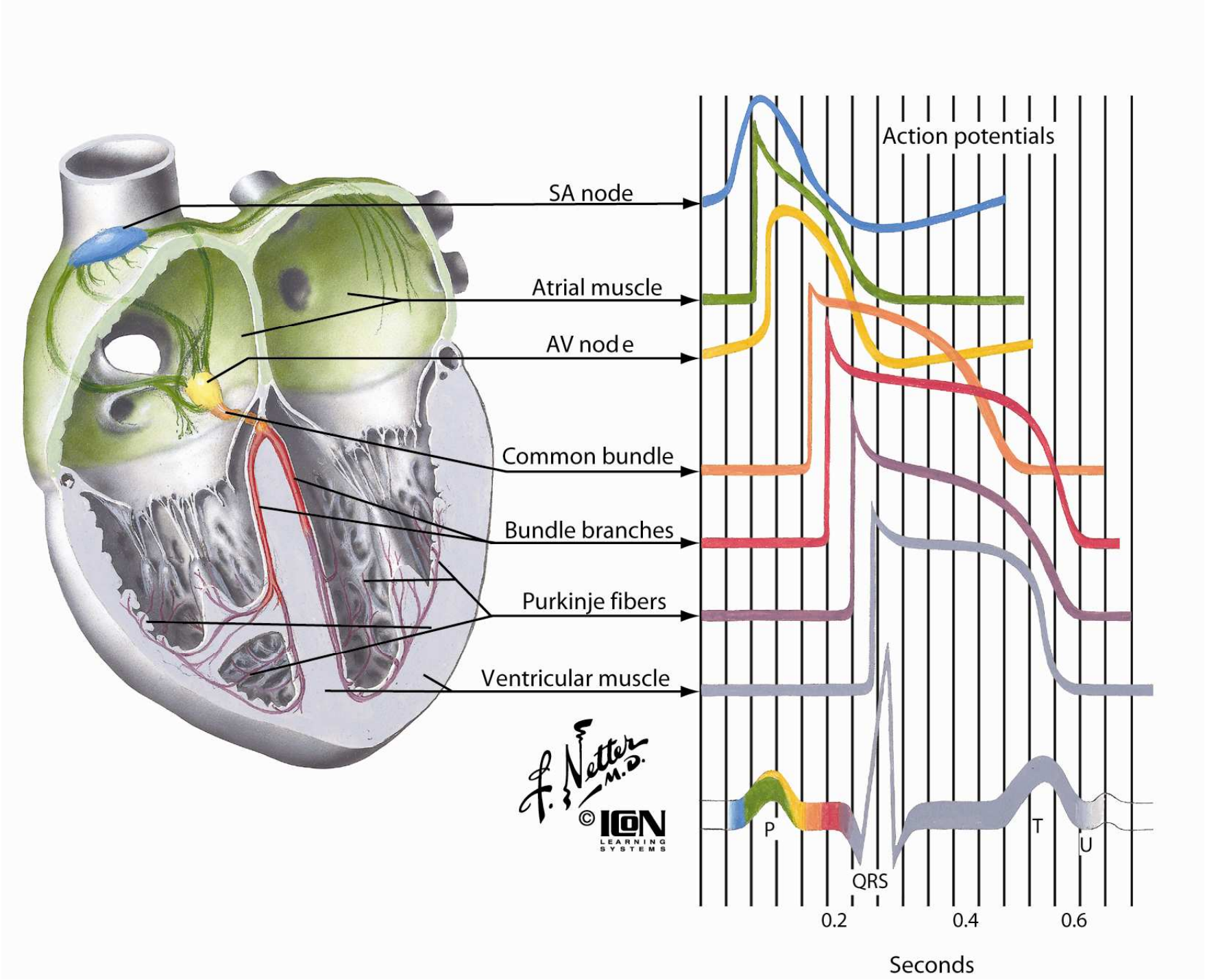
Arun Holden
(Leeds)

Jules Hancox
(Bristol)

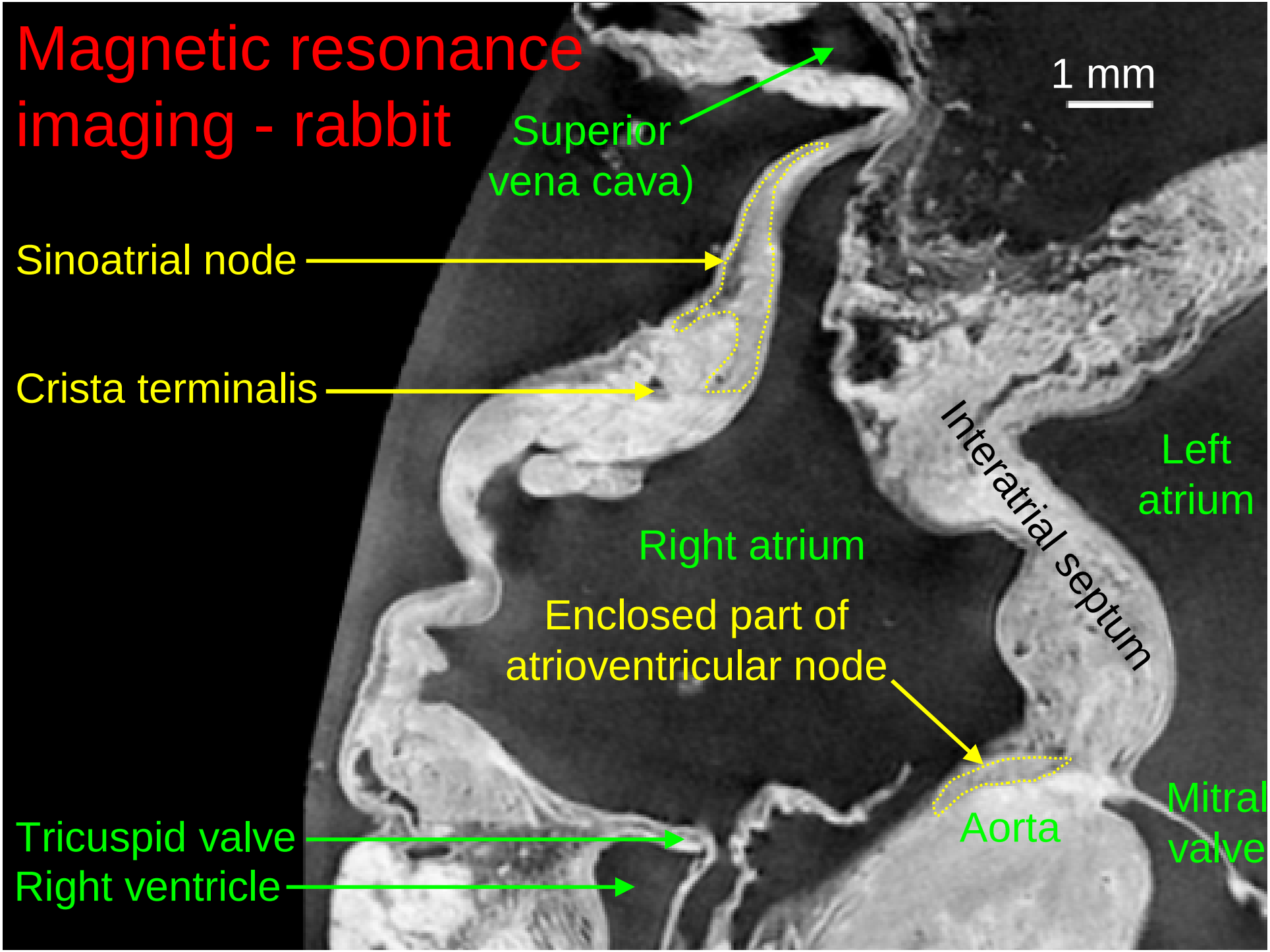
John Tucker
(Swansea)

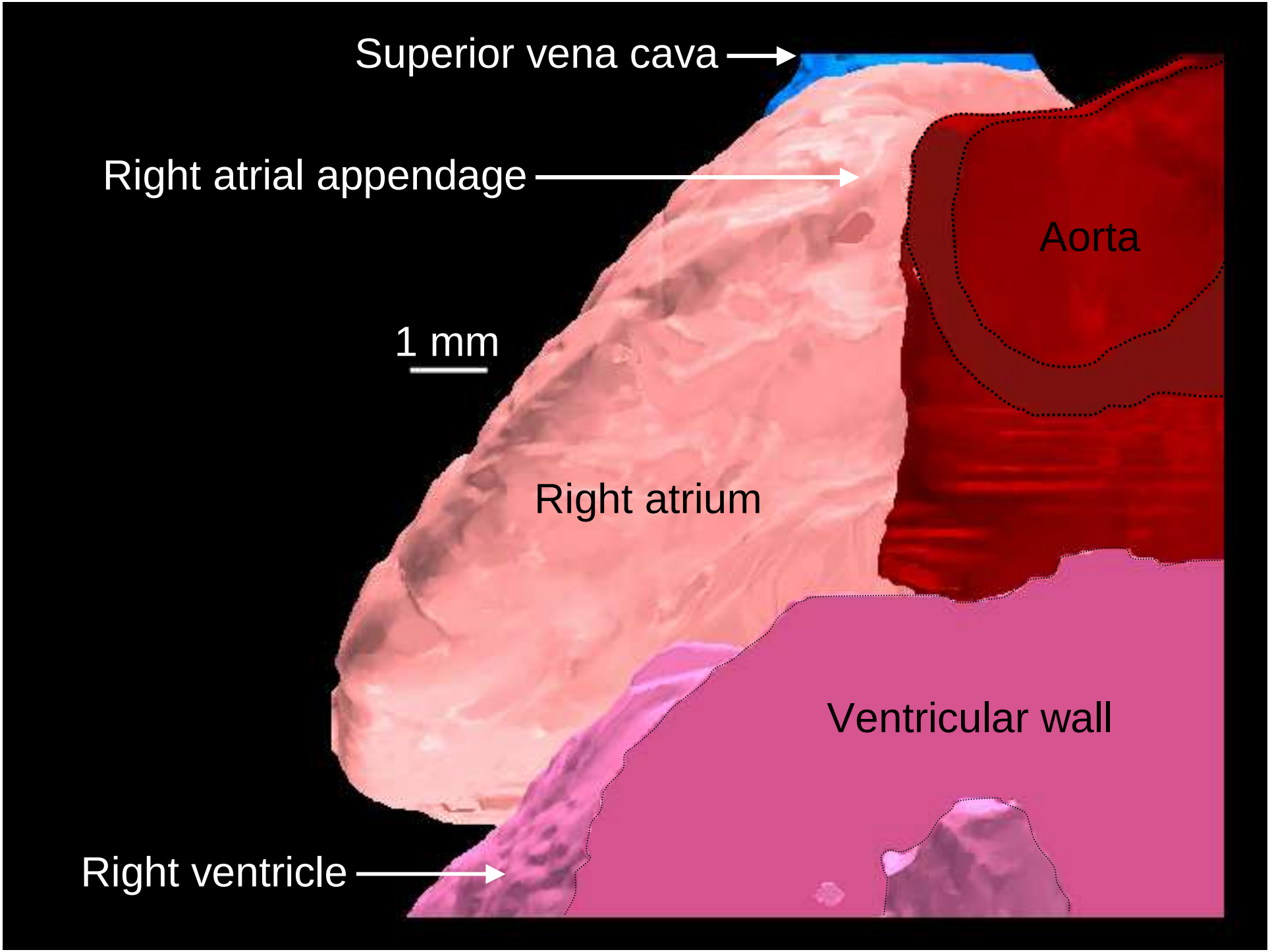
Min Chen
(Swansea)

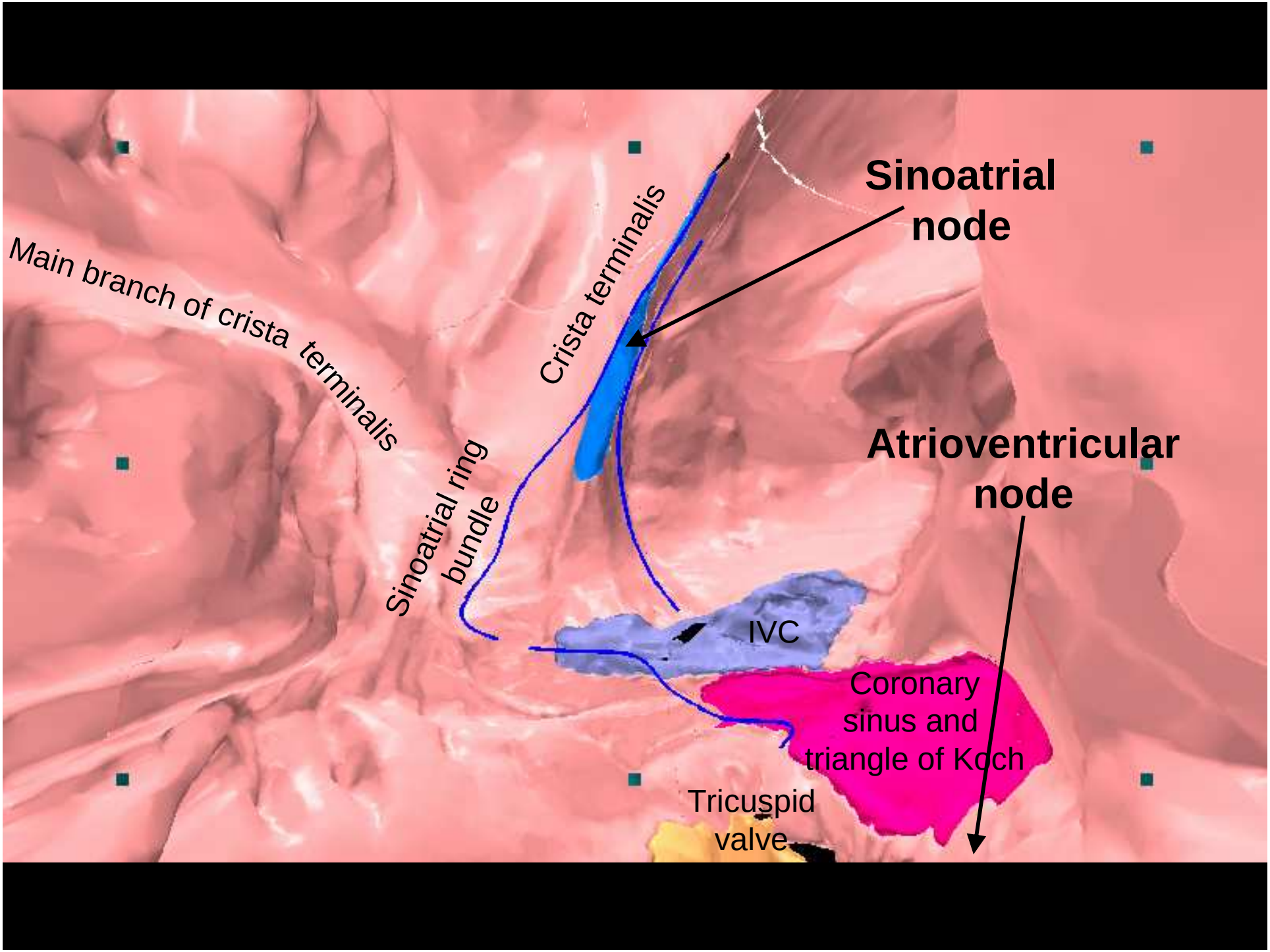


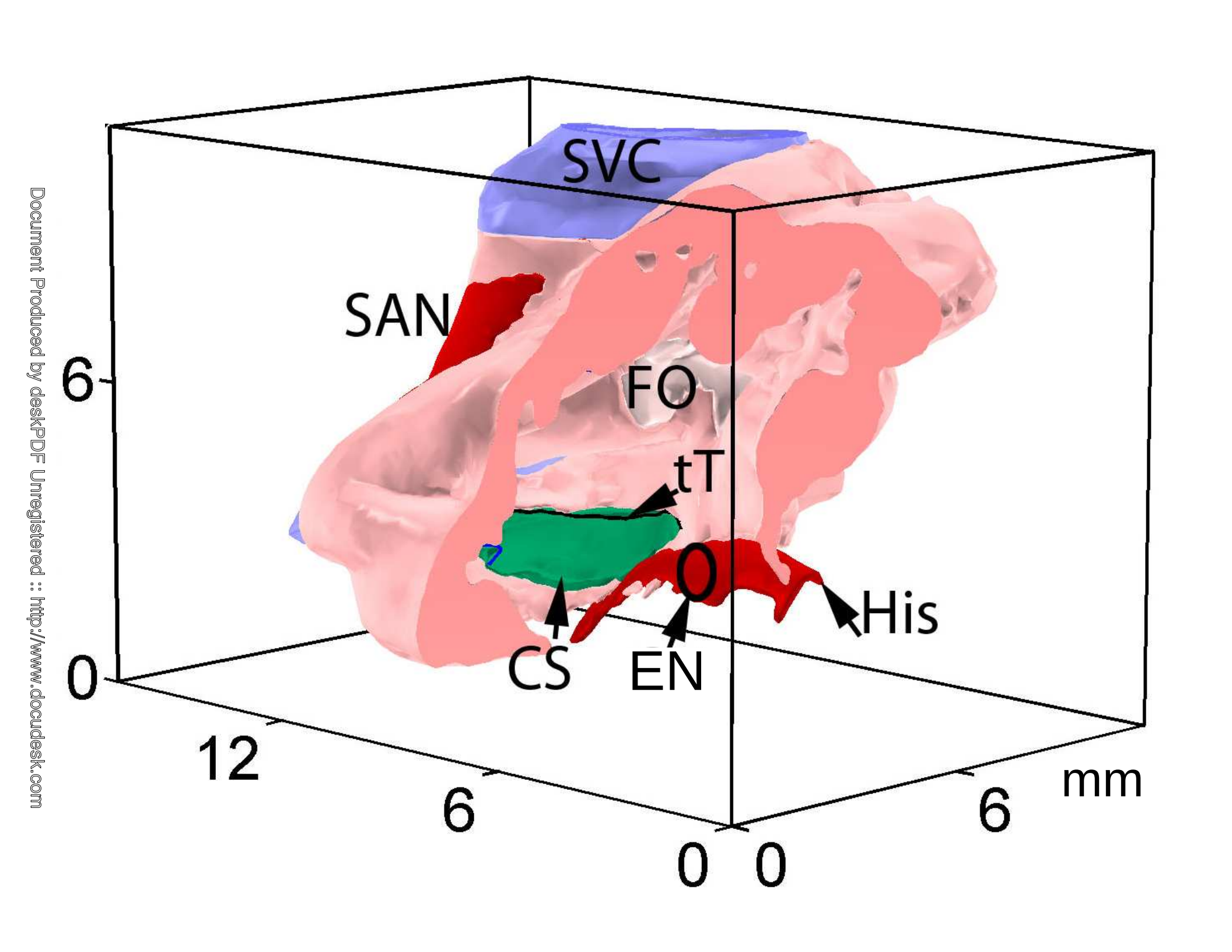
Model of right atrium of rabbit

Jue Li, Jurgen Schneider, Mitsuru Yamamoto and Halina Dobrzynski



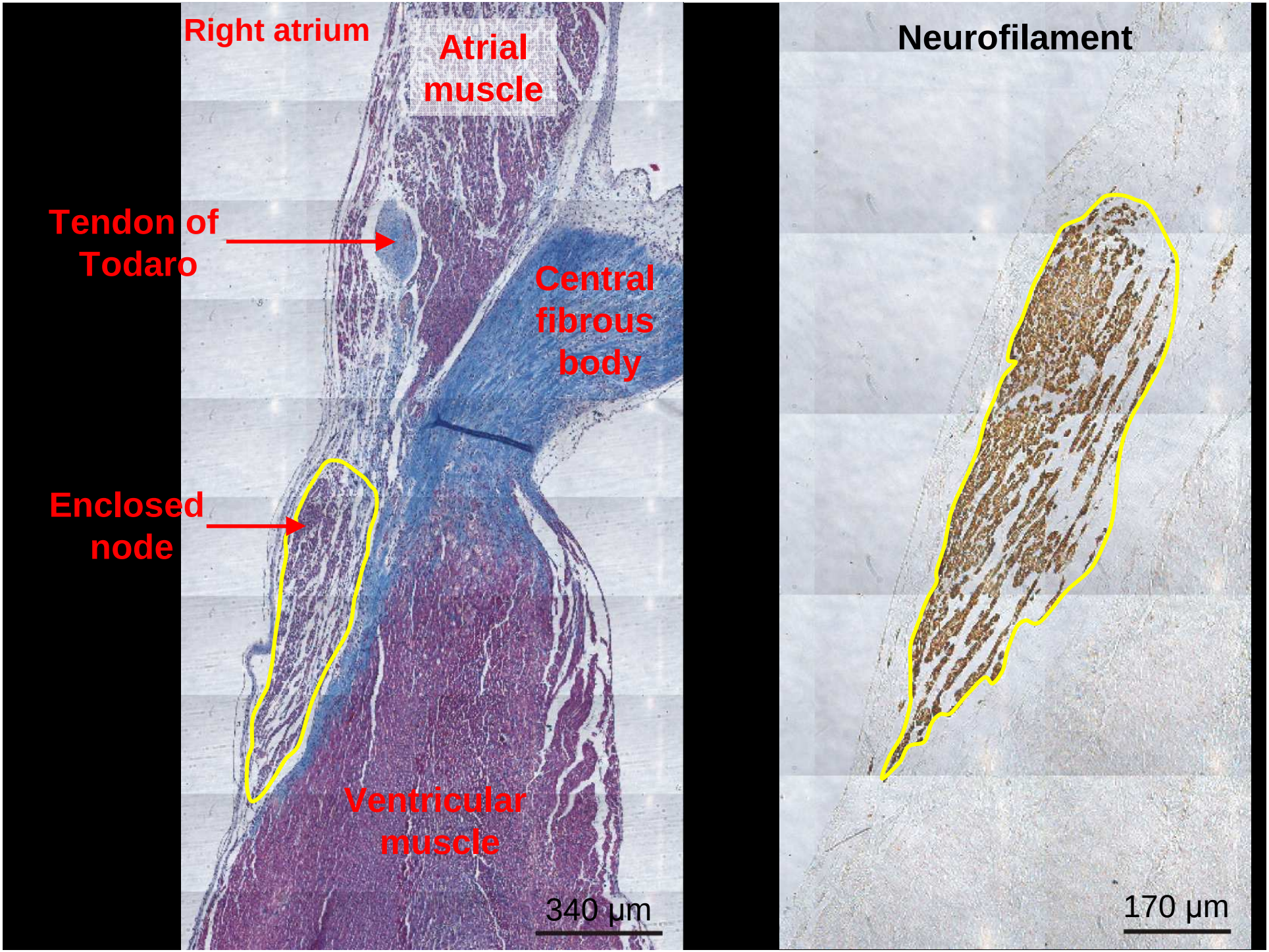




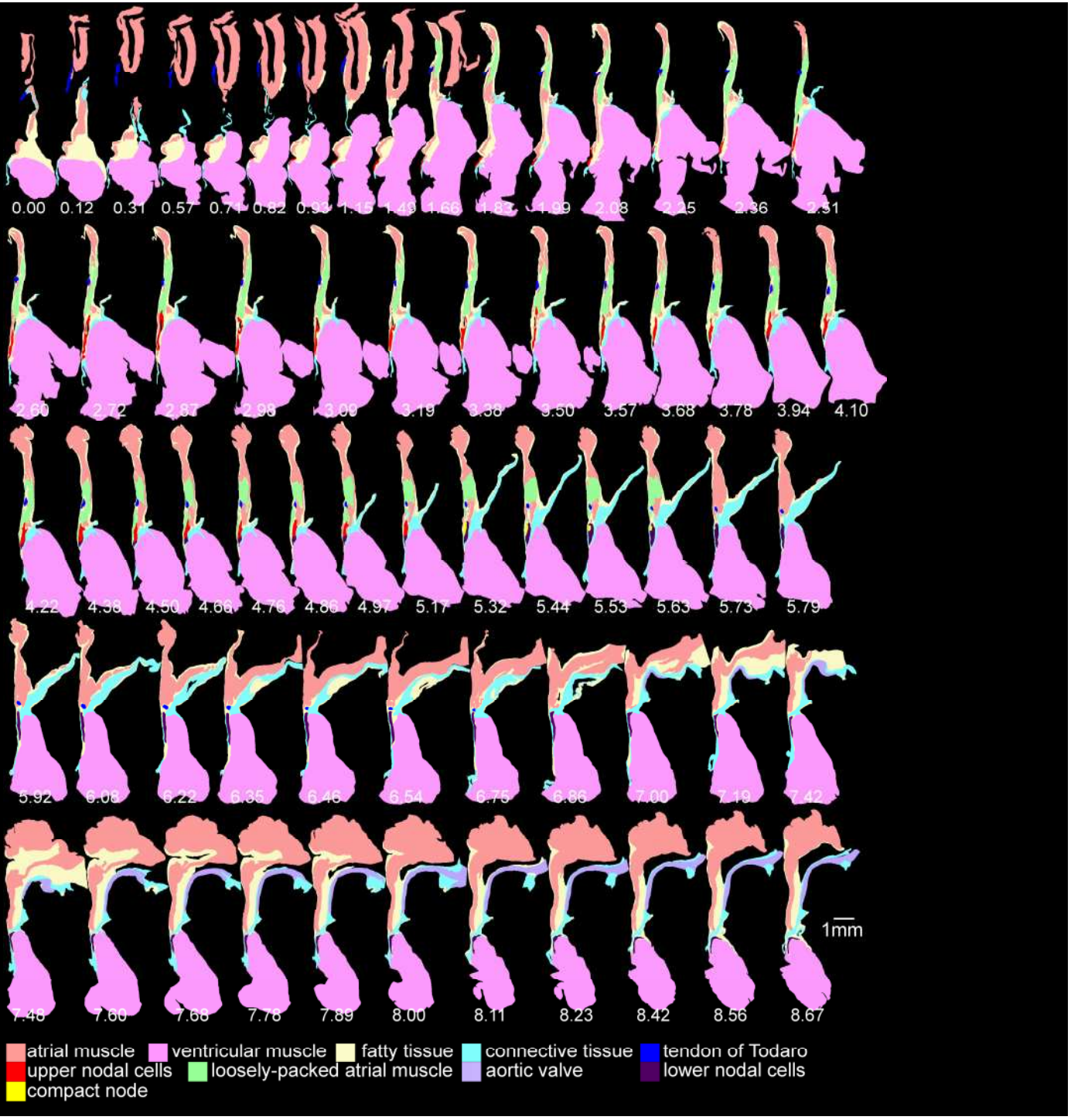


Model of atrioventricular node of rabbit

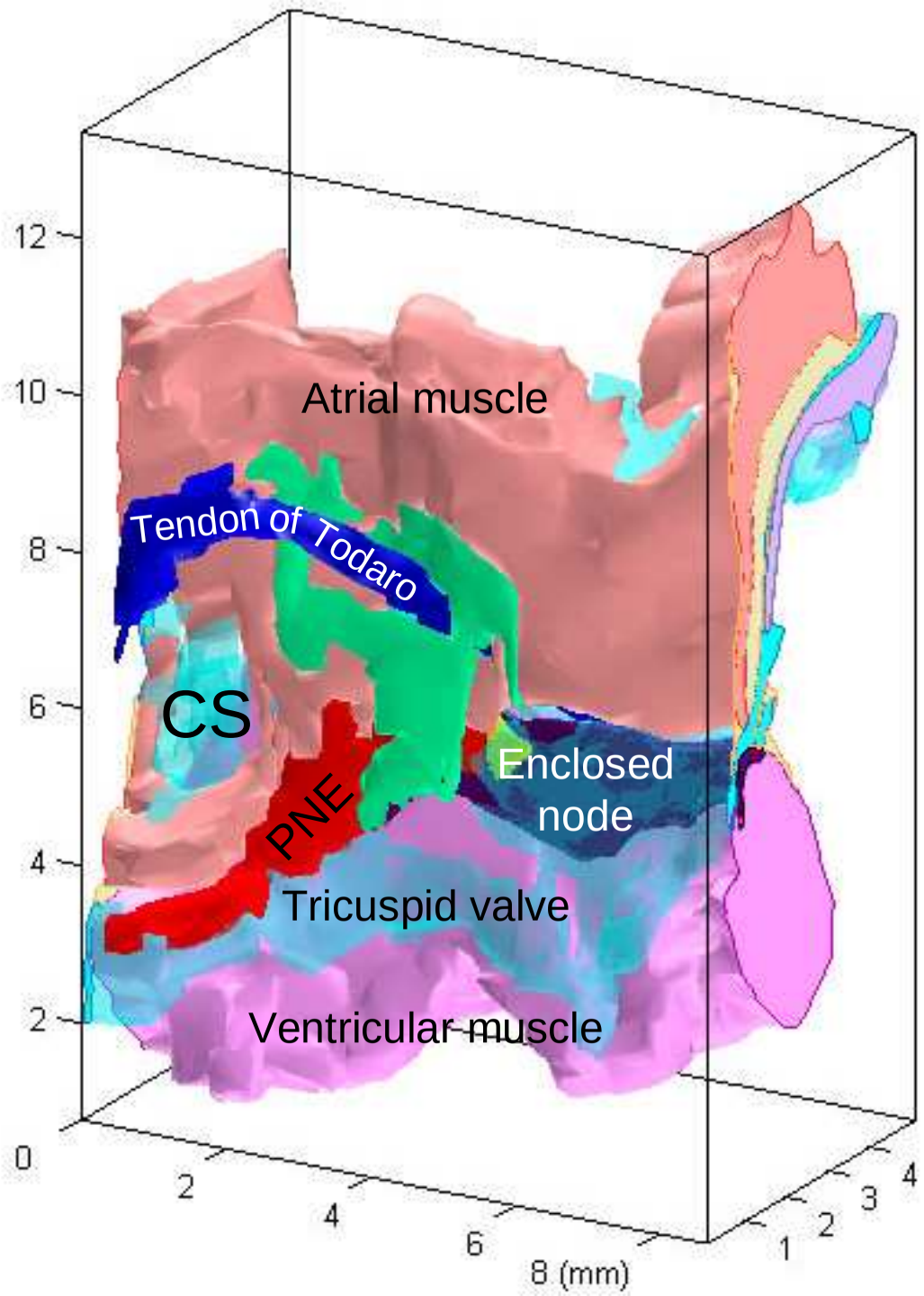
Jue Li, Halina Dobrzynski, Ian Greener, Vladimir Nikoloski and Igor Efimov



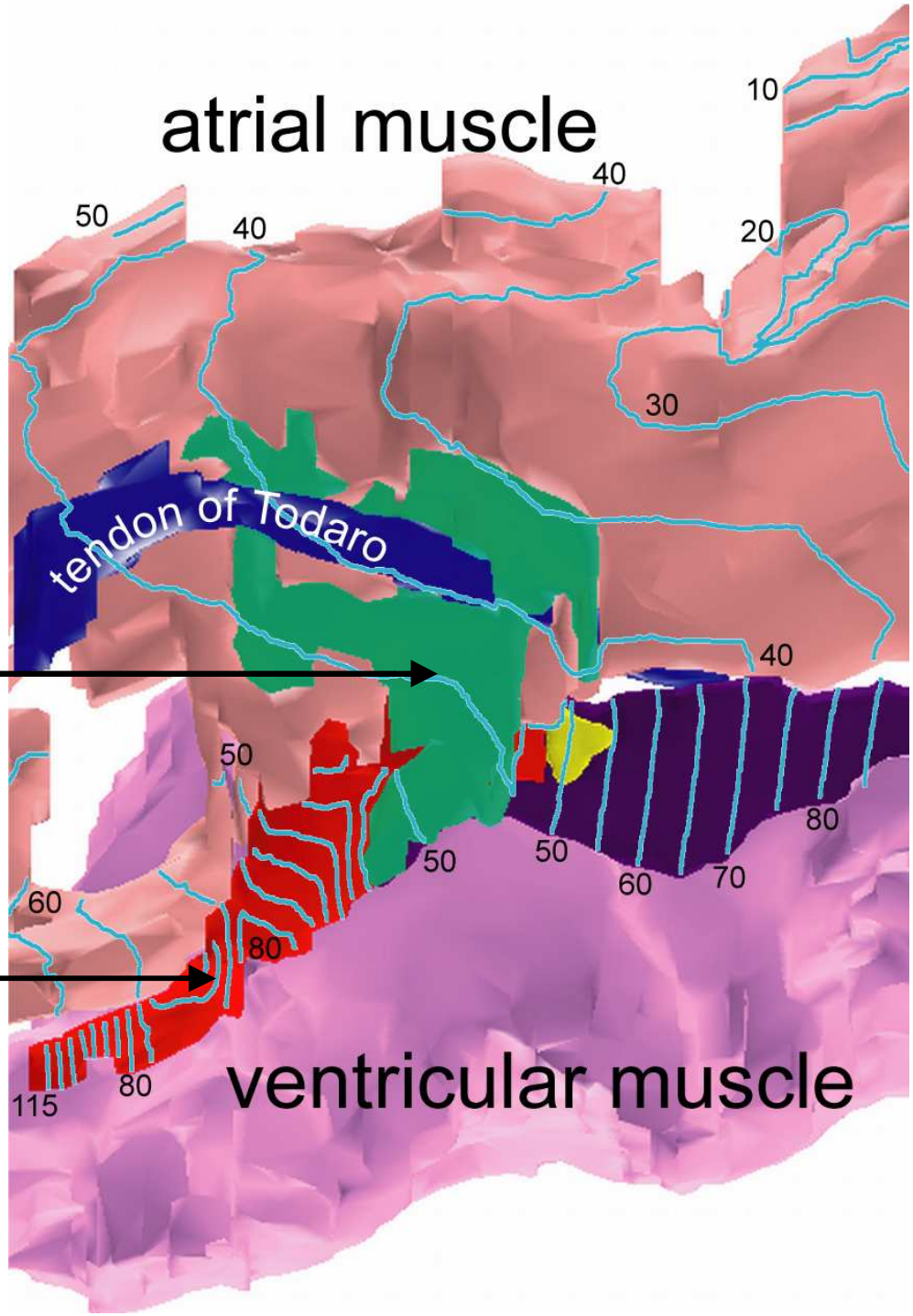
AV node



AV node

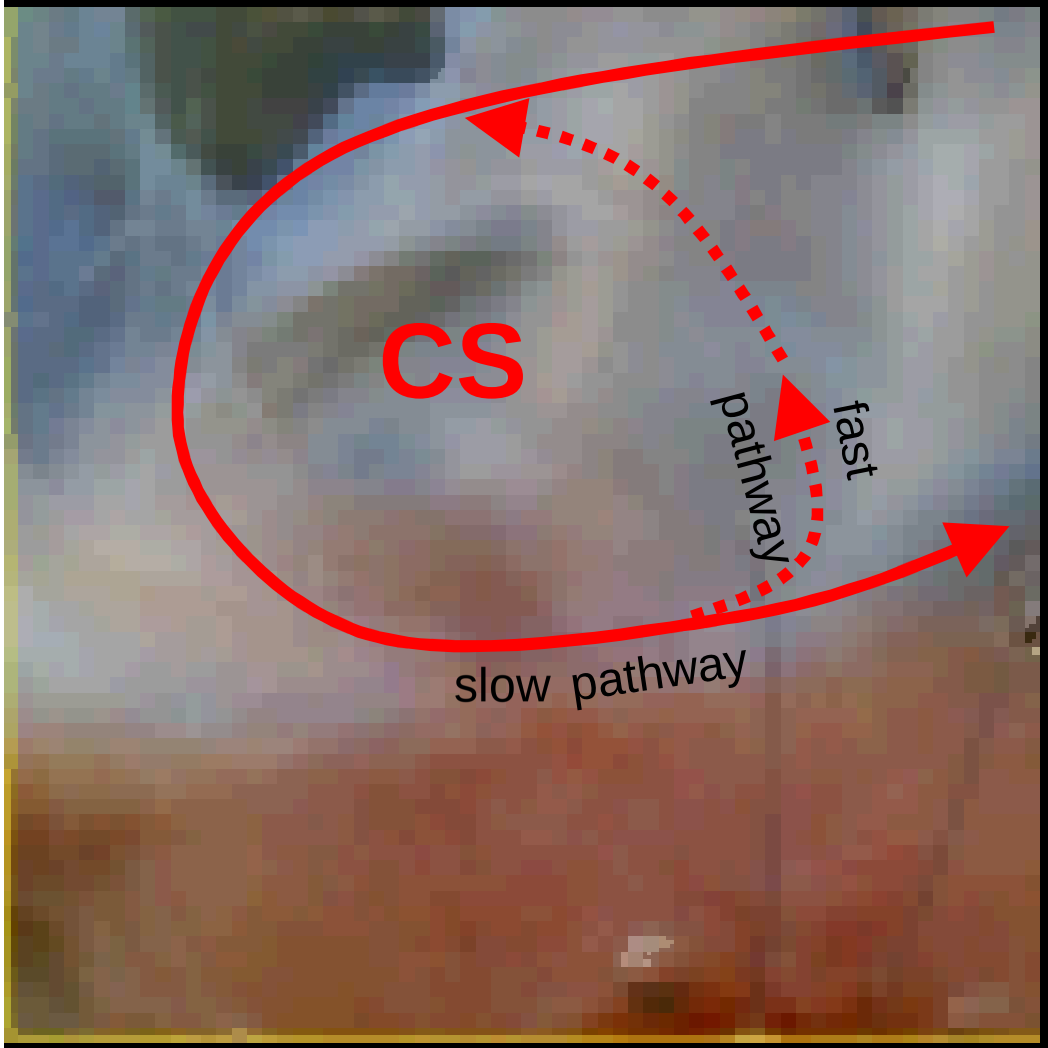


AV node activation sequence (cellular automaton model)

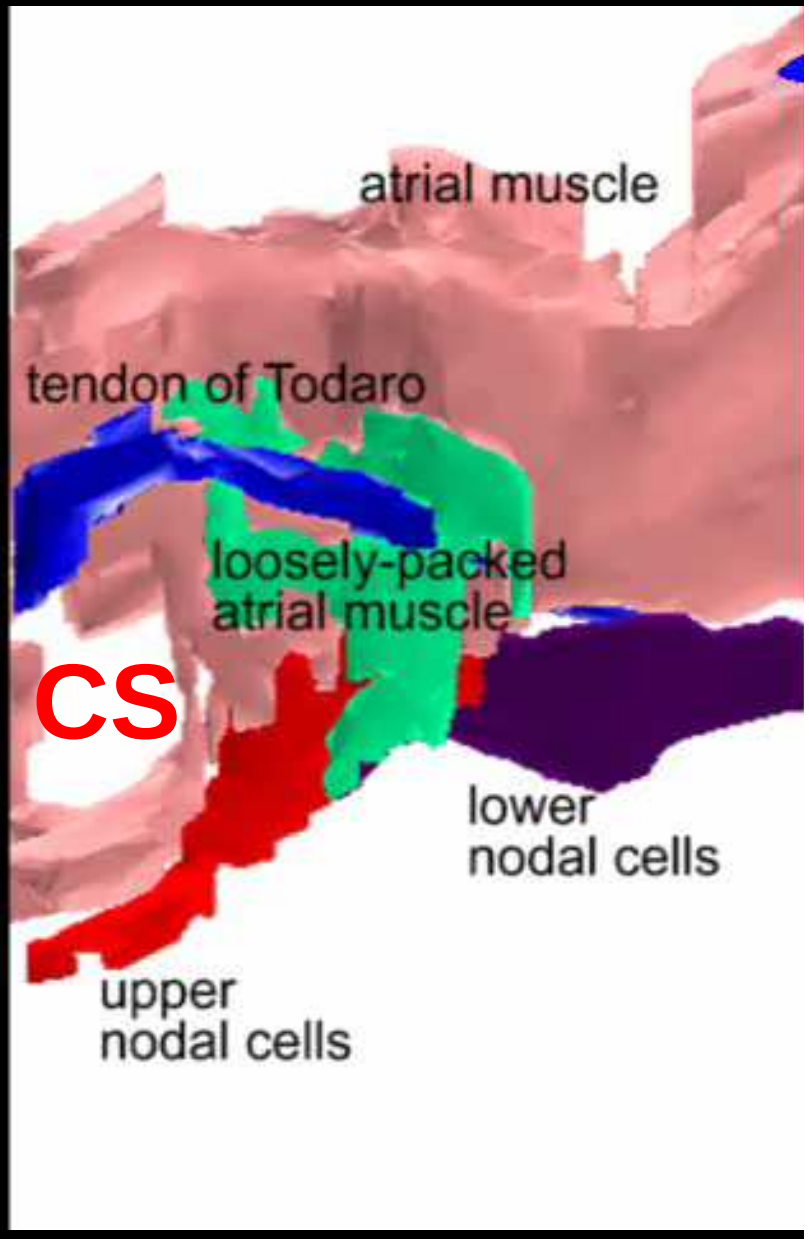


AV nodal reentry

Experiment

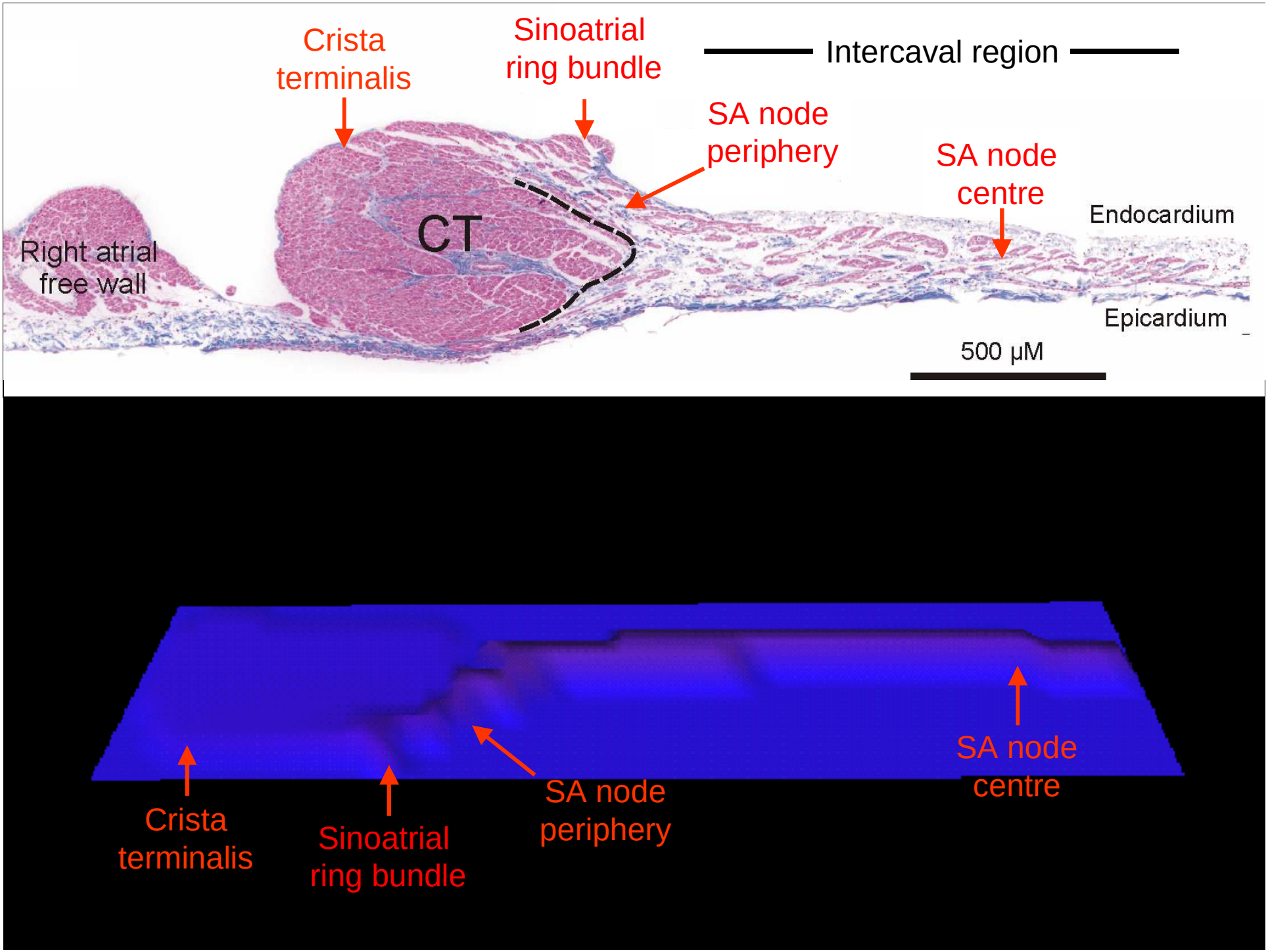


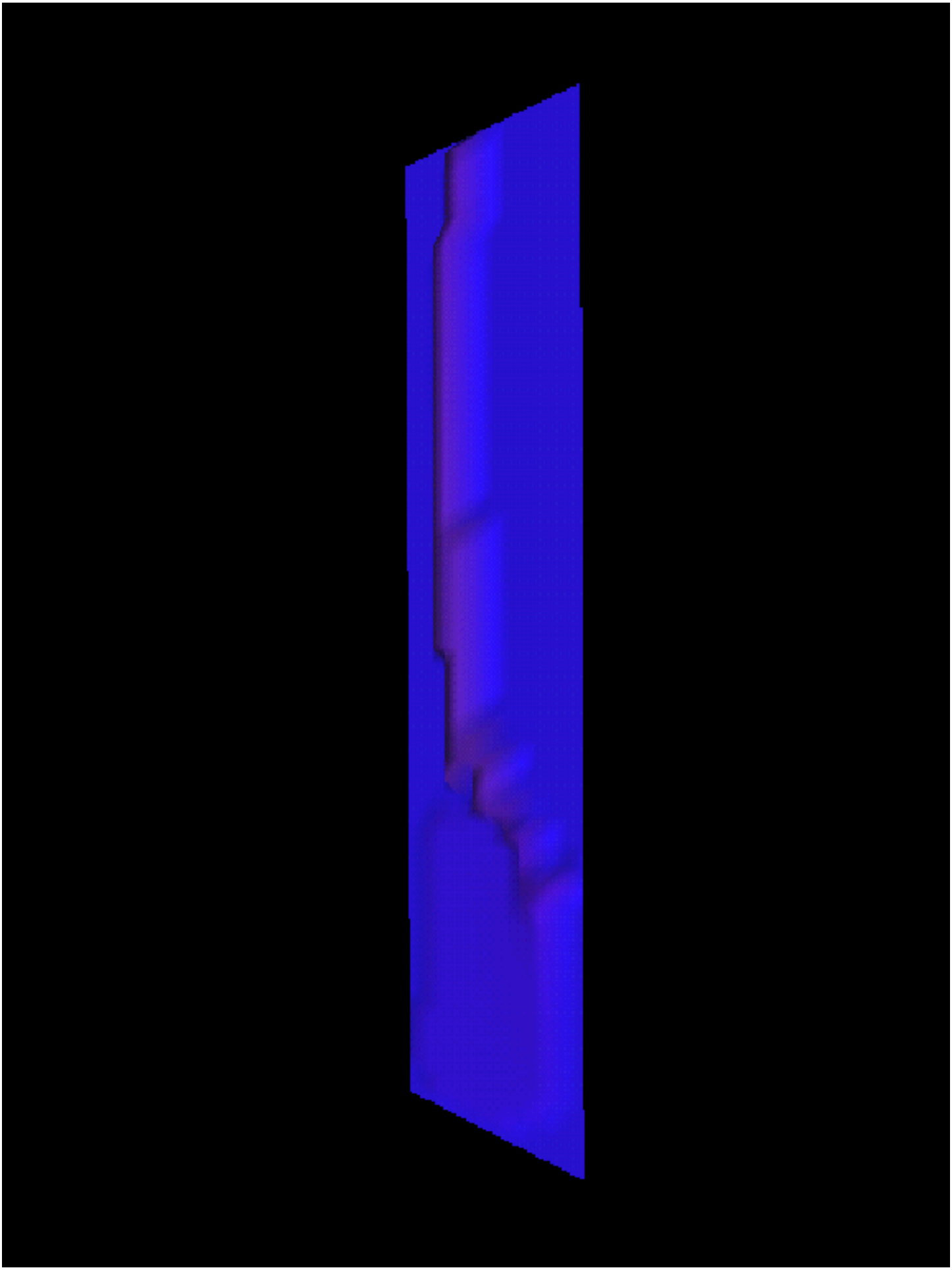
Model (cellular automaton model)



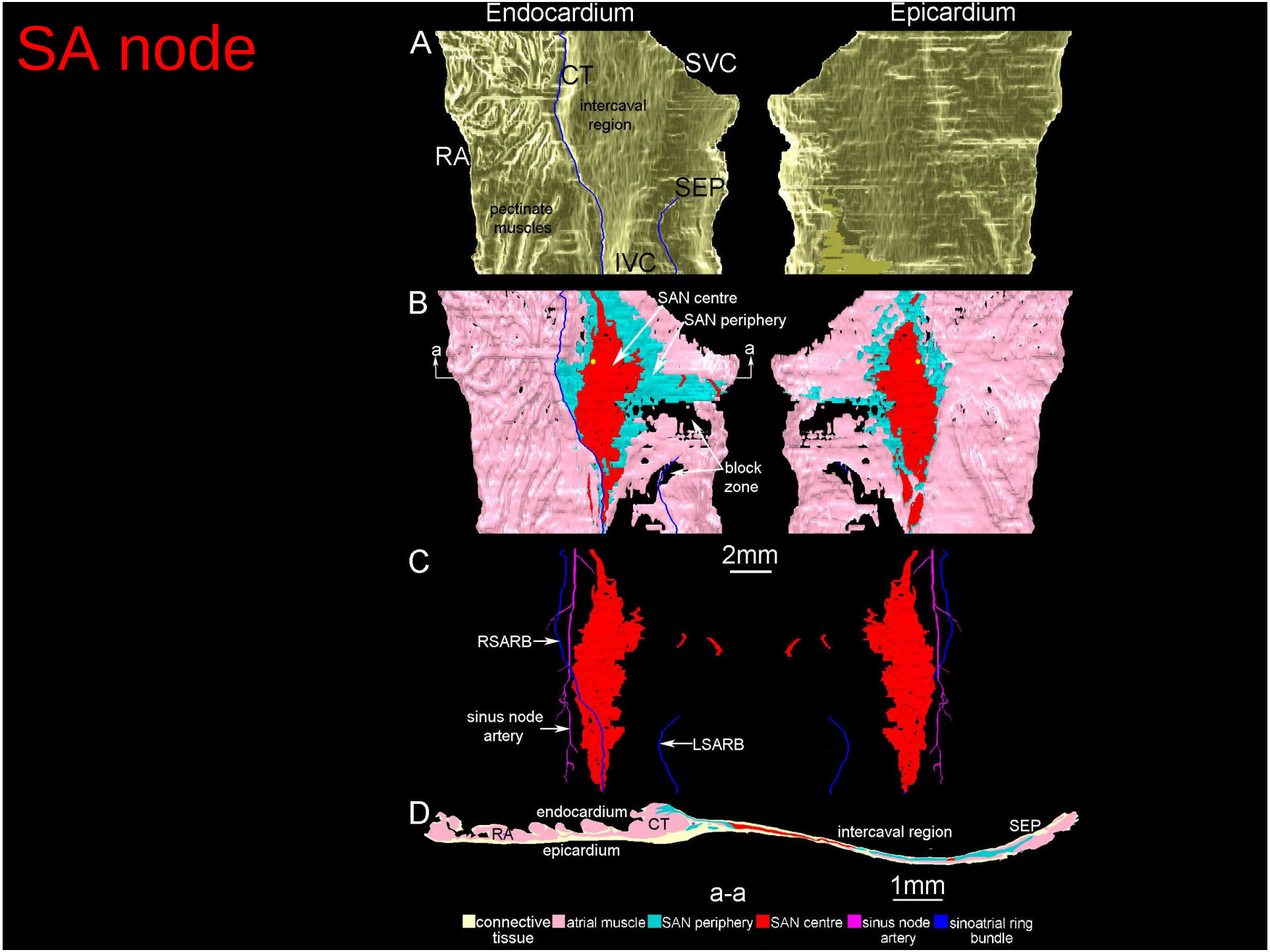
Model of sinoatrial node of rabbit

Halina Dobrzynski, Jue Li and Henggui Zhang





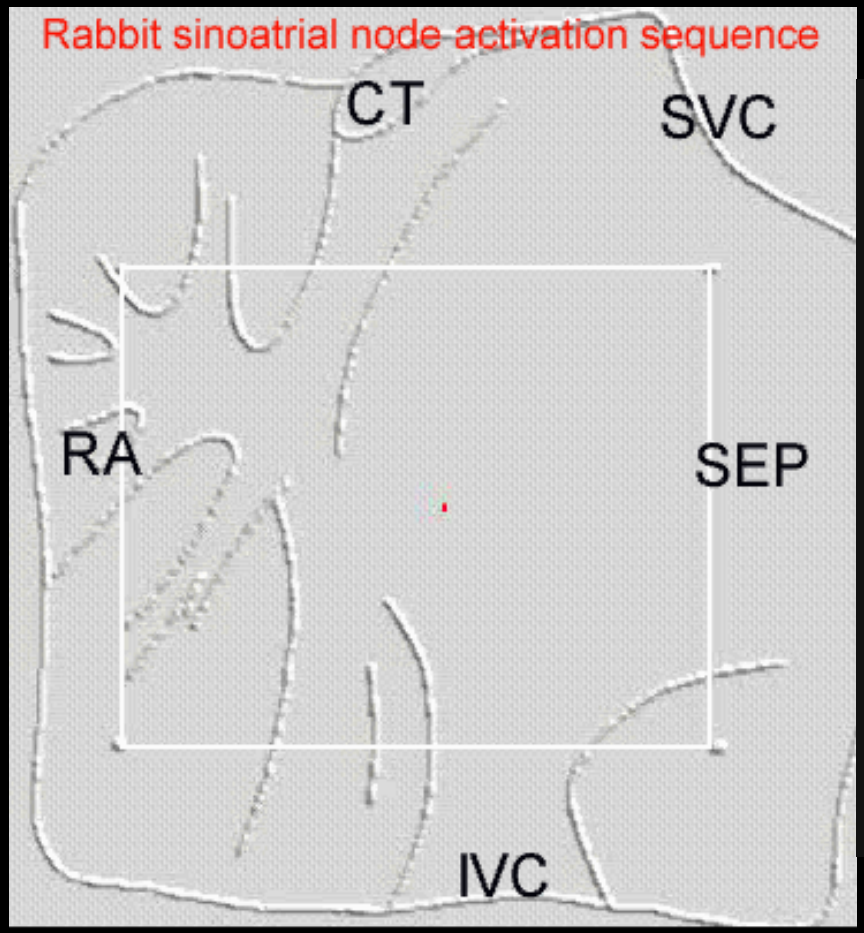
SA node

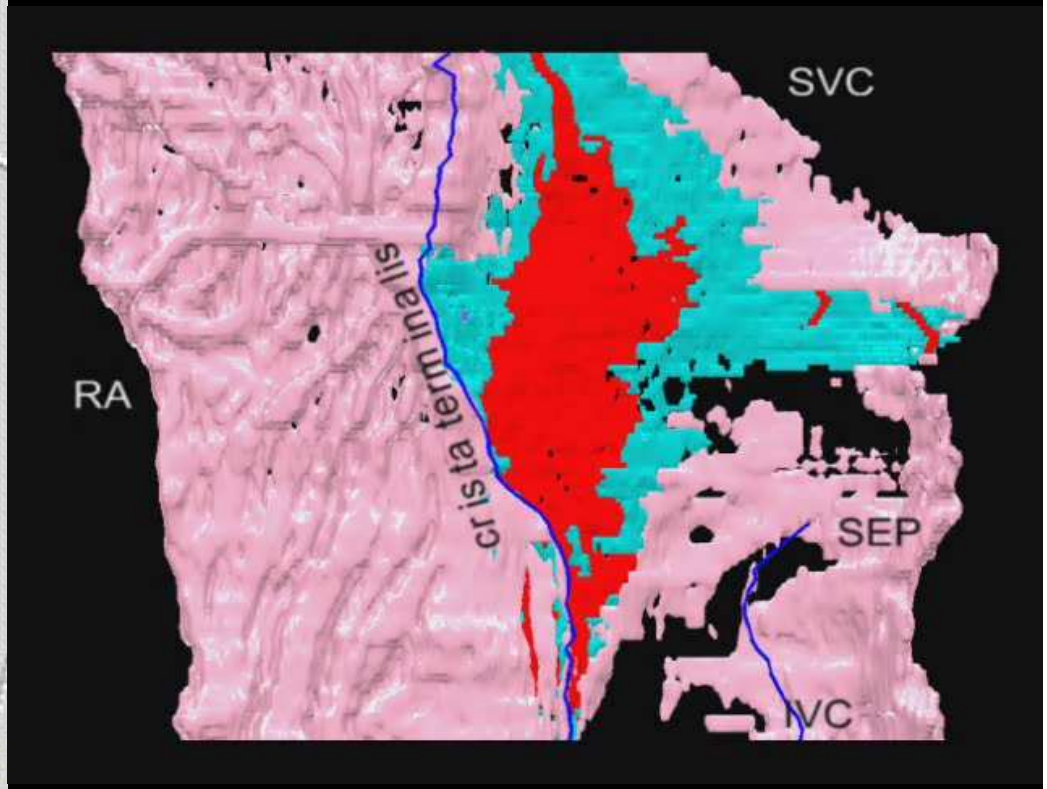


SA node activation sequence

Experiment

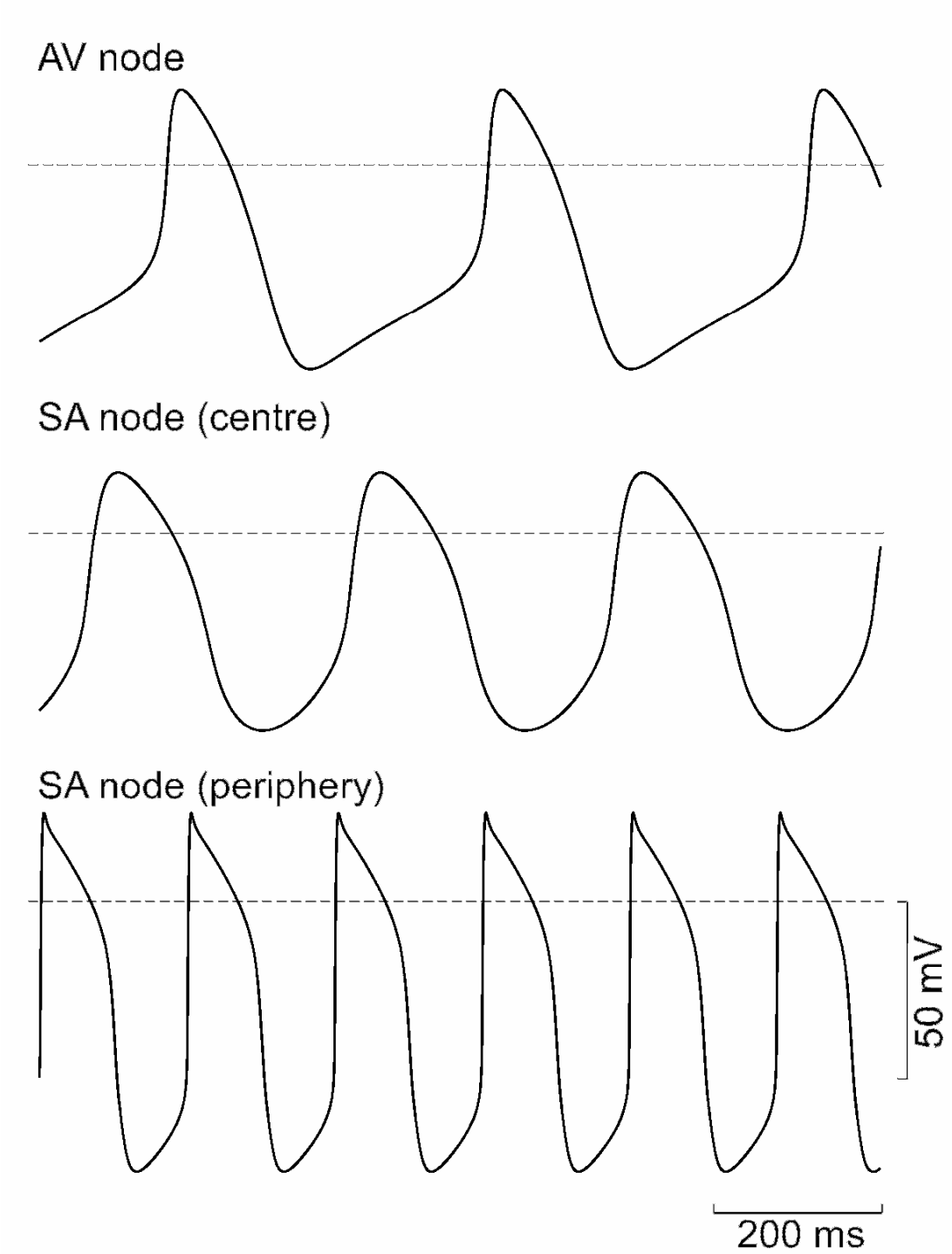
Model (cellular automaton model)

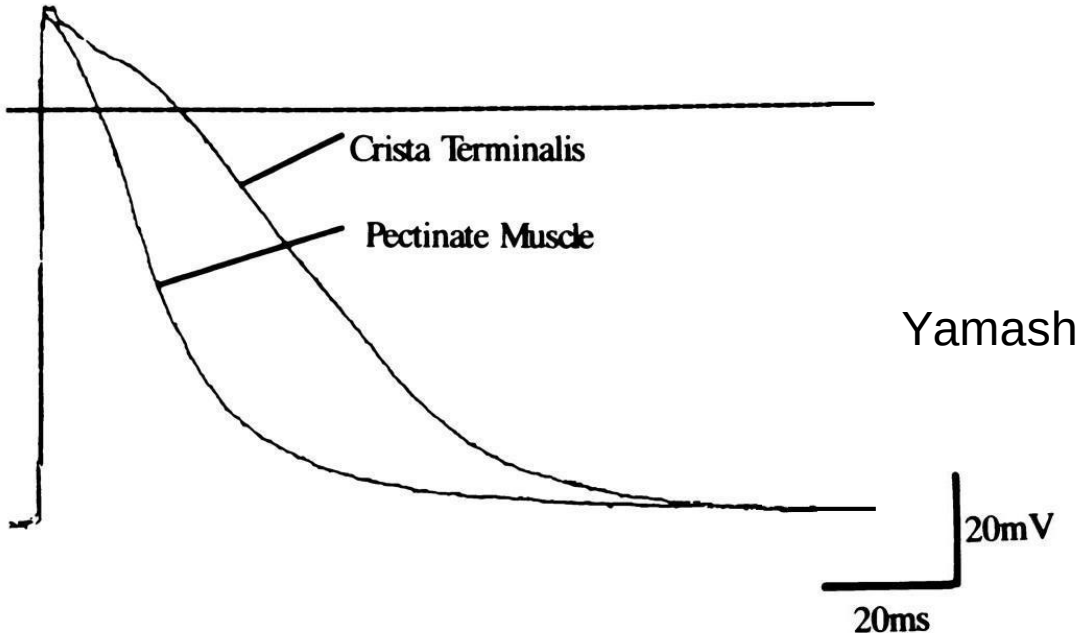




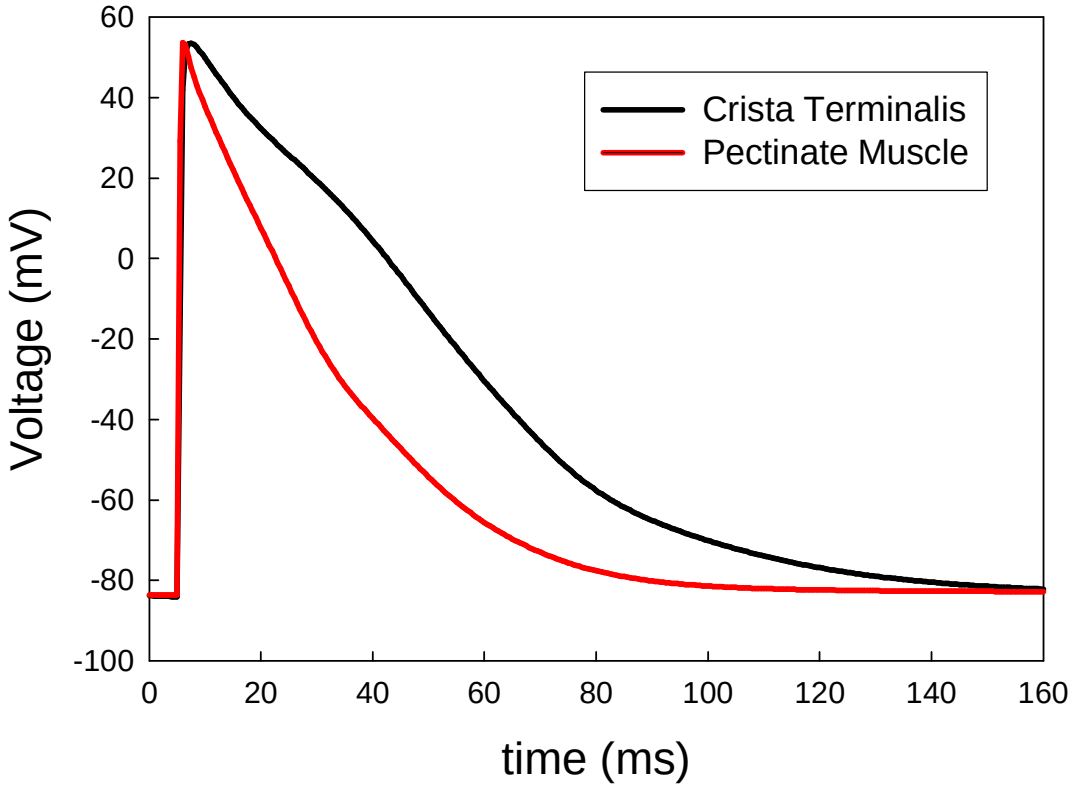
Models of action potentials of rabbit

Shin Inada, Jules Hancox and Henggui Zhang





Yamashita et al., 1995

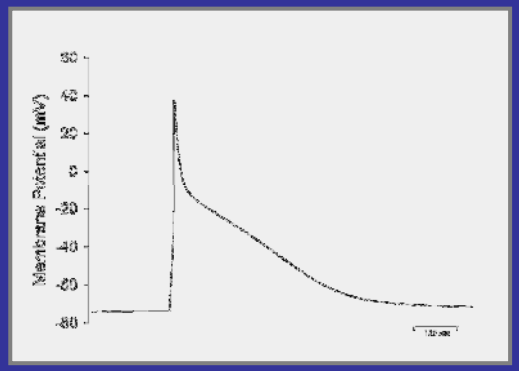


Reconstruction of Clinical Electrophysiology of Human Atrium

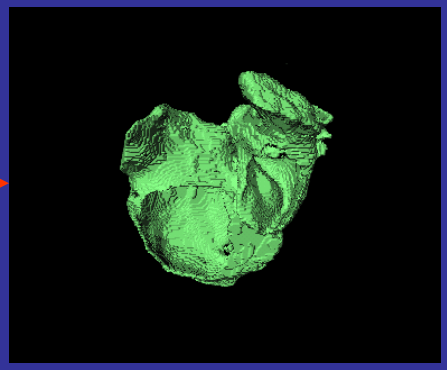
Development of Hierarchical Models of Human Atrium

•Chronic human atrial fibrillation (AF) and AF remodelling
(BHF: 2004 – 2007; Collaborator: Prof. CJ Garratt, Manchester Royal Infirmary)

•Effects of beta-blocker on human atrial excitation
(Collaborators: Dr. A Workman and A Rankin, Glasgow Royal Infirmary)



Cellular Electrical model



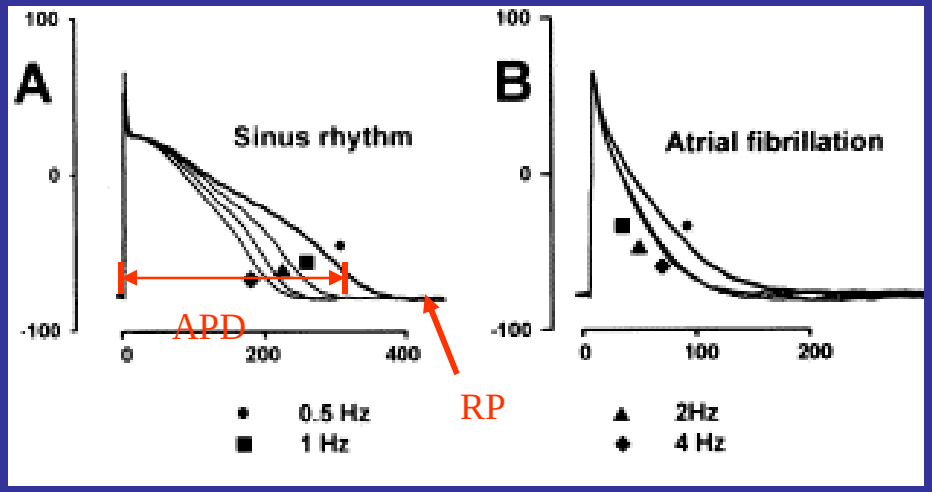
Anatomic Geometrical Model

- Anatomic model of atrium
- Ionic mechanisms underlying
  - initiation
  - termination

  of atrial arrhythmias
- Complexity association between distortion of chambers and arrhythmias
- Actions of anti-arrhythmia drugs

Simulation of AF-induced Ion Channel Remodelling

Chronic AF-induced changes in the electrical activity of human atrial myocyte



	RP (mV)	APD_{90} (ms) (0.2 Hz)
SR	-76.3±2.2	319 ±48
AF	-78.9 ±2.9	134 ±12
Change	-2.6 ↓	-58% ↓

SR: sinus rhythm
AF: atrial fibrillation
RP: resting potential

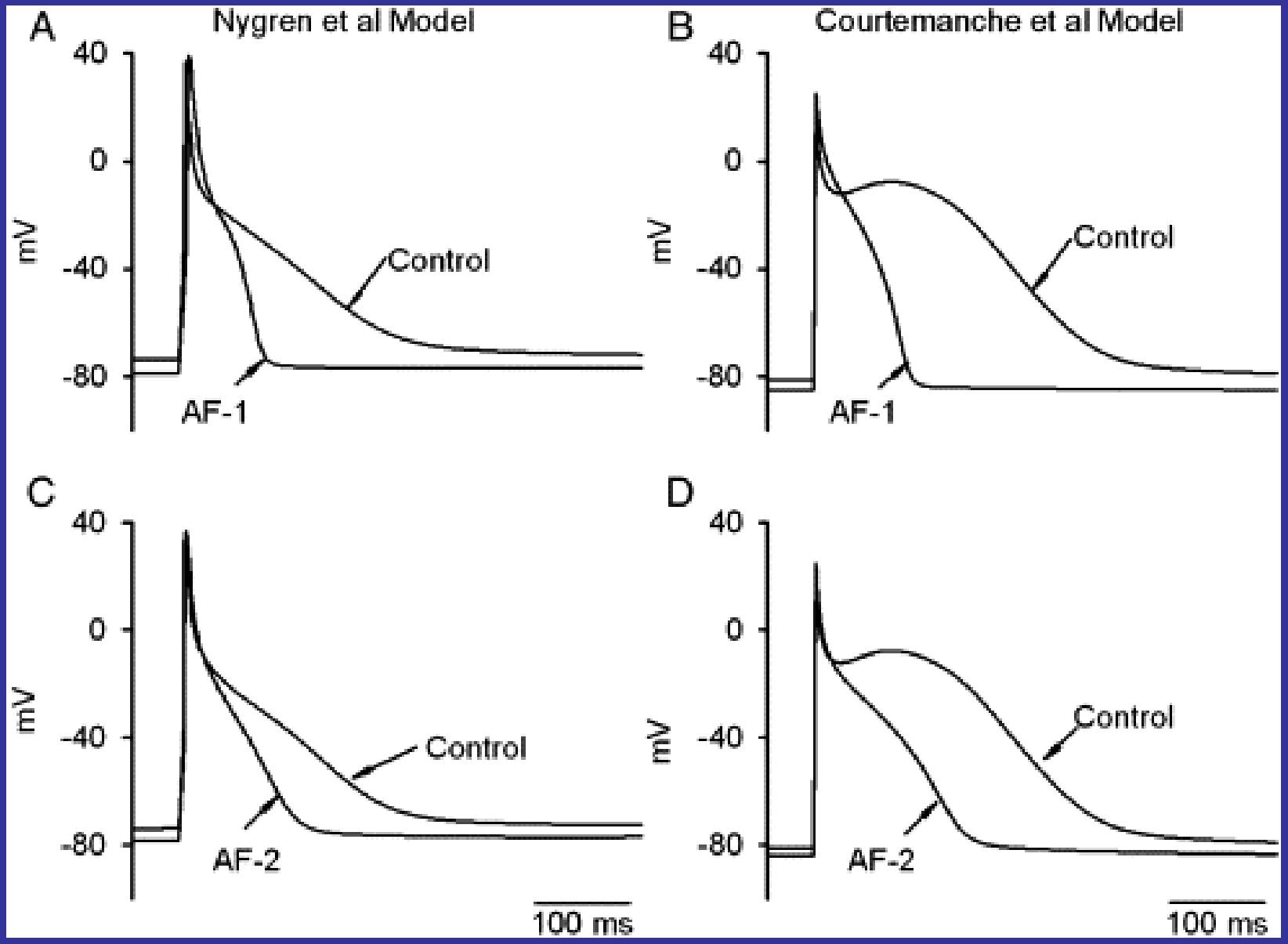
Bosch et al. (1999)
Cardiovasc Res 44: 121-131

Chronic AF-induced remodelling of ionic channels

	Regulation	Current density	Channel kinetics
$i_{Ca,L}$	Down ↓	↓ 74%	$\tau_{inact,fast}$ ↑ 62%
i_{to}	Down ↓	↓ 85%	Activation curve shifted by 16 mV
$i_{K,sus}$	--	--	--
i_{Na}	--	--	Inactivation curve shifted by 10 mV
$i_{K,1}$	UP ↑	250% (-90 mV) ↑ ~~235%~~ (-20 mV)	--

Bosch et al. (1999) Cardiovasc Res 44: 121-131

RESULTS Simulation of AF-remodelling

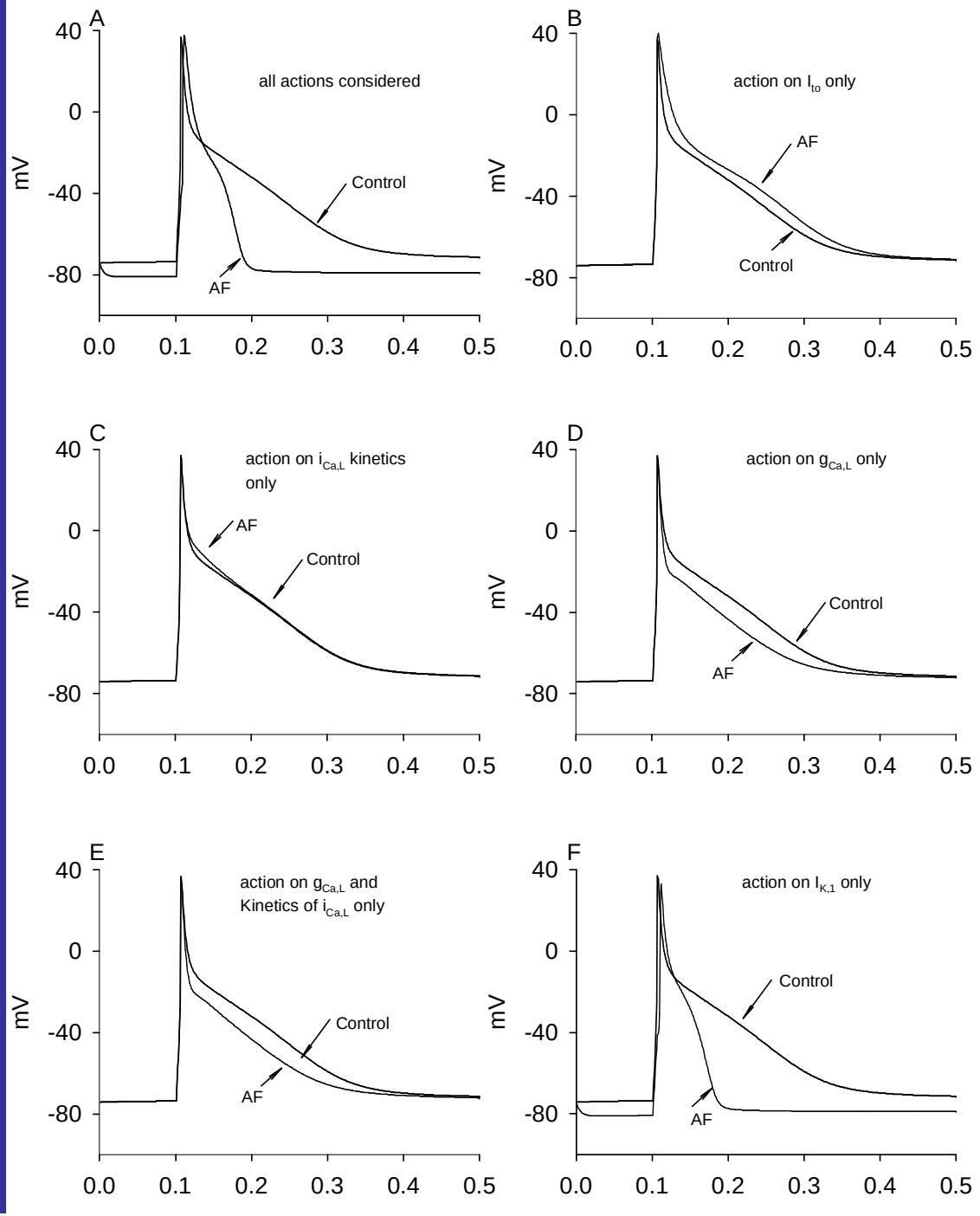


Role of each individual AF remodelled ionic channels

Exclusive method:

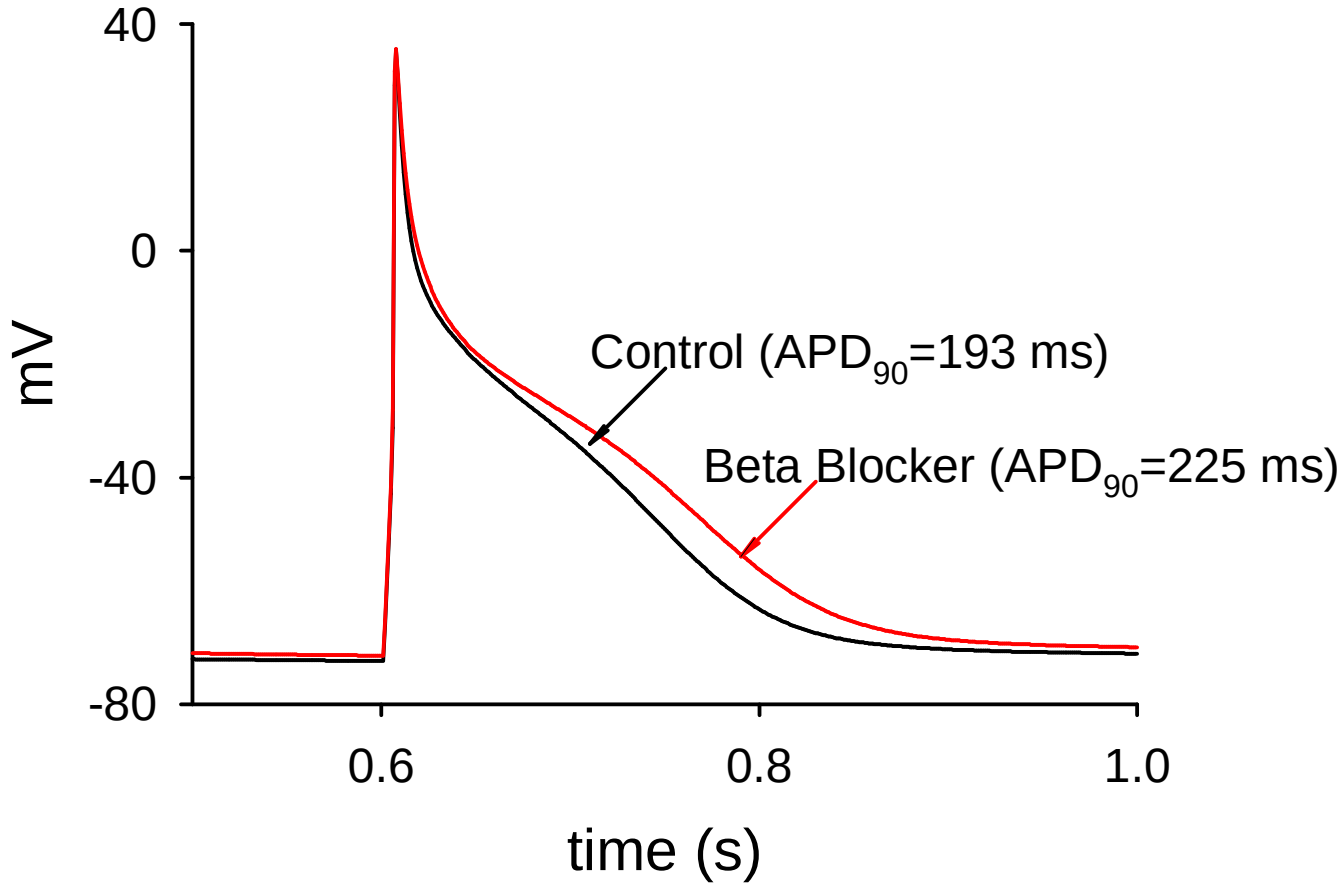
all other actions are removed while only the interested action is considered.

Zhang et al.
Cardiovascular Research (2005)



Effects of BB Induced Ionic Channel Remodelling on Human Atrial AP & Conduction

Effects of BB on normal human atrial APs



Control

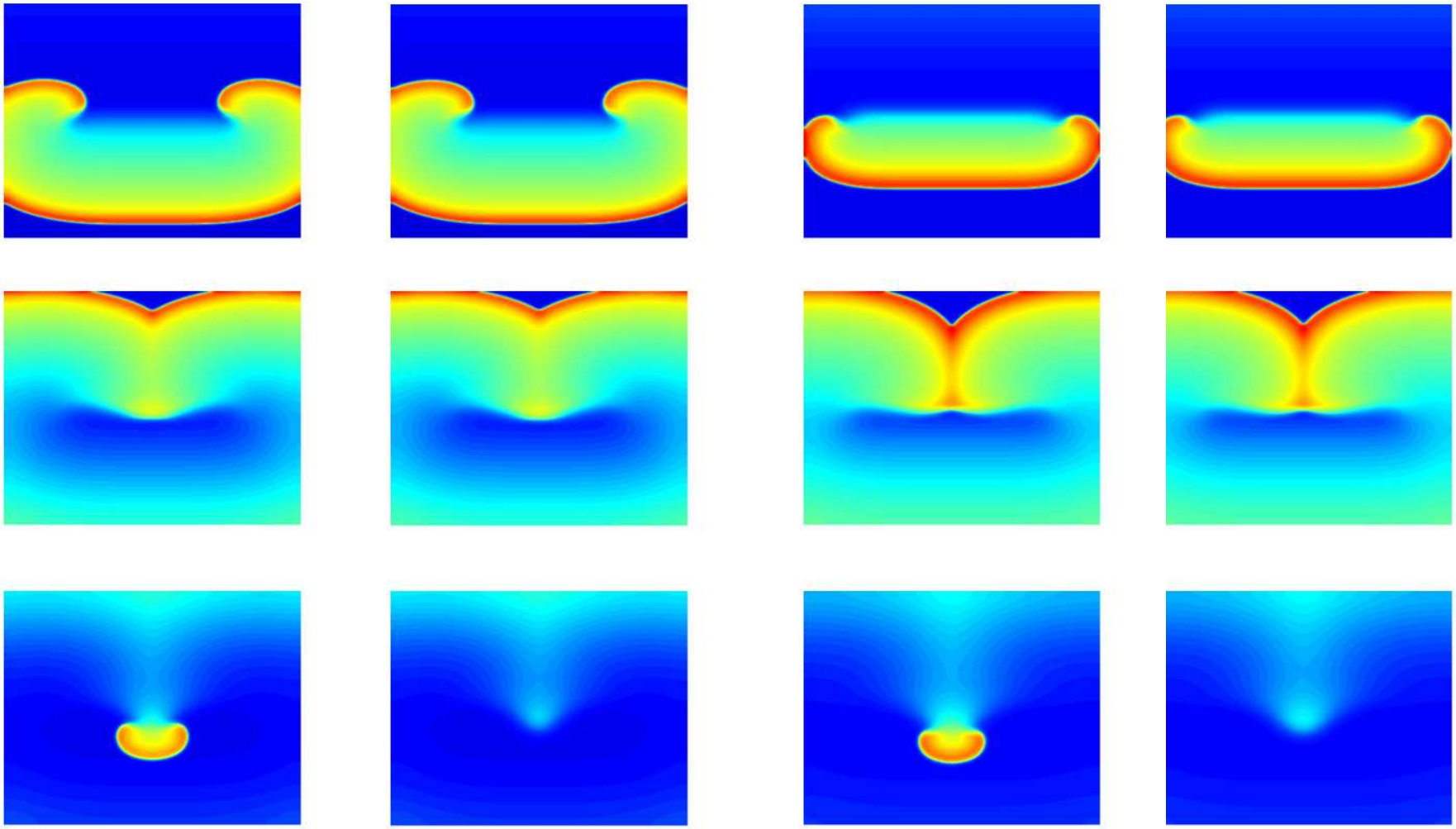
Beta Blocker

L = 55.04 mm

l = 54.62 mm

L = 67.2 mm

l =66.88 mm



Reconstruction of Electrophysiology of Ventricle

Current projects on ventricle modelling

- Short QT syndrome and gene mutation of potassium channels
(Collaborator: Prof. JC Hancox, Bristol) (Zhang & Hancox Biochem, Biophy Res Commun 2005)

- Acute ischemia
(Collaborators: Prof. JC Hancox, Bristol)

- Exercise remodelling
(Dr. E White, Leeds)

- Effects of volatile anesthetics
(Dr. S Harrison, Leeds)

Sub-cellular modelling
Intracellular cardiac Ca^{2+} handling

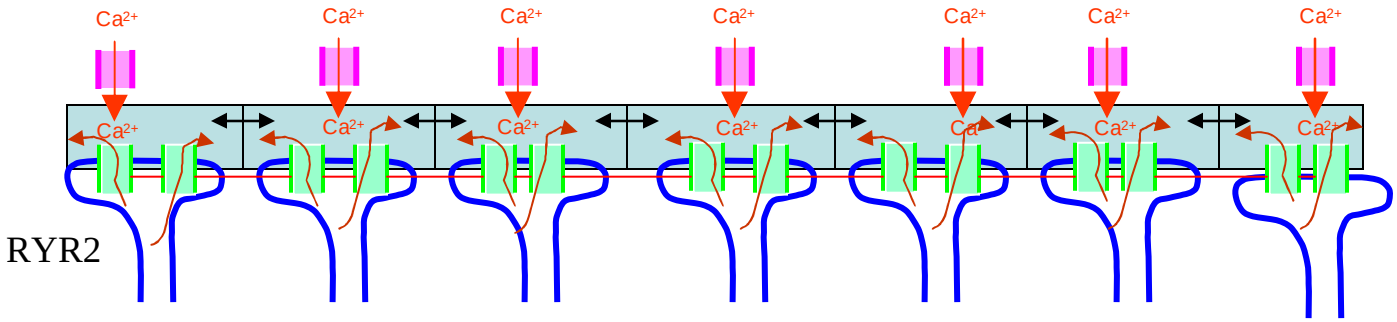
Modelling team

Dr. H Zhang
(Manchester)

Experimental team

Prof. D. Eisner & Dr. S. O'Neil
(Manchester)

Model of cluster of RyRs



$$\frac{d[Ca^{2+}]_{sub}}{dt}(x) = J_{Ca,\,L} + J_{Ca,\,T} + J_{rel} - J_{NaCa} - J_{Ca,\,diff} - J_{Ca,\,spacial\_diff} - J_{buffer,\,sub}$$

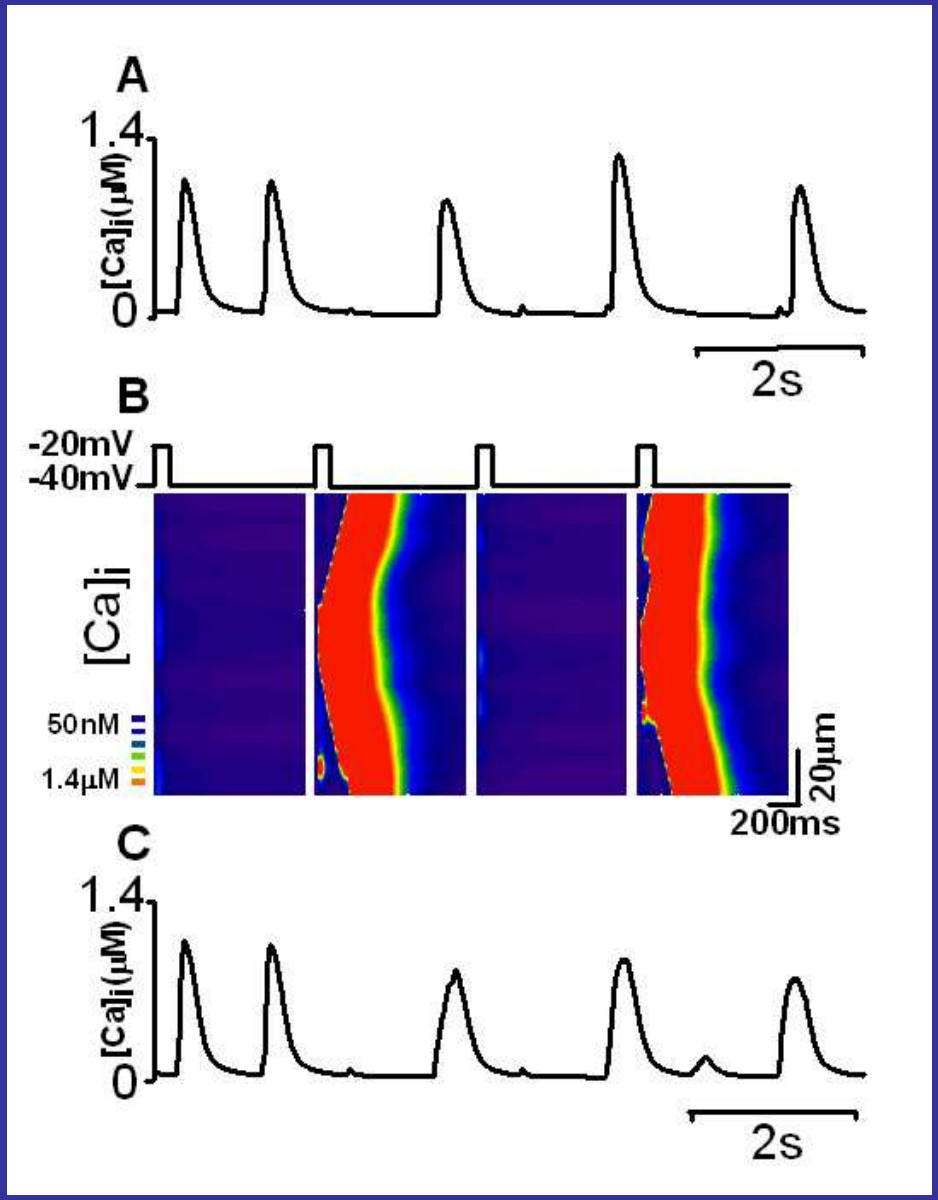
$$\frac{d[Ca^{2+}]_{i}}{dt}(x) = J_{Ca,\,diff} + J_{Ca,\,spacial\_diff} - J_{up} - J_{Ca,\,P} - J_{buffer,\,i}$$

$$\frac{d[Ca^{2+}]_{rel}}{dt}(x) = J_{tr} - J_{rel} - J_{buffer,\,rel}$$

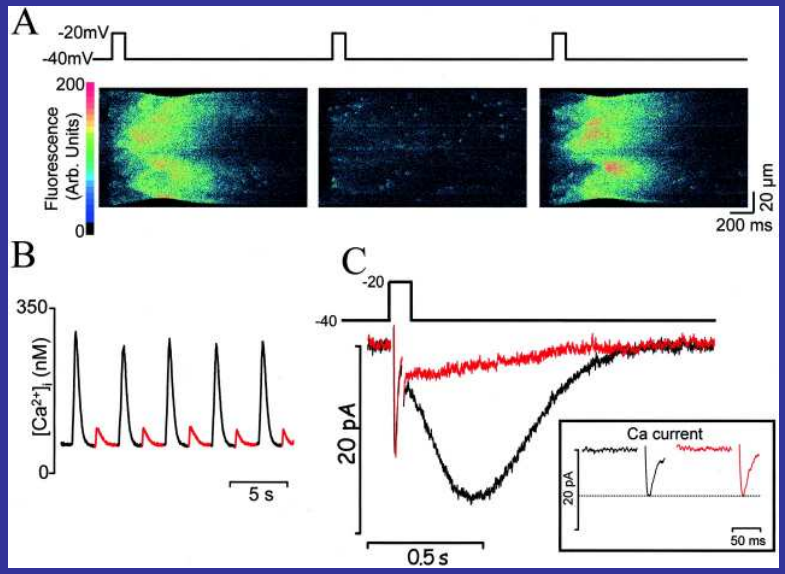
$$\frac{d[Ca^{2+}]_{up}}{dt}(x) = J_{up} - J_{tr} - J_{buffer,\,up}$$

(1)

Simulation of intracellular Ca spark and waves



Simulation



Diaz, M. E. et al. Circ Res 2004;94:650-656

Experiment