

# CORAZÓN VIRTUAL: APLICACIÓN DE LOS MODELOS MATEMÁTICOS EN EL ESTUDIO Y TRATAMIENTO DE LAS ARRITMIAS

Discurso de entrada como Académico Correspondiente

**Francisco Javier Saiz Rodríguez**



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## Ingeniería Biomédica

Es un área científico-tecnológica en la que se aplican los **principios y métodos propios de la ingeniería** a la definición, análisis y resolución de problemas en biología y medicina, y a la mejora de los métodos de prevención, diagnóstico y tratamiento.

## Modelos matemáticos

Matemáticas

Ciencias de la Computación

## Ventajas

Ayudar a entender el comportamiento de un sistema

Someter al sistema a diferentes condiciones, incluso extremas

Sugerir nuevos experimentos o estudios clínicos

## Limitaciones

Es una aproximación de la realidad

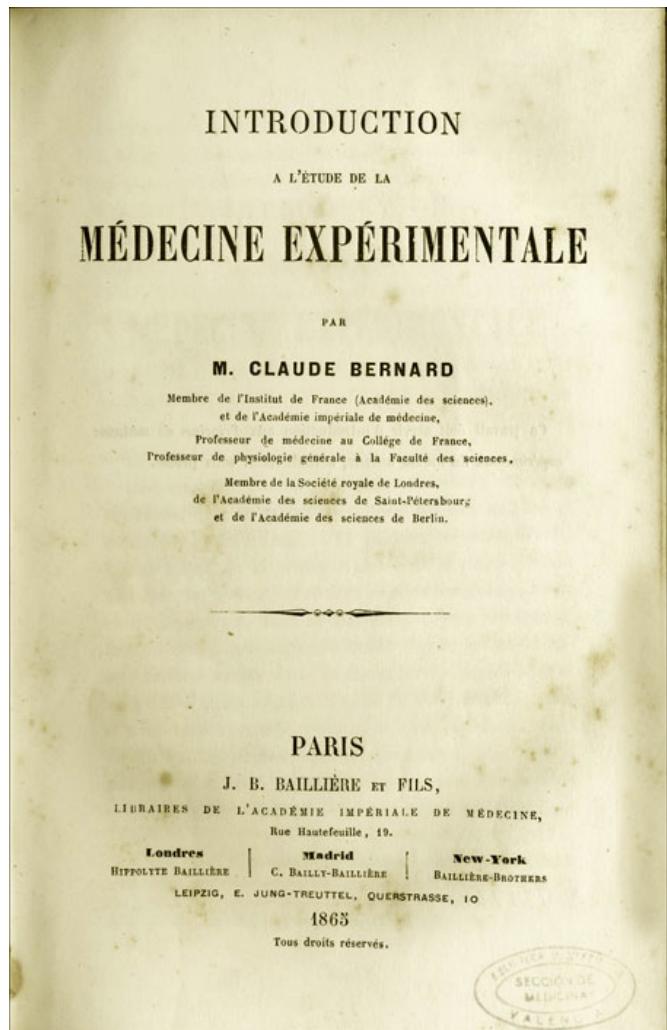
En ciertos casos, el coste computacional es importante

**No se debe olvidar que....**

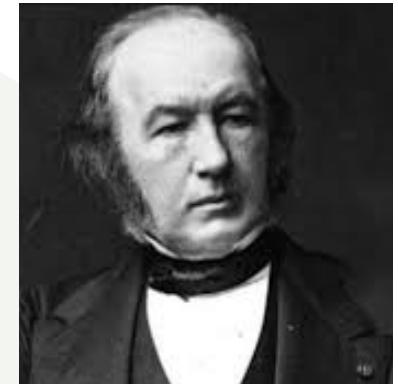
*Essentially, all models are wrong  
but some are usefull.*

Prof. George E.P. Box

# BREVE RESEÑA HISTORICA



Claude Bernard



“Cette application des mathématiques aux phénomènes naturels est le but de toute science, parce que l'expression de la loi des phénomènes doit toujours être mathématique”

“Or je pense que les tentatives de ce genre sont prématurées dans la plupart des phénomènes de la vie, précisément parce que ces phénomènes sont tellement complexes.....”



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# BREVE RESEÑA HISTORICA

J. Physiol. (1952) 117, 500-544

## A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

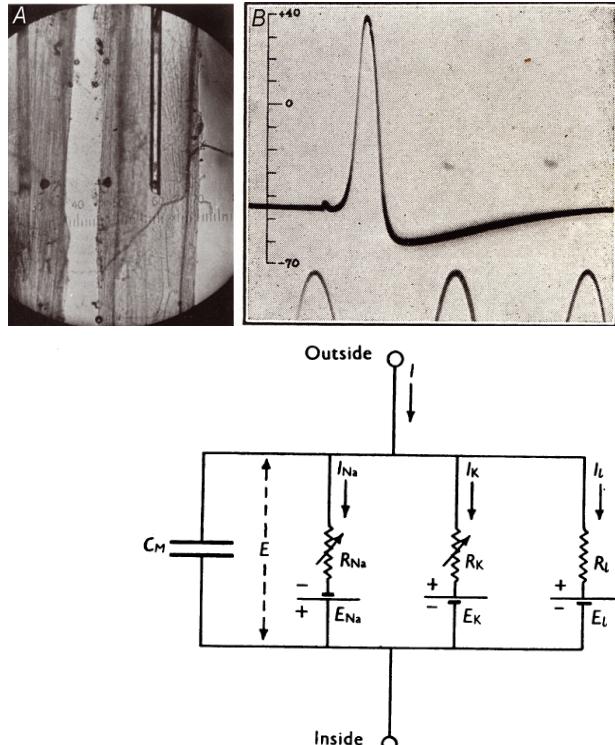
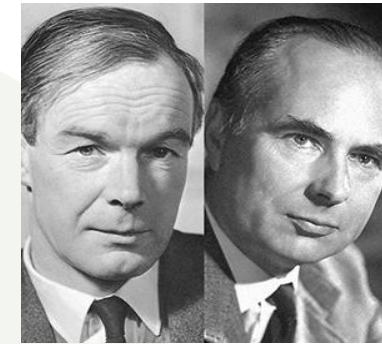


Fig. 1. Electrical circuit representing membrane.  $R_{Na} = 1/g_{Na}$ ;  $R_K = 1/g_K$ ;  $R_l = 1/g_l$ .  $R_{Na}$  and  $R_K$  vary with time and membrane potential; the other components are constant.

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n (1 - n) - \beta_n n,$$

$$dm/dt = \alpha_m (1 - m) - \beta_m m,$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h,$$

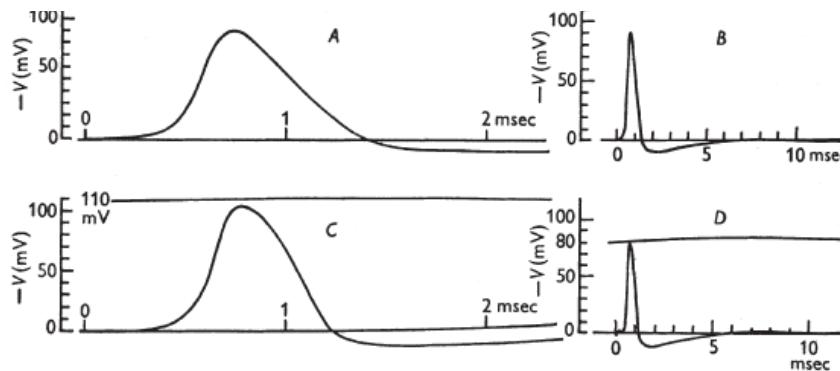
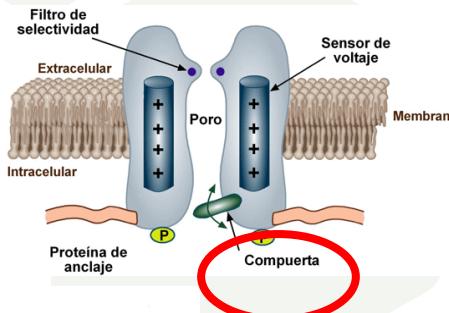


Fig. 15. A, solution of eqn. (31) calculated for  $K$  of  $10.47 \text{ msec}^{-1}$  and temperature of  $18.5^\circ \text{ C}$ . B, same solution plotted on slower time scale. C, tracing of propagated action potential on same vertical and horizontal scales as A. Temperature  $18.5^\circ \text{ C}$ . D, tracing of propagated action potential from another axon on approximately the same vertical and horizontal scales as B. Temperature  $19.2^\circ \text{ C}$ . This axon had been used for several hours; its spike was initially  $100 \text{ mV}$ . Reprinted from Hodgkin & Huxley (1952).

# BREVE RESEÑA HISTORICA

NO 4749

November 5, 1960

N A T U R E

## Cardiac Action and Pacemaker Potentials based on the Hodgkin-Huxley Equations



Células musculares cardiacas

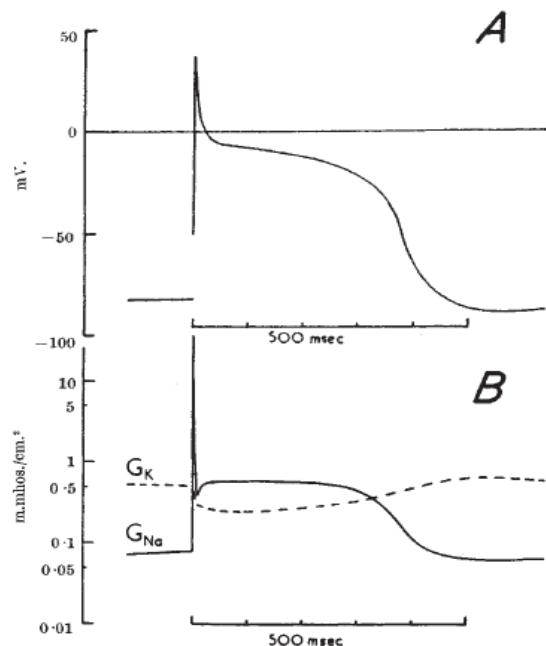


Fig. 1. A, Computed action potential. The integration was started by displacing the membrane potential to  $-50$  mV, which is equivalent to a very short cathodal pulse of  $3.6 \times 10^{-7}$  coulombs/cm.<sup>2</sup>. B, Time course of computed conductance changes on a logarithmic scale.  $G_K$ , potassium conductance;  $G_Na$ , sodium conductance. The potassium and sodium equilibrium potentials were set at  $-100$  mV. and  $+40$  mV, respectively.

Células marcapasos

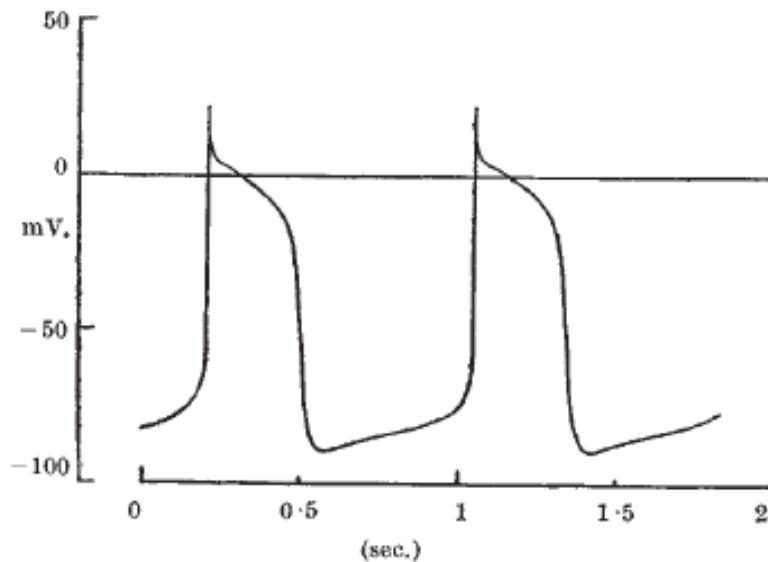


Fig. 2. Solution to equations in which the membrane potential is unstable in diastole so that pacemaker activity occurs. In this case, the potential at which the steady state sodium and potassium currents are equal and opposite is  $-38$  mV, and an unstable state at this potential corresponds to a second solution to the equations



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# BREVE RESEÑA HISTORICA

## A computer model of atrial fibrillation

Gordon K. Moe, M.D.\*

Werner C. Rheinboldt, Ph.D.\*\*

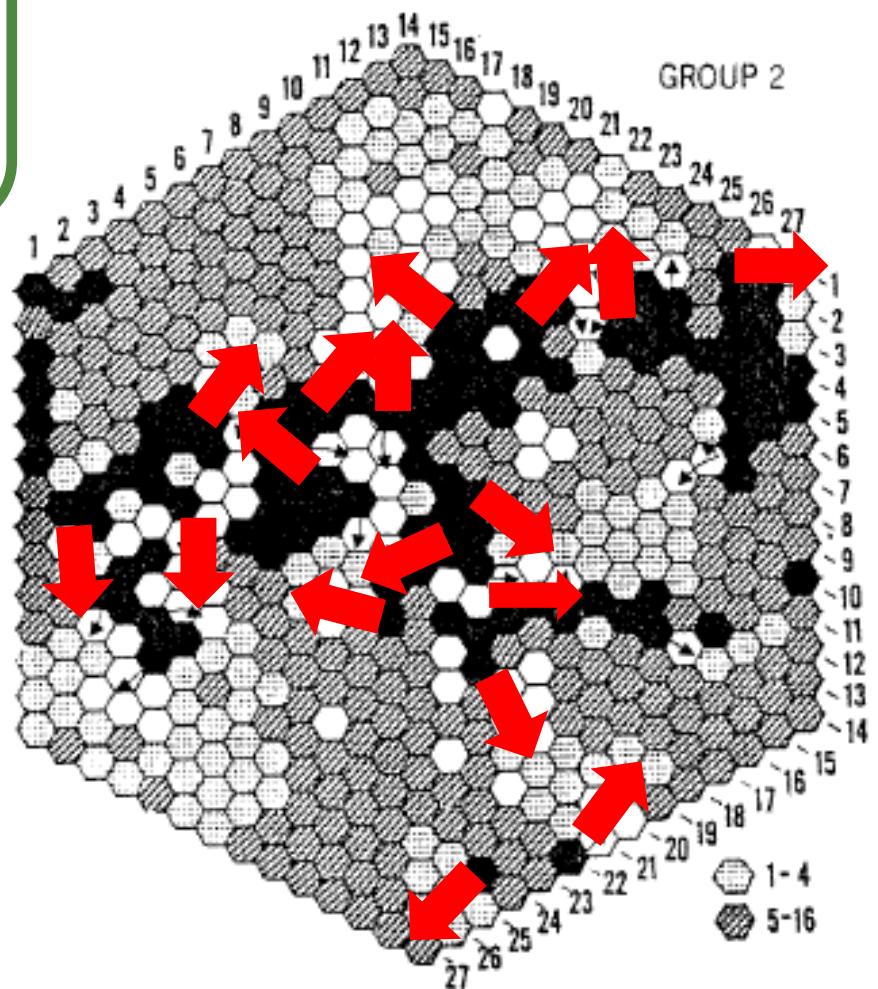
J. A. Abildskov, M.D.\*\*\*

Utica, N. Y.



### Methods

*A. The mathematical model.* The model was designed on the basis of a number of simplifying assumptions: (1) The piece of atrial tissue under consideration consists of a finite number of discrete "units." No fine structure is considered within a unit.



G K. Moe y col, 1964



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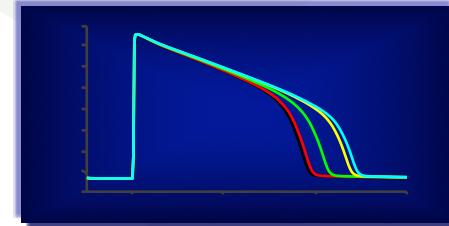
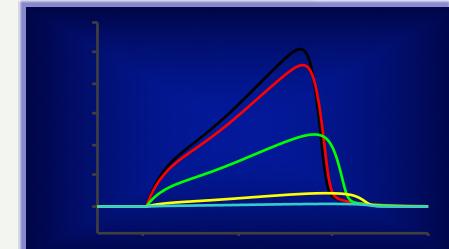
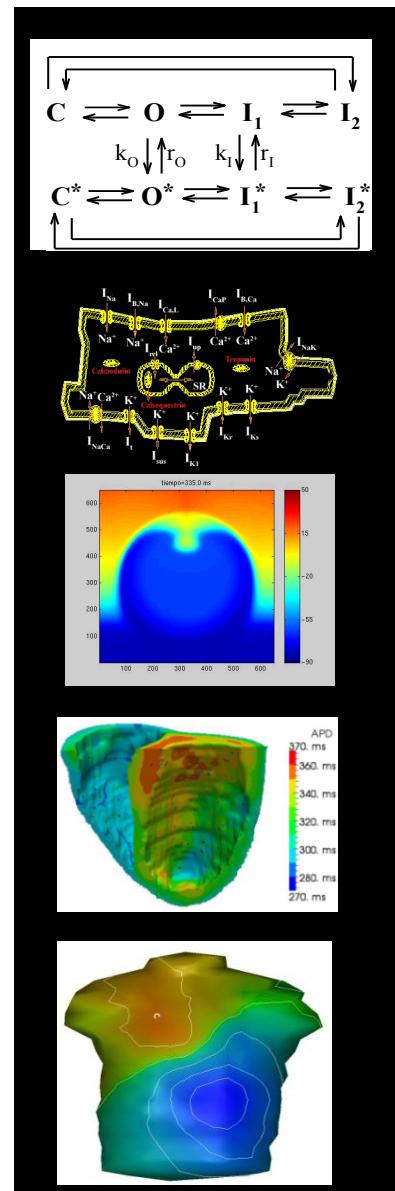
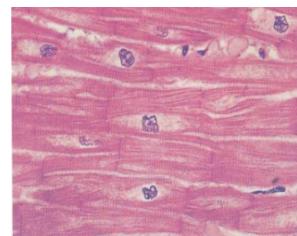
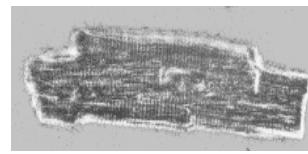
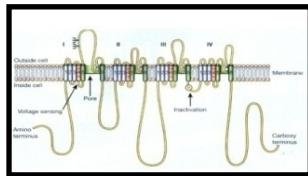
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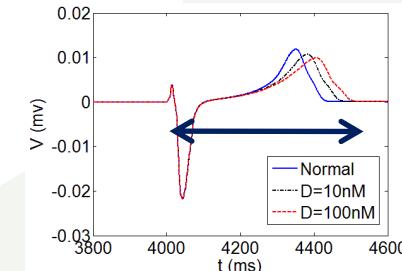
# COBÁZÓN MULTIESCALA DEL CORAZÓN

[farm., gen., pat.]

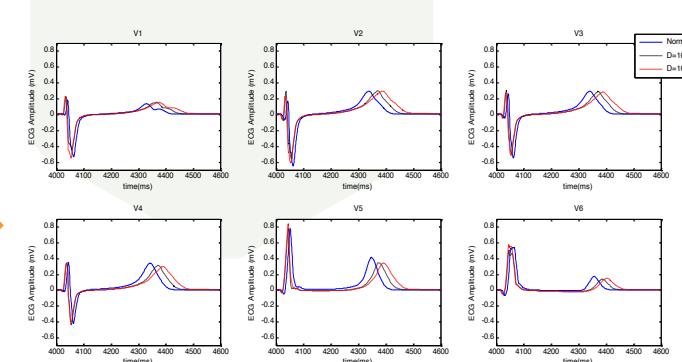
Canal Célula Tejido Órgano Cuerpo



Biomarcadores



QT



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# CORAZÓN VIRTUAL

## Objetivos:

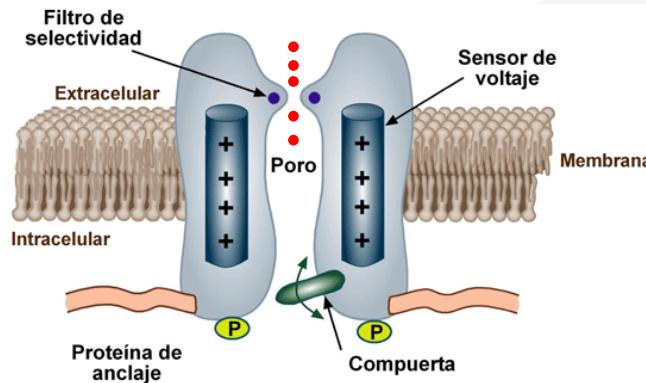
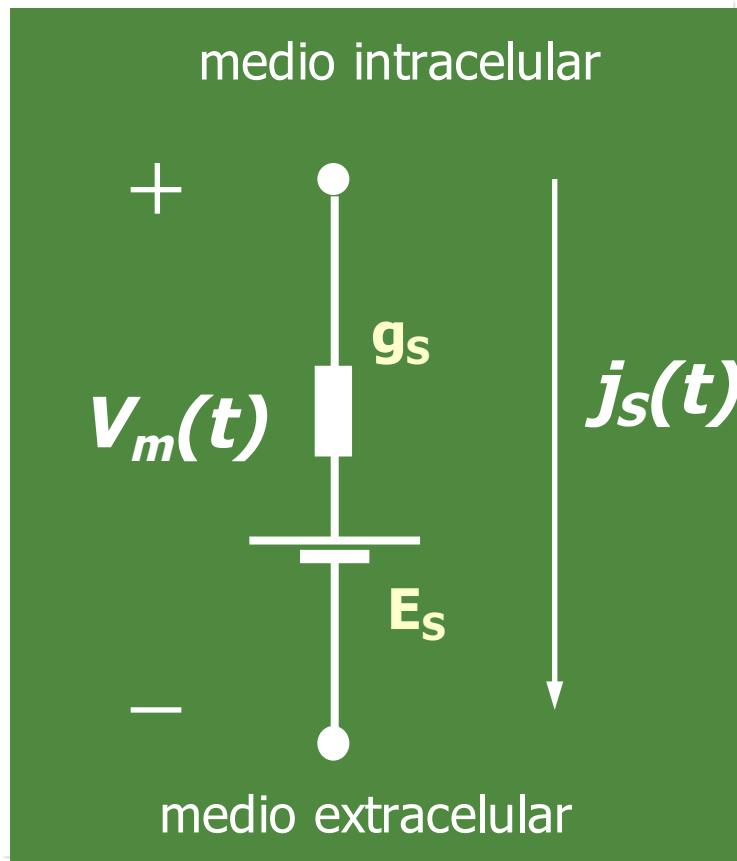
Ayudar a

Entender las condiciones que facilitan el desarrollo de las arritmias cardíacas mediante la integración de información disponible desde el nivel molecular hasta el torso.

Diseñar nuevos y seguros métodos de prevención, diagnóstico y tratamiento.

# CORAZÓN VIRTUAL

○ Nivel canal



$$E_S = -\frac{RT}{FZ_S} \ln \frac{[S]_i}{[S]_e}$$

$$g_s = g_s (V_m, t, [X]_i, [X]_e, T, pH, far...)$$

$$j_s = g_s (V_m - E_S)$$

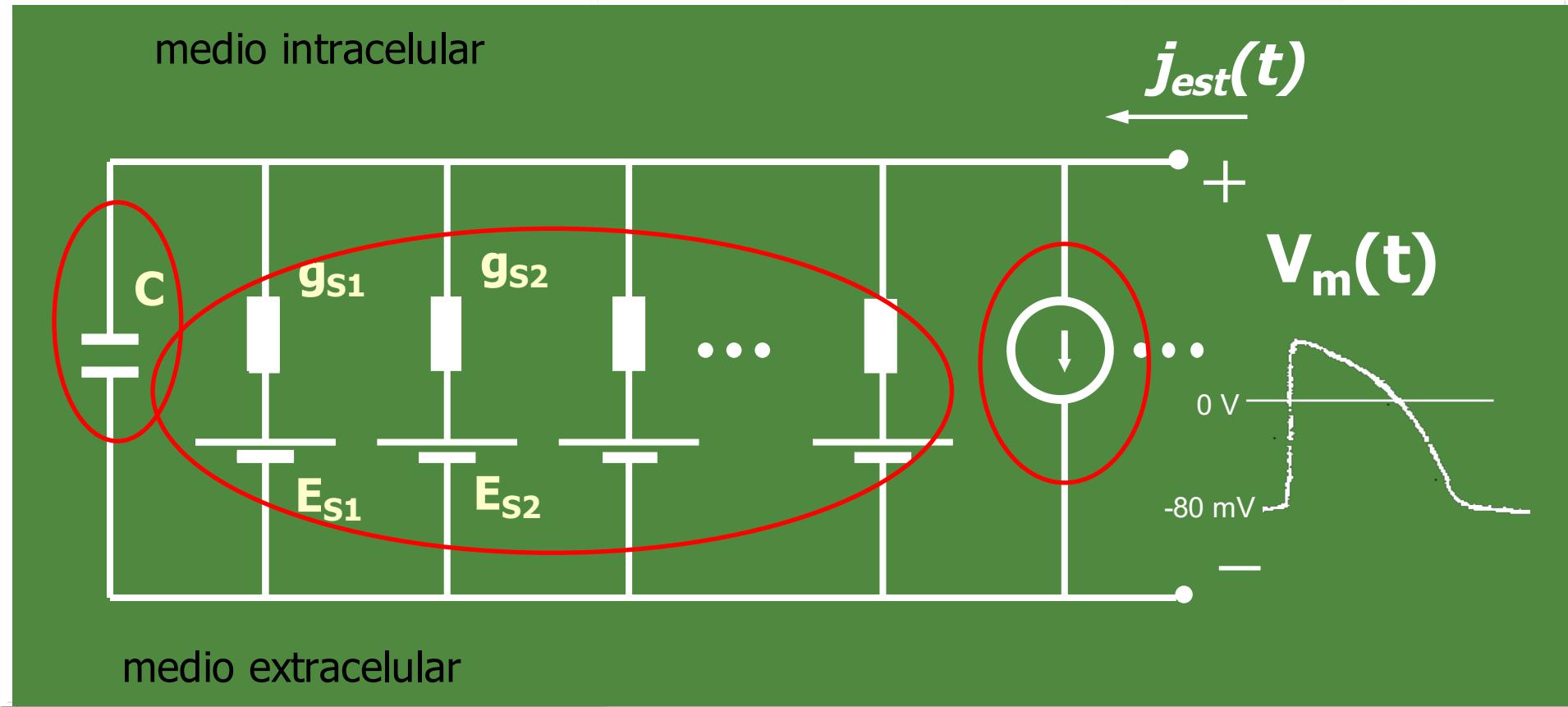
$$V_m = u_i - u_e$$

# CORAZÓN VIRTUAL

○ Nivel celular

Capacidad de membrana ( $V_m$ ,  $t$ ) + Bombas e intercambiadores iónicos

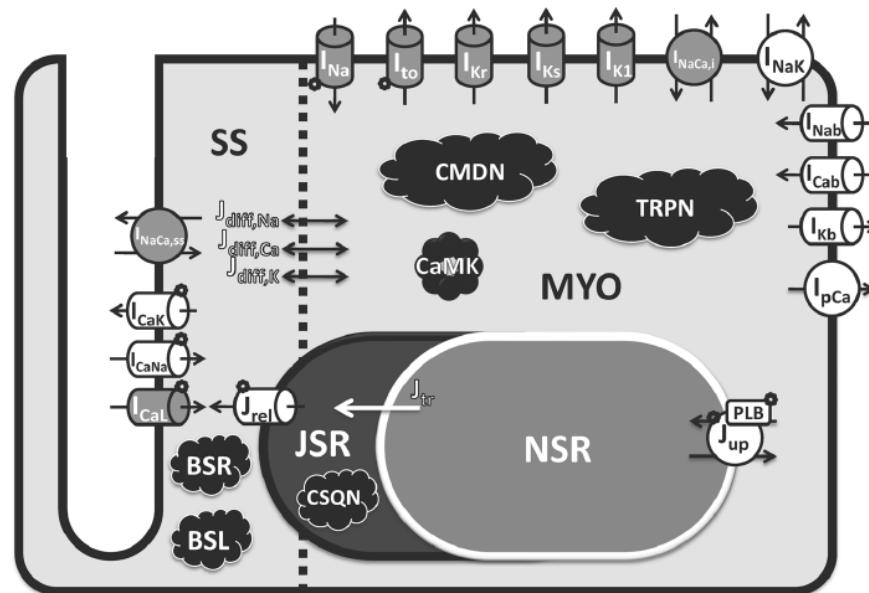
$$C_m \frac{dV_m}{dt} = \sum_i j_{Si}(V_m, t) - \sum_p j_p(V_m) - j_{est}(t) = 0$$



# CORAZÓN VIRTUAL

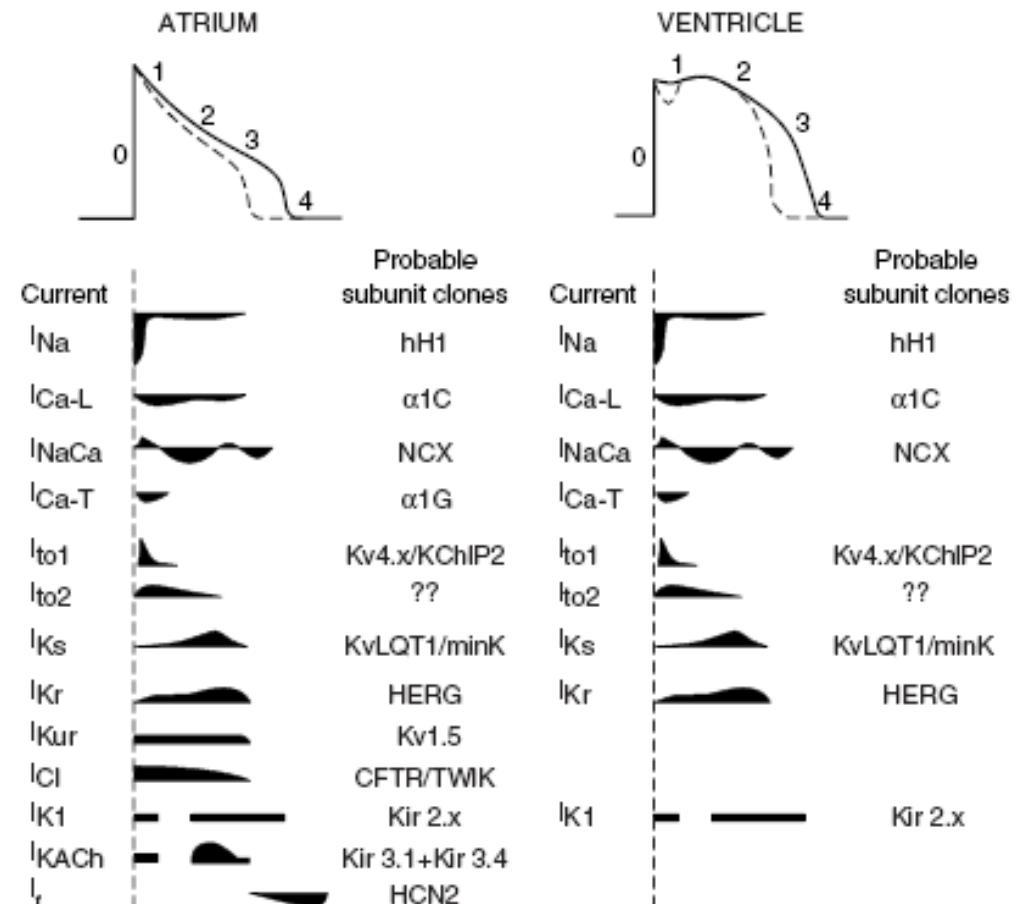
○ Nivel celular

## Modelo de célula del músculo ventricular humano



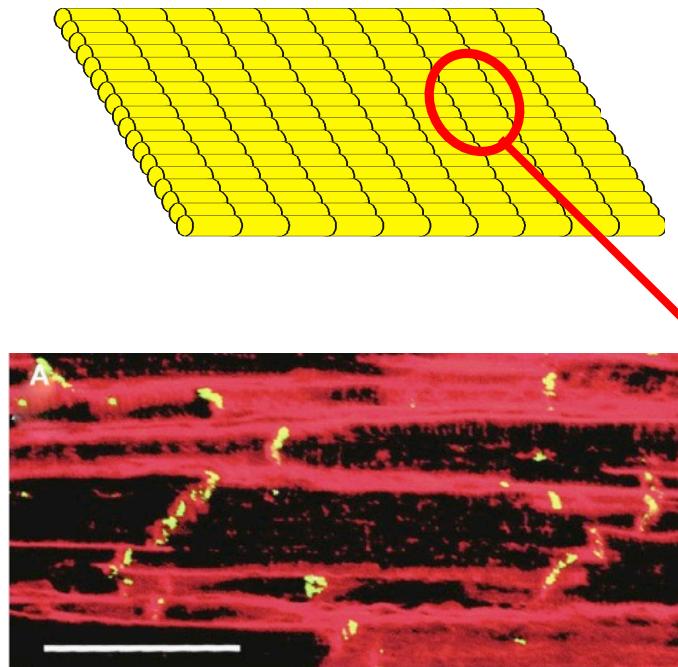
O'Hara y col. 2011

## Heterogeneidad electrofisiológica



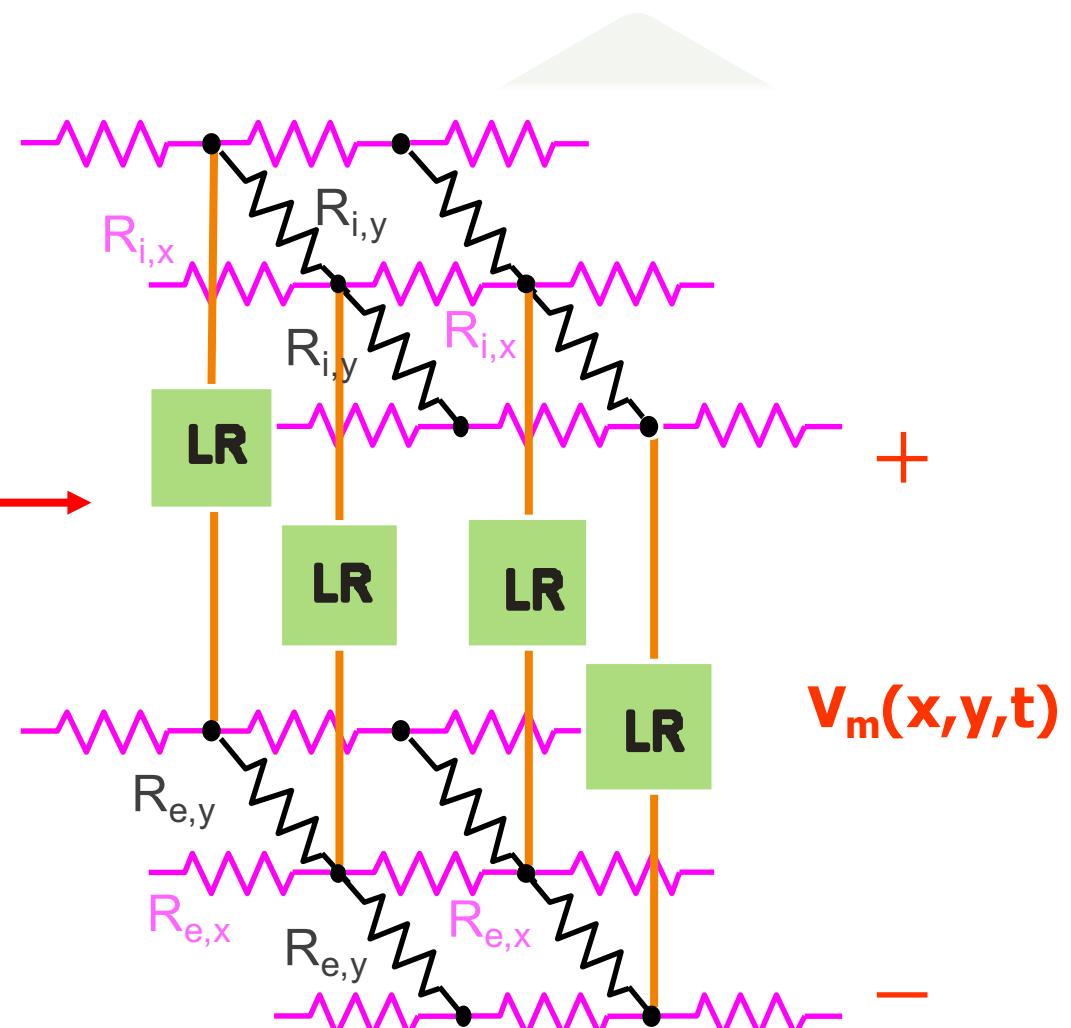
# CORAZÓN VIRTUAL

○ Nivel tejido



Valderrábano, 2007

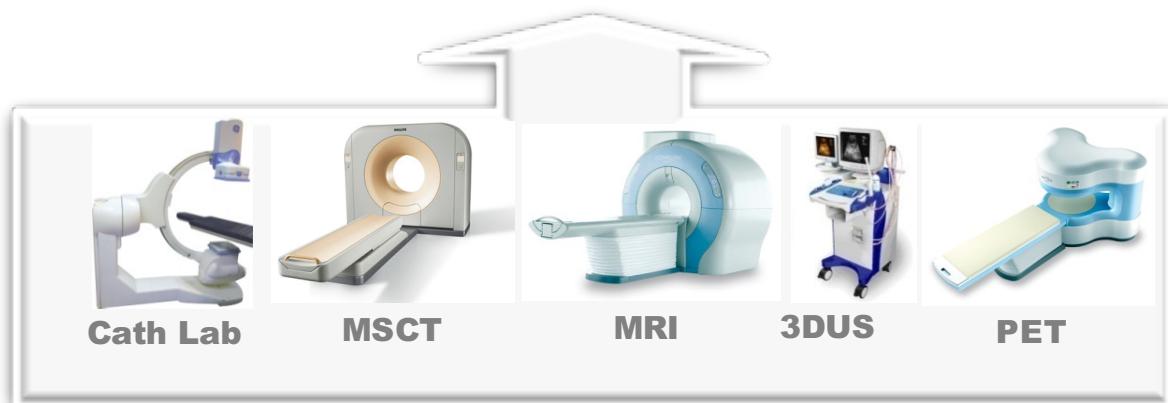
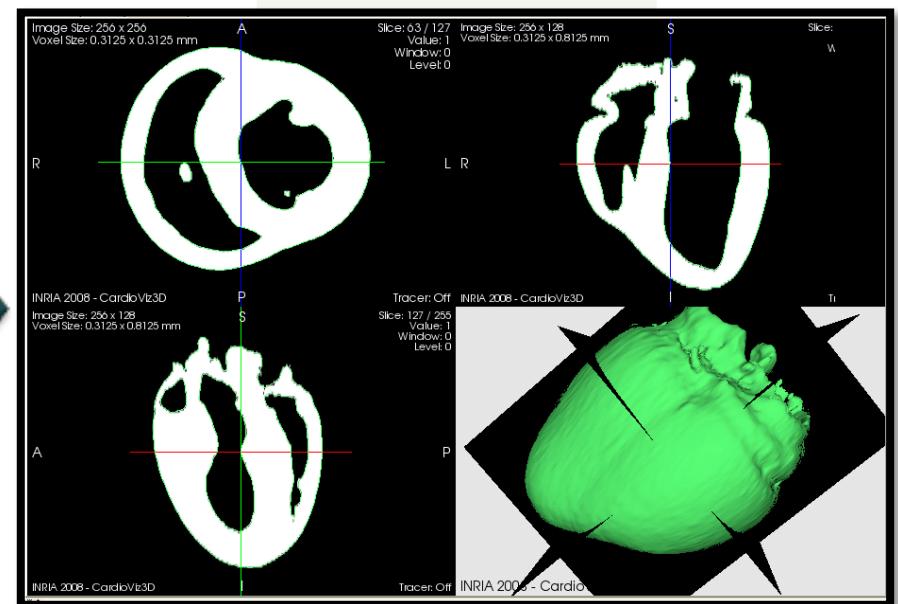
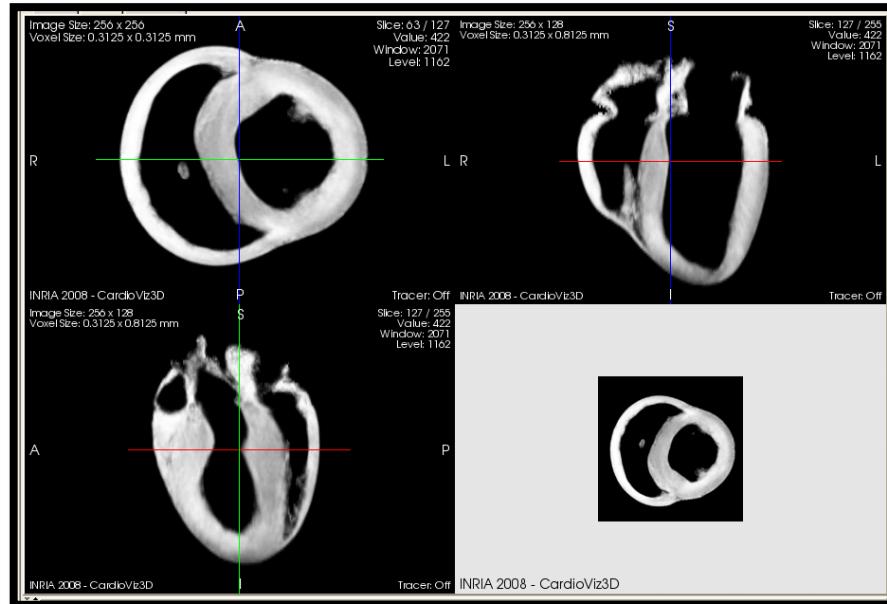
tejido anisótropo



$$\frac{1}{S_V} \left( \frac{1}{\rho_{ix}} \frac{\partial^2 V_m}{\partial x^2} + \frac{1}{\rho_{iy}} \frac{\partial^2 V_m}{\partial y^2} \right) = C_m \frac{\partial V_m}{\partial t} + \sum_i I_{S,i} + \sum_{B,I} I_{B,I} + I_{est}$$

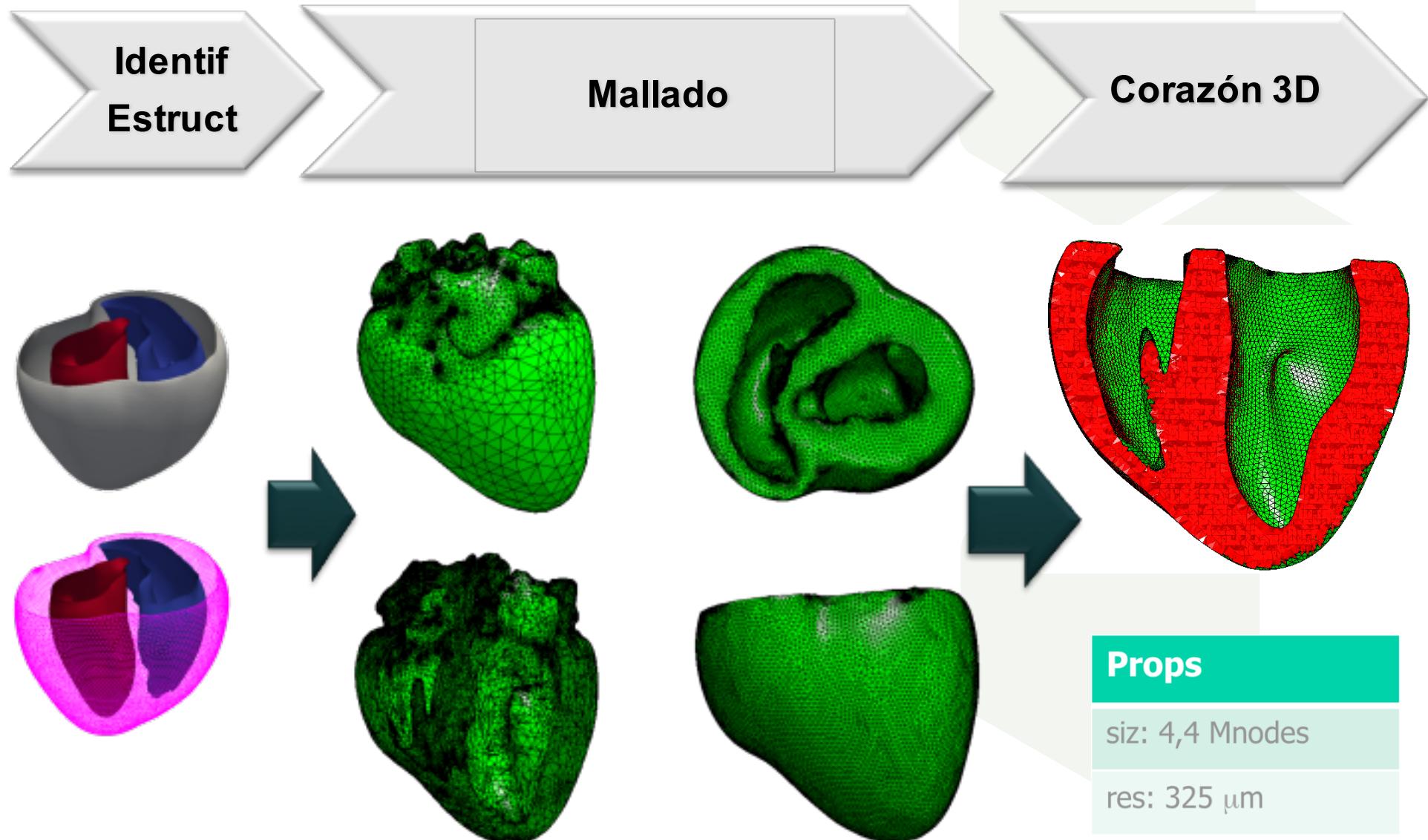
# CORAZÓN VIRTUAL

○ Nivel de órgano. Geometría realista



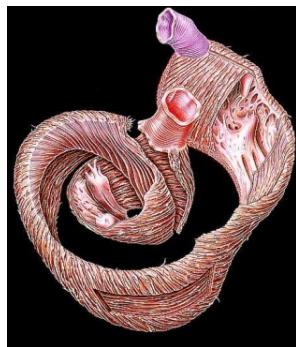
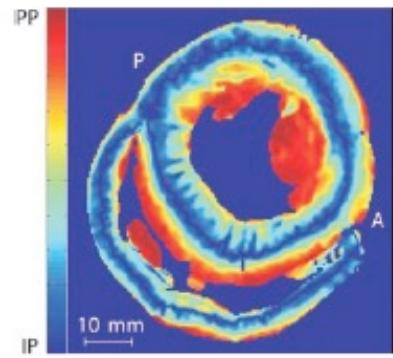
# CORAZÓN VIRTUAL

○ Nivel de órgano. Geometría realista



# CORAZÓN VIRTUAL

○ Nivel de órgano. Geometría realista



Endo  
+ 60

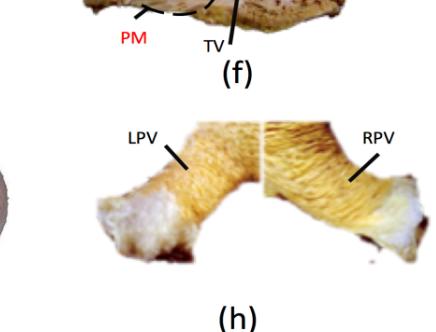
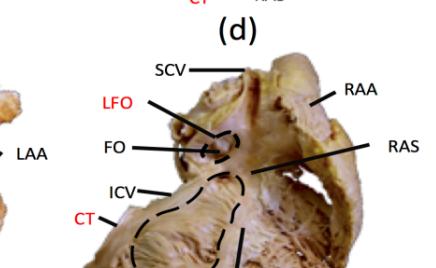
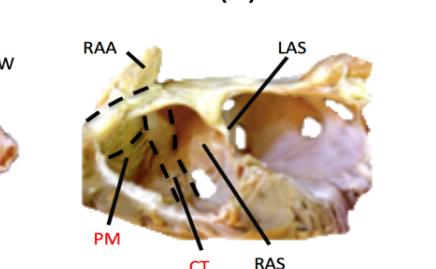
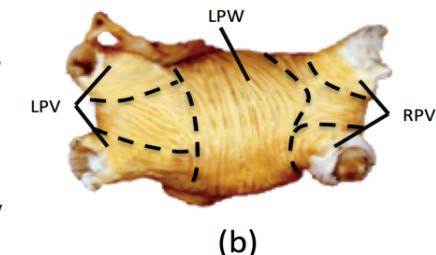
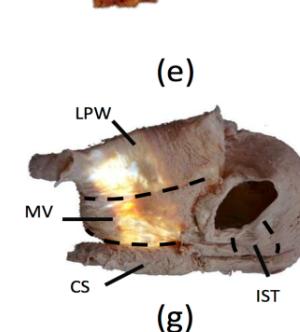
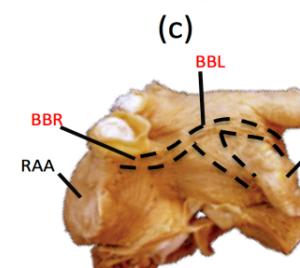
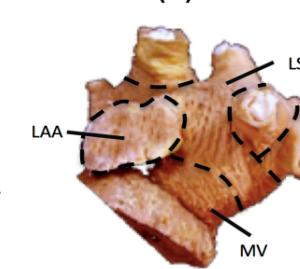
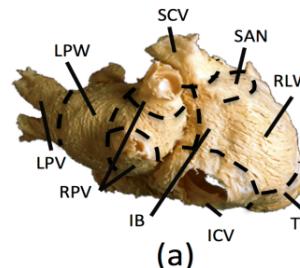


Torrent-Guasp, 1950

Epi

Geerts y col 2002

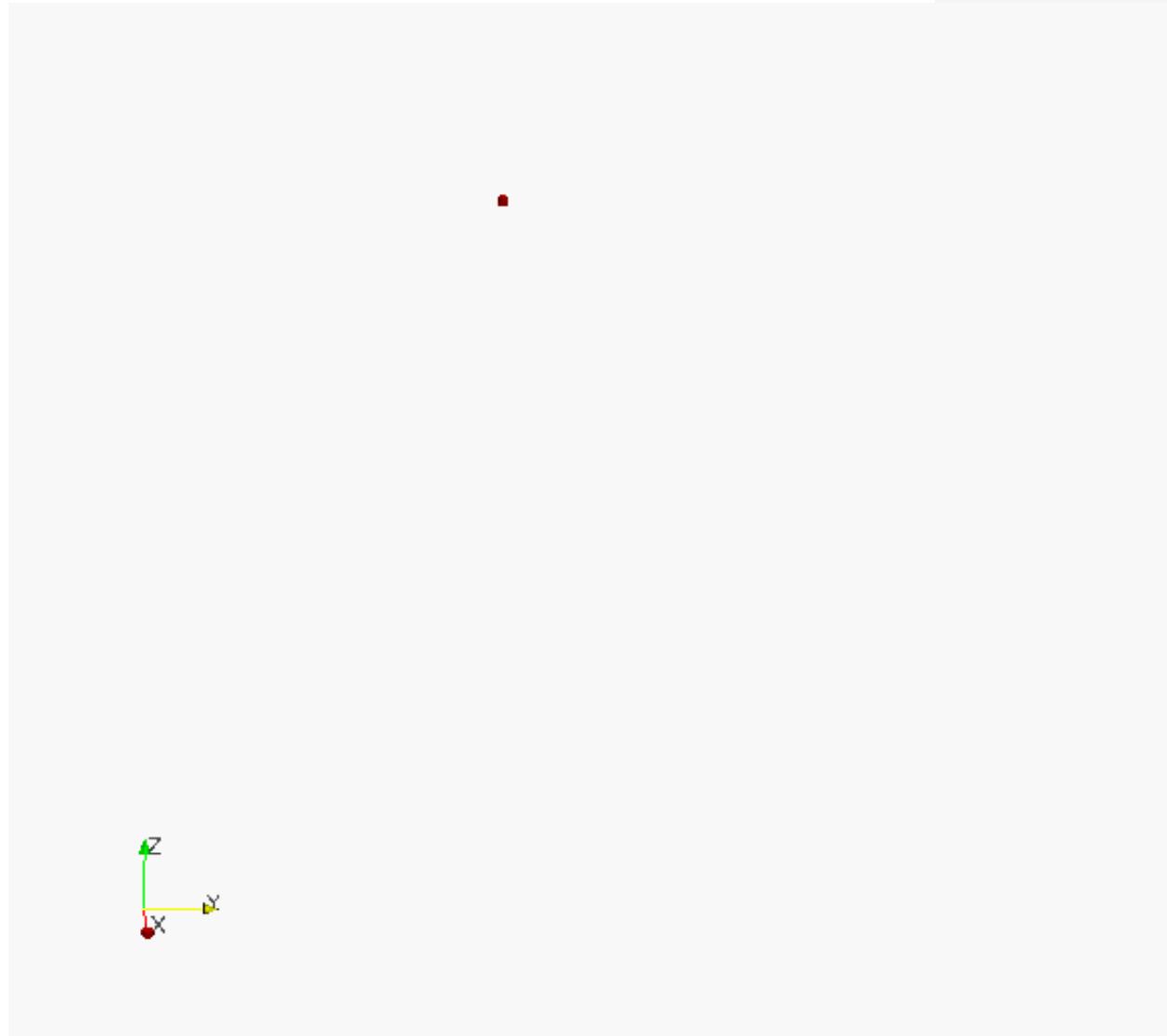
Streeter y col, 1969



Sanchez-Quintana y col

# CORAZÓN VIRTUAL

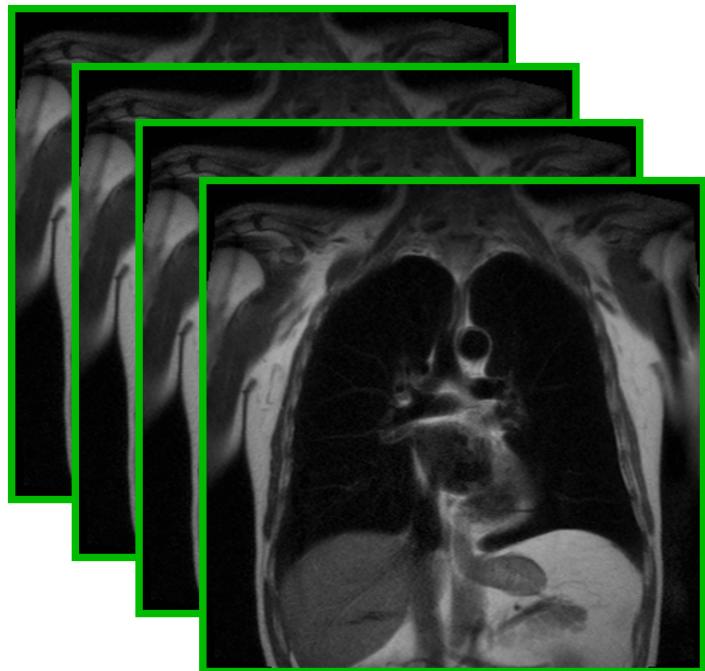
○ Fibras de purkinje



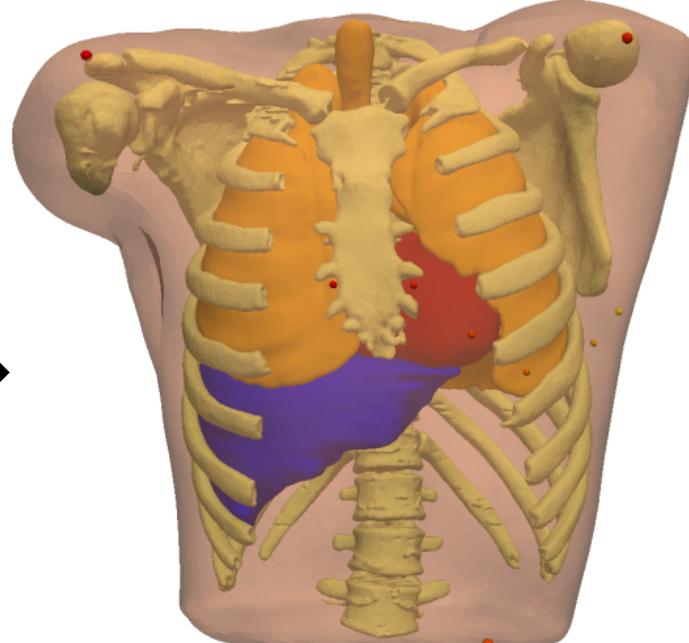
# CORAZÓN VIRTUAL

○ Nivel torso

Imágenes RMN



Modelo de torso  
Específico del paciente



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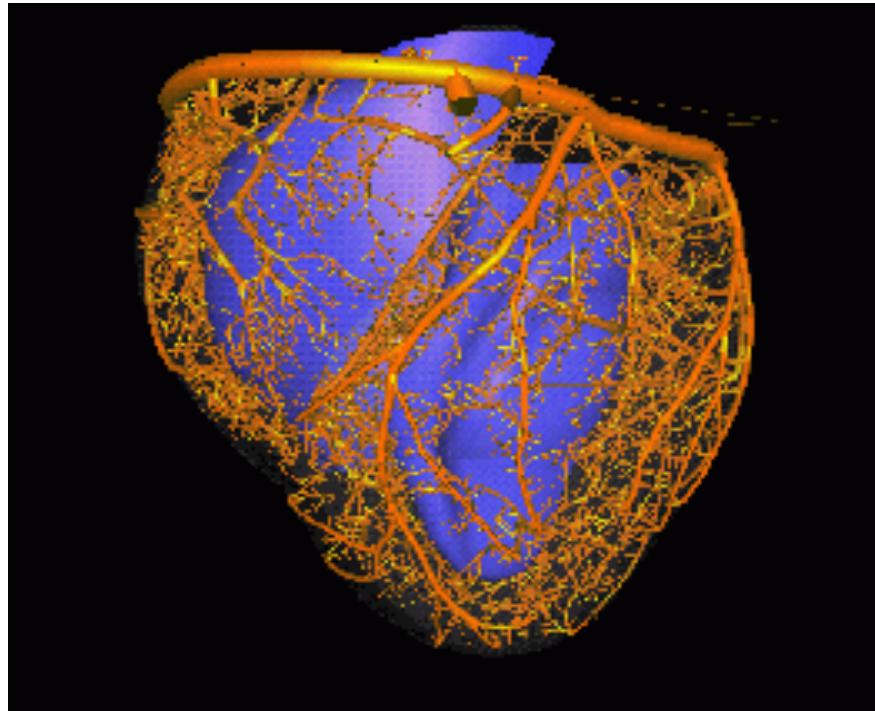


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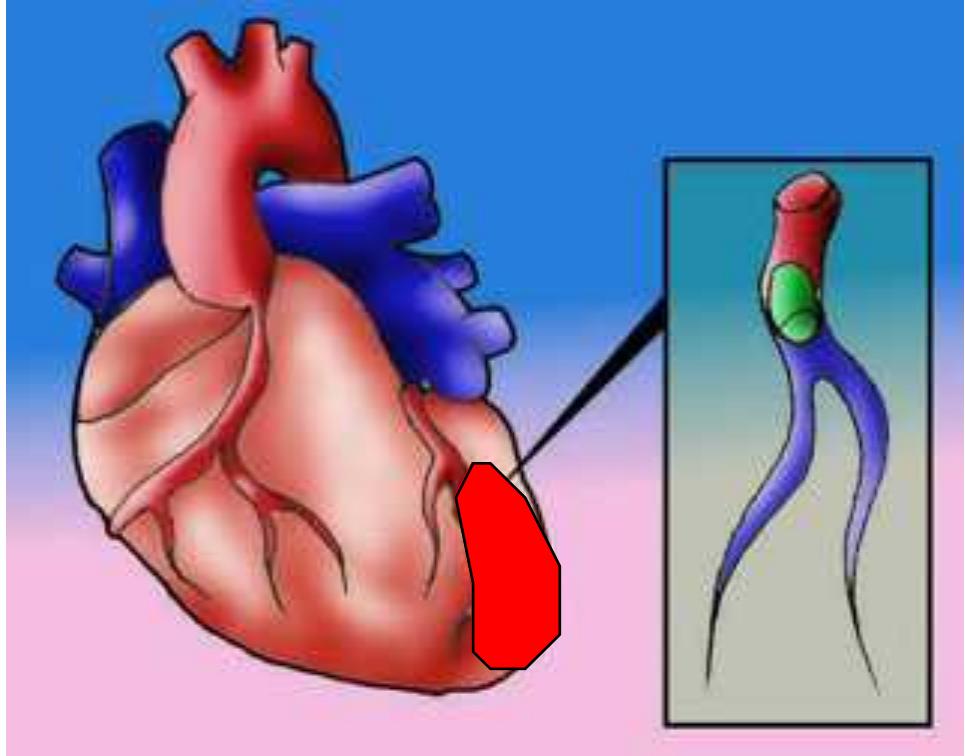


# CASO 1. ARRITMIAS VENTRICULARES

## Arritmias en isquemia



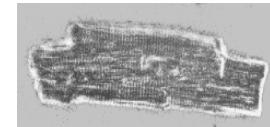
Arterias coronarias



Oclusión coronaria (infarto)

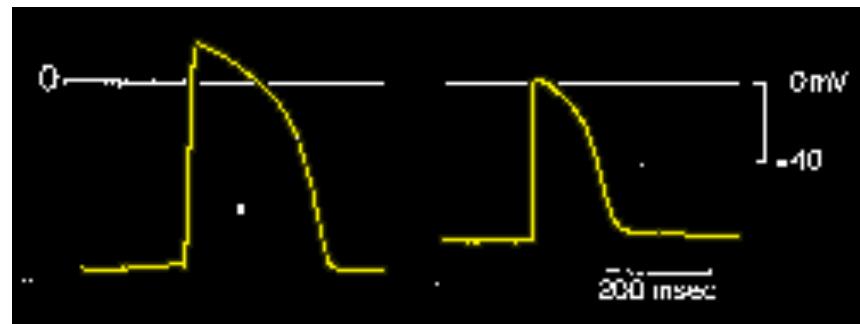
*Isquemia: anemia local y temporal en el miocardio causada por la falta de riego sanguíneo.*

# CASO 1. ARRITMIAS VENTRICULARES



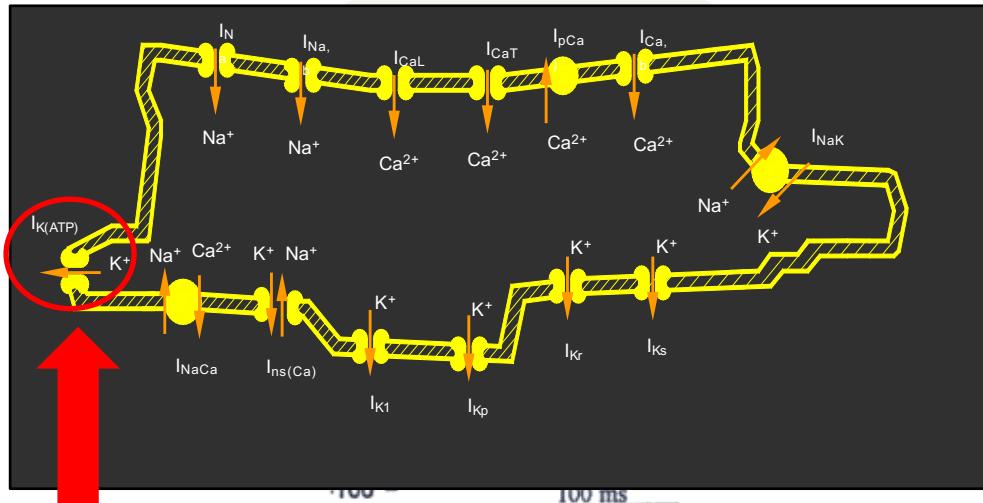
## Arritmias en isquemia

Control



10' Hypoxia

Morena y col 1980

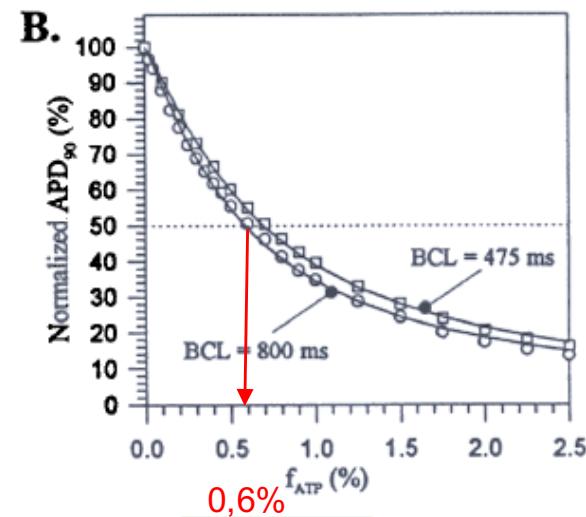


$$I_{K(ATP)} = g_{K(ATP)} f_{ATP} (V_m - E_K)$$

$$g_{K(ATP)} = 35.3 \cdot \left( \frac{[K^+]_o}{5^4} \right)^{0.24} \cdot \frac{1}{1 + \frac{[Ca^{2+}]_i}{K_{h,Mg}(V_m, [K^+]_o)}} \cdot \frac{1}{1 + \left( \frac{[K^{+}]_i}{K_{h,Na}(V_m)} \right)^2}$$

¿Papel de la corriente  $I_{KATP}$ ?

$$f_{ATP} = \frac{1}{1 + \left( \frac{[ATP]_i}{K_{h,Mg}([ADP]_i)} \right)^H([ADP]_i)}$$



Ferrero J.M., Saiz J., Ferrero J.M., Thakor N. V.

Simulation of Action Potentials From Metabolically Impaired Cardiac myocytes,  
Circulation Research 1996



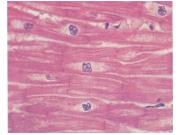
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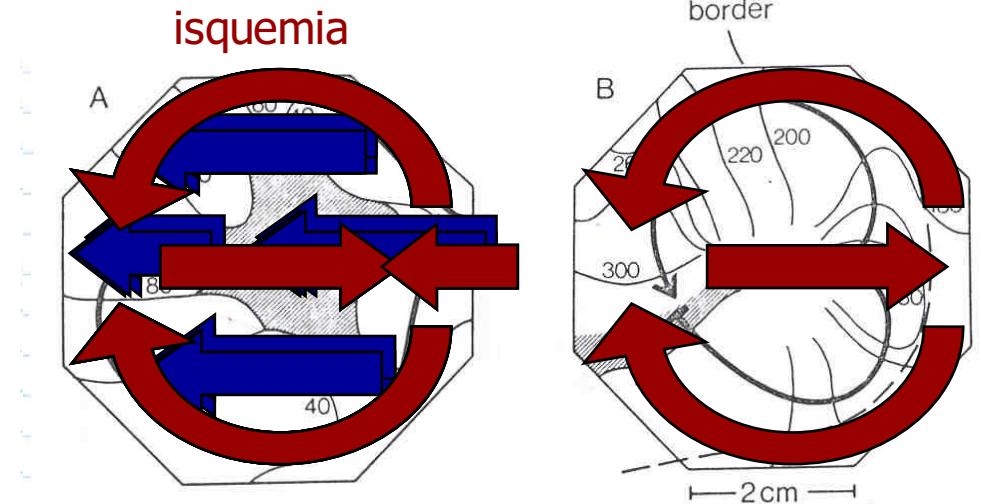
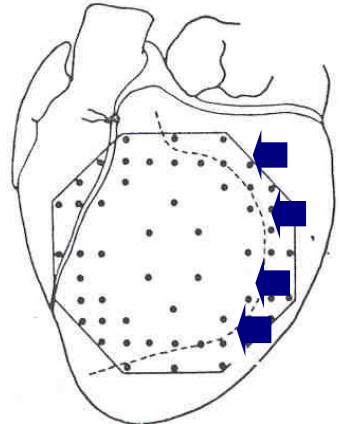


# CASO 1. ARRITMIAS VENTRICULARES



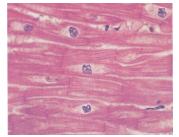
## Arritmias en isquemia

[Janse et al, 1978]

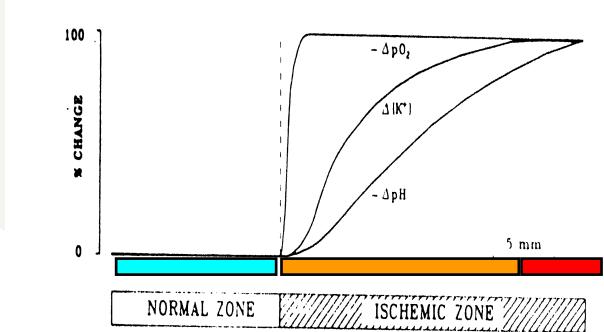
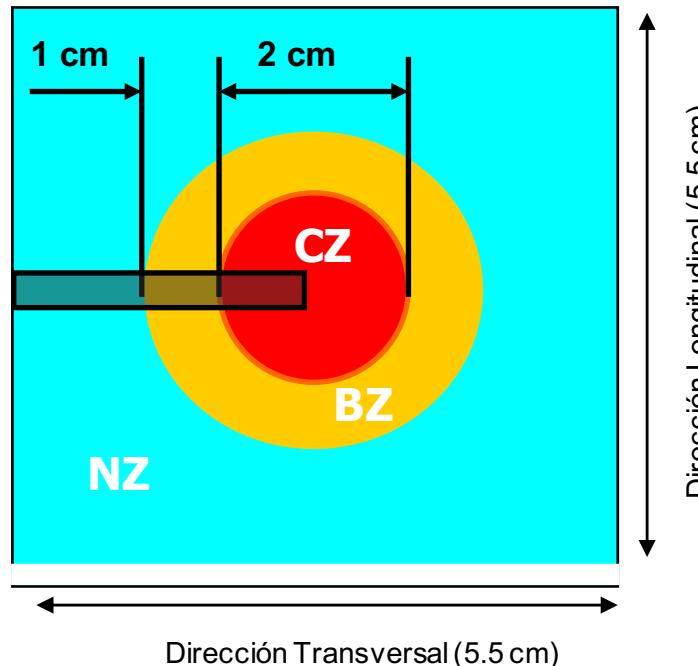
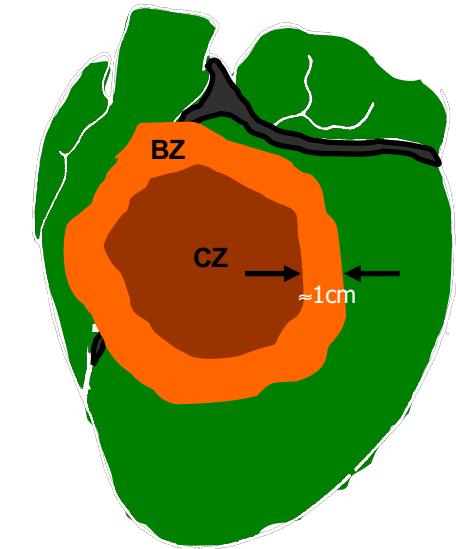


- ✓ Es posible registrar la actividad eléctrica en el tejido miocárdico, sin embargo...
- ✓ *“In vivo”* durante la isquemia es imposible registrar los PA, corrientes iónicas y concentraciones.

# CASO 1. ARRITMIAS VENTRICULARES



## Arritmias en isquemia



Coronel et al, 1988

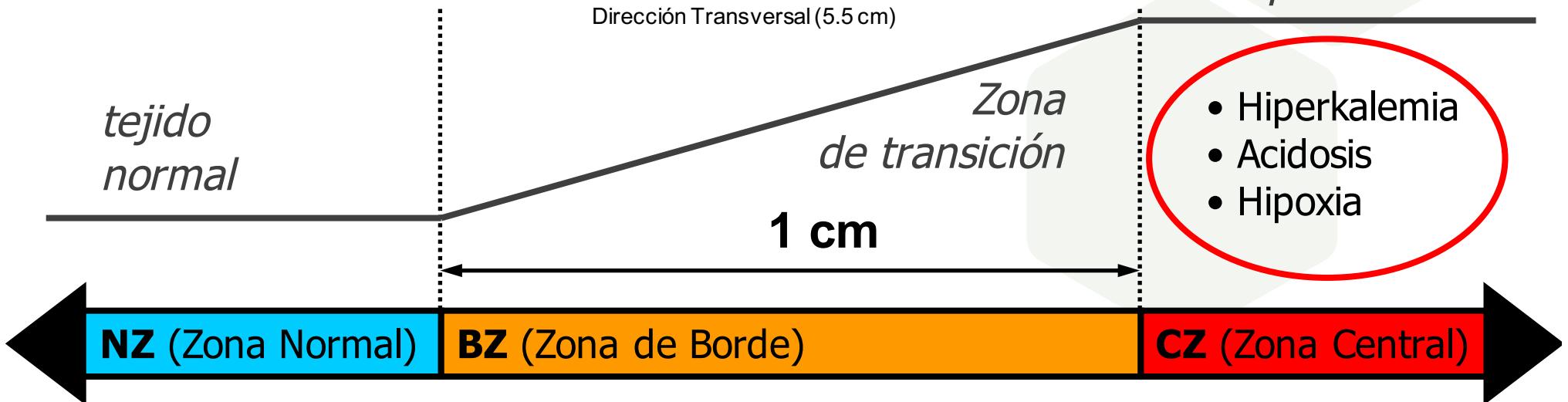
*tejido  
isquémico*

*tejido  
normal*

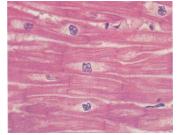
Zona  
de transición

1 cm

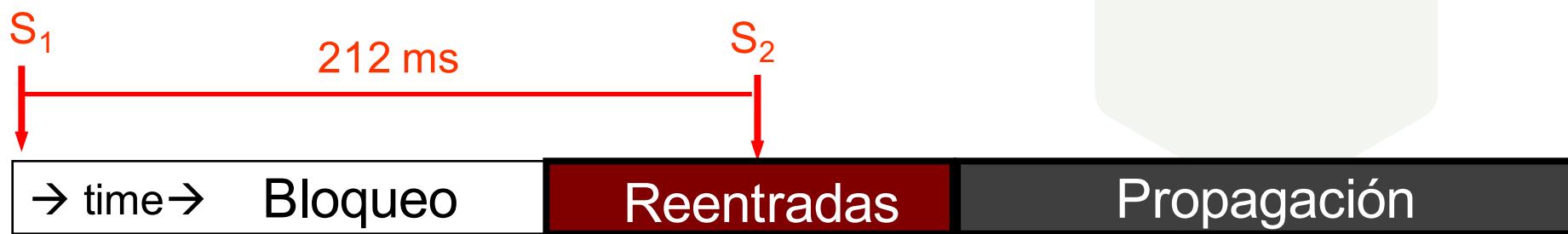
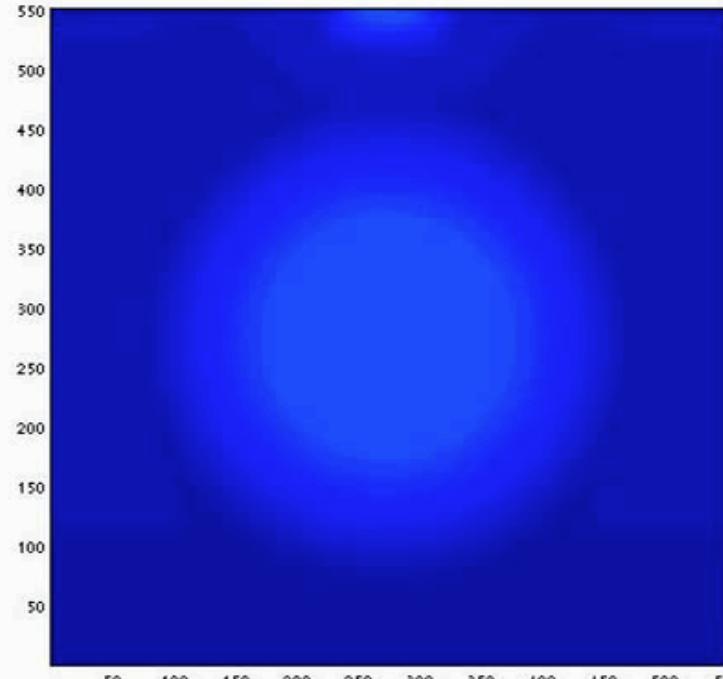
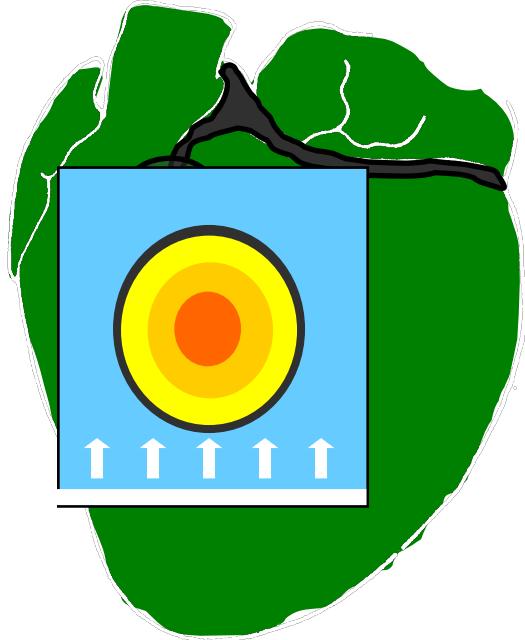
- Hiperkalemia
- Acidosis
- Hipoxia



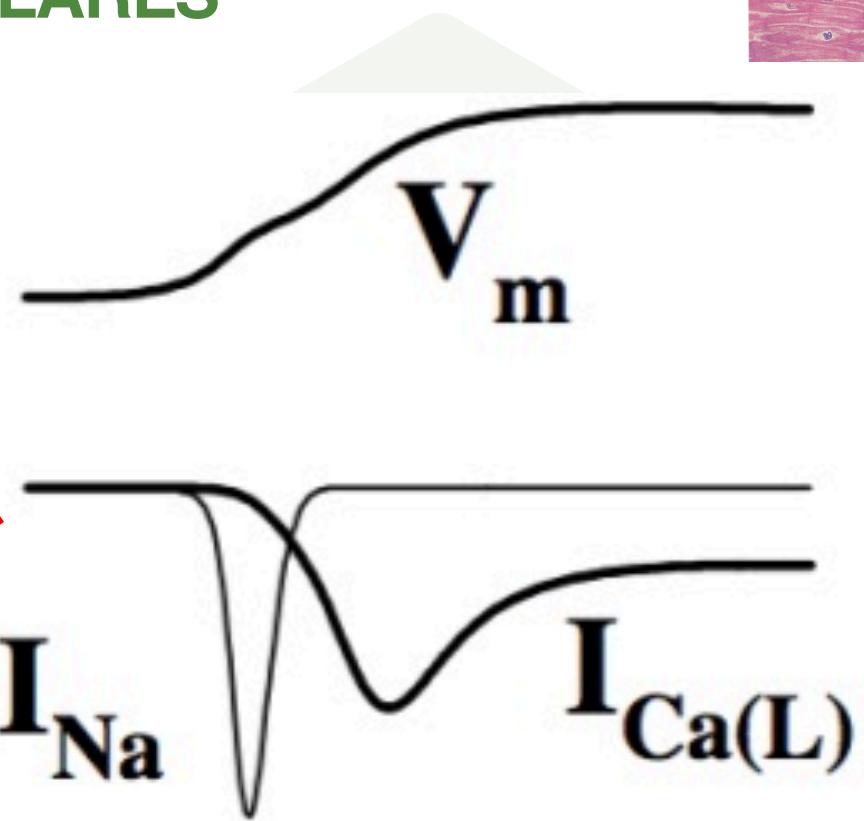
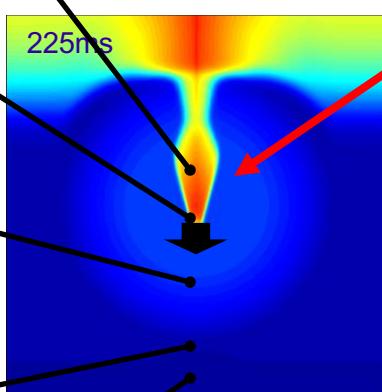
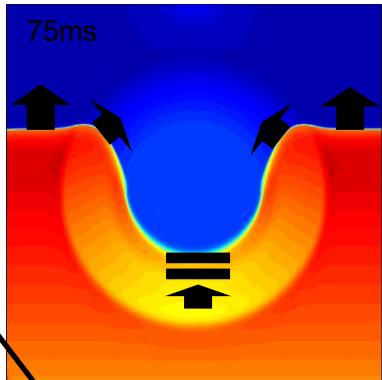
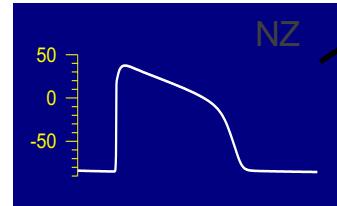
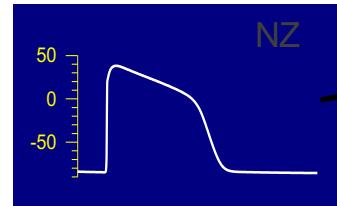
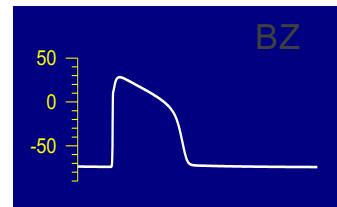
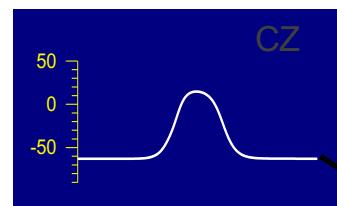
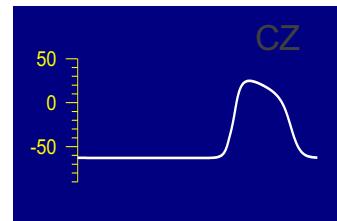
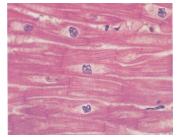
# CASO 1. ARRITMIAS VENTRICULARES



# Arritmias en isquemia



# CASO 1. ARRITMIAS VENTRICULARES

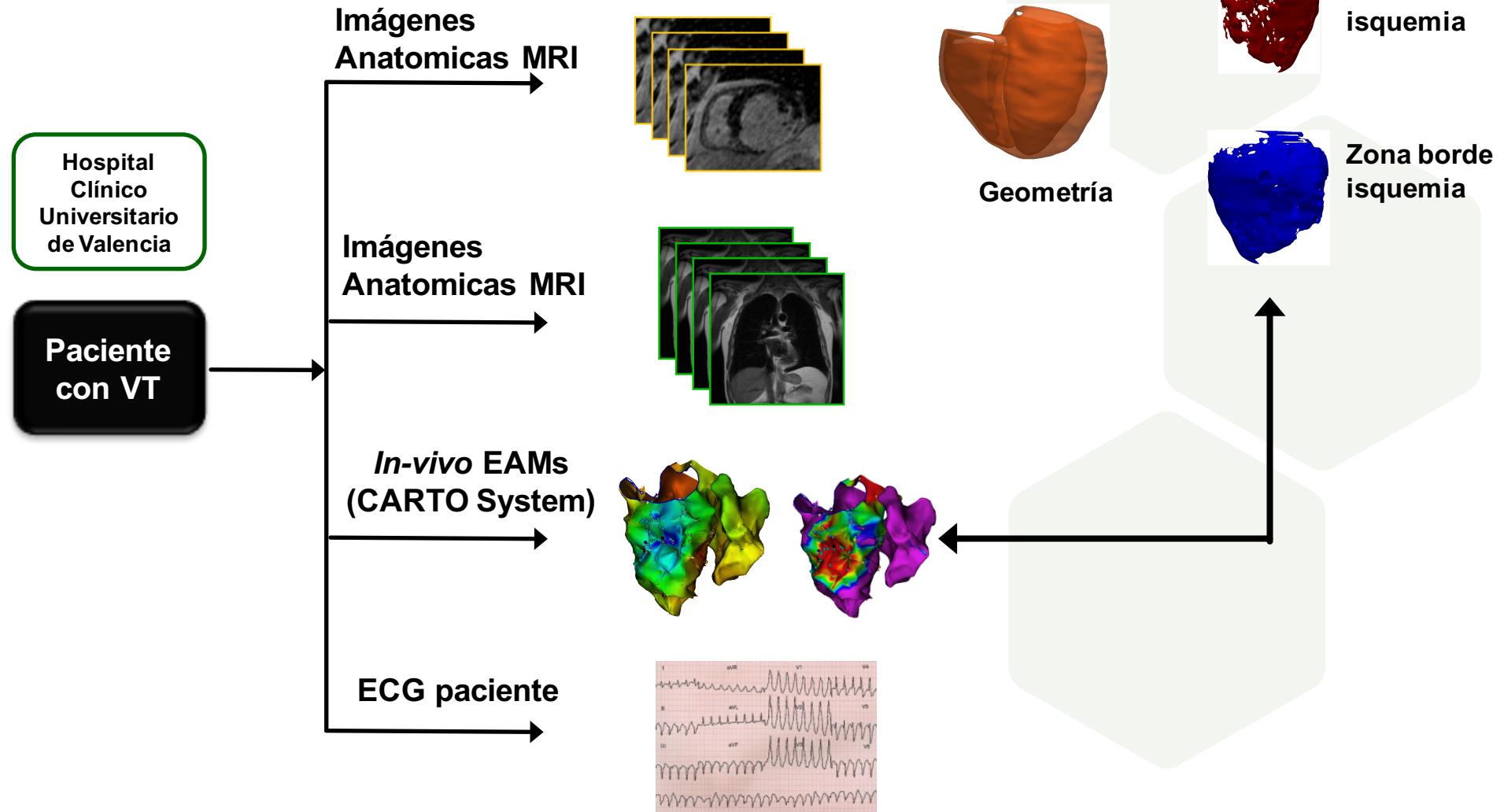


# CASO 1. ARRITMIAS VENTRICULARES

## Papel de los canales de conducción

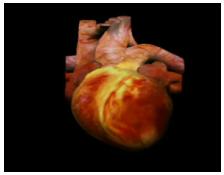


- Desarrollo del modelo personalizado a paciente

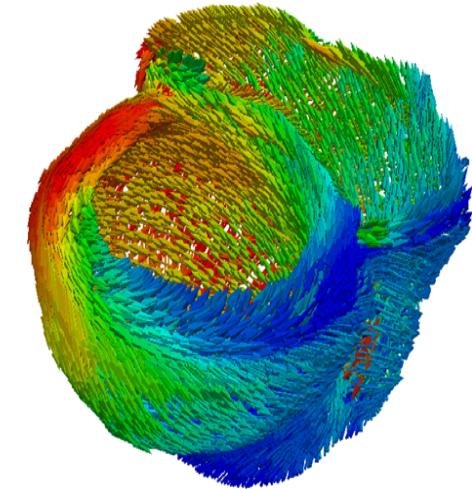
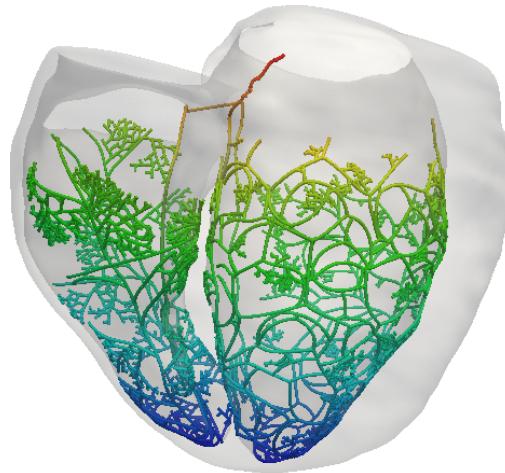
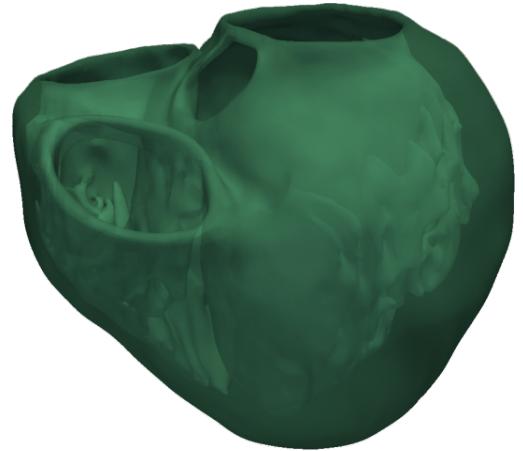


# CASO 1. ARRITMIAS VENTRICULARES

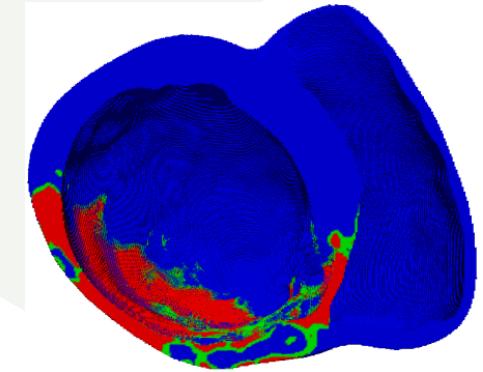
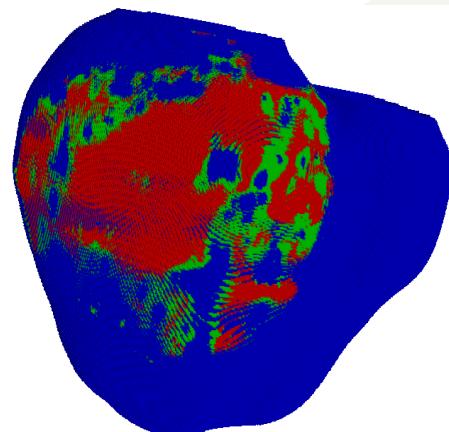
## Papel de los canales de conducción



- Desarrollo del modelo personalizado a paciente

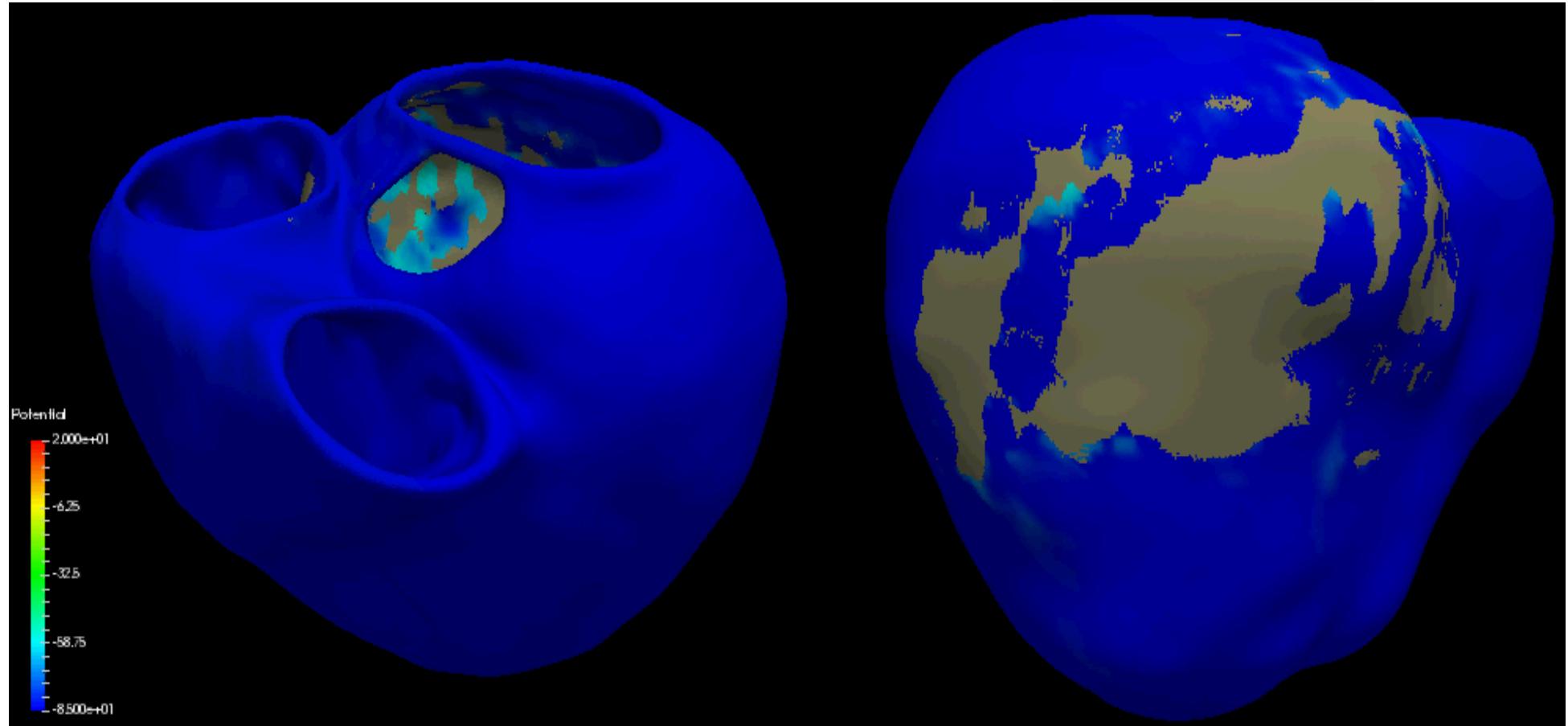
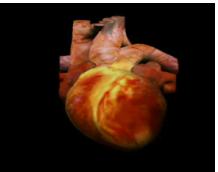


Anatomía cardiaca



# CASO 1. ARRITMIAS VENTRICULARES

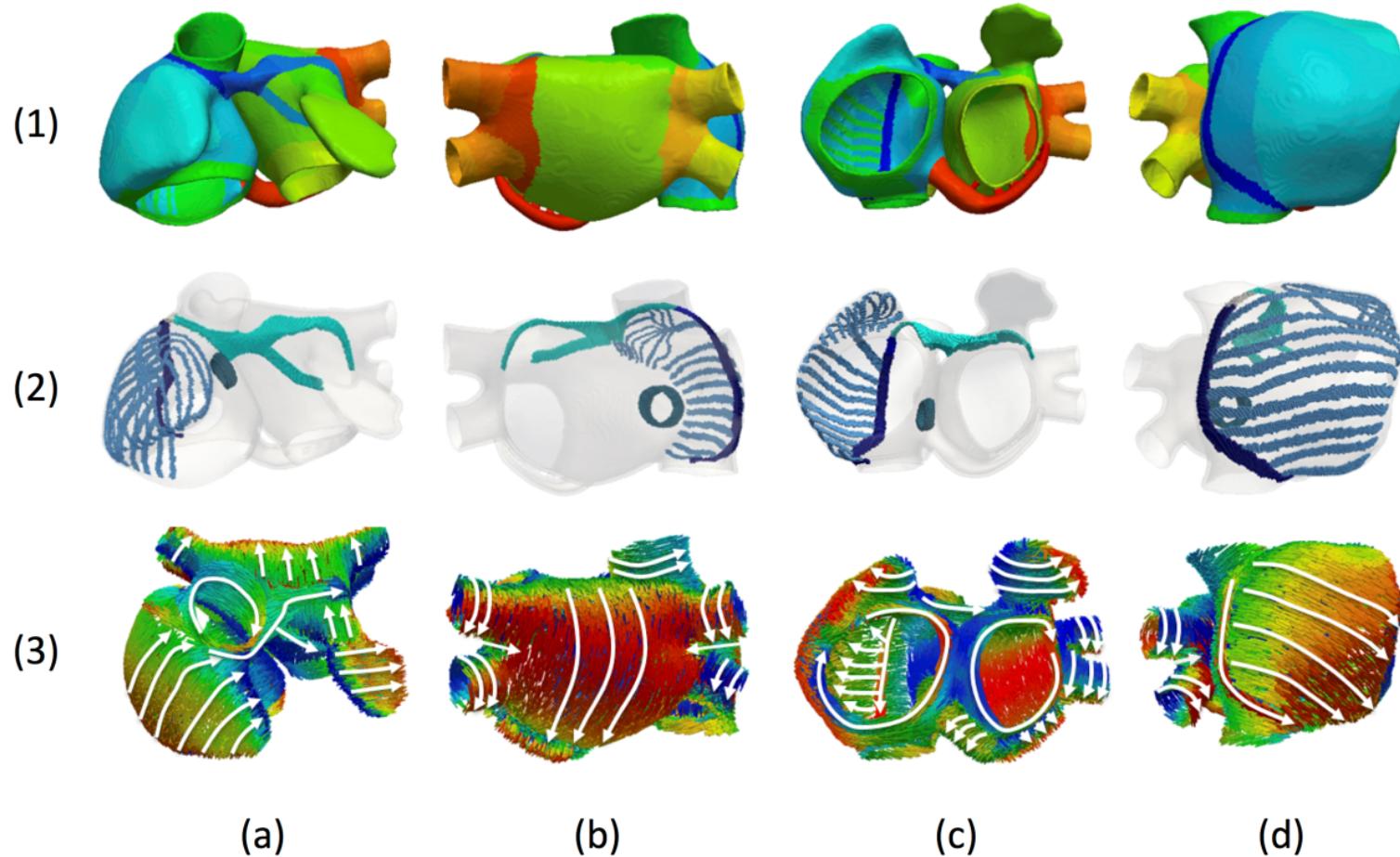
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López A. Tesis Doctoral. No publicado

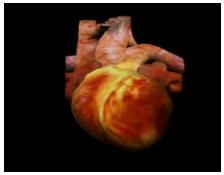
# CASO 2. ARRITMIAS AURICULARES

## Modelo realista de las aurículas

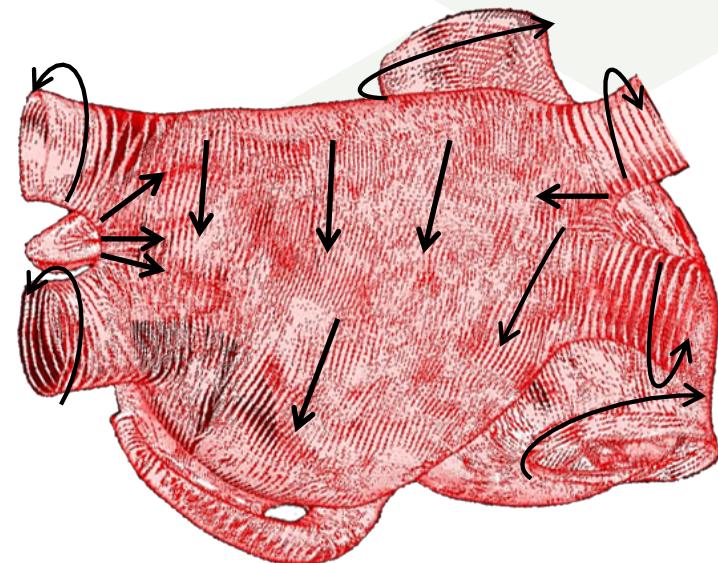
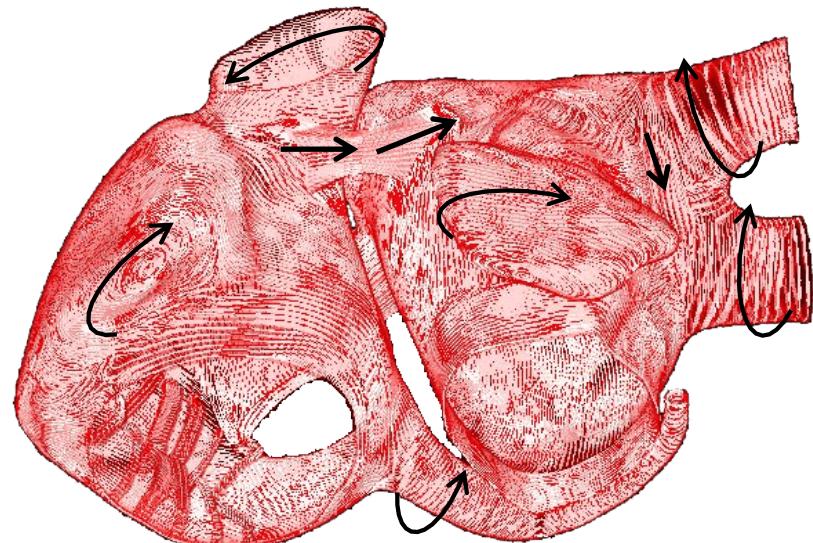
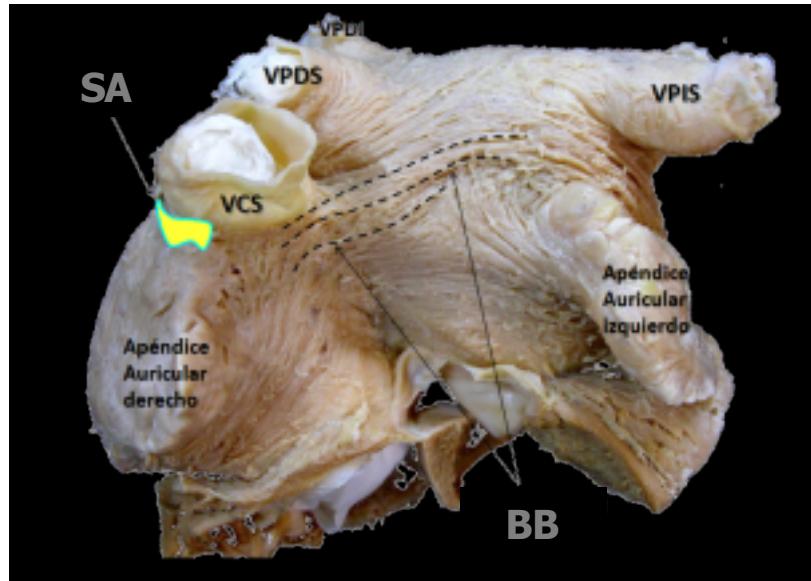


Ferrer A., Sebastián R., Sánchez-Quintana D., Rodríguez J. F., Godoy E.J., Martínez L., Saiz J.,  
*Detailed Anatomical and Electrophysiological Models of Human Atria and Torso for the  
Simulation of Atrial Activation* PLOS ONE, 2015

# CASO 2. ARRITMIAS AURICULARES



## Modelo realista de las aurículas



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DE VALÈNCIA

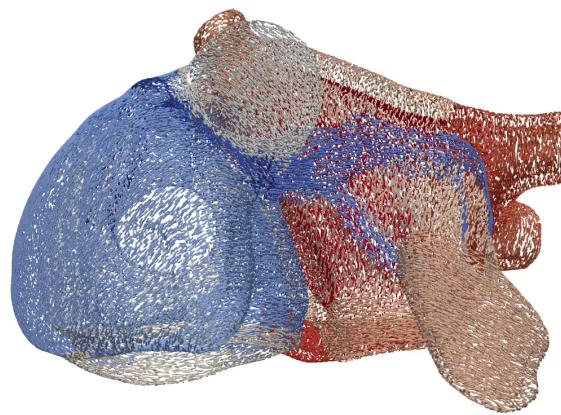
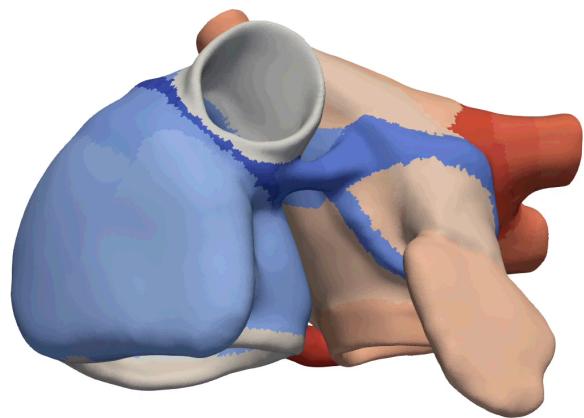
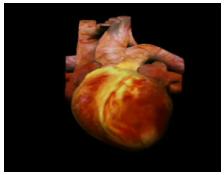


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# CASO 2. ARRITMIAS AURICULARES

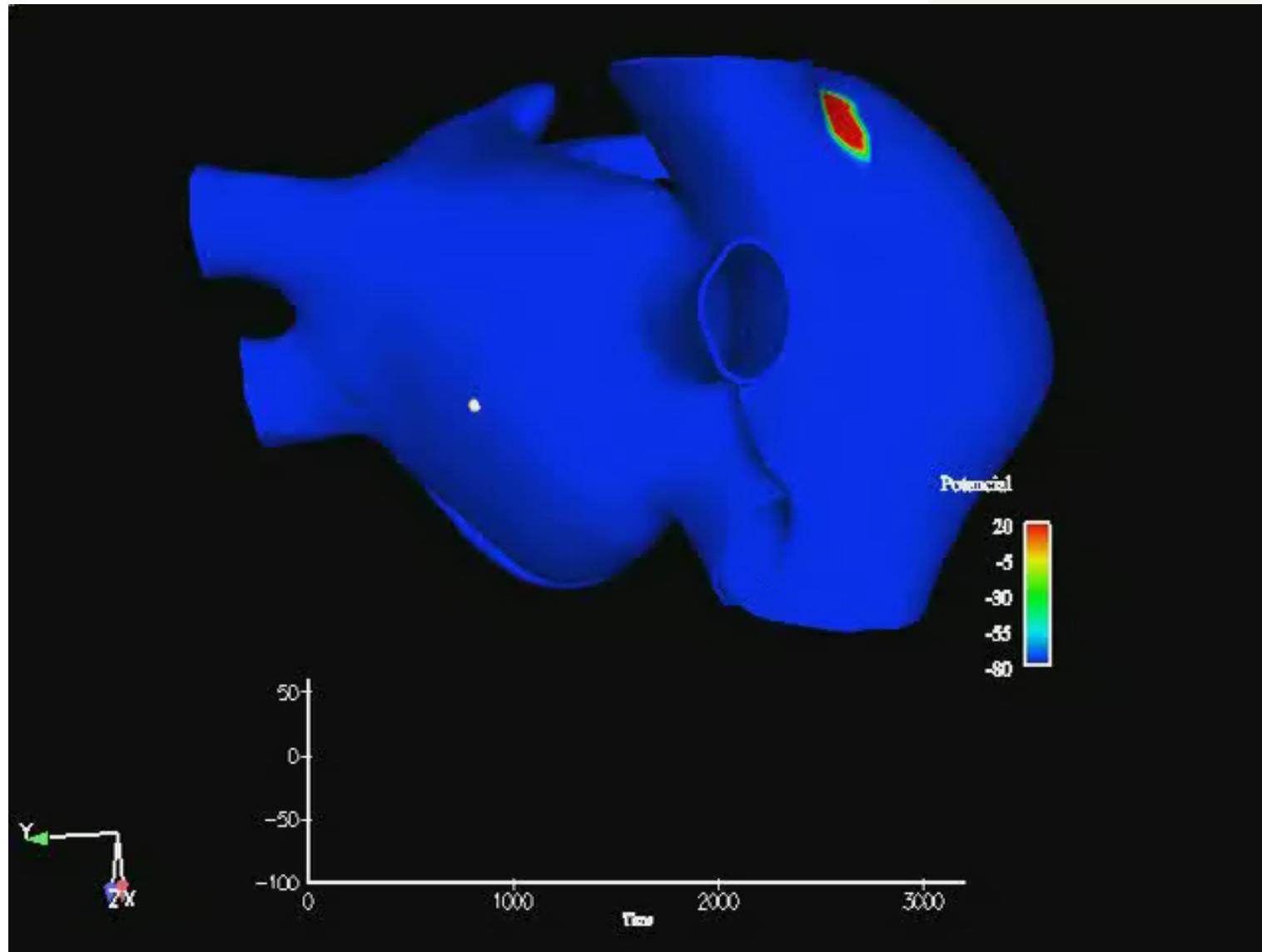
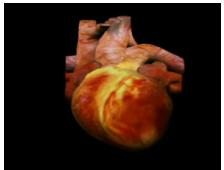
## Modelo realista de las aurículas



Rocher S. Tesis Fin Master. No publicado

# CASO 2. ARRITMIAS AURICULARES

## Propagación normal cAF



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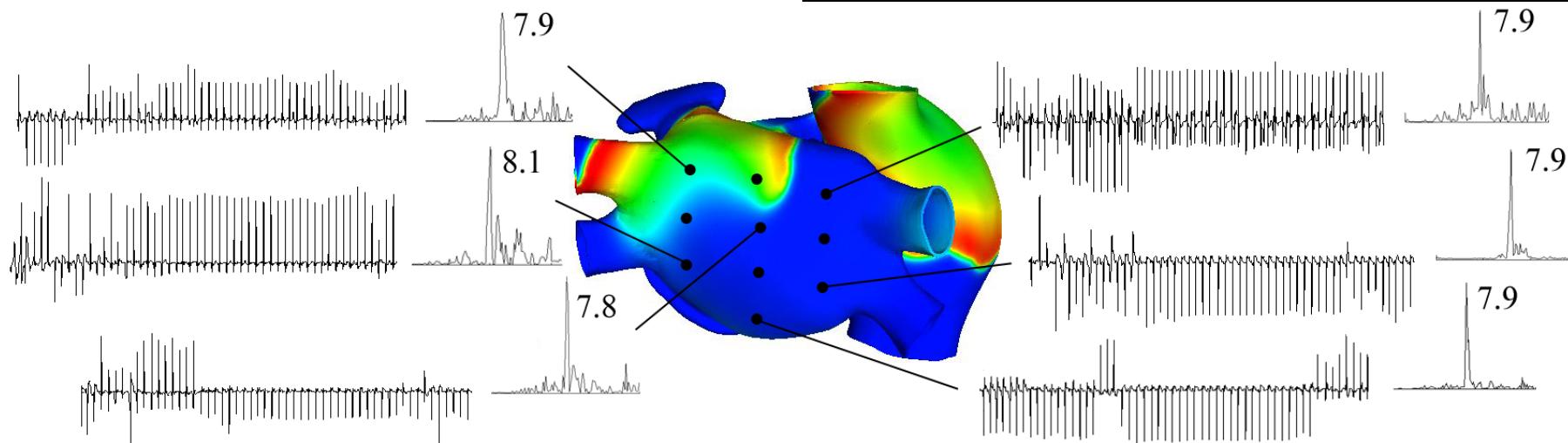
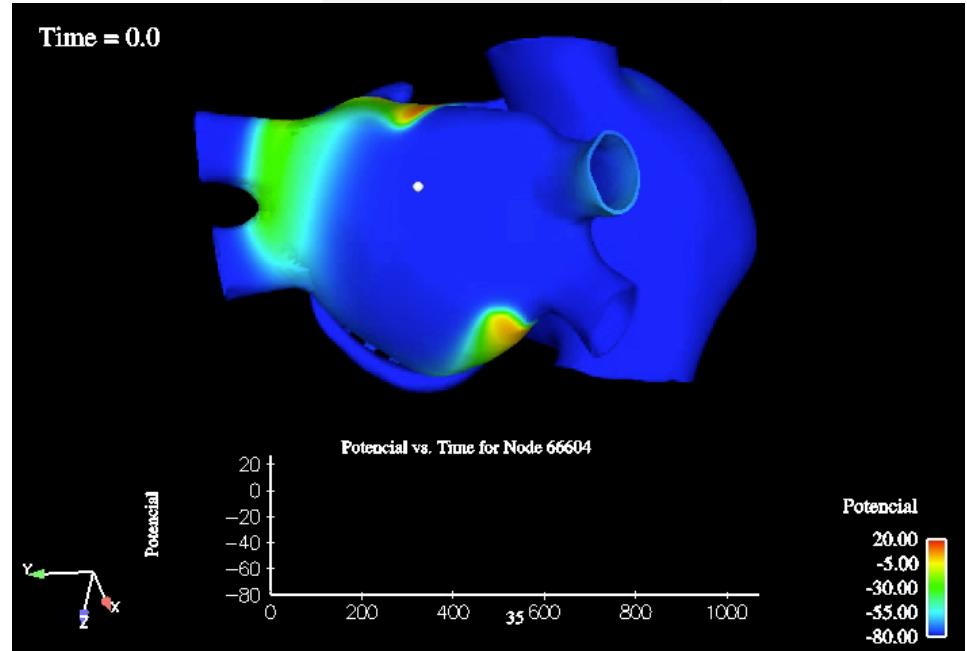
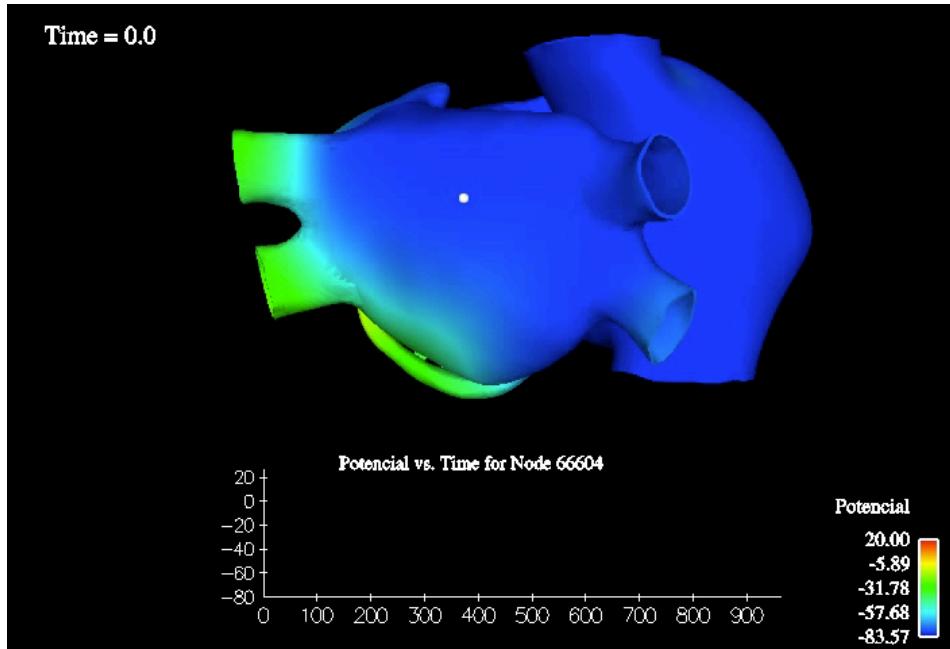


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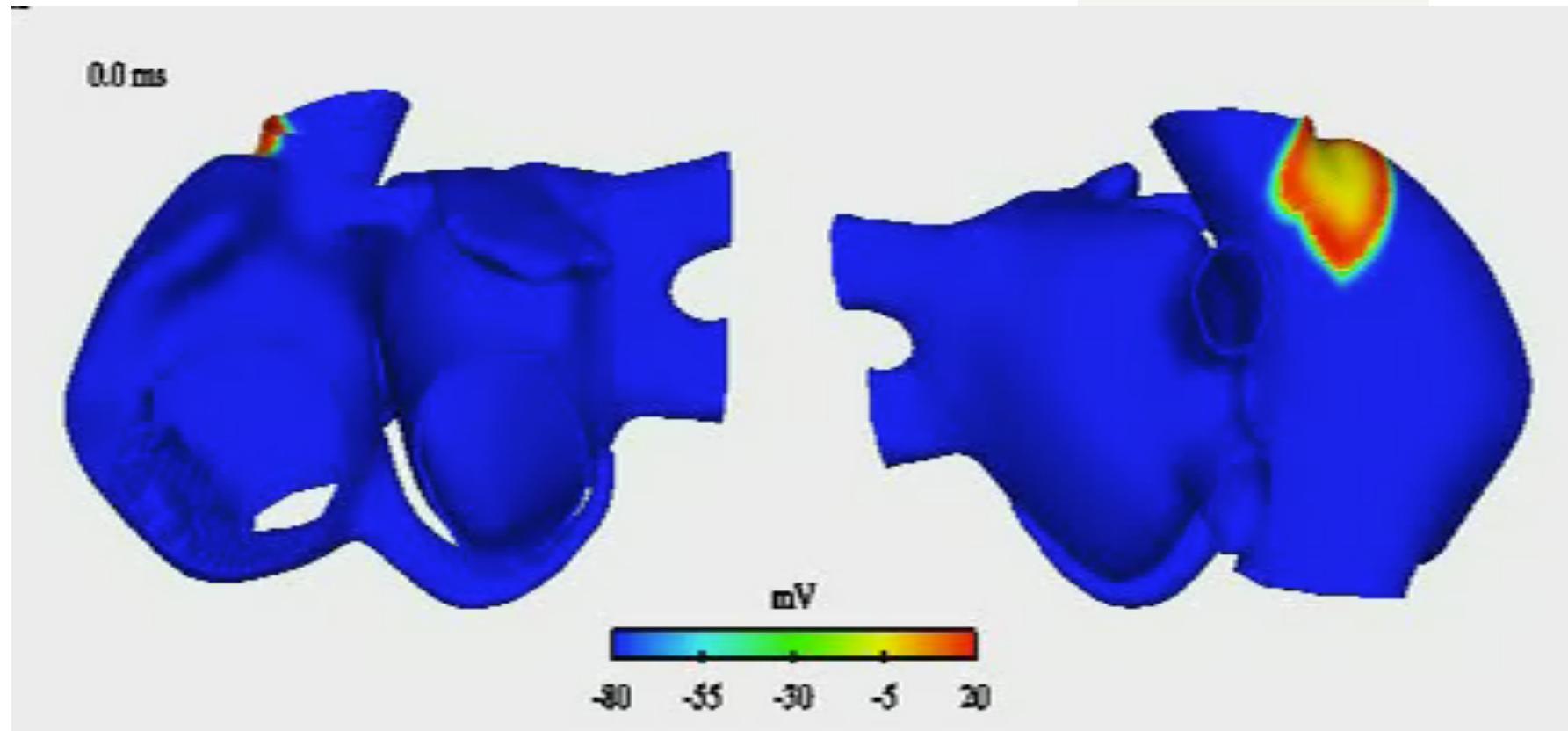
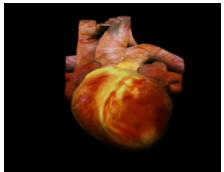
# CASO 2. ARRITMIAS AURICULARES

## Fibrilación auricular



# CASO 2. ARRITMIAS AURICULARES

## Foco ectópico en VPD



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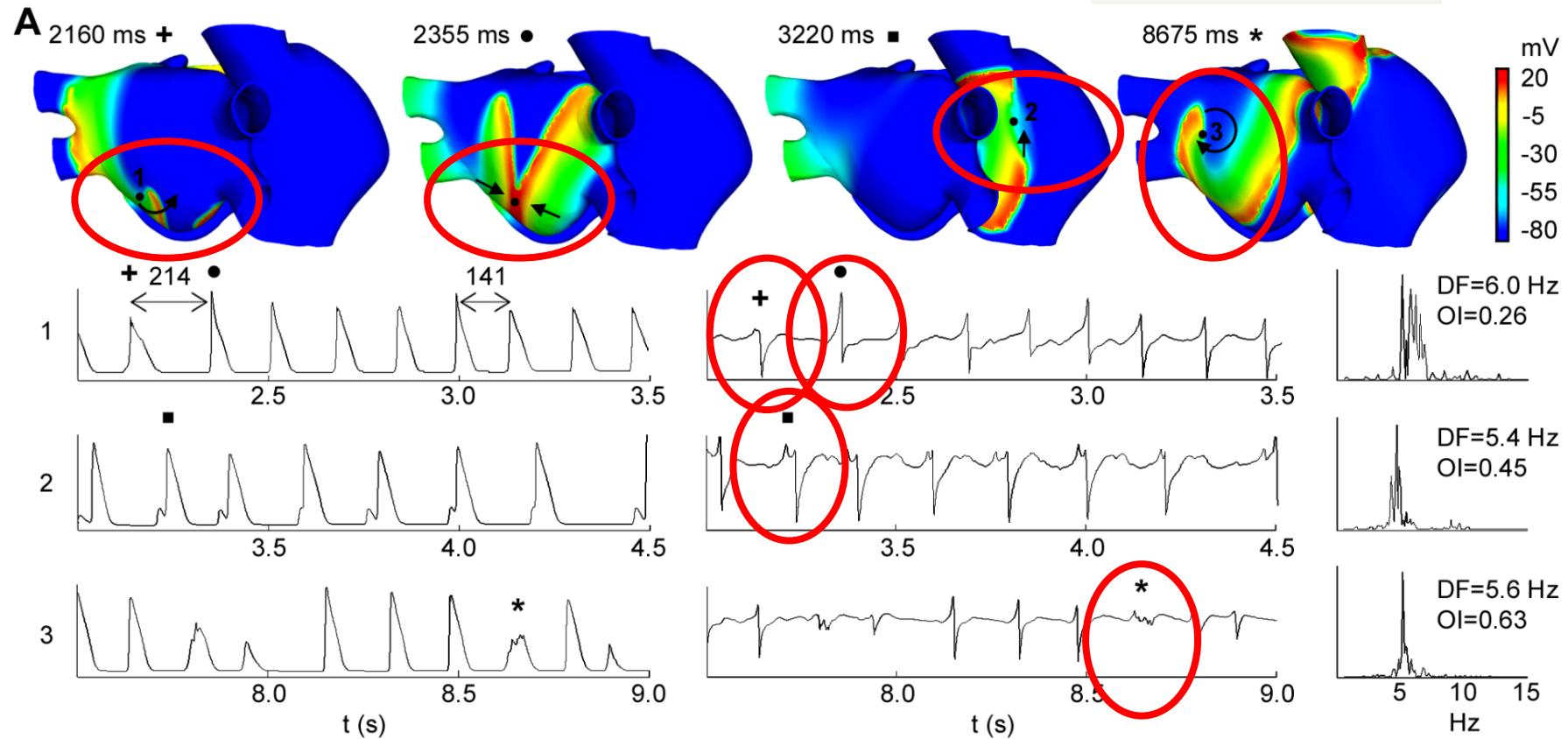


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# CASO 2. ARRITMIAS AURICULARES

## Foco ectópico en VPD



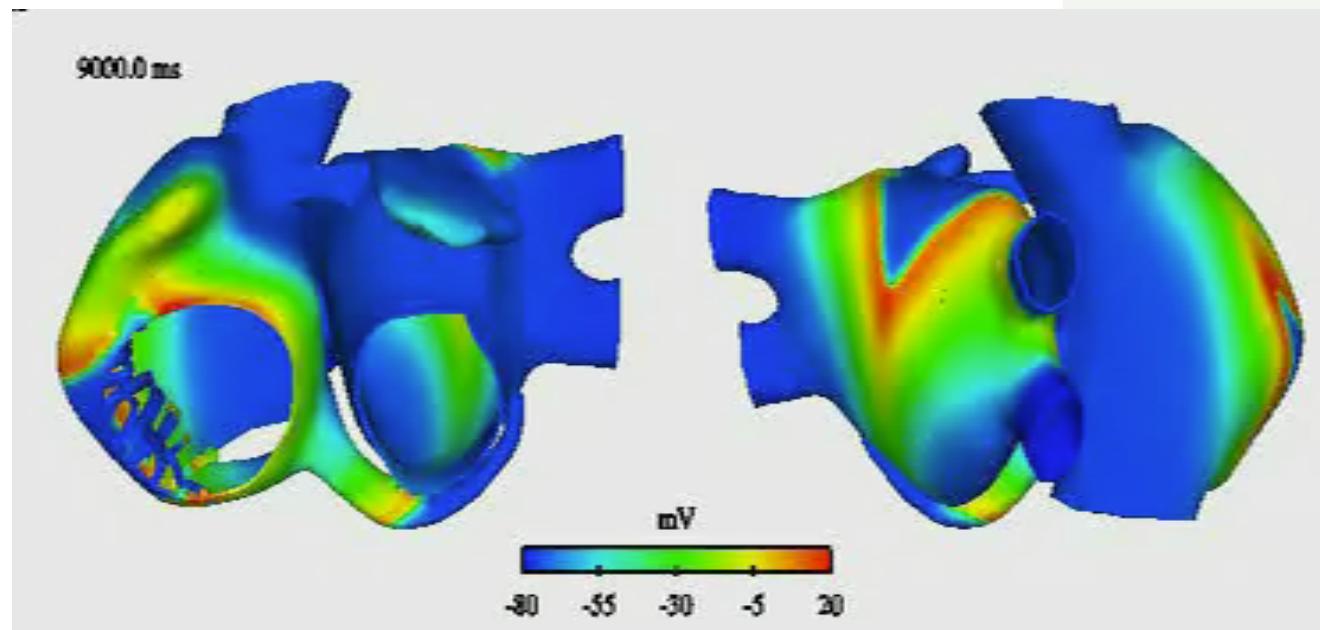
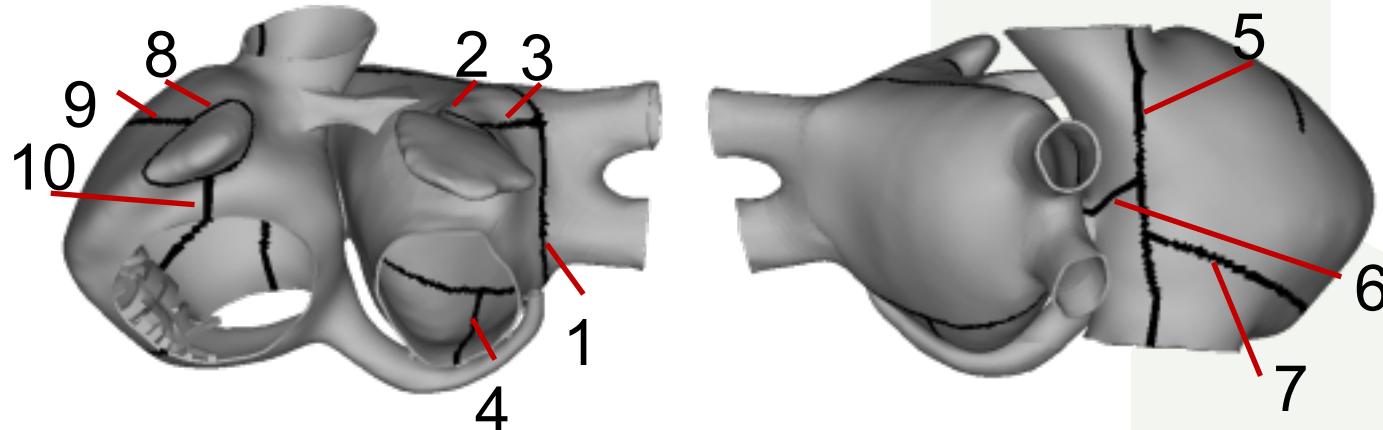
Tobón C., Ruiz-Villa C.A., Heidenreich E., Romero L., Hornero F., Saiz J.  
*A Three-Dimensional Human Atrial Model with Fiber Orientation. Electrograms and Arrhythmic Activation Patterns Relationship* PLOS ONE, 2010

# CASO 2. ARRITMIAS AURICULARES

## Foco ectópico en VPD

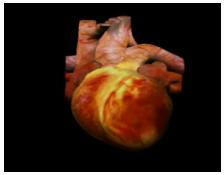


Maze III

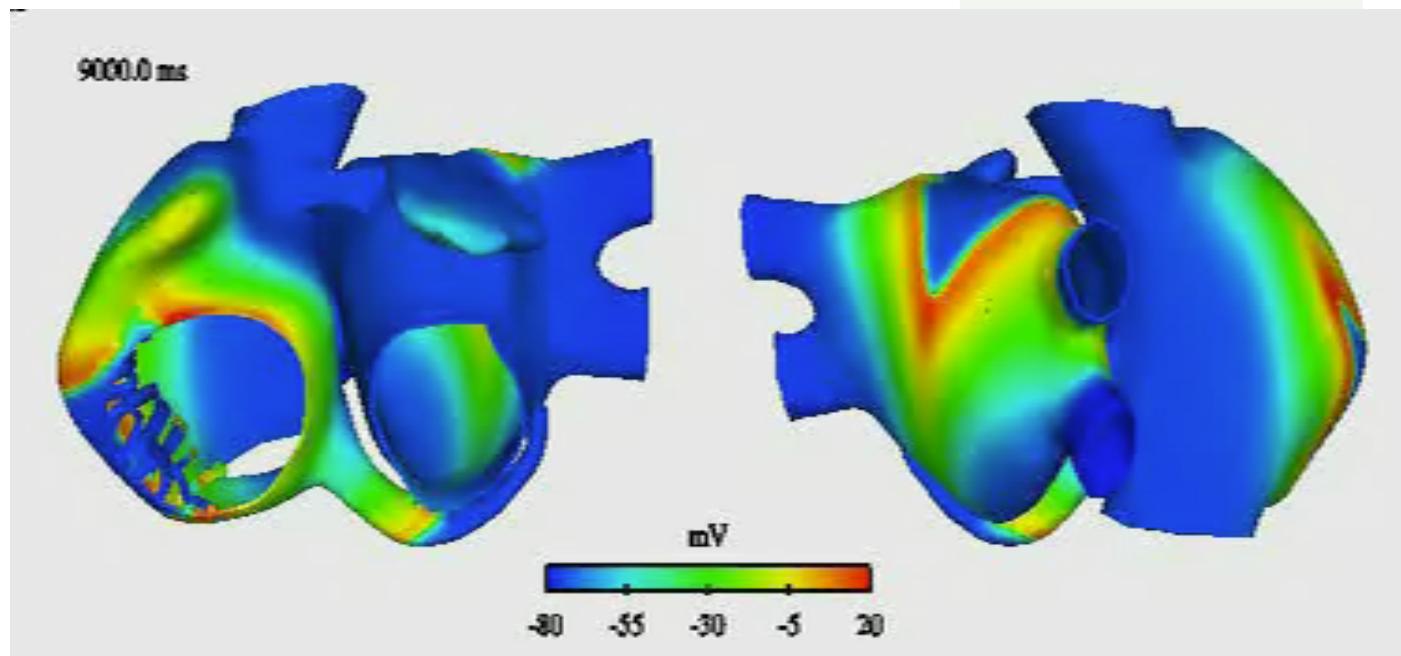
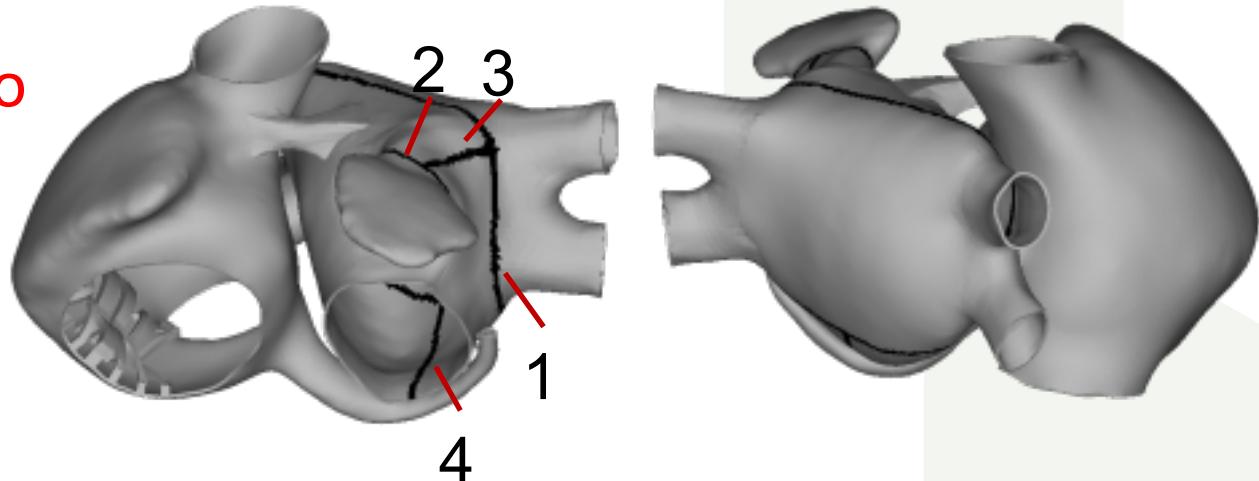


# CASO 2. ARRITMIAS AURICULARES

## Foco ectópico en VPD



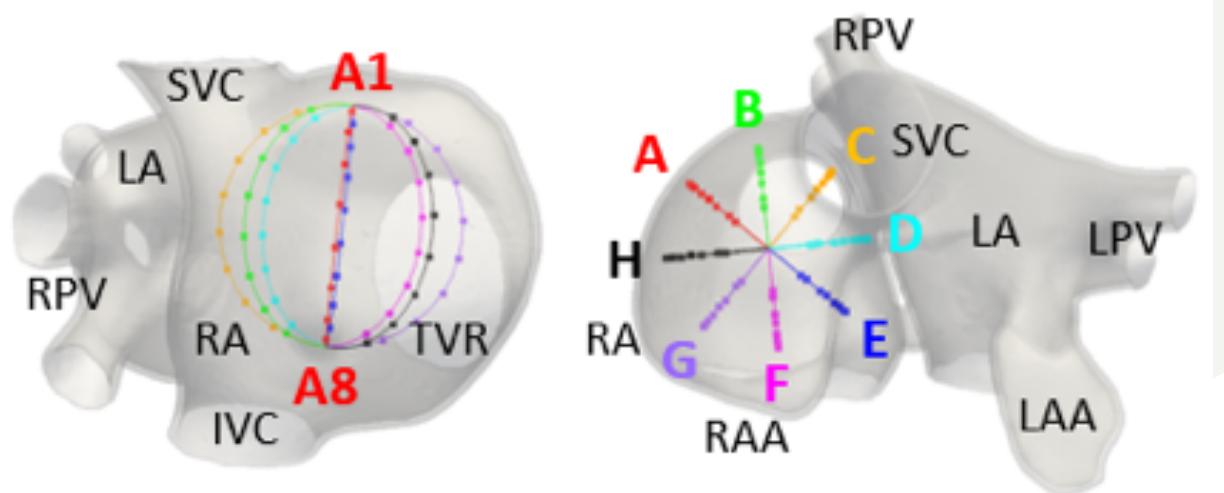
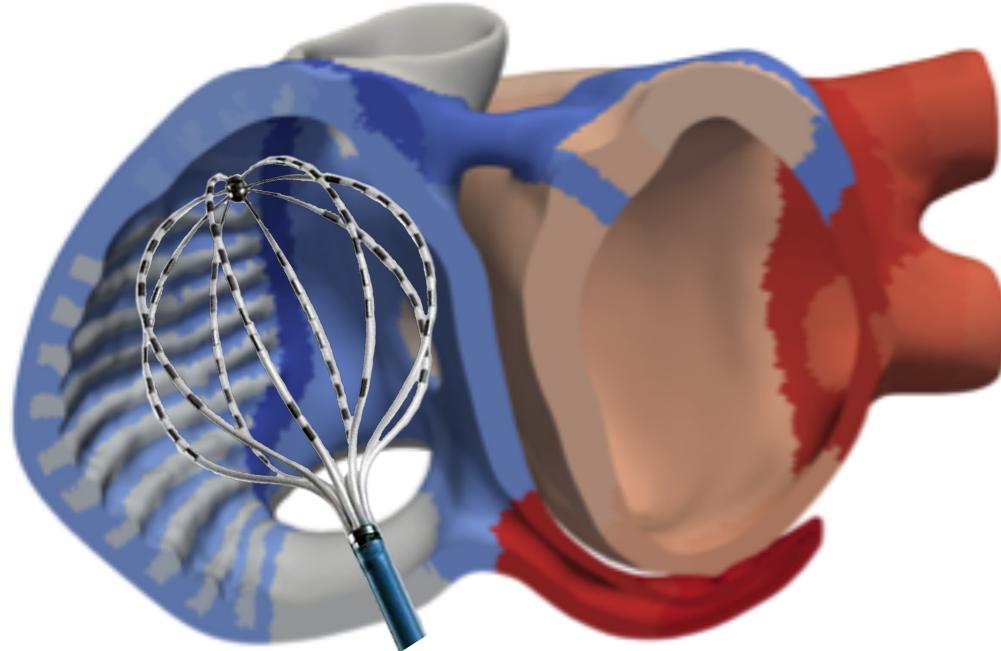
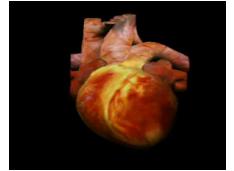
Maze parcial izquierdo



Saiz J., Tobón C.,  
*Supraventricular Arrhythmias in a  
realistic 3D Model of the Human  
Atria.*  
Cardiac Electrophysiology. From Cell  
to Bedside. 6th Edition.  
Ed. Dr Zipes and Dr Jalife

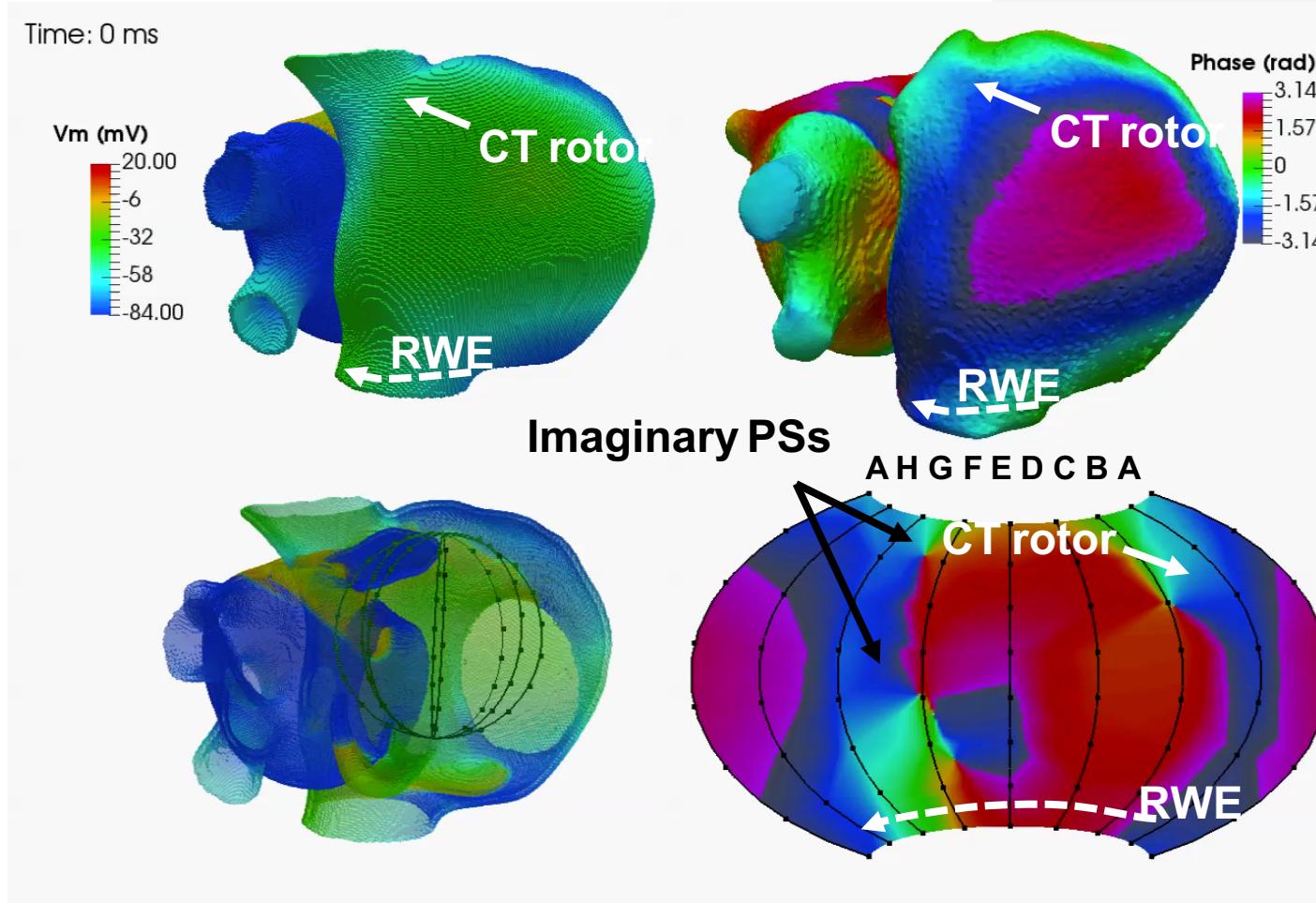
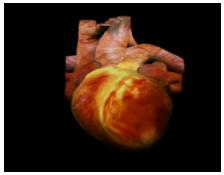
# CASO 2. ARRITMIAS AURICULARES

## Mapeo de rotores



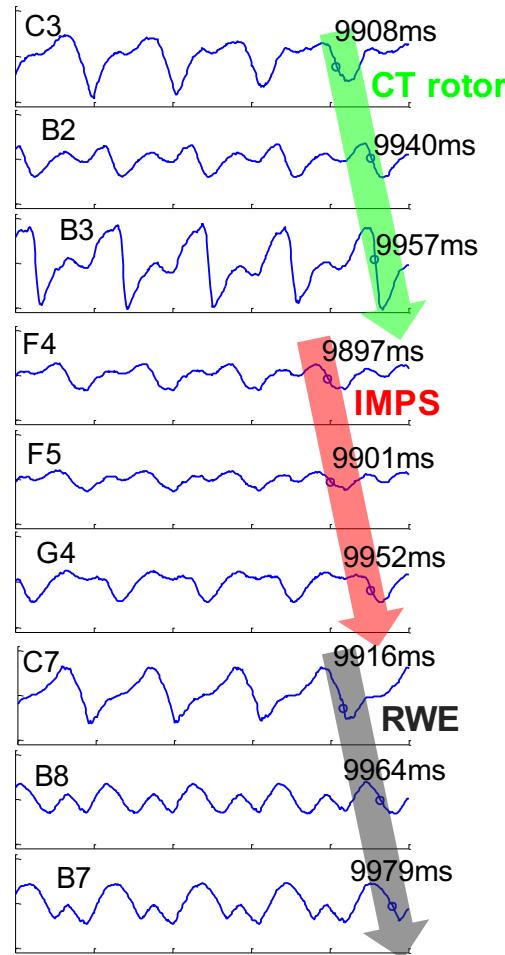
# CASO 2. ARRITMIAS AURICULARES

## Mapeo de rotores

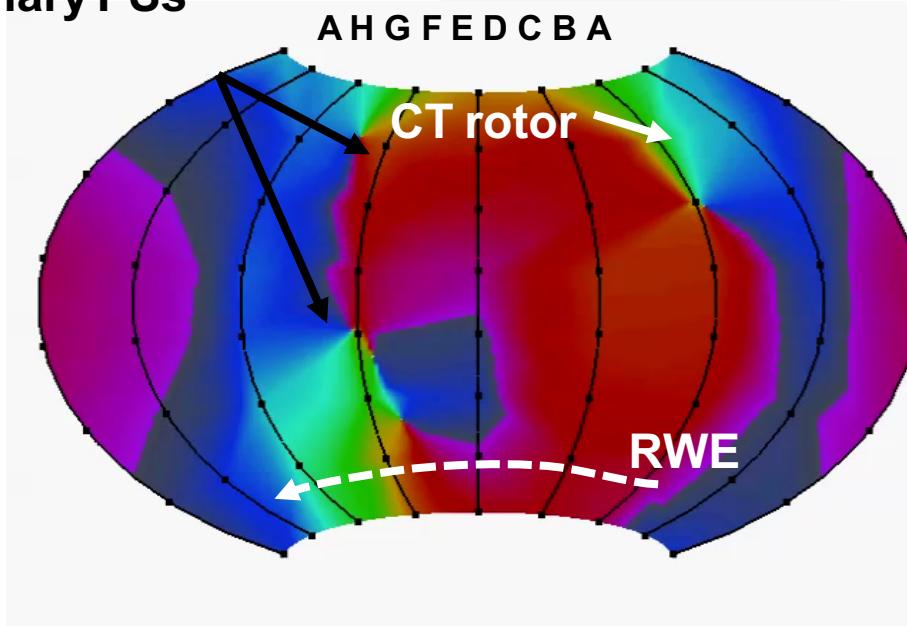


# CASO 2. ARRITMIAS AURICULARES

## Mapeo de rotores



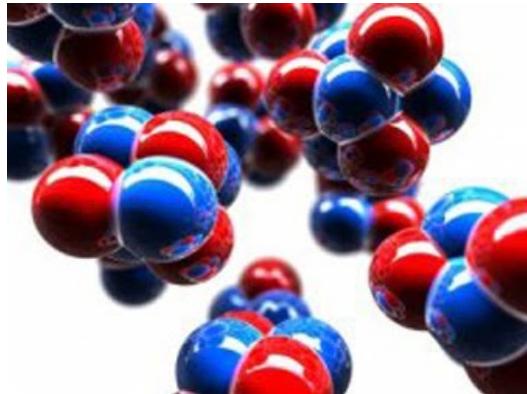
Imaginary PSs



Martinez-Mateu L., Romero L., Ferrer-Albero A., Sebastian R., Rodriguez-Matas J.F., Jalife J., Berenfeld O., Saiz J.  
*Factors affecting basket catheter detection of real and phantom rotors in the atria: A computational study.*

PLOS Computational Biology, en revision.

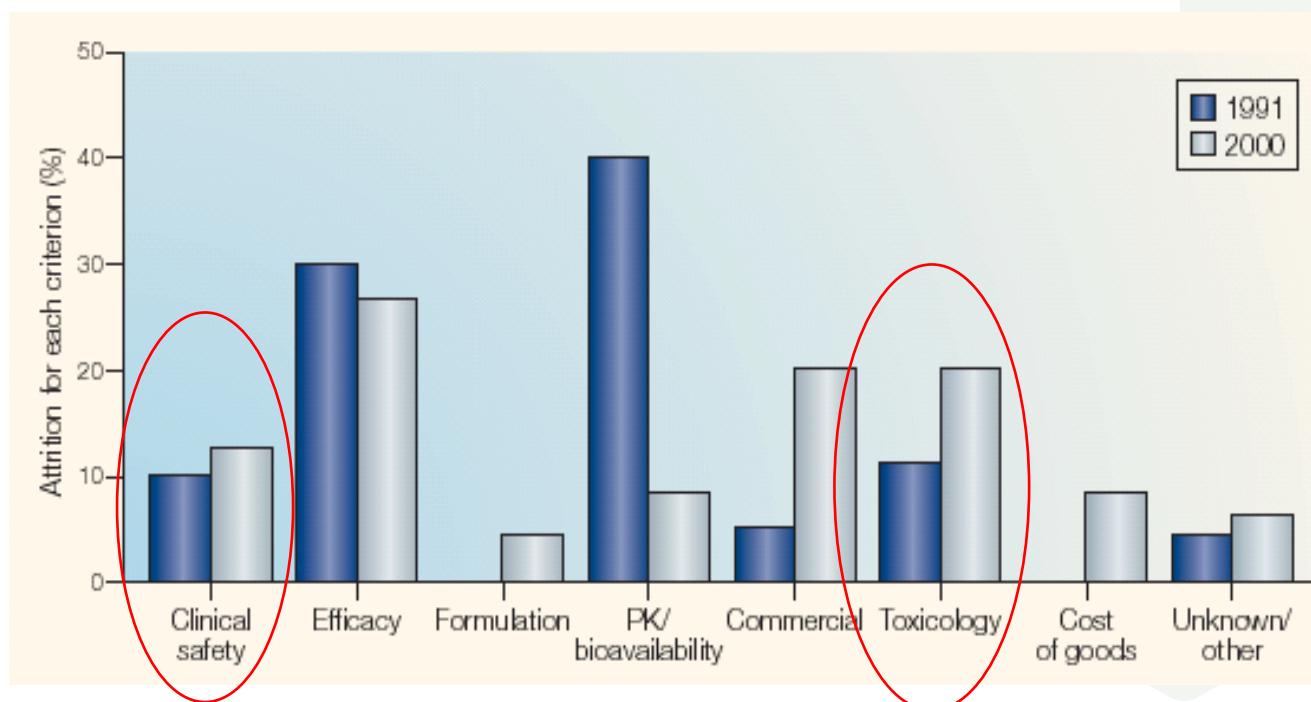
## CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS



- ◆ La utilización de fármacos es una de las terapias más extendidas en el tratamiento de diferentes patologías.
- ◆ Sin embargo, muchos de estos fármacos pueden inducir arritmias cardíacas, incrementando el riesgo de mortalidad.

# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

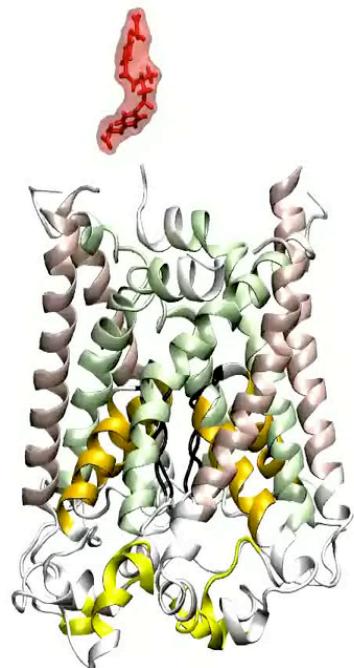
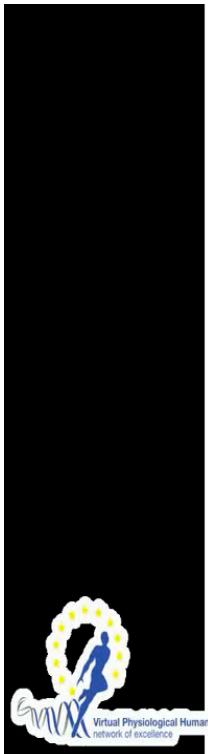
- ◆ Biomarcadores obtenidos en ensayos preclínicos y clínicos
- ◆ Estos **biomarcadores** tienen limitaciones y presentan FN (fármacos peligrosos alcanzan el mercado) y FP (fármacos beneficiosos no alcanzan el mercado).



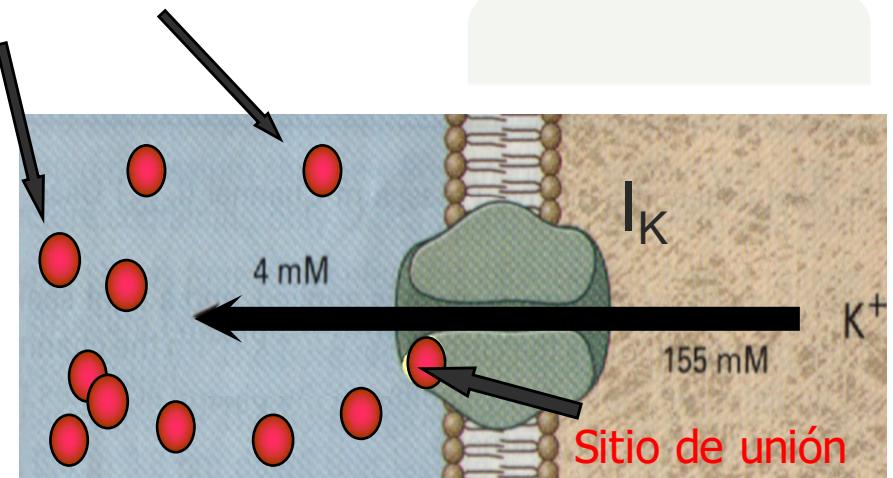
Kola and Landis 2004

# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

## Ensayos virtuales



Moléculas de fármaco



Fármacos modifican la conductancia de los canales



RESEARCH  
PROGRAMME  
ON BIOMEDICAL  
INFORMATICS

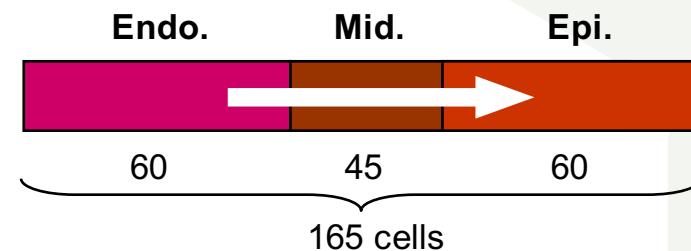
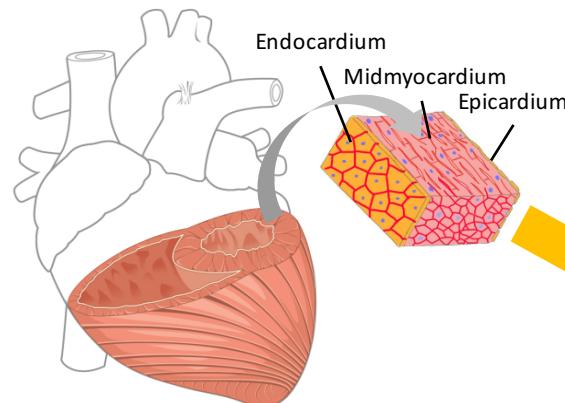
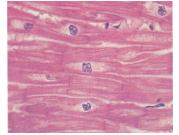


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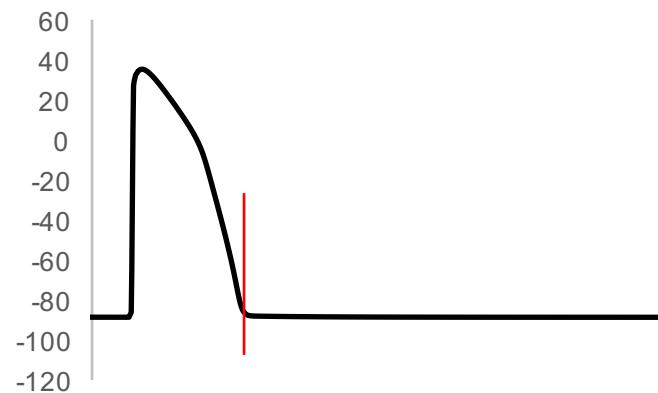


# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

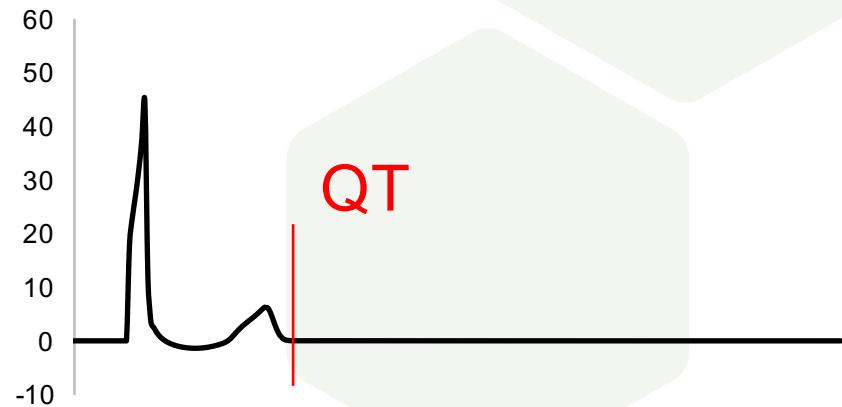
## Ensayos virtuales



PA

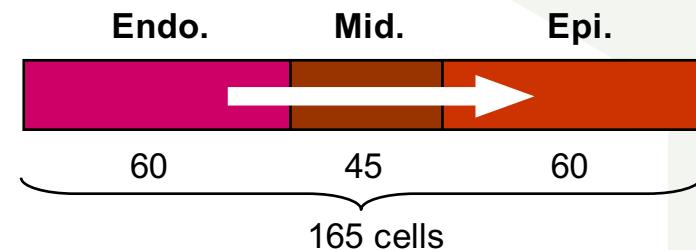
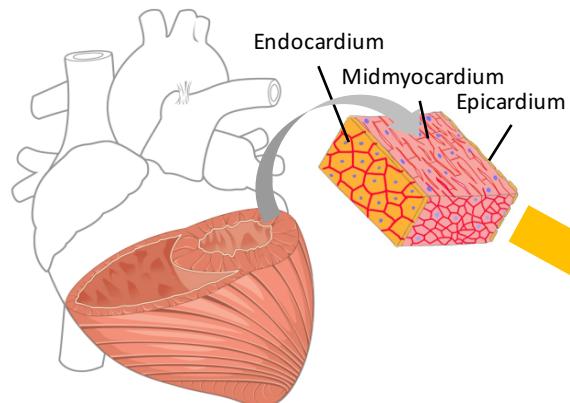
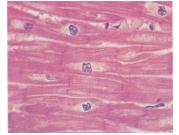


Pseudo ECG

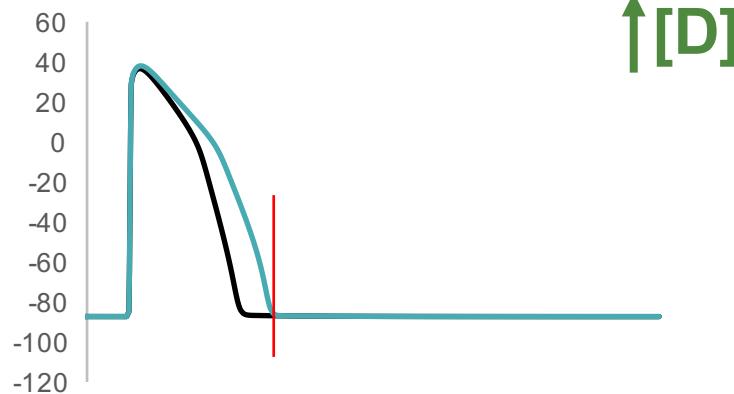


# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

## Ensayos virtuales

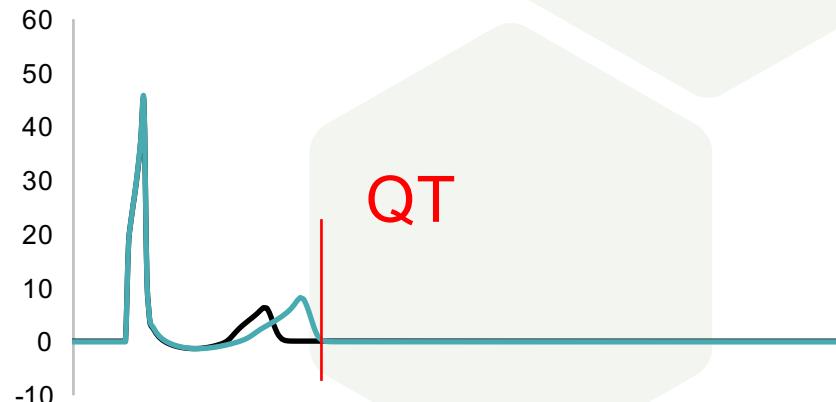


PA



↑[D]

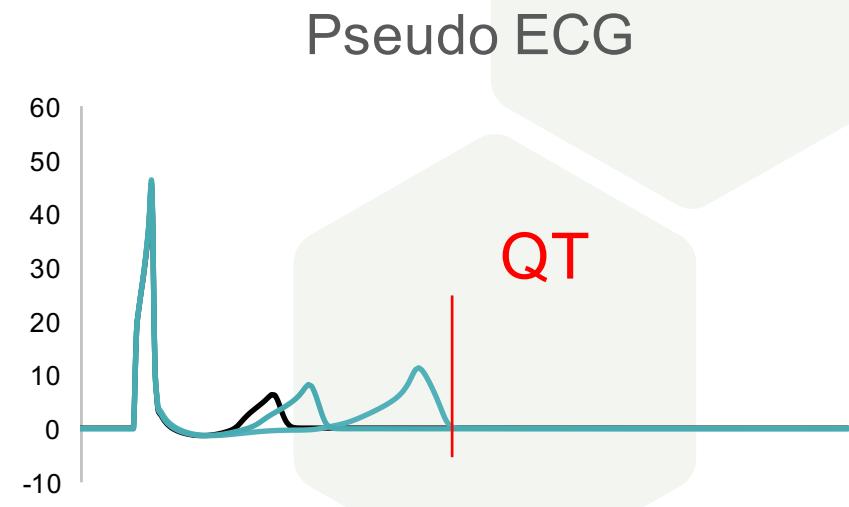
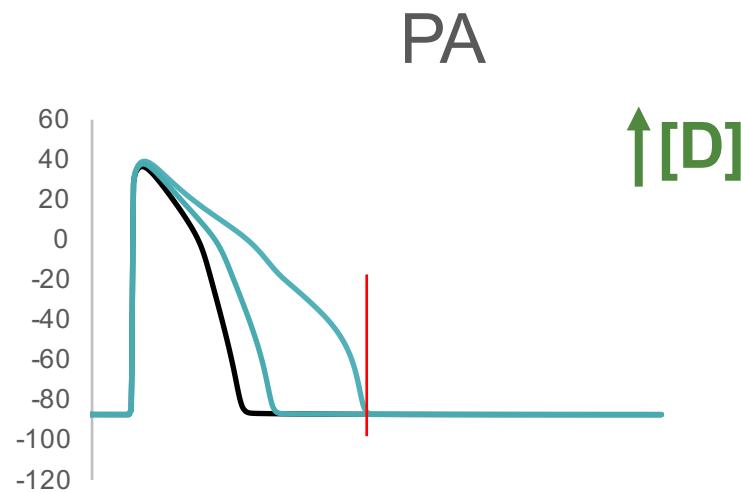
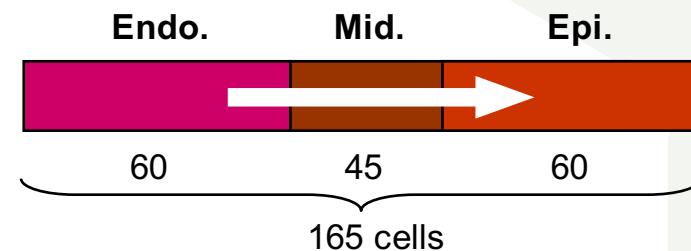
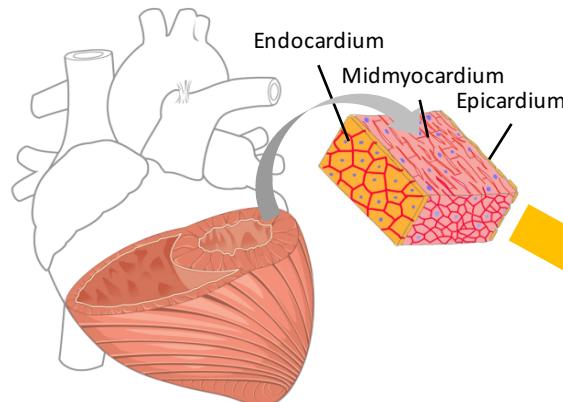
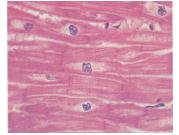
Pseudo ECG



QT

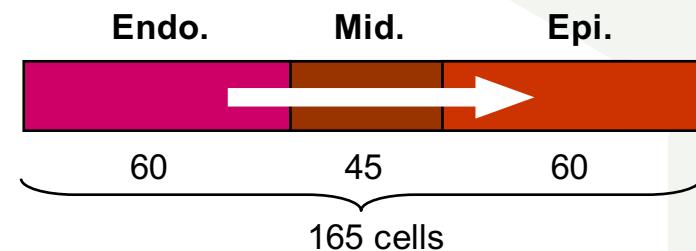
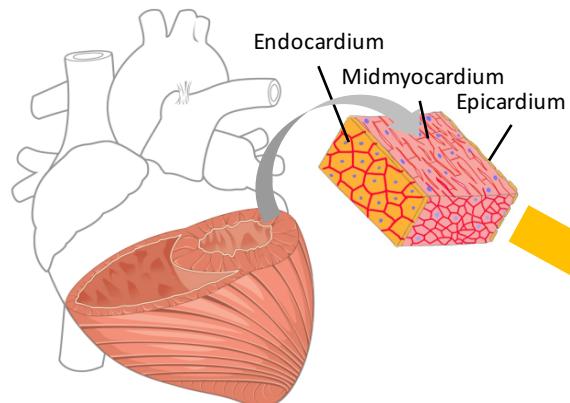
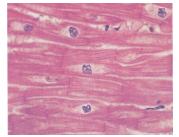
# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

## Ensayos virtuales

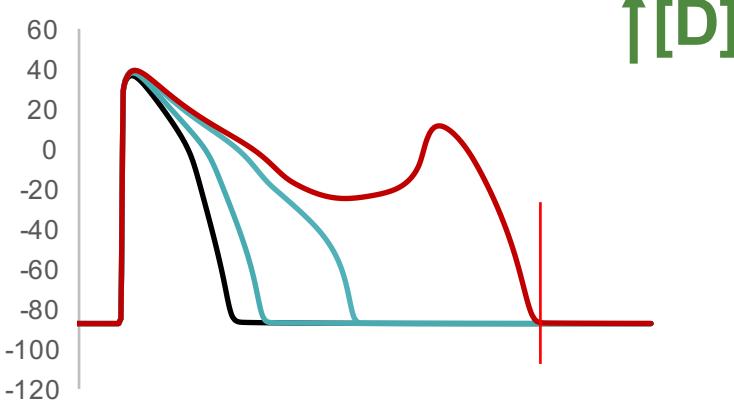


# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

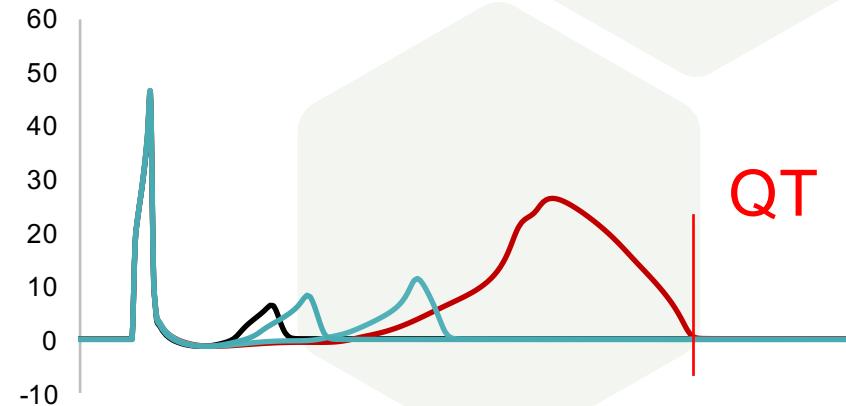
## Ensayos virtuales



PA

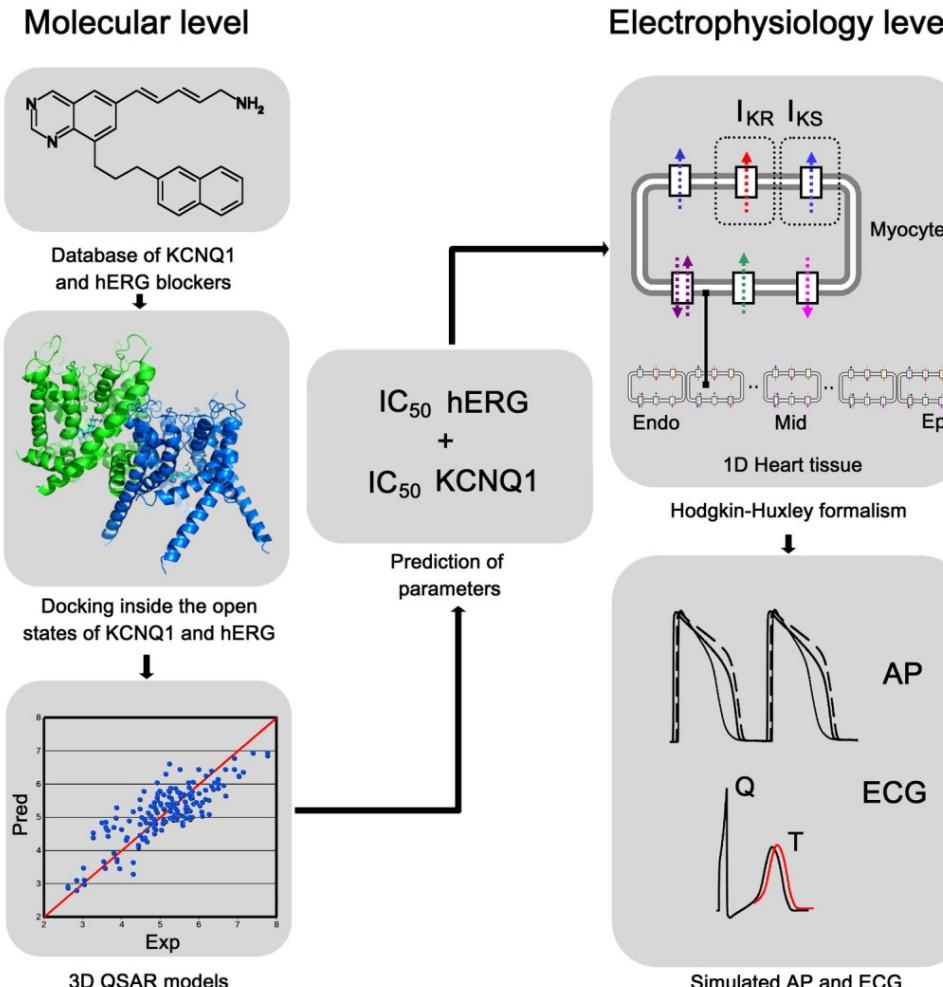


Pseudo ECG



# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS

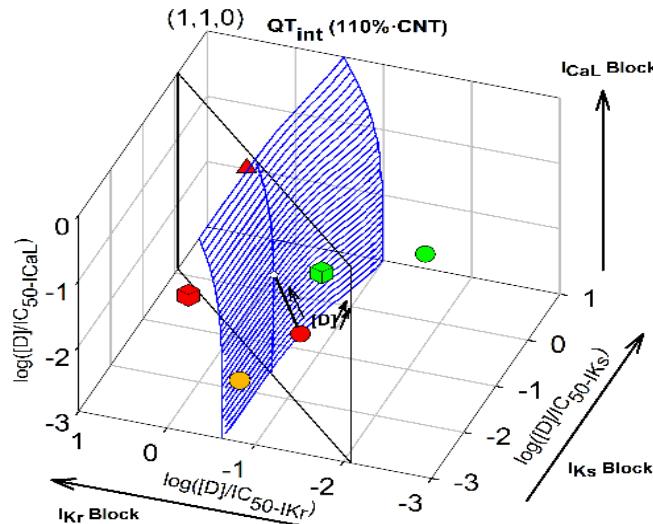
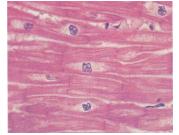
## Desarrollo virtual de fármacos



Obiol-Pardo C., Gomis-Tena J., Sanz F., Saiz J., Pastor M  
*A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity*  
Journal of Chemical Information and Modelling 2011, 51:483-492

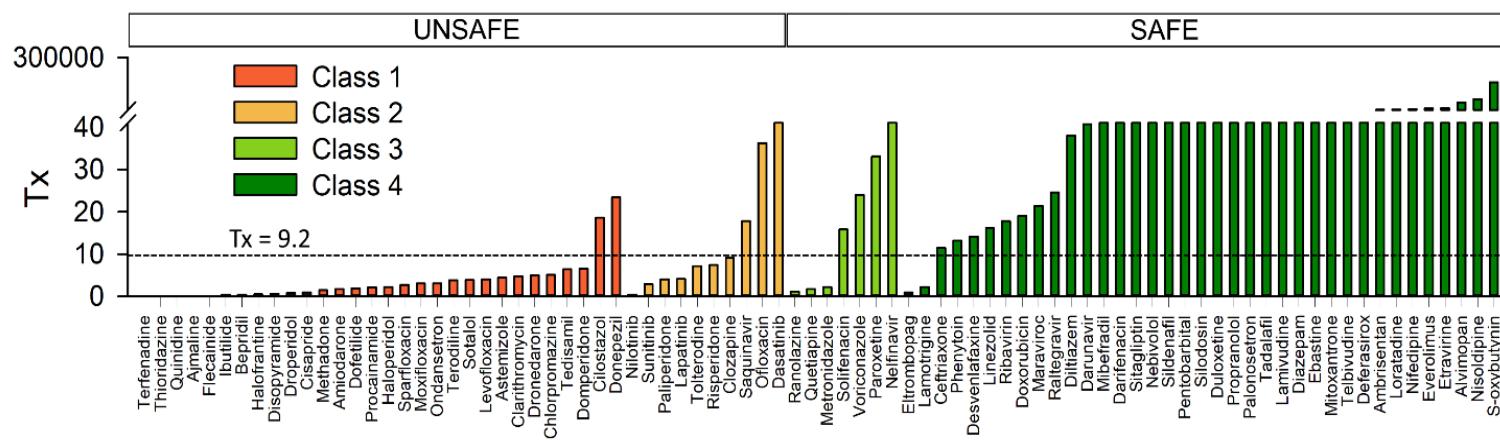


# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS



	TdP+	TdP-
+	22	5
-	18	39
<b>A</b>	TPR	TNR
0.73	0.55	0.89

**Riesgo basado en hERG**  
**Seguro pIC50 <6**



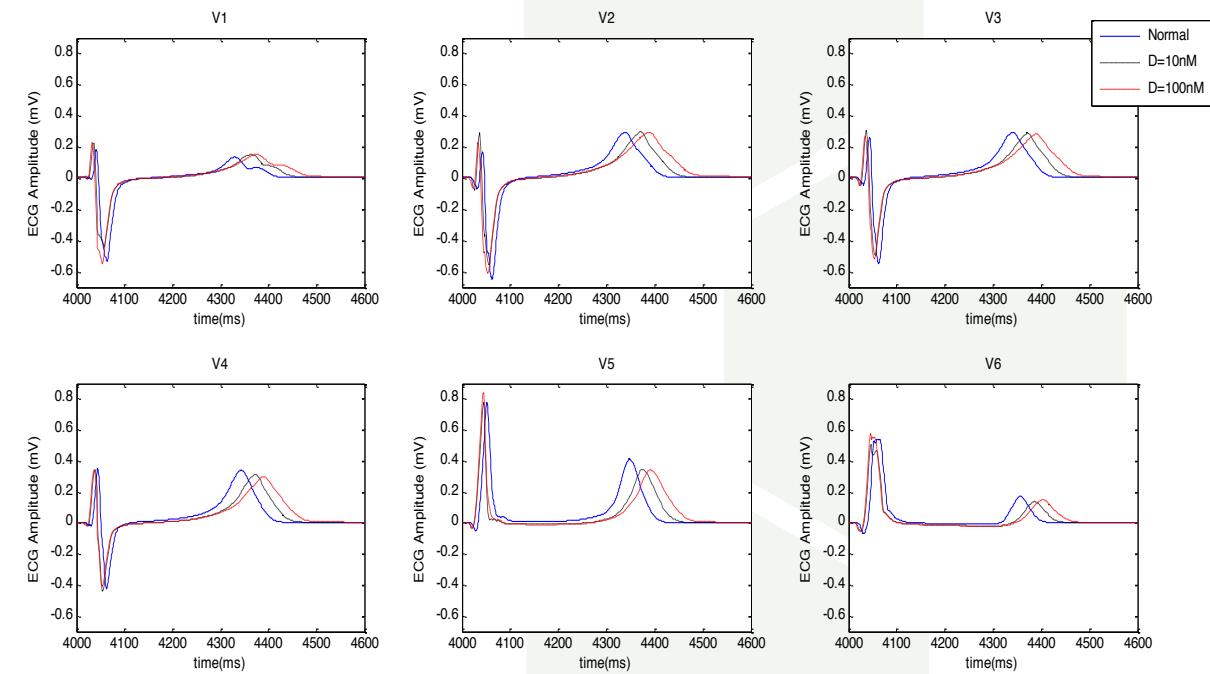
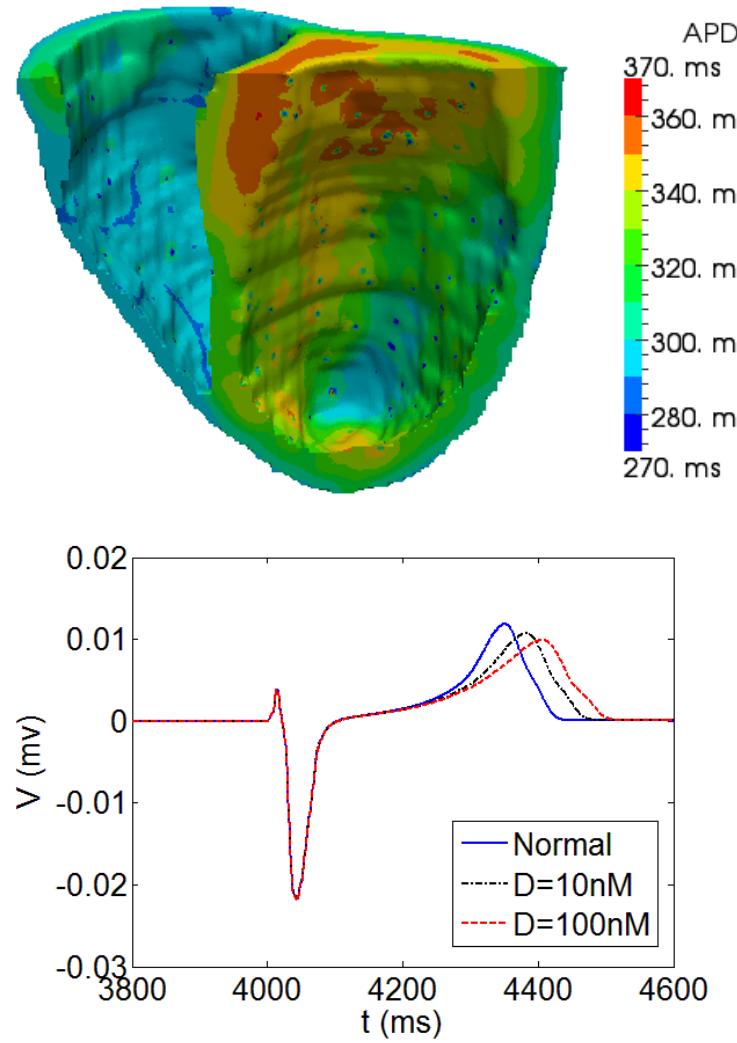
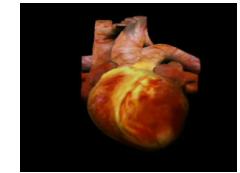
Romero L., Cano J., Gomis-Tena J., Trenor B., Sanz J., Pastor M., Saiz J.

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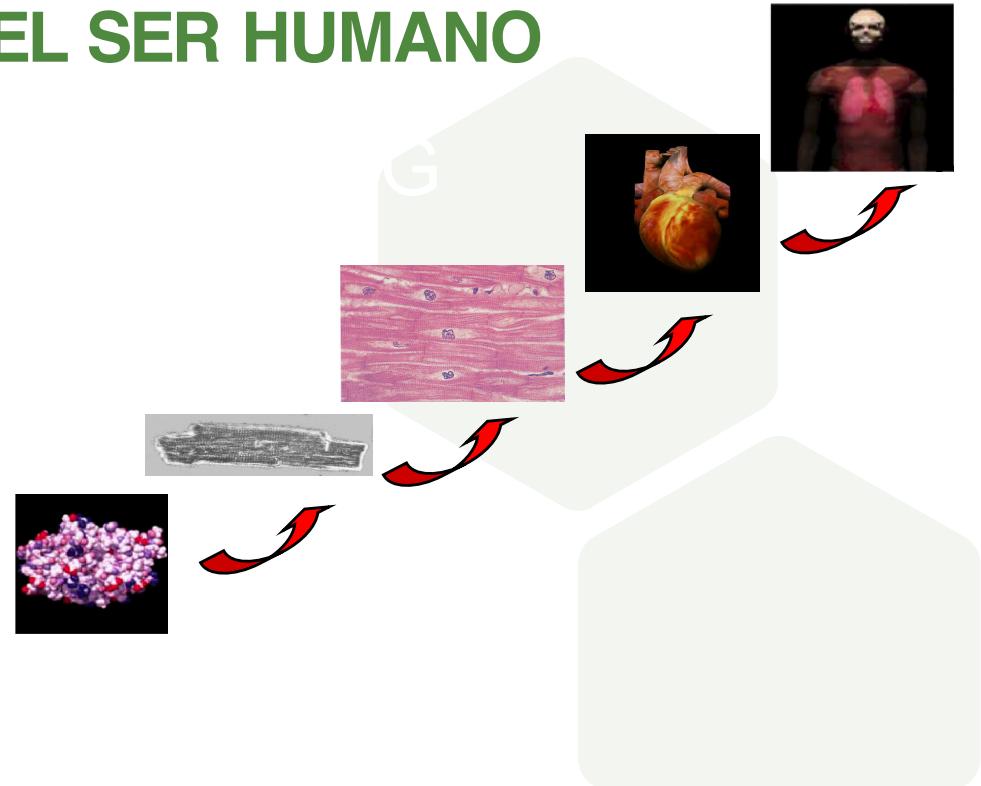
Journal of Chemical Information and Modelling, segunda revisión



# CASO 3. PRO-ARRITMICIDAD DE LOS FÁRMACOS



# MODELO MULTIESCALA DEL SER HUMANO



## Medicina Computacional

*Virtual Physiological Human*

*International Union of Physiological Societies (IUPS)*

# AGRADECIMIENTOS

## Miembros Ci<sup>2</sup>B

Chema Ferrero  
Beatriz Trenor  
Lucia Romero  
Julio Gómis-Tena  
Rafael Sebastián

## Alumnos

Sara Rocher  
Alejandro López  
Maite Mora  
Jordi Cano  
Jorge Sánchez  
Laura Martínez  
Ana Ferrer  
Juan F. Gómez  
Catalina Tobón  
Rodolfo González  
Oscar A. Henao  
Carlos A. Ruiz  
Esteban Ramírez  
Marta Monserrat  
Vicente Torres  
Edison Carpio  
Karen Cardona

## Colaboradores Externos

José Jalife  
Omer Berenfeld  
Denis Noble  
Wayne Giles  
Collen Clancy  
Igor Efimov  
Andras Varro  
Blanca Rodríguez  
Javier Chorro  
Felipe Atienza  
Jesús Almendral  
Fernando Hornero  
Damián Sánchez-Quintana  
Ricardo Ruiz  
Manuel Pastor



# CORAZÓN VIRTUAL: APLICACIÓN DE LOS MODELOS MATEMÁTICOS EN EL ESTUDIO Y TRATAMIENTO DE LAS ARRITMIAS

Discurso de entrada como Académico Correspondiente

**Francisco Javier Saiz Rodríguez**



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POLITÈCNICA  
DE VALÈNCIA