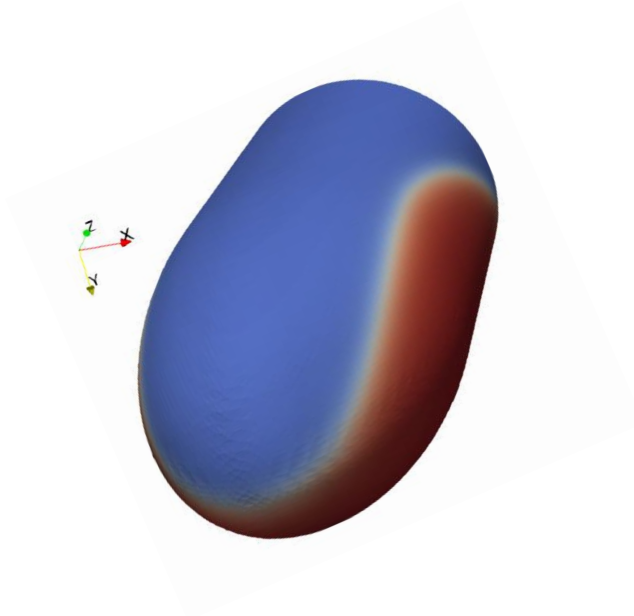

FROM CARDIAC STEM CELL IONIC MODELS TO ISOGEOMETRIC SIMULATIONS OF 3D CARDIAC TISSUE

Sofia Botti

UNIPV-USI Ph.D. Program in Computational mathematics and decision sciences
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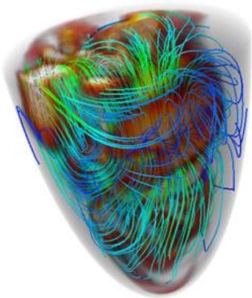
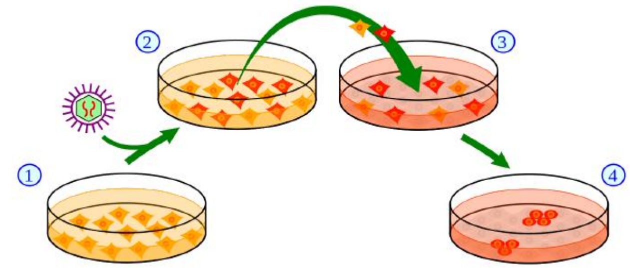
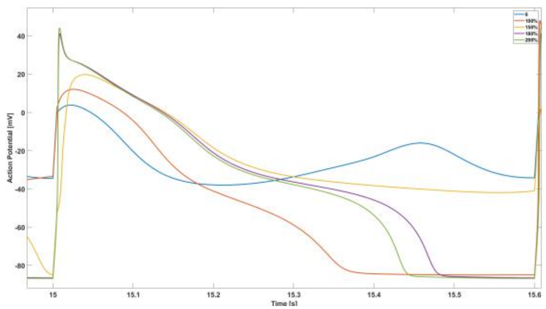
Spring Workshop 2022
March 16-17



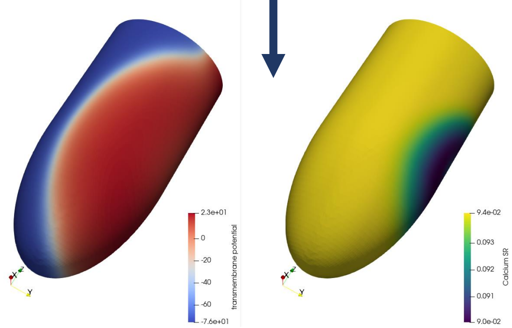
Cardiac physiology formalism and mathematical models



Human induced pluripotent stem cell and regenerative medicine



New generation of ionic models



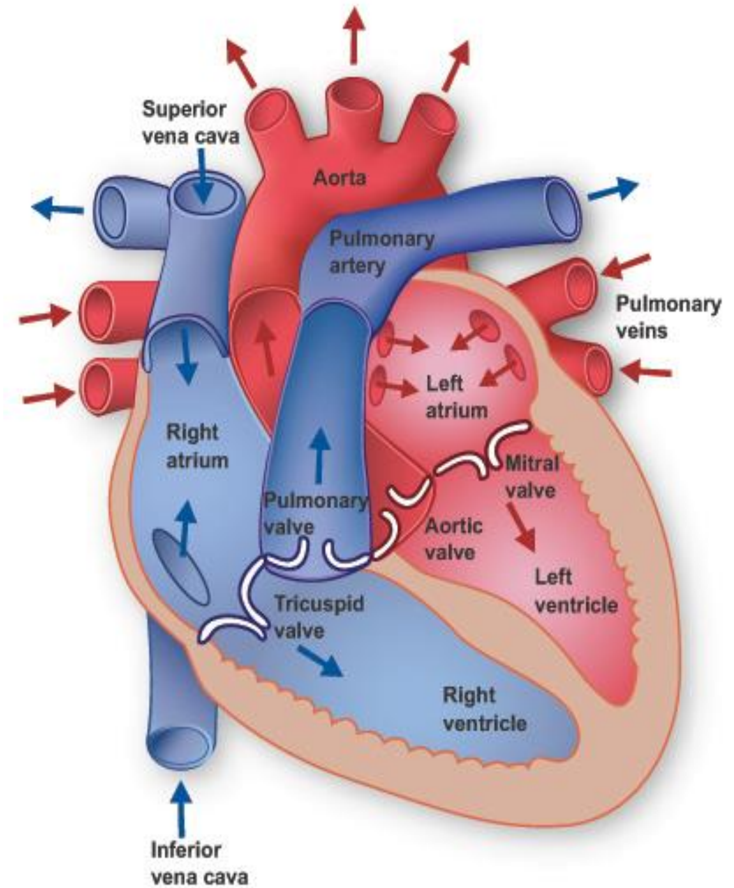
3D simulations of cardiac tissue, using isogeometric analysis framework

Elements of Cardiac Physiology

Cardiac physiology studies the healthy (or unimpaired) cardiac function of the heart.

This includes:

- The electrical conduction system
- The myocardium structure (relaxation and contraction)
- Blood flow
- Valves
- Mutual interaction of components



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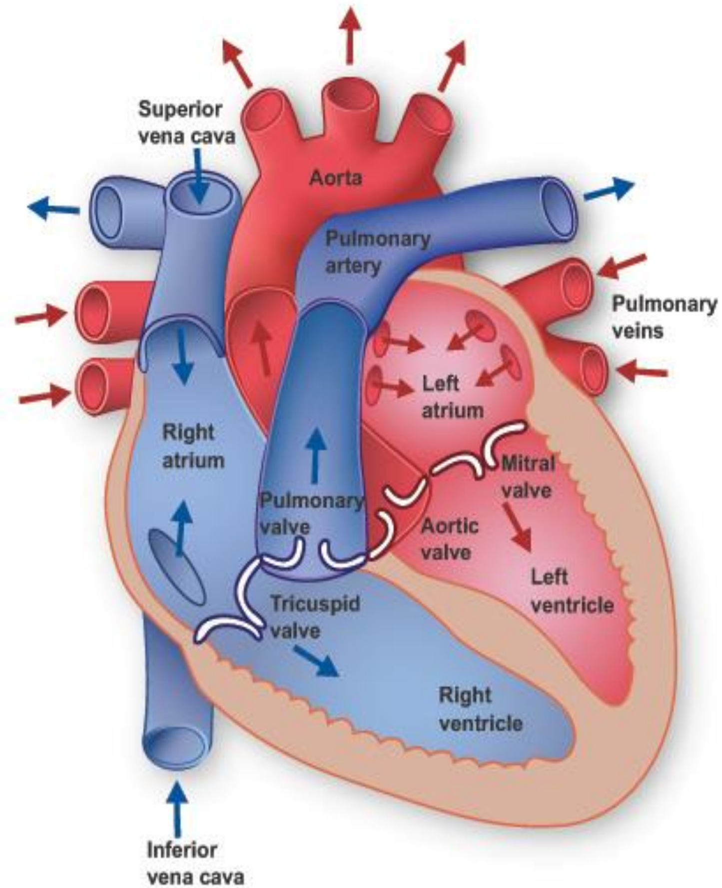
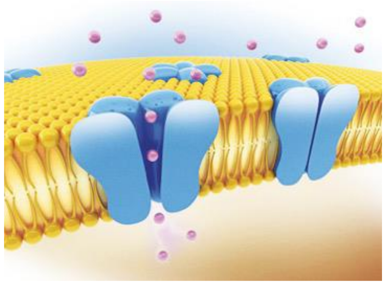
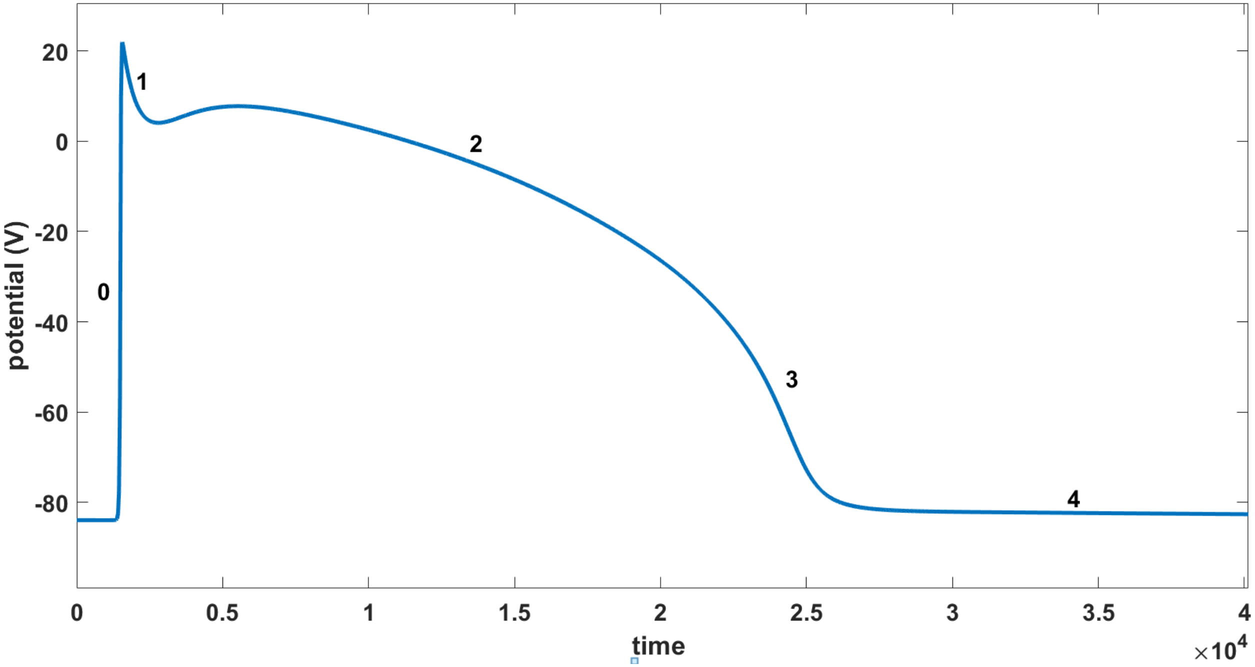


The Action Potential



Cardiomyocytes are excitable cells, i.e. they have the ability to respond actively to electric stimuli. In resting condition, the cells maintain ionic concentrations (different from those outside).

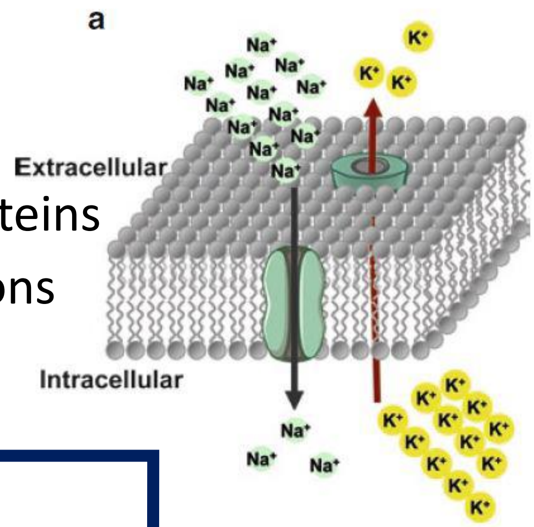
The action potential of charged ions through the membrane determines an electric potential difference across the membrane, called **transmembrane potential**.



This phenomenon is described by the **action potential**

0 Depolarization
1 Early repolarization
2 Plateau
3 Repolarization
4 Resting

Cardiac models

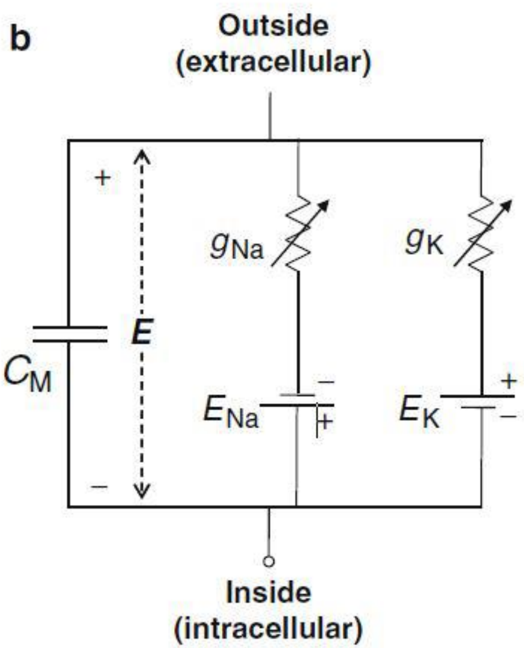


PHYSIOLOGICAL PERSPECTIVE

Cellular membrane = lipid bilayer in which are immersed proteins

Ionic channels = exchangers for the flow of Na^+, K^+, Ca^{2+} ions

Electrical activity modeled by a resistor-capacitor circuit + Conservation law, Definition of capacitance



$$C_m \frac{dv}{dt} + I_{ion} = I_{app}$$

General equation that describes the electrical activity of the cellular membrane, where:

C_m	membrane capacitance
v	voltage potential
I_{ion}	sum of ionic currents
I_{app}	applied current

Mathematical formulation

The modern and general cardiac membrane model, with N ionic currents, M gating variables and $\boldsymbol{w} = (w_1 \dots w_M)$, S ionic concentrations, $\boldsymbol{c} = (c_1 \dots c_s)$, can be written as a system of ODEs

$$\begin{cases} C_m \dfrac{dv}{dt} + I_{ion}(v, \boldsymbol{w}, \boldsymbol{c}) = I_{app} \\ \dfrac{d\boldsymbol{w}}{dt} = R(v, \boldsymbol{w}) \\ \dfrac{d\boldsymbol{c}}{dt} = S(v, \boldsymbol{w}, \boldsymbol{c}) \\ v(0) = v_0, \qquad \boldsymbol{w}(0) = \boldsymbol{w}_0, \qquad \boldsymbol{c}(0) = \boldsymbol{c}_0, \end{cases}$$

Where R and S are specific functions, v_0, $\boldsymbol{w}_0, \boldsymbol{c}_0$ are the initial conditions and

$$I_{ion}(v, \boldsymbol{w}, \boldsymbol{c}) = \sum_{k=1}^{N} G_k(v, \boldsymbol{c}) \sum_{j=1}^{M} w_j^{p_{j_k}} \big(v - v_k(\boldsymbol{c})\big) + I_n(v, \boldsymbol{w}, \boldsymbol{c})$$

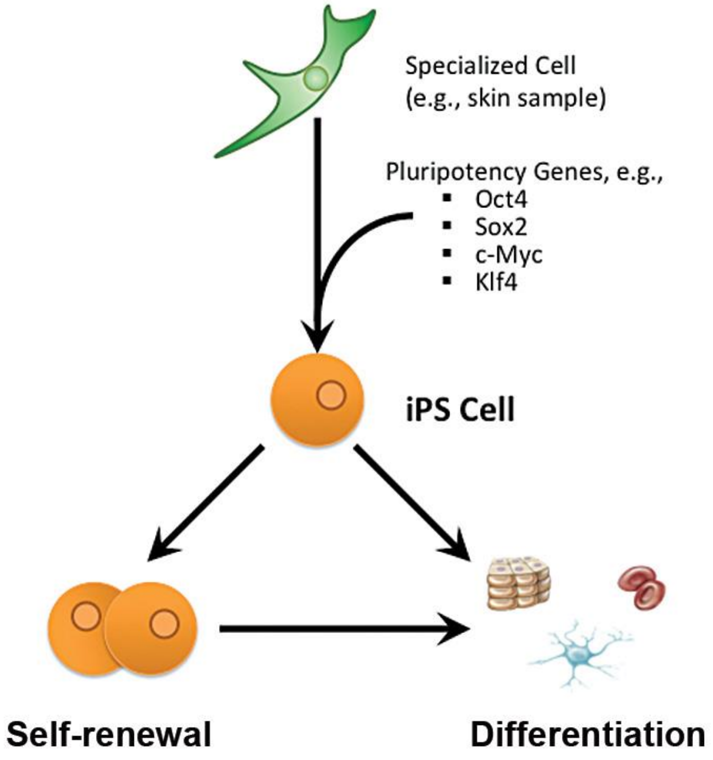
Cardiac stem cells ionic models

Human Induced Pluripotent Stem Cells (hiPSCs):

A kind of human pluripotent stem cells that can be directly generated from adult cells

- In 2006 S. Yamanaka and J. Gordon (Nobel Prize for Medicine), created iPSCs starting from mouse somatic cells

- hiPSCs can be propagated almost indefinitely and provide a constant source of differentiated cells, including Cardiac Myocytes (CMs)



S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embrionic and Adult Fibroblast Cultures by Dened Factors*, in Cell, 2006

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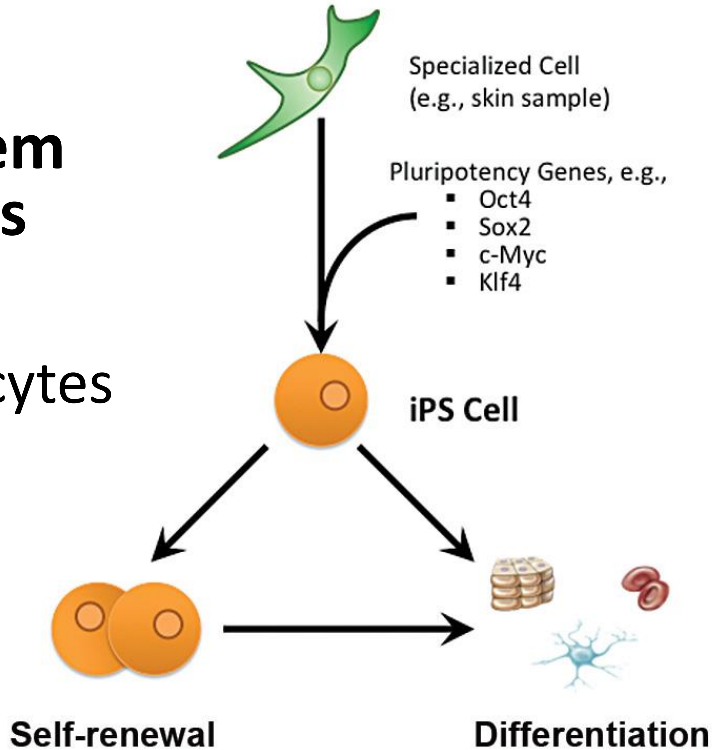
A kind of human pluripotent stem cells that can be directly generated from adult cells

Human Induced Pluripotent Stem Cells – derived cardiomyocytes (hiPSC-CMs):

Spontaneous beating cardiomyocytes derived from hiPSCs

They are functionally similar to adult human cardiomyocytes and exhibit expected responses to cardiac stimuli



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Ionic model for Ventricle-like hiPSC-CMs

The current model for hiPSC-CMs with a ventricle phenotype was published in 2018 by M. Paci and S. Severi.

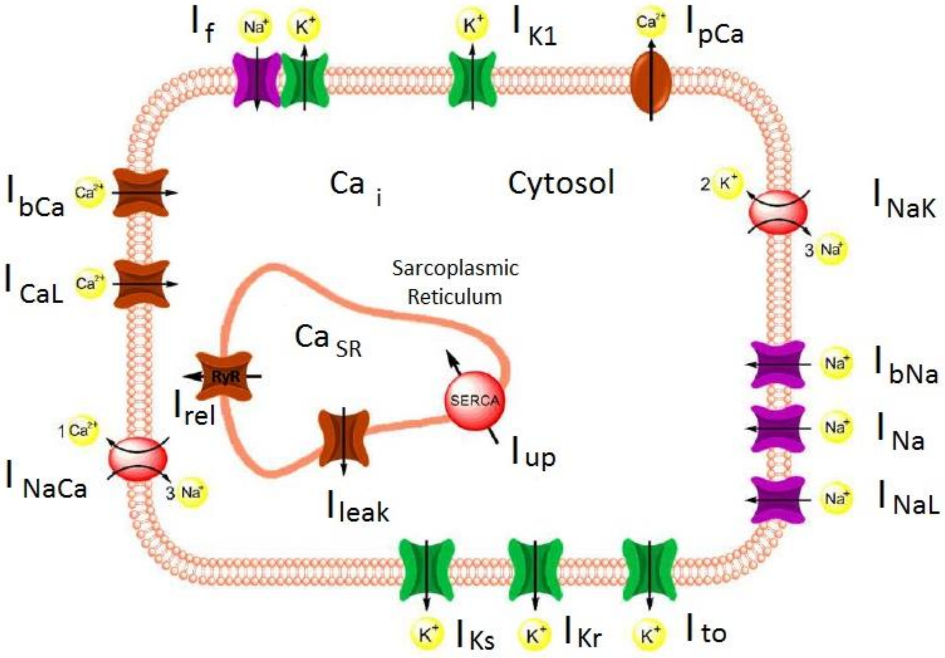
The model consists in a set of **22 ODEs for 22 variables**:

15 gating variables

for **membrane currents**

3 gating variables

involved in **calcium dynamic**



M. Paci et al., *Automatic Optimization of an in Silico Model of Human iPSC Derived Cardiomyocytes Recapitulating Calcium Handling Abnormalities*, in Frontiers in Physiology 9 (2018)

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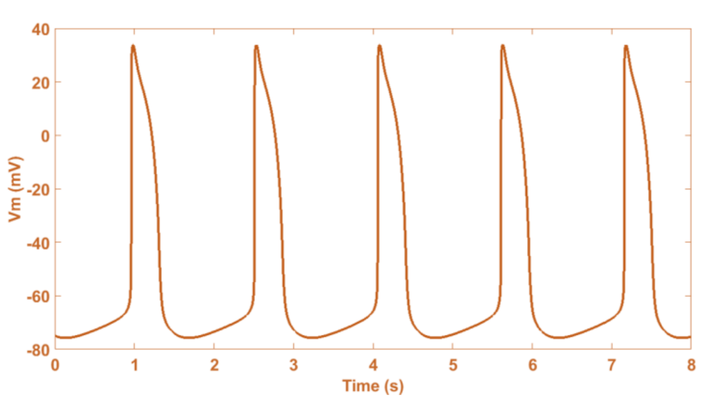
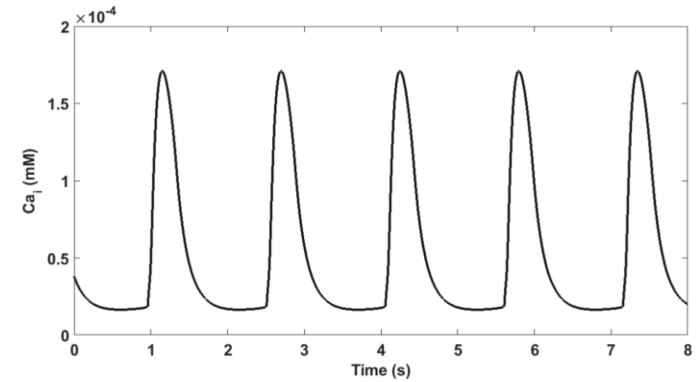
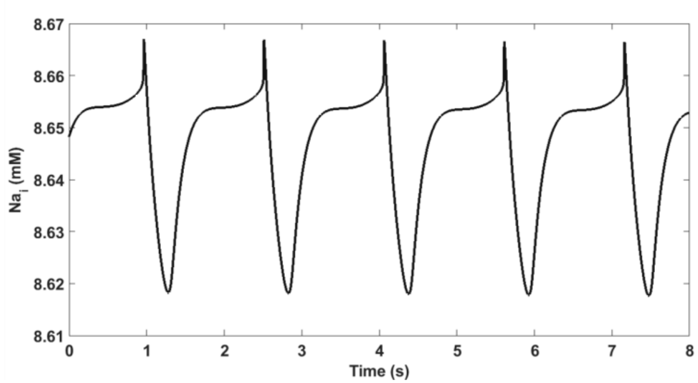
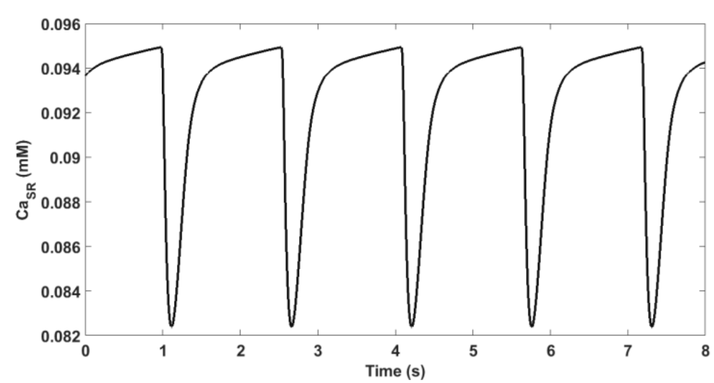
Action potential





3 ionic concentrations





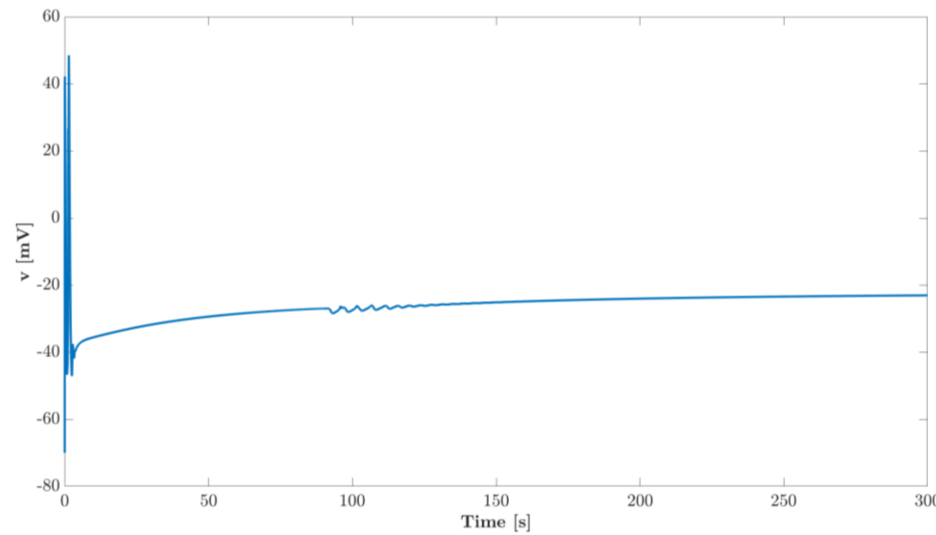
Analysis are numerically simulated by Matlab ode15s

Experimental background

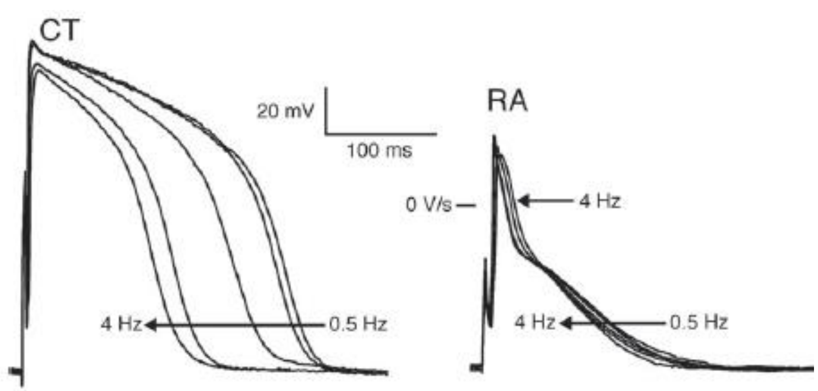
Atrial like hiPSC-CMs increasing interest to study atrial fibrillation

In undifferentiated hiPSC-CMs the *Inward Rectifier Potassium Current (IK1)* expression is still too low or lacking

$\Rightarrow I_{K1} = 0$



Treatment of differentiating hiPSC-CMs with *Retinoic acid* promotes atrial specification



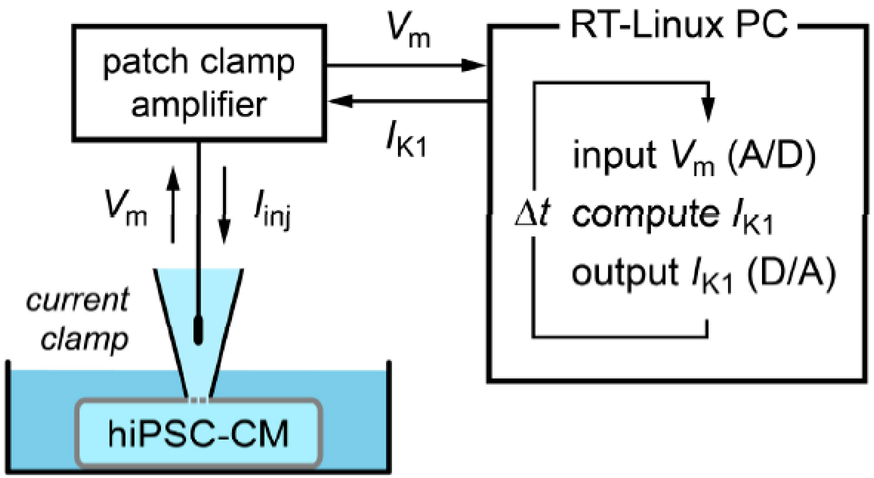
Devalla et al., *Atrial-like cardiomyocytes from human pluripotent stem cells are robust preclinical model for assessing atrial-selective pharmacology,* in Embo Molecular Medicine (2015)

Dynamic clamp

Several attempts have been proposed to mature hiPSC-CMs through an increase of I_{K1}

The dynamic clamp (DC) uses computer simulation to introduce artificial membrane currents into the cell and create hybrid circuits of real and model cells.

The membrane potential V_m is continuously sampled into a Real-Time Linux based pc. The V_m-dependent current I_{K1} is computed and injected with the stimulus current I_{stim}



Virtual dynamic clamp

In-silico **replica of the dynamic clamp, performing the Atrial Paci 2013 and the Ventricular Paci 2013, published by Paci et al.** (first generation models, without calcium dynamic)

<u>I step</u>: Evaluation of 6 different I_{K1} model structures available in the literature

Ten-Tusscher $$I_{K1} = G_{K1}\sqrt{\frac{K_o}{5,4}}\, x_{K1\infty}(V - E_K)$$

Fink 2013 $$I_{K1} = G_{K1}\frac{G}{G_{max}}(V - E_K)$$

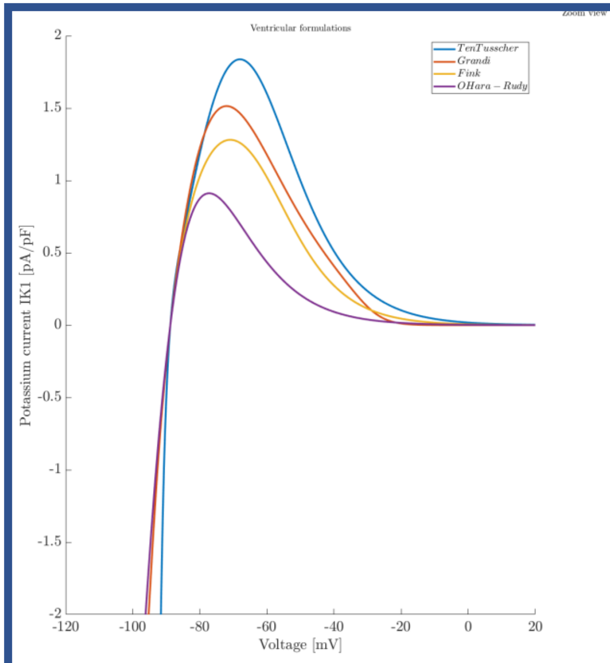
Grandi 2011 $$I_{K1} = 0,35\sqrt{\frac{K_o}{5,4}}\, K1_{ss}(V - E_K)$$

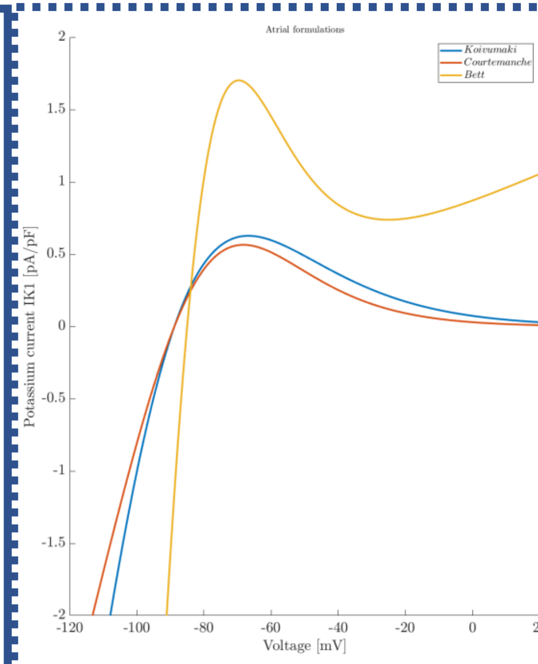
O’Hara-Rudy 2011 $$I_{K1} = \overline{G_{K1}}\sqrt{K_o}\, x_{K1}R_{K1}(V - E_K)$$

Koivumaki 2014 (Nygren 1997)
$$I_{K1} = G_{K1}K_O^{0,4457}\left(\frac{V - E_K}{1 + e^{1,5(V - E_K + 3,6)F/RT}}\right)$$

Courtmanche 1998
$$I_{K1} = \frac{g_{K1}(V - E_K)}{1 + \exp[0,07(V - E_K)]}$$

Bett 2013
$$I_{K1} = \left(\frac{V + 85}{1 + \exp[0,0896(V + 85)]}\right) + 0,01(V + 85)$$

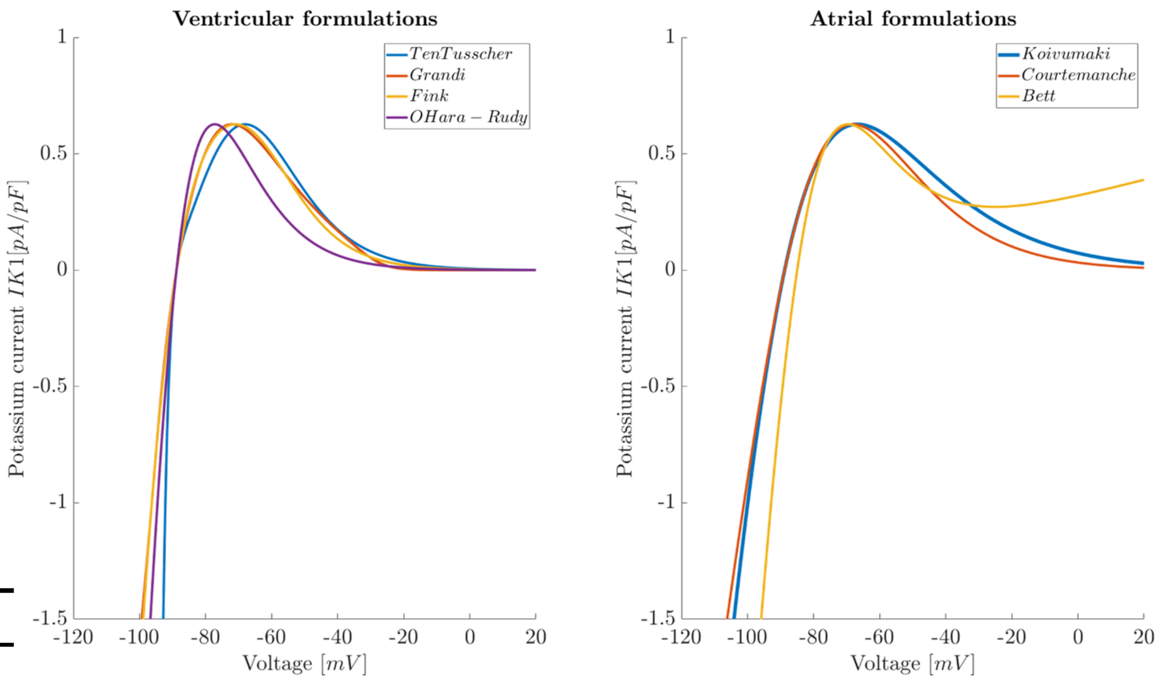




Virtual dynamic clamp

***In-silico* replica of the dynamic clamp, performing the Atrial Paci 2013 and the Ventricular Paci 2013, published by Paci et al.** (first generation models, without calcium dynamic)

<u>II step</u>: G_{K1} (Maximum conductance) scaling, in order to obtain the same higher current value



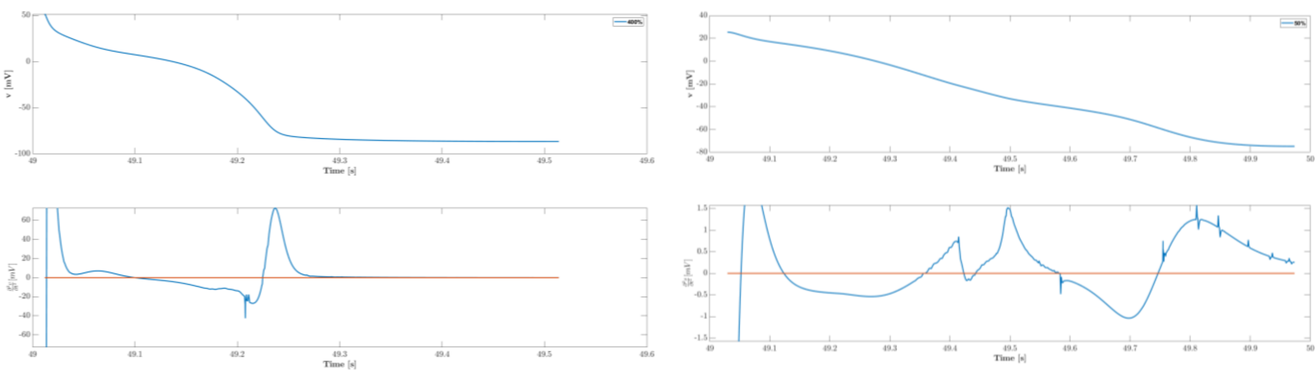
Model	Scaling factor	Normalized g_{K1} $[nS/pF]$
Ten Tusscher	0.34109	1.8436
Fink	0.48919	0.3337
Grandi	0.41384	0.41384
O'Hara-Rudy	0.68753	0.1312
Courtemanche	1.1101	0.0999
Bett	0.36827	0.36827

Toward Atrial ionic model (i)

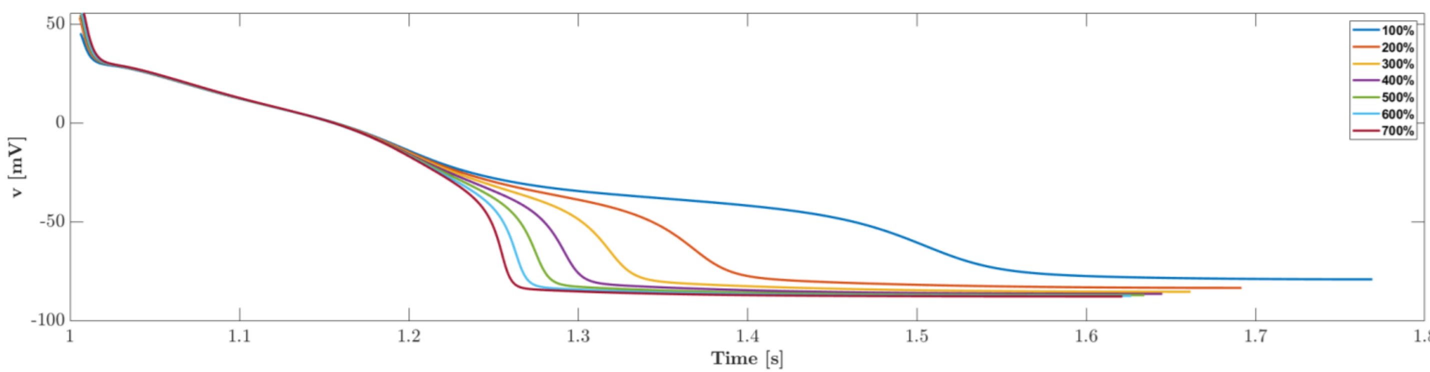
Virtual dynamic clamp

***In-silico* replica of the dynamic clamp, performing the Atrial Paci 2013 and the Ventricular Paci 2013, published by Paci et al.** (first generation models, without calcium dynamic)

III step: Physiological and non-physiological AP morphology definition, mathematically discriminated by the number of inflections



Increasing the percentage of the injected current, the morphology is driven to a physiological AP



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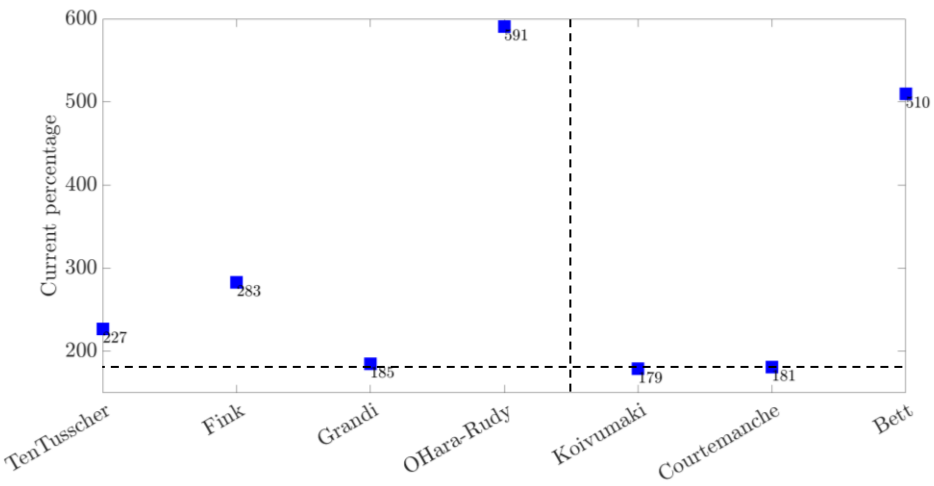
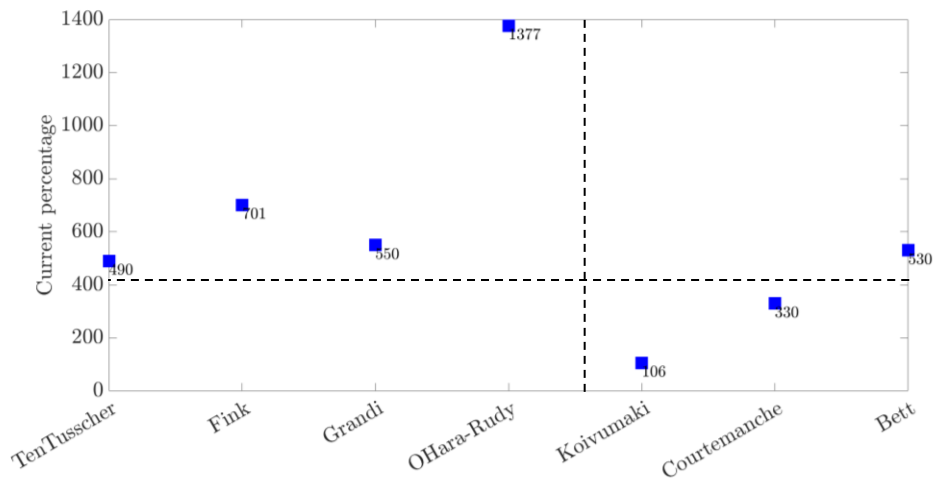


Ventricular like hiPSC-CMs



Atrial like hiPSC-CMs

Results: Required I_{K1} percentages are higher for atrial like formulations
⇒ The same injected current could produce non physiological action potential in the atrial like cell ⇒ **Atrial like potassium formulations are elegible in the DC**

Ionic model for Atrial-like hiPSC-CMs

Starting from *Cardiocentrum Ticino* biomarkers…

Create a new ionic model for Atrial like hiPSC-CMs

Ionic model for Atrial-like hiPSC-CMs

I step: Parameters update of the best Ventricular model, Paci 2020, using the same scaling of Paci 2013, considering virtual basic fitting parameters of mixed phenotypes

$$f: \alpha_{bf} \mapsto \alpha_v$$

$$g: \alpha_{bf} \mapsto \alpha_a$$

$$\rightarrow \alpha_a \mapsto g(f^{-1}(\alpha_v))$$

Current	Year	Basic fitting	Ventricular	Atrial	Units
I_{Na}	2013	$G_{Na} = 6329.7$	$0.58 * G_{Na} = 3671.2$	$1.05 * G_{Na} = 6646.2$	S/F
	2020	$G_{Na} = G_{Na,v}/0.58$	$G_{Na,v} = 64471.1896$	$G_{Na,a} = 1.05 * G_{Na} = 116720$	S/F
I_{CaL}	2013/2020	$Vh_d = -9.1$	$Vh_{d,v} = Vh_d = -9.1$	$Vh_{d,a} = Vh_d + 3.114 = -5.986$	mV
	2013/2020	$Vh_f = -26$	$Vh_{f,v} = Vh_f = -26$	$Vh_{f,a} = Vh_f + 0.774 = -25.226$	mV
	2013/2020	$Vh_{f2} = -32$	$Vh_{f2,v} = Vh_{f2} = -32$	$Vh_{f2,a} = Vh_{f2} + 0.774 = -31.226$	mV
	2013/2020	τ_{f2}	$\tau_{f2,v} = tau_{f2}$	$\tau_{f2,a} = 2 * \tau_{f2}$	ms
I_f	2013	$G_f = 53.76$	$0.56 * G_f = 30.10$	$0.56 * G_f = 30.10$	S/F
	2020	-	$G_{f,v} = 22.2763088$	$G_{f,a} = 22.2763088$	S/F
I_{to}	2013	$G_{to} = 59.81$	$0.5 * G_{to} = 29.9$	$G_{to,a} = G_{to} = 59.81$	S/F
	2020	$G_{to} = G_{to,v}/0.5$	$G_{to,v} = 29.9038$	$G_{to,a} = G_{to} = 59.8076$	S/F
I_{K1}	2013	$G_{K1} = 25.59$	$1.1 * G_{K1} = 28.15$	$0.75 * G_{K1} = 19.19$	S/F
	2020	$G_{K1} = G_{K1,v}/1.1$	$G_{K1,v} = 28.1492$	$G_{K1,a} = 0.75 * G_{K1} = 19.1926$	S/F
C_m	2013	$C_m = 88.7$	$1.113 * C_m = 98.71$	$0.887 * C_m = 78.66$	pF
	2020	$C_m = C_m/1.113$	$C_{m,v} = 98.7109$	$C_{m,a} = 0.887 * C_m = 78.6672$	pF

Ionic model for Atrial-like hiPSC-CMs

<u>II step:</u> Additional atrial specific current: *ultrarapid outward current* I_{Kur}

Koivumaki Maleckar formulation

$$I_{Kur} = g_{Kur} \cdot a_{ur} \cdot i_{ur} \, (VmV - E_K \cdot 10^3)$$

$$a_{ur,\infty} = \frac{1.0}{1.0 + \exp - \frac{VmV \cdot 10^3 + 6.0}{8.6}}$$

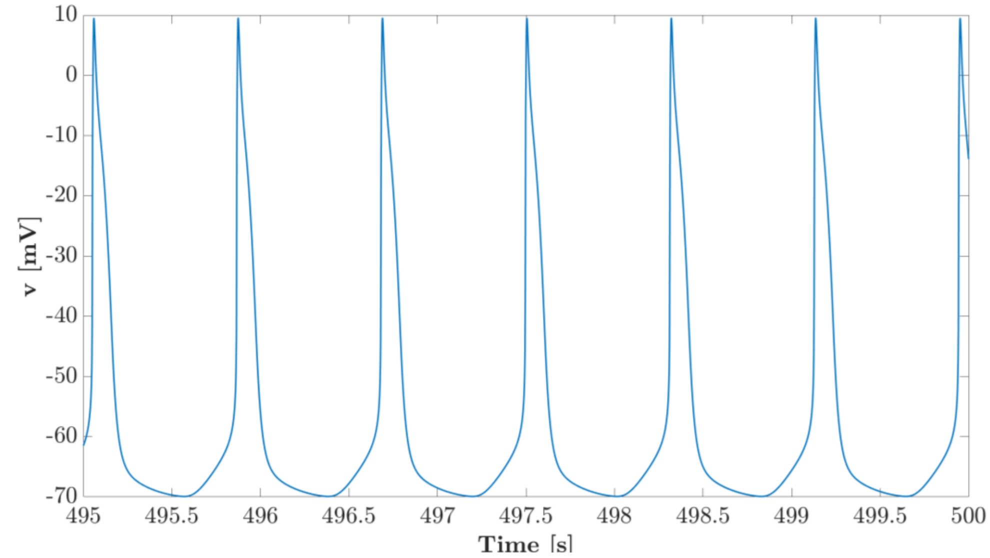
$$\tau_{aur} = \frac{0.009}{1.0 + \exp \frac{VmV + 5.0}{12.0}} + 0.0005$$

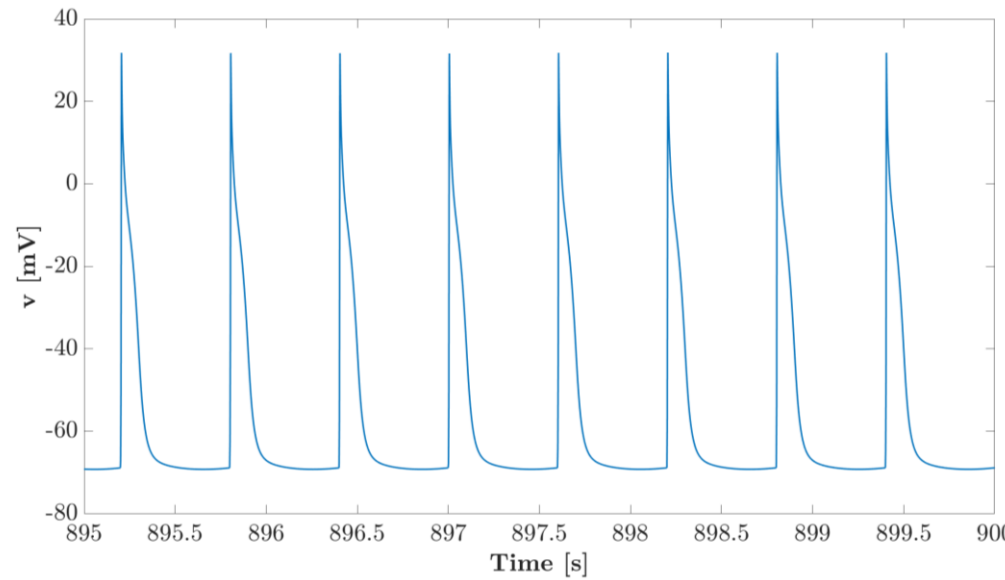
$$\frac{da_{ur}}{dt} = \frac{a_{ur,\infty} - a_{ur}}{\tau_{aur}}$$

$$i_{ur,\infty} = \frac{1.0}{1.0 + \exp \frac{VmV + 7.5}{10.0}}$$

$$\tau_{iur} = \frac{0.59}{1.0 + \exp \frac{VmV + 60.0}{10.0}} + 3.5$$

$$\frac{di_{ur}}{dt} = \frac{i_{ur,\infty} - i_{ur}}{\tau_{iur}}$$





Ionic model for Atrial-like hiPSC-CMs

II step: Additional atrial specific current: *ultrarapid outward current* I_{Kur}

Courtemanche formulation

$$I_{Kur} = g_{Kur} \cdot u_a^3 \cdot u_i \cdot (VmV - E_K \cdot 10^3)$$

$$g_{Kur} = 0.005 + \frac{0.05}{1.0} + \exp\left(-\frac{VmV - 15.0}{13.0}\right)$$

$$\alpha_{u(a)} = 0.65\left[\exp\left(-\frac{VmV + 10.0}{8.5}\right) + \exp\left(-\frac{VmV - 30.0}{59.0}\right)\right]^{-1}$$

$$\beta_{u(a)} = 0.65 \cdot \left[2.5 + \exp\left(-\frac{VmV + 82.0}{17.0}\right)\right]^{-1}$$

$$\tau_{u(a)} = \frac{K_{Q,10}}{\alpha_{u(a)} + \beta_{u(a)}}$$

$$\frac{du_a}{dt} = \frac{u_{a(\infty)} - u_a}{\tau_{u(a)}}$$

$$u_{a(\infty)} = \left[1.0 + \exp\left(-\frac{VmV + 30.0}{9.6}\right)\right]^{-1}$$

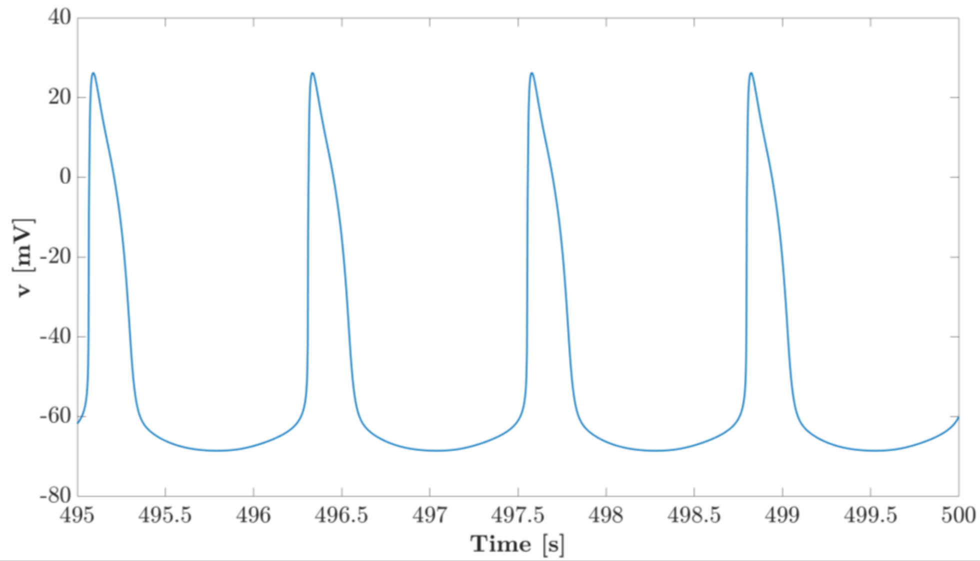
$$\alpha_{u(i)} = \left[21.0 + \exp\left(-\frac{VmV - 185.0}{28.0}\right)\right]^{-1}$$

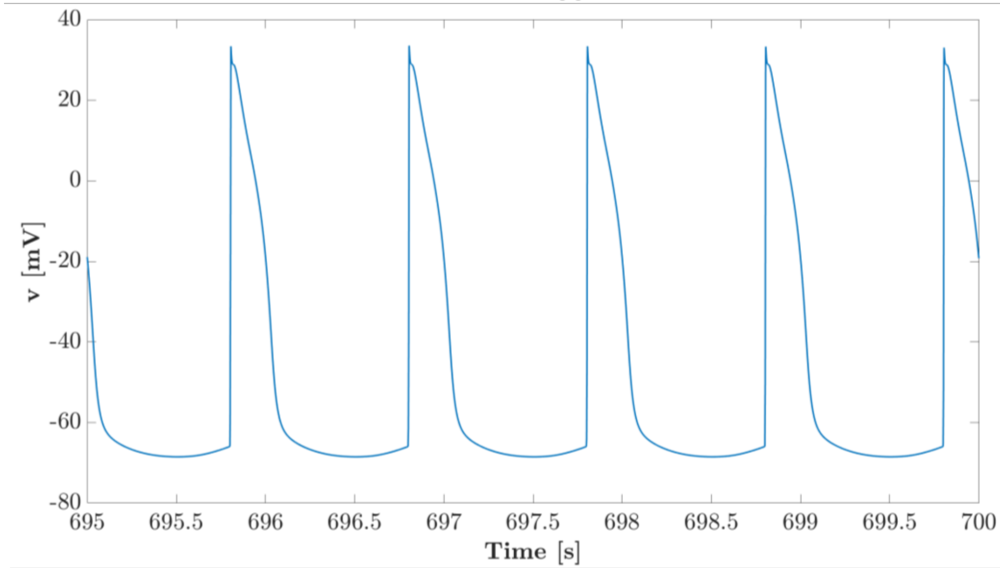
$$\beta_{u(i))} = \exp\left(-\frac{VmV + 158.0.0}{16.0}\right)$$

$$\tau_{iur} = \frac{K_{Q,10}}{\alpha_{u(i)} + \beta_{u(i)}}$$

$$\frac{du_i}{dt} = \frac{u_{i(\infty)} - u_i}{\tau_{u(i)}}$$

$$u_{i(\infty)} = \left[1.0 + \exp\left(-\frac{VmV - 99.45}{27.48}\right)\right]^{-1}$$





Ionic model for Atrial-like hiPSC-CMs

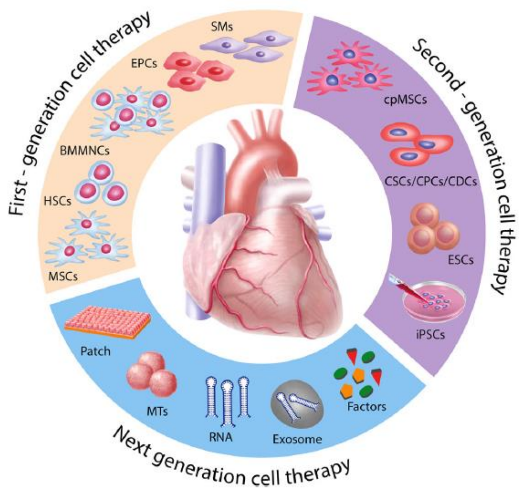
Next steps: **1.** Parameters calibration, using literature and CCT biomarkers

Tested models	Exp data	Atrial		Atrial Koivumaki		Atrial Courtemanche	
	Unpaced	Unpaced	Paced	Unpaced	Paced	Unpaced	Paced
MDP [mV]	-73.5 ± 1.5	-74.858	-66.5490	-69.9388	-68.9266	-68.5498	-68.4722
dV/dt_{max}	–	20.3890	64.3703	24.8421	119.1028	22.10128	107.1832
APA [mV]	100.2 ± 2.1	102.030	100.5526	79.5101	99.7257	94.82082	101.8640
$Peak$ [mV]	26.7 ± 1.4	27.1675	33.98477	9.55838	30.7271	26.26785	33.0917
$APD10$ [ms]	60.8 ± 5.5	87.1589	84.3750	14.4785	3.8715	60.40387	47.4125
$APD20$ [ms]	–	167.596	137.6229	28.7482	8.7657	103.4678	84.8394
$APD30$ [ms]	123.1 ± 10.3	223.993	192.8139	49.6623	19.5967	144.2292	127.6341
$APD50$ [ms]	–	300.578	264.8854	84.0664	62.9016	199.4379	191.8454
$APD70$ [ms]	–	334.647	306.3398	106.888	93.0400	231.2435	226.4829
$APD90$ [ms]	286.9 ± 21.2	390.518	340.6575	138.714	128.3481	274.9456	263.8436
$RateAP$	–	35.0233	60.00175	73.6341	100.0003	48.23846	59.9990
$RappAPD$	1.1 ± 0.1	2.79240	2.6392	1.6364	1.4785	2.152	2.5525
CL [ms]	1200 ± 200	1713.14	999.9713	814.839	599.9981	1243.820	1000.0158

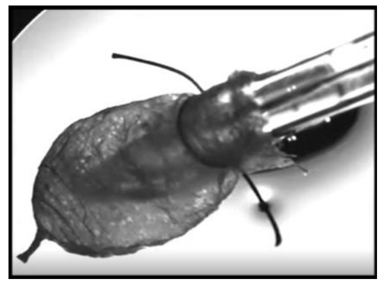
2. Model validation, performing current block and dynamic clamp expertiments

Isogeometric simulations of 3D cardiac tissue

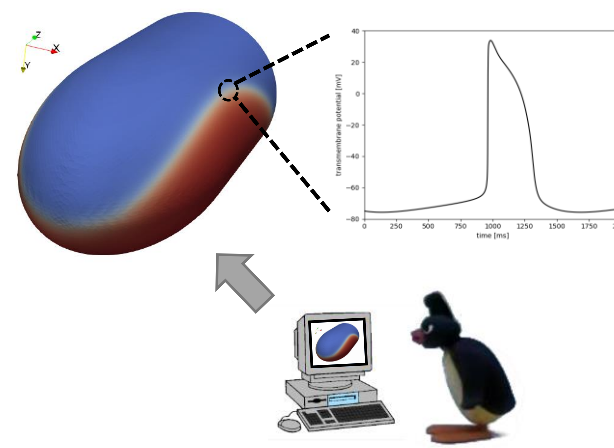
Isogeometric simulations of hiPSC-CM tissue



Cambria et al., Nat. Reg. Med., **2**, (2017)



MacQueen et al., Nat. Bio. Eng., **2**, 930, (2018)



Regenerative medicine

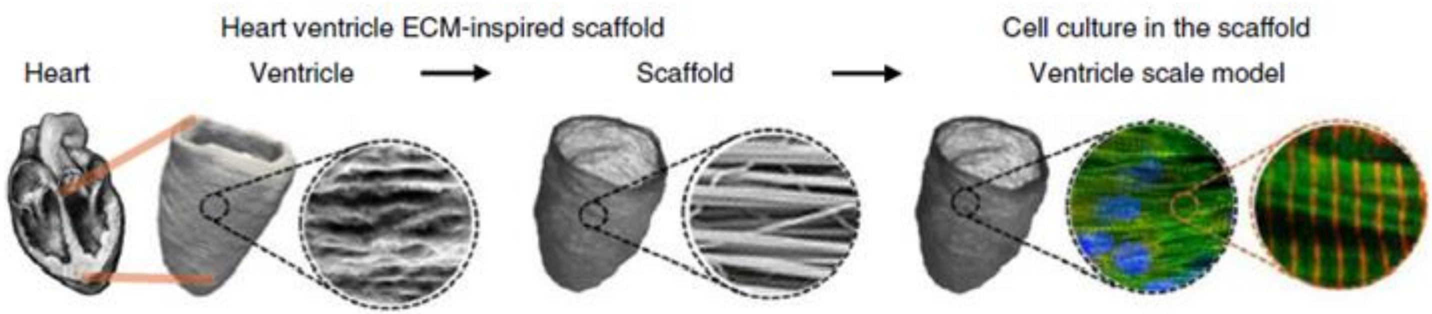
***In-vitro* model**

Framework for *in-silico* replicas

In-vitro ventricle manufactured on a scaffold

Ellipsoidal heart tissue (ventricle scaffold)

Human left ventricle with ellipsoidal shape and circumferentially oriented nanofibers was produced by pull spinning nanofibers onto ellipsoidal collection mandrels



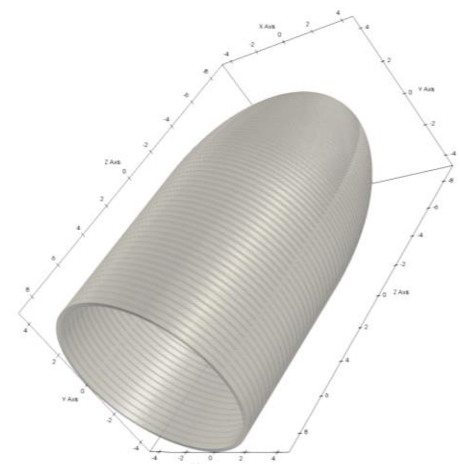
MacQueen et al., Nat. Bio. Eng., **2**, 930, (2018)

From the ellipsoidal collector

Half ellipsoid with
Radius 4,5 mm
Heigh 9 mm

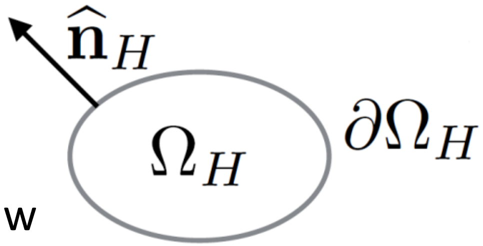
Cylinder with
Radius 4,5 mm
Heigh 9 mm

To the *in-silico* ventricle mesh



Reaction-Diffusion Cardiac models

Cardiomyocytes are connected by means of gap junctions allowing flux of electric current in form of ions.



Continuous intercellular space approximation
Volume-average approach for a generic domain Ω_H

+

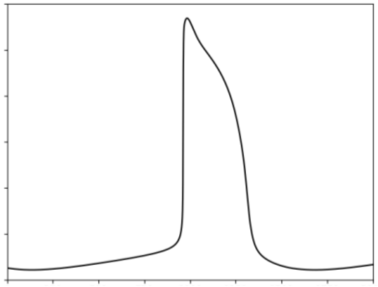
Ohm's law
Kirchhoff's law

Monodomain equation

Diffusion — Reaction

$$
\begin{cases}
\dfrac{\partial v}{\partial t} = \nabla \cdot (\sigma \nabla v) - \dfrac{I_{ion}(v,\boldsymbol{w},\boldsymbol{c})}{C_m} + I_{app} & in\ \Omega_H \\
\dfrac{d\boldsymbol{w}}{dt} = R(v,\boldsymbol{w}) & in\ \Omega_H \\
\dfrac{d\boldsymbol{c}}{dt} = S(v,\boldsymbol{w},\boldsymbol{c}) & in\ \Omega_H \\
\dfrac{\partial v}{\partial \widehat{\boldsymbol{n}}_H} = 0 & on\ \partial\Omega_H
\end{cases}
$$

Tissue description



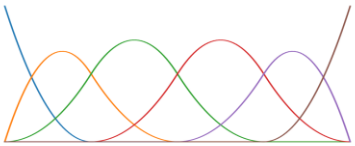
Paci et al. cellular model

Shape functions for Space discretization

$$v\left(x,t\right)=\mathrm{N}\left(x\right)\hat{\mathrm{v}}\left(t\right)$$

FEM → 

Element-wise
linear polynomials
p=1

IGA → 

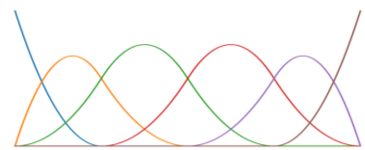
Patch-wise
B-splines
p=2-3

Shape functions for Space discretization

$$v(x,t) = \mathrm{N}(x)\,\hat{\mathrm{v}}(t)$$

FEM → 

Element-wise
linear polynomials
p=1

IGA → 

Patch-wise
B-splines
p=2-3

Operator splitting for Time discretization

Given the generic evolution linear model

$$\begin{cases} \dfrac{\partial u}{\partial t} + \mathcal{L}\mathrm{u} = f \\ u(t=0) = u_0 \end{cases}$$

Where the linear operator is

$\mathcal{L} = \mathcal{L}_1 + \mathcal{L}_2$

First solve

$$\begin{cases} \dfrac{\partial w_1}{\partial t} = \mathcal{L}_1 w_1 \quad \mathrm{t} \in (0, \Delta t] \\ w_1(t=0) = u_0 \end{cases}$$

Then solve

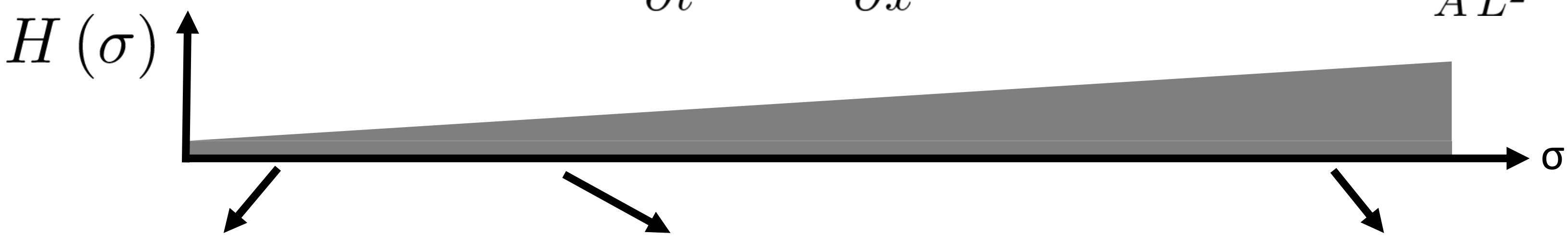
$$\begin{cases} \dfrac{\partial w_2}{\partial t} = \mathcal{L}_2 w_2 \quad \mathrm{t} \in (0, \Delta t] \\ w_2(t=0) = w_1(\Delta t) \end{cases}$$

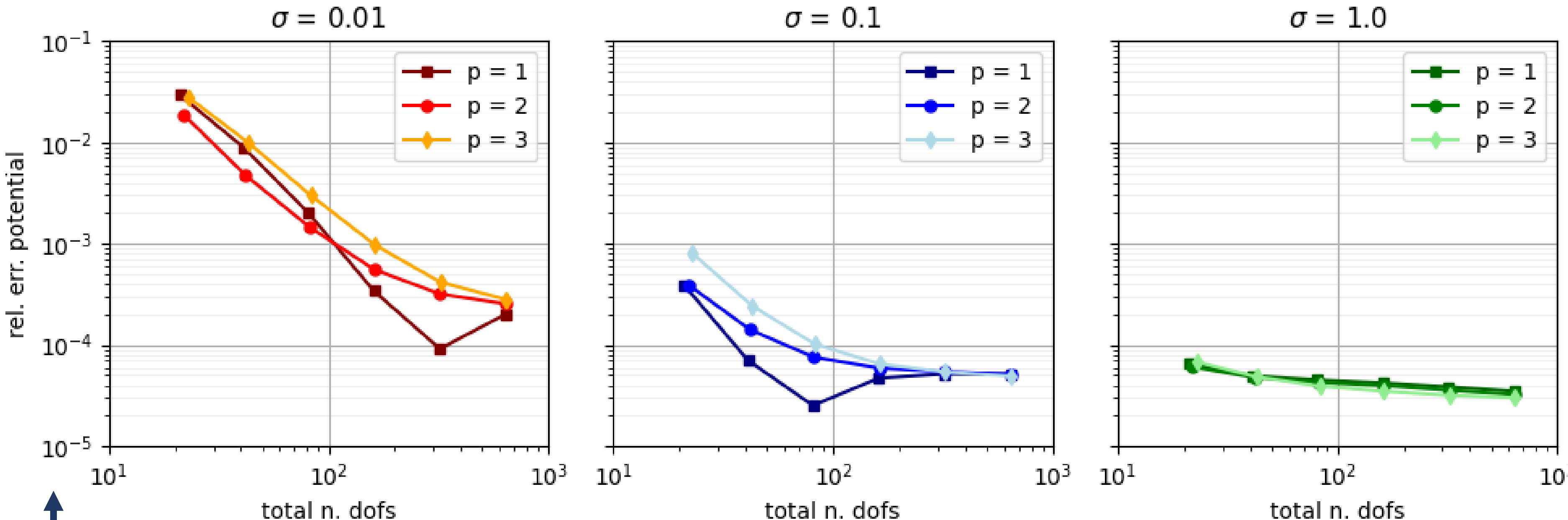
Comparison IGA-FEM on a cable (1)

Adimensional equation: $$\frac{\partial v^*}{\partial t^*} = H \frac{\partial^2 v^*}{\partial x^{*2}} - I^*_{ion} \qquad H = \frac{C_m \, V \, S}{A \, L^2} \sigma$$

Comparison IGA-FEM on a cable (1)

Adimensional equation: $$\frac{\partial v^*}{\partial t^*} = H\frac{\partial^2 v^*}{\partial x^{*2}} - I^*_{ion}$$ $$H = \frac{C_m\, V\, S}{A\, L^2}\sigma$$

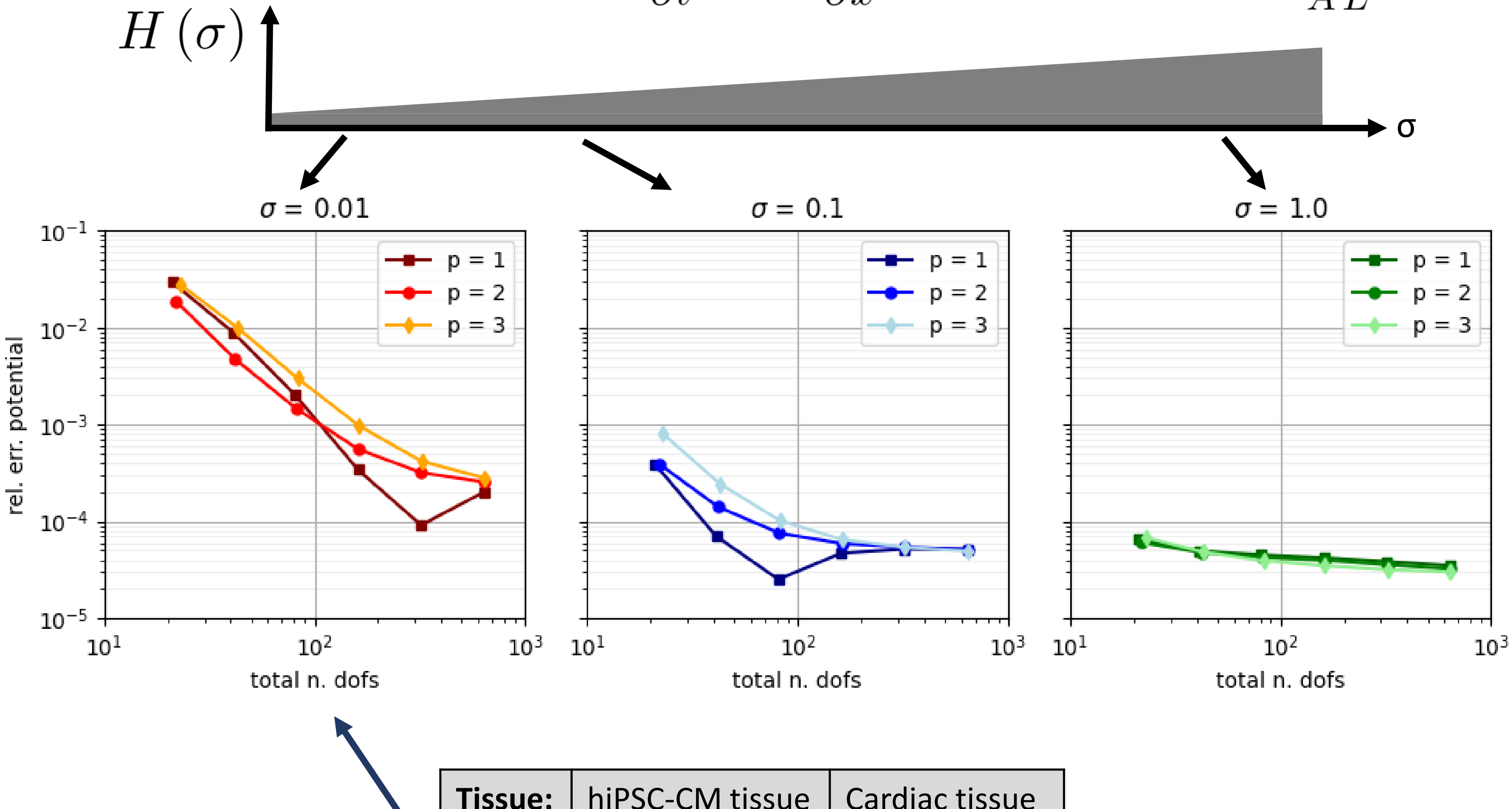




relative error: $$V_{err} = \left.\frac{\int_0^{T_{max}} \left|v\left(\boldsymbol{x},t\right) - v_{ref}\left(\boldsymbol{x},t\right)\right|\, dt}{\int_0^{T_{max}} \left|v_{ref}\left(\boldsymbol{x},t\right)\right|\, dt}\right|_{\boldsymbol{x}=\mathbf{x}_p}$$

Comparison IGA-FEM on a cable (1)

Adimensional equation: $$\frac{\partial v^*}{\partial t^*} = H \frac{\partial^2 v^*}{\partial x^{*2}} - I^*_{ion}$$ $$H = \frac{C_m\, V\, S}{A\, L^2}\sigma$$

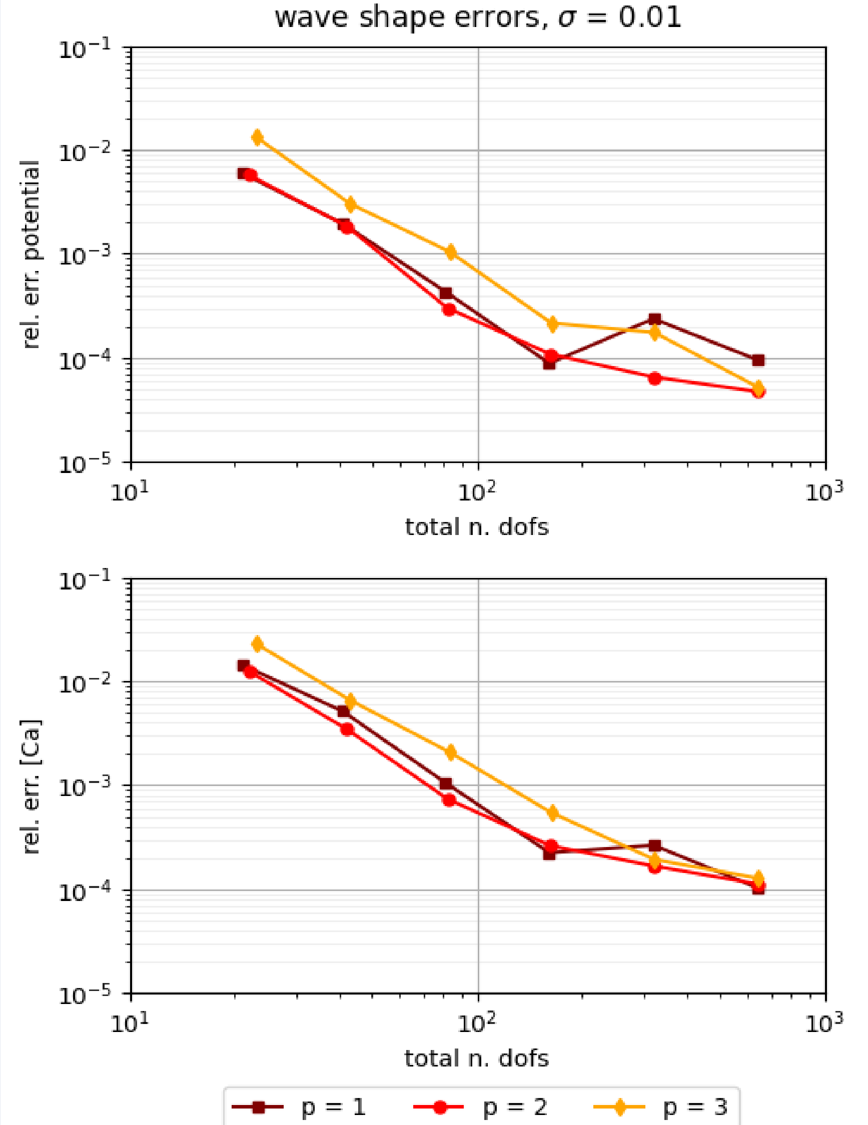


Tissue:	hiPSC-CM tissue	Cardiac tissue
CV:	5÷15 [cm/s]	50÷100 [cm/s]

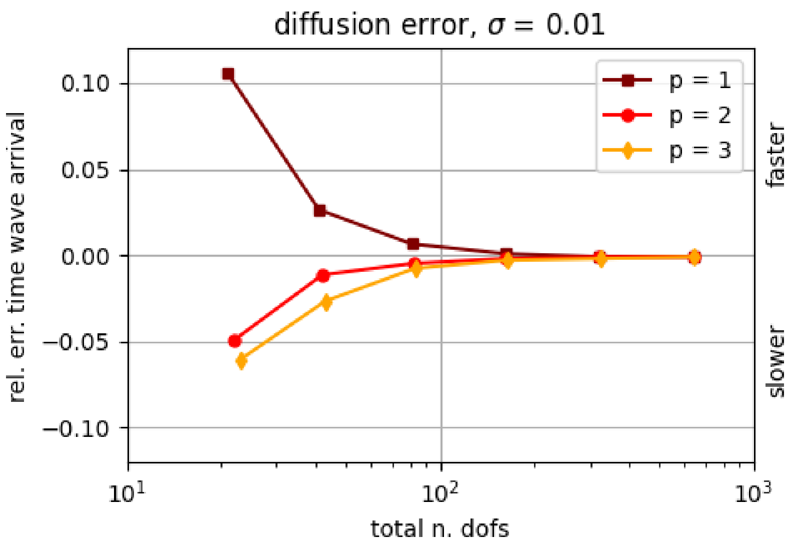
Comparison IGA-FEM on a cable (2)

For limited values of *H*:

- p=1 and p=2 have the same accuracy on reaction



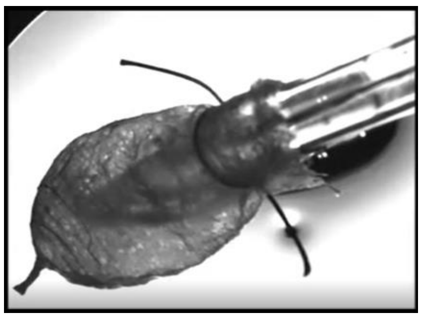
- p=2 increase the accuracy on diffusion

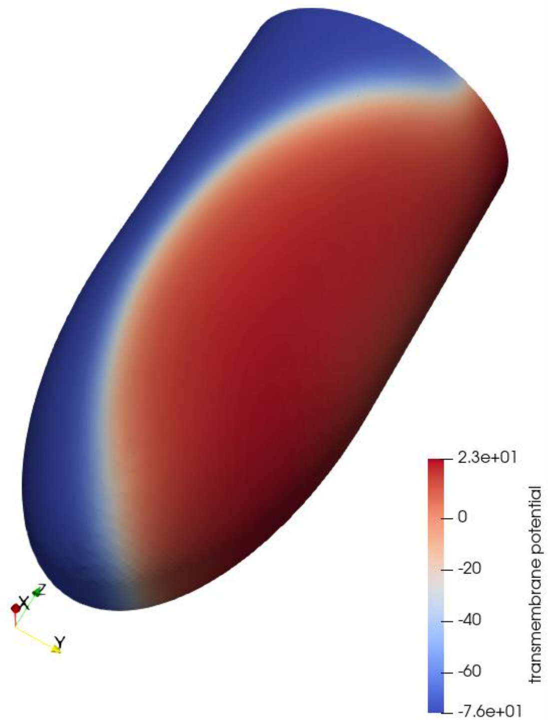


<u>p=2</u> is the best choice

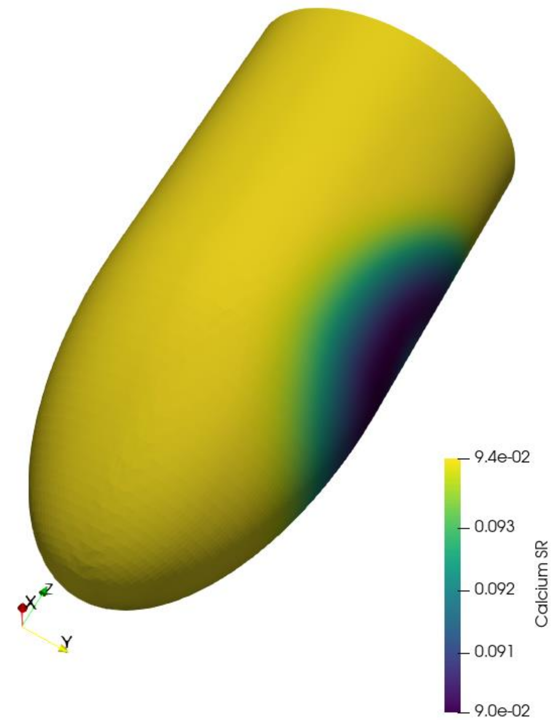
In-silico replica of the engineered ventricle

Computational framework for preclinical cardiology



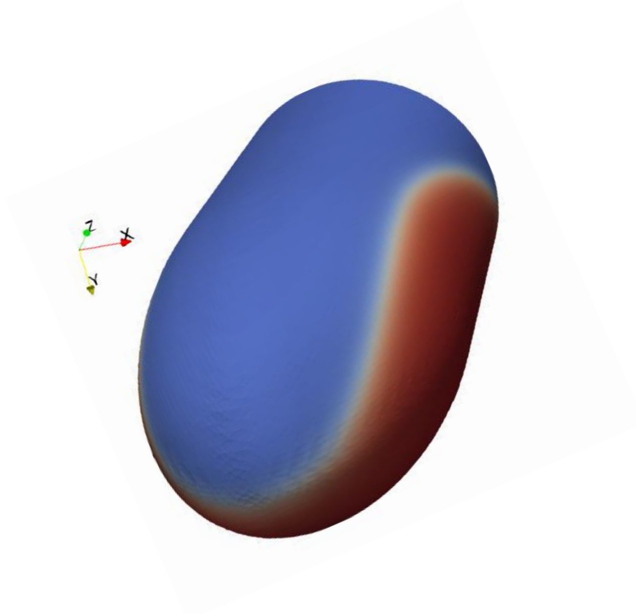


Transmembrane potential



Calcium concentration

Thanks for your attention



FROM CARDIAC STEM CELL IONIC MODELS TO ISOGEOMETRIC SIMULATIONS OF 3D CARDIAC TISSUE

Sofia Botti

UNIPV-USI Ph.D. Program in Computational mathematics and decision sciences

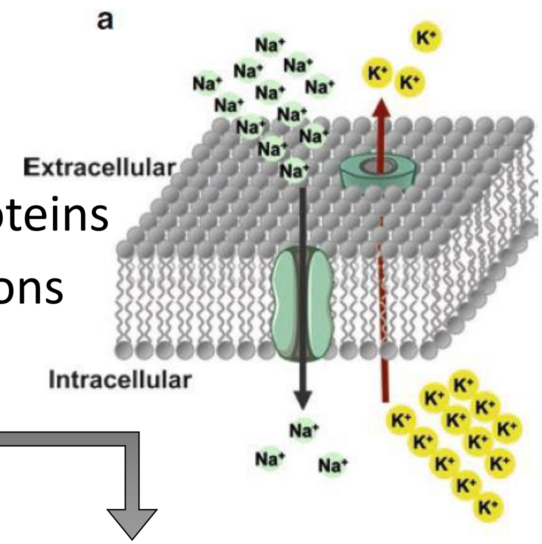
Supervisor: Prof Luca F. Pavarino

Spring Workshop 2022

March 16-17

Backup

Cardiac models

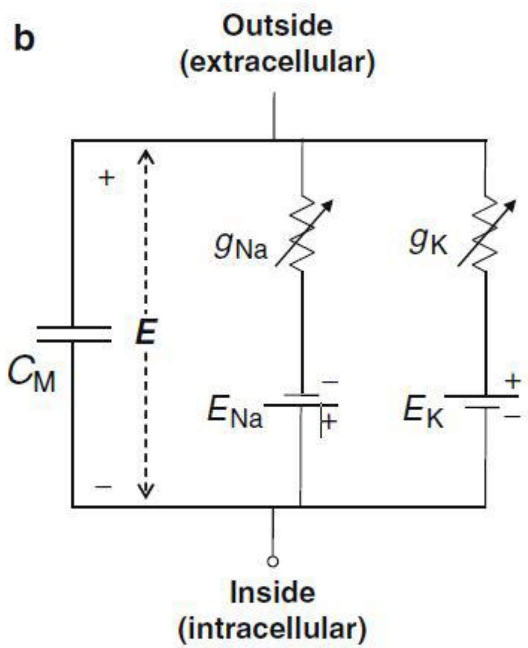


PHYSIOLOGICAL PERSPECTIVE

Cellular membrane = lipid bilayer in which are immersed proteins

Ionic channels = exchangers for the flow of Na^+, K^+, Ca^{2+} ions

Electrical activity modeled by a resistor-capacitor circuit + Conservation law, Definition of capacitance

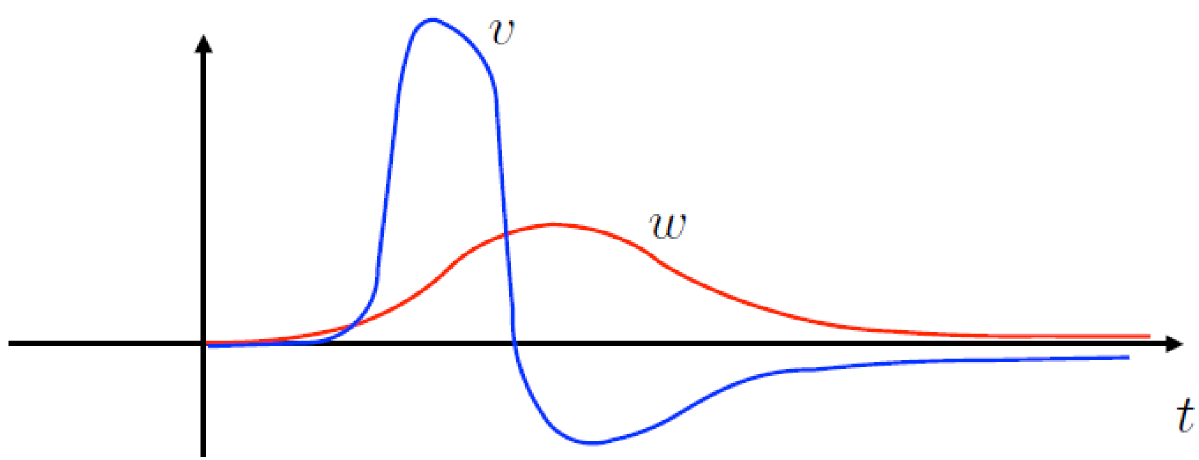


$$C_m \frac{dv}{dt} + I_{ion} = I_{app}$$

Variable accuracy of the membrane description → Different number of ionic channels and **gating variables** → Different **ionic current I_{ion} formulations** → **DIFFERENT CARDIAC MODELS**

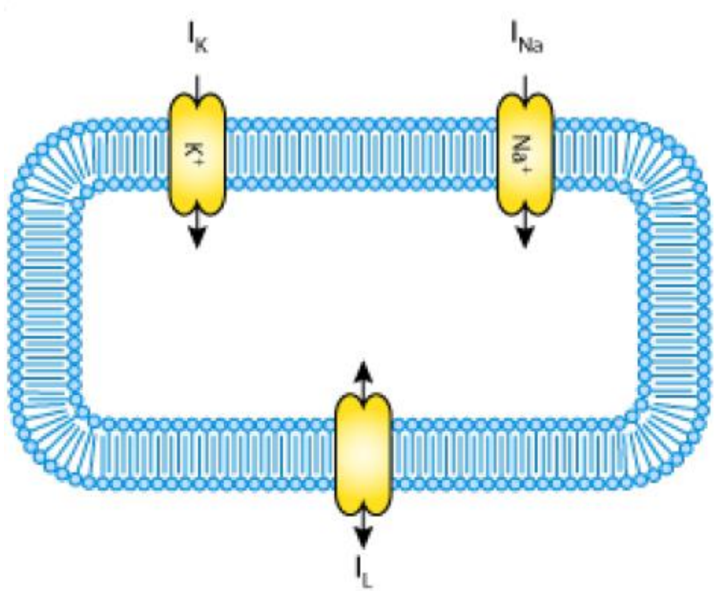
Models formalism

Generation	Representative model	Gating variables number	Equations number
Phenomenological approach	FitzHugh-Nagumo (1955)	1	2



Models formalism

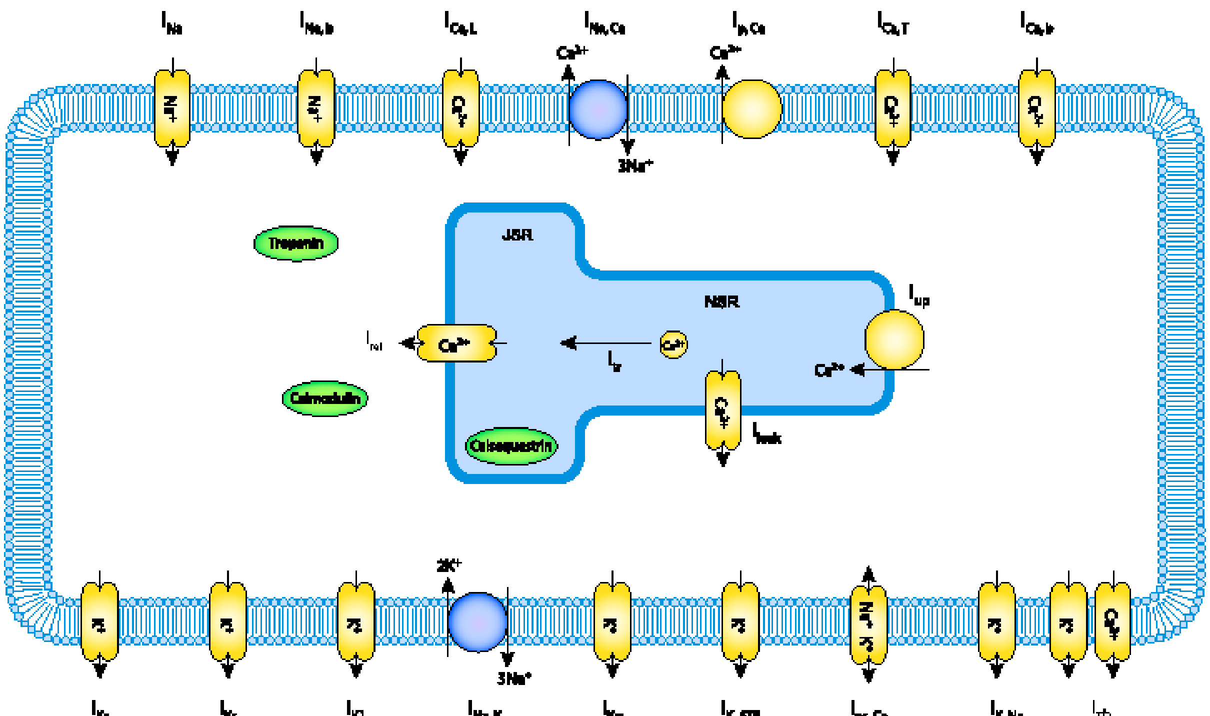
Generation	Representative model	Gating variables number	Equations number
Phenomenological approach	FitzHugh-Nagumo (1955)	1	2
First Generation models	Hodgkin-Huxley (1952)	3	4



A.L. Hodgkin, A. F. Huxley, *A quantitative description of the membrane current and its application to conduction and excitation in nerve*, in The Journal of Physiology, 1952

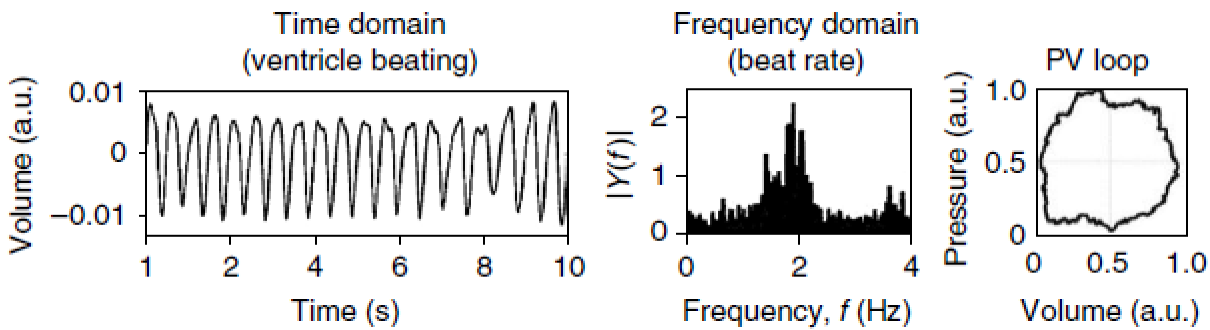
Models formalism

Generation	Representative model	Gating variables number	Equations number
Phenomenological approach	FitzHugh-Nagumo (1955)	1	2
First Generation models	Hodgkin-Huxley (1952)	3	4
Second Generation models	O'Hara-Rudy (2011)	12	41



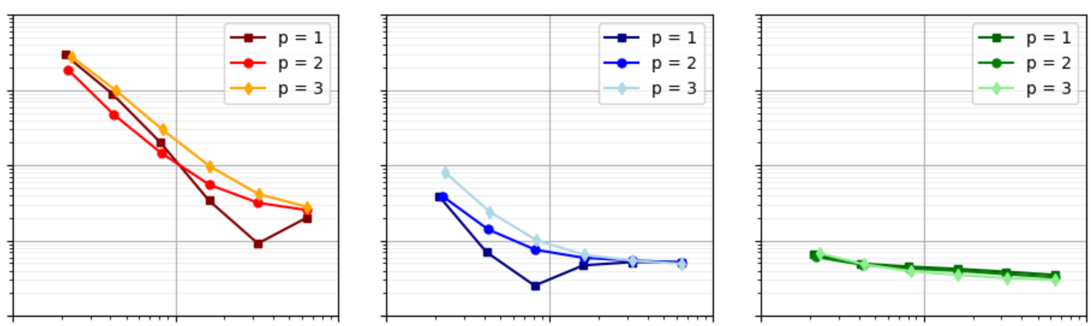
T. O'Hara et al., *simulation of the undiseased Human Cardiac Ventricular Action Potential: Model formulation and Experimental Validation*, in PLoS Computational Cardiology, 2011

- **Coupled electro-mechanical simulations**

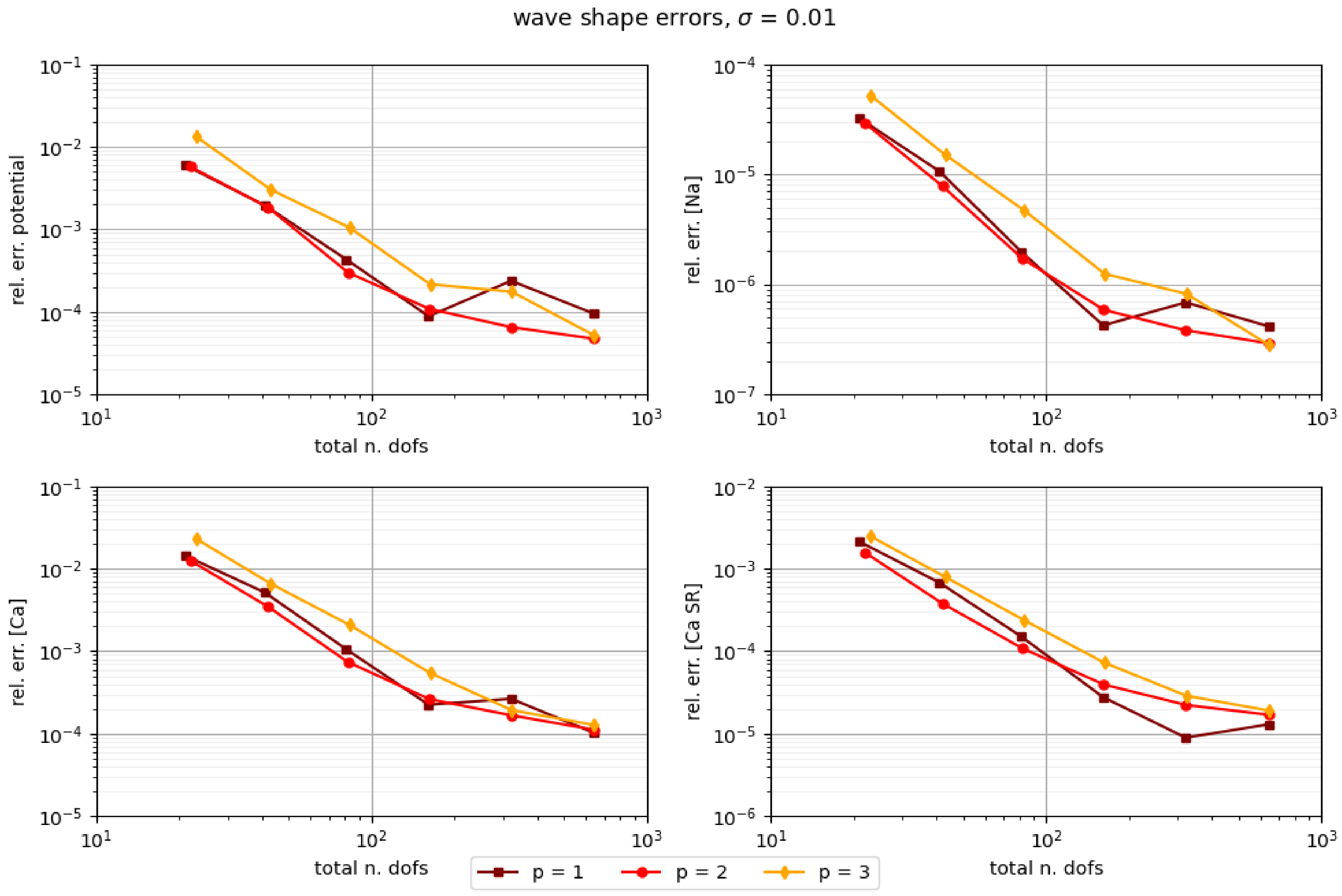


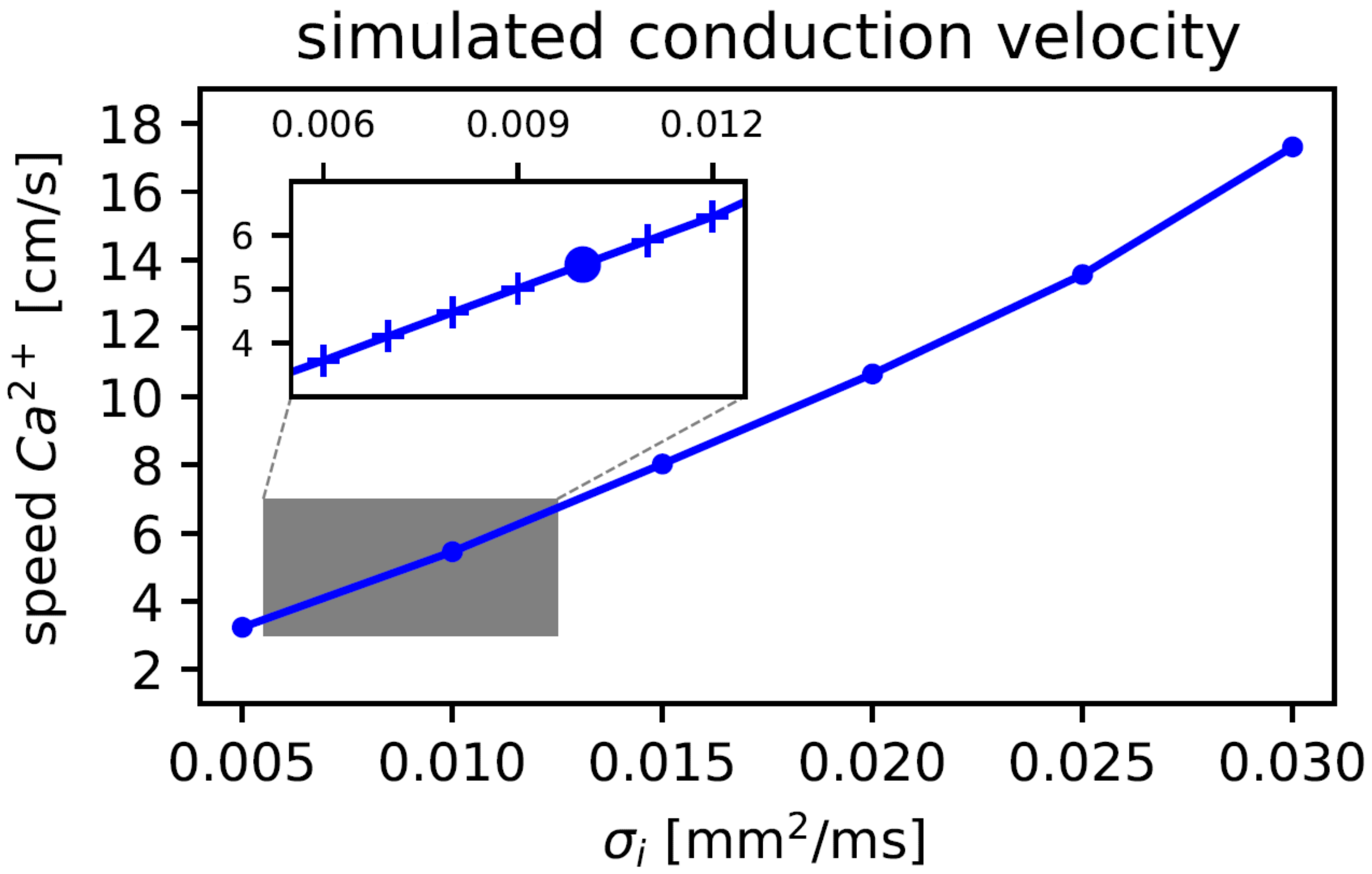
MacQueen et al., Nat. Bio. Eng., **2**, 930, (2018)

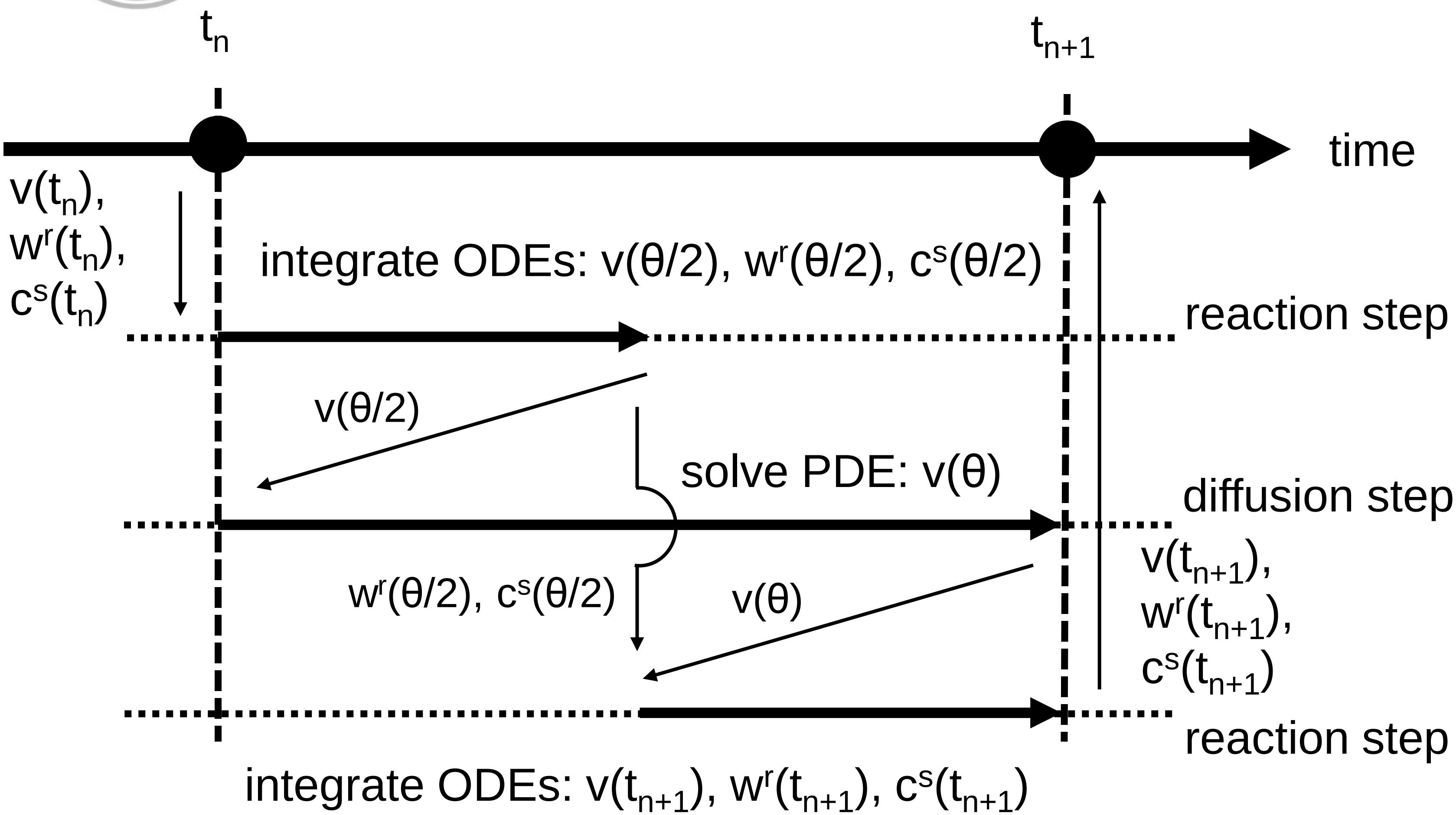
- **Further investigations on *H*(σ)**



Error on concentrations

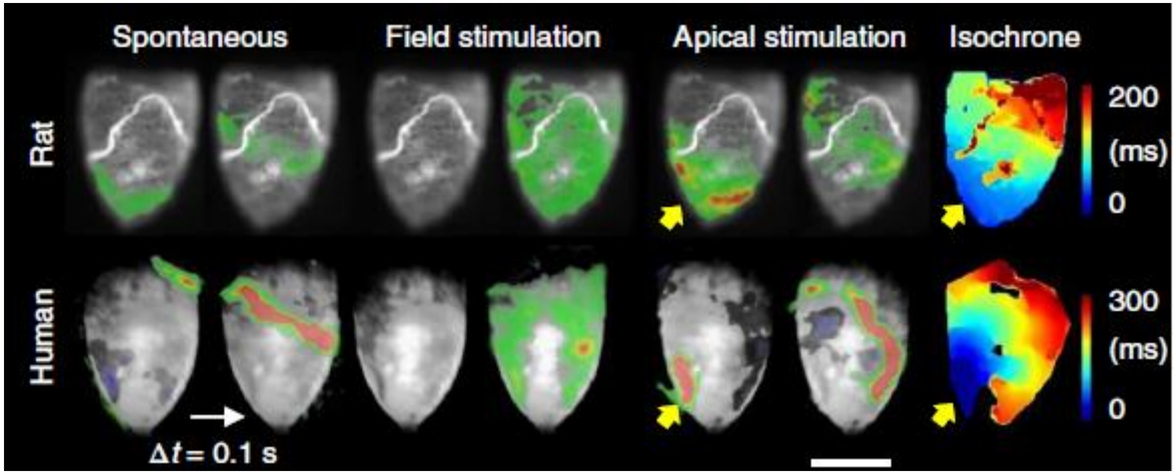



simulated conduction velocity
speed Ca^{2+} [cm/s]
18
16
14
12
10
8
6
4
2
0.005
0.010
0.015
0.020
0.025
0.030
σ_i [mm^2/ms]
0.006
0.009
0.012
6
5
4


t_n
t_{n+1}
time
$v(t_n)$,
$w^r(t_n)$,
$c^s(t_n)$
integrate ODEs: $v(\theta/2)$, $w^r(\theta/2)$, $c^s(\theta/2)$
reaction step
$v(\theta/2)$
solve PDE: $v(\theta)$
diffusion step
$v(t_{n+1})$,
$w^r(t_{n+1})$,
$c^s(t_{n+1})$
$w^r(\theta/2)$, $c^s(\theta/2)$
$v(\theta)$
reaction step
integrate ODEs: $v(t_{n+1})$, $w^r(t_{n+1})$, $c^s(t_{n+1})$

Engineered heart tissue

Three-dimensional, muscle strips, that can be generated from isolated heart cells or hiPSC-CMs



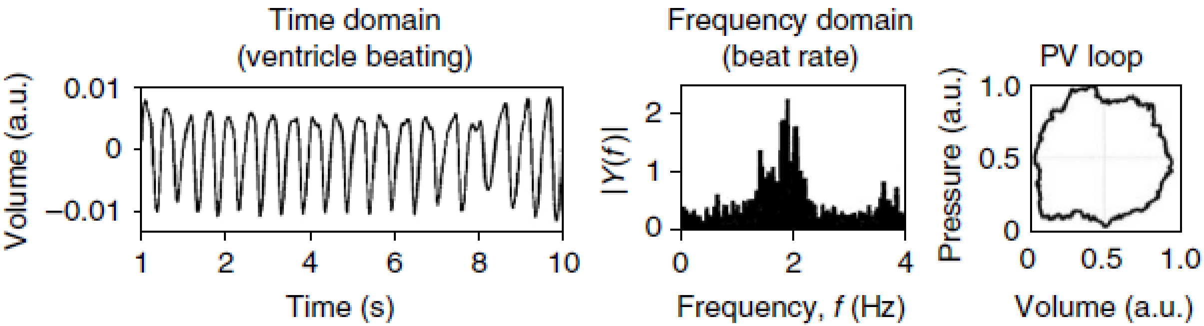
MacQueen et al., Nat. Bio. Eng., **2**, 930, (2018)

Goal 1

Spontaneous calcium activity measurements, useful for Cardiac arrhythmia studies

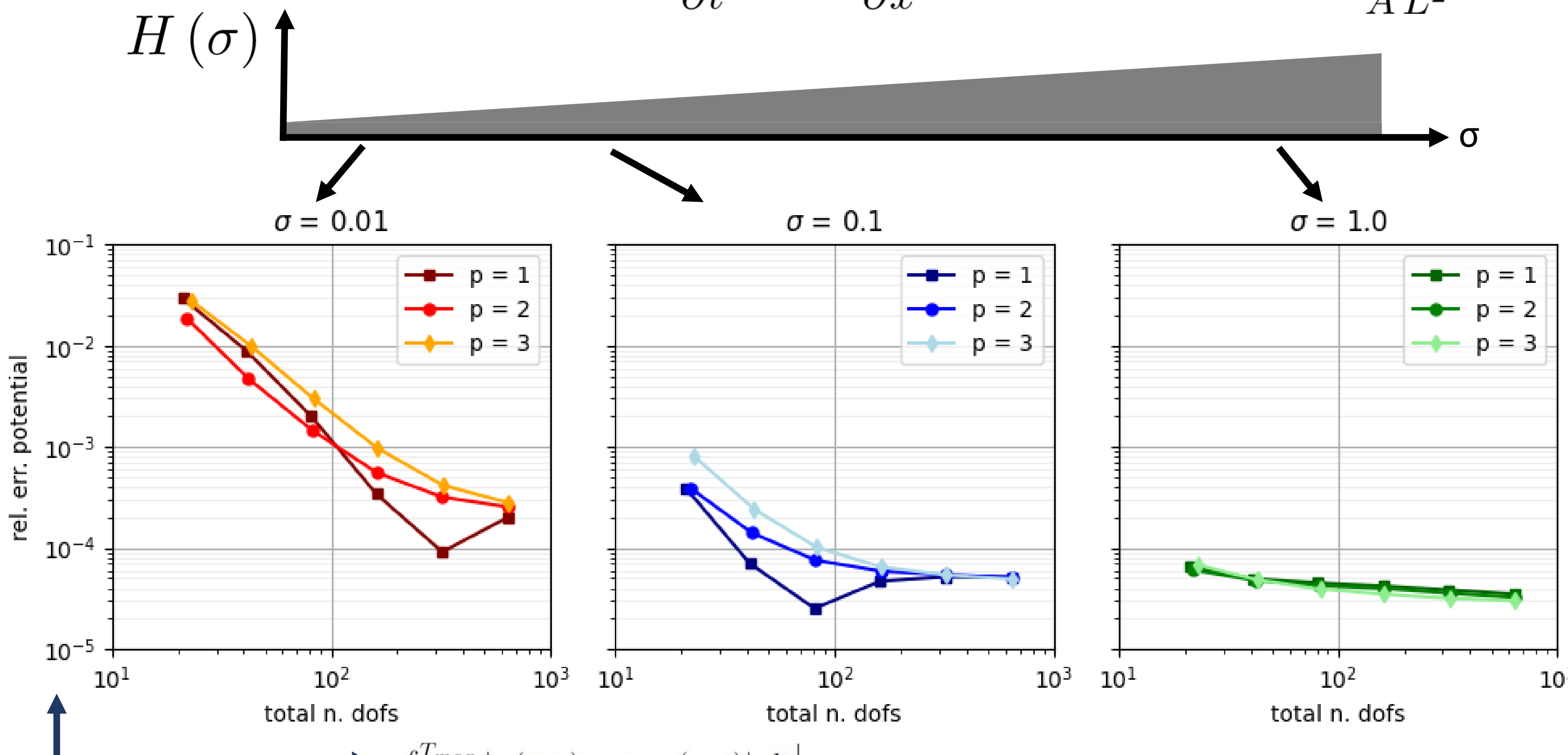
Goal 2

Time – dependent pressure and volume measurements



Comparison IGA-FEM on a cable (1)

Adimensional equation: $\frac{\partial v^*}{\partial t^*} = H \frac{\partial^2 v^*}{\partial x^{*2}} - I_{ion}^*$ $\quad H = \frac{C_m V S}{A L^2}\sigma$



relative error: $V_{err} = \frac{\int_0^{T_{max}} |v(\boldsymbol{x},t) - v_{ref}(\boldsymbol{x},t)|\, dt}{\ldots}$

Tissue:	hiPSC-CM tissue	Cardiac tissue
CV:	5÷15 [cm/s]	50÷100 [cm/s]

HIPSC derived Cardiomyocytes

Spontaneous beating cardiomyocytes

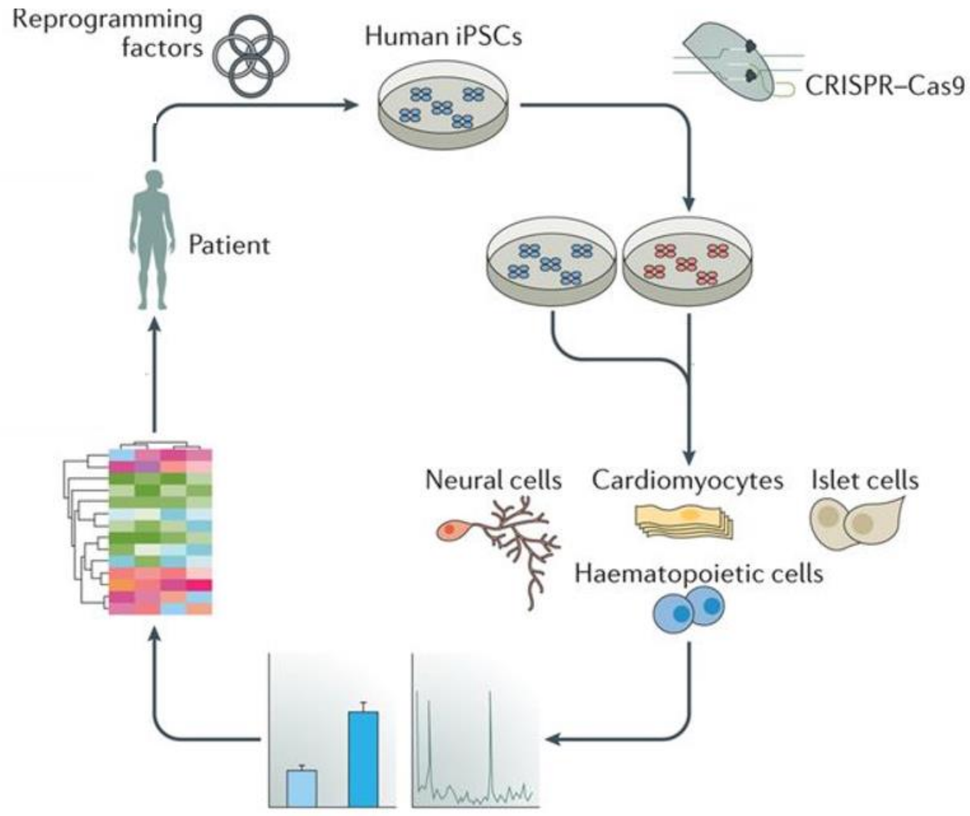
hiPSC-CMs successfully replicate the fundamental cellular characteristics of patients CMs in vitro

↓

High control on functionally healthy and diseased human CMs

↓

In vitro drug tests and preclinical cardiology



Ionic model for Atrial-like hiPSC-CMs

<u>I step:</u> Parameters update of the best Ventricular model, Paci 2020, using the same scaling of Paci 2013, considering virtual basic fitting parameters of mixed phenotypes

$$f: \alpha_{bf} \mapsto \alpha_v$$

$$g: \alpha_{bf} \mapsto \alpha_a$$

$$\alpha_a \mapsto g(f^{-1}(\alpha_v))$$