Computational model of defibrillation: Importance of fibrotic content in modifying the virtual electrode strengths

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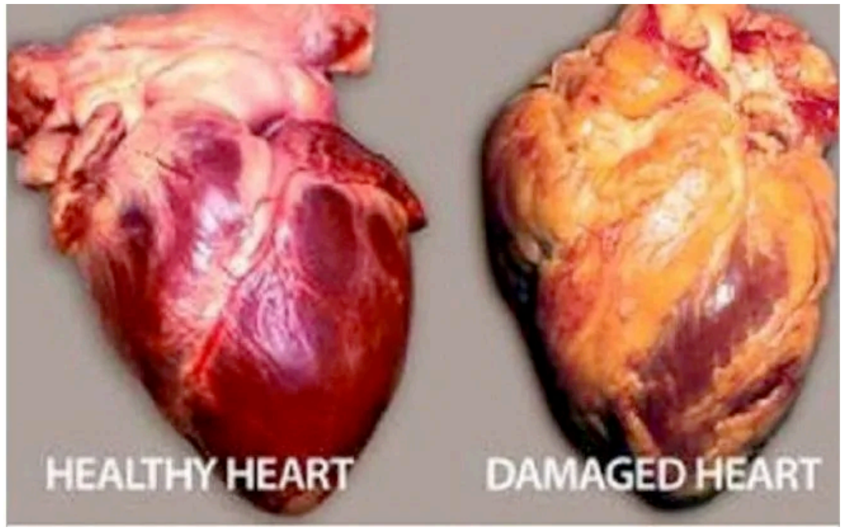
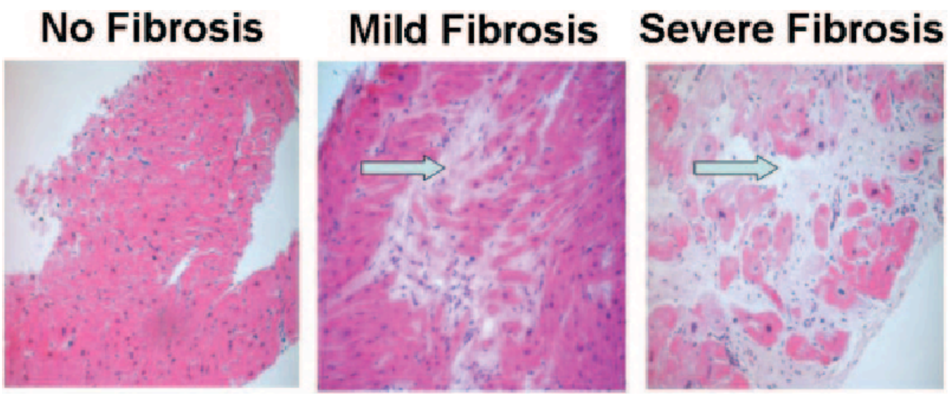
2nd TRANSCARDIO, Translational Sciences in Cardiology
BCN, Wednesday 19/12/2018

Are defibrillators working better on a damaged heart ?



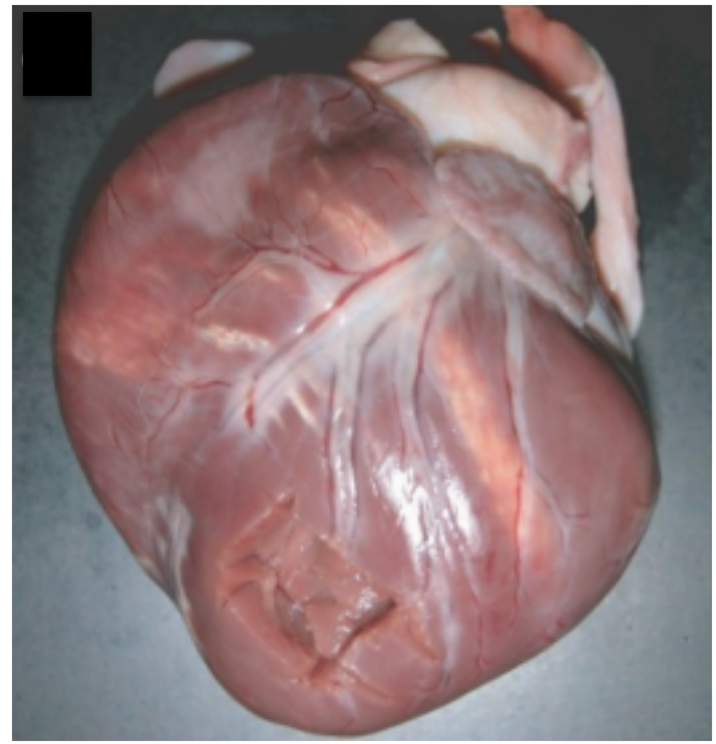
If yes, quantify to which extend ?

Is the defibrillatory shock more efficient in presence of fibrotic tissue ?



Cardiac fibrosis refers to proliferation
of cardiac fibroblasts.
The cardiac muscle is stiffer and
it is seen in the progression to heart failures.

Fibrotic (canine) heart



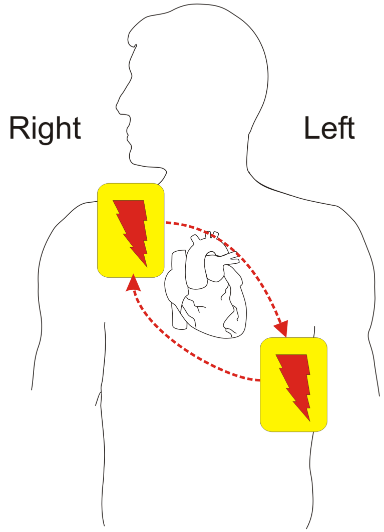
Fibrotic sheep hearts (CVRTI, courtesy of Chao Huang)

Outline of the talk

- Introduction & motivations
- The mathematical model and the geometrical set-up (1D and 2D)
- Results from the simulations
- Discussions
- Conclusions & outlook

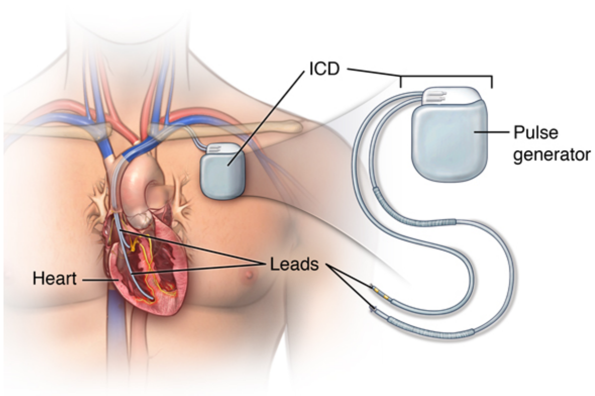
Cardiac defibrillation to restore the correct function

A controlled electric shock is applied to the heart in order to terminate the unstable or pulseless rhythm.

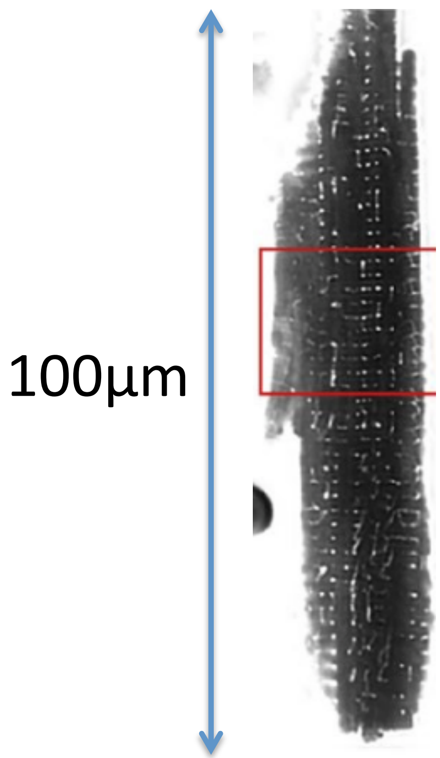


External shock ~ 150 Joules

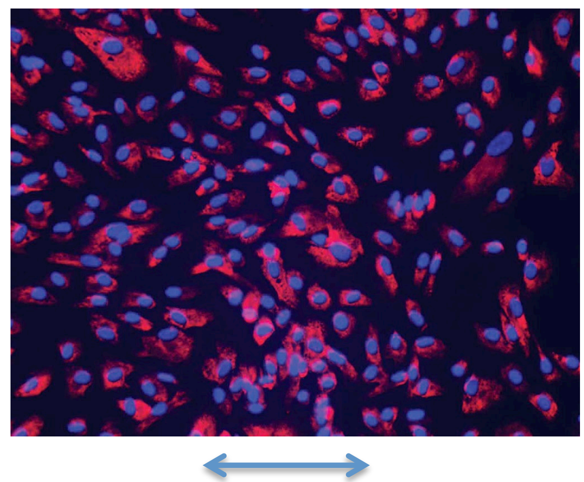
Internal shock ~ 25 Joules



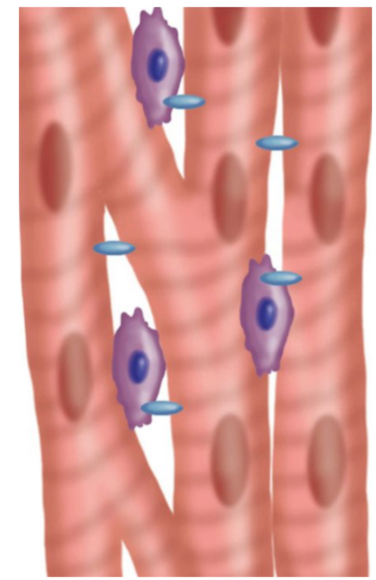
The cardiac tissue model will contain 3 “species”



Rabbit ventricular myocytes

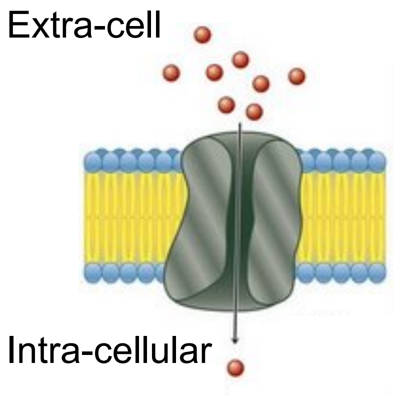


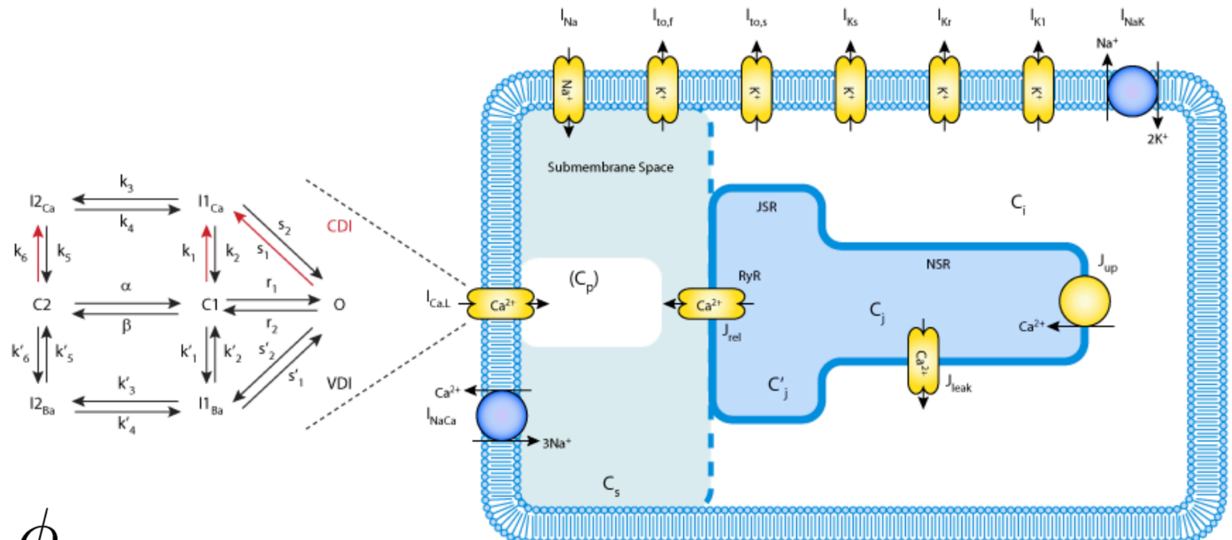
Ventricular cardiac fibroblasts



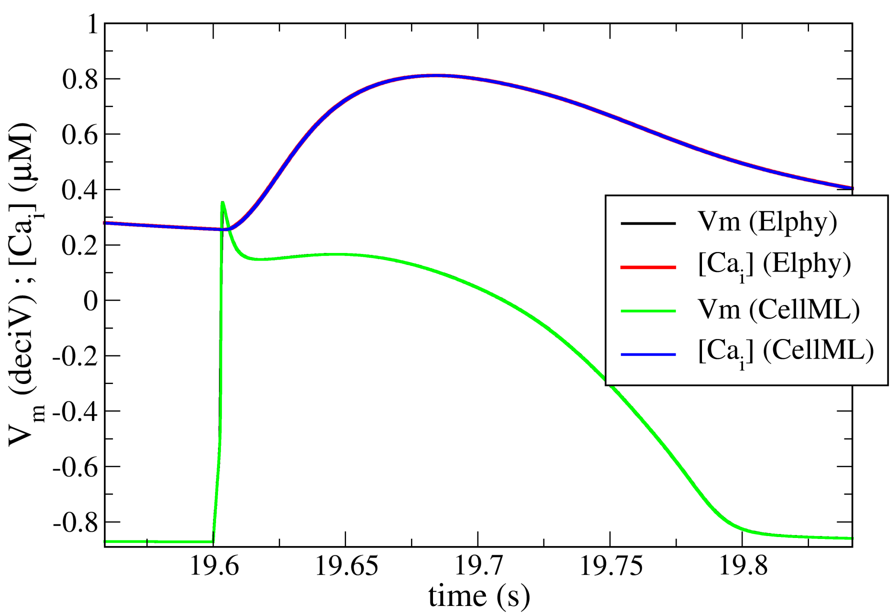
Extra-Cellular Matrix
(Blood, capillaries, proteins,...)

We use the Mahajan *et al*. rabbit model to describe the cell membrane for the cardiomyocytes





$$V_{myo} = \phi_{myo} - \phi_e$$



The Mahajan model was developed

to model the rabbit myocyte at high pacing.

26 State Variables

(V_{myo}) + 16 gate Variables (m, h, j, …) ;

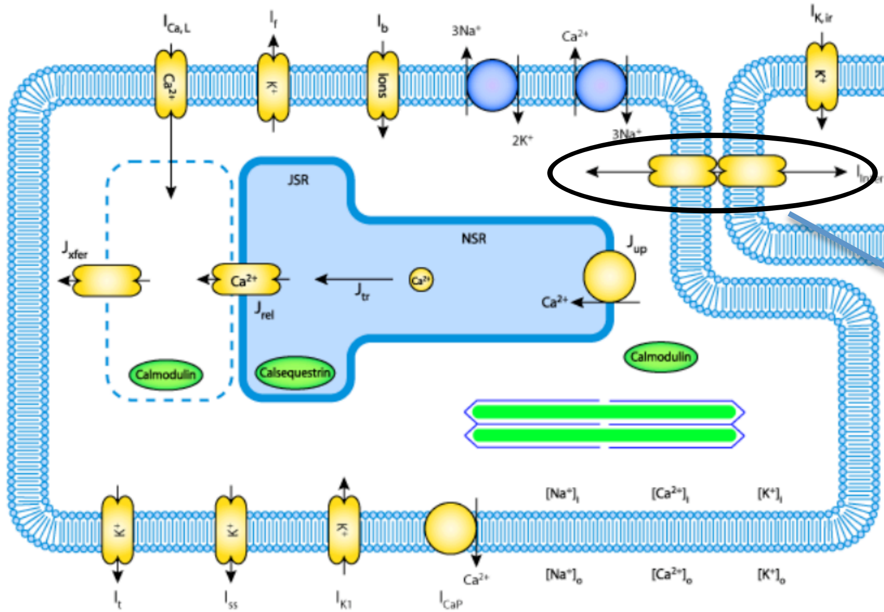
8 concentration Variables.

Mahajan et al. ,
2008 *Biophysical Journal*, 94(2):392-410
PubMed ID: 18160660

We use the Sachse *et al.* model to describe the cell membrane for the cardio-fibroblast

NB: The fibroblasts are not excitable cells unlike the cardio-myocytes

V_{myo}



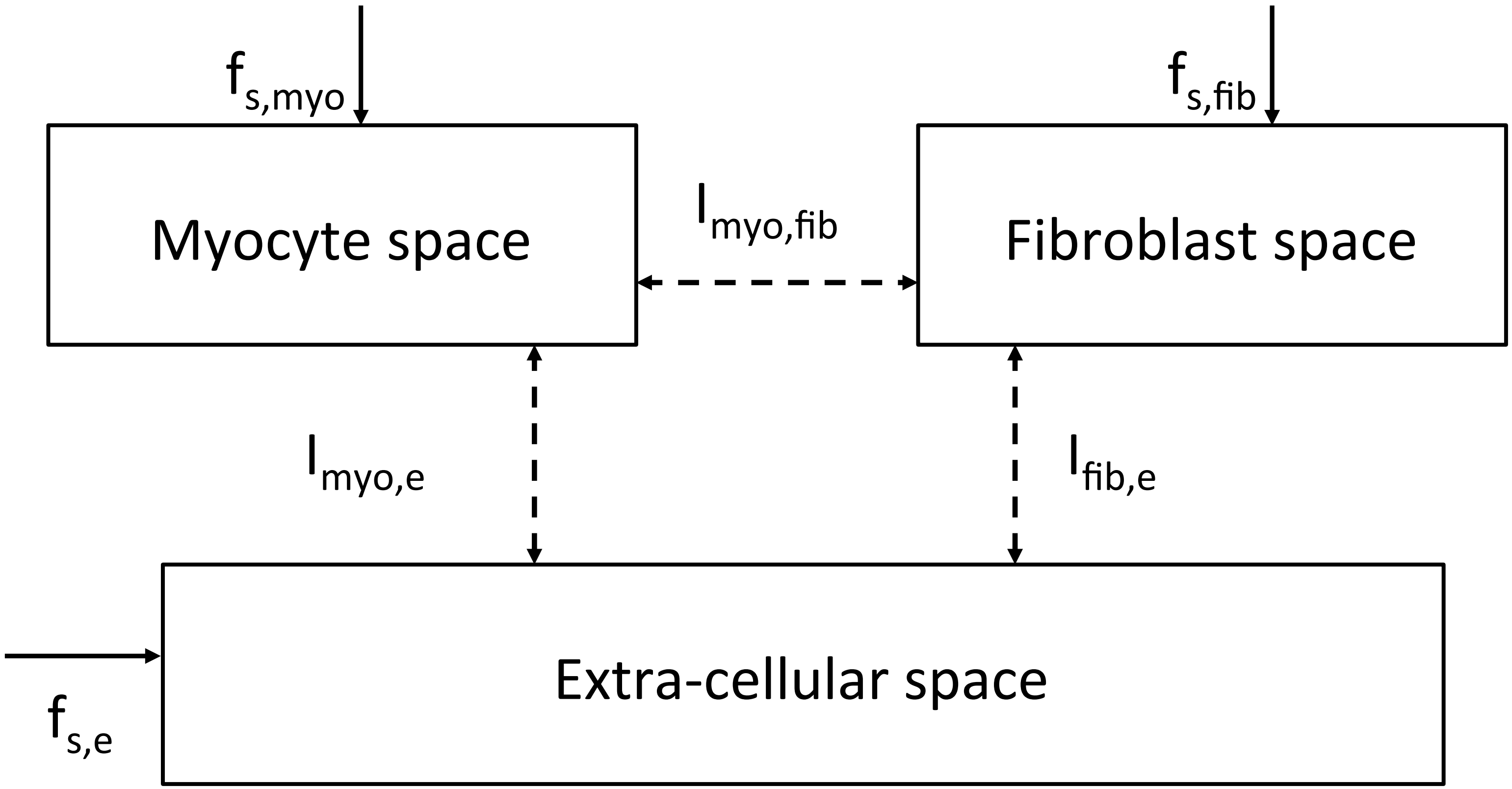
$$V_{fib} = \phi_{fib} - \phi_e$$

$$I_{myo,fib} = \frac{\phi_{myo} - \phi_{fib}}{R_{myo,fib}}$$

The electric coupling term between the myocytes and the fibroblasts is a crucial parameter of our study. Rmyo,fib is not easily determined experimentally !

Electrophysiological Modeling of Fibroblasts and Their Interaction with Myocytes, F.B. Sachse et al.,2008, Annals of Biomedical Engineering PubMed ID: 17999190

We use the extended bidomain model to implement the spatial coupling between the model constituents

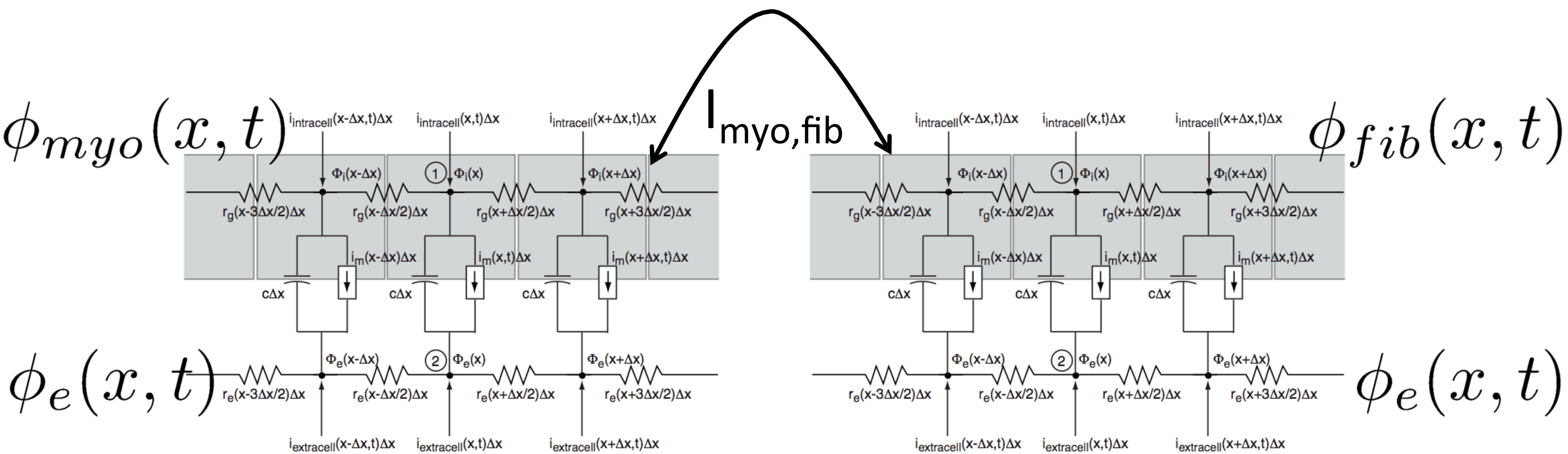


Sachse et al. (2009) A model of electrical conduction in cardiac tissue including fibroblasts. Ann Biomed Eng, 37, 874-889.

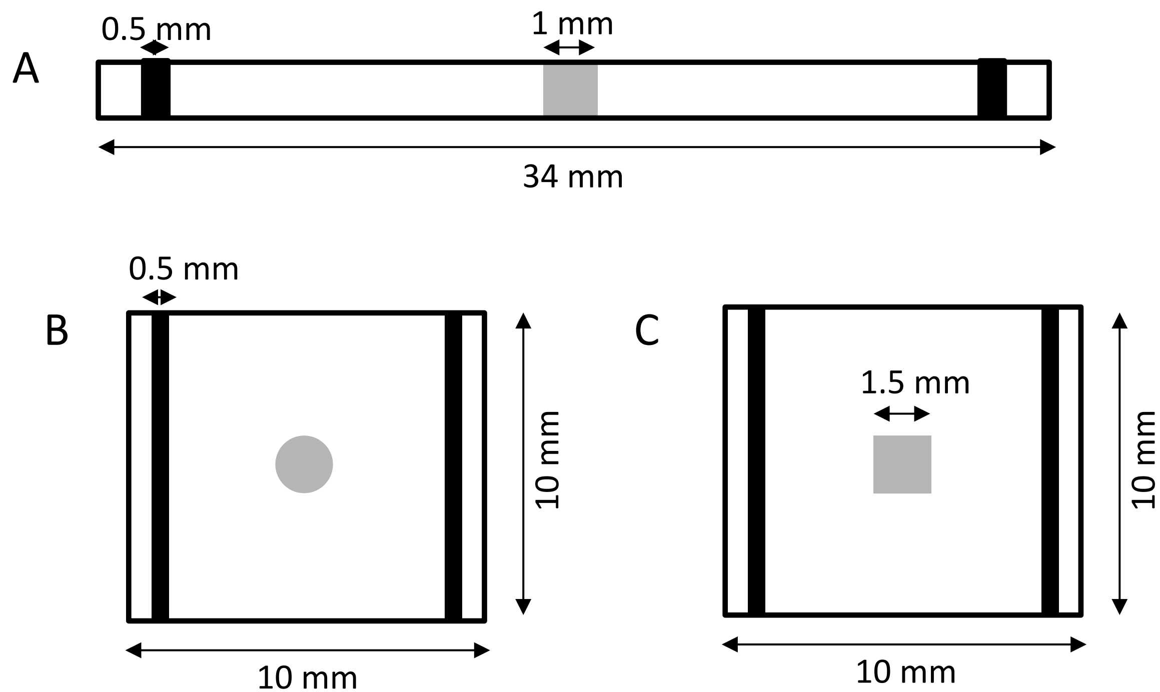
Extended Bidomain model at the tissue level

Based on current conservation (Kirchhoff's laws)
we can write 3 Poisson equations (1 for each domain)

$$\begin{cases} \nabla\cdot(\sigma_{myo}\nabla\phi_{myo}) = -f_{s,myo} + \beta_{myo,fib}\, I_{myo,fib} + \beta_{myo}\, I_{myo,e} \\ \nabla\cdot(\sigma_{fib}\nabla\phi_{fib}) = -f_{s,fib} - \beta_{myo,fib}\, I_{myo,fib} + \beta_{fib}\, I_{fib,e} \\ \nabla\cdot(\sigma_{e}\nabla\phi_{e}) = -f_{s,e} - \beta_{myo}\, I_{myo,e} - \beta_{fib}\, I_{fib,e} \end{cases}$$



The geometrical set-ups



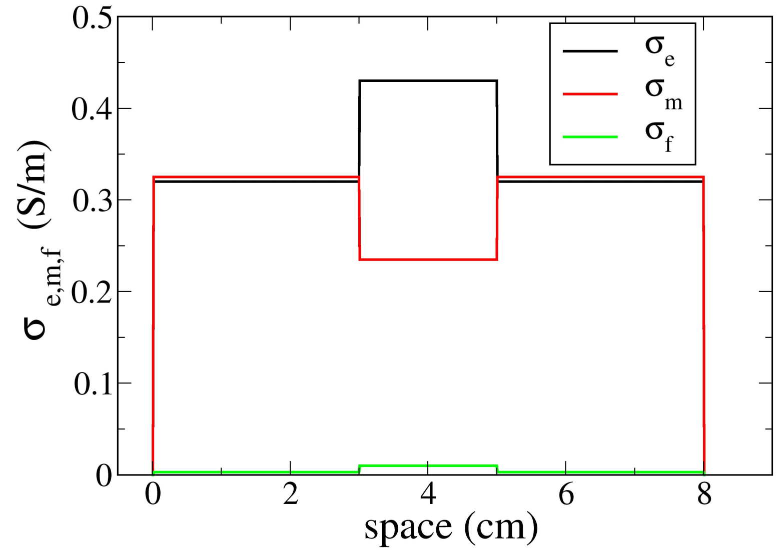
We will study 1D and 2D fibrotic patches immersed in a normal “control” tissue.
The characteristic of the fibrotic patch are determined by the volume fractions of the 3 species.
The conductivities are assumed to vary linearly with the volume fractions.

$$\sigma_{fib} = Vol_{fib}\,\bar{\sigma}_{fib}$$

The 3 sets of parameter values

Volume fractions used here

Domain	Control	Patch (mild)	Patch (severe)
Extra.	0.32	0.43	0.60
Myo.	0.65	0.47	0.20
Fib.	0.03	0.10	0.20

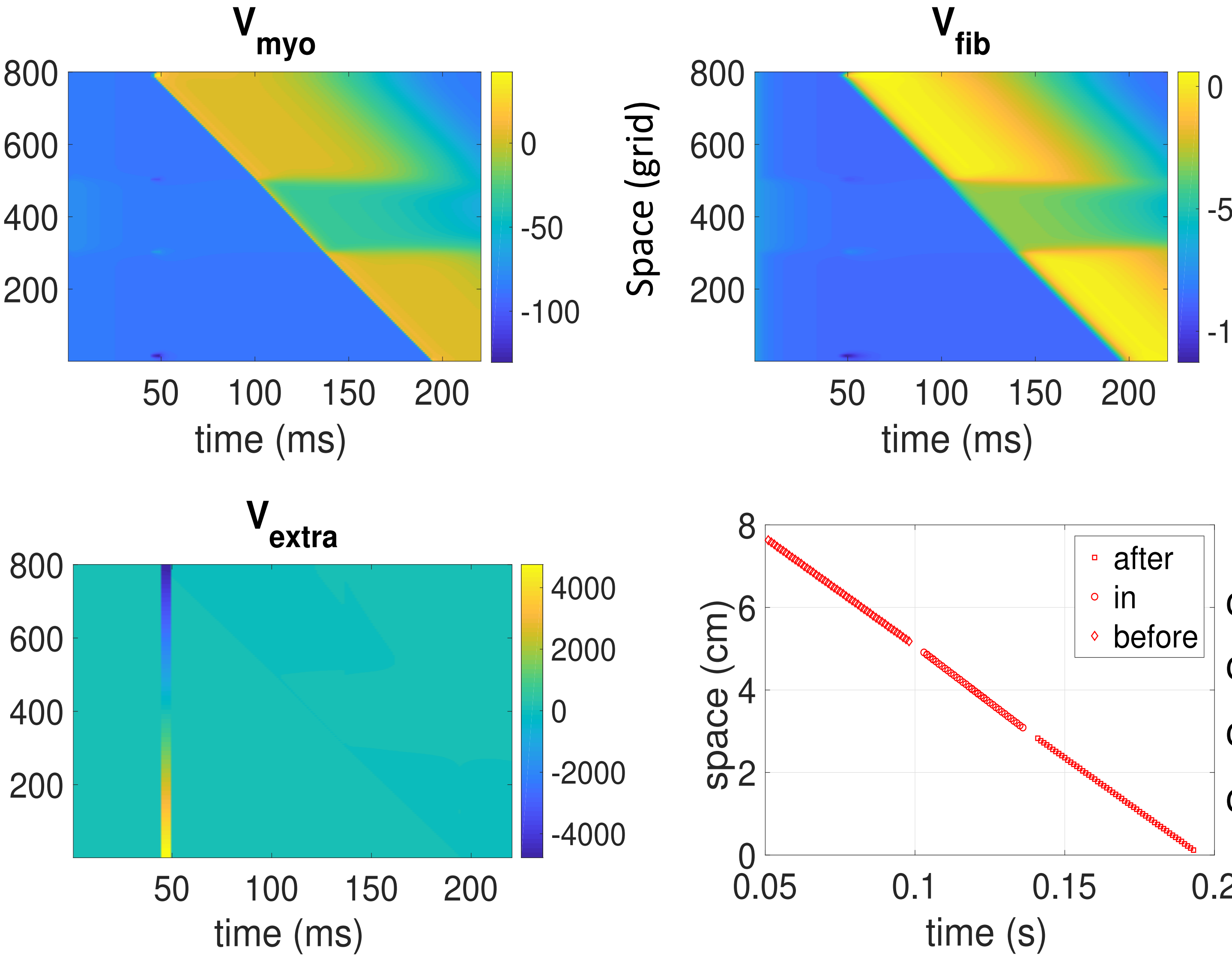


	Myocyte	Fibroblast	Extra-cellular
Conductivity (S/m)	0.5	0.1	1
Beta (cm)^(-1)	2500	16800	-

V_{fib}= 0.268 pL
$R_{myo\text{-}fib}$ varied (MΩ—TΩ)
$Stim_{duration}$ = 5 ms
$E_{applied}$ = 0.546 (V/cm)
δx = 0.01 cm
δt = 0.001 ms
C_m = 1 $\mu F/cm^2$
$Elect_{width}$=0.5 mm

Greiner et al. Frontiers in Physiol., 04 April 2018 | https://doi.org/10.3389/fphys.2018.00239.

A benchmark simulation (mild fibrotic patch)



C_{myo} (bef.) = 52.14 (cm/s)

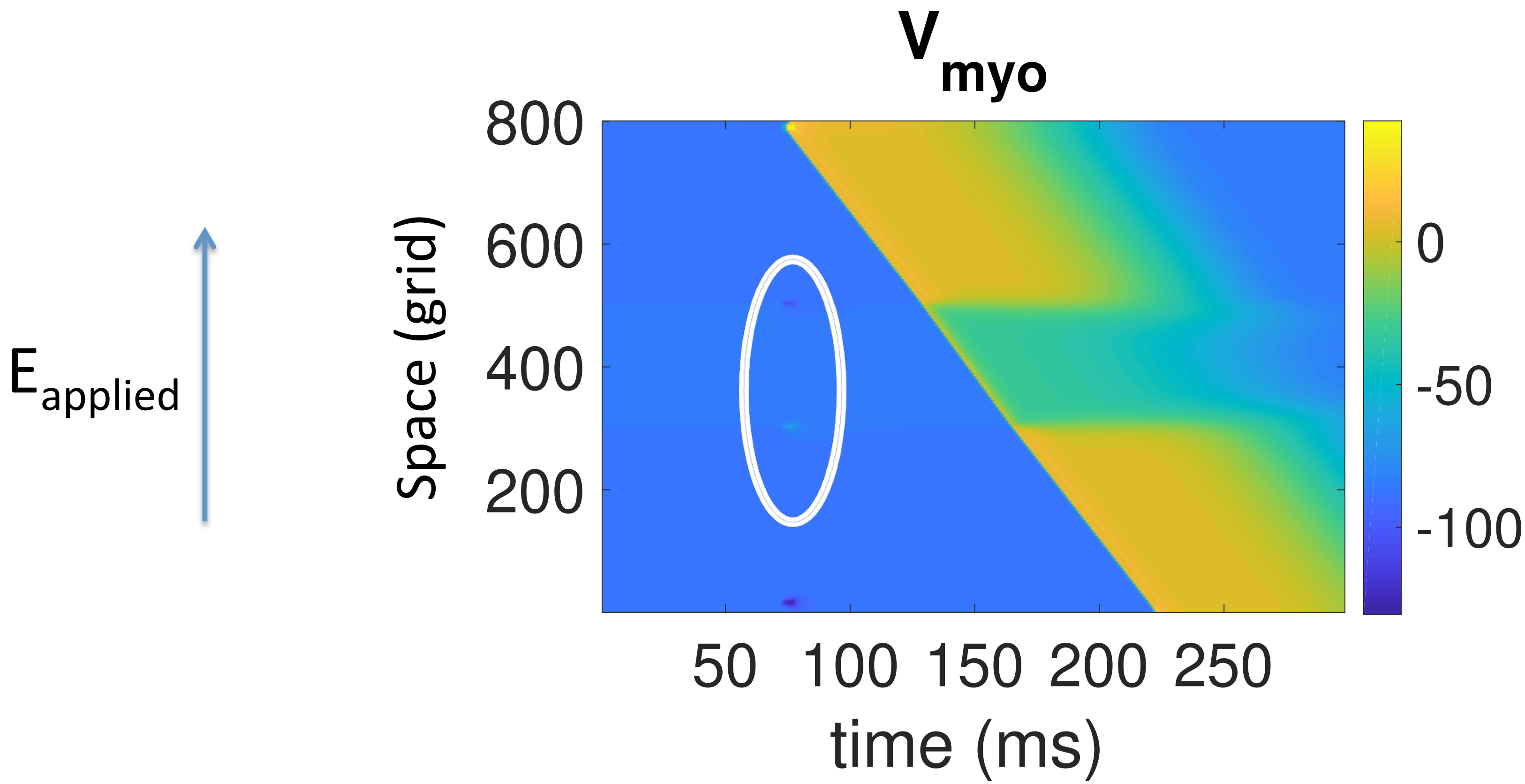
C_{myo} (in) = 55.26 (cm/s)

C_{myo} (after) = 52.07 (cm/s)

CPU_{time}= 92 s (single proc.)

mpiexec -np 1 ./**tridom_cabl_inhom_V1** -ksp_rtol 1.e-11 -ksp_type gmres -ksp_max_it 25000 -log_summary -pc_type asm -sub_pc_factor_levels 1

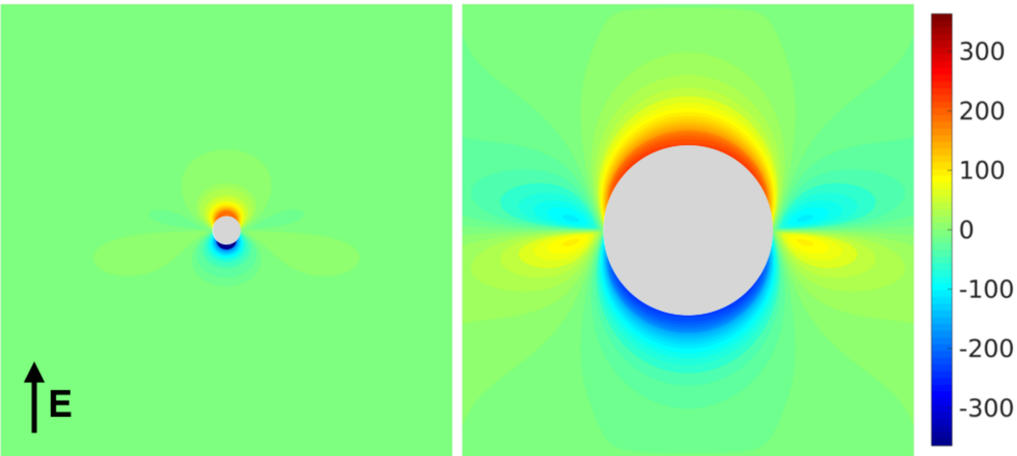
2 virtual electrodes (VE) are created at the patch boundaries during the shock stimulus



$$\frac{\partial V_{myo}}{\partial t} \propto -\left(\nabla \sigma_{myo}\right) \cdot E + \sigma_{myo} \nabla^2 \phi_e$$

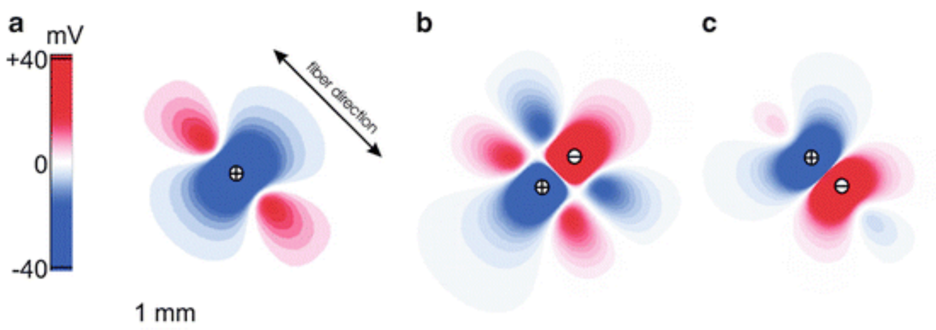
These VE are susceptible to elicit new action potentials during a defibrillatory shock

Virtual electrodes (VE) are important actors in defibrillation



Reference 1

"Virtual electrodes around anatomical structures and their roles in defibrillation"
Plos One 2017,
Adam Connolly , Edward Vigmond, Martin Bishop



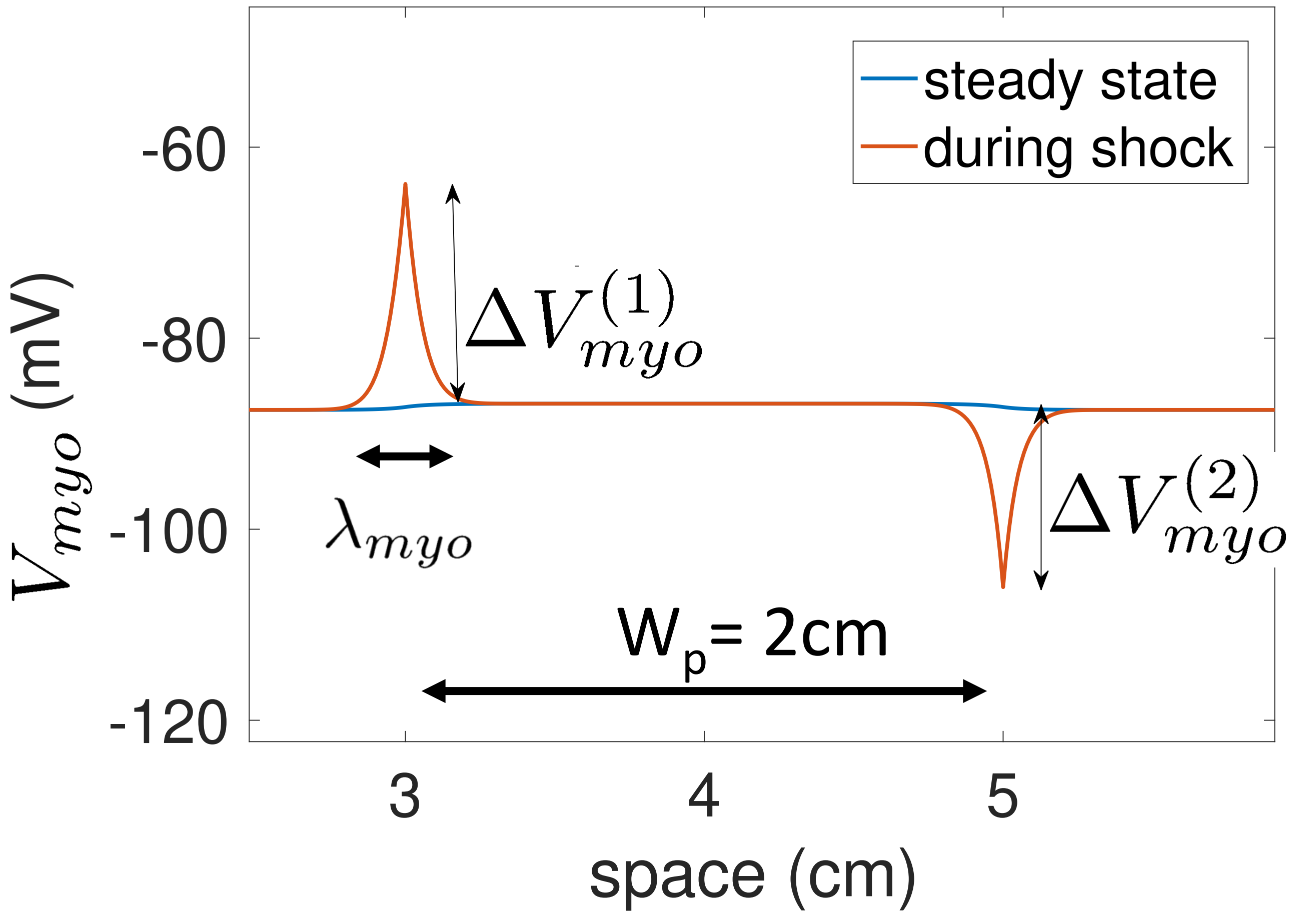
anodal current

bipolar stimulation

Reference 2

Imaging of Ventricular Fibrillation and Defibrillation: The Virtual Electrode Hypothesis
Advances in Experimental Medicine and Biology,
Boukens B.J., Gutbrod S.R., Efimov I.R. (2015)

We quantify the virtual electrode strengths at the fibrotic patch boundaries

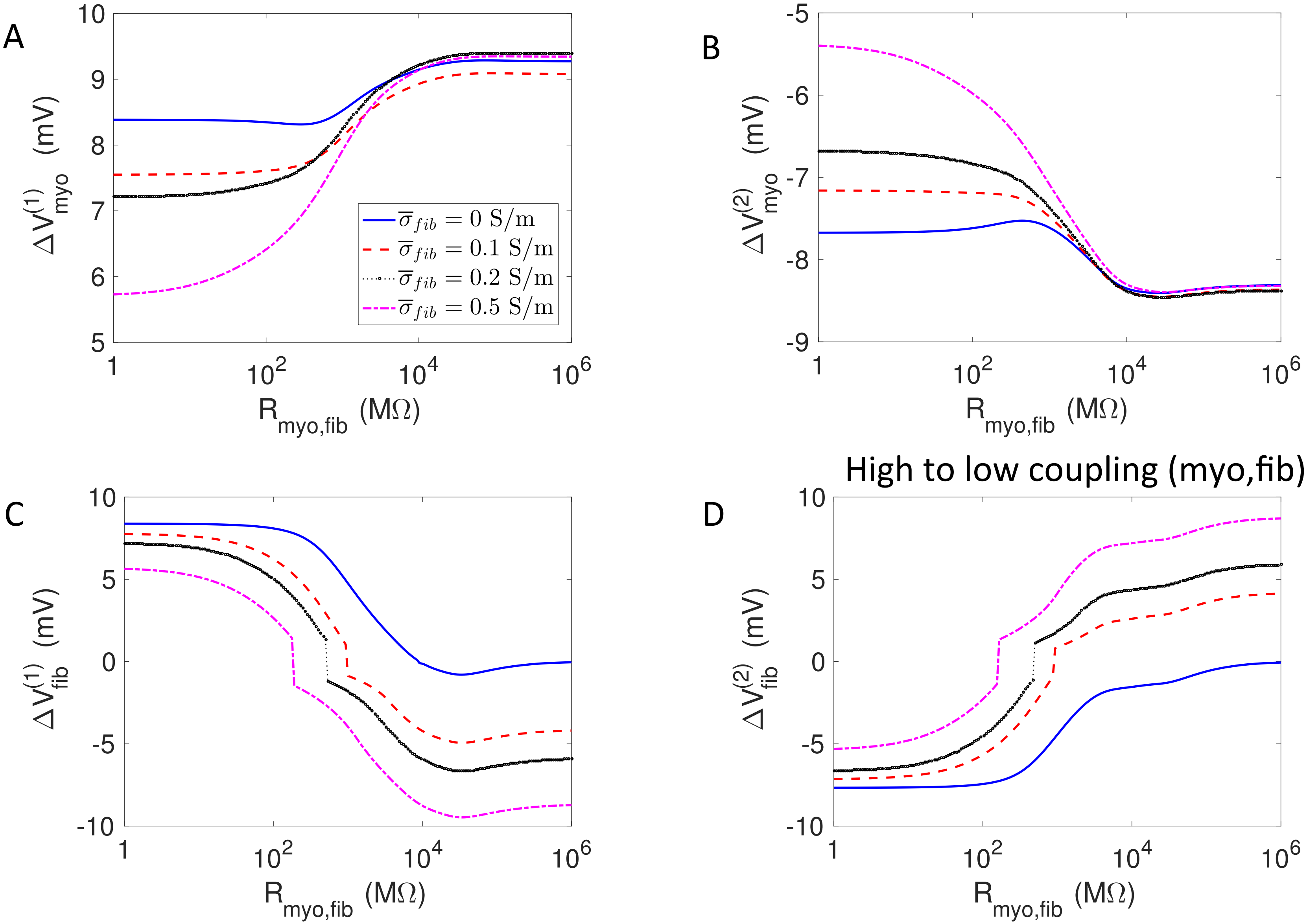


λ_{myo} is the electrotonic constant for the myocytes (≈ 0.6 mm)

Results for the virtual electrode strengths

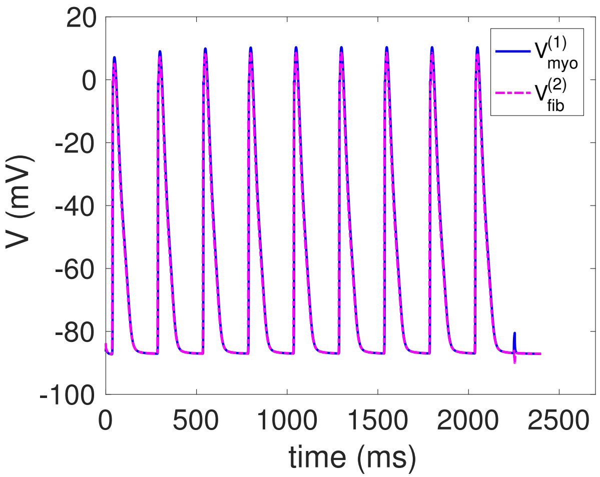
Protocol:
Transient of 9 waves followed by a sub-threshold excitation with current of 0.7e+5 (A/m^3) where we measure VE strengths

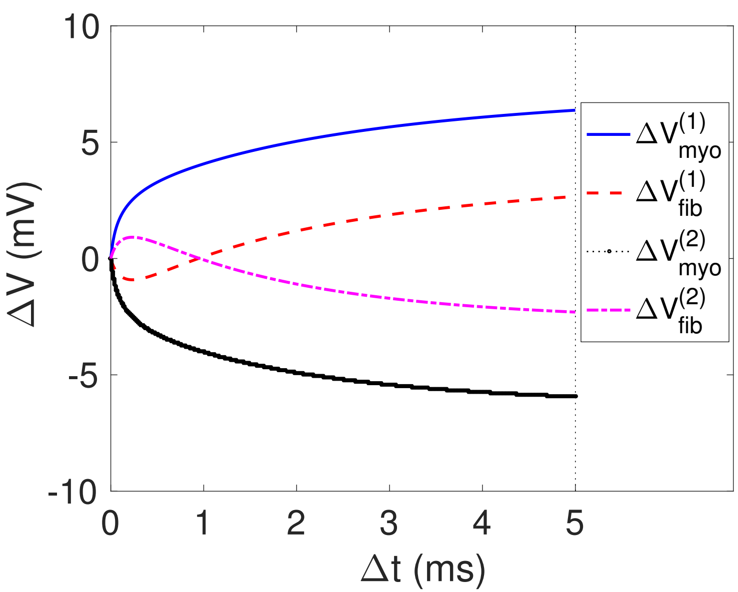
Average fibrotic patch results



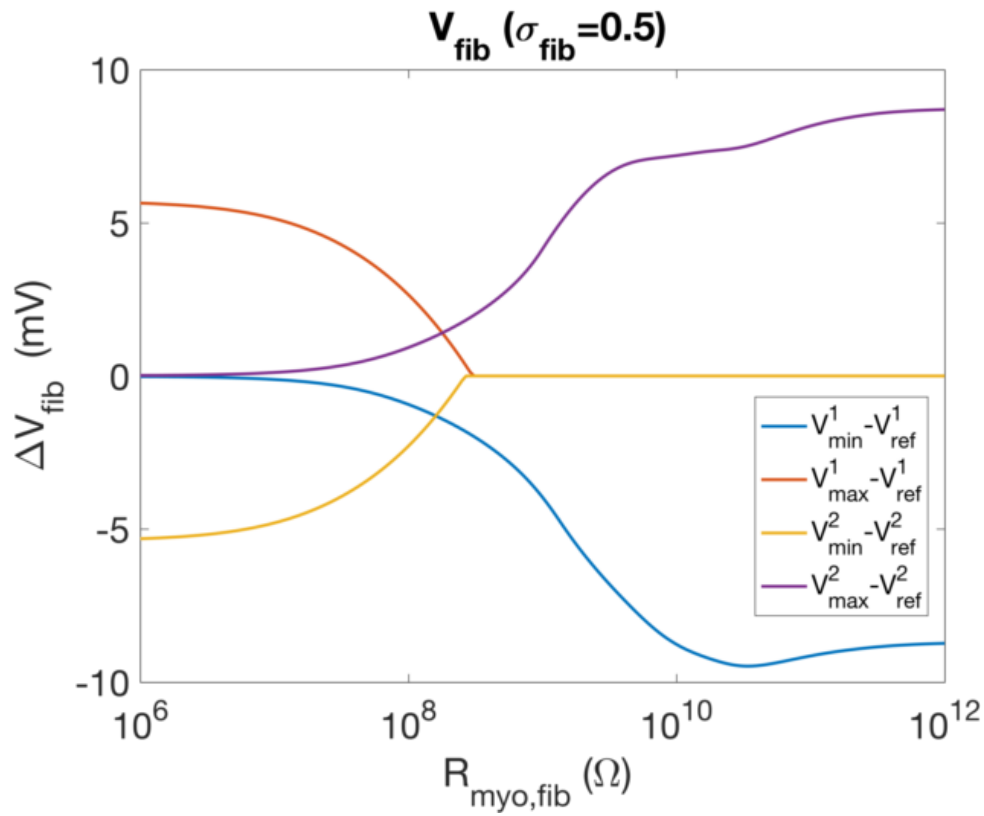
Increased electrical coupling of myocytes with fibroblasts reduced the virtual electrode strength.

Non-monotonous behavior for V_{fib} during the shock





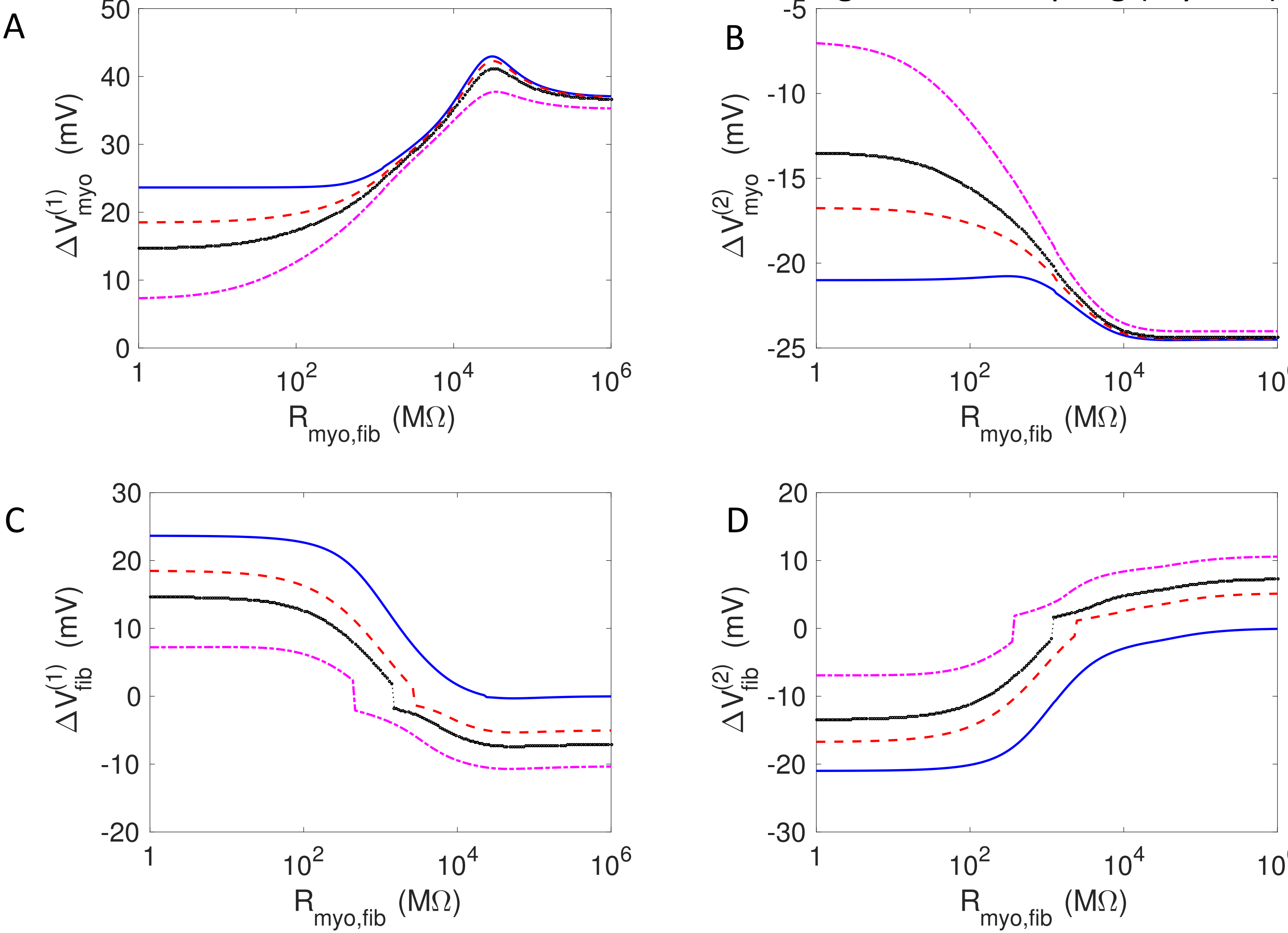
← Rmyo,fib=1e+8 Ω



This is a result of different terms with different time scales that are competing

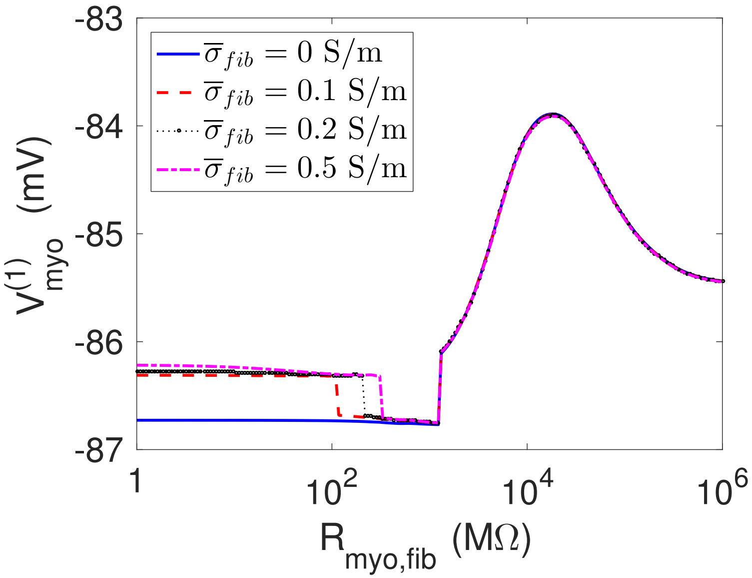
Extreme fibrotic patch results

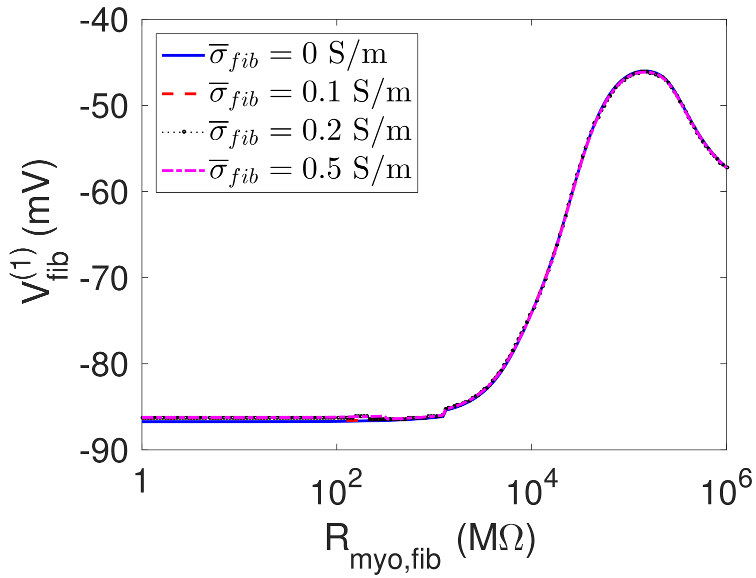
High to low coupling (myo,fib)



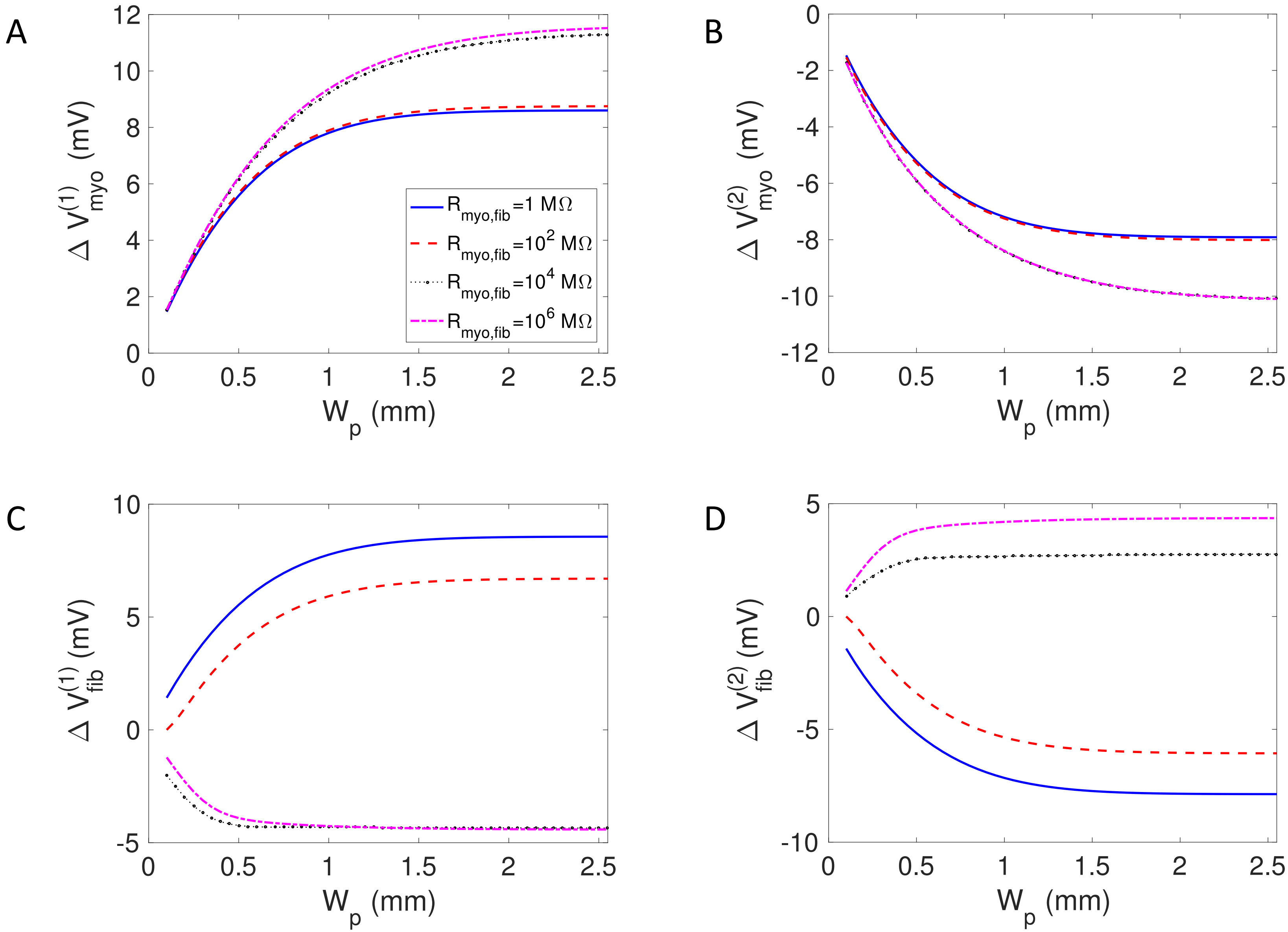
Intra-fibroblast coupling reduced VE strength in case of high myocyte-fibroblast coupling.

Extremum for $\Delta V_{myo}^{(1)}$ is explained by different initial states before applying the shock



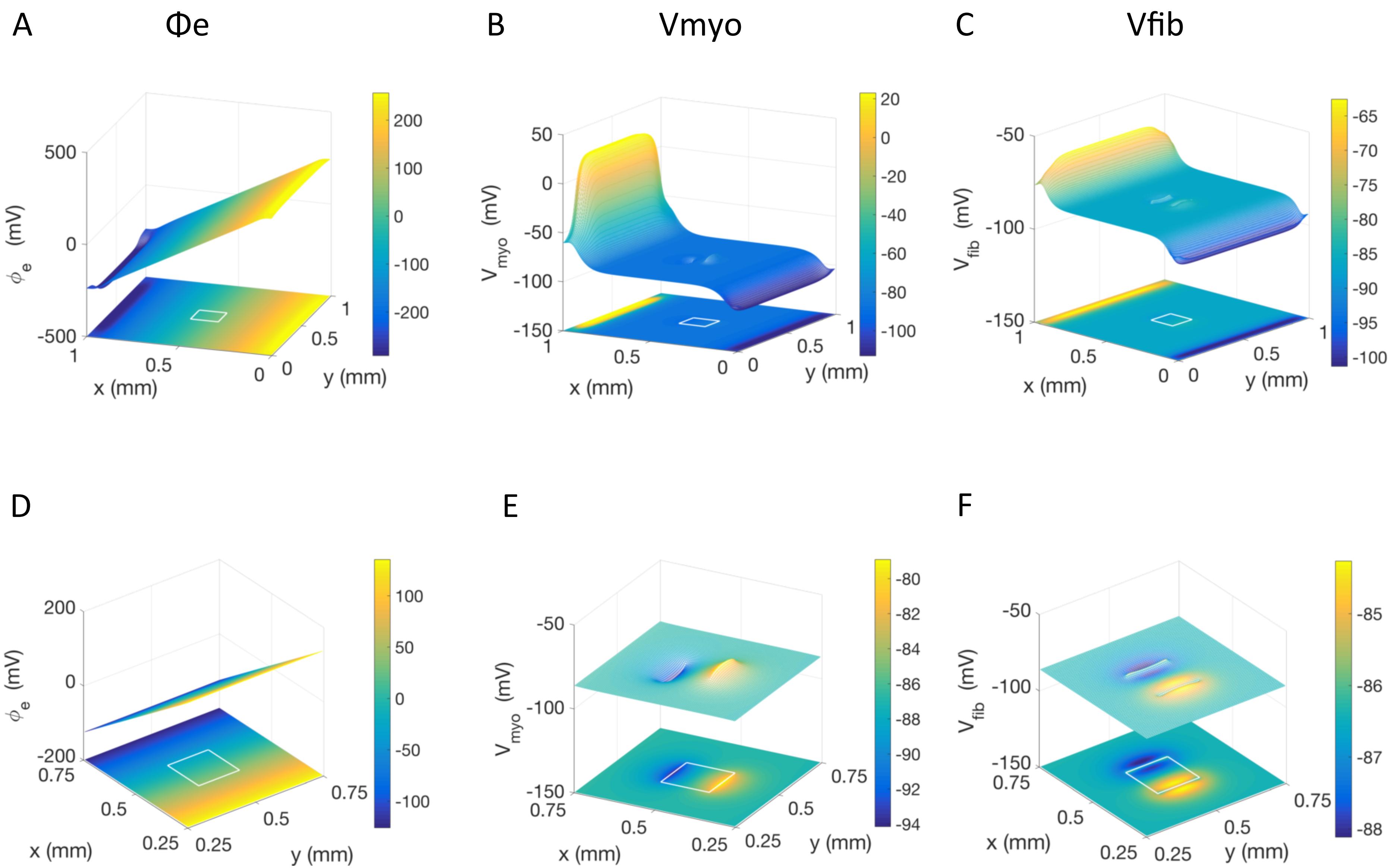


Fibrotic patch size W_p is a crucial parameter

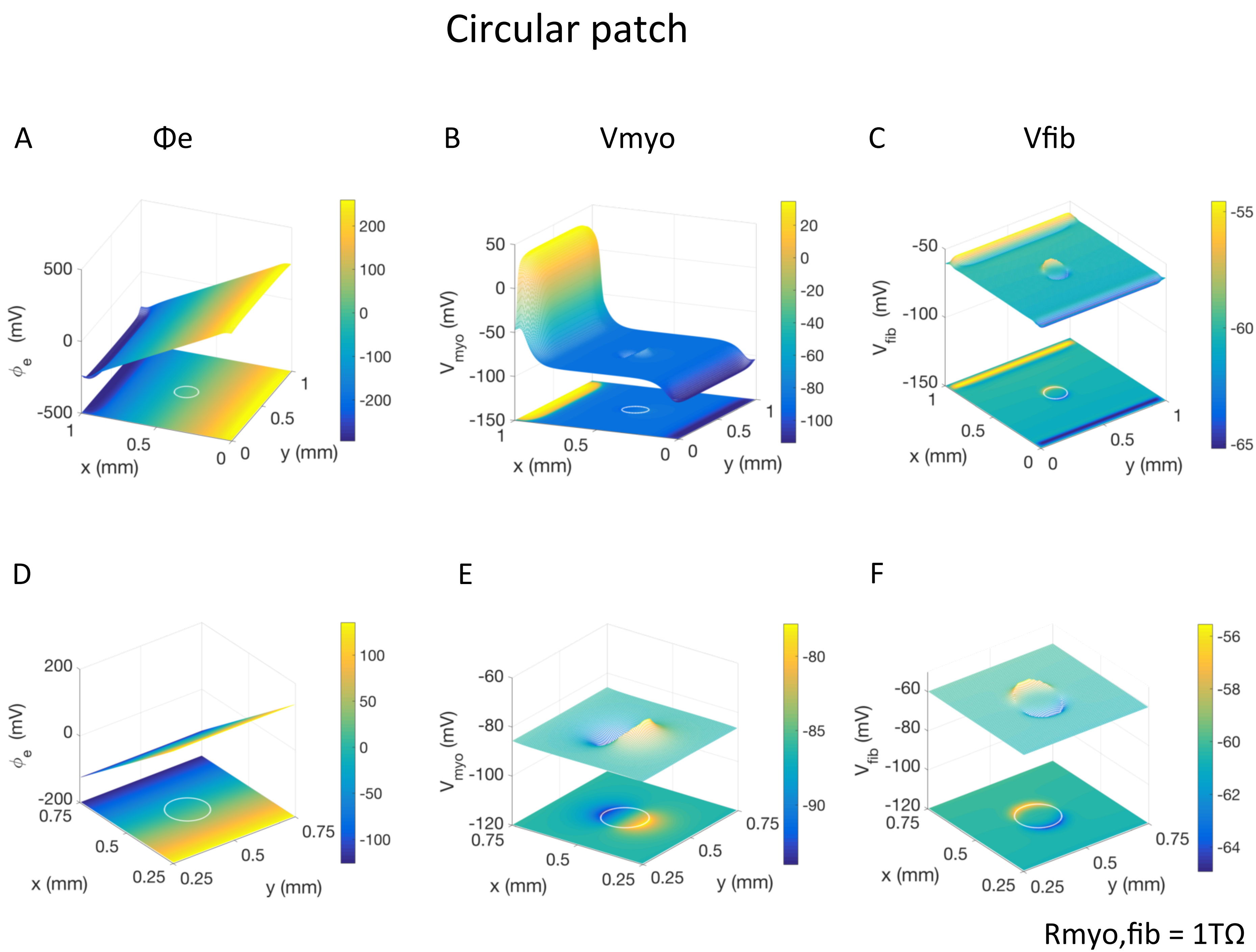


2D simulations

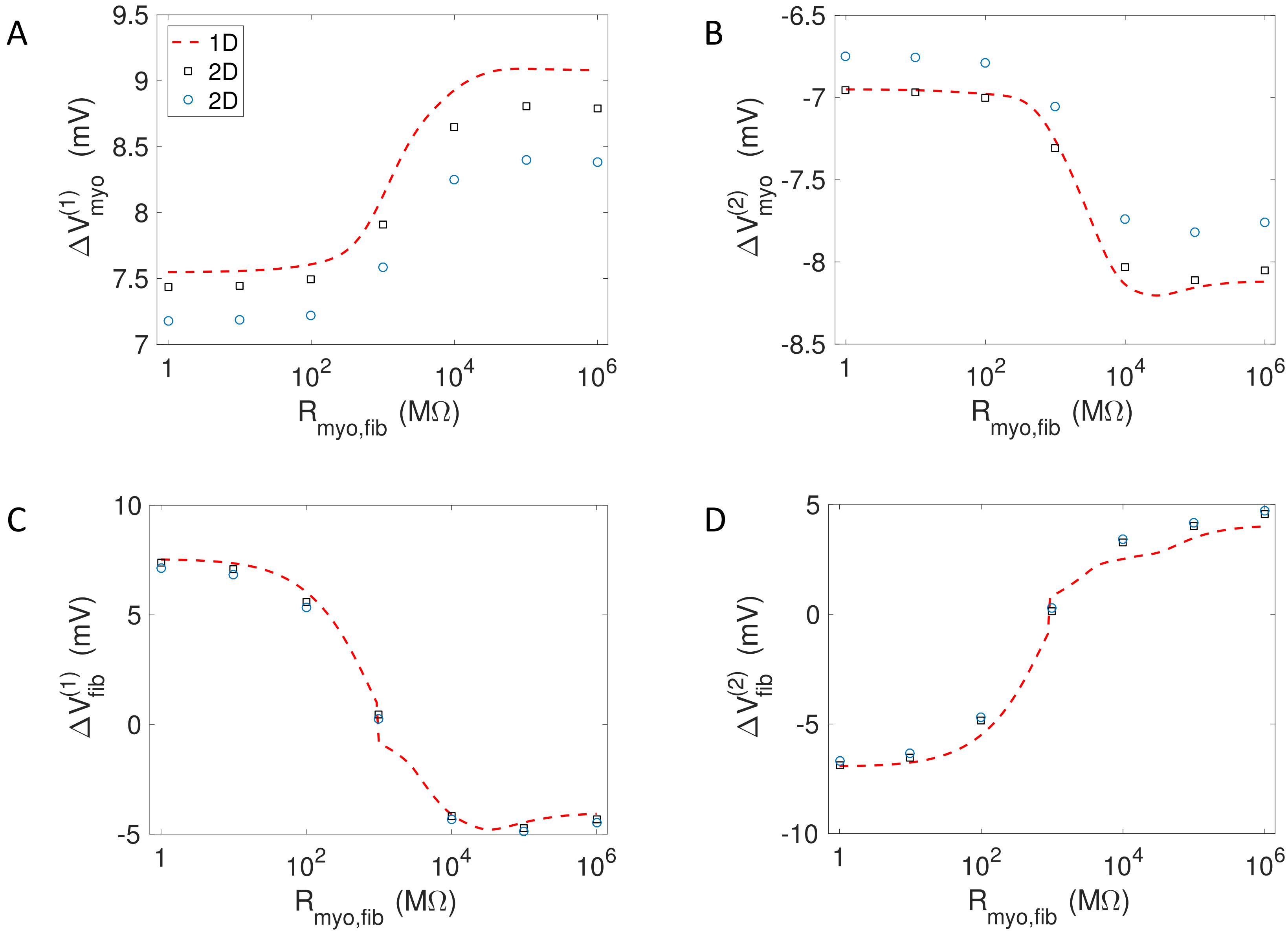
Square patch



Rmyo,fib = 1GΩ


Circular patch
A
Φe
B
Vmyo
C
Vfib
D
E
F
ϕ_e (mV)
V_{myo} (mV)
V_{fib} (mV)
x (mm)
y (mm)
Rmyo,fib = 1TΩ

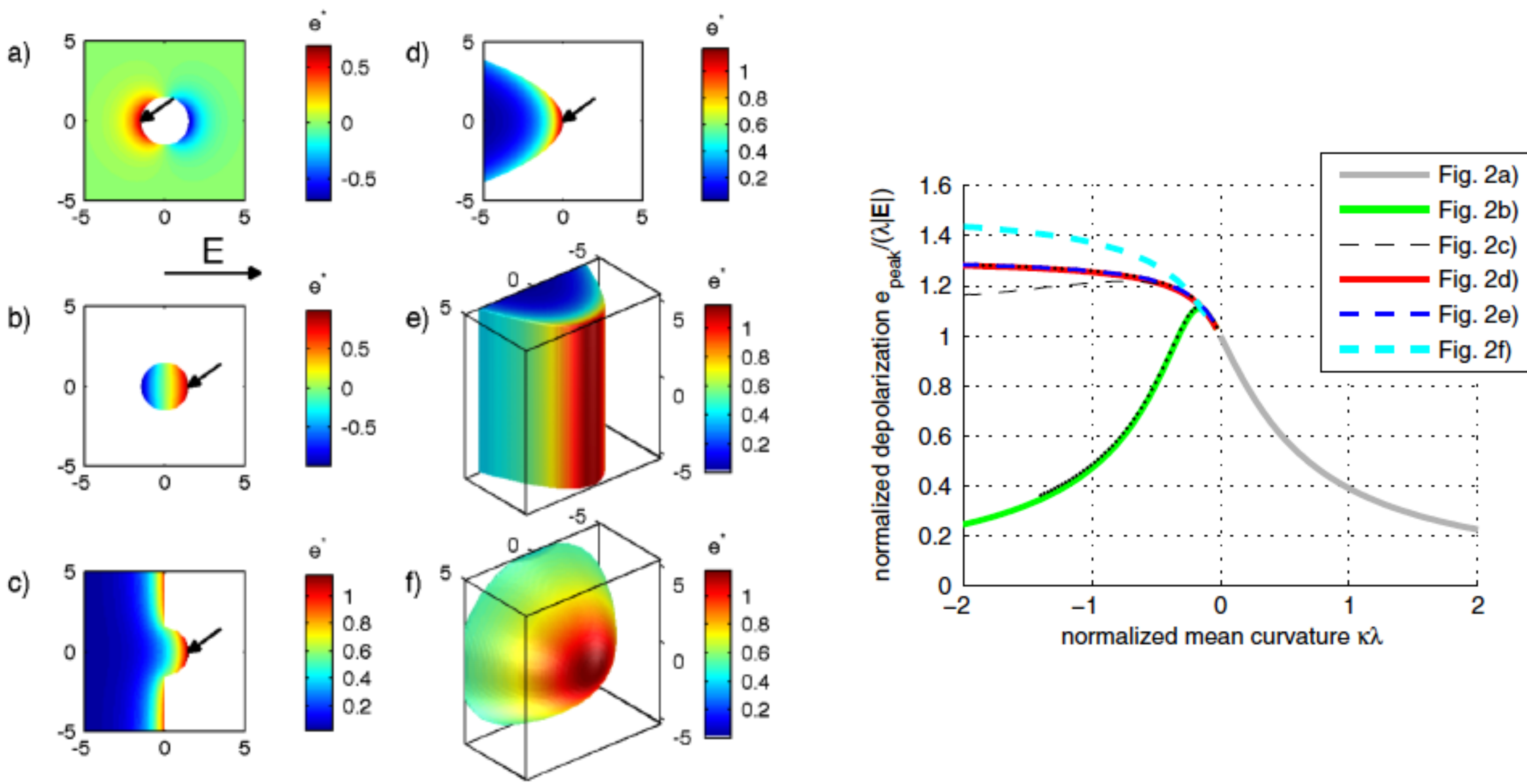
Comparison between the 1D and 2D results



PRL 109, 118106 (2012) PHYSICAL REVIEW LETTERS week ending 14 SEPTEMBER 2012

Negative Curvature Boundaries as Wave Emitting Sites for the Control of Biological Excitable Media

Philip Bittihn,[1,2,3,*] Marcel Hörning,[4,5] and Stefan Luther[1,2,3,6]



Conclusions

- Fibrotic patches constitute potential sites for wave initiation in response to defibrillation.
- Our study showed that an increased degree of fibrosis

and an increased size of the fibrotic patch cause an increased strength of virtual electrodes.

- Increased electrical coupling of myocytes with fibroblasts

reduced the virtual electrode strength.

- Intra-fibroblast coupling reduced virtual electrodes

in case of high myocyte-fibroblast coupling.

- Geometrical (curvature) factors are important
- Future…better design for optimized “low energy” defibrillation.

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Max Planck Göttingen (A. Witt, S. Luther,...)

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