Comparison of defibrillation protocols through a simple cardiac dynamical model

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Outline of the talk

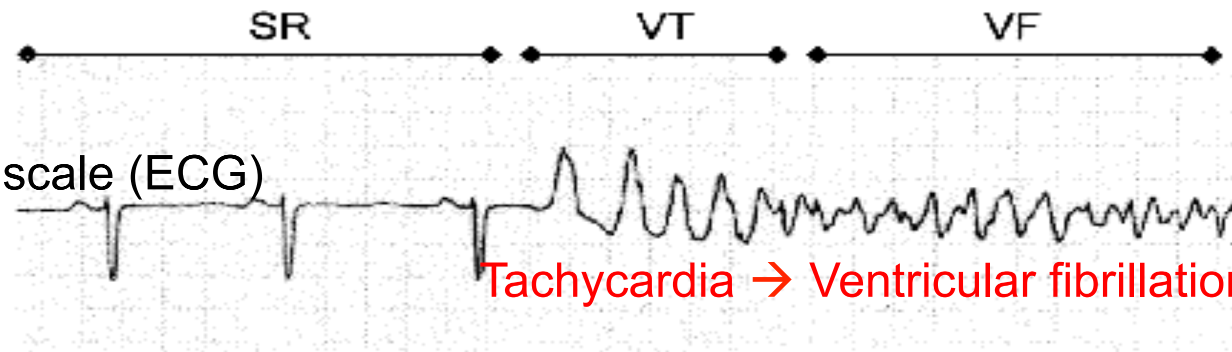
- Introduction (Cardiac (de)-fibrillation)
- A 3D mathematical model
- The simpler one-dimensional model

Applications

- Two-electrode defibrillator
- Four-electrode defibrillator
- Statistical considerations
- Conclusions & Outlook

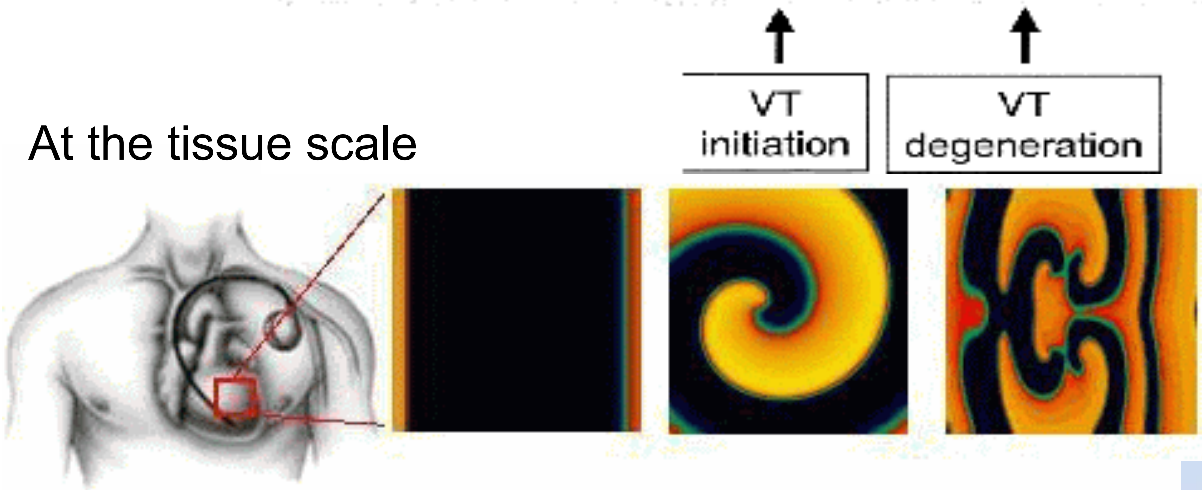
Cardiac fibrillation is a wrong electrical activity

At the body scale (ECG)



Tachycardia → Ventricular fibrillation

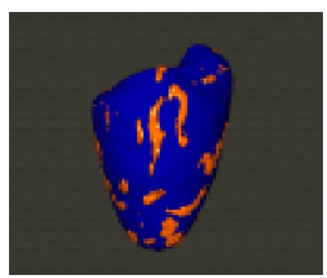
At the tissue scale

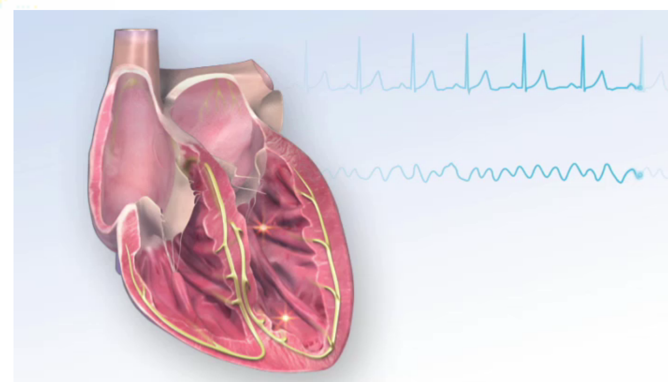


Color coding represents the cardiac electrical activity

Action Potentials

= Nonlinear Waves



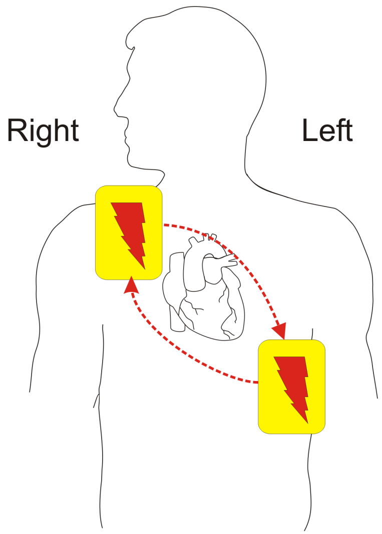


Cherry *et al*. New J. Phys. **10** (2008) 125016

AHA movie

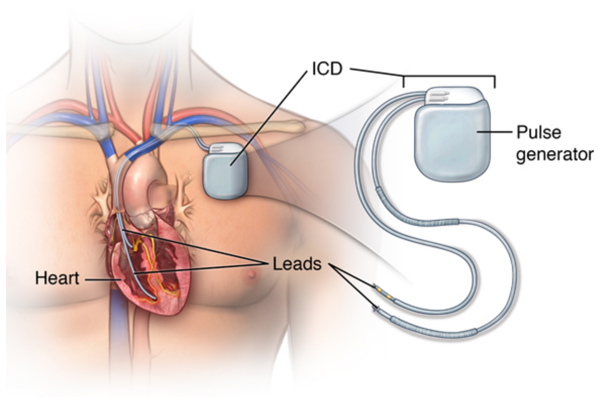
Cardiac defibrillation to restore the correct function

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

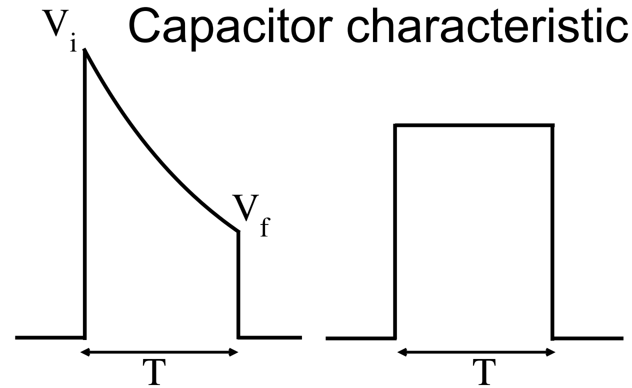


The design of new defibrillators is a complex problem

Many parameters enter in the design of new defibrillator devices.
Since the 1990's all the defibrillators are biphasic.

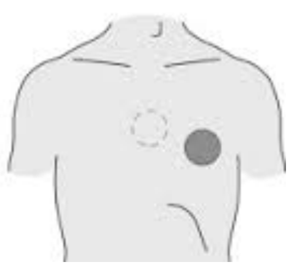
- Waveform design (shape, simple models)
- Shock timing
- Biphasic versus Monophasic
- Placement of the electrodes
- …

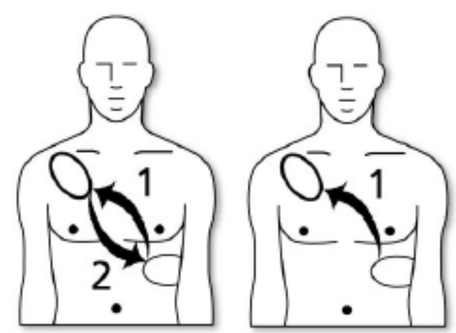
Capacitor characteristic



Anterior-apex

Anterior-posterior

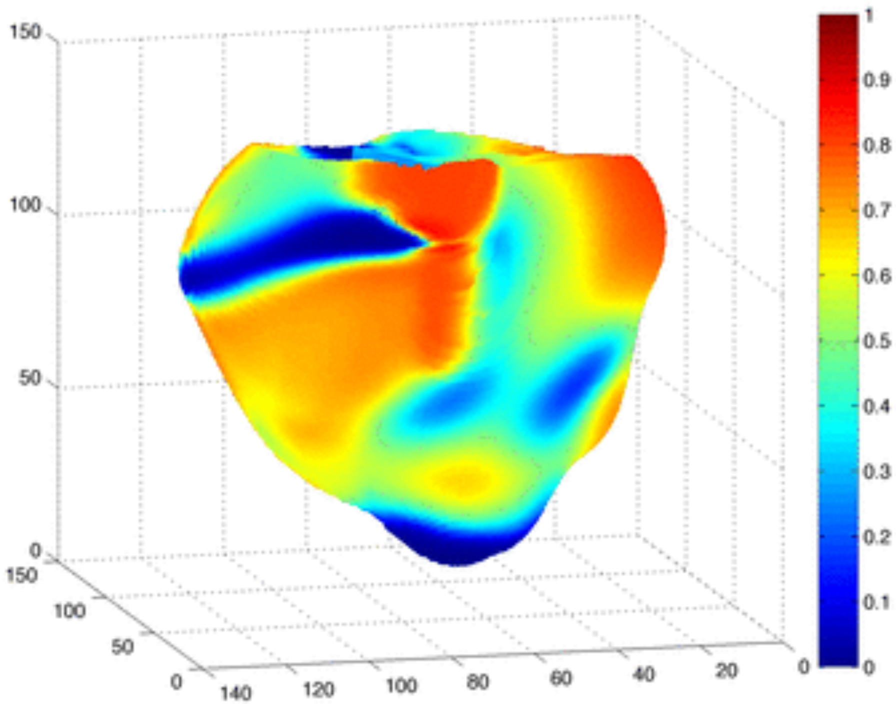


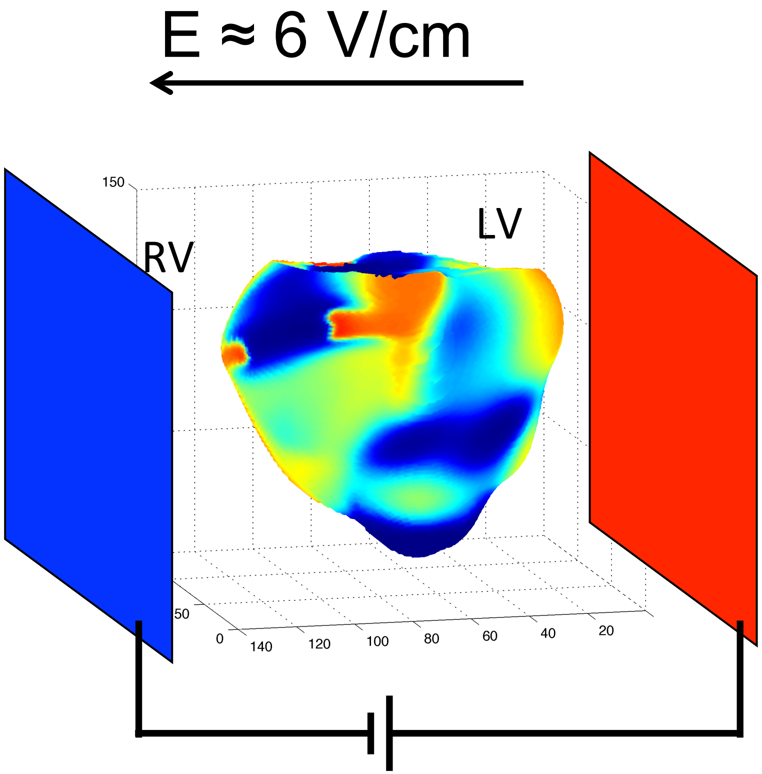


Biphasic ~ 150 J

Monophasic ~ 200 J

A 3D numerical model of cardiac defibrillation

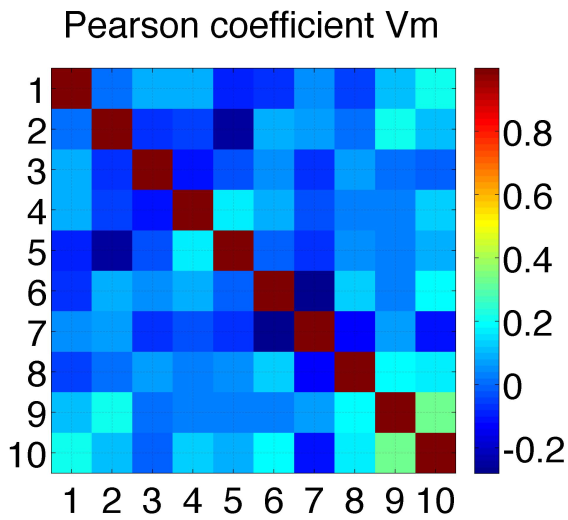


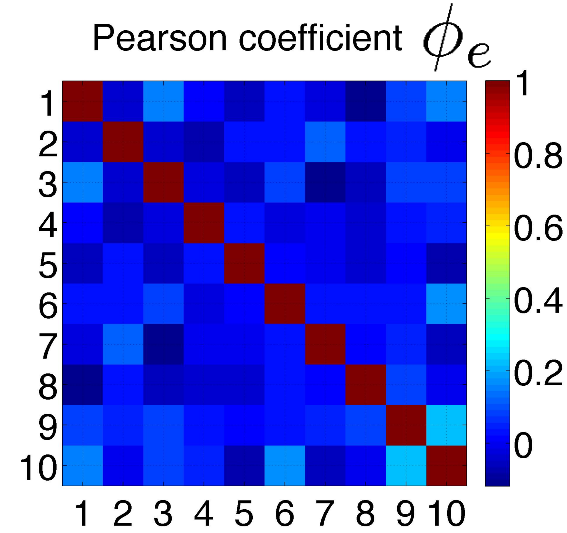


CPU time ~ 4 hours on a 8-core fast computer (2 x i7).

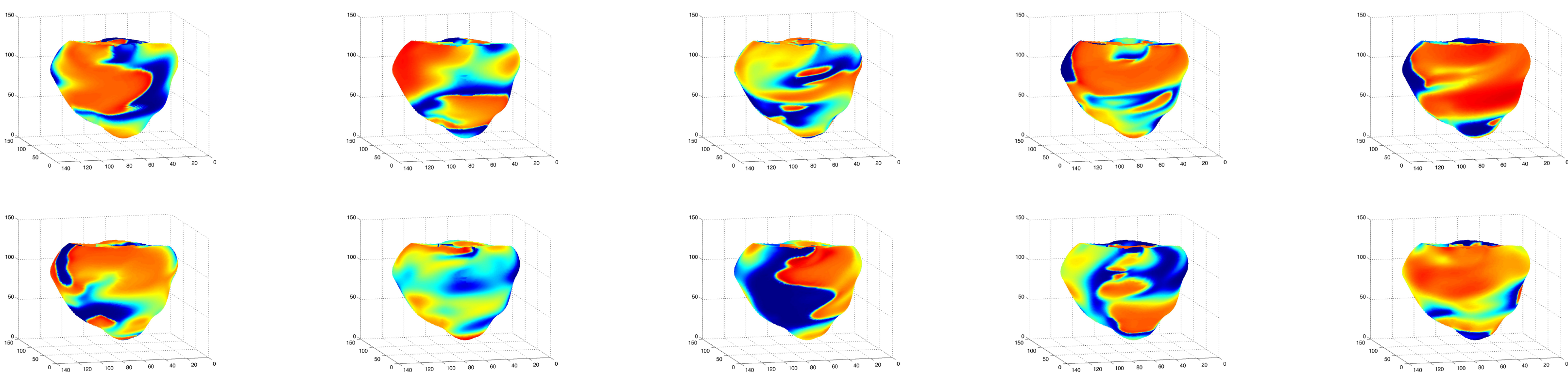
Bragard *et al*. (CinC), 2013, 851-854.

For testing 3D defibrillation, 10 ICS were selected

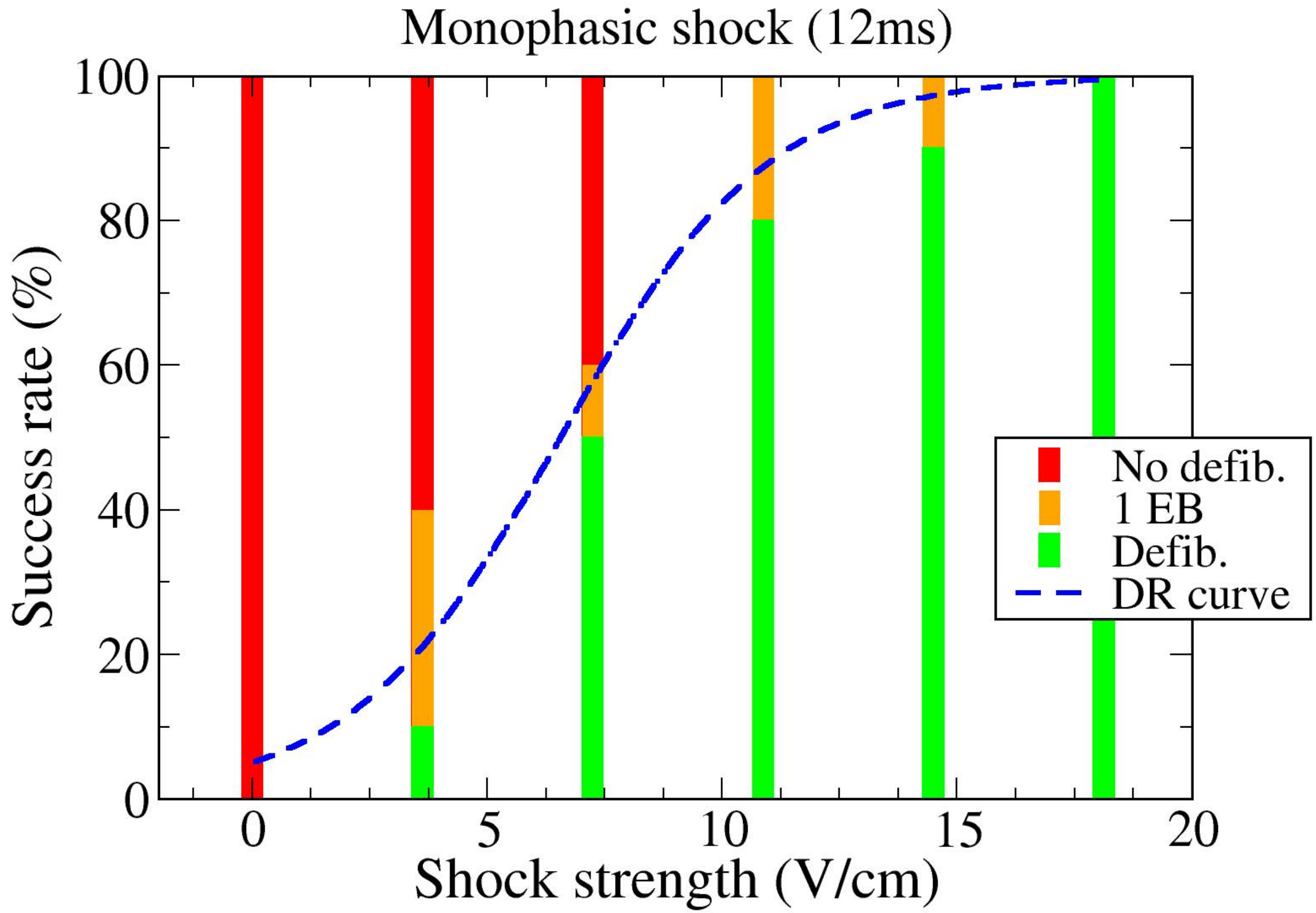




$$\rho_{i,j} = \frac{< (\phi^{(i)} - < \phi^{(i)} >)(\phi^{(j)} - < \phi^{(j)} >) >}{\sigma_{\phi^{(i)}} \sigma_{\phi^{(j)}}}$$



Monophasic shock results



Resultados :choques monofasicos

Dose-Response Curva :

$$P(I) = \frac{1}{1 + \exp[k(I_{50} - I)]}$$

I_{50}= 6.6 (V/cm)
k=0.45 (cm/V)

Energía en el choque:

$$E = \Delta\phi_e \, I_e \, \tau$$

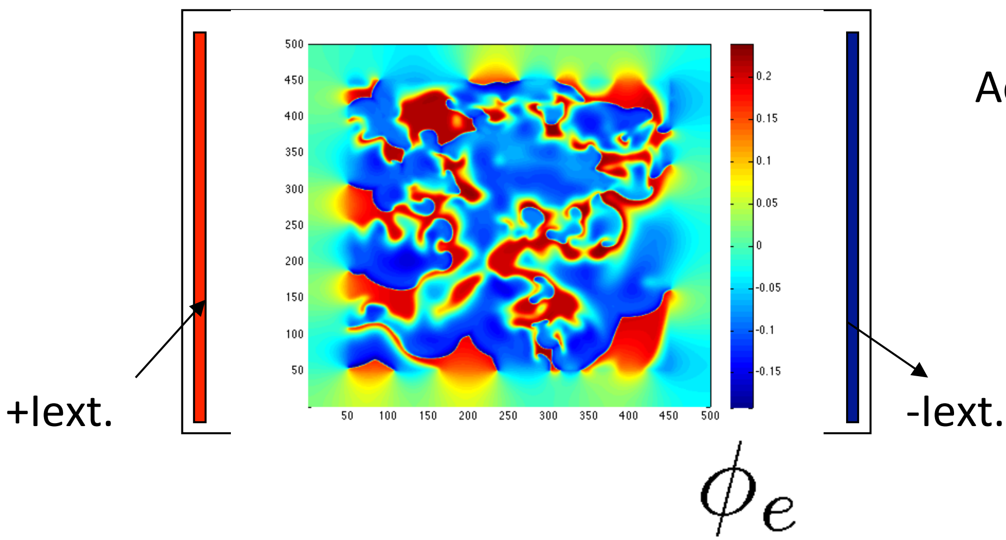
Aquí: Ie= 1.81 (A/cm^3) ;

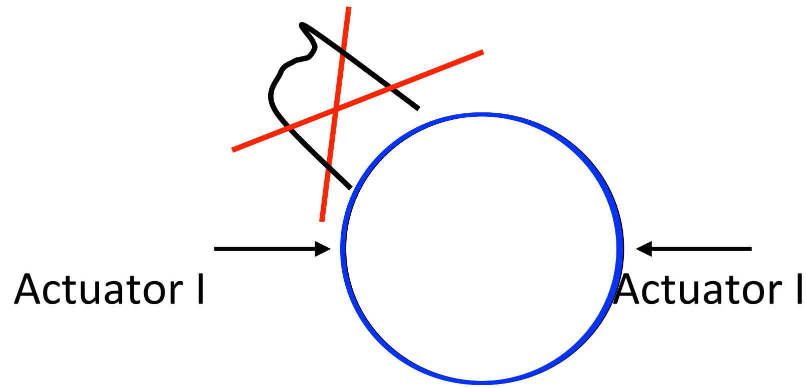
$$\Delta\phi_e = 18.1 \, Volt \qquad \tau = 12 \, ms$$

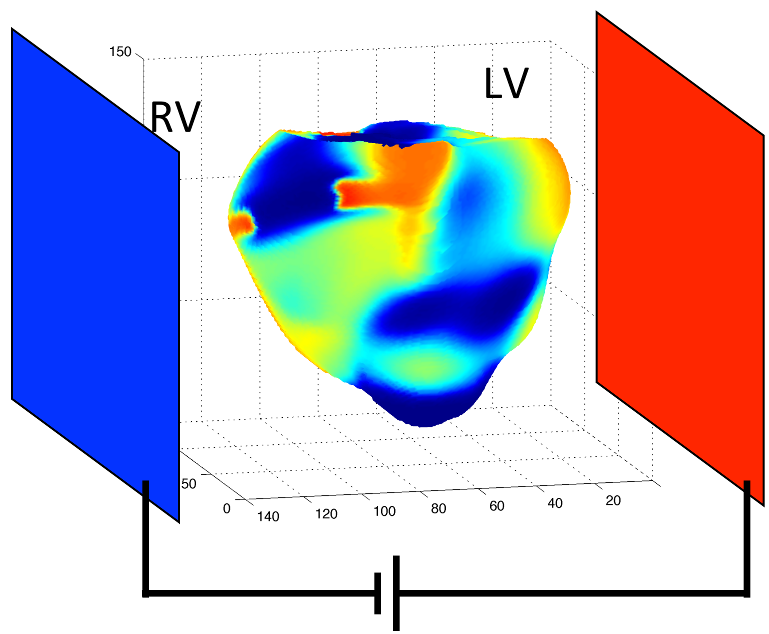
Energía en el choque: 0.286 (A) 18.1 (V) 0.012 (s) = 0.062 (Joule)

NB: Energía ~ L^3 ; L_rabbit= 2 cm ; L_human= 10 cm

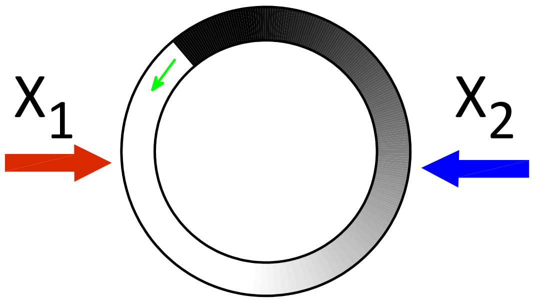
There exist 1D, 2D and 3D models for defibrillation



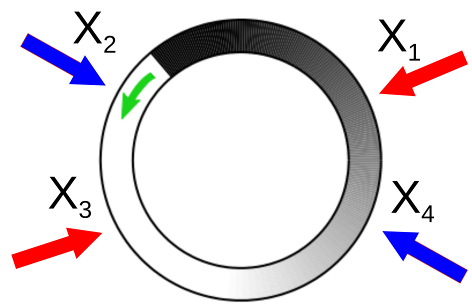




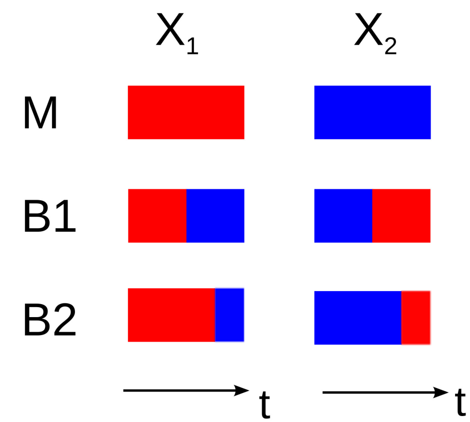
One-dimensional ring as a model to study defibrillation



2 electrode system



4 electrode system



3 protocols

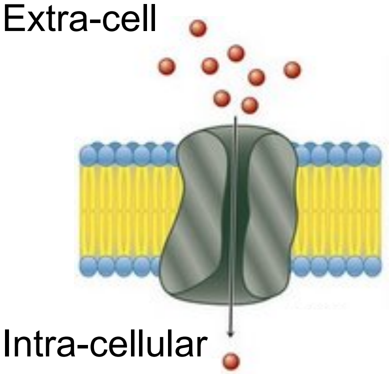
Numerical experiment setup :

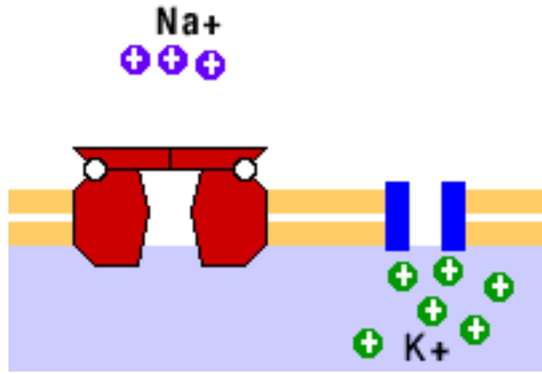
- A reentrant wave is induced on the ring
- An external shock is applied through the electrodes
- The outcome is classified as :
    1) successful (reentrant dynamics is removed)
    2) unsuccessful (reentrant wave is still present)

L. Glass & M. Josephson, Phys. Rev. Lett. **75** (1995)

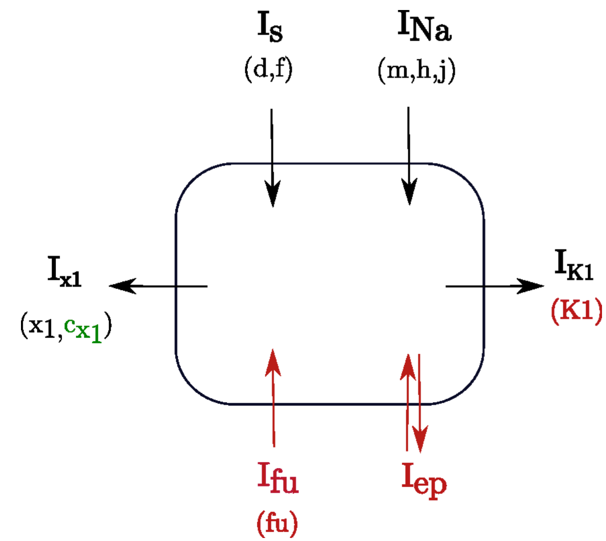
We use the B-R model to describe the cell membrane

The difference in ionic concentrations between the intra- and extra-cellular regions leads to the presence of a membrane electric potential.





$$V_m = \phi_i - \phi_e$$



$$I_{BR} = I_{Na} + I_s + I_{x1} + I_{K1}$$

$$\frac{d[Ca]_i}{dt} = -10^{-7} I_s + 0.07(10^{-7} - [Ca]_i)$$

$$I_j = G_j\, y_1\, y_2 \ldots y_n (V_m - E_j)$$

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}$$

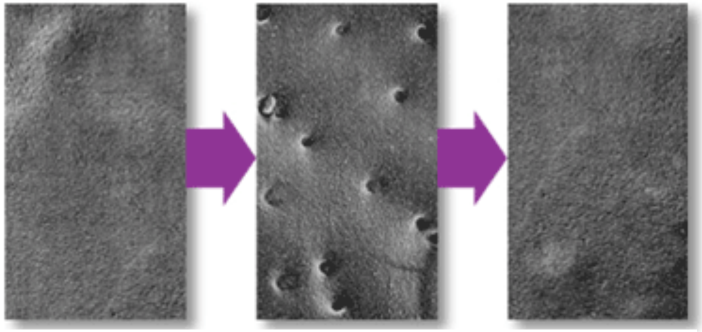
Beeler-Reuter model **+ modifications**:

1. Electroporation current
2. Anode break phenomenon (fu current)
3. (Chaotic dynamics by modifying x_1)

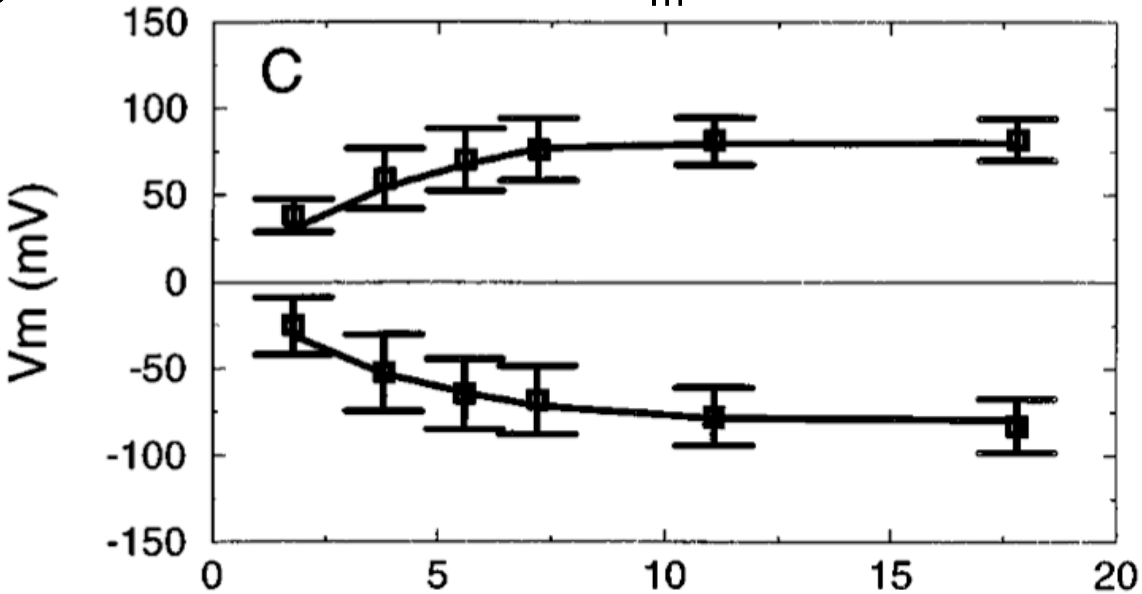
G. Beeler & H. Reuter, J. Physiol. **268** (1977)
M. Courtemanche, Chaos **6** (1996)

Electroporation phenomenon

Reversible openings of pores in the cell membrane



Saturation of V_m with E (V/cm)



Applied electric field E (V/cm)

$$I_{ep} = g_p(V_m) N V_m$$

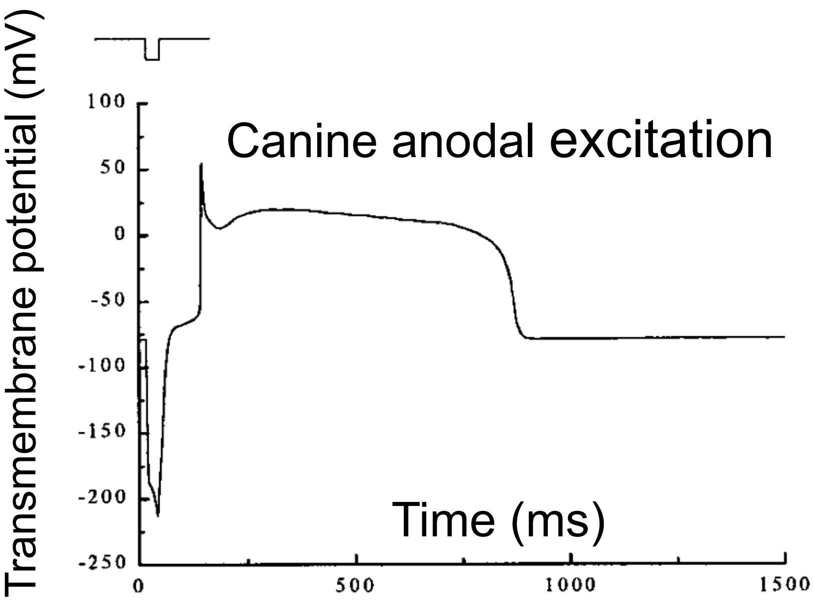
$$\frac{dN}{dt} = \alpha \exp(\beta V_m^2)\left(1 - \frac{N}{N_0}\exp(-q\beta V_m^2)\right)$$

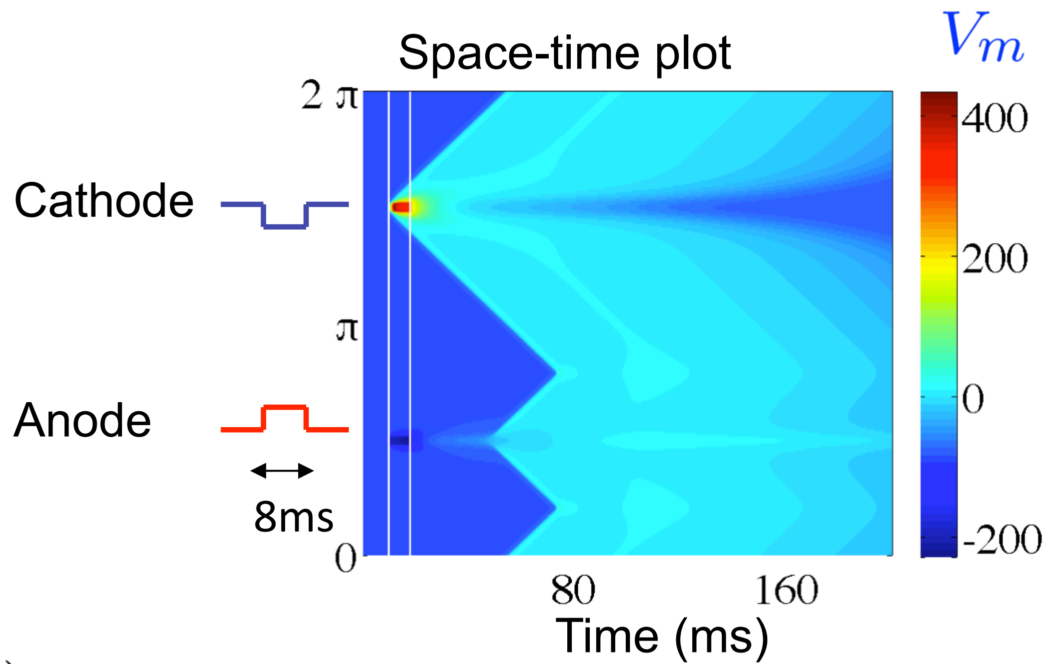
The electroporation protects the myocyte !

K. DeBruin & W. Krassowska, Ann. Biomed. Eng. **26(4)** (1998)

Anode-break phenomenon

A strong anodal excitation can elicit an action potential (here E=18 V/cm)





$$I_{\rm fu} = 0.1\,{\rm fu}\,(V_m - E_{\rm fu})$$

Following the study of Ranjan *et al*. we add the "funny current" and modify the time constant associated with the I_{K1} current.

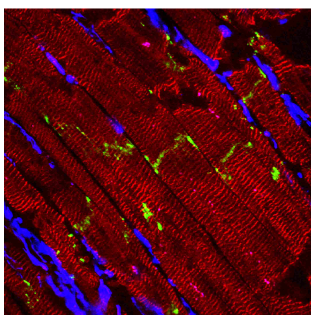
Ranjan *et al.*, Biophys. J. **74** (1998)
Brown *et al.*, Nature **280** (1979)

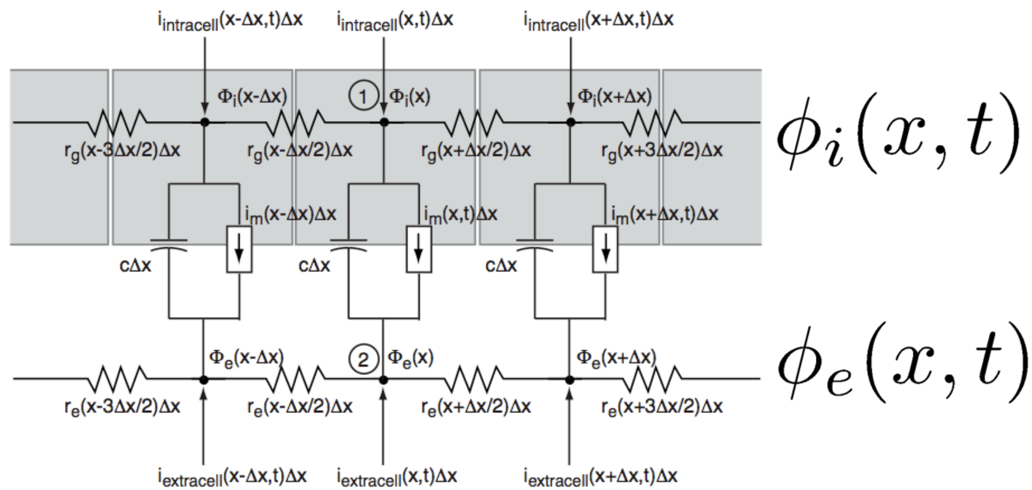
Bidomain model at the tissue level

The dynamics at the tissue level is computed through a set of coupled PDEs

The Poisson equation is the most time consuming (CPU)

$$\begin{cases} \dfrac{\partial V_m}{\partial t} = \dfrac{-i_m}{c} + \nabla \cdot (\mathbf{D_g} \cdot \nabla V_m) + \nabla \cdot (\mathbf{D_g} \cdot \nabla \phi_e) + \dfrac{i_{intra}}{\tilde{S}c} \\ \nabla \cdot [(\mathbf{D_e} + \mathbf{D_g}) \cdot \nabla \phi_e] = -\nabla \cdot (\mathbf{D_g} \cdot \nabla V_m) - \dfrac{i_{intra}}{\tilde{S}c} - \dfrac{i_{extra}}{\tilde{S}c} \\ \dfrac{\partial \mathbf{s}}{\partial t} = \mathbf{f}(\mathbf{s}, t; \mu) \end{cases}$$





$$D_g(x_k) = \bar{D}_g(1 + \sigma \; r_k)$$

$$D_e = \bar{D}_g = 1.5\,10^{-3}\,\mathrm{cm}^2/\mathrm{ms}$$

← Tissue heterogeneities are included in the model

$\sigma = 0.15$ $\qquad r_k \sim \mathcal{N}(0,1)$

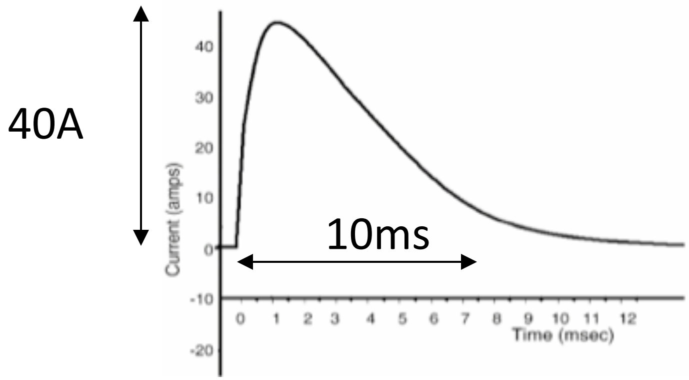
C. Henriquez, Crit. Rev. Biomed. Eng. **21** (1993)

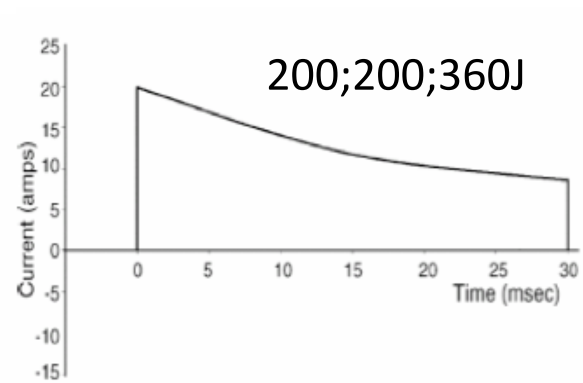
N. Otani, Lecture Notes.

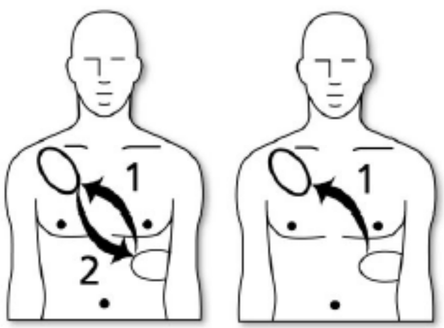
Application I

Two-electrode system

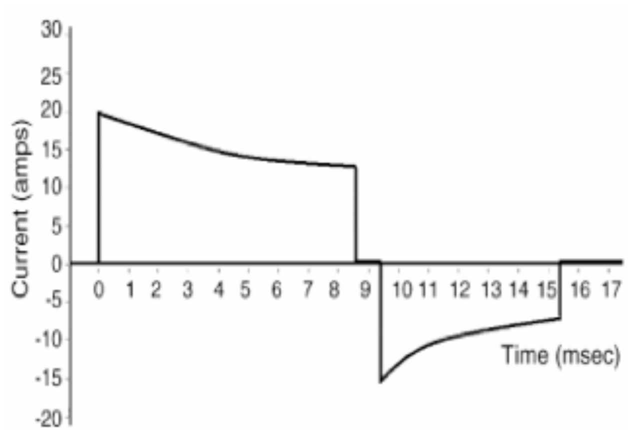
Objective: Understand why biphasic shocks are more efficient than monophasic shocks in order to defibrillate the heart.

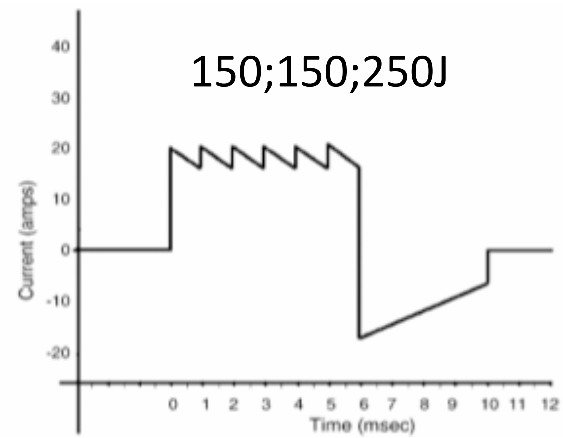






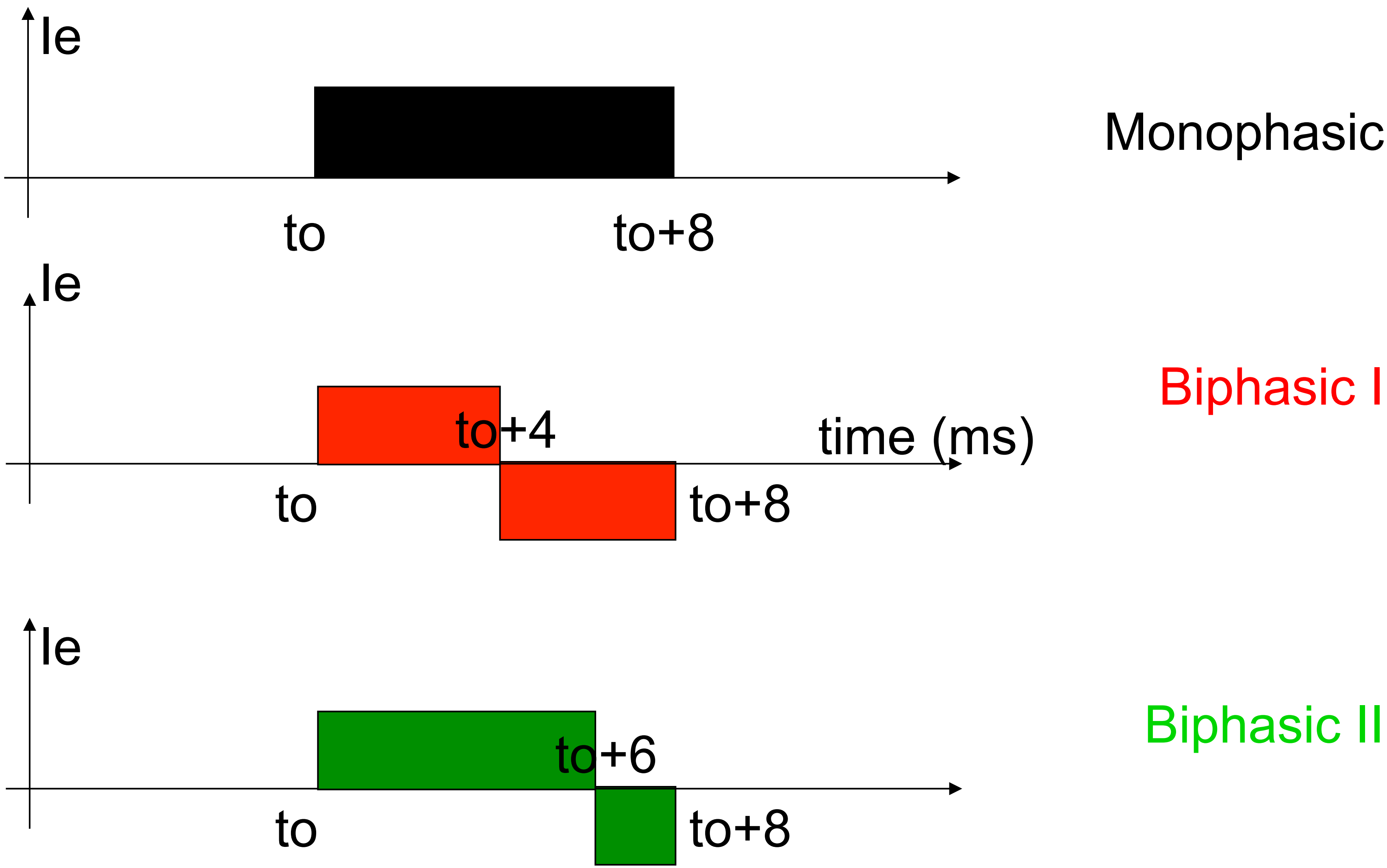
biphasic monophasic



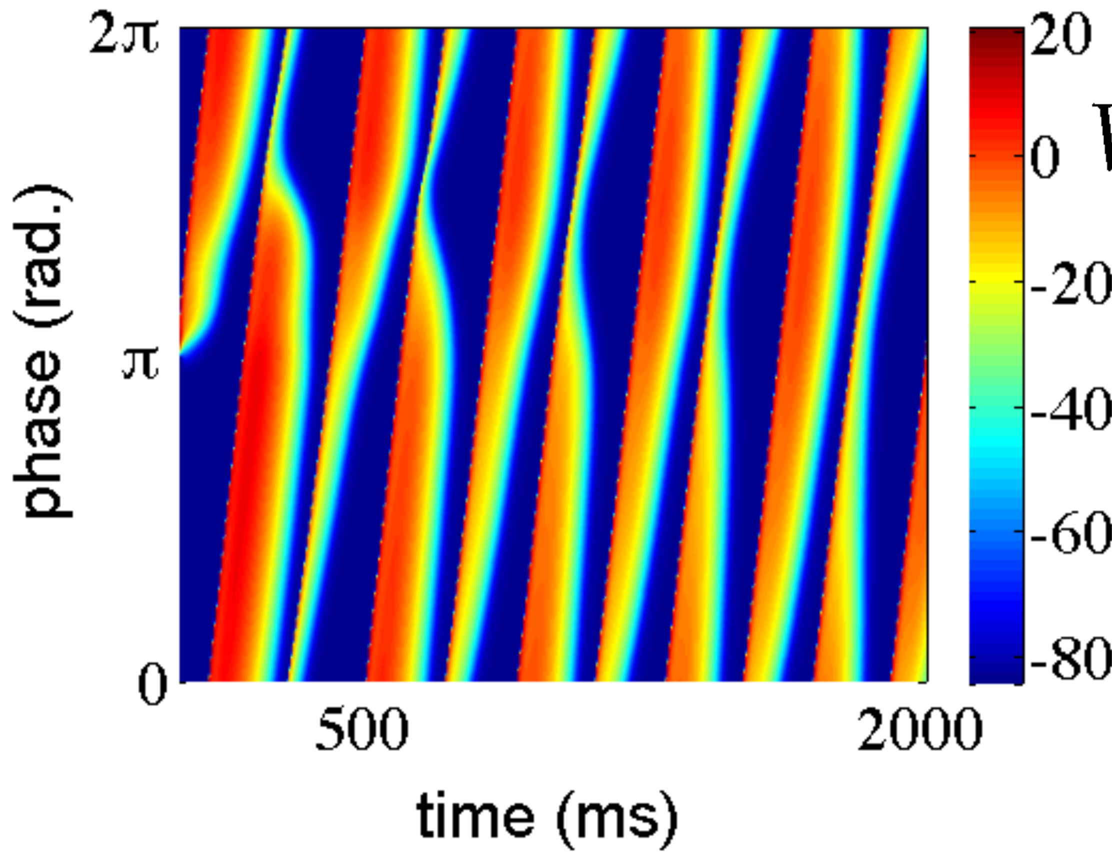


Since 1990, all the new defibrillators are biphasic !

Once the model is ready 3 shock protocols are tested



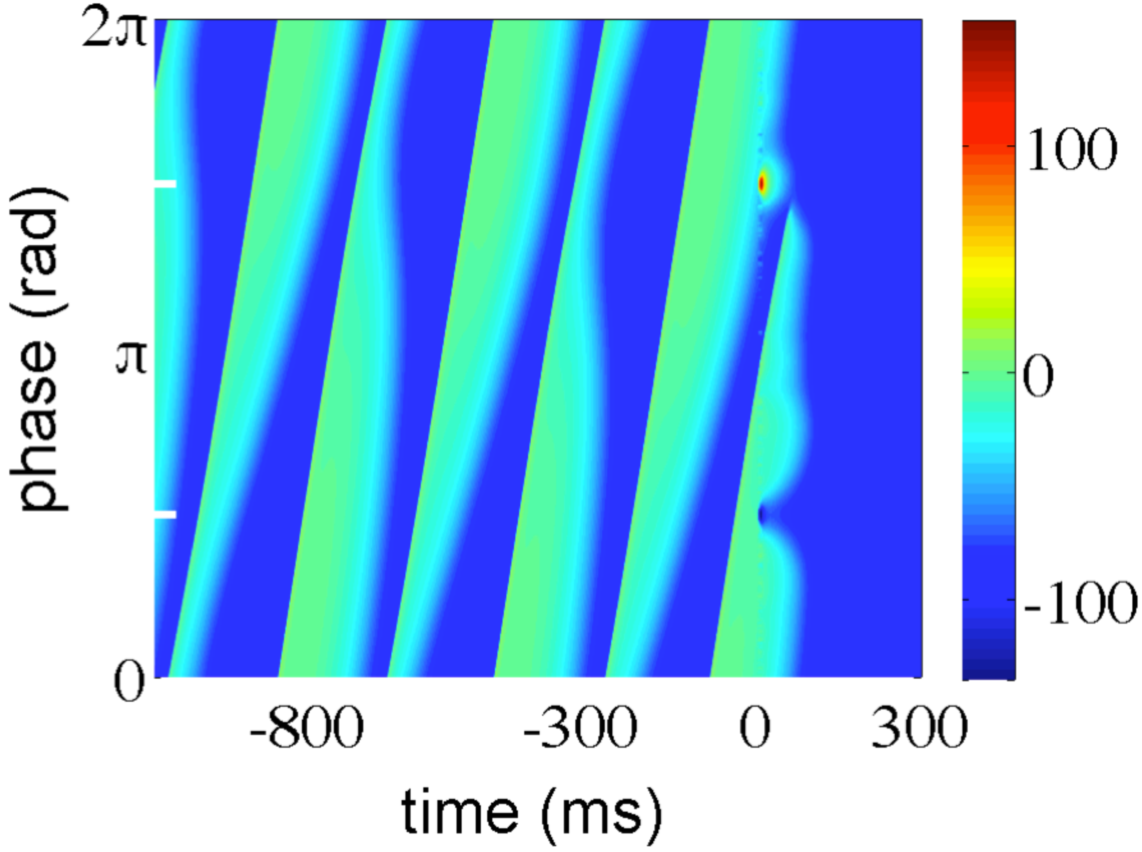
We select L=6.7 cm



$$V_m = \phi_i - \phi_e$$

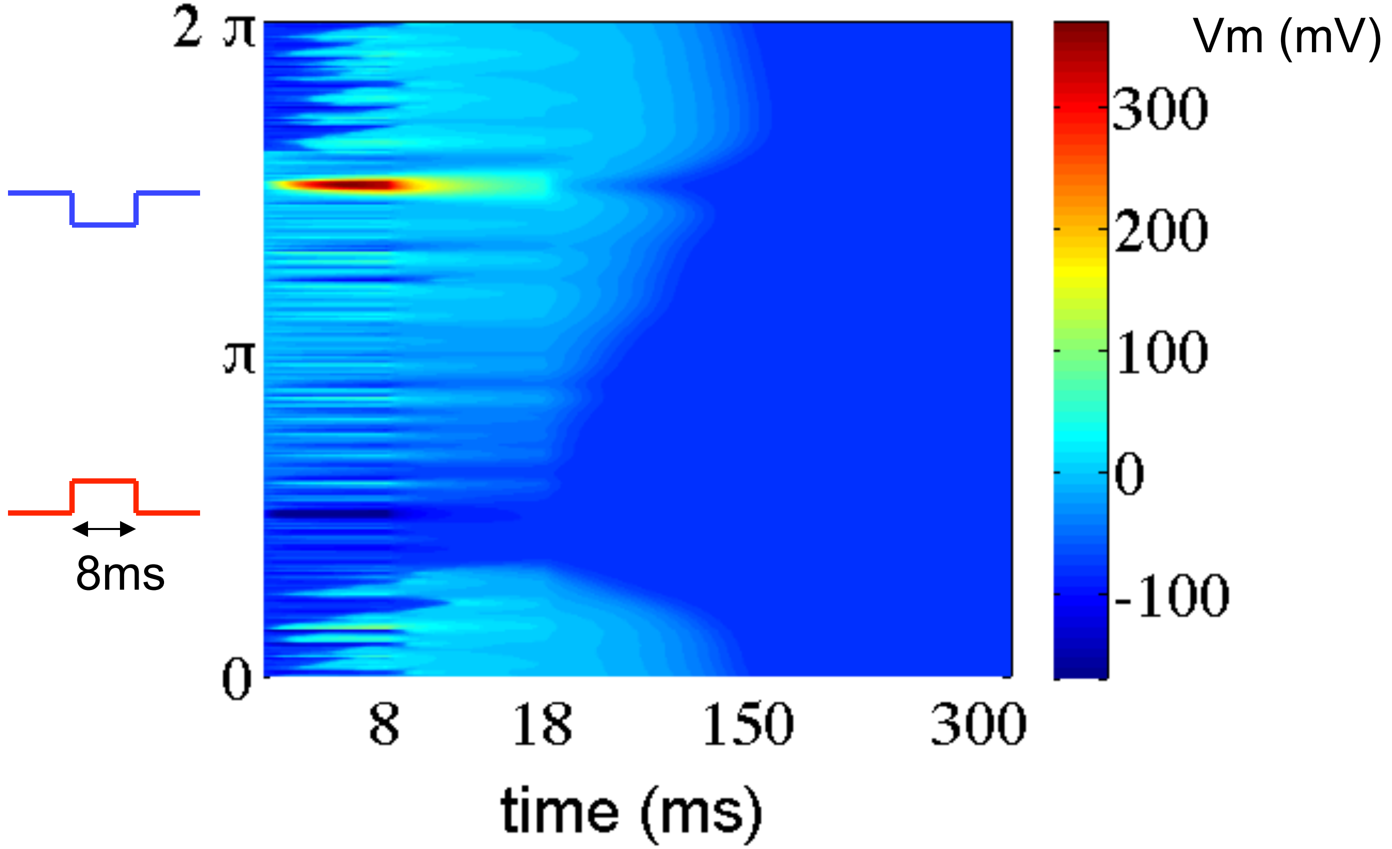
- Discordant-alternans are known to be precursors to cardiac fibrillation ($T_1 \approx 200$ ms ; $T_2 \approx 3000$ ms)

Monophasic shock of 8 ms duration (E=2 V/cm)



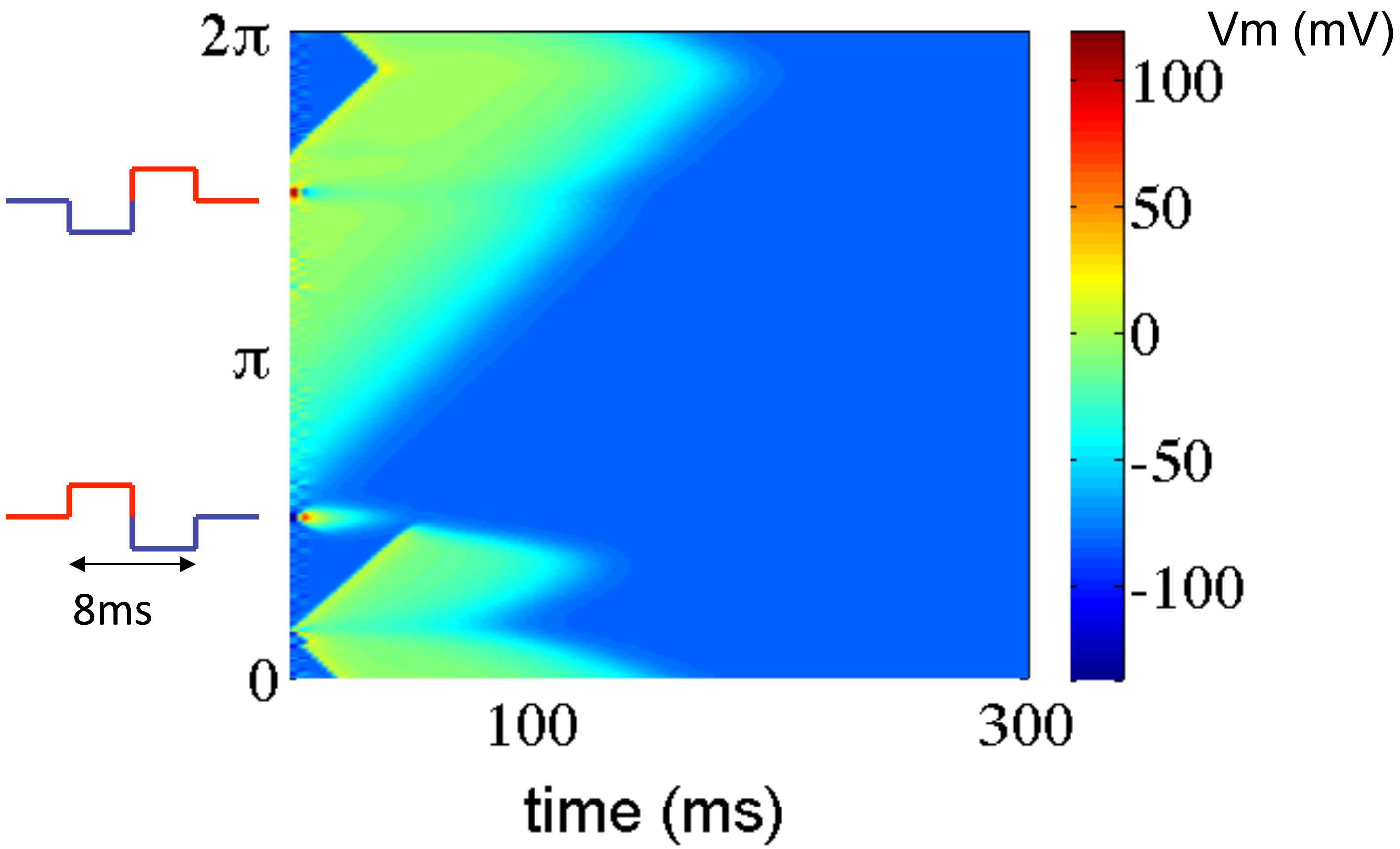
One example of a 1D simulation

Successful Monophasic shock (E=6V/cm)



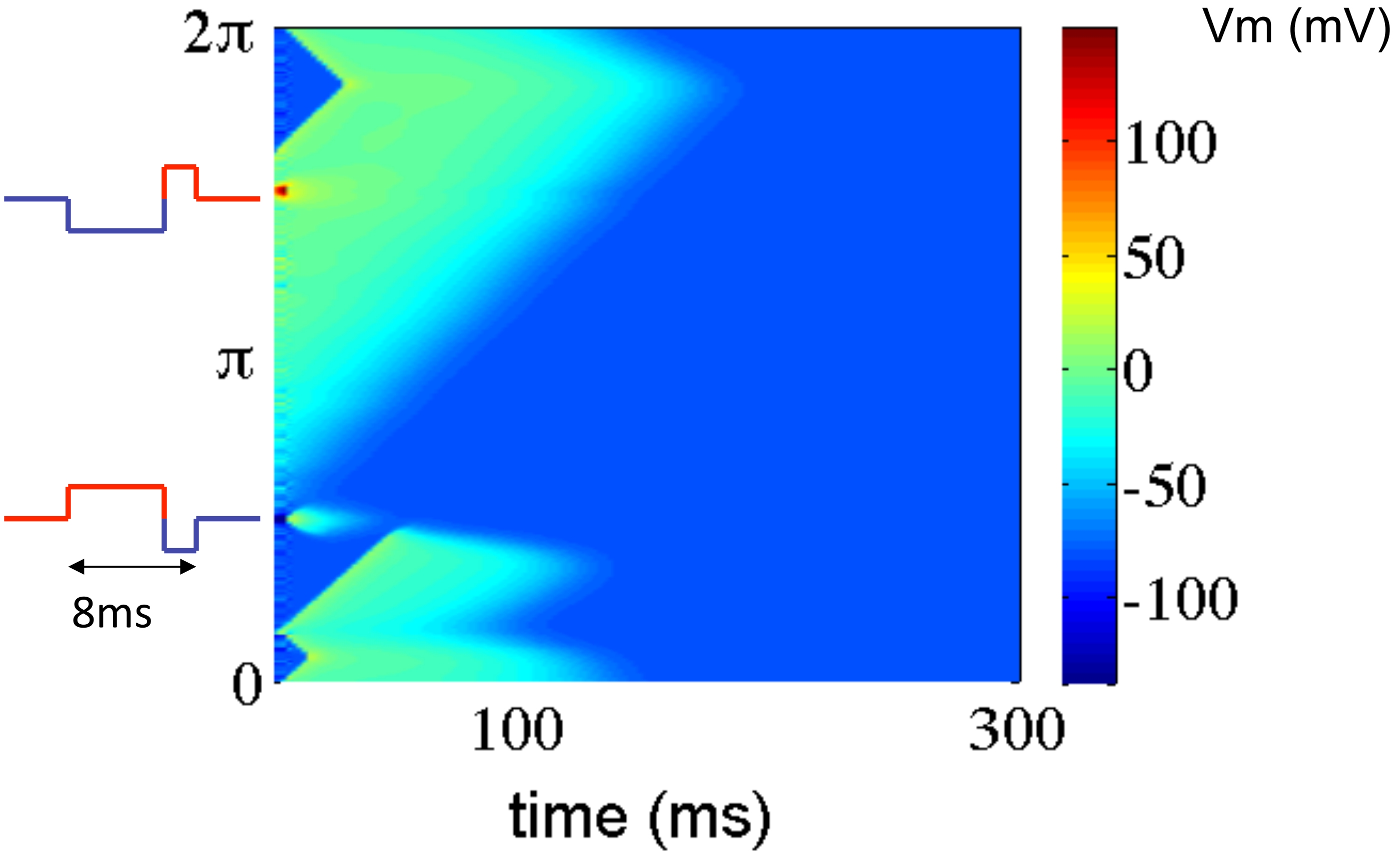
$E_{applied}$=6 V/cm

Successful Biphasic shock type I (E=2V/cm)



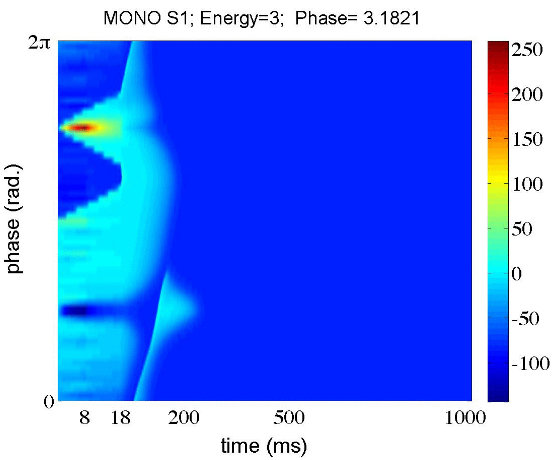
$E_{applied}$=2 V/cm

Successful Biphasic shock type II (E=2V/cm)

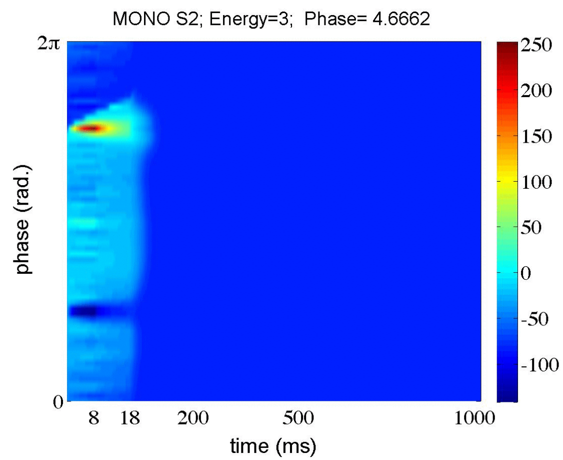


$E_{applied}$=2 V/cm

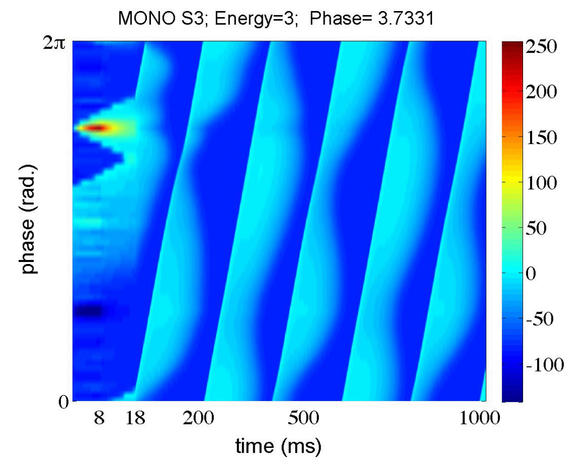
Different initial phases and initial conditions lead to different defibrillation mechanisms



IC1
Medium



IC2
Large

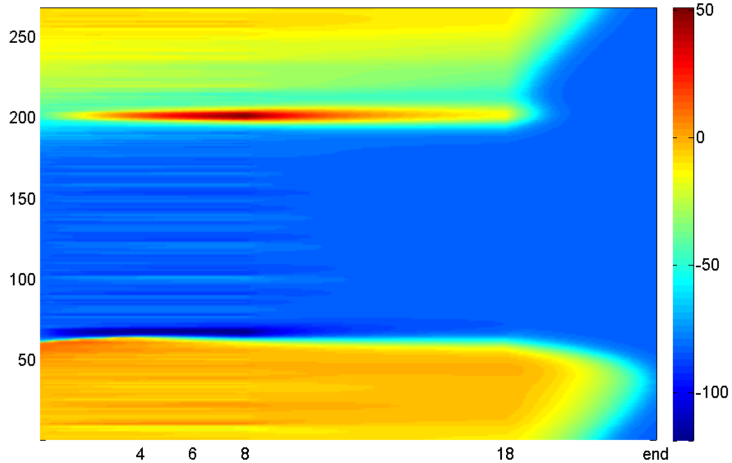


IC3
Short

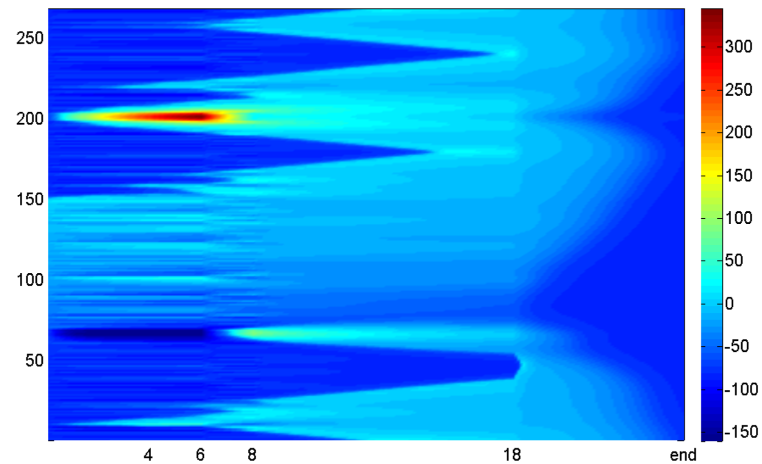
Monophasic shocks at E=3V/cm

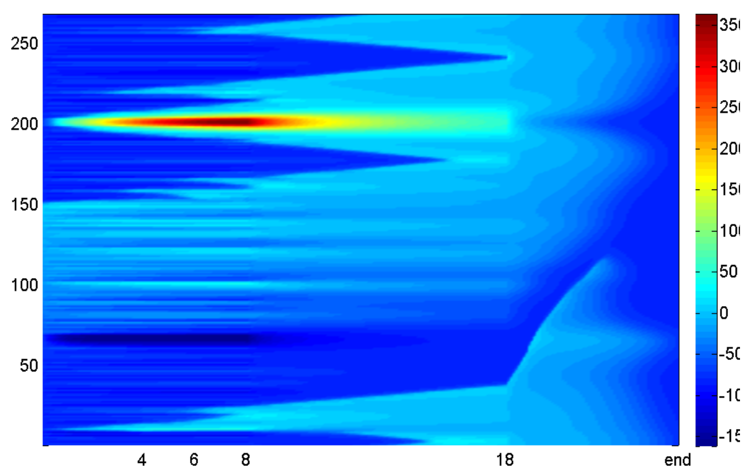
Different initial phases and initial conditions lead to different defibrillation mechanisms

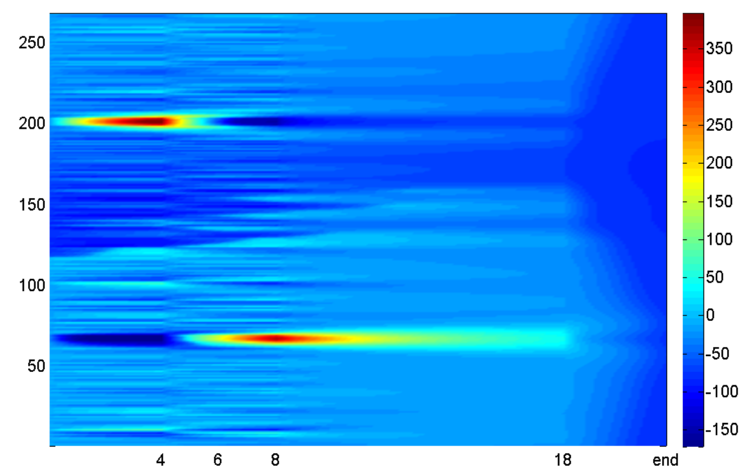
Direct block (1V/cm)



Annihilation (5V/cm)







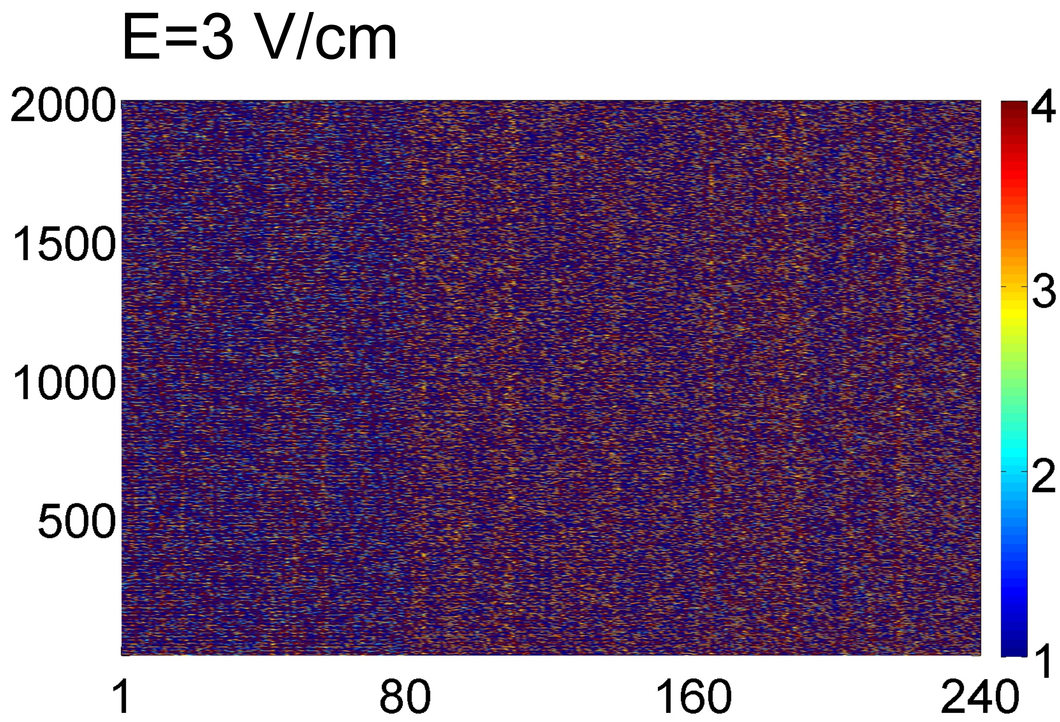
Delayed block (5V/cm)

Direct activation (8V/cm)

What are the parameters that influence the success or failure of the shock ?

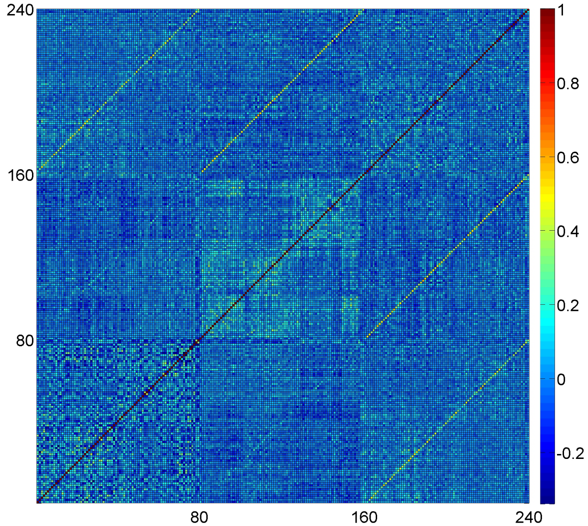
1. Shock duration → we fix it to 8 ms
2. Shock energy → we explore E = [1 ; 10] V/cm
3. Shock timing (wave front or wave back)
4. Dynamical state at the time of the shock application
5. Level of heterogeneities in the cardiac tissue (σ=0.15)
6. Random realizations of the heterogeneities (80)
7. System size → we fix L=6.7 cm
8. Defibrillation protocol used (Mono. ; B I ; B II)
9. …

(10x2000x80x3=4,800,000 simulations)

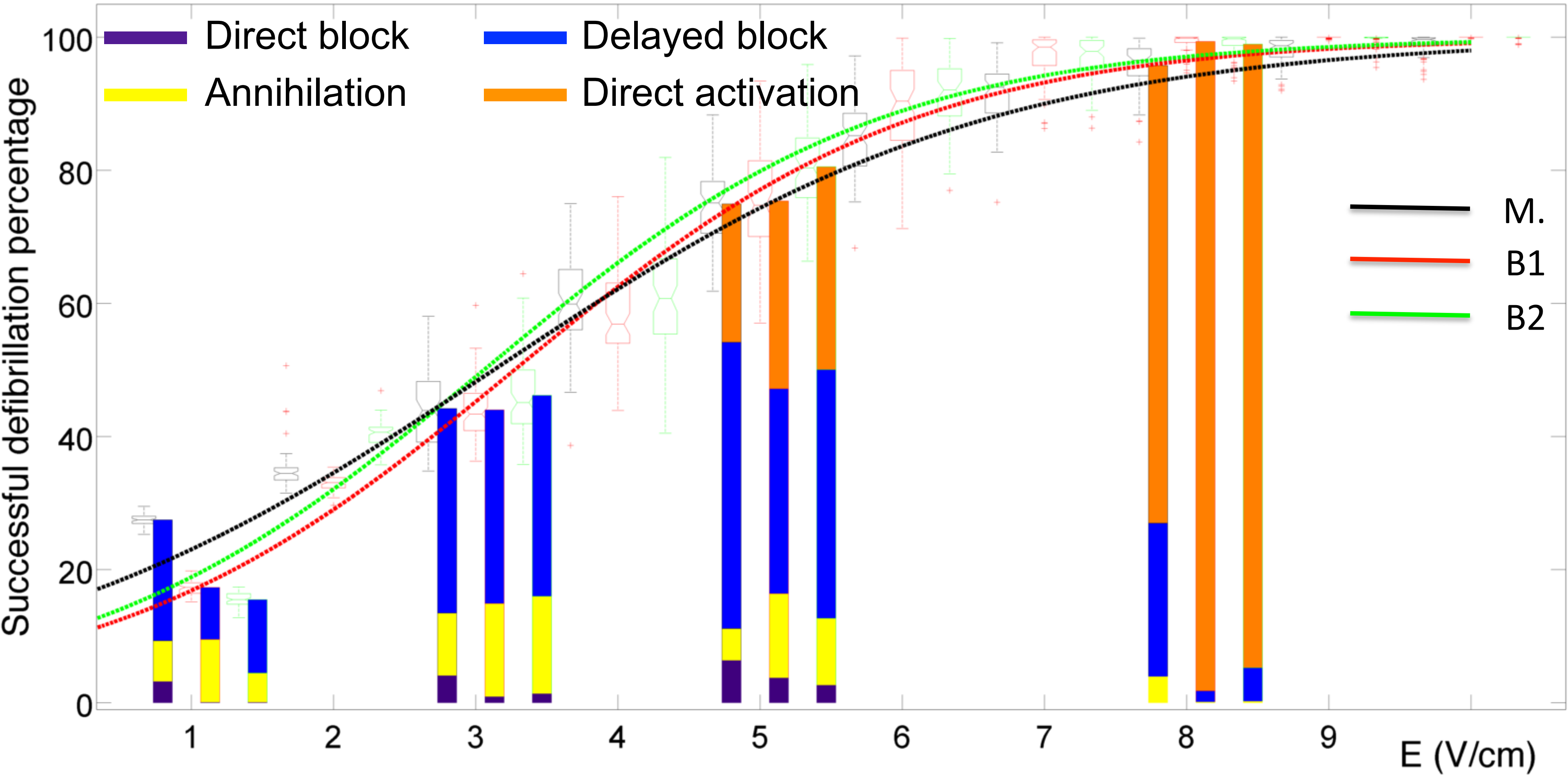


1->80 : Mono
81->160: Biph. I
161->240: Biph. II

1 -> No defibril.
2->Direct block
3->Annihilation
4->Delayed block



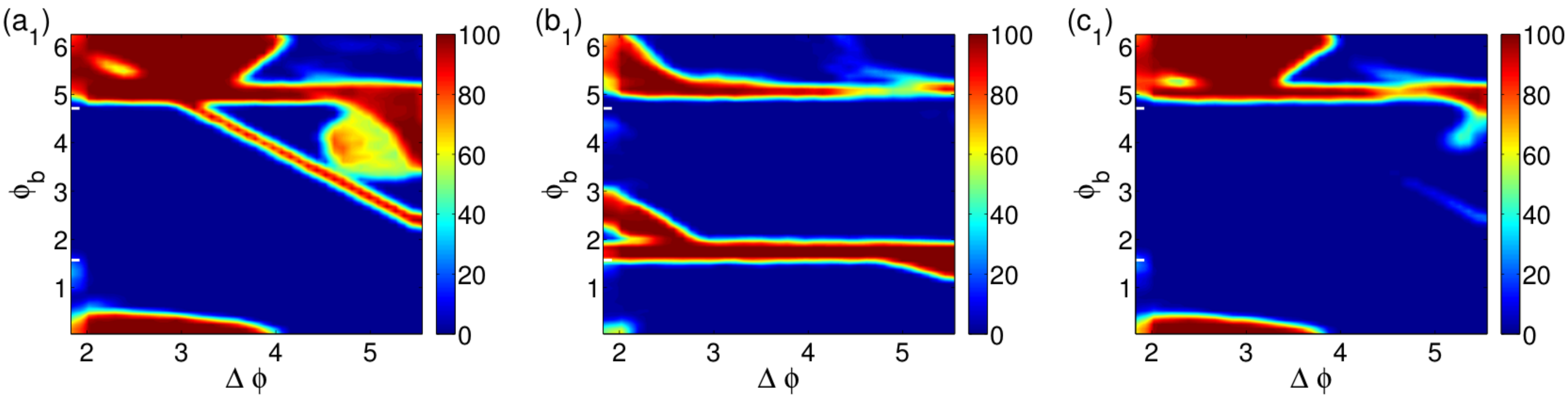
Results for 1D simulations (2 electrodes)



We have performed a total of (10 x 2,000 x 80 x 3 = 4,800,000 simulations)

NB: CPU time ~ 3h40' for 300 simulations on 1-core of a fast computer (i7).

2D histograms (Low energy E=1 V/cm)



Monophasic

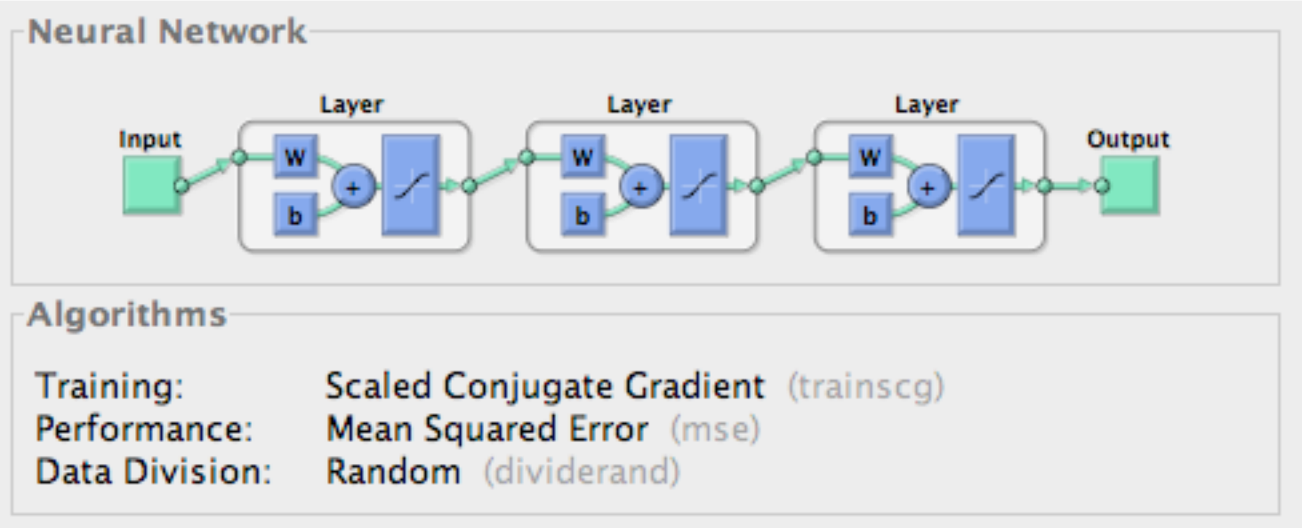
Biphasic I

Biphasic II

Now, we want to separate into the different mechanisms

Automatic Mechanism Classification

Matlab Neural Network Tool for automatic pattern classification



Direct block

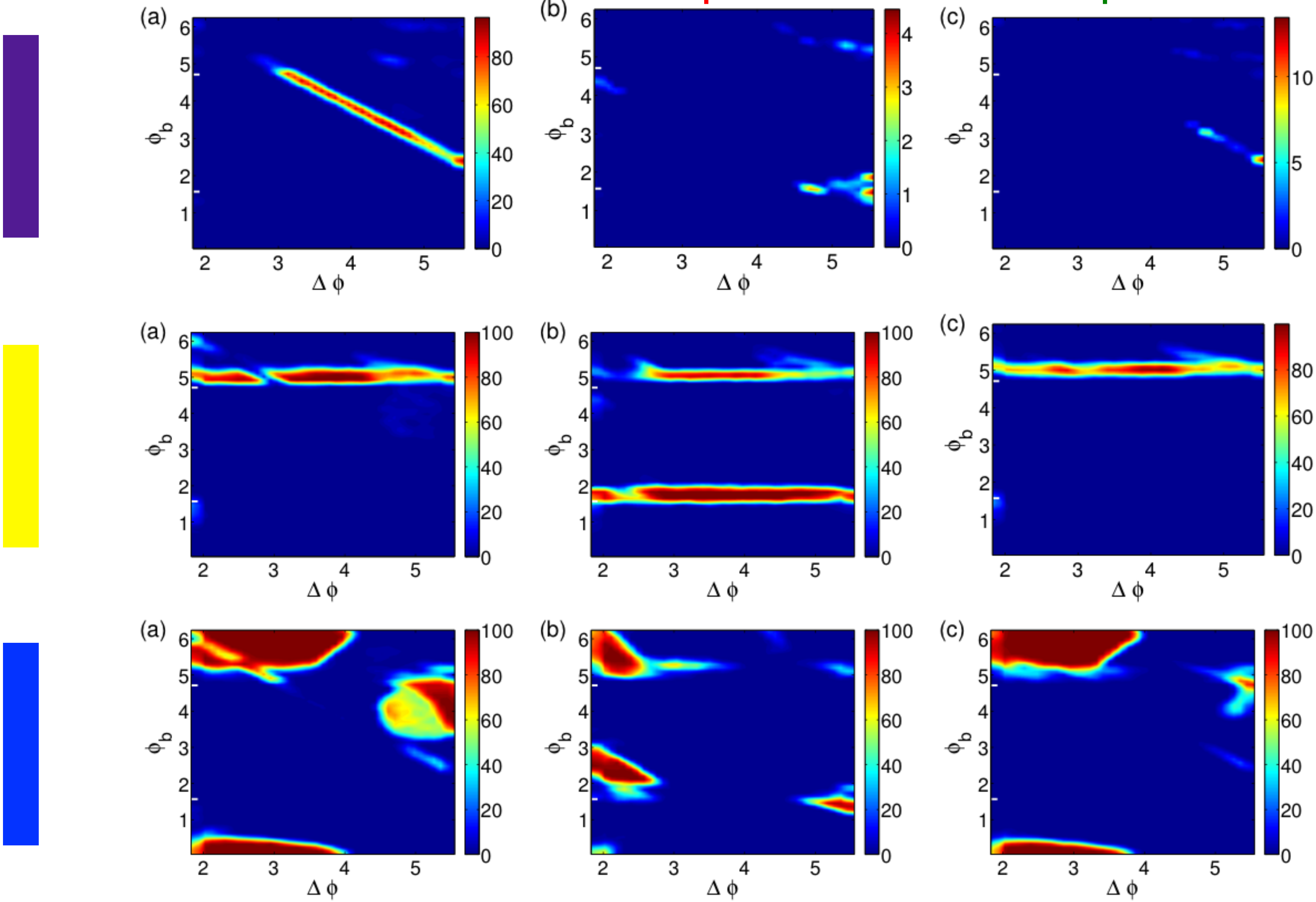
Delayed block

Annihilation

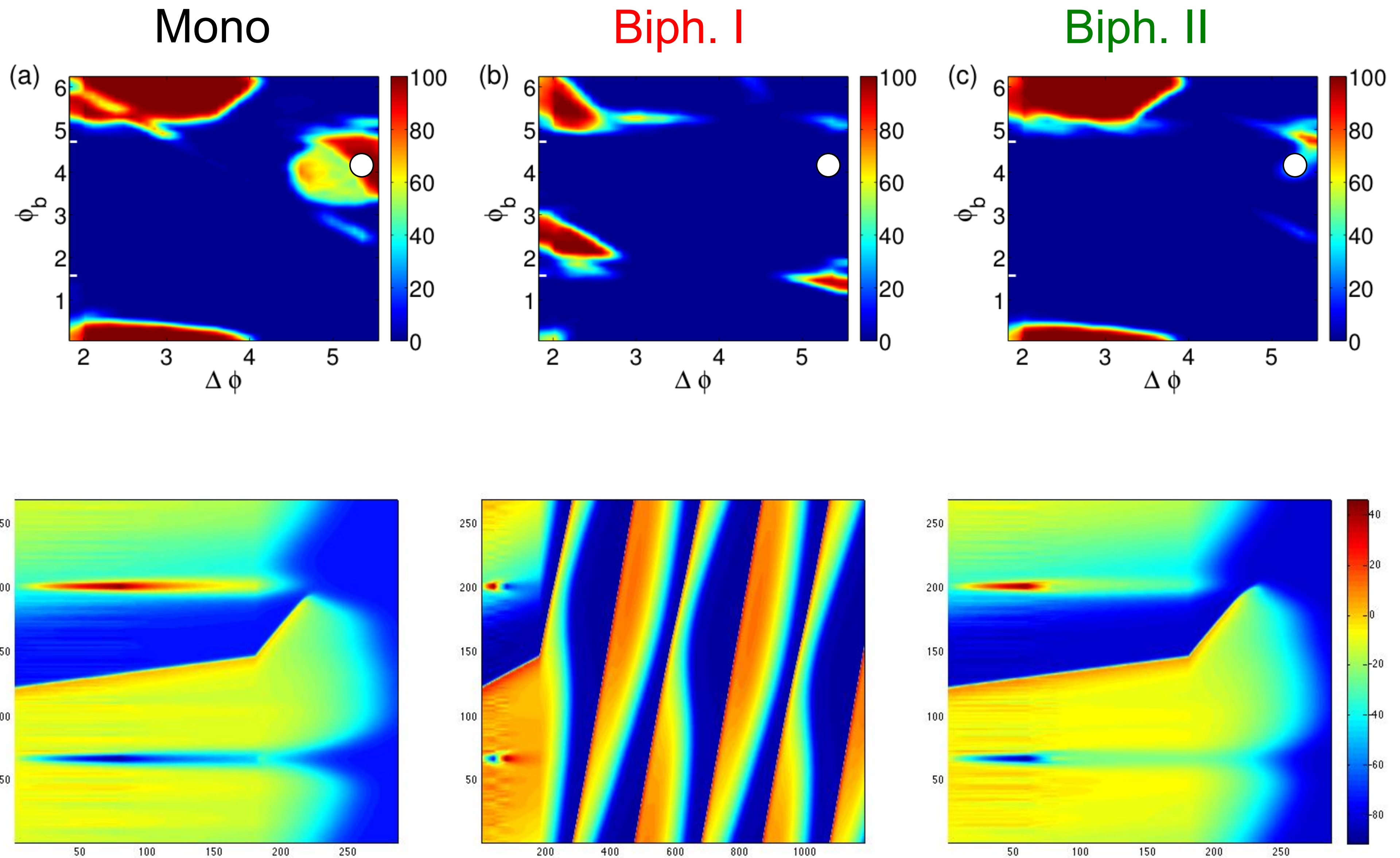
Direct activation

2D histograms (E=1 V/cm)

Mono | Biph. I | Biph. II



Example (ϕ_b =4; ϕ_i = 2.9 ; $\Delta\phi$=5.18)



Median of the 80 trials (2000 i.c.)

Energy (V/cm)	Monophasic	Z(Mo-BI)	Biphasic I	Z(BI-BII)	Biphasic II	Z(Mo-BII)
1	0.2750	10.9196	0.1732	8.5157	0.1550	10.9198
2	0.3448	6.5650	0.3310	-10.9192	0.4065	-9.9448
3	0.4392	-0.3191	0.4338	-2.4316	0.4512	-2.1364
4	0.5992	2.0698	0.5693	-2.1073	0.6078	-0.3481
5	0.7510	-0.2286	0.7475	-3.8410	0.8035	-5.2913
6	0.8522	-4.7590	0.9042	-1.6432*	0.9213	-6.9415
7	0.9250	-8.0970	0.9852	0.8108	0.9788	-7.7097
8	0.9657	-8.9189	0.9990	1.4119	0.9978	-7.8431
9	0.9875	-10.0976	1.0000	1.0661	1.0000	-8.7257
10	0.9968	-9.2650	1.0000	0.0673	1.0000	-8.9123

Pair-wise Wilcoxon rank sum test for equal medians

Z_{score}=1.6449 (α=0.05, one sided)

*red color means not significant difference

Statistical results (2 electrode system)

Protocols	$E_{90\%}$ (V/cm)	Energy (J)
Monophasic	6.787 ± (0.080)	200
Biphasic I	6.028 ± (0.062)	158
Biphasic II	5.839 ± (0.062)	148

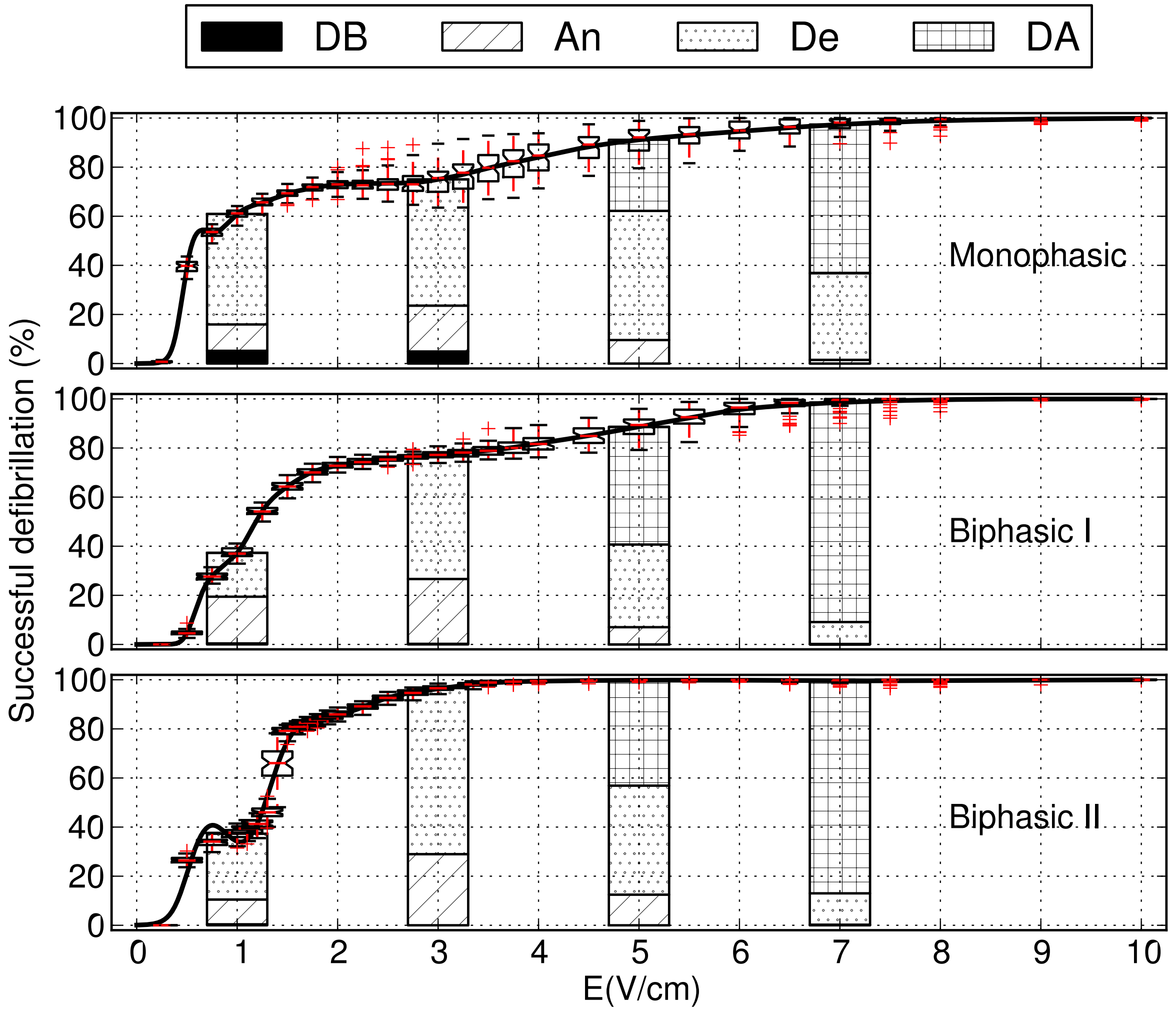
(standard errors are computed with Bootstrap technique)

We observe a reduction of 25 % between Biphasic II and Monophasic
This is due to high level of the DA mechanism at high energy for the biphasic shocks.

Application II

Four-electrode system

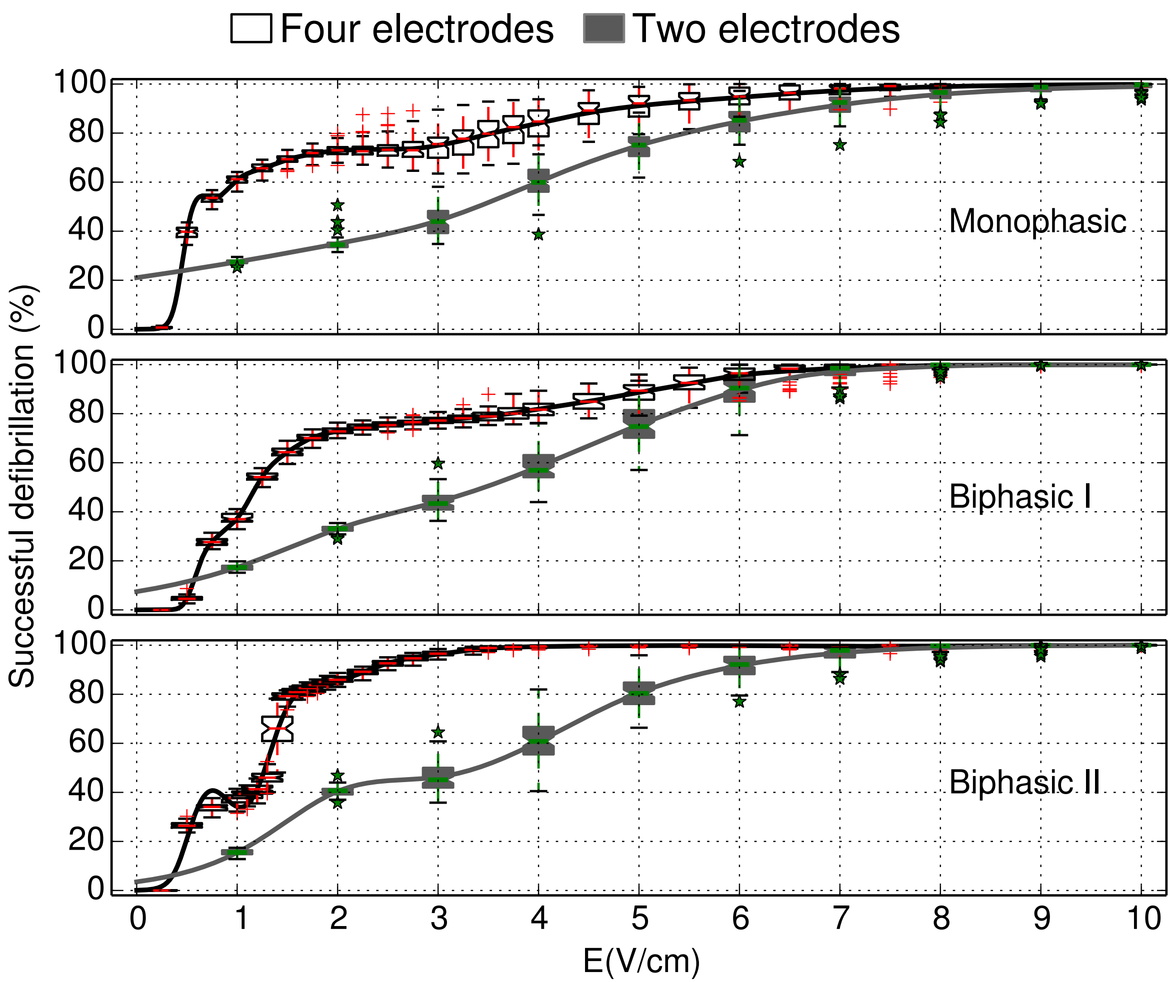
Results for 1D simulations (4 vs 2 electrodes)



In the 4 electrode case, we have performed a total of

(28 x 2,000 x 50 x 3 = 8,400,000 simulations)

Results for 1D simulations (4 vs 2 electrodes)



In the 4 electrode case, we have performed a total of

(28 x 2,000 x 50 x 3 = 8,400,000 simulations)

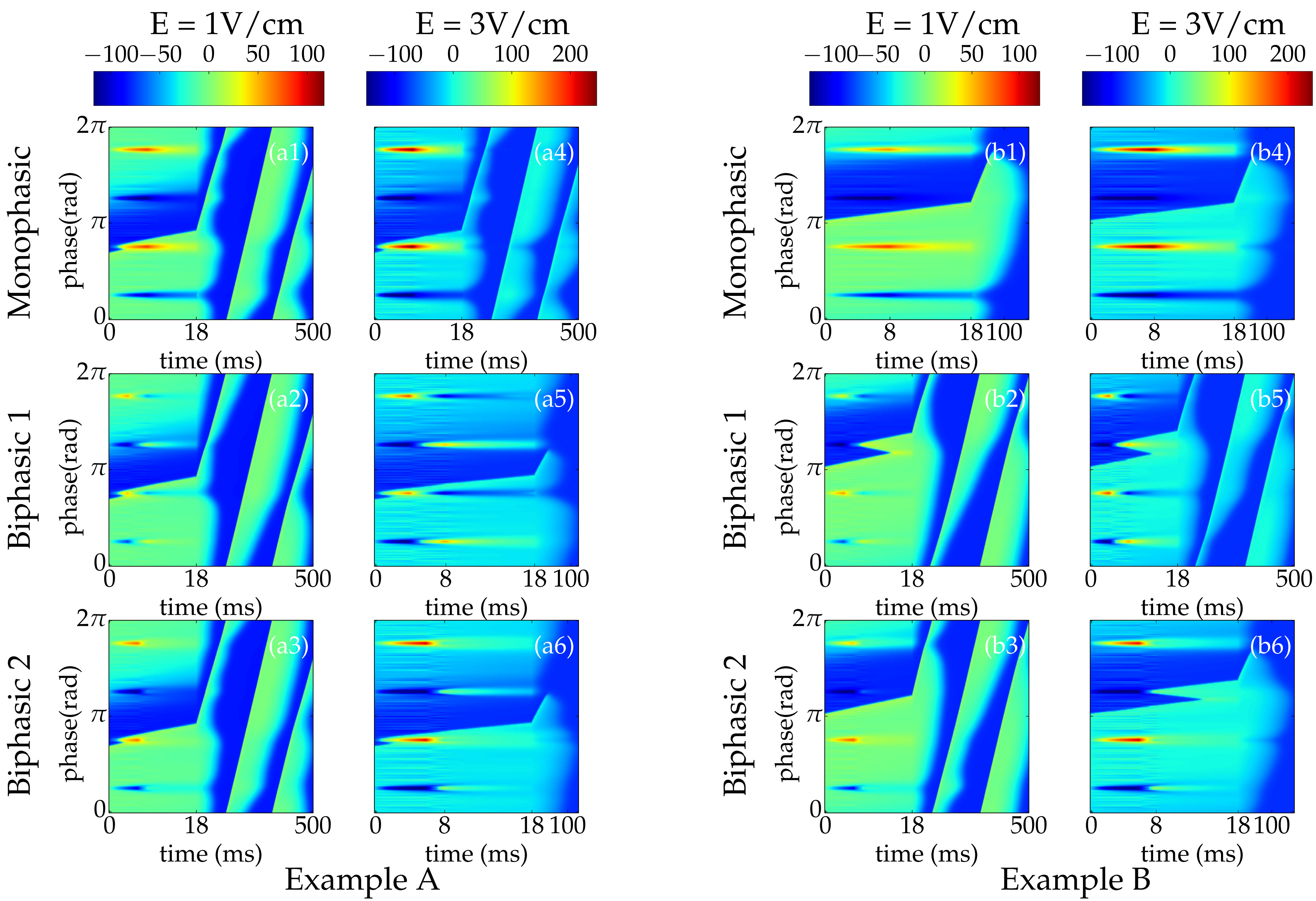
Comparing the 2- versus the 4-electrode system

Protocols	$E_{90\%}$ (V/cm) (2 electrodes)	$E_{90\%}$ (V/cm) (4 electrodes)	Energy Reduction
Monophasic	6.787 ± (0.080)	4.752 ± (0.150)	- 51%
Biphasic I	6.028 ± (0.062)	5.193 ± (0.083)	- 26 %
Biphasic II	5.839 ± (0.062)	2.320 ± (0.013)	- 84 %

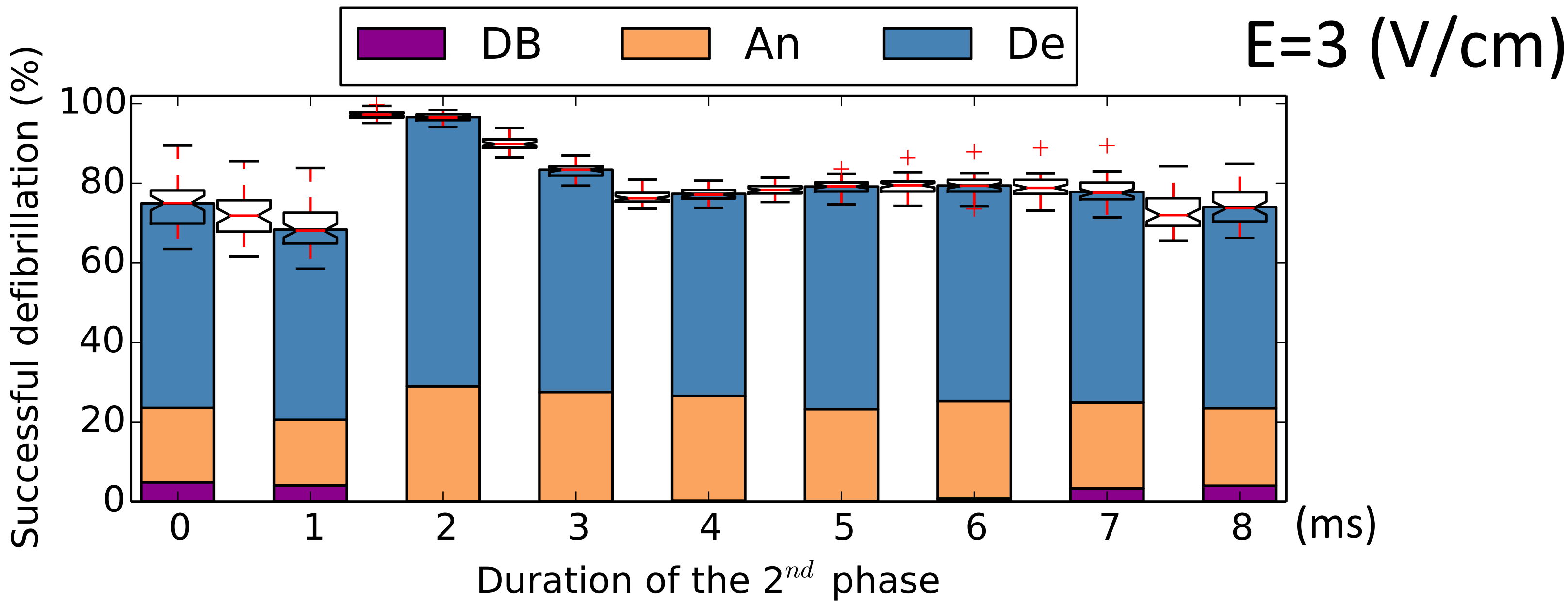
(standard error computed with Bootstrap technique)

We observe a huge benefit for the 4-electrode system (Biphasic2)

Explanation of why Biphasic II is so efficient (4 electrodes)

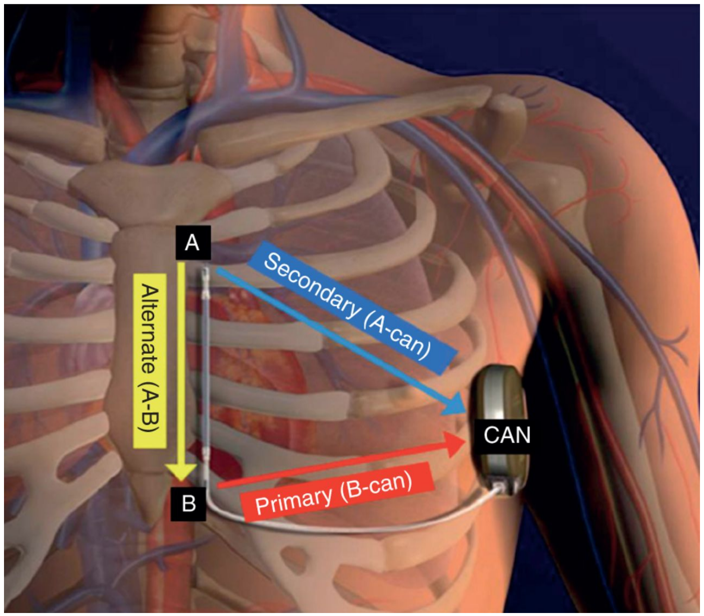


Importance of the second phase duration (4 electrodes)



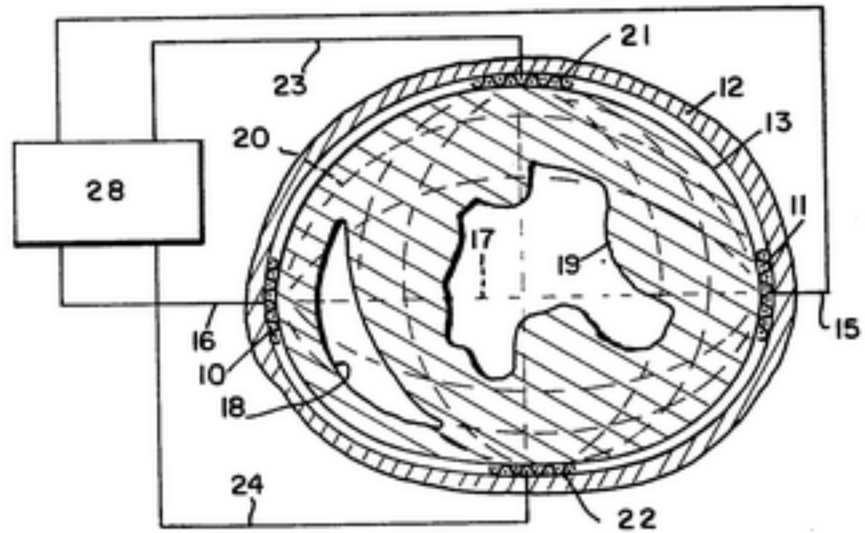
The Delayed block (De) mechanism is much more efficient in the Biphasic II protocol (4 electrodes) if the correct duration is selected. (Here around 2 ms for the second phase duration)

Patents and commercial defibrillators



3 leads ICD (Boston Scientific)

FIG 2



“two current pulses to separate pairs of electrodes orthogonally placed around the heart”

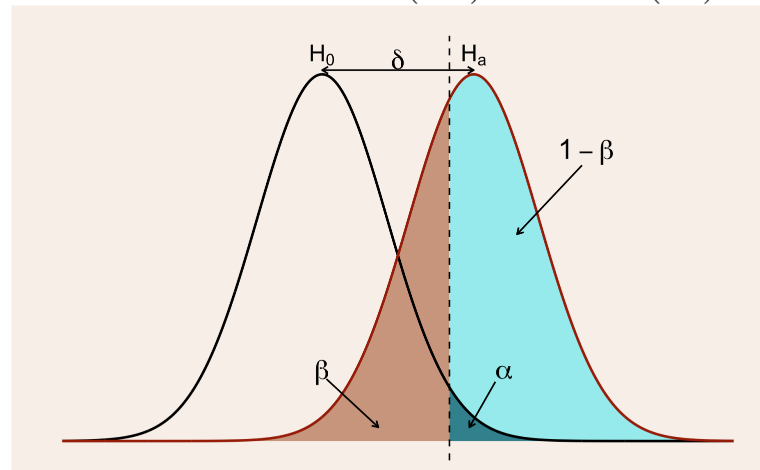
Patent: Apparatus for controlling cardiac ventricular tachyarrhythmias
EP 0095726 A1 (**1983**)
W. A. Tacker, Jr., C. F. Babbs, J. D. Bourland, L.A. Geddes.
Medtronic, Inc.

Do we really need so many simulations ?

Here we compare protocol efficiencies

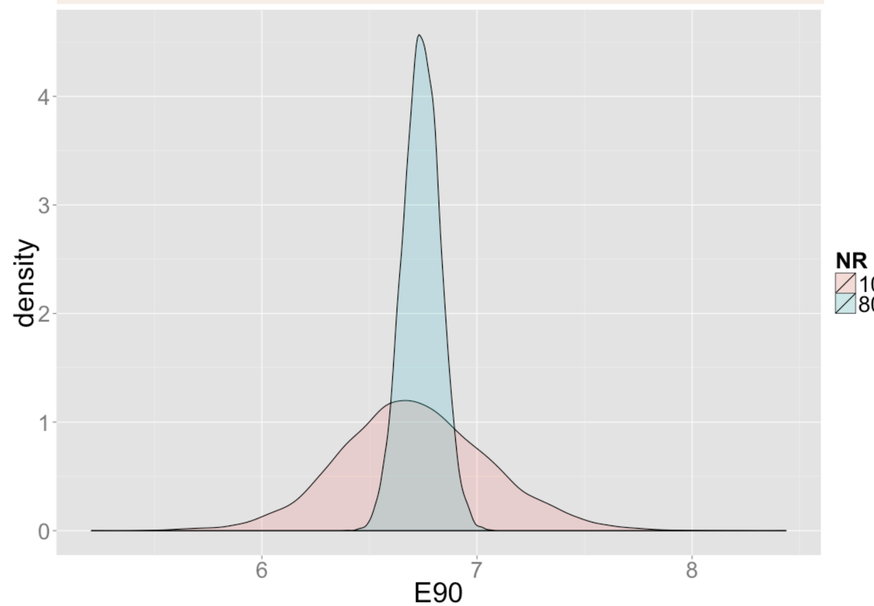
		Truth	
		H_o True	H_o False
Your Findings	H_o True	Correct	**Type II Error (β)**
	H_o False	**Type I Error (α)**	Correct

$$H_0 \equiv \mu_{E_{90(\mathrm{BII})}} = \mu_{E_{90(\mathrm{M.})}}$$
$$H_a \equiv \mu_{E_{90(\mathrm{BII})}} < \mu_{E_{90(\mathrm{M.})}}$$



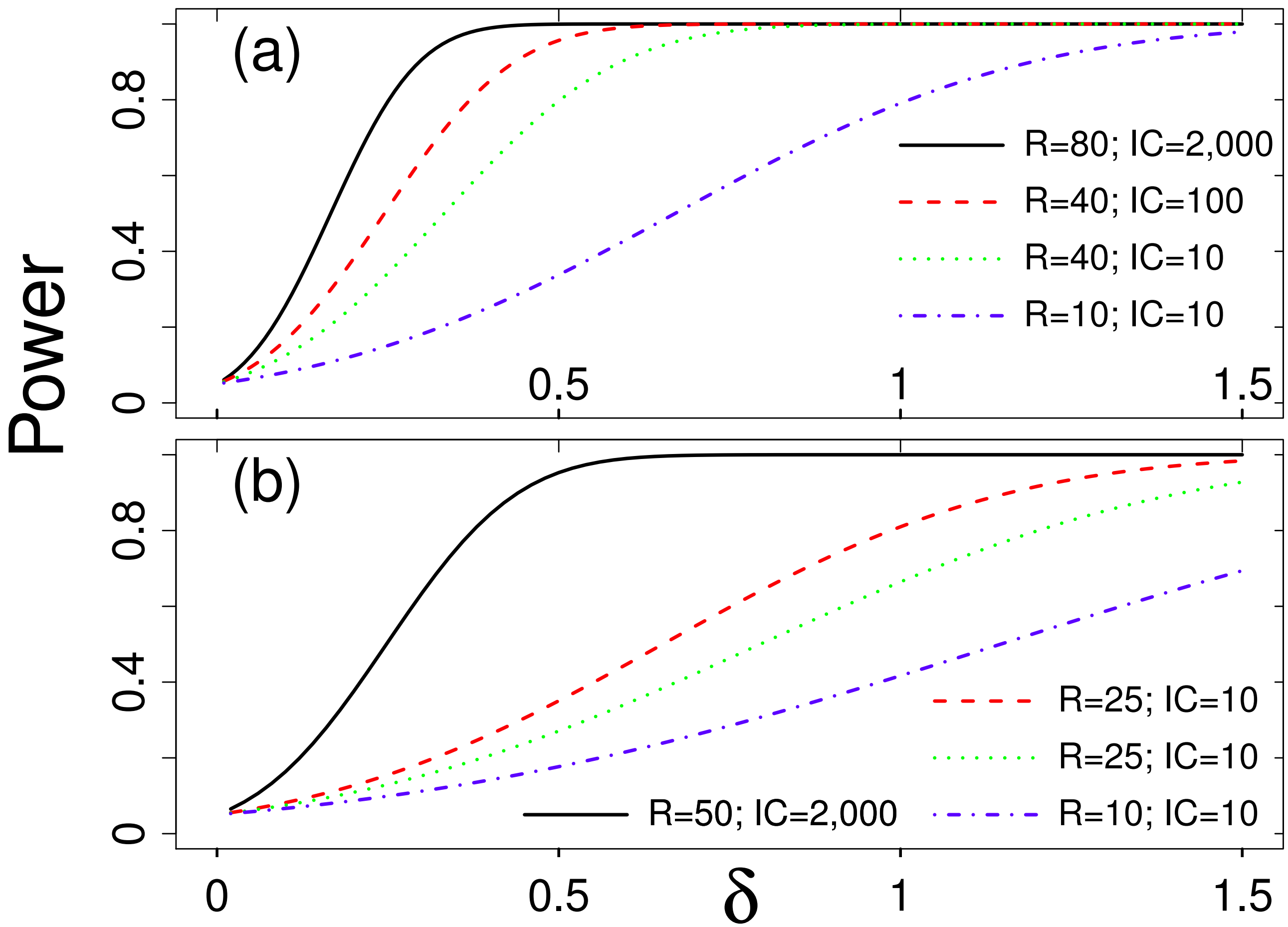
Monophasic 2 electrodes (Varying NR & NICS)

	E50(CI=2000)	E90(CI=2000)	E50(CI=100)	E90(CI=100)	E50(CI=10)	E90(CI=10)
NR 80 GLM GAM R2(GLM) R2(GAM)	3.08877 (0.02970) 3.39714 (0.04769) 9.38e-01 (3.87e-03) 9.47e-01 (4.35e-03)	6.78660 (0.07977) 6.7416 (0.0860)	3.0889 (0.0344) 3.3826 (0.0574) 8.41e-01 (4.91e-03) 8.49e-01 (5.47e-03)	6.7868 (0.0836) 6.7295 (0.0958)	3.0875 (0.0626) 3.3330 (0.1063) 0.5620 (0.0120) 0.5683 (0.0124)	6.7852 (0.1123) 6.714 (0.135)
NR 40 GLM GAM R2(GLM) R2(GAM)	3.08910 (0.04161) 3.39653 (0.06737) 9.38e-01 (5.47e-03) 9.47e-01 (6.14e-03)	6.78669 (0.11281) 6.7409 (0.1210)	3.0892 (0.0481) 3.3748 (0.0798) 8.41e-01 (6.90e-03) 8.50e-01 (7.73e-03)	6.7866 (0.1181) 6.7250 (0.1318)	3.0879 (0.0891) 3.308 (0.145) 0.5623 (0.0174) 0.5691 (0.0178)	6.786 (0.161) 6.717 (0.182)
NR 10 GLM GAM R2(GLM) R2(GAM)	3.0899 (0.0840) 3.3947 (0.1370) 9.40e-01 (1.06e-02) 9.51e-01 (1.19e-02)	6.7820 (0.2246) 6.7363 (0.2435)	3.0890 (0.0965) 3.355 (0.155) 0.8433 (0.0135) 0.8539 (0.0151)	6.7815 (0.2357) 6.717 (0.255)	3.085 (0.178) 3.250 (0.290) 0.5648 (0.0340) 0.5746 (0.0353)	6.777 (0.321) 6.712 (0.346)



Bootstrap simulations to determine the distribution of E_{50} & E_{90} (10,000 repetitions)

Statistical power (1-β)



2 electrodes

4 electrodes

$\alpha = 0.05$

If the true difference δ is large enough (δ ~ 1, same order as in 1D), one can do the 2D and 3D simulations with much less repetitions (/ 1,000) and still have a “decent” statistical power (0.8).

Conclusions

- We have used the “bidomain” model on a ring for comparing the efficiency of different defibrillation protocols and comparing the two and the four-electrode defibrillators.

- The biphasic shocks are proven to be more efficient (at high energy) because extra tissue is activated through the direct activation mechanism (2 electrodes).

- The 4 electrode defibrillator (biphasic II) offers a reduction of 80 % in energy with respect to its 2 electrode counterpart.

- Future…2D & 3D more realistic simulations are ongoing.
- Design of new protocols for lower energy defibrillation.

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Advantage of four-electrode over two-electrode defibrillators

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