Ectopic activity in 2-dimensional cultures of cardiac cells

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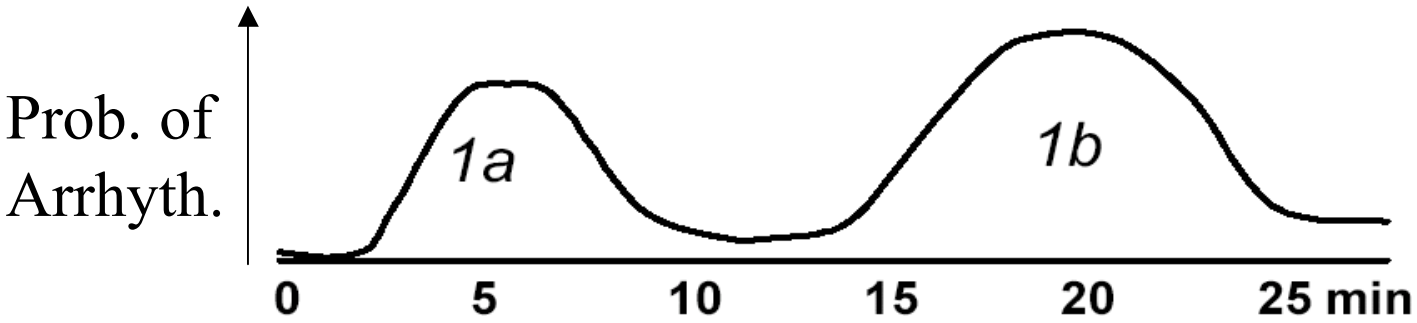
Medical context of the study (1)

Infarcts are caused by the clogging of blood vessels, which results in an inappropriate irrigation of the heart.

Arrhythmias occur very shortly after the infarct, or ~20 minutes after.



1a : mostly (~75%) reentrant arrhythmias

1b : mostly (~75%) ectopic arrhythmias (Janse and Wit, 1989)

Dynamics during an infarct ??

Medical context of the study (2)

Ischemia-Reperfusion arrhythmias :

- During the initial phase of an infarct, inadequate supply of blood and nutrients of the tissue leads to abnormal properties – cells become *spontaneously oscillatory*, and *uncoupled*.

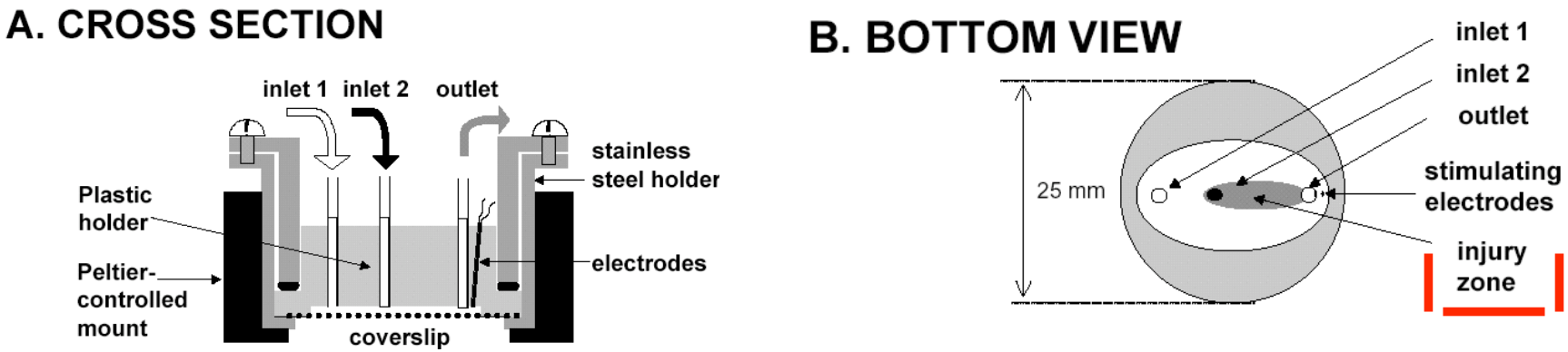
- After ~10 mn, at the boundary of the infarcted zone, partial recovery (reperfusion) is observed.

Arrhythmias occur mostly during the reperfusion, due to ectopic sources at the border between ischemic and normal tissue

Biological context of the study (1)

It is difficult to study the problem *in-vivo*; study it *in-vitro*, with 2-d cell cultures.

Experimental set-up (Arutunyan and Sarvazyan, 2000)



Effectively, create a geometrically and biochemically "well-controlled" infarct (see also Bub et al.).

Biological context of the study (2)

Main biochemical ingredients :

- The ischemia-mimicking solution contains uncouplers, which reduce the coupling between myocytes (Heptanol).

- The solution also contains factors that make myocytes *spontaneously oscillatory* (Isoproterenol; Barium).

Arrhythmias result from the interaction between the two effects.

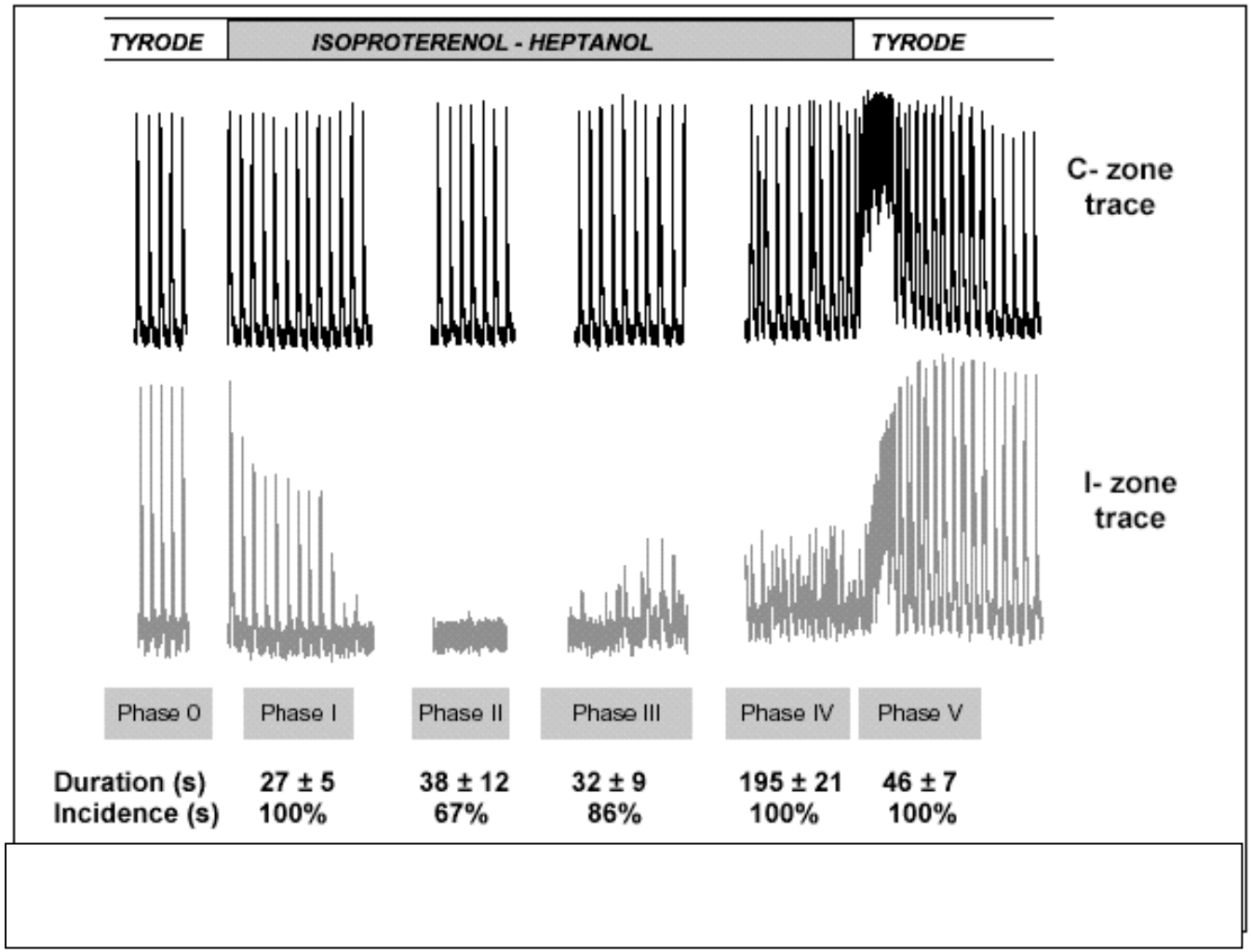
Protocol : add the ischemic solution, then wash it off to model the ischemia-reperfusion process.

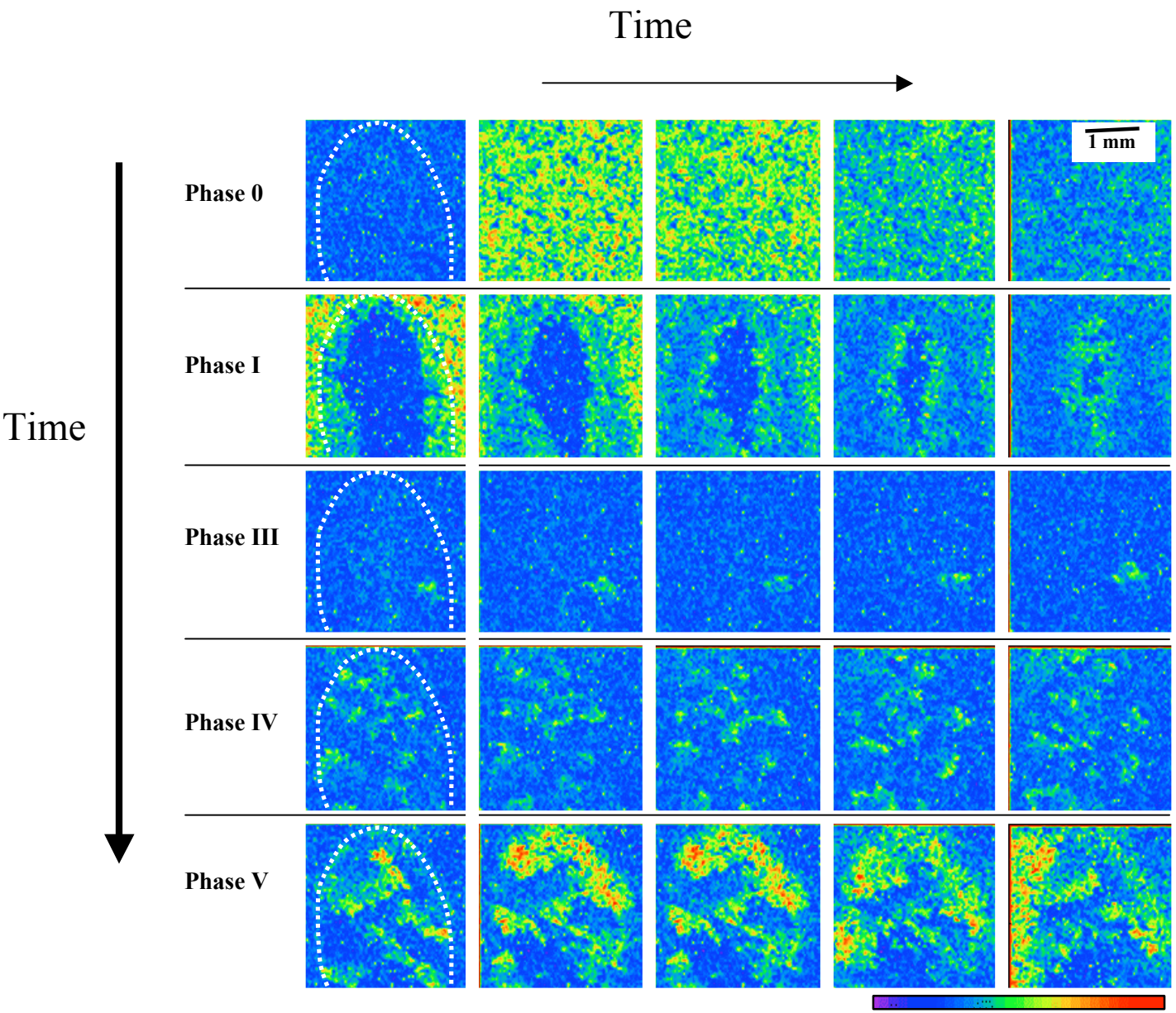
Biological context of the study (3)

Summary of the experimental results

Arrhythmias !

Pacing on the C-side.

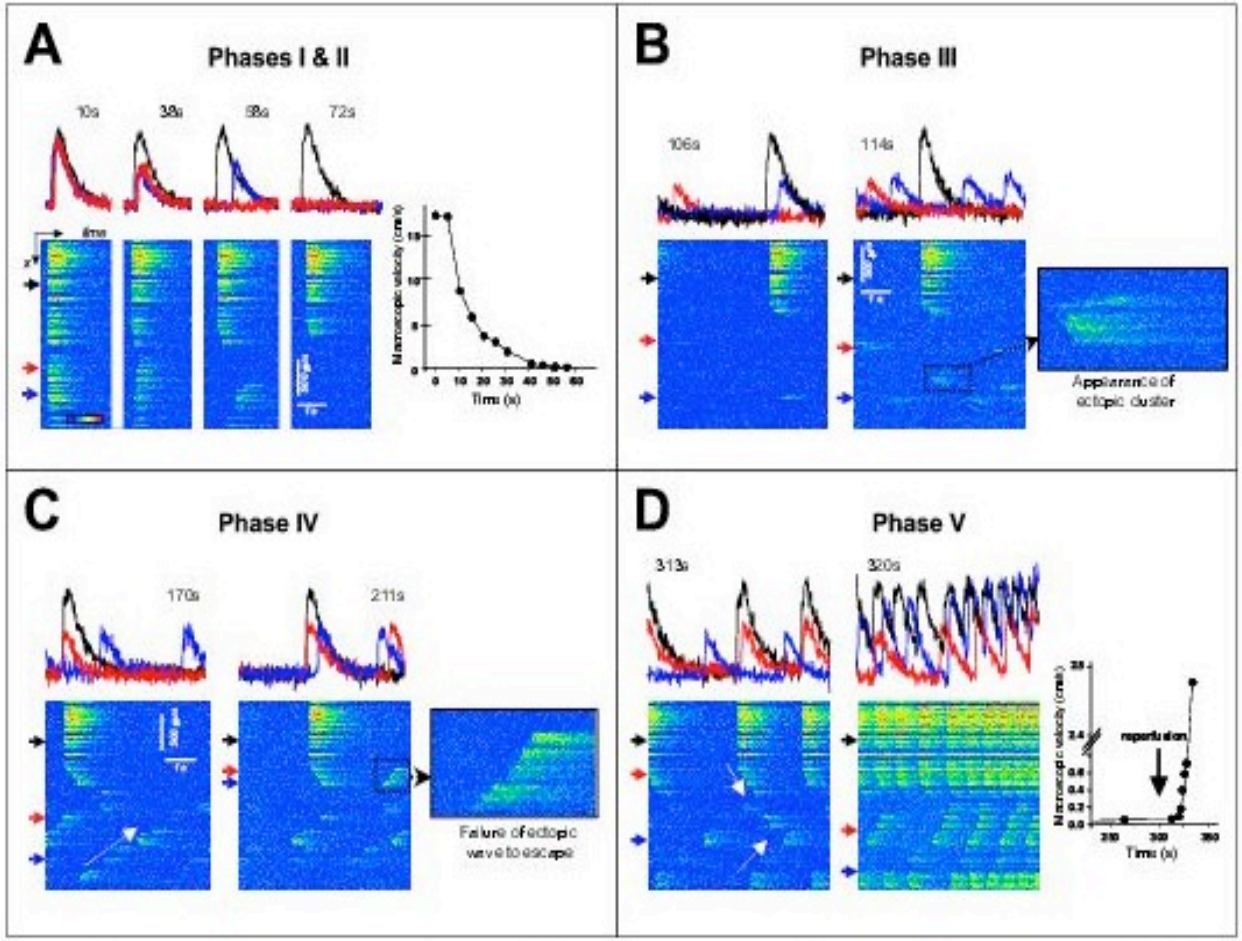




Arutunyan et al, AJP2003

Biological context of the study (4)

Summary of the results :



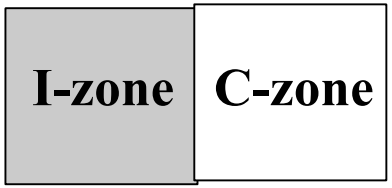
Purposes of the theoretical study:

- Identify the key ingredients of the dynamics leading to arrhythmias.

- Study the dynamics as a function of the concentrations of uncouplers (HEPT) and ISO/Barium (map out the 'phase diagram')

Modelling assumptions

• Simplified geometry :



• Ignore the real shape of the cells; model the cell network as a square lattice, coupled through a diffusive term $D\nabla^2$. Uncouplers (heptanol) block gap junctions, resulting in a much lower value of the diffusion term.

• Assume that after a change of uncouplers concentration, D relaxes towards the new equilibrium value with a characteristic time constant

$$\tau_D$$

We used two models: FitzHugh - Nagumo model (FHN)
Beeler - Reuter model (BR)

Beeler-Reuter model

$$C\partial_t e = -(I_{Na} + I_{K1} + I_{x1} + I_{Ca}) + D\nabla^2 e$$

Observation (Silva and Rudy, 2003) : the cells become spontaneously oscillating when the potassium current I_{K1} is inhibited. This corresponds precisely to the action of barium.
Simply use :

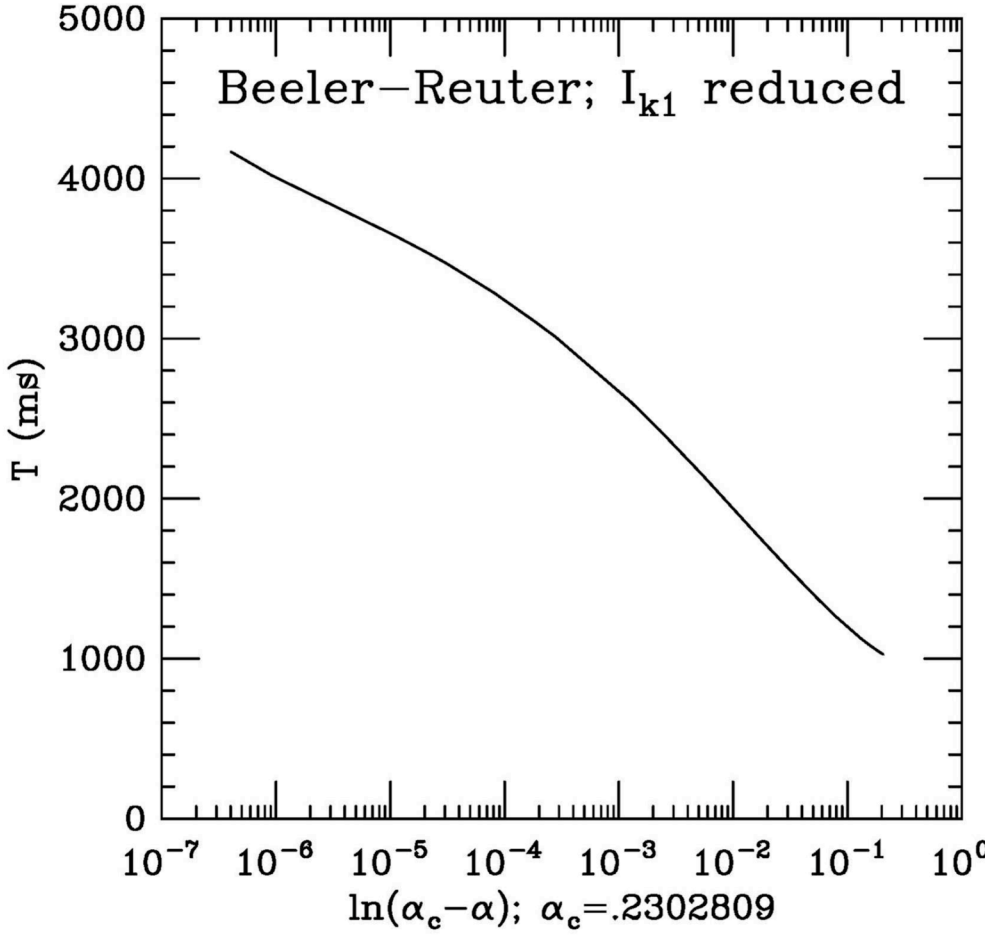
$$C\partial_t e = -(I_{Na} + (1-\alpha)\ I_{K1} + I_{x1} + I_{Ca}) + D\nabla^2 e$$

Transition from an excitable to an oscillatory state: Homoclinic bifurcation.

The period diverges logarithmically close to the transition.

The amplitude of the oscillation is constant.

Dependence of the oscillation period on Ik1 inhibition



Similar behavior observed in experiments (logarithmic divergence of the period of oscillation when the barium concentration goes to 0).

FitzHugh Nagumo model

For a normal excitable tissue, the model reads (e : membrane potential; w : slow variable following the fast depolarisation of e; assume here that $Ca \propto w$).

$$\partial_t e = A\ e\ (1-e)\ (e-u) - w + D\nabla^2 e$$

$$\partial_t w = \epsilon(e - kw)$$

To model the injured tissue with spontaneous activity, simply modify the equation for w by :

$$\partial_t w = \epsilon \times (e - \alpha u - kw)$$

Heterogeneity and temporal change in oscillatory behavior

Both for the FitzHugh-Nagumo and Beeler-Reuter models, increasing the parameter α leads from an excitable state to an oscillatory state.

The experiments suggest that cells do not all become spontaneously active at the same rate, and with the same frequency.

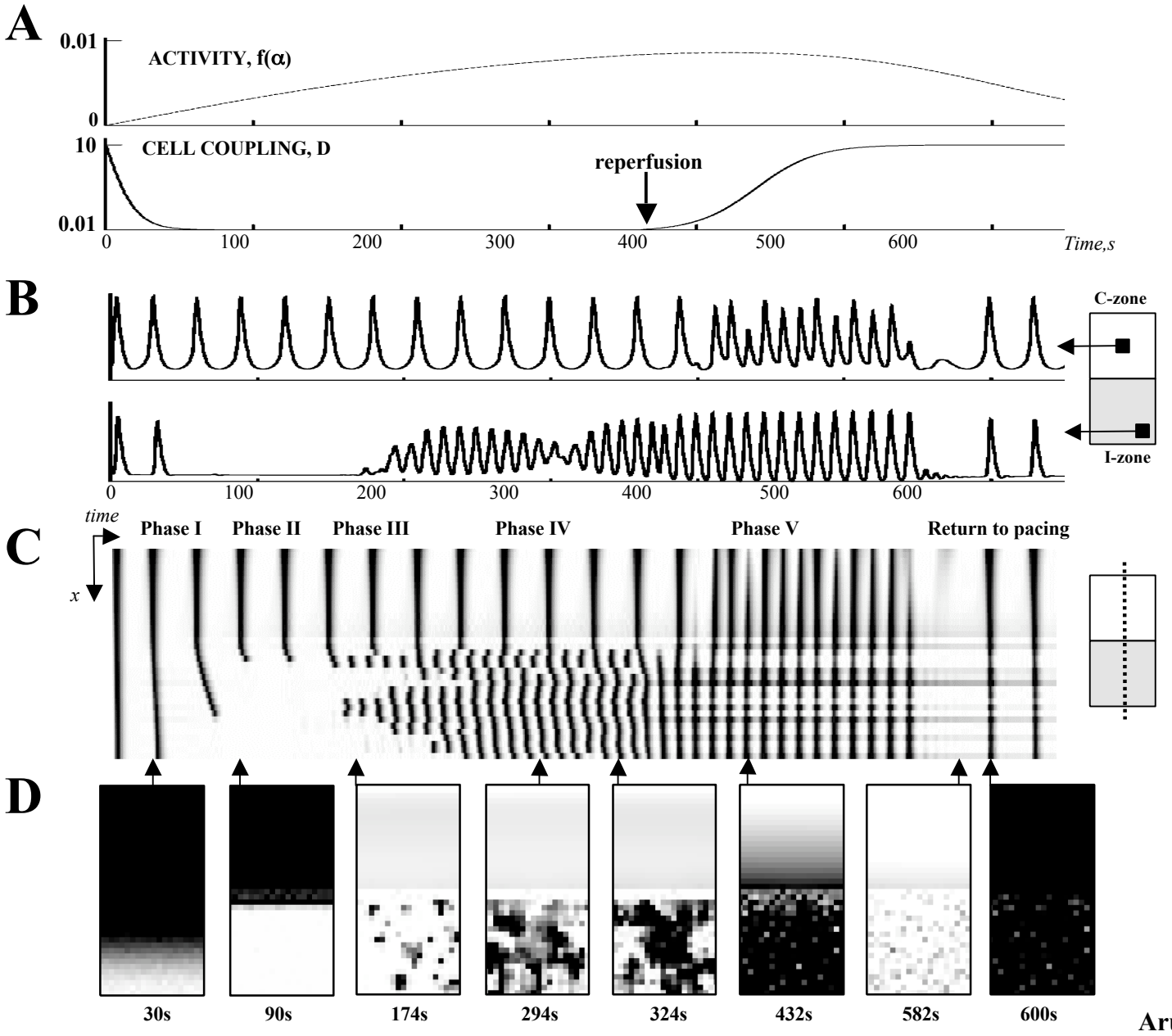
Therefore we introduce a dispersion of the values of $\alpha(i, j)$:

A random, spatially uncorrelated, gaussian distribution of $\alpha_0(i, j)$, with a mean value, $\langle\alpha\rangle$ and a rms, α_{rms} was used

Change in time during the experiment was modeled by

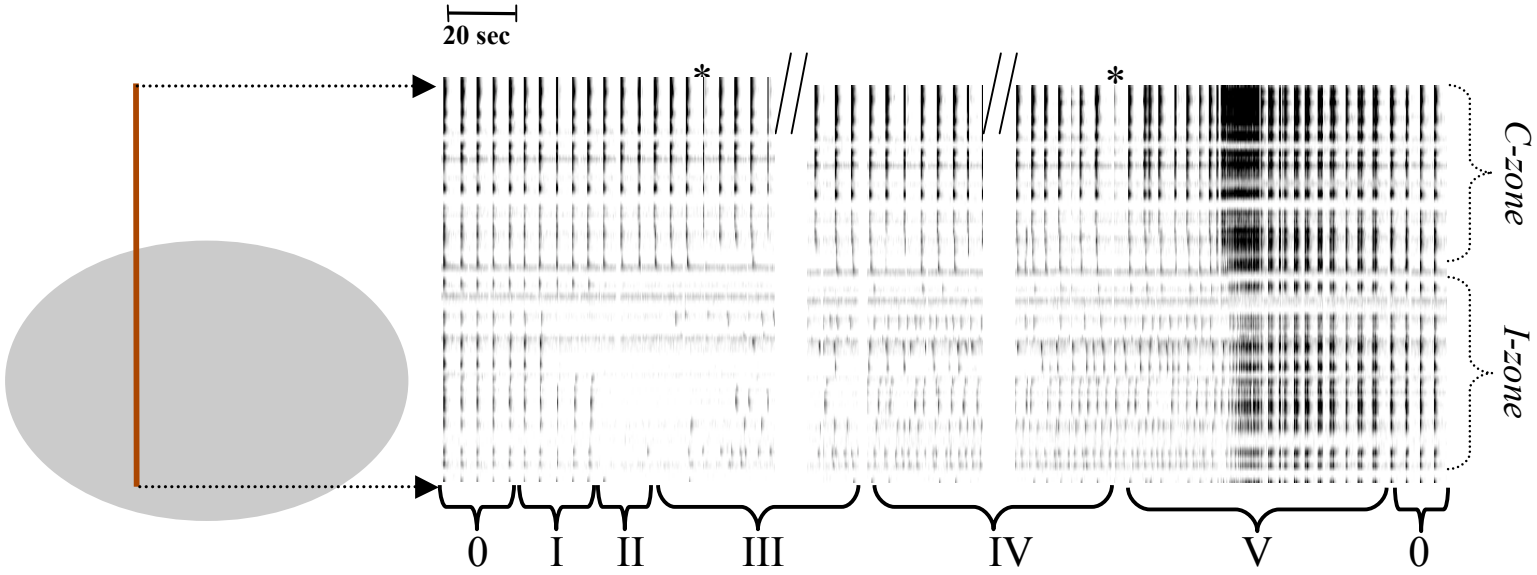
$$\alpha(i, j) = \alpha_0(i, j) \times f_\alpha(t)$$

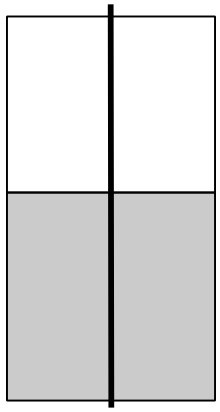
Modeling ISO-HEPT protocol using FHN model

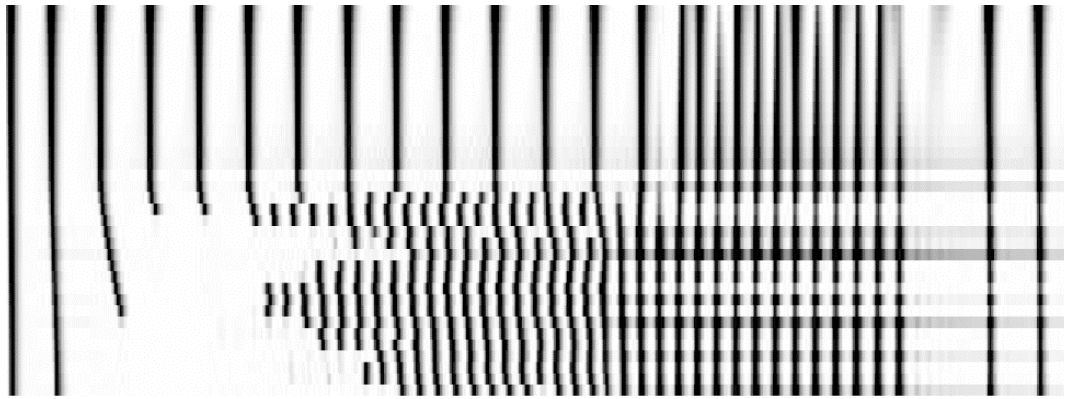


Arutunyan et al, 2003

Confrontation Experiment/Model :



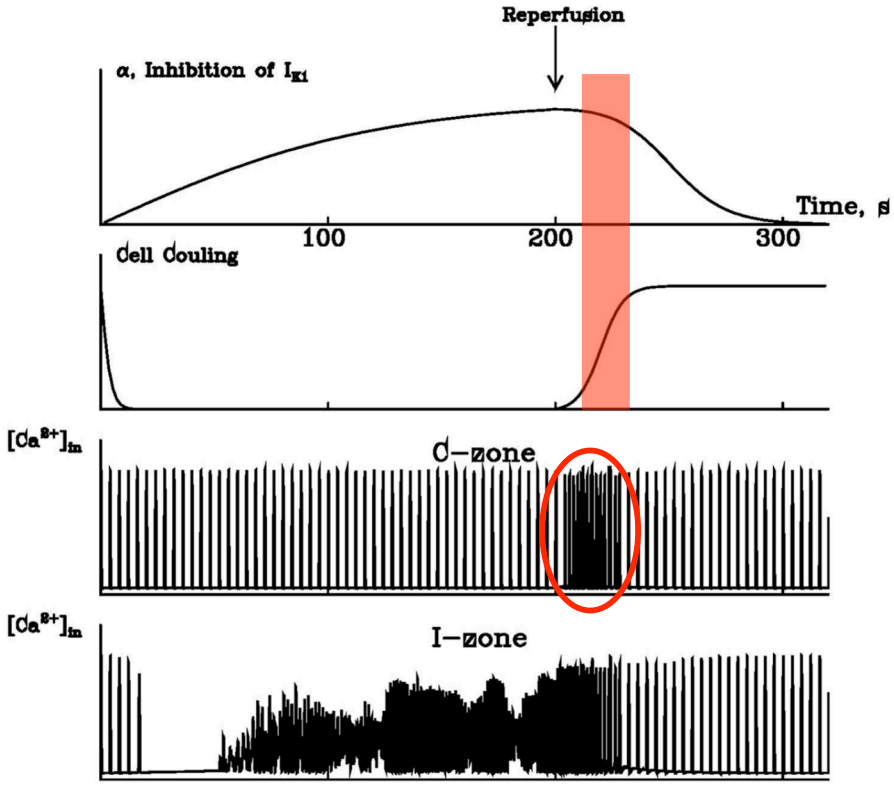




(Arutunyan et al, AJP2003)

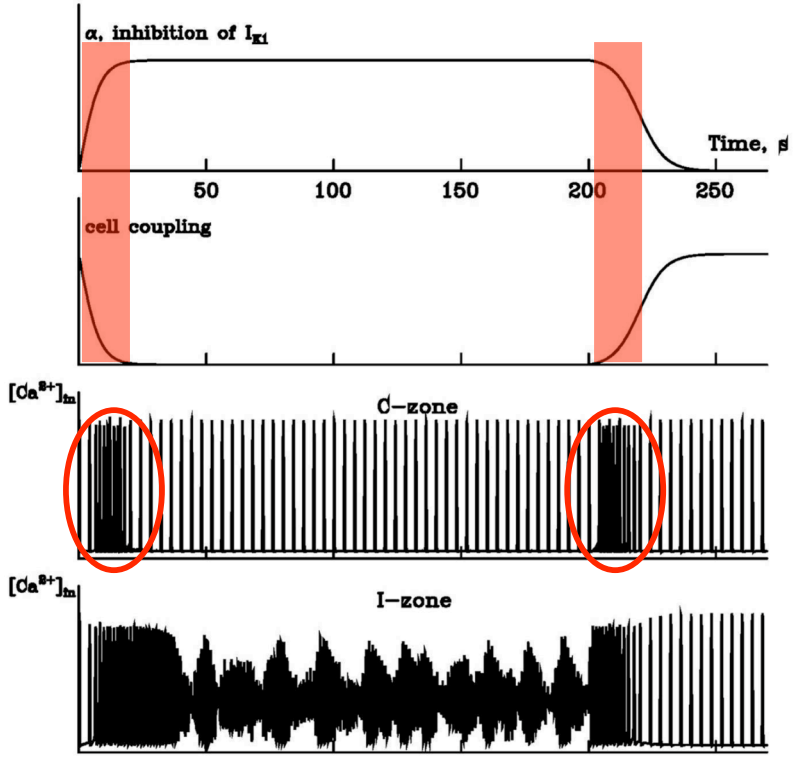
Modeling ISO-HEPT & Ba-HEPT using BR model

$\tau_D \ll \tau_\alpha$



ISO-HEPT

$\tau_D \sim \tau_\alpha$



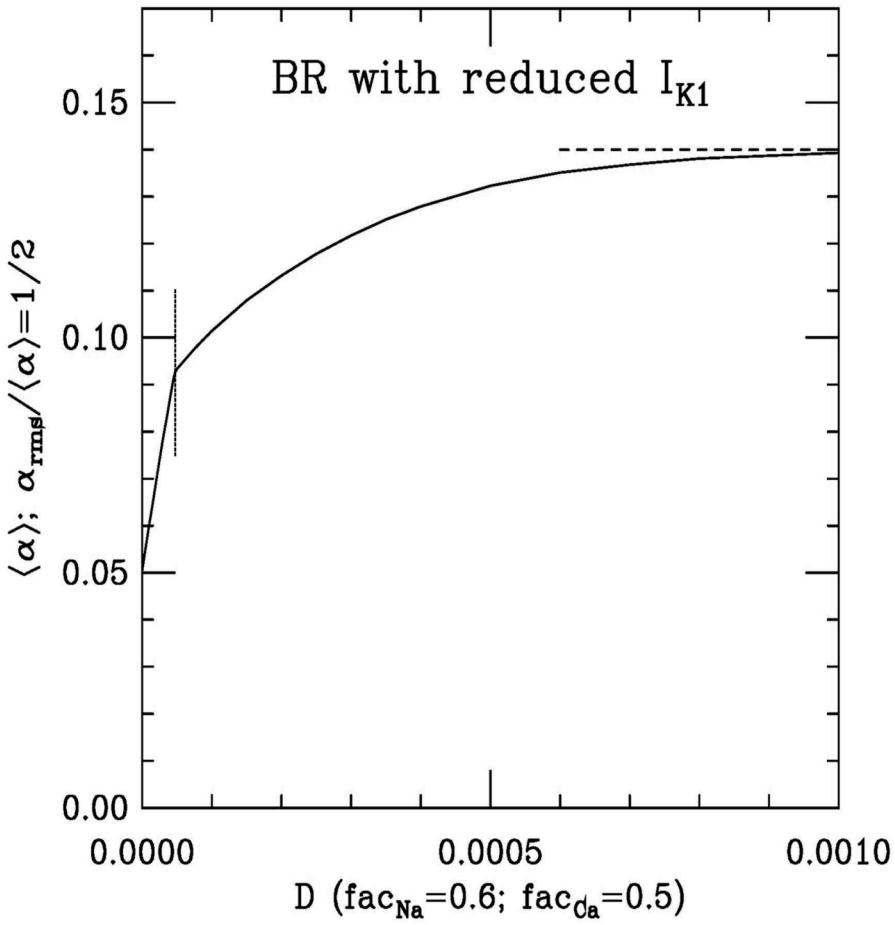
Ba-HEPT

Transition to oscillatory states

Question studied : nature of the transition between a uniformly quiescent state (all cells at rest) and a state when cells become active.

Parameters varied : the diffusion coefficient, D, and the parameters characterizing the cells' activity, <α> and α_{rms}

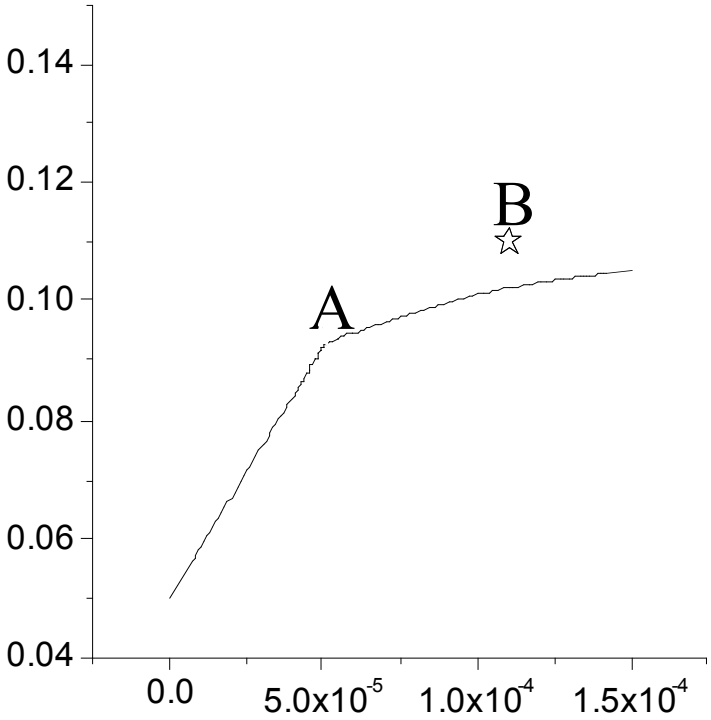
(for simplicity, the ratio <α>/ α_{rms} is held constant)

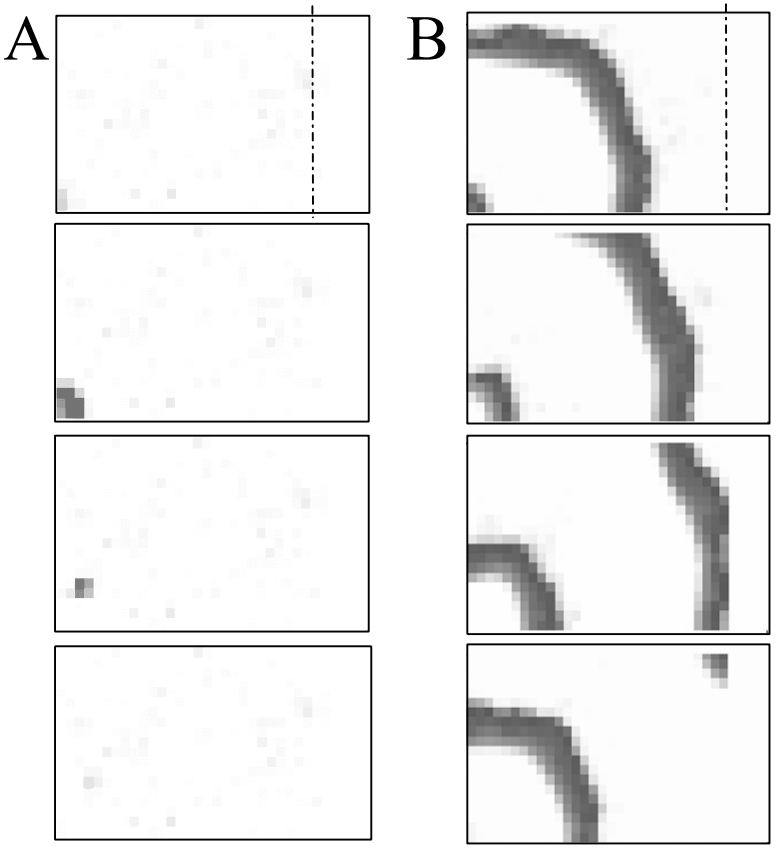


Propagating and non-propagating ectopic sources

Point B: α =0.11±0.055, D=11E-5

Point A: α =0.094±0.047, D=5E-5





Length of ectopic waves: effect of increasing excitability α.

Point F: α =0.10±0.05, D=5E-5

Point G: α =0.12±0.06, D=5E-5

Point H: α =0.14±0.07, D=5E-5